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2018 ASPHO ABSTRACTS

Plenary Paper # 2001 | EXCELLENT EVENT-FREE (EFS) AND OVERALL SURVIVAL (OS) FOR CHILDREN WITH DOWN SYNDROME (DS) WITH STANDARD RISK B-ACUTE LYMPHOBLASTIC LEUKEMIA (SR B-ALL): RESULTS OF CHILDREN'S ONCOLOGY GROUP (COG) AALL0331

Kelly Maloney, Meenakshi Devidas, Leonard Mattano, Alison Friedmann, Karen Rabin, Patrick Buckley, Michael Borowitz, Andrew Carroll, Julie Gastier-Foster, Nyla Heerema, Nina Kadan-Lottick, Mignon Loh, Yousif Matloub, David Marshall, Linda Stork, Elizabeth Raetz, Brent Wood, Naomi Winick, Stephen Hunger, William Carroll

University of Colorado, Children's Hospital Colorado, Aurora, Colorado, United States

Background: Survival for SR (age 1-9.99 yrs. and initial white blood cell count <50,000/microliter) B-ALL patients with DS has improved over time through enrollment on therapeutic trials and enhanced supportive care.

Objectives: To assess contemporary outcomes for DS patients with SR-ALL.

Design/Method: COG AALL0331 utilized a 3-drug induction (IND), with post-induction assignment into refined risk groups (SR-Low, SR-Average (Av), SR-High) based on leukemia genetics and early response. DS patients received risk-stratified therapy with additional supportive care guidelines, including leucovorin rescue after intrathecal methotrexate until maintenance, and highly encouraged hospitalizations during high-risk blocks until neutrophil recovery. SR-Av patients underwent a 2 × 2 randomization at end-IND to standard (SC) vs. intensified consolidation (IC) and standard interim maintenance (IM)/delayed intensification (DI) vs. intensified IM/DI. The IM/DI randomization was closed in 2008 due to superior results of escalating IV methotrexate (MTX) during IM for SR ALL patients treated on CCG 1991; all patients enrolled in AALL0331 subsequently received escalating IV MTX during IM. SR-high DS patients nonrandomly received IC and a single intensified IM/DI vs double IM/DI given to non-DS patients. SR-Low DS and non-DS patients participated in a randomization to additional pegaspargase doses during consolidation and IM.

Results: AALL0331 enrolled 5311 SR B-ALL patients (4/2005-5/2010), 141 (2.7%) had DS. 129 DS patients were CNS1 (91.5%), 11 CNS2 (7.7%) and 1 was CNS3. 138 patients were M1 at end induction, 3 did not have available results. There was no difference in the proportion of patients with a rapid early response or slow early response between DS and non-DS patients ($p = 0.578$). Risk distribution was significantly different ($p<0.0001$) for DS vs non-DS patients: SR-Low (15% vs. 47.3%), SR-Av (66.7% vs. 36.9%), and SR-High (18% vs. 15.8%). The 5-year EFS for all SR B-ALL patients with DS vs non-DS was 86%±3.1% vs 89%±0.45% ($p = 0.025$), and OS for DS vs non-DS patients was 90%±2.7% vs 96%±0.28% ($p<0.0001$). IND mortality for DS patients was initially excessive (11.5%), but after additional treatment modifications were made, decreased to 1.7%, 5-year EFS by risk groups for DS vs. non-DS patients was: SR-Low 100.00%±0.00% vs 95.35%±0.51%; SR-Av 88.07%±4.35% vs 89.63%±0.84%, and SR-High 82.35%±9.25% vs 86.18%±1.44%. DS was not prognostic in multivariate analyses that accounted for risk group.

Conclusion: With treatment modifications and additional supportive care, SR-ALL DS patients had excellent EFS and OS, similar to patients without DS in equivalent risk groups.

Plenary Paper # 2002 | INDUCED PLURIPOTENT STEM CELL MODEL OF 7Q DELETION IN BONE MARROW FAILURE IDENTIFIES A NOVEL THERAPEUTIC STRATEGY

Melisa Ruiz-Gutierrez, Cailin Joyce, Ozge Vargel Bolukbasi, Adriana Kotini, Gabriela Alexe, Jennifer Whangbo, David Russell, Kimberly Stegmaier, Carl Novina, Akiko Shimamura

Boston Children's Hospital, Boston, Massachusetts, United States

Background: Monosomy 7 or deletion of 7q (del(7q)) are common cytogenetic abnormalities in pediatric

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myelodysplastic syndrome (MDS) and frequently arise in the context of inherited bone marrow failure (BMF) syndromes, such as Shwachman Diamond Syndrome (SDS). Monosomy 7/del(7q) is associated with high grade MDS and propensity to progress to acute myelogenous leukemia, a major cause of morbidity and mortality for patients with inherited BMF. Development of non-transplant strategies to treat bone marrow failure without simultaneously stimulating outgrowth of malignant clones remains a major challenge.

Objectives: The aim of this study is to investigate the molecular consequences of del(7q) in the context of BMF with the goal of developing more effective treatments.

Design/Method: To study the biological and molecular consequences of monosomy/del(7q) in BMF, induced pluripotent stem cells were generated from SDS patients (SDS-iPSC). A deletion of the MDS-associated region of the long arm of chromosome 7 was then introduced using a previously published modified Cre-Lox approach.

Results: The SDS iPSC phenocopied bone marrow failure with slow proliferation and impaired hematopoietic differentiation. We next explored whether deletion of 7q conferred a relative fitness advantage within the context of bone marrow failure. Proliferation of the SDS-del(7q) iPSCs was reduced below that of both the isogenic SDS iPSCs and normal controls without an increase in cell death. SDS-del(7q) demonstrated reduced hematopoietic differentiation compared with isogenic SDS cells. These data demonstrate that deletion of 7q fails to confer a relative growth advantage relative to isogenic SDS iPSCs and results in further impairment of hematopoiesis. To gain insight into the mechanisms of del7q-associated clonal evolution in SDS, we performed RNA sequencing (RNAseq) of SDS+/-del(7q) iPSC. Expression of TGFβ pathways and their downstream targets were reduced in SDS-del(7q) iPSCs compared to isogenic SDS iPSC. Single cell RNAseq analysis of primary SDS bone marrow cells confirmed that the TGFβ pathway is hyperactivated in SDS. Western blot analysis showed increased phospho-SMAD2 levels in SDS iPSCs compared to SDS-del(7q) and normal controls, while total levels of SMAD2 were unchanged. Pharmacological targeting of TFGβ with small molecule inhibitors resulted in selective improvement of SDS hematopoietic colony formation and myeloid differentiation without stimulating outgrowth of the isogenic SDS-del(7q) cells or normal controls.

Conclusion: These results demonstrate that del(7q) reverses the TGFβ pathway hyperactivation of SDS. Furthermore, inhibition of TGFβ selectively rescues hematopoiesis in SDS but not in isogenic del7q cells, suggesting a potential strategy to treat bone marrow failure without stimulating del7q clonal outgrowth.

Paper Session # 2003/Young Investigator Award Recipient | CAR T CELLS TARGETING B7-H3, A PAN-CANCER ANTIGEN, DEMONSTRATE POTENT PRECLINICAL ACTIVITY AGAINST PEDIATRIC SOLID TUMORS AND BRAIN TUMORS

Robbie Majzner, Anandani Nellan, Sabine Heitzeneder, Johanna Theruvath, Crystal Mackall

Stanford University School of Medicine, Palo Alto, California, United States

Background: Patients with relapsed pediatric solid tumors and CNS malignancies have few therapeutic options and frequently die of their disease. Chimeric antigen receptor (CAR) T cells have shown promise in treating hematologic malignancies, but this has not yet translated to success in solid tumors. This is partially due to a paucity of identified differentially expressed cell surface molecules on solid tumors.

Objectives: Using a tumor specific anti-B7-H3 antibody (MGA271, Loo et al., 2012), we aimed to generate a novel CAR targeting B7-H3, a checkpoint molecule overexpressed at high levels on many pediatric solid tumors.

Design/Method: Pediatric tumor microarrays were stained for B7-H3 expression by immunohistochemistry (IHC). A second-generation CAR containing the 41BB and CD3-zeta endodomains was generated using the variable regions of MGA271. The MGA271 antibody was previously shown to have tumor specific binding and has been used in a clinical setting without off-tumor effects. The B7-H3-CAR was tested in several models of lethal pediatric malignancies.

Results: B7-H3 was expressed on 84% of tumors stained, with most samples demonstrating high and homogeneous levels of expression, including Ewing sarcoma, rhabdomyosarcoma, diffuse intrinsic pontine glioma, Wilms tumor, and medulloblastoma. B7-H3-CAR T cells demonstrated robust cell killing and cytokine production in vitro against cell lines derived from these histologies. A single dose of intravenously administered B7-H3-CAR T cells mediated complete regression of established osteosarcoma (MG63.3) and Ewing sarcoma (EW8) orthotopic xenografts, resulting in significantly improved survival in both models. All mice treated with control CD19-CAR T cells died of tumor. Additionally, the B7-H3-CAR was tested in a universally fatal metastatic model of osteosarcoma. Whereas all untreated mice died from lung metastases, 9/10 B7-H3-CAR treated mice survived for greater than six months. In order to test if the CAR can traffic to the CNS and cross the blood brain barrier, mice were orthotopically injected with medulloblastoma in the posterior fossa and then treated with B7-H3-CAR or control CD19-CAR T

cells. In two different xenograft models of medulloblastoma (D425 and DAOY), the B7-H3-CAR mediated regression of tumors and significantly extended survival.

Conclusion: We have generated an effective, novel therapeutic for many pediatric solid tumors and brain tumors. This is the first reported CAR targeting B7-H3. This therapy could be transformative for children with high risk diseases who lack effective therapeutic options. A clinical trial in relapsed pediatric solid tumors and CNS malignancies is planned.

Paper Session # 2004/Young Investigator Award Recipient | NATURAL KILLER CELLS TARGETING THE SUPPRESSIVE IMMUNE MICROENVIRONMENT OF PEDIATRIC SOLID TUMORS RESCUE THE IMPAIRED ACTIVITY OF CAR-T CELLS

Robin Parihar, Charlotte Rivas, Stephanie Fetzko, Anna Cole, Stephen Gottschalk, Cliona Rooney

Baylor College of Medicine, Houston, Texas, United States

Background: Immunotherapy with chimeric antigen receptor-bearing T (CAR-T) cells directed against the leukemia/lymphoma antigen CD19 has produced impressive clinical responses. In contrast, CAR-T cells directed against solid tumors have produced few durable clinical responses, in part, due to a solid tumor microenvironment (TME) that inhibits the activity of T cells. Myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and inhibitory macrophages (M2s) contribute to the immunosuppressive TME by secreting suppressive cytokines and expressing inhibitory ligands. To increase the efficacy of CAR-T therapies for pediatric solid tumors, approaches to reverse TME-mediated immune suppression are needed. Human MDSCs, Tregs, and M2s express ligands for the activating receptor, NKG2D, found on natural killer (NK) cells. To target these suppressive components of the TME, we have generated NK cells expressing a highly cytotoxic version of this activating receptor, comprising the ectodomain of NKG2D fused to the CD3-zeta endodomain (termed NKG2D.zeta).

Objectives: (1) To define the mechanisms by which MDSCs, Tregs, and M2s within the solid TME inhibit CAR-T cell anti-tumor activity, and (2) To test an approach to reverse CAR-T impairment by targeting MDSCs, Tregs, and M2s using NKG2D.zeta-expressing NK cells. We hypothesized that NK cells expressing NKG2D.zeta would kill NKG2D ligand-expressing MDSCs, Tregs, and M2s, and secrete pro-inflammatory cytokines and chemokines that would alter the TME and recruit and activate CAR-T cells.

Design/Method: To assess the effects of the suppressive immune microenvironment on CAR-T function, we established a novel in vivo TME model of neuroblastoma in which human MDSCs, Tregs, or M2s co-implanted with a neuroblastoma cell line induce tumor supportive stroma and immune suppression. In this model, we examined the ability of NKG2D.zeta-expressing NK cells to eliminate MDSCs, Tregs, or M2s, and improve the anti-tumor function of CAR-T cells targeting the GD2 neuroblastoma antigen (GD2.CAR-T).

Results: Tumors containing MDSCs or M2s inhibited GD2.CAR-T homing and expansion at tumor sites, whereas Tregs only inhibited local expansion, which resulted in impaired GD2.CAR-T cell-mediated tumor control. Pre-infusion of NKG2D.zeta NK cells reduced intra-tumoral MDSCs, Tregs and M2s, led to accumulation of an array of T cell-attracting chemokines, and rescued homing and expansion of subsequently infused GD2.CAR-T cells.

Conclusion: NKG2D.zeta NK cells reduced the immunosuppressive burden within the solid TME, resulting in enhanced CAR-T cell function. We provide a rationale for a novel combination therapy utilizing the anti-TME effects of NKG2D.zeta NK cells with the anti-tumor activity of CAR-T cells for the treatment of pediatric solid tumors.

Paper Session # 2005 | MUTATIONAL SIGNATURES AND IMMUNOPHENOTYPE IN RECURRENT MEDULLOBLASTOMA: AN INDICATION FOR NOVEL THERAPEUTIC APPROACH

Aditi Bagchi, Megan Bowman, Galen Hostetter, Scott Jewell

Helen DeVos Children's Hospital Van Andel Research Institute, Grand Rapids, Michigan, United States

Background: Standard therapy of medulloblastoma consists of treatment with alkylating agents and radiation after surgical resection. Although a statistically significant increase in survival is reported with this regimen, 1/3rd recur and become resistant this class of agents ultimately leading to mortality. Large numbers of somatic mutations were observed in recurrent medulloblastoma (RM) after alkylating agent and radiation treatment. High mutation rates in tumors can have twofold effect; 1) a large number of non-synonymous mutations that have no role as drivers can still cause functional tumor antigens increasing the neoantigen burden and immunogenicity.

Moreover, 2) such tumors can gain mutations in canonical or non-canonical DNA repair pathways leading to a gain in the number of mutations as seen in case of glioblastoma, this can lead to even higher accelerated mutational rate. Evidences suggest that high mutational load can cause higher neoantigen burden thereby making the tumor more susceptible to immune checkpoint inhibition. We propose that post therapy recurrent medulloblastoma gain mutational signature and Immunophenotype of malignancies demonstrating clinical response to Immune checkpoint therapy.

Objectives: 1) RM has molecular signatures identical to tumors with high immunogenicity and clinical response to immune check point inhibition. 2) RM has the immune inflammatory phenotype; harboring high percentage of tumor infiltrating lymphocytes (TILs), macrophages and monocytes.

Design/Method: To test our hypothesis, we downloaded the raw BAM files of previously published data from International Cancer Genome consortium (ICGC). This set of about 30 matched primaries and recurrent medulloblastoma cases forms our discovery cohort. We have called somatic variants using the GATK pipeline by the Broad Institute. To validate our key findings, we have procured human medulloblastoma specimens and are conducting whole exome sequencing. The primary assays utilized to assess immunogenicity are immunohistochemical (IHC) staining of formalin fixed and embedded recurrent medulloblastoma tissue to identify TILs, tumor associated macrophages and other markers.

Results: Genomic data was aligned to hg38 genome reference the analysis, validated previously published results and identified mutations in genes of interest (repair pathway genes, immune related). We identified higher proportion of SNPs were missense mutations in RM, indicating higher burden of neoepitopes. The preliminary IHC staining shows increase tumor infiltrations of TILs and macrophages indicating immune inflammatory phenotype of RM.

Conclusion: RM are resistant to standard chemotherapies and radiation, there is a critical need for alternative strategies. Our preliminary analysis indicates a potential role of immune check point inhibitors for treating recurrence. Further validation of the results is being conducted.

Paper Session # 2006/Early Career Travel Stipend Award Recipient | EX VIVO EXPANDED MULTI-ANTIGEN SPECIFIC LYMPHOCYTES FOR THE TREATMENT OF SOLID TUMORS

Amy Houghtelin, C. Russell Cruz, Robert Ulrey, Barbara O'Brien, Maja Stanojevic, Shuroug Albihani, Fahmida Hoq, Maria Fernanda Fortiz, Haili Lang, Patrick Hanley, Catherine Bollard, Holly Meany

Children's National Medical Center, Washington, District of Columbia, United States

Background: Patients with solid tumors refractory to standard therapies have poor prognoses, and most salvage therapies are toxic and ineffective. T cell therapies, which have been successful in hematologic malignancies, offer a promising alternative for targeted therapy. While immunotherapy such as chimeric-antigen receptor (CAR) T cells have had only limited success in solid tumors, antigen-specific T cells offer the ability to target multiple antigens with minimal toxicity seen in early clinical trials. We hypothesize that patient-derived tumor-associated antigen-specific T cells (TAA-T) targeting WT1, PRAME, and survivin, antigens expressed by many pediatric solid tumors, can be safely administered to treat relapsed/refractory disease.

Objectives: The objective of this phase I clinical trial is to determine the safety of administering TAA-T to patients with a high-risk solid tumor due to the presence of refractory, relapsed and/or residual detectable disease. Secondary objectives include determination of disease response and immune reconstitution following infusion.

Design/Method: T cells expanded from patient peripheral blood are stimulated weekly with antigen presenting cells expressing an overlapping peptide library spanning the tumor antigens WT1, PRAME, and survivin. Following release testing (cytotoxicity assay, culture, flow cytometry), patients are infused with TAA-T on a dose escalation study ranging from a dose of 1 × 107/m2 (level 1) to a maximum dose of 4 × 107/m2 (level 3), potentially every 4 weeks. Clinical and immune reconstitution studies are performed post-infusion to monitor for adverse effects and assess immune and disease responses.

Results: We have generated TAA-T products from 14 patients with relapsed/refractory solid tumors (neuroblastoma, osteosarcoma, Wilms tumor, Ewing sarcoma, soft tissue sarcoma, rhabdomyosarcoma), all passing release criteria. We have infused 12 patients with a median of 2 (range 1–8) infusions without product-related severe adverse events post-infusion. Epitope spreading to tumor-associated antigens beyond WT1, PRAME, and survivin was identified in 86% of responding patients, supporting TAA-T persistence and in vivo efficacy. Preliminary outcome data (N = 10) shows overall survival of 90% and 78% at 3 months and 6 months, respectively; event-free survival is 60% and 25% at 3 months and 6 months, respectively.

Conclusion: This unique immunotherapeutic has been well tolerated without causing life-threatening cytokine release syndrome. Despite aggressive and multiply relapsed disease, 60% of patients have demonstrated evidence of disease control

after TAA-T with epitope spreading identified in a majority of patients post-infusion. These clinical and laboratory data suggest that this therapy may have efficacy in patients with relapsed refractory solid tumors.

Paper Session # 2007 | PHASE 1 STUDY OF THE EZH2 INHIBITOR, TAZEMETOSTAT, IN CHILDREN WITH RELAPSED OR REFRACTORY INI1-NEGATIVE TUMORS INCLUDING RHABDOID TUMORS, EPITHELIOID SARCOMA, CHORDOMA; AND SYNOVIAL SARCOMA

Susan Chi, Maryam Fouladi, Neerav Shukla, Franck Bourdeaut, Ashley Margol, Guy Makin, Geoff McCowage, Cynthia Wetmore, Margaret Macy, Ted W. Laetsch, Darren Hargrave, Navin Pinto, Joanna Yi, Dave Ebb, Giles Robinson, Maria Roche, Benjamin Suttle, Alicia Clawson, Peter Ho, Jill Rodstrom, Scott Daigle, Karsten Nysom

Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: The defining molecular feature of rhabdoid tumors, epithelioid sarcomas (ES), and poorly differentiated chordomas is the absence of tumor INI1 expression, which induces dependence on EZH2 through transcriptional repression caused by aberrant H3K27me3. Tazemetostat, a potent and selective EZH2 inhibitor, has demonstrated tumor regression in INI1-negative preclinical models and durable objective responses in adults with certain INI1-negative tumors.

Objectives: To determine the recommended Phase 2 dose (RP2D) and interim results from the dose escalation (DEsc) cohorts of a Phase 1 pediatric study.

Design/Method: EZH-102 (NCT02601937) is a Phase 1, multi-center study of tazemetostat continuously dosed through an oral suspension administered BID in patients aged 6 months to 21 years with synovial sarcoma, or INI1-negative tumors. The DEsc was a "Rolling 6" design and objective response were assessed every 8 weeks using disease appropriate response criteria i.e. RANO or RECIST 1.1. Primary endpoints included identification of dose-limiting toxicities (DLT) and RP2D. Secondary endpoints included safety/tolerability, pharmacokinetics (PK), and duration of response. Exploratory endpoints assessed the relationship between tazemetostat exposure and the pharmacodynamic (PD) marker H3K27me3 in peripheral blood.

Results: Forty-six patients were treated in 7 dose cohorts: 240 (n = 8), 300 (n = 6), 400 (n = 6), 520 (n = 7), 700 (n = 6), 900 (n = 6) and 1200 (n = 7) mg/m2 BID. One patient at 300 mg/m2 had DLTs of dyspnea (grade 4)/hypoxia (grade 3) but no DLTs were observed in any other cohort. Adverse events were generally mild to moderate, consistent with the safety profile observed in adults. Across the DEsc cohorts, plasma concentrations were dose-proportional and steady state concentrations were lower on Day 15 vs. Day 1. Mean systemic exposure in the 1200 mg/m2 cohort was ~ 4-fold greater compared with the adult RP2D of 800 mg BID. A PK:PD relationship between tazemetostat exposure and H3K27me3 levels in peripheral blood monocytes and granulocytes was observed in the DEsc phase. Consistent and significant post-dose reductions in H3K27me3 occurred at doses ≥900 mg/m2. Further analysis of twelve patients treated at the RP2D confirmed that H3K27me3 inhibition was maximally inhibited. Doses 520–900 mg/m2 showed confirmed objective responses (CR/PR) per RECIST/RANO in patients with ES (n = 1), chordoma (n = 2), and ATRT (n = 1).

Conclusion: Tazemetostat was generally well tolerated in children and showed promising anti-tumor activity including CRs in patients with INI1-negative tumors. The RP2D of 1200 mg/m2 BID was defined on the basis of PK, PD, and clinical safety, and resulted in higher systemic exposure than in adults. Dose expansion cohorts are currently enrolling.

Paper Session # 2008 | CHANGES IN ANTIEMETIC PRESCRIBING PRACTICES FOR CHILDREN RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY

Matthew Davis, Marc Rosenman, Anne Bendelow, Stewart Goldman

Ann & Robert H. Lurie Children's Hospital, Chicago, Illinois, United States

Background: Acute chemotherapy-induced nausea and vomiting occurs among greater than 90% of children who receive chemotherapeutic agents rated at National Comprehensive Cancer Network (NCCN) Level 5 for emetogenicity. Although some antiemetics are formally endorsed in consensus guidelines, use of antiemetic regimens for children is complicated by few randomized clinical trials in children and lack of formal FDA labeling for indications for use in children under age 12 years for some agents. In this context, we sought to characterize evolving antiemetic prescribing practices by physicians and advanced practice nurses at a major pediatric oncology program.

Objectives: To compare frequencies of different antiemetic regimens prescribed for children receiving highly emetogenic

chemotherapy in an outpatient day hospital setting, over the most recent 4 years (2013-2017).

Design/Method: We retrospectively identified children who received NCCN Level 5 chemotherapy in the outpatient day hospital at our children's hospital from July 2013 through June 2017. Through review of electronic medical records, we categorized antiemetic regimens based on administration in the infusion suite at the time of chemotherapy and prescriptions issued to patients for outpatient use. Using published consensus guidelines and clinical evidence, we specified 10 mutually exclusive antiemetic prescribing patterns, focusing on key agents and combinations including ondansetron, aprepitant, dexamethasone, and olanzapine. Given evidence published in late 2014 about safety of olanzapine, we compared the periods 2013–14 versus 2015–17 regarding the most commonly prescribed regimens. We used likelihood ratio chi-squared tests of proportions to assess statistical significance.

Results: For 121 patients treated during the study period with Level 5 chemotherapy, we identified 337 separate encounters for chemotherapy in the outpatient day hospital. For encounters in 2013–14 (n = 75), the most commonly prescribed regimens were ondansetron + aprepitant (36%), ondansetron IV/PO only (23%), ondansetron IV only (17%), and ondansetron + aprepitant + dexamethasone (11%). For encounters in 2015–17 (n = 262), the most commonly prescribed regimens were ondansetron + olanzapine (22%), ondansetron + multiple other emetics other than olanzapine (22%), ondansetron IV only (18%), and ondansetron + aprepitant (13%). The frequencies of specific antiemetic regimens differed significantly in 2015–17 versus 2013–14 ($p<0.001$).

Conclusion: Evidence suggesting safety of olanzapine as an antiemetic for children has led to a significant shift in prescribing practices over the last 4 years among oncology clinicians, toward olanzapine-containing regimens and away from the previously predominant combination of ondansetron + aprepitant. Further investigations must examine the relative antiemetic effectiveness of these distinct regimens.

Paper Session # 2009 |

NEUROPROTECTIVE EFFECTS OF HYDROXYUREA IN SICKLE CELL ANEMIA: MAINTENANCE OF NORMAL CEREBRAL OXYGENATION

Charles Quinn, Adriane Hausfeld, Amanda Pfeiffer, Omar Niss, Russell Ware, Patrick McGann

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Children with sickle cell anemia (SCA) have a very high risk of cerebral ischemia and infarction. Desaturation of hemoglobin (Hb) in cerebral tissue, a physiologic marker of brain that is vulnerable to ischemic injury, can be measured non-invasively by transcranial near-infrared spectroscopy. Consequently, cerebral oximetry could be used to monitor primary neuroprotective therapy in SCA. Without disease-modifying therapy, the oxygen saturation of Hb in cerebral tissue (SCTO2) in SCA is markedly decreased and declines further with increasing age (Quinn 2012).

Objectives: We hypothesized that early initiation of hydroxyurea therapy with sustained treatment at maximum tolerated dose can prevent the expected, age-related decline in SCTO2 and maintain normal values in most children with SCA.

Design/Method: TREAT is an ongoing, prospective cohort study of children with SCA receiving pharmacokinetics-based dosing of hydroxyurea (NCT02286154). We used the FORESIGHT cerebral oximeter to measure SCTO2 with bi-frontal probes immediately before initiation of hydroxyurea and every 3–4 months thereafter. The mean of the right and left SCTO2 values was calculated. Comparison groups included children with SCA without disease-modifying therapy and controls without SCA (Quinn 2012).

Results: We studied 36 children (50% male) who initiated hydroxyurea therapy at 1.5±0.3 (mean ± SEM) years of age (range 0.5 - 6.9), of whom 23 (64%) initiated hydroxyurea before 1 year of age. Mean duration of hydroxyurea therapy was 1.2±0.2 years (range: 0.1 - 2.8), giving a total of 44.3 patient-years of hydroxyurea therapy. Before initiation of hydroxyurea, mean SCTO2 was 66.4±1.6% (range 52.3 - 78.0%; lower limit of normal = 65%). At the last visit, mean SCTO2 was 70.9±1.2% (range 53.8 - 86.5%), a statistically significant increase from before initiation of hydroxyurea therapy ($P<0.001$). In longitudinal analysis, the mean slope of SCTO2 over time was positive at 3.2±3.1% per year (range: -30 to 71.4), indicating that SCTO2 did not decrease with age, as would be expected without disease-modifying therapy. Considering all SCTO2 values from TREAT participants measured after initiation of hydroxyurea, 79% were in the normal range (65-80%) and 93% were above the age-related mean for children with SCA without disease-modifying therapy.

Conclusion: Hydroxyurea therapy appears to prevent the progressive, age-related decline in cerebral tissue Hb saturation (SCTO2) that occurs in children with SCA. Overall, SCTO2 increased with hydroxyurea therapy, mostly into the normal range. These data suggest that hydroxyurea may be neuroprotective by improving the balance between oxygen supply and demand within cerebral tissue. (Quinn, Pediatr Blood Cancer, 2012).

Paper Session # 2010/Early Career Travel Stipend Award Recipient | OUTCOMES OF UNRELATED DONOR PERIPHERAL STEM CELL TRANSPLANTATION FOR PATIENTS WITH NON-MALIGNANT HEMATOLOGIC DISORDERS USING TWO PARTIAL T CELL DEPLETION STRATEGIES

Joseph Oved, Yongping Wang, Yanping Huang, Dimitri Monos, David Barrett, Stephan A. Grupp, Nancy Bunin, Timothy Olson

Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States

Background: Partial T cell depletion (pTCD) of mobilized peripheral stem cells (PSC) may allow successful engraftment with high doses of CD34+ stem cell doses and limit severity of graft versus host disease and graft failure in patients with non-malignant hematologic diseases. Consequently, this allows expansion of unrelated donor peripheral stem cell transplantation (URD-PSCT) as curative therapy for this pediatric patient population. We present outcomes of 15 patients with non-malignant hematologic diseases who received URD-PSCT with pTCD performed using CliniMACS and either CD3+/CD19+ depletion with T cell addback or T cell receptor (TCR)$\alpha\beta$+ T cell/CD19+ depletion.

Objectives: To determine whether pTCD and URD-PSCT in patients with non-malignant hematologic diseases results in durable donor engraftment with minimal GVHD.

Design/Method: Fifteen patients with non-malignant hematologic diseases lacking matched related donors received URD-PSCT with disease-specific conditioning using 10/10 (5), 9/10 (9), or 8/10 (1) HLA-matched URD PSC's. Donor PSC's underwent either CD3+/CD19+ depletion, with 1 × 10^5 CD3+ cell/kg addback per an expanded access study (n = 12) or TCR$\alpha\beta$+ T cell/CD19+ depletion (n = 3) per a prospective clinical trial.

Results: Patients with acquired aplastic anemia (6), paroxysmal nocturnal hemoglobinuria (1), Diamond-Blackfan Anemia (2), Beta Thalassemia Major (2), and congenital bone marrow failure syndrome (1) received CD3+/CD19+ depletion and T cell addback. They received a median of 12 × 10^6 CD34+ cells/kg (2.4 × 10^6-19.3 × 10^6). Median follow-up is 479 days (35-1241). All 12 patients demonstrated rapid, durable trilinear engraftment. Median time to neutrophil and platelet engraftment was 13.5 (11-20) and 15 (13-31) days per CIBMTR criteria. All are currently alive, transfusion independent, and have greater than 95% donor chimerism. Mild acute skin GvHD (grade II) occurred in 1 patient and 2 others developed eczema as the only manifestation of limited chronic skin GvHD. No patient is currently receiving systemic GvHD treatment. CMV and EBV reactivations occurred, but no patient developed symptomatic disease. 3 patients with SAAA received TCR$\alpha\beta$+ T cell/CD19+ depletion. They received a median 14.6 × 10^6 cells/kg CD34+ cells and 6.85 × 10^4 cells/kg TCR$\alpha\beta$+ T cells. All patients are alive without graft rejection with follow-up range of 183 to 253 days. Each achieved rapid trilinear engraftment with median neutrophil and platelet engraftment on days 15 and 14. They remain transfusion-independent and are off systemic immune suppression.

Conclusion: URD PSCT with pTCD performed either by CD3+/CD19+ depletion with CD3+ T cell addback or by TCR$\alpha\beta$+ T cell/CD19 depletion is associated with excellent failure-free survival and minimal GvHD in patients with non-malignant hematologic diseases.

Paper Session # 2011 | CAREGIVER PERCEPTIONS OF IRON DEFICIENCY ANEMIA AND IRON REPLACEMENT THERAPIES IN YOUNG CHILDREN WITH NUTRITIONAL IRON DEFICIENCY ANEMIA

Jacquelyn Powers, Margaret Nagel, Jean Raphael, George Buchanan, Donald Mahoney, Deborah Thompson

Baylor College of Medicine; Texas Children's Cancer and Hematology Center, Houston, Texas, United States

Background: In the U.S., approximately 3% of young children develop iron deficiency anemia (IDA), with Hispanic/Latino children disproportionately affected. IDA is associated with inferior neurodevelopmental outcomes. Oral iron therapy mitigates its consequences yet over one-third of patients are non-adherent or lost-to-follow-up, resulting in treatment failure.

Objectives: To characterize caregiver perspectives of barriers to and facilitators of oral iron therapy in young children with nutritional IDA.

Design/Method: Infants and children aged 9 months to 4 years with nutritional IDA (assessed by history and laboratory criteria) and treated with oral iron in the outpatient hematology clinic at a large U.S. tertiary care pediatric hospital were identified. In person audio-recorded semi-structured interviews were conducted with caregivers using an interview guide developed by a multidisciplinary research team. Verbatim transcripts were reviewed manually by 2 research team members to perform thematic analysis and identify common

patterns in responses. Clinical data were abstracted from the electronic medical record.

Results: Eighteen patient-caregiver dyads enrolled. Patients' median age was 23 months (range 12 to 40); half were male. The majority self-identified as White and Hispanic/Latino (n = 15). Eighteen interviews were completed (13 English; 5 Spanish). Median hemoglobin concentration at first hematology visit was 8.3 g/dL (range 5.4 to 10.4 g/dL). Median duration of oral iron therapy at time of interview was 2 months (range 1 to 10). Caregivers expressed fear, anxiety, stress, and surprise at time of diagnosis and optimism with treatment resolution. Many wished they had been better informed about preventive dietary measures. Most had a basic understanding of IDA, though some misinformation was present. Widely variable IDA consequences included: changes in skin color, energy, and potential for more severe disease. Negative features of iron therapy, specifically poor taste and difficulty in getting child to take the medication, were barriers. Specific administration instructions, caregiver support, and transition to better tasting formulations were facilitators. Motivation to adhere to treatment included desire for their child to be healthy (e.g. increased energy, activity) and avoidance of traumatic experiences, such as additional blood draws or blood transfusion. Most demonstrated willingness for their child to receive intravenous iron if necessary but deferred decision-making to the provider.

Conclusion: Knowledge regarding IDA and its consequences was not a consistent treatment barrier. Most caregivers deferred treatment-related decision-making to the recommendation of the provider. Interventions that increase caregiver motivation by emphasizing health benefits and avoidance of more invasive interventions should be explored in order to improve adherence to oral iron therapy.

Paper Session # 2012 | CLINICAL EFFECT OF SC411 (ALTEMIA TM) ON CHILDREN WITH SICKLE CELL DISEASE IN THE SCOT TRIAL: A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, DOSE-FINDING MULTI-CENTER STUDY

Ahmed Daak, Mathew Heeney, Carlton Dampier, Beng Fuh, Julie Kanter, Ofelia Alvarez, Vandy Black, Melissa McNaull, Michael Callaghan, Alex George, Lynne Neumayr, Lee Hilliard, Fredrick Sancilio, Adrian Rabinowicz

Sancilio Pharmaceutical Company, Rivera Beach, Florida, United States

Background: Blood cell membranes of sickle cell disease (SCD) patients have low docosahexaenoic acid (DHA) and eicosatetraenoic acid (EPA) levels. Previous studies showed that treatment with DHA reduces the rate of sickle cell crises (SCC). AltemiaTM is a novel highly purified DHA ethyl ester formulation with a proprietary delivery platform (Advanced Lipid Technology® (ALT®). The SCOT trial investigated the therapeutic effects of AltemiaTM in children with SCD.

Objectives: To investigate safety, tolerability and clinical effect of treatment with AltemiaTM on patients with SCD.

Design/Method: Children with SCD (HbSS, HbSC or S/β° thalassemia) aged 5–17 years were enrolled from 11 U.S. centers. Subjects had experienced between two and ten (inclusive) documented SCC during the 12 months prior to screening, and had either not received, or were on a stable regimen of hydroxyurea (HU). SCC was defined as painful crisis or acute chest syndrome. Painful crisis was defined as new onset of pain that lasted two or more hours for which there was no explanation other than vaso-occlusion, and which required therapy with oral or parenteral opioids, non-steroidal anti-inflammatory drugs, or other analgesics prescribed by a healthcare provider in a medical setting such as a hospital, clinic, or emergency room, or documented telephone management. Subjects were randomized to either daily oral placebo or AltemiaTM for two months. The rate ratio (RR) of selected clinical and eDiary patient-reported outcomes were investigated in the Intention-To-Treat (ITT) population using a Poisson regression model with log-link, including terms for treatment, disease severity (based on the number of crises during the year prior to enrollment), age at baseline, and prior HU use.

Results: Sixty-seven (n = 67) subjects were randomized, 50 to AltemiaTM at 3 dose levels. Fifty-one subjects (76%) were on HU treatment. Sixty-two subjects (93%) completed the blinded portion of the study. The adjusted RRs of AltemiaTM (pooled all dose levels) versus placebo on analgesic use, acute SCC, hospitalization due to SCD-related complications and eDiary-recorded pain, were 0.71 (95% CI: 0.58-0.87), 0.45 (95% CI: 0.19-1.07), 0.40 (95% CI: 0.15-1.05) and 0.87 (95% CI: 0.63-1.2), respectively. No treatment-related adverse events were seen.

Conclusion: The SCOT trial reveals that 2 months of AltemiaTM treatment reduced home analgesic use for sickle cell pain. Treatment with AltemiaTM also revealed trends in reduction of SCC rate and hospitalization due to SCD-associated complications. These results support proceeding to a phase 3 pivotal study to confirm the clinical therapeutic effects of AltemiaTM in children with SCD.

Paper Session # 2021 | THE SIX1 HOMEOBOX GENE IS A NOVEL CRM1-DEPENDENT TARGET IN CALM-AF10 LEUKEMIAS

Waitman Aumann, Amanda Conway, Catherine Lavau, Dan Wechsler

Aflac Cancer & Blood Disorders Center and Emory University Department of Pediatrics, Atlanta, Georgia, United States

Background: The CALM-AF10 translocation is detected in 5 to 10% of pediatric and adult T-cell acute lymphoblastic leukemias (T-ALLs), and more rarely in acute myeloid leukemias (AMLs). CALM-AF10 leukemias are characterized by high expression of proleukemic HOXA genes, similar to leukemias that harbor Mixed Lineage Leukemia (MLL) translocations. Since HOXA genes are difficult to target, we hypothesized that the identification of other, non-HOXA CALM-AF10 effector genes could potentially yield novel therapeutic targets. To discover novel CALM-AF10-regulated genes, we took advantage of our prior observation that the nuclear export factor CRM1/XPO1 tethers CALM-AF10 to HOXA genes by interacting with a nuclear export signal (NES) in CALM. Using RNA-sequencing and Affymetrix microarray studies, we found that, similar to HOXA genes, SIX1, a homeobox gene that is highly expressed during embryogenesis, is increased in CALM-AF10 leukemias and decreased in response to the CRM1 inhibitor, Leptomycin B (LMB).

Objectives: To evaluate the role of SIX1 in CALM-AF10 leukemias.

Design/Method: RT-qPCR was performed on both bone marrow progenitors and murine embryonic fibroblasts (MEFs) transduced with CALM-AF10 or an empty vector, with and without Leptomycin B. Chromatin Immunoprecipitation (ChIP) using an anti-Six1 antibody was performed on MEFs transduced with CALM-AF10. The ability of SIX1 to enhance the self-renewal of hematopoietic progenitors was examined by measuring the colony forming ability of transduced fetal liver progenitors upon serial replating in methylcellulose.

Results: Similar to HOXA genes, RT-qPCR confirmed overexpression of SIX1 in both CALM-AF10 transduced MEFs and CALM-AF10 leukemias, with decreased expression in response to LMB. Furthermore, ChIP analysis revealed that CALM-AF10 binds to the SIX1 gene locus. Finally, overexpression of SIX1 in fetal liver cells was sufficient to increase the self-renewal potential of these colony forming progenitors.

Conclusion: SIX1 is a homeobox gene that is highly expressed during embryogenesis and is involved in the epithelial mesenchymal transition (EMT) and organogenesis. While SIX1 expression is silenced post embryogenesis, increased expression has been reported in numerous solid tumors; however, a potential role for SIX1 in leukemias is less clear. We have now determined that SIX1 is upregulated in the presence of CALM-AF10, and that SIX1 increases the self-renewal potential of hematopoietic progenitors. These observations indicate that SIX1 may play a pathogenic role in leukemogenesis, and that SIX1 could be a novel therapeutic target in CALM-AF10 leukemias. The fact that SIX1 is not expressed post-embryonically suggests that inhibition of SIX1 might be effective in impairing CALM-AF10 leukemia cell proliferation, with few off-target effects.

Paper Session # 2022 | TRANSCRIPTIONAL CO-REGULATION BY IKAROS AND RUNX1 IN MYELOID LEUKEMIA

Jessica Heath, Jamie Deutsch, Gabriel Cohn, Shelby Fertal, Janet Stein, Gary Stein, Sayyed Zaidi, Seth Frietze

University of Vermont, Burlington, Vermont, United States

Background: IKAROS is a transcription factor that plays an essential role in normal lymphopoiesis, and mutations of IKZF1, the gene encoding IKAROS, are frequently seen in acute lymphoblastic leukemia (ALL). Despite reports of the presence of IKZF1 mutations in acute myeloid leukemia (AML), there remains a paucity of information regarding a possible role for disrupted IKAROS function in AML. RUNX1 is critically important for normal hematopoiesis within both the lymphoid and myeloid lineages. Mutations or translocations involving RUNX1 have been identified in a variety of myeloid and lymphoid lineage hematopoietic malignancies.

Objectives: Emerging evidence indicates that the transcriptional programs of IKAROS and RUNX1 converge on critical pathways in hematopoiesis. We hypothesize that IKAROS contributes to a gene regulatory program in AML, and that the IKAROS and RUNX1 regulatory networks intersect in the pathogenesis of myeloid malignancies.

Design/Method: Chromatin immunoprecipitation followed by next generation sequencing (ChIP-Seq) was utilized to identify the genome-wide binding sites of IKAROS, RUNX1, and a panel of activating and repressive histone modifications in the human myeloid sarcoma U937 cell-line. The genes bound by IKAROS and RUNX1 as well as the chromatin patterns of these binding sites were analyzed to understand the mutual and shared roles of these transcription factors.

Results: We identified that greater than 30% of RUNX1 binding sites in this myeloid sarcoma cell line are also bound by IKAROS. These sites of co-occupancy are enriched at

distal sites marked by the enhancer histone mark H3K27ac. Of the high-confidence IKAROS-RUNX1 shared binding sites, RUNX1 binding motifs predominate; while ETS, IRF4 and CEBPA motifs are also present. A Genome Regions Enrichment of Annotations (GREAT) analysis of the IKAROS-RUNX1 shared binding sites reveals enrichment for several biological associations, including leukocyte activation, migration, and chemotaxis. Importantly, genes associated with the regulation of chromatin organization and Notch1 signaling cascades are also co-bound by these factors.

Conclusion: We begin to define a role for IKAROS in myeloid leukemogenesis by delineating the IKAROS cistrome in malignant myeloid cell lines. We also identified cross talk between IKAROS and RUNX1 in myeloid malignancy by showing bidirectional transcriptional regulation between these two tumor suppressors, and defining overlapping transcriptionally regulated genes. Ongoing studies, including RNA-Seq experiments in the presence and absence of IKAROS and RUNX1 knockdown, will define the transcriptome, explore the functional consequences of co-occupancy at these identified binding sites, and characterize the relationship between IKAROS and RUNX1 in the context of AML.

Paper Session # 2023 | NOVEL BIOLOGIC FOR THE TREATMENT OF PH-LIKE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA WITH OVER EXPRESSION OF CRLF2

Cornelia Stoian, Jacqueline Coats, Hossam Alkashgari, Veriah Vidales, Ineavely Baez, Juliette Personius, Hannah Choi, WayAnne Watson, Brandon Ng, Benjamin Becerra, Rishikesh Chavan, Muhammad Kamal, Shadi Farzin Gohar, Sinisa Dovat, Kimberly Payne

Loma Linda University, Loma Linda, California, United States

Background: Approximately half of all Ph-like B cell acute lymphoblastic leukemia is characterized by overexpression of CRLF2 (CRLF2 B-ALL). CRLF2 B-ALL is associated with poor outcome, high relapse rate, and health disparities in Hispanic children. CRLF2, together with the IL-7 receptor alpha (IL-7Ra), comprises a receptor complex that is activated by the cytokine, TSLP. Receptor activation induces JAK2/STAT5 and PI3/AKT/mTOR signals that promote survival and proliferation of leukemia cells. To study the role of TSLP in CRLF2 B-ALL, we developed a patient-derived xenograft (PDX) model of CRLF2 B-ALL that allows us to vary circulating levels of human TSLP (hTSLP). We generated PDX from primary CRLF2 B-ALL cells and compared leukemia burden in mice with varying levels of hTSLP. CRLF2 B-ALL cells were essentially eliminated in PDX with elevated physiological levels of hTSLP but grew robustly in mice with hTSLP levels at or below physiological levels present in pediatric cancer patients.

Objectives: The objective of the proposed research was to evaluate whether TSLP anti-leukemia effects are mediated via upregulation of Suppressor of Cytokine Signaling (SOCS) which are known to regulate cytokine signaling via negative feedback through multiple mechanisms including cytokine receptor degradation.

Design/Method: Whole genome microarray was used to evaluate SOCS genes upregulation by TSLP. TSLP dose response studies were performed and flow cytometry was used to evaluate the effect of TSLP on SOCS protein expression, CRLF2 signaling shutdown, and loss of TSLP receptor components.

Results: Whole genome microarray showed that SOCS1, SOCS2, SOCS3 and CISH mRNA were upregulated in primary CRLF2 B-ALL cells cultured with high dose hTSLP. Flow cytometry analysis showed that high-dose TSLP upregulated SOCS1 and SOCS3 proteins CRLF2 B-ALL cells, and studies to evaluate TSLP effects on CISH and SOCS2 are ongoing. CRLF2 B-ALL cells cultured with TSLP showed a dose-dependent loss in the ability to induce STAT5 and S6 phosphorylation following TSLP stimulation. This loss was correlated with the loss of IL-7Ra, and maintained for 24–48 hours following a pulse of high-dose, but not low-dose, hTSLP. The loss of signaling and surface IL-7Ra was prolonged if high-dose hTSLP levels were maintained.

Conclusion: These data provide evidence that TSLP exerts anti-leukemia effects by shutting down CRLF2-mediated signals and that these effects are at least partially mediated by the loss of the IL-7Ra component, and potentially through SOCS family proteins. These studies identify the human TSLP cytokine as a potential biologic therapy to treat CRLF2 B-ALL. Supported by 1R01CA209829.

Paper Session # 2024 | UNIVERSAL PRETREATMENT FOR ASPARAGINASE-BASED THERAPY SHOULD BE STANDARD OF CARE

David Young, Caitlin Bowen, Nicole Arwood, Sarah Poggi, Stacy Cooper, Patrick Brown

Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, United States

Background: Asparaginase is a critical component of acute lymphoblastic leukemia (ALL) therapy. The current standard product is intravenous pegaspargase (IV-PEG). IV-PEG causes acute adverse events (aAEs) that occur during the infusion and are difficult to interpret, representing a mix of

drug-inactivating hypersensitivity and non-inactivating reactions. Erwinia (ERW) is approved for PEG hypersensitivity, but is less convenient, costs more and results in lower serum asparaginase activity (SAA). Premedication for PEG has been avoided for fear of "masking" hypersensitivity and drug inactivation. With available SAA assays, however, we began premedicating and re-challenging with IV-PEG after aAEs, and found IV-PEG tolerable and associated with excellent SAA. We began universal premedication and SAA testing for all IV-PEG doses, hypothesizing this would reduce aAEs and unnecessary drug substitutions.

Objectives: Assess the impact of universal IV-PEG premedication and SAA testing upon the rate of drug substitution, rate and severity of aAEs, and drug cost.

Design/Method: Retrospective chart review of patients receiving IV-PEG before and after implementation of premedication with diphenhydramine and famotidine. Hydrocortisone was added when patients with a history of previous aAEs. SAA was tested 1 week after IV-PEG to detect subclinical drug inactivation. We excluded patients who had asparaginase discontinued due to non-allergic AEs (pancreatitis, etc.). The primary end-point was substitution of ERW for IV-PEG. Secondary end-points included grade of aAEs, drug inactivation per SAA testing, and drug cost (2017 adjusted cost).

Results: Pre-policy, we substituted ERW in 21 of 123 (17%) patients, all for aAEs. Post-policy, we substituted 5 of 62 patients (8%; RR 0.472, 95%-CI 0.29-0.76, NNT 11.1, P = 0.048), 4 for severe breakthrough aAEs and 1 for silent inactivation. All non-substituted patients had excellent SAA (mean 0.91 units/mL), especially compared to levels seen with ERW (mean 0.15 units/mL). Silent inactivation rate post-policy was 1 of 62 (1.6%). Rate of aAEs pre/post-policy was 17% versus 6.5% (RR 0.378, 95%-CI 0.22-0.64, NNT 9.4, P = 0.022). Proportion of grade 4 aAEs pre/post-policy was 15% versus 0%. All pre-policy grade 4 aAEs required ICU admission. Cost analysis predicts $107,000 savings per drug substitution prevented, or $9,636 per patient premedicated.

Conclusion: Universal IV-PEG premedication reduced the need for ERW substitutions and acute adverse events. SAA testing demonstrated very low rates of silent inactivation, and superior SAA levels for IV-PEG compared to ERW. A substantial cost savings was achieved. Given these reasons, we propose universal premedication for IV-PEG to be standard of care.

Paper Session # 2025/Early Career Travel Stipend Award Recipient | MECHANISMS LINKING FIBRIN(OGEN) STRUCTURE/FUNCTION TO TUMOR METASTASIS

Allison Remiker, Leah Rosenfeldt, Gregory Adams, Matthew Flick, Malinda Frederick, Joseph Palumbo

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Previous studies established that the platelet/fibrin(ogen) axis promotes metastatic potential by impeding the clearance of newly formed micrometastases by natural killer (NK) cells. However, multiple important questions remain, including the potential of fibrin(ogen) to promote metastasis through interactions with cells other than platelets (e.g., inflammatory cells), and the fundamental question of whether fibrin polymerization is required for metastasis.

Objectives: Determine the role of fibrin polymerization and fibrin(ogen) engagement of integrins αIIbβ3 and αMβ2 in metastasis.

Design/Method: We performed experimental and spontaneous metastasis assays in immunocompetent mice carrying specific fibrinogen structure/function alterations.

Results: Expression of a mutant fibrinogen lacking the binding motif for the leukocyte integrin αMβ2 (Fibγ390-396A) significantly decreased metastatic potential relative to wildtype fibrinogen, suggesting a role for fibrin(ogen)-inflammatory cell interactions mediated by αMβ2 in metastasis. To directly determine the importance of thrombin-mediated fibrin polymerization in metastasis, we analyzed metastatic potential in FibAEK mice, which carry a form of fibrinogen essentially "locked" in the soluble state due to a mutation in the Aα chain thrombin cleavage site. Metastatic potential in FibAEK mice was diminished relative to control mice, speaking to the importance of thrombin-mediated fibrin polymerization in the metastatic process. However, the FibAEK mice retained significant metastatic potential relative to complete fibrinogen deficiency, indicating that fibrinogen monomer retains significant prometastatic properties. In order to better define the role of fibrin(ogen)-platelet interactions in metastasis, we compared metastatic potential in control and Fib$\gamma\Delta$5 mice, carrying a form of fibrinogen lacking the γ chain binding motif for the platelet integrin αIIbβ3. Surprisingly, this mutation had no impact on metastatic potential.

Conclusion: Together, these studies suggest fibrinogen plays a multifaceted role in metastasis. Fibrin(ogen)-leukocyte interactions mediated by αMβ2 appear to have a role in metastasis. Previous studies showed that macrophages promote the metastatic potential of circulating tumor cells, which may represent at least one important αMβ2 expressing cell type whose prometastatic behavior is influenced by fibrin(ogen) interactions. These studies show that thrombin-mediated fibrin polymerization promotes metastasis, but soluble fibrinogen retains some significant prometastatic capacity. Surprisingly, loss of the fibrinogen γ chain αIIbβ3 binding motif had no impact on metastasis. Given the established importance of platelets in

metastasis, these findings suggest that fibrin (ogen) is capable of platelet stabilization through mechanism(s) independent of this αIIbβ3 binding motif. Platelets may bind polymerized fibrin at other sites, and/or fibrin interactions with other matrix proteins capable of binding αIIbβ3 are sufficient to support platelet functions required for metastasis.

Paper Session # 2026 | SAFETY AND PATIENT-REPORTED EFFICACY OF SIROLIMUS IN 120 PATIENTS WITH VASCULAR ANOMALIES: A REPORT FROM THE LYMPHATIC ANOMALIES REGISTRY

Meghan O'Hare, Richard Griewe, Katherine Broecker, Hasan Al-Sayegh, Clement Ma, Steven Fishman, Denise Adams, Cameron Trenor

Boston Children's Hospital, Boston, Massachusetts, United States

Background: Sirolimus is increasingly utilized for a variety of vascular anomalies complications. Available data about safety and efficacy are drawn from case series and one phase 2 study of 57 patients. Off label use is increasing and additional safety and efficacy data are urgently needed.

Objectives: To determine safety and patient-reported efficacy in real world, off-label use of sirolimus for vascular anomalies

Design/Method: Patients in an IRB-approved, international registry who received systemic sirolimus therapy for at least 6 months were retrospectively reviewed for adverse events, goals and outcomes of sirolimus therapy.

Results: 120 patients received sirolimus for at least six months. Sirolimus therapy was utilized for several different vascular anomalies, mostly with lymphatic complications. Specific diagnoses treated were lymphatic malformation (n = 31), generalized lymphatic anomaly (n = 19), CLOVES (n = 18), Gorham-Stout disease (n = 15), central conducting lymphatic anomaly (n = 10), kaposiform lymphangiomatosis (n = 9), blue rubber bleb nevus syndrome (n = 5), Klippel-Trenaunay syndrome (n = 4), kaposiform hemangioendothelioma (n = 3), and other (n = 6). Median age at initiation of therapy is 7.5 years (range = 0.1-52.6) and 45% were female. Median total duration of sirolimus therapy was 24 months (range = 6-90). Similar to prior reports, the more common adverse events occurring at least once and attributed to sirolimus were mucositis (31%), headache (8%), diarrhea (4%) and nausea (4%). The following goals of therapy were predetermined: improved swelling (40%), improved quality of life (38%), improved pain (31%), improved functionality (26%), fewer infections (23%), improved bleeding (23%), other (21%), improved effusion (19%), stable effusion (13%), improved bone mineralization (13%), stable bone mineralization (13%), decreased transfusions (9%), improved imaging (3%), and stable imaging (3%). Using patient/parent reported outcomes, 99% (112/113) reported any one or more positive responses to sirolimus. Analyzing response based on goals of therapy, highest responses to sirolimus were reported for bleeding (78.6%), pain (62.2%), stable bone involvement (60%), fewer transfusions (54.6%), fewer infections (50%), improved swelling (50%), improved effusion (39.1%) and improved quality of life (35.6%).

Conclusion: Oral sirolimus is a well-tolerated and effective therapy for complications of vascular anomalies, especially bleeding, pain, infections and swelling. Sirolimus therapy needs further multidisciplinary, prospective study for patients with vascular anomalies.

Paper Session # 2027 | PERIPHERAL ARTERIAL THROMBOSIS IN HOSPITALIZED CHILDREN: CHARACTERISTICS AND SHORT-TERM OUTCOMES OF EXTENDED ANTICOAGULATION

Julie Weisman, Carrie Diamond, Carole Hennessey, Christine Guelcher, Suvankar Majumdar, Jennifer Meldau, Yaser Diab

Children's National Health System, Washington, District of Columbia, United States

Background: Peripheral arterial thrombosis (PAT) which is increasingly encountered in hospitalized children can lead to serious complications, including threatened limb or organ viability, leg length discrepancy, claudication, and loss of arterial access. Anticoagulation is the mainstay therapy. However, there is limited data on optimal duration of anticoagulation.

Objectives: To describe characteristics of PAT at a tertiary care pediatric hospital and report short-term outcomes with an extended anticoagulation protocol.

Design/Method: We performed a retrospective analysis of a prospectively maintained institutional thrombosis database. We identified all patients with a PAT confirmed by ultrasound at our institution over a 6-year period (2011-2017). Patients were managed according to an institutional protocol in which patients received therapeutic enoxaparin from the time of diagnosis until complete radiologic resolution of thrombosis and for a maximal duration of 3 months with assessment of clinical and radiologic response at 2 weeks, 6 weeks and 3 months. Relevant data were collected and summarized using descriptive statistics.

Results: A total of 65 patients developed a PAT at our institution during the study period which accounted for 11%

of all thrombotic events. The median age at diagnosis was 1.8 months [Interquartile range (IQR) 0.4-5.5]. Thirty-five patients (54%) were males. PATs were completely occlusive in 30 patients (46%). Of 65 PATs, 53 (88%) were catheter-related PATs (CR-PATs). CR-PATs were caused by an indwelling catheter (IC) in 34 patients (64%) or cardiac catheterization (CC) in 19 patients (36%). CR-PATs were diagnosed at a median of 8 days (IQR 2–16) after catheter insertion. Forty-nine of 53 CR-PATs (92%) involved the lower extremity arteries. Most patients diagnosed with PAT were critically ill (77%), on mechanical ventilation (69%) and had a cardiac disease (65%), most commonly a cyanotic congenital heart disease (64%). Initial treatment consisted of therapeutic anticoagulation [58 patients (94%)], systemic thrombolysis (2 patients) and catheter-directed thrombolysis (2 patients). Complete radiologic resolution in patients who received anticoagulation per our protocol occurred in 24%, 73% and 88% of patients after 2 weeks, 6 weeks and 3 months of anticoagulation, respectively. Two patients lost their limbs due to reperfusion injury. No patient experienced anticoagulation-related major bleeding.

Conclusion: PAT is most commonly encountered in critically ill infants with cardiac disease who require an IC or CC. Extended anticoagulation for up to 3 months was safe and was associated with high rates of complete resolution. Multicenter, prospective studies are needed to confirm our results and for developing more optimal evidence-based risk stratified management approaches.

Paper Session # 2028 | PLATELET ONTOGENY: A CLOSER LOOK AT PLATELET IMMUNE FUNCTION

Akua Asante, Zachary Hilt, Daphne Pariser, Jacqueline Lillis, Sara Ture, Kate Fegan, Seana Catherman, Leah Vit, Anne Koniski, Paul Kingsley, Kathleen McGrath, Craig Morrell, James Palis

University of Rochester Medical Center, Rochester, New York, United States

Background: The role of platelets in hemostasis and thrombosis is well defined, but it is becoming increasingly evident that platelets also assist in host defense and inflammation. Platelets participate in the innate immune system through direct antimicrobial activity and interactions with effector cells (Chapman2012, Garlanda2013, Kapur 2016). In the adaptive immune system, platelets recruit and co-stimulate T-cells, and promote B-cell differentiation and antibody class switching (Kapur2016, Morrell2017). The question remains: which mechanisms influence platelet immune function and are they developmentally regulated? Preliminary studies in the Palis lab have revealed significant differences in embryonic versus adult platelet gene expression, including regulators of immune and inflammatory responses such as Beta2-microglobulin (B2M) and Major Histocompatibility Complex class I (MHC1). MHC1 is expressed on all cell surfaces except red blood cells and its molecular chaperone B2M is a marker of inflammation highly expressed in platelet alpha granules (Zufferey2014). Preliminary data from the Morrell lab reveals a mass release of B2M during platelet activation, which drives monocyte differentiation to an inflammatory phenotype through TGFB receptor signaling. We therefore sought to determine whether developmental changes in platelet B2M expression mediate differences in platelet-mediated monocyte activation.

Objectives: To understand developmental regulation of platelet immune function by: 1. Evaluating B2M expression in embryonic, postnatal and adult platelets. 2. Assessing postnatal and adult platelet effect on monocyte differentiation.

Design/Method: Experiments conducted with C57Bl/6 mice and platelet-specific B2M knockout mice (PF4^Cre+ - B2M^flox/flox). Blood samples from embryonic, postnatal, and adult mice were treated with PGI2 and apyrase to prevent platelet activation during isolation. Transcript levels from platelets were determined using qRT-PCR with PF4 as a control. B2M serum protein levels determined by ELISA. Platelets and adult bone marrow monocytes were co-incubated for 48-hours. Monocyte surface markers and serum cytokine levels were assessed using flow cytometry and ELISA, respectively.

Results: Platelet B2M gene expression was significantly lower in the B2M KO, embryonic and postnatal platelets compared to adult platelets. A similar pattern was seen with platelet B2M protein expression and plasma levels. Adult monocytes co-incubated with activated adult platelet releasate become pro-inflammatory. However, monocytes become anti-inflammatory, as evidenced by IL-10 secretion, when incubated with postnatal or B2M KO platelet releasates. Anti-TGFB antibody limited B2M KO platelet releasate-mediated anti-inflammatory monocyte phenotype.

Conclusion: This study provides evidence that murine B2M platelet transcript and plasma protein levels are developmentally regulated. Additionally, postnatal platelets are less immunogenic compared to their adult counterparts and tend to promote monocyte differentiation to the anti-inflammatory phenotype.

Poster # 001 | IDIOPATHIC HYPERAMMONEMIC ENCEPHALOPATHY: DIAGNOSTIC COMPLEXITIES AND MANAGEMENT OPTIONS

Ross Mangum, Alexandra Stevens

Texas Children's Hospital/Baylor College of Medicine, Houston, Texas, United States

Background: We present the case of a 19 year-old female with low risk acute myeloid leukemia (AML) who developed progressive altered mental status and respiratory alkalosis with eventual diagnosis of idiopathic hyperammonemic encephalopathy while awaiting count recovery following her final round of cytoreductive chemotherapy. The patient developed persistently increasing ammonia levels with abrupt neurologic deterioration in the absence of hepatic dysfunction. Extensive diagnostic work-up included metabolic screen for urea cycle disorders such as ornithine transcarbamylase deficiency, genetic screen with whole exome sequencing, thorough infectious work-up, and evaluation for cerebrovascular accident. Neuroimaging demonstrated evidence of metabolic encephalopathy. Continuous renal replacement therapy (CRRT) was initiated to limit the potentially lethal toxicities of hyperammonemia. While the exact etiology remains elusive, this complex case is being actively discussed by the Undiagnosed Disease Network, illustrating an exciting new era of medicine where collaboration and shared expertise can lead to expanded understanding of previously undiagnosed conditions.

Objectives: Due to the exceedingly rare, and often fatal, nature of idiopathic hyperammonemic encephalopathy, poor symptom recognition can lead to delayed diagnosis and worse patient outcomes. Further understanding of this phenomenon will allow practitioners to expedite optimal therapies and potentially improve overall prognosis.

Design/Method: We describe the presenting symptoms and work-up leading to the diagnosis of hyperammonemic encephalopathy, including the patient's associated multiorgan system dysfunction. The differential diagnosis and treatment options will be delineated followed by a review of the limited current literature on isolated hyperammonemia.

Results: A rare case of isolated hyperammonemia following completion of chemotherapy in a teenage patient with AML. The onset of increasing ammonia levels well outside the typical time period for chemotherapy-induced hyperammonemia and otherwise negative diagnostic work-up highlights both the diagnostic complexity and importance of early recognition of this unique condition. This case also offers a framework to discuss the range of management options for hyperammonemia such as nutrition modification, lactulose, rifaximin, sodium benzoate, and CRRT/hemodialysis.

Conclusion: Idiopathic hyperammonemic encephalopathy is an uncommon and potentially lethal cause of neurologic deterioration associated with anti-neoplastic chemotherapy. With new technologies and improved initial management, we are better able to prevent immediate neurologic devastation and facilitate a more in-depth investigation of underlying etiologies. Nonspecific presenting symptoms and an extensive differential diagnosis can lead to delay in disease recognition and missed opportunities for prompt treatment and improved patient outcomes.

Poster # 002 | MAMMARY ANALOGUE SECRETORY CARCINOMA IN CHILDREN: A REPORT FROM THE TEXAS CHILDREN'S RARE TUMOR REGISTRY

Priya Mahajan, Daniel Chelius, Norma Quintanilla, Angshumoy Roy, Rajkumar Venkatramani

Baylor College of Medicine, Houston, Texas, United States

Background: Mammary analogue secretory carcinoma (MASC) is an uncommon salivary gland malignancy with morphologic and molecular similarities to secretory carcinoma of the breast. MASC is characterized by the ETV6-NTRK3 fusion gene, and management includes surgical excision. MASC is rare in children with few pediatric cases reported in literature.

Objectives: To present a case series of two patients with MASC.

Design/Method: Case series.

Results: We report two pediatric patients with MASC. The first patient is a 13-year-old male who presented with a painless left preauricular mass. Magnetic resonance imaging (MRI) of the face showed a heterogeneous, enhancing 2.1 cm mass in the anterior segment of the superficial left parotid gland. He underwent a left parotidectomy, and pathology demonstrated MASC with tumor focally positive at the resection margins. TNM staging was T3N0M0. FISH analysis showed ETV6 gene rearrangement and ETV6-NTRK3 fusion was demonstrated by reverse-transcriptase-PCR. The second patient is a 16-year-old male with a history of standard risk B-acute lymphoblastic leukemia at age four who presented with right facial and neck swelling. MRI of the face showed a $2.2 \times 2 \times 2.5$ cm well defined partially cystic and solid lesion in the superficial aspect of the right parotid gland and enlarged submental and submandibular lymph nodes. He underwent a parotidectomy with selective lymph node dissection. Pathology revealed a low-grade salivary gland carcinoma consistent with MASC with infiltrative margins. Of the five lymph nodes sampled, two had MASC metastases and two had incidental foci of papillary thyroid carcinoma (PTC). ETV6-NTRK3 was detected in the parotid tumor tissue and TFG-MET fusion was detected in the PTC. TNM staging was T2N2M0. He subsequently underwent a total thyroidectomy,

and central and left lateral lymph node dissection, followed by radioactive iodine for management of PTC. Both patients have been disease free at 3 months and 24 months respectively.

Conclusion: Surgical resection is the preferred treatment for MASC. Given the distinct translocation seen in MASC, NTRK inhibitors may have a role in unresectable or recurrent disease. Further studies are necessary to better define the natural history, effective treatments, and long-term outcomes of MASC in children.

Poster # 003 | A RARE CASE OF IMMUNODEFICIENCY, CENTROMERE INSTABILITY, AND FACIAL ANOMALIES TYPE I SYNDROME IN A MALE INFANT

Priyal Patel, Lubna Mehyar, Rolla Abu-Arja, Elizabeth Varga, Benjamin Prince, Melissa J. Rose

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: Immunodeficiency, Centromere Instability, and Facial anomalies (ICF) syndrome is a rare autosomal recessive immunodeficiency reported in less than 100 individuals worldwide. Affected individuals present with recurrent infections, poor growth, facial dysmorphism, intellectual disability, and psychomotor retardation with neutropenia, hypogammaglobulinemia and absence of memory B cells. ICF syndrome is the result of epigenetic dysregulation, leading to hypomethylation, centromeric instability, and chromosome decondensation. ICF syndrome is most commonly due to biallelic mutations in DNMT3B, a DNA methyltransferase gene. Opportunistic infections typically result in mortality before the 3rd decade of life. Treatment includes immunoglobulin replacement, prophylactic antibiotics and hematopoietic stem cell transplant (HSCT).

Objectives: To expand the differential diagnosis of a patient who presents with frequent infections, neutropenia and hypogammaglobulinemia, we report a case of ICF type 1 (ICF1) syndrome due to biallelic mutations in DNMT3B.

Design/Method: A 6 month old male with gross motor delays presented with several weeks of cough, emesis, and diarrhea. On admission, he was febrile and neutropenic, with an absolute neutrophil count (ANC) of 0. Testing was positive for coronavirus, adenovirus and astrovirus; his ANC gradually normalized. Subsequently, he exhibited a cyclical pattern to neutropenia and respiratory infections prompting further evaluation.

Results: Anti-neutrophil antibodies were not identified. A bone marrow biopsy revealed a normocellular marrow with trilineage hematopoiesis with a predominance of early myeloid precursors, with full maturation. Microarray, ELANE and SBDS sequencing and deletion/duplication analyses were negative. Immunologic evaluation was significant for agammaglobulinemia and an absence of memory (CD19+CD27+) B cells. A 207 gene primary immunodeficiency panel revealed two variants of unknown significance- c.1957G>A and c.2292G>T in DNMT3B; one previously reported in association with ICF1. Parental testing demonstrated parental heterozygosity. Centromeric instability was confirmed in mitogen stimulated lymphocytes showing characteristic, multibranched chromosomes containing at least 3 arms of chromosome 1 and 16 joined near the centromere. Decondensation of the 1qh and 16qh regions and triradial configuration of chromosome1 was noted, and a diagnosis of ICF1 syndrome was made. The patient was started on monthly intravenous immunoglobulin (IVIG). Prophylaxis for Pneumocystis jiroveci pneumonia and respiratory syncytial virus was initiated. A 10/10 matched sibling HSCT is being planned.

Conclusion: Our aim is to increase awareness of ICF1, prompting inclusion in the differential diagnosis for patients with recurrent infections, neutropenia and hypogammaglobulinemia. This phenotypically variable disease carries significant morbidity and mortality despite immunoglobulin replacement and prophylactic antibiotics. As an intention for cure, HSCT should be considered in patients with ICF1.

Poster # 004 | A CASE REPORT OF SPONTANEOUS EXPECTORATION OF PULMONARY METASTASES IN A CHILD WITH OSTEOGENIC SARCOMA

Hamza Gorsi, Shamlal Mangray, Bradley DeNardo, Jennifer Welch

Hasbro Children's Hospital/Rhode Island Hospital, Providence, Rhode Island, United States

Background: Pulmonary metastases from solid tumors can be parenchymal (peripheral) or endobronchial (central). Endobronchial metastases are rare events; most frequently reported in breast, colorectal, kidney, stomach and prostate malignancies. Occasionally, endobronchial metastases present with spontaneous expectoration of the metastatic tissue. To date such examples have been limited to adult patients and have not been reported in osteogenic sarcoma (OGS).

Objectives: To review clinical presentation and treatment course of a child with OGS who spontaneously expectorated metastatic tumor.

Design/Method: Case report.

Results: A 9-year-old female presented with OGS of distal right femur with numerous bilateral pulmonary metastases. She was treated with methotrexate, doxorubicin, cisplatin (MAP) plus zoledronic acid with addition of ifosfamide and etoposide (IE) following local control (rotationplasty). Her pulmonary lesions were not resectable. Due to persistent pulmonary disease, she received maintenance sorafenib, everolimus and zoledronic acid after completion of MAP/IE. At 22 months from diagnosis, routine imaging showed new FDG-avid pulmonary lesions and increased FDG-avidity in older lesions. One week later, she presented to the hospital for respiratory distress secondary to complete collapse of right lung from a new metastatic lesion in the right main stem bronchus. She received targeted 3000 cGy local radiation and her respiratory distress improved significantly. Post-radiation CT scan showed partial opening of right main stem bronchus. She was treated with gemcitabine and docetaxel. At 27 months from diagnosis, she expectorated a piece of necrotic tissue with degenerate cells and intermixed arborizing matrix (osteoid), consistent with post radiation necrotic changes in the tumor tissue. Post expectoration CT scan showed complete opening of the right main stem bronchus. At 30 months from diagnosis, routine imaging documented development of new liver metastasis, which was treated with heat ablation. Systemic chemotherapy was changed to high dose methotrexate followed by liposomal muramyl tripeptide phosphatidyl ethanolamine (L-MTP-PE) as Single Patient Investigational New Drug (SPIND) after FDA and IRB approval. At 34 months, patient developed back and abdominal pain and spontaneously expectorated pieces of tissue two times in an interval of two weeks. Pathology evaluation of one of these specimens was again consistent with metastatic OGS making a total of three episodes of expectoration of tissue from metastatic OGS. Subsequently, L-MTP-PE was discontinued and she continues to pursue alternative treatment options.

Conclusion: Airway obstruction from endobronchial metastasis should be considered if a patient with pulmonary metastases presents with acute worsening of respiratory symptoms. Appropriate treatment can result in alleviation of obstruction and resolution of symptoms.

Poster # 005 | MUTATION OF CEP72 GENE MAY PREDISPOSE PATIENTS TO HEPATOTOXICITY

Robin Pham, Alice Hoeft, Carol Roberts, Charles Maloy, Anish Ray

Cook Children's Medical Center, Fort Worth, Texas, United States

Background: Approximately 4,000 cases of acute lymphoblastic leukemia (ALL) are diagnosed in the United States annually. The manifestation of drug toxicities, which varies among patients receiving similar doses of therapeutic agents, plays a pivotal role in influencing outcome as certain toxicities may impair treatment compliance.

Objectives: Polymorphisms in CEP72 have been linked to increased incidence of vincristine-induced toxicities, namely peripheral neuropathy. We hypothesize that polymorphisms in the same gene may also increase a patient's risk of developing hepatotoxicity when receiving potentially hepatotoxic agents during chemotherapy. This report describes drug-induced cholestasis noted with the use of vincristine and 6-mercaptopurine (6-MP) in a patient homozygous for the CEP72 risk alleles.

Design/Method: This report employed the use of electronic medical records for the review of this patient's diagnosis, treatment, and outcome at Cook Children's Medical Center.

Results: A 10-year-old female with high-risk B-precursor ALL entered remission after induction therapy. She developed acute hepatic injury with elevated direct bilirubin during weeks five and six of consolidation. These weeks exposed her to 6-MP, vincristine, and PEG-asparaginase. We held 6-MP due to its hepatotoxic potential, and reduced the vincristine dose by 75%. Direct bilirubin normalized over time. Cytogenetic testing revealed homozygous CEP72 risk alleles and normal TPMT*1 alleles. During interim maintenance and delayed intensification, the patient received 50% dose reduction of vincristine due to the association between CEP72 mutations and vincristine-induced toxicities. Given normal TPMT status, she received protocol-guided full doses of 6-MP. During maintenance, she proceeded to receive 50% dose reduction of vincristine and full dosing of 6-MP as well as weekly methotrexate. The patient again developed jaundice and elevated direct bilirubin, which normalized following a renewed 50% dose reduction of 6-MP. The patient continues to tolerate therapy well with full doses of vincristine and methotrexate while the dose of 6-MP remains at 50%.

Conclusion: Patients who possess polymorphisms in CEP72 may be at higher risk for developing hepatotoxicity when receiving chemotherapy agents for acute leukemia. Animal studies suggest that intact microtubular function enables hepatic uptake of bilirubin. Disruption/inhibition of microtubular polymerization has been shown to interfere with hepatic function. These may form the basis for CEP72 mutations leading to peripheral neuropathy and additionally hepatic injury. In this report we describe a novel adverse effect in association with polymorphism in the promoter region of CEP72. If replicated among other patients, detection of this mutation may allow the treating clinician to dose modify during therapy and improve overall therapeutic outcome.

Poster # 006 | AN EXTRA-RENAL WILMS TUMOR PRESENTING AS A UTERINE MASS

Simone Chang, Warren Alperstein, Claudia Rojas, Antonello Podda, Matteo Trucco

University of Miami, Miami, Florida, United States

Background: Wilms tumor (WT) is the most common renal tumor in children, while rarely seen in adults. It is not limited to the kidney but can rarely present as an extra-renal Wilms tumor (ERWT).

Objectives: Describe the presentation of a uterine ERWT and its differential.

Design/Method: Case Report

Results: A 33-year-old female presented with menorrhagia of four weeks. Pelvic examination revealed a fungating mass obscuring the cervical os. The differential entertained at initial appearance included more common uterine cancers adenocarcinomas such as endometrioid carcinoma or a possible squamous cell carcinoma of the cervix or uterine sarcoma such as a leiomyosarcoma. Imaging demonstrated a mass arising from the mid-uterus extending to the cervix and vagina. There was no evidence of extension to the adnexae or surrounding tissues. She subsequently had an exploratory laparotomy performed with modified radical hysterectomy. The mass involved the lower uterine segment extending from the endometrial surface with superficial invasion (<50%) into the myometrium with no lymphovascular involvement. Histology showed the presence of blastemal components, epithelial/tubular elements and a significant stromal constituent warranting the diagnosis of ERWT. ERWT's can originate at the retroperitoneum, inguinal area, female and male genital organs. Theories regarding its origin remain controversial and it is hypothesized that it arises from ectopic nephrogenic rests that persist and develop into a nephroblastoma. It manifests usually as an asymptomatic mass or with fullness, abdominal pain and discomfort. Given the location in our patient, she presented with heavy prolonged vaginal bleeding. ERWT is primarily a disease of childhood and thus made it an unexpected diagnosis. Relevant differentials include squamous cell carcinoma of the cervix, an embryonal rhabdomyosarcoma, uterine sarcomas, malignant mixed mullerian tumor and less likely in her age an endometrial adenocarcinoma. Criteria for pathologic diagnosis of ERWT described by Beckwith and Palmer include (1) extrarenal site of the primary lesion, (2) primitive blastemous spindle or round cell component, (3) abortive or embryonal tubular or glomeruloid structure and (4) no evidence of teratoma or renal carcinoma. The diagnosis is almost exclusively made postoperatively which can jeopardize treatment and contributes to the poorer prognosis in this population.

Conclusion: The prognosis of ERWT is comparable to the excellent prognosis of intra-renal WT. However, this is dependent on the timely and accurate diagnosis and the implementation of appropriate treatment. Therefore, early identification of this rare and unexpected entity is critical to providing optimal outcomes, along with a multidisciplinary can maximize the survival for these patients.

Poster # 007 | A CLINICAL DESCRIPTION AND MEDICAL MANAGEMENT OF "STIGMATA"

Amanda Lipsitt, Emily Carrol, Florisa Lubrin, Sulakshana Ranjan, Chatchawin Assanasen

University Health System, University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States

Background: Hematidrosis is a rare condition that has historically been associated with body marks or bleeding from sites associated with the crucifixion of Jesus Christ and culturally popularized in movies and texts. Dramatic descriptions generally include individuals bleeding from their tears or sources associated with crucifixion wounds. Though a true medical condition, the cultural stigma associated with the presentation has limited opportunities for appropriate medical evaluation and disease management.

Objectives: We describe the case of a child with progressive hematidrosis and non-epileptiform seizure activity, who was successfully treated with propranolol.

Design/Method: A 13 yo female with a history of depression, anxiety, PTSD, and non-epileptiform seizure activity presented with nine months of progressive episodic bleeding from her skin and eyes. The bleeding first presented as bloody tears and then progressed to bloody secretions from her forehead, palms, soles, mouth, and ears. Her episodes were consistently preceded by extreme emotional stress, excitement, or physical exertion. She reported a minimum of seven episodes a day. She was evaluated by multiple providers of various specialties that were unable to identify an etiology and on many occasions challenged the validity of her symptoms. Her mother was also accused of Munchausen's by proxy.

Results: With appropriate suspicion for organic etiology the patient was seen in our facility and a bleeding episode from the palms was induced and its validity confirmed. The sample was collected and sent to pathology for analysis. 1.52 M/mcl RBC were noted in the expelled fluid confirming a true blood source with further workup ruling out any coagulopathies. In an attempt to mitigate symptomatology, 30mg of Propranolol twice a day was started. With consideration of tranexamic acid to be added as well. After the initiation of treatment, the

bleeding episodes improved significantly with decrease to one episode a day.

Conclusion: There is no confirmed cause of hematidrosis, though a few theories have been proposed, such as rupture of the capillaries near the sweat glands, dermal defects leading to blood filled spaces that empty in the hair follicles, or a vasculitis. We report a case presenting with severe psychosocial comorbidities that significantly improved with medical intervention. It is important that the pediatric hematologist have familiarity with this rare disease as cultural morays may influence initial medical impressions and impact patient care.

Poster # 008 | DESMOPLASTIC SMALL ROUND CELL TUMOR OF THE CENTRAL NERVOUS SYSTEM

Michael Pavio, Ellen Chung, Kimberly Fagen, James League-Pascual, Kip Hartman

Walter Reed National Military Medical Center, Bethesda, Maryland, United States

Background: Desmoplastic small round cell tumors (DSRCT) are extremely rare, aggressive soft tissue sarcomas that arise predominantly within the abdominal-pelvic cavity. They occur in both pediatric and adult populations with a median age of 19 years and a strong male predominance of 4:1. Approximately 200 cases are described in the literature, with two prior case reports of intracranial DSRCT.

Objectives: Due to DSRCT's aggressive behavior and usual significant disease burden at presentation, the prognosis typically remains poor. A case series of both pediatric and adult patients report 3- and 5- year survival of 44% and 15% respectively; the median survival from diagnosis is 22–29 months. We report a case of intracranial DSRCT with favorable outcome to date.

Design/Method: Case Report.

Results: A 6 year-old male presented with complaints of daily headaches and sleeping difficulties. Neuro-ophthalmology exam revealed a visual field defect. MRI demonstrated a heterogeneous mass with solid and cystic components measuring $6.3 \times 4.4 \times 4.8$cm centered in the left occipital lobe, displacing the posterior temporal horn. The mass displayed diffusion restriction and avid post-Gadolinium enhancement of the solid and peripheral components, reflecting dense cellular packing and high vascularity, respectively. PET/CT and spine MRI showed no systemic metastatic disease or drop metastasis. The initial differential diagnosis included primitive neuroectodermal tumor, atypical teratoid/rhabdoid tumor, and ependymoma. The patient underwent a left parieto-occipital craniotomy and gross total resection. The initial pathologic diagnosis was a high-grade embryonal tumor of uncertain differentiation; subsequent molecular testing showed an EWSR1-WT1 fusion consistent with the diagnosis of DSRCT. The patient was treated with 10 cycles of Ifosfamide, Etoposide, Carboplatin (ICE) chemotherapy repeated at 21 to 28 day intervals. Following the second chemotherapy cycle, the patient was treated with Proton Beam Radiation. The initial field was treated with 5040cGy in 28 fractions, followed by a boost to the tumor bed of 900cGy in 5 fractions, for a total dose of 5940cGy. Our patient shows no evidence of recurrent or residual disease 20 months after diagnosis. Neurologic sequelae include a persistent right homonymous hemianopsia, while neuropsychiatric testing has been normal.

Conclusion: This case demonstrates that molecular testing is essential for the precise pathologic diagnosis of poorly differentiated tumors. DSRCT is rare but should be included in the differential diagnosis of aggressive intracranial malignancies. Factors that may have contributed to the favorable treatment outcome in the current case include the initial gross total surgical resection, the use of Proton Beam Radiation, and the pulse-intensive ICE chemotherapy regimen.

Poster # 009 | SIADH DUE TO HIGH-DOSE METHOTREXATE

Paul Kent, Kelsey Romatoski, Allison Byrne, Sara Brown, Ariana Pavlopoulos, Jennifer Misasi

Rush Medical College, Chicago, Illinois, United States

Background: The standard chemotherapy regimen for pediatric patients with osteosarcoma includes high dose methotrexate (HD-MTX), doxorubicin, and cis-platinum. Side effects commonly cited with these medications include alopecia, mucositis, nausea, vomiting, myelosuppression, cardiotoxicity, nephrotoxicity, and ototoxicity. Although syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been associated with several cancers and chemotherapy drugs, the relationship between SIADH and high dose methotrexate is not well understood or documented among the pediatric population being treated for osteosarcoma.

Objectives: Describe two cases of SIADH following administration HD-MTX.

Design/Method: We conducted a literature search via PubMed using the terms "methotrexate," "SIADH," and "osteosarcoma." We were unable to identify any literature demonstrating SIADH after HD-MTX in patients with osteosarcoma undergoing treatment.

Results: Case Reports: A 14-year-old female and 17-year-old male, both with right tibia osteosarcoma undergoing standard therapy of HD-MTX, doxorubicin, and cis-platinum, were

diagnosed with SIADH following administration of HD-MTX as evidenced by fluid overload symptoms and confirming laboratory values. The 14-year-old female experienced edema, weight gain of 2.0kg, and mild increase in blood pressure (97/61 to 109/61). Specific gravity increased from 1.006 to 1.017 within 2 hours of administration of HD-MTX with stable creatinine (0.78 to 0.64) indicating normal renal function. Symptoms resolved and lab values normalized following treatment with low dose furosemide. She was diagnosed with SIADH following her next HD-MTX treatment with resolution after low dose furosemide treatment. Subsequently, she was scheduled for low dose furosemide with future HD-MTX administration and had no further episodes of SIADH. The 17-year-old male experienced edema, weight gain of 3.7kg, and increase in blood pressure (129/66 to 159/77). Specific gravity increased from 1.007 to 1.016 within 4 hours of administration of HD-MTX with stable creatinine (0.98 to 0.85) indicating normal renal function. Symptoms resolved and lab values normalized following treatment with low dose furosemide. During his next HD-MTX treatment, he was diagnosed with SIADH and successfully treated with low dose furosemide again. In both cases, there was no delay in subsequent chemotherapy or noted side effects following administration of low dose furosemide.

Conclusion: Pediatric oncologists caring for patients undergoing treatment for osteosarcoma with HD-MTX who observe signs and symptoms of fluid retention should consider SIADH as a possible side effect. Fluid retention has the potential to cause prolonged exposure to methotrexate and thus, increase risk of toxicity. In select cases, furosemide may be an effective treatment for methotrexate-induced SIADH preventing delay in chemotherapy or undue toxicity.

Poster # 010 | MALIGNANT DISSEMINATED GLIONEURONAL TUMOR WITH BRAF-KIAA1549 FUSION AND 1p DELETION RESPONDS TO MEK-INHIBITOR: A CASE REPORT

Avani Mangoli, Amy Smith, Ana Aguilar-Bonilla

Arnold Palmer Hospital, Orlando, Florida, United States

Background: Low-grade glioneuronal tumors with malignant transformation are uncommon in childhood and young adults as are disseminated glioneuronal tumors of childhood. Recent studies have identified BRAF alterations in low-grade gliomas; two commonly described aberrations are KIAA1549-BRAF fusion and BRAFV600E mutation. BRAF fusion is more commonly seen in pilocytic astrocytomas and BRAFV600E mutations in pleomorphic xanthoastrocytomas and gangliogliomas. In fact, genetic alterations that result in upregulation of the MAPK/ERK pathway dominate the landscape of pediatric low-grade gliomas and low grade glioneuronal tumors, found in 82% of tumors. We present the case of a 20 year-old patient diagnosed initially with a right parietal lobe low-grade glioneuronal tumor with BRAF-KIAA1549 fusion and 1 p deletion.

Objectives: To evaluate the effect of MEK inhibitor on a patient with low-grade glioneuronal tumor with BRAF-KIAA1549 fusion and 1 p deletion who subsequently developed disseminated leptomeningeal disease.

Design/Method: We present the case of a 20 year-old patient diagnosed initially with a right parietal lobe low-grade glioneuronal tumor with BRAF-KIAA1549 fusion and 1 p deletion. He initially underwent a gross total resection and was followed with serial MRIs. He subsequently developed hydrocephalus requiring VP shunt placement. Approximately 4 months later, he was found to have abdominal distention with malignant ascites. MRI brain and spine showed new disseminated leptomeningeal disease. He was treated with cisplatin, CCNU, Vincristine, Cytoxan and IV Cetuximab as well as intrathecal triple therapy (Hydrocortisone, Methotrexate and Cytarabine). His ascites improved and his MRI showed stable CNS disease, however he developed significant malnutrition and refractory nausea/vomiting requiring inpatient rehabilitation. Subsequently, he was started on oral Trametinib (MEK-inhibitor) 2mg PO daily and currently on cycle 8.

Results: After starting on oral Trametinib (MEK-inhibitory) 2 mg PO daily, he has had remarkable clinical and radiographic response of his leptomeningeal disease and no re-accumulation of ascites. He has shown improvement in MRI and quality of life.

Conclusion: Some small molecule inhibitors have been developed to target both BRAFV600E mutations and targets downstream of BRAF, such as MEK inhibitors to target increased signaling due to BRAF duplications and are in early phase clinical trials for children. In our patient, we were able to obtain trametinib and fortunately he has had a dramatic response which has lasted for over 8 months. Although it is still early to know the long term effect of this medication, these agents are showing some exciting responses and certainly have shown benefit in the metastatic melanoma population.

Poster # 011 | WOLMAN DISEASE AND HLH, A CASE OF OVERLAPPING CLINICAL FEATURES

Krupesh Patel, Katharine Hodock

Hackensack University Medical Center, Hackensack, New Jersey, United States

Background: Wolman disease is a rare autosomal recessive condition characterized by lysosomal acid lipase deficiency. Lysosomal acid lipase is crucial for the breakdown of cholesterol esters and triglycerides within the lysosomes of cells located throughout the body. Lysosomal acid lipase deficiency leads to cholesterol esters and triglycerides accumulating in many different organ systems causing irreversible damage. Without therapy, consisting of enzyme replacement therapy or bone marrow transplantation, there can be irreversible organ damage and developmental interruption. Hemophagocytic lymphohistiocytosis (HLH) is characterized by abnormal activation of macrophages and lymphocytes. HLH can be inherited or can occur secondary to metabolic disorders, malignancies, infections or autoimmune conditions.

Objectives: This case report discusses a patient with clinical features of both Wolman disease and HLH. Rare cases have been discussed in the past, suggesting a cholesterol ester-induced inflammasome activation of macrophages in Wolman disease leading to secondary HLH. This case is unique since the patient had overlapping symptoms and is likely the youngest to be treated with enzyme replacement therapy to treat the underlying Wolman disease.

Design/Method: A 2 month old female initially presented with fevers, cough, failure to thrive, noted hepatosplenomegaly, abdominal distension, a reducible umbilical hernia, a systolic murmur, microcephaly, leukocytosis, anemia, thrombocytopenia, and decreased tone. Abdominal ultrasound was significant for bilateral adrenal calcifications. Patient was evaluated by multiple specialties and Wolman disease was considered the likely diagnosis. Patient was noted to have an elevated ferritin and hypertriglyceridemia. The patient also met criteria for HLH and was started on steroids. Patient was additionally started on weekly sebelipase alfa (recombinant lysosomal acid lipase) infusions as therapy for her Wolman disease. She has tolerated treatment and is showing clinical and laboratory improvement.

Results: The patient showed much improvement with decreases in ferritin, triglycerides, and soluble IL-2 receptor. To date, patient has tolerated sebelipase alfa infusions well. Her HLH has been well treated with steroids.

Conclusion: This case illustrates a rare condition in Wolman disease and the concurrence of hemophagocytic lymphohistiocytosis in an infant. Therapy for Wolman disease outside of bone marrow transplantation has been successful in our case with the utilization lysosomal acid lipase enzyme replacement. This patient is the youngest documented case of Wolman disease to successfully receive and tolerate lysosomal acid lipase therapy. Furthermore, this is one of the rare cases in which HLH is secondary to a lipid storage disease. The clinical feature overlap can make treatment and prognosis discussions difficult.

Poster # 012 | PEPTIDE RECEPTOR RADIONUCLIDE THERAPY FOR METASTATIC PANCREATIC NEUROENDOCRINE TUMOR

Samara Potter, Danielle Johnston, Priya Mahajan, Rajkumar Venkatramani

Baylor College of Medicine/Texas Children's Hospital, Houston, Texas, United States

Background: Non-appendiceal neuroendocrine tumors (NETs) are uncommon in children, with an incidence rate of 0.1 per million in children under 10 years of age. There is no known curative therapy for patients presenting with unresectable metastatic gastro-pancreatic NETs. Peptide receptor radionuclide therapy (PRRT) employs radiolabeled somatostatin analogues, which bind to somatostatin receptors expressed by the NET cells. 177Lu-Dotatate based PRRT therapy showed significant improvement in both progression free survival and response rate in adults with progressive somatostatin receptor positive midgut neuroendocrine tumors. The safety and efficacy of this agent in children is unknown.

Objectives: To report a case of pediatric metastatic neuroendocrine tumor with clinical improvement with PRRT.

Design/Method: Case report

Results: An 8 year-old male presented with 6 months of severe, intermittent abdominal pain. Computed tomography of the abdomen demonstrated multiple low-attenuation liver lesions and periportal lymphadenopathy without a definite primary site. Biopsy of a liver lesion revealed a grade 2 stage IV NET. Octreotide scan did not show any uptake. Endoscopic biopsy of a concerning lesion in the pancreatic head confirmed NET. Chemotherapy was initiated with capecitabine and temozolomide for 4 cycles without clinical improvement. Surgical resection was attempted, but was discontinued due to extensive lymphadenopathy surrounding the pancreatic head. Subsequently, the patient was treated with everolimus for two months; however, he continued to have worsening abdominal pain. DOTATATE PET scan showed uptake in all known lesions. Based on emerging adult data and lack of other therapeutic options, 177Lu-Dotatate therapy was administered at 81 mCi. The patient received an amino acid infusion to protect his kidneys prior to therapy which was well tolerated with no acute side effects. Post treatment scans showed uptake of the agent in all tumor sites. Blood counts and liver and kidney

function tests did not show any abnormalities in the post treatment period. The patient received a second 177Lu-Dotatate therapy two months later with improvement in pain control. The chromogranin level decreased from 149 ng/ml prior to therapy to normal levels (70 ng/ml) after two treatments. We plan to administer two more doses of 177Lu-Dotatate prior to repeating the DOTATATE PET scan.

Conclusion: We present the first report of a child with metastatic neuroendocrine tumor whose disease showed clinical improvement after treatment with PRRT with 177Lu-Dotatate. PRRT therapy should be considered in pediatric patients with refractory neuroendocrine malignancies and further investigations are warranted in other populations that might potentially benefit, such as patients with refractory neuroblastoma.

Poster # 013 | UNIQUE PRESENTATIONS OF ATAXIA-TELANGIECTASIA IN TWO BROTHERS

Christopher Ours, Ashley Cunningham, Zeinab Afify

University of Utah, Salt Lake City, Utah, United States

Background: Ataxia-Telangiectasia (A-T) is a disorder that consists of cerebellar degeneration, telangiectasia, immunodeficiency, radiation sensitivity, and cancer susceptibility. These clinical manifestations are the result of an autosomal recessive defective ataxia-telangiectasia mutated (ATM) gene responsible for DNA repair. Patients with classic A-T typically present in the first decade of life with ataxia and abnormal eye movements. It is often associated with telangiectasia, frequent respiratory infections, lab abnormalities (IgA deficiency, lymphopenia, and increased alpha-fetoprotein (AFP) levels). We describe two brothers both with ataxia but with unique hematologic presentations: one who presented with Burkitt lymphoma, and the other with chronic parvovirus induced anemia.

Objectives: To describe a novel pathogenic variant of ATM and two unique presentations of A-T in two brothers.

Design/Method: Case report and review of literature. The medical record, pathologic studies and immune work up followed by next generation sequencing were reviewed.

Results: A 7-year-old Burundi immigrant male presented with a croup-like cough and was discovered to have a mediastinal mass. Biopsy confirmed EBV-positive Burkitt lymphoma. He was treated as per ANHL1131 Group B therapy. During therapy, he developed severe dysphagia, ataxia, as well as persistent tachycardia and heart failure. His 8-year-old brother later presented with ataxia, fatigue, and pallor and was found to be severely anemic with parvovirus viremia. Bone marrow aspirates and biopsies revealed erythroblastopenia and viral inclusions. He received intravenous immunoglobulin (IVIG) 1gm/kg and had temporary improvement of his reticulocytopenia. He continues to require monthly IVIG. Additionally, both brothers had elevated AFP levels. They are followed by neurology, pulmonology, and medical genetics for comprehensive care. Genetic testing of the younger brother confirmed ataxia-telangiectasia with a paternally inherited c.3667_3668dupAA not previously described in the literature and a maternally inherited c.6415_6416delGA that has been reported in multiple other cases. These mutations result in a frameshift and premature termination. Immunoblot assay for the ATM protein on older brother confirmed absence of ATM protein.

Conclusion: We present two brothers with unique presentations of ataxia-telangiectasia and describe a novel genetic variant. In patients who experience excessive chemotherapy toxicity it is important to investigate for an underlying disorder. In our patients, a history of neurologic symptoms led to suspicion and ultimate diagnosis of ataxia-telangiectasia.

Poster # 014 | OSTEOSARCOMA IN A CHILD WITH NEUROFIBROMATOSIS TYPE 1: A CASE REPORT AND REVIEW OF THE LITERATURE

Gino Jose Bardi Lola, Adriana Trabal, Maggie Fader, Jorge Galvez-Silva, Carole Brathwaite, Ossama Maher

Nicklaus Children's Hospital, Miami, Florida, United States

Background: Neurofibromatosis type 1 (NF1) is an autosomal dominant condition that has been strongly associated with the development of malignancy. Although reported in adults, the occurrence of osteosarcoma in children with NF1 is extremely uncommon.

Objectives: We report a case of osteosarcoma of the left femur in a pediatric patient with NF1 and a review of the literature of osteosarcoma diagnosed in patients with NF1.

Design/Method: A PubMed search was conducted for queries including "Neurofibromatosis type 1" "Osteosarcoma", and "Outcomes" Relevant papers were selected for literature review.

Results: A 6 year-old Hispanic female diagnosed with NF1 at 2 months of age, presented with a 5 × 5 cm left thigh mass. Imaging studies revealed an extensive infiltrative bone lesion involving the whole femur with a soft tissue component. Fluoroscopy guided needle biopsy was performed and

demonstrated the diagnosis of high grade osteosarcoma. The patient was started on multi-agent chemotherapy with planned a whole femur prosthesis at time of local control. 7 cases of osteosarcoma have been described in the literature in patients with NF1 (median age; 25 years, range 17–37 years) with slightly male predominance (4 cases). The femur was the most common site of involvement (5 cases). Four patients died of metastatic disease despite surgery and multi-agent chemotherapy.

Conclusion: NF1 represents a major risk factor for development of malignancy and uncommonly osteosarcoma in adolescents and adults. We report a rare case of an extensive involvement of osteosarcoma of the left femur in a child with known diagnosis NF1. This presentation should alert the pediatric oncologists to monitor for bone tumors in patients with NF1 by physical exam and detailed medical history.

Poster # 015 | SIGNIFICANT IMPROVEMENT IN PARANEOPLASTIC DYSAUTONOMIA WITH RITUXIMAB THERAPY

Nicole Muhlbauer, Thomas Renaud, Jennifer Welch

Hasbro Children's Hospital, Providence, Rhode Island, United States

Background: Dysautonomia is a paraneoplastic syndrome most commonly described in adult malignancies. Despite current therapies aimed at symptoms management, it is often debilitating. We present a case of a 16-year-old girl who initially presented with autonomic dysfunction and was subsequently found to have Hodgkin Lymphoma.

Objectives: Describe Hodgkin Lymphoma presenting with dysautonomia and discuss symptom management with rituximab

Design/Method: Case report

Results: A 16 year-old-girl presented with severe symptoms of orthostatic hypotension necessitating prone positioning to prevent syncopal episodes. Additionally, she reported anhidrosis, xerostomia, urinary retention, and constipation. She had unmanageable peripheral neuropathic pain despite multiple analgesia medications. Initially, it was suspected that her symptoms were caused by an atypical presentation of Guillain-Barre Syndrome. She was treated with intravenous immunoglobulin G, without response. Due to a suspicion of a paraneoplastic syndrome a positron emission test/cat scan (PET/CT) was performed and revealed widespread FDG-avid nodal and splenic disease. Pathology from a thoracoscopic biopsy of a mediastinal lymph node demonstrated classical Hodgkin Lymphoma. She was classified as Stage IVB. A paraneoplastic panel obtained during the first cycle of chemotherapy revealed elevated anti-amphiphysin antibodies and glutamic acid decarboxylase (GAD) antibodies. Therapy was initiated with ABE-PC (doxorubicin, bleomycin, etoposide, prednisone, cyclophosphamide); vincristine was held given her significant neuropathy. Due to persistence of autonomic symptoms following her first cycle and presence of anti-amphiphysin and GAD antibodies, rituximab was incorporated into her treatment. Following two cycles ABE-PC, she had a rapid early response by FDG-PET/CT. She completed an additional three cycles of ABD-PC. End of therapy imaging demonstrated complete response with a single persistent mildly FDG-PET avid lymph node (Deauville 2) and her antibodies were negative. She continues treatment of maintenance rituximab with significant improvement, but not resolution, of her orthostatic hypotension. At this time, the patient can ambulate with assistance. Constipation and urinary retention have fully resolved and, her peripheral neuropathy, xerostomia, anhidrosis have improved.

Conclusion: This is rare case of a pediatric Hodgkin Lymphoma patient developing dysautonomia associated with anti-amphiphysin and glutamic acid decarboxylase antibodies and subsequently managed with chemotherapy and rituximab. Clinicians should be suspicious of a paraneoplastic syndrome when a neurologic disorder fails to improve with standard treatment.

Poster # 016 | A LOW-GRADE GLIOMA HISTOLOGICALLY DIAGNOSED AS AN EPENDYMOMA: HOW MOLECULAR DATA IS SHAPING THE WAY WE DIAGNOSIS AND TREAT BRAIN TUMORS

Jessica Lake, Andrew Donson, Davis Witt, Nicholas Foreman, Lindsey Hoffman

University of Colorado Anschutz Medical Campus, Aurora, Colorado, United States

Background: Molecular diagnostics can augment the histopathological diagnosis of pediatric brain tumors. The BRAF:KIAA1549 fusion (B-K fusion) is considered a useful diagnostic marker for low-grade gliomas (LGGs), the least aggressive category of pediatric brain tumors. We report a case of an infant with a histological diagnosis of ependymoma, which was retrospectively found to harbor the B-K fusion.

Objectives: To review the presentation and diagnosis of a brain tumor and how new molecular data may inform diagnosis.

Design/Method: Case report

Results: A 6 month-old male presented with a several month history of vomiting, weight loss, increasing head circumference, and loss of milestones. His exam was significant for macrocephaly, irritability, poor neck control, and poor visual tracking. CT scan of the brain revealed a 5.6 × 5.3 × 5 cm posterior fossa mass and marked hydrocephalus. A difficult pathologic diagnosis of his subtotally resected tumor was made as anaplastic ependymoma (WHO grade III). He received 2 rounds of chemotherapy, followed by second look surgery; the second surgery was undertaken because complete tumor resection is prognostically favorable for ependymoma. After complete resection, he continued with chemotherapy until his first birthday, after which he received focal radiation. At age six years old, this patient is cancer-free but has significant sequelae from his tumor and therapies, including developmental delay, dysarthria, hearing loss, ataxia, and persistent bilateral cranial nerve VI and VII palsies. Retrospective assessment of this patient's tumor tissue using a CLIA-certified RNA-based fusion panel developed at the University of Colorado revealed a B-K fusion, characteristic of LGG.

Conclusion: Treatment for ependymoma, which includes maximal surgical resection and focal radiation therapy, is much more aggressive than for LGG, which can often be managed with surgery followed by observation. Since B-K is a known molecular driver of LGG, real-time molecular characterization of this patient's tumor would have dramatically altered therapeutic management, likely sparing much of his therapy-associated morbidity. This case emphasizes how molecular characterization of brain tumors can be an extremely important diagnostic tool to limit unnecessary interventions and improve morbidity for pediatric patients with brain tumors.

Poster # 017 | EXPLORING WHY PEDIATRIC CANCER PATIENTS ARE DYING IN THE INTENSIVE CARE UNIT WITH LONGSTANDING DO NOT RESUSCITATE ORDERS

Valeria Smith, Heidi Russell

Baylor College of Medicine, Houston, Texas, United States

Background: Although there has been significant improvement in the overall survival rates of children with cancer many children will still die from their illness or complications secondary to treatment. Research surrounding the deaths of children who succumb to their disease is warranted to ensure we are providing the best care possible for these patients.

Objectives: This case series aims to explore pediatric cancer deaths by focusing on perhaps the most extreme cases of high intensity end of life care. We explore those patients whom we know are dying or our very likely to die as evidence by their do not resuscitate (DNR) orders. In all of these cases despite the patients very grim prognosis, their great likelihood of death and limitations placed of resuscitation methods all patients continued end of life care in the pediatric intensive care unit (PICU).

Design/Method: The primary medical records of all children with a cancer diagnosis who died between February 1, 2011 and January 31, 2017 in the PICU with a DNR order seven days or earlier prior to death. Each medical history included disease-directed treatment history and response with particular attention to the events surrounding the terminal admission.

Results: Eight patients met criteria for this study representing 1.9% of all cancer patients who died during this time period and 7.4% of those who died in the ICU. The average time between DNR and death is 19.6 days (7 days – 32 days). The average length of terminal admission was 43.5 days (1 day – 153 days). The average time between diagnosis and DNR is 10.75 months (0 months – 22 months). The average time between diagnosis and death is 11.25 months (0 months – 23 months).

Conclusion: These cases highlight the journey that patients, families and providers endure leading up to death. Medical care is complex, there are very few absolutes that are encountered when caring for patients and decisions around limiting or withdrawing medical care are made in a context of the prior journey. These cases help to understand the complexity of death and how two seemingly opposite ideals can be congruent in the event of an anticipated death. Most of these cases show the need for improved anticipatory guidance surrounding death and greater consideration for de-escalation of care when death is expected.

Poster # 018 | A CASE OF RUBINSTEIN-TAYBI SYNDROME PRESENTING WITH NEUROBLASTOMA AND MALIGNANT HYPERTENSION

Meera Srikanthan, Lindsey Murphy, Navin Pinto

Seattle Children's Hospital, Seattle, Washington, United States

Background: Rubinstein-Taybi syndrome (RSTS) is a genetic disorder associated with growth retardation, dysmorphic facial features, and an increased risk of malignancy. RSTS is associated with gene mutations encoding cyclic-AMP regulated enhancer binding protein (CREBBP) or E1A binding

protein p300 (EP300). CREBBP and EP300 are both transcriptional co-activators of p53, the tumor suppressor gene, potentially explaining why RSTS patients are predisposed to cancer. These tumors are typically of neural or developmental origin, including neuroblastomas, pheochromocytomas, medulloblastomas, and seminomas. Neuroblastoma is a neuroendocrine tumor where hypertension is a feature in only 10–20% of patients, and usually secondary to vascular compression. In pheochromocytoma, catecholamine containing storage granules are released, causing hypertension. However, in more primitive neuroblastic cells there is a defect in catecholamine synthesis resulting in the accumulation and excretion of catecholamine metabolites, homovanillic acid (HVA) and vanillylmandelic acid (VMA). Only a small proportion of neuroblastomas are capable of catecholamine synthesis and may present similarly to pheochromocytoma.

Objectives: Describe a unique case of RSTS presenting with neuroblastoma and concurrent hypertension secondary to catecholamine excess.

Design/Method: Case report

Results: A 2-year-old female with RSTS and confirmed CREBBP gene mutation presented with 3 weeks of fevers, cough, and irritability. Imaging revealed a posterior paramediastinal mass without evidence of distant metastatic disease. During her initial evaluation, she was observed to have significant hypertension. Labs confirmed the suspicion of a catecholamine mediated process with elevated homovanillic acid, vanillylmandelic acid, free metanephrine, and free normetanephrine. Thoracotomy and biopsy was performed, revealing a poorly differentiated neuroblastoma, without MYCN amplification. Full resection was unsuccessful due to the friable nature of the tumor. Treatment was initiated per our institutional standard for intermediate-risk neuroblastoma with two cycles of chemotherapy. Breakthrough hypertension secondary to tumor lysis was observed with initial administration of chemotherapy. Surgical resection was performed four weeks after completion of chemotherapy with a gross total resection. She was normotensive postoperatively. She currently is clinically asymptomatic and off antihypertensives.

Conclusion: Here we describe a rare case of a RSTS patient presenting with hypertension from a catecholamine secreting neuroblastoma. Chemotherapy triggering tumor lysis or surgical manipulation of these tumors can cause catecholamine release, as both occurred in our patient. It is unclear whether patients with RSTS are predisposed to forming catecholamine secreting tumors specifically and whether the CREBBP pathway is implicated in this process. Neuroblastoma should be on the differential for RSTS patients who develop tumors, and catechol excess may be a presenting sign in these individuals.

Poster # 019 | ATAXIA TELANGIECTASIA PRESENTING WITH SEVERE NEUTROPENIA AND INVASIVE ACTINOMYCES INFECTION

Stacy Snyder, Jason Newland, Marwan Shinawi, Toni Pearson, Elizabeth Nieman, Carrie Coughlin, Jeffrey Bednarski, Alok Kothari, Maleewan Kitcharoensakkul, Melanie Fields

Washington University School of Medicine, St. Louis, Missouri, United States

Background: Ataxia-telangiectasia (AT) is an autosomal recessive disorder resulting from mutations in the ATM gene that is characterized by progressive cerebellar ataxia, telangiectasias, immunodeficiency, radiation sensitivity, and cancer predisposition. Most commonly, patients with AT are diagnosed after presenting with neurologic abnormalities.

Objectives: We aim to highlight the importance of including primary immunodeficiencies in the differential diagnosis of severe neutropenia.

Design/Method: We report a case of a 14-month-old female with a history of recurrent otitis media who presented with sepsis, severe neutropenia, oral lesions, and circumferential perianal ulceration due to an underlying diagnosis of AT.

Results: Labs obtained at an outside hospital one month prior to presentation showed absolute neutrophil count (ANC) 78 and hemoglobin 10.2 g/dL. She presented to our institution with 11 days of fever, hepatomegaly 1 cm below costal margin, a white plaque on her tongue, and circumferential perianal ulceration. Labs were significant for ANC 0 and hemoglobin 7.8 g/dL. Anti-granulocyte antibody testing was positive. Bone marrow biopsy showed arrest of neutrophil maturation. After initiation of filgrastim (2.7 mcg/kg/day), her ANC increased to >500 and repeat bone marrow biopsy demonstrated left shifted myelopoiesis. Biopsy of her oral lesion demonstrated invasive actinomyces prompting a prolonged course of antibiotics. Biopsies of her oral and anal lesions were reported as myeloid sarcoma without MLL rearrangement. Chemotherapy was not initiated due to complete resolution of both lesions within 6 weeks of initiating filgrastim and appropriate antibiotic coverage. She has not developed any further lesions concerning for malignancy. Testing for common genes associated with severe congenital neutropenia and autoimmune lymphoproliferative syndrome was negative. Her immunoglobulin levels and the measurement of age-appropriate vaccine responses were normal. After her lymphocyte subpopulation analysis indicated a selective deficiency in CD8 positive T-lymphocytes (absolute CD8 cell count 185), the Severe Combined Immunodeficiency panel from GeneDx showed compound heterozygous mutations in

the ATM gene, c.6916_6917delAG (p. L2307C_fsX65) and c. 4632_4635delCTTA (p. Y1554X), which are both pathogenic for AT. Following identification of the ATM mutations, alpha-fetoprotein was found to be elevated at 77.8 ng/mL (normal < 8.3). Following diagnosis of AT, the patient was evaluated by a multidisciplinary team including a neurologist (who identified truncal ataxia), immunologist, ophthalmologist, geneticist and cancer predisposition service.

Conclusion: Primary immunodeficiencies should be considered in patients presenting with severe neutropenia.

Poster # 020 | PROLONGED SURVIVAL AND EVENTUAL DEATH BY DISSEMINATED PULMONARY METASTASIS IN A PEDIATRIC PATIENT WITH DIFFUSE PONTINE H3.1K27M GLIOMA: A CASE REPORT

Christina Coleman Abadi, Tabitha Cooney, Arie Perry, Hua Guo, David Solomon, Joseph Torkildson

UCSF Benioff Children's Hospital Oakland, Oakland, California, United States

Background: Diffuse intrinsic pontine gliomas (DIPG) with H3.1K27M mutation are associated with dismal prognosis and median survival of 15.0 months.

Objectives: To describe a case of DIPG with an unusual natural history.

Design/Method: Case Report

Results: In this case report, we present a patient with diffuse H3.1K27M pontine glioma treated with craniospinal irradiation and anti-angiogenic therapy, who survived 38 months and ultimately died of pulmonary disease. A previously healthy 7-year-old female presented with headache and altered mental status. Neuroimaging revealed T2/FLAIR hyperintensity centered within and expanding the pons, as well as enhancement along pituitary infundibulum and ventral C6-T5 spinal cord concerning for synchronous metastatic disease. Ventriculoperitoneal shunt placement and brainstem biopsy were performed, biopsy revealed infiltrative astrocytoma with positive nuclear histone H3-K27M staining. She received 6 weeks of craniospinal irradiation followed by 10 months of triple anti-angiogenic medication with thalidomide, celecoxib and etoposide per modified Angiocomb protocol. She eventually developed progressive interstitial lung disease with no concurrent clinical signs of CNS disease progression. She ultimately died of respiratory failure 38 months from diagnosis. Next generation sequencing performed on diagnostic tissue found HIST1H3B p.K28M hotspot and PTPN11 gene missense mutations, lung biopsy tissue prior to death revealed the same H3.1K27M and PTPN11 mutations, as well as frameshift mutations in NF1 and CREBBP genes. Postmortem examination revealed presence of metastases in lungs, kidneys, liver, fallopian tube, perihepatic soft tissue, diaphragm, as well as progression of her primary disease.

Conclusion: Our case is the first report of documented DIPG pulmonary metastasis and subsequent death by pulmonary disease, and the longest documented survival of HIST1H3B K27M pontine glioma by several months.Further thought should be given to whether cerebrospinal fluid diversion and radiation strategy affected her clinical course. References: 1 Mackay A, et al. Integrated molecular meta-analysis of 1000 pediatric high-grade and diffuse intrinsic pontine glioma. Cancer Cell. 2017 Oct 9; 32(4):520-537. 2 Castel D, et al, Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. Acta Neuropathol. 2015; 130(6):815-827. 3 Barajas Jr, R, et al. Metastatic diffuse intrinsic pontine glioma to the peritoneal cavity via ventriculoperitoneal shunt: case report and literature review. J Neurol Surg Rep. 2015 Jul;76(1):e91-e96. 4 Porkholm M, et al. Radiation therapy and concurrent topotecan followed by maintenance triple anti-angiogenic therapy with thalidomide, etoposide, and celecoxib for pediatric diffuse intrinsic pontine glioma. Pediatr Blood Cancer. 2014 Sep;61(9): 1603-9.

Poster # 021 | DIAGNOSIS AND MANAGEMENT OF VON WILLEBRAND DISEASE TYPE 2B IN A PATIENT WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Kathleen Felton, Sarah McKillop, Hanan Gerges, Mark Belletrutti, Aisha Bruce

University of Alberta, Edmonton, Alberta, Canada

Background: Acute lymphoblastic leukemia (ALL) is the most common type of cancer diagnosed in children; treatment involves multiple intrathecal chemotherapy administrations. Von Willebrand disease (VWD) is the most common bleeding disorder seen in children and caused by either decreased quantity or abnormal function of von Willebrand factor (VWF). VWD Type 2B, is a rare qualitative defect, with increased VWF and platelet binding, leading to depletion of large, functional VWF multimers. There are no guidelines on the management of patients with VWD undergoing ALL therapy.

Objectives: To describe the diagnostic process and management of VWD in a patient with newly diagnosed B-cell ALL.

Design/Method: Case report.

Results: A 15-year-old male presented with a spontaneous tonsillar bleed and history of recurrent epistaxis. Initial hemostasis investigations revealed normocytic anemia, normal PTT, INR, white blood count, platelet count. The patient underwent partial tonsil resection and tranexamic acid to achieve hemostasis and was discharged on 3 days post operatively with no complications. Following discharge additional results revealed decreased Factor VIII (0.47U/ml), ristocetin (0.16U/ml) and von willebrand factor antigen (0.23U/mL). Three weeks later when presenting for routine follow up there were blasts on his blood smear. He was subsequently diagnosed with B-cell ALL. Repeat testing confirmed VWD. The patient received tranexamic acid and Humate P 60 units/kg IV prior to IVAD insertion and lumbar puncture with intrathecal chemotherapy, followed by 30 units/kg IV every 12 hours for three doses. Platelet aggregation testing demonstrated increased aggregation with ristocetin (0.5mg/ml) between control platelets and patient plasma and no ristocetin induced aggregation between patient platelets and control plasma, leading to the diagnosis of VWD Type 2B. Multimer studies demonstrated loss of high molecular weight multimers. Genetic studies are pending. Half-life study demonstrated VWF antigen level of 32% at 48 hours. Therefore, Humate P infusion was changed to pre-procedure only. In addition, the patient will receive Humate P infusion prior to platelet transfusions, due to increased risk of VWF clearance. To date, the patient has tolerated therapy well, with no bleeding or thrombotic complications.

Conclusion: This case represents the concurrent diagnosis of VWD Type 2B and B-cell ALL. The use of factor prophylaxis for a major procedure was used successfully to prevent bleeding in frequent intrathecal chemotherapy administrations. A half-life study was used to reduce the number of Humate P doses required to prevent procedural bleeding. The coordination between laboratory medicine, hematology and oncology was key to provide optimal patient care.

Poster # 022 | DESCRIPTION OF A NOVEL BRAF MUTATION IN CHILD WITH FIBROUS HAMARTOMA OF INFANCY

William Thomsen, Luke Maese, Douglas Fair

Primary Children's Hospital, University of Utah, Salt Lake City, Utah, United States

Background: Fibrous hamartoma of infancy (FHI) is a rare benign soft tissue tumor defined by triphasic morphology consisting of adipose, fibroblastic and mesenchymal components and rare sarcomatous-appearing foci. Surgical resection is curable; however when resection is not feasible other treatment options must be considered. B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF) is a well-characterized oncogene in the RAS/RAF/MEK/ERK signaling pathway. Somatic activating mutations in BRAF have been reported in numerous cancers. Inhibition of BRAF and downstream signaling pathway components have produced promising clinical results. To date BRAF mutations have not been reported in FHI.

Objectives: Describe case of an infant with an unresectable FHI with somatic BRAF mutation.

Design/Method: Case report and literature review

Results: A male infant was born with a large thigh mass. The child was clinically well aside from restricted movement of affected leg. MRI showed mass expanding into pelvis without other lesions. An interventional-radiology guided core biopsy of the mass was reported as high-grade spindle cell sarcoma without ETV6 rearrangement. Surgery was deferred because of concern that it would result in excessive morbidity. The mass was treated with vincristine and dactinomycin per infantile fibrosarcoma protocols. After 3 months of therapy, no significant change in size of the mass was noted on physical exam or imaging. Repeat biopsy was obtained to confirm diagnosis and allow for expanded tumor testing. This biopsy showed triphasic distribution of adipose, fibrous and mesenchymal tissue consistent with FHI with rare sarcomatous foci. Additional chemotherapy was deferred and the child was followed clinically. His tumor has remained approximately the same size and still unresectable. Next generation sequencing of tumor utilizing panel based technology revealed BRAF-ERC1 fusion consistent with BRAF activating mutation. This mutation was confirmed by fluorescent in situ hybridization (FISH) probe for BRAF. BRAF and MEK inhibitors have been pursued as treatments to decrease size of tumor and allow for resection.

Conclusion: BRAF mutations have been characterized in a variety of malignancies. Inhibition of BRAF and downstream signaling components has produced promising results in a variety of patients. This is the first case report of a BRAF mutation in a FHI. Although management of FHI is typically surgical, this does suggest a potential therapeutic target and may allow for improved surgical outcomes especially in cases where up-front surgery would result in unacceptable morbidity. Genetic sequencing of FHI and other rare tumors is an important tool and has the potential to identify mutations amenable to targeted therapies.

Poster # 023 | DIAGNOSIS AND MANAGEMENT OF A NOVEL PHENOTYPE OF IMMUNODEFICIENCY, CENTROMERIC INSTABILITY, AND FACIAL ANOMALY SYNDROME (ICF) TYPE 4 WITH NEUTROPENIA AND NEUROBLASTOMA

Katie Greenwood, Jennifer Miller, Rosa Diaz, Jennifer Foster, Caridad Martinez, Sarah Nicholas

Baylor College of Medicine, Houston, Texas, United States

Background: ICF is a rare autosomal recessive disorder characterized by hypo- or agammaglobulinemia and often opportunistic infections suggesting T-cell dysfunction. It is further categorized into subtypes 1–4 based on mutations in DNA methylation. Mutations in the helicase-lymphoid specific (HELLS) gene, which is required for T-cell proliferation and participates in de novo DNA methylation, are characteristic of ICF type 4 (ICF4). Of approximately 70 reported cases of ICF, less than 10 percent are characterized as ICF4. While malignancy has been reported in ICF1 (angiosarcoma, acute lymphoblastic leukemia), and ICF2 (Hodgkin lymphoma), here we describe the diagnosis and management of an ICF4 patient with neuroblastoma and neutropenia, which has not been previously described.

Objectives: Describe a novel phenotype and mutation of ICF4 and its management to further expand our understanding of this disease.

Design/Method: Retrospective chart review.

Results: A 6 month ex-31 week premature male with bronchopulmonary disease and failure to thrive presented with acute respiratory failure in the setting of recent viral bronchiolitis with associated chronic diarrhea. He was subsequently diagnosed with multiple infections including PJP pneumonia, norovirus, parainfluenza, rhinovirus, and pseudemonal cellulitis. He presented with profound neutropenia and agammaglobulinemia with presence of B and T cells on lymphocyte phenotyping. CT revealed a paraspinal mass that was MIBG-avid on further study, strongly suggesting neuroblastoma. Bone marrow was normocellular and negative for malignancy, however revealed marked granulocytic hypoplasia and maturation arrest concerning for severe congenital or, less likely, immune-mediated neutropenia. Metastatic workup was negative. Whole exome sequencing revealed a homozygous variant of unknown significance (c. 668T>C) in the HELLS gene, portending a working diagnosis of ICF4 syndrome. Immunoglobulin supplementation, pentamidine prophylaxis, and G-CSF were initiated. He was able discontinue G-CSF after 4 months of treatment. His neuroblastoma, initially categorized as L1, met criteria for observation. However, followup MRI revealed interval growth nearing the spinal canal. He underwent tumor resection, confirming MYCN non-amplified, favorable histology neuroblastoma. After infectious prophylaxis and immunologic support were initiated, he incurred two other hospitalizations, the first for G-tube cellulitis and the second for parainfluenza respiratory illness. He now has stable neutrophil counts off G-CSF and remains in remission from neuroblastoma. Current plan is to proceed with bone marrow transplantation for immunodeficiency.

Conclusion: ICF4 has not previously been described with neutropenia or neuroblastoma. This report not only describes a novel mutation and phenotype of ICF4 and the management thereof, but also reveals the potential curative role of bone marrow transplantation in such disease.

Poster # 024 | A NOVEL APC MUTATION IN A TEENAGE PATIENT WITH A LARGE INTRA-ABDOMINAL DESMOID TUMOR

Ivana Capin, Eleny Romanos-Sirakis

Staten Island University Hospital - Northwell Health, Staten Island, New York, United States

Background: Desmoid tumors are rare tumors that arise from highly differentiated fibroblasts. They occur in isolation or as part of the disease spectrum of familial adenomatous polyposis (FAP). FAP mutations between codons 1445–1578 typically correlate with increased extraintestinal disease such as desmoid tumors and upper gastrointestinal polyps. We describe a patient with a large intra-abdominal desmoid tumor who is heterozygous for a c.8161C>T (p.Arg2721Cys) APC gene mutation. We are not aware of any other patients reported with this germline APC mutation presenting with a desmoid tumor.

Objectives: To discuss a novel APC mutation and the presentation of a rare case.

Design/Method: Review of clinical presentation, genetic analysis and management of a rare tumor.

Results: A 17-year-old female with no significant medical history presented with abdominal asymmetry and intermittent pain. She reported urinary urgency, shortness of breath, early satiety, decreased appetite and a 20-pound weight loss over the course of 7 months. CT scan of the abdomen demonstrated a 24 × 15cm abdominal tumor abutting the local organs but no presence of bowel obstruction. A biopsy revealed a

spindle cell neoplasm favoring fibromatosis. There was no known family history of FAP, colon cancer, or desmoid tumors. APC gene mutation analysis demonstrated a c.8161C>T (p.Arg2721Cys) heterozygous gene variant. Due to size and location of the tumor, it was initially deemed unresectable. The patient was started on a course of monthly liposomal doxorubicin. She tolerated the initial cycles well and interval CT after 3 cycles of chemotherapy revealed a 40% decrease in tumor volume. Variability exists in phenotypic presentation with regards to the location of the AFP mutation locus. While FAP mutations associated with desmoid tumors typically have changes in the 1445–1645 codon region, our patient presented with a heterozygous mutation resulting in a missense mutation at codon 2721. Due to the change in polarity and size, the mutation is not considered to be of conservative nature. We are only aware of one other report of this mutation, which occurred in an individual with a personal and family history of colon cancer. We are not aware of any patients with desmoid tumors who also have this germline APC gene mutation.

Conclusion: Our case report highlights an APC gene mutation that is not well-described; we are not aware of any other cases of this mutation reported in patients with desmoid tumors. Future evaluation and tracking of this mutation may lead to the determination of further clinical significance.

Poster # 025 | PEDIATRIC USE OF A DENVER SHUNT: ANSWER TO A FAMILY'S GOALS OF CARE

Haroon Ali, Billie Winegard, Jaime Libes

University of Illinois College of Medicine at Peoria, Peoria, Illinois, United States

Background: Over time, advanced care planning for location of death has been associated with increased deaths at home rather than in the hospital. In some cases, however, complex management and symptom control can prevent families from achieving their goal of keeping their child out of the hospital and at home at the end of life. Ascites is a sequelae of many conditions including malignancy that might lead to significant morbidity. Increasingly, interventional procedures are being utilized. Peritoneovenous "Denver" shunts are placed internally with one end in the peritoneal space and the other buried within a major vessel such as the SVC. A one-way valve and pump buried under the skin allows the patient to pump fluid from the peritoneal to the vascular space. The shunt is used frequently in adults, but has not seen much use in pediatric oncology patients.

Objectives: To describe a case of a terminally ill patient with refractory Wilms tumor with IVC involvement who received symptomatic relief with Denver shunt placement.

Design/Method: Case Report

Results: An 8-year-old female was diagnosed with relapsed, refractory, metastatic Wilms tumor with pulmonary and hepatic involvement, with tumor extension to the hepatic veins and IVC. Multiple chemotherapeutic regimens and palliative radiation to the IVC were administered, but her disease continued to progress, leading to pressure on the portal vein and portal hypertension. The resulting ascites was causing the patient significant pain and was difficult to manage. The patient's code status was changed to DNR/DNI after discussion with her mother, who identified a desire to have the child die at home as comfortably as possible. A peritoneovenous shunt was placed in order to control the patient's pain and avoid frequent medical procedures and therapies. Despite initial anxiety, the patient was able to utilize the pump and achieve significant improvement in her ascites and pain. She was able to spend the remaining six weeks of her life at home.

Conclusion: Ascites is a common phenomenon of end stage disease. Peritoneovenous shunts are a treatment modality that may be considered to allow for pain control at the end of life for pediatric oncology patients with ascites. The procedure is relatively low risk, allows for self-control of the pump to maintain comfort, and is easy enough to use by the patient or family.

Poster # 026 | EXTRANEURAL METASTASES IN PEDIATRIC GLIOBLASTOMA MULTIFORME - A CASE REPORT AND LITERATURE REVIEW

Sameer Farouk Sait, Tanya Trippett, David Lyden, Sofia Haque, Marc Rosenblum

Memorial Sloan Kettering Cancer Centre/Weil Cornell Medical Centre, New York, New York, United States

Background: Extraneural metastases (ENM) from pediatric glioblastoma multiforme (GBM) are rare, with an estimated frequency of 0.3%. Etiologic factors include multiple neurosurgical procedures and sarcomatous dedifferentiation. Their occurrence can seriously affect the patient's quality of life and survival. While ENMs have been well documented in adults, pediatric cases have not been previously summarized.

Objectives: A 15 year old male with a cerebral GBM developed extension of disease outside of the neuraxis approximately 18 months post initial presentation and at the time of disease progression. Metastases included exracranial temporal lesions, cervical and mediastinal lymph nodes and

bilateral lung nodules. A large pleural-based soft tissue metastatic focus was identified on imaging when the patient presented with respiratory distress secondary to a right tension pneumothorax, which was recognized and managed promptly. We summarize the main reported cases in literature to better define risk factors for and evaluate the proposed mechanisms underlying these systemic metastases.

Design/Method: We performed a literature review on the PubMed database using the terms GBM and ENM. Patients under 21 years of age who met the Weiss criteria for the diagnosis of ENM from primary CNS tumors were included.

Results: Our patient fulfilled two of the three Weiss criteria with confirmed GBM at the primary site with all ENM in the temporal soft tissue and cervical lymph nodes displaying histopathologic features similar to the primary CNS tumor. The intrathoracic adenopathy and lung nodules detected upon chest imaging during workup for respiratory distress were assumed to represent additional metastatic foci. Our literature review identified 22 pediatric patients with ENM from GBM with a median age of 12 years (range 3.5 - 21 years) and a slight female predominance (55% females vs. 45% males). The most common sites of metastases reported were pleura/lungs, bones, lymph nodes and liver. In 9 of 22 patients, metastases were associated with CSF shunting.

Conclusion: Pediatric oncologists should have an increased index of suspicion when caring for patients with GBM, particularly those who have undergone shunting procedures and present with systemic symptoms including bony pain, respiratory changes, transaminitis or cytopenias which should prompt timely investigation for ENM. Although ENM of CNS tumors carry very poor prognosis, their diagnosis has potential therapeutic importance because treatment of metastatic lesions may alleviate symptoms and improve the quality of life. Additional studies may be warranted to evaluate the incidence of ENM that can provide valuable insight into the pathogenesis and biology of high-grade gliomas.

Poster # 027 | SINUSOIDAL OBSTRUCTION SYNDROME AND SUSCEPTIBILITY TO BLEEDING AFTER GASTRIC TUBE PLACEMENT

Adriana Trabal, Gino Bardi, Ossama Maher, Roberto Gomara, Ziad Khatib, Guillermo DeAngulo

Nicklaus Children's Hospital, Miami, Florida, United States

Background: Sinusoidal Obstruction Syndrome (SOS) has been reported in patients undergoing intensive chemotherapy and as a complication post-hematopoietic stem cell transplantation. SOS may be complicated by portal hypertension, hepatorenal disease or multi-organ failure. However, despite treatment, there may be further potential complications that can be anticipated in patients with history SOS.

Objectives: We report two patients with history of SOS presented with post-procedural bleeding after gastric tube placement. We believe that their presentations may be associated to their previous diagnosis of SOS.

Design/Method: PubMed search was done with search for terminology including "Sinusoidal Obstruction Syndrome" "Defibrotide", and "Bleeding". Papers relevant to our cases were selected for literature review.

Results: Case 1: A 4 year-old female with history of desmosplastic medulloblastoma status-post resection and intensive chemotherapy was diagnosed with SOS one month after her second part of planned tandem transplant. She was managed with paracentesis and defibrotide. Due to malnourishment, patient had a gastric tube placement 5 months after she completed therapy and had an episode of upper gastrointestinal bleeding postoperatively from the G tube site. Case 2: Similarly, a 4 year-old male diagnosed with anaplastic medulloblastoma status post resection and adjuvant multiagent chemotherapy. His treatment course was complicated with SOS after the second cycle of induction chemotherapy which responded to 21-day course of Defibrotide. Likewise, the patient had a major bleeding event from the G-tube site approximately two months after SOS diagnosis.

Conclusion: Defibrotide was discontinued in both cases before G-tube placement. Both patients had no previous history of bleeding disorders or relevant family history. In addition, comprehensive laboratory evaluations were within normal limits before both procedures. In SOS, there is blockage of fluid out of the liver that leads to congestion, ascites, ischemia of the liver, and post-sinusoidal portal hypertension. Two related causes of SOS should be considered as an explanation for G-tube bleeding. Similar patients should have close monitoring postoperatively or if possible surgical intervention should be delayed until the SOS process has been evolved.

Poster # 028 | OCCURRENCE OF CUTANEOUS MYELOID SARCOMA IN A PATIENT WITH A HISTORY OF OVARIAN YOLK SAC TUMOR

Michell Lozano Chinga, Maggie Eidson Fader, Carole Brathwaite, Ossama Maher

Nicklaus Children's Hospital, Miami, Florida, United States

Background: The development of treatment related Acute Myeloid Leukemia (t-AML) and Myelodysplastic Syndromes

(t-MDS) is a potential complication after cytotoxic chemotherapy or radiation therapy. The incidence of development of t-AML/t-MDS varies from 1–20% depending on the treatment regimen used. Cutaneous myeloid sarcoma (MS) is a common presentation of extramedullary leukemia and usually occurs in the setting of AML.

Objectives: We report a rare case of cutaneous MS in an adolescent female after successful treatment for Ovarian Yolk Sac Tumor (YST) Stage I with BEP (Bleomycin, Etoposide and Cisplatin) therapy. The MS was managed only with biopsy and close observation.

Design/Method: A PUBMED search was conducted for queries including t-AML/t-MDS, cytotoxic agents, cutaneous myeloid sarcoma, regression. Relevant papers were selected for literature review.

Results: A 13 year-old female was diagnosed with a left ovarian yolk sac tumor, for which she underwent left salpingo-oophorectomy and successfully completed 4 cycles of BEP over 4 months. During routine follow-up 8 months after initiation of treatment for Ovarian YST, she was noted to have a small, non-tender, indurated nodule on the left side of her upper back approximately 1cm in diameter. Punch biopsy of the skin nodule was performed and pathology was positive for cutaneous myeloid sarcoma. At the time of next follow-up less than one month later, the skin lesion had resolved. Two subsequent bone marrow aspirates were performed one month apart and were negative for leukemic involvement or MDS. Examinations and work-up including whole body PET with CT scan were negative for evidence of disease.

Conclusion: Although cutaneous MS can be regarded as the herald of systemic myeloid disease rather than a localized process, our patient was monitored periodically with physical exam and laboratory evaluations. She remains free of disease more than four years after the presentation of cutaneous MS without any further treatment. Spontaneous regression MS has been previously reported. The authors would like to stress that a conservative approach with close observation could be an option in cutaneous MS even with history of chemotherapy exposure.

Poster # 029 | HEMOPHILIA AND CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Nesreen Ali, Iman Sidhom, Sonia Soliman, Sherine Salem

National Cancer Institute, CairoUniversity, Egypt Children Cancer Hospital Egypt, Egypt

Background: Acute leukemia is the commonest malignancy in childhood. The coincidental occurrence of leukemia with hemophilia is extremely rare. Hemophilia is a congenital rare X linked bleeding disorder. The main complication of the two diseases is bleeding diathesis which may be life-threatening due to many factors, deficiency of coagulation factors in hemophilic patients, thrombocytopenia from disease and chemotherapy in leukemic patients, certain cytotoxic drugs such as asparaginase which may result in coagulation disorders and infection which may lead to disseminated intravascular coagulation.

Objectives: Reporting such a case is imperative to set up treatment guidelines for prevention of bleeding and to optimize the therapeutic approach for these patients.

Design/Method: Seventeen years old boy, presented to children cancer hospital Egypt in June 2015 with pallor and multiple ecchymoses.He was diagnosed with Precursor B Acute lymphoblastic leukemia, cerebrospinal fluid (CSF) was free, the chromosomal analysis revealed hypodiploidy 36, XY. He had moderate type of Hemophilia A since birth, factor VIII level was 1.5 % at time of diagnosis, coagulation profile revealed prolonged partial thromboplastin time 89 (normal 26–45), factor VIII was low 1%, prothrombin concentration and prothrombin time were normal100% and 13 seconds, virology screening for hepatitis B core IgG/IgM, HBS Ag, HIV and HC IgG /IgM were negative.The patient started Induction Total XV SJCRH protocol, factor VIII 40 unit/kg was given at presentation before doing bone marrow aspiration(BMA), CSF and as a prophylactic before intramuscular asparaginase injection, intrathecal and BMA. It was given immediately within 2 hours before the procedures and platelets transfusion was given regularly to maintain platelets count about 50,000. The minimal residual disease by flow cytometry was 0.81% and 0.11% at D15 and D42 induction.

Results: Our patient received his induction and re-intensification chemotherapy without any major bleeding event which reveals the success of our guidelines for the prevention of bleeding. He developed very early relapse at W7 maintenance by the same clone. He received salvage chemotherapy but didn't achieve remission and died out of disease and resistant clone.

Conclusion: The development of leukemia on top of hemophilia is a major problem. Bleeding complication during chemotherapy can be prevented by regular prophylactic factor VIII and platelets concentrate transfusion with good supportive care. Life threating bleeding complication may be correlated with the severity of hemophilia. We need to collect data about the biology of leukemic cells, complications, and cause of death to optimize care for these patients.

Poster # 030 | MUCOEPIDERMOID CARCINOMA: CASE REPORT AND ANALYSIS OF MECT1-MAML2 FUSION TRANSCRIPT IN CASES FROM IOWA

Neeraja Swaminathan, Sue O'Dorisio, Charles Lynch, Deqin Ma

University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States

Background: Mucoepidermoid carcinoma (MEC) is a rare malignancy that arises from exocrine glands in the upper aerodigestive tract and tracheobronchial tree. Conventionally, MEC diagnosis is based on histology, with prognosis based on the extent of resection and detection of metastases. MEC is characterized by a translocation of chromosomes 11q and 19p resulting in a fusion between the MECT1 and MAML2 genes, that occurs in 38–81% of cases. This fusion transcript has been recognized to have a favorable impact on disease features and prognosis of MEC. However, recent studies indicate that high grade MEC can have MECT1-MAML2 fusion positivity and multiple other genomic imbalances that have not been studied in much detail. Owing to the rarity of MEC tumors, more definitive data related to the clinical and prognostic significance of these molecular markers are limited.

Objectives: 1. Identify the presence or absence of MECT1-MAML2 fusion in the tissue of our patient. 2. Analyze the incidence of the fusion in 25 MEC cases in children and young adults retrieved from the Iowa Cancer Registry. 3. Determine if fusion status correlates with clinical, pathological and outcome data in our cohort.

Design/Method: We describe the case of a 12 year-old Caucasian male who presented with recurrent pneumonia, persistent cough and radiographic evidence of right lobar collapse. Bronchoscopy revealed an endobronchial lesion and the patient underwent right upper lobe sleeve resection. Pathology report was consistent with low grade muco-epidermoid carcinoma. We retrieved 25 archived formalin-fixed paraffin-embedded (FFPE) specimens of pediatric and young adult MEC cases (ages 0–29) reported in Iowa from 1973–2016 using the Iowa Cancer registry. Testing for the MECT1-MAML2 fusion in the index case and 25 FFPE specimens will be done using a custom-designed laboratory validated next generation sequencing (NGS) assay with the ability to detect novel fusion partners. Clinical, pathological and outcome data (age, sex, tumor site, tumor size, nodal metastases, clinical stage, histologic grade, treatment and follow up) will be analyzed to correlate with fusion status.

Results: The MECT1- MAML2 fusion tested positive in our index patient. We will obtain IRB approval to test for the fusion in the 25 archived FFPE specimens and correlate clinical, pathological and outcome data.

Conclusion: MECT1-MAML2 fusion is a frequent event in MEC that has prognostic and potential therapeutic applications in adults. The results of this study may enlighten the clinical management of MEC in children and young adults.

Poster # 031 | SAMD9 MUTATION ASSOCIATED BONE MARROW FAILURE TREATED WITH BONE MARROW TRANSPLANT: A UNIQUE TREATMENT APPROACH TO A RARE CASE

Sana Farooki, Keith August, Ibrahim Ahmed

Children's Mercy Hospital, Kansas City, Missouri, United States

Background: Mutations in the SAMD9 gene are associated with a rare syndrome comprising of myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes and enteropathy (MIRAGE syndrome). Diagnosis is made through exome sequencing. In the largest reported case series, of eleven patients diagnosed with MIRAGE syndrome, two developed loss of chromosome 7. Given the potent growth restricting activity of SAMD9 mutants, the loss of chromosome 7 is considered the first documentation of adaptation by aneuploidy mechanisms in humans and led to myelodysplastic syndrome (MDS), with deaths occurring from related complications at 2 and 5 years of age.

Objectives: To report a case of MIRAGE syndrome with congenital thrombocytopenia progressing to bone marrow failure, managed uniquely with bone marrow transplantation.

Design/Method: Case report

Results: Male born at 29 weeks gestation with prenatal diagnosis of IUGR, two vessel cord, oligohydramnios was found to have ambiguous genitalia, adrenal insufficiency, partial panhypopituitarism and congenital thrombocytopenia with bone marrow showing absence of megakaryocytic precursors. Severe thrombocytopenia was present from birth. Bone marrow evaluation demonstrated a hypocellular marrow with markedly reduced megakaryocytic and myeloid precursors and no evidence of myelodysplasia. He required gastric tube placement for failure to thrive, had a laryngeal cleft repaired and developed focal segmental glomerulosclerosis. MPL gene testing for congenital amegakaryocytic thrombocytopenia was negative. Testing for Fanconi anemia, Shwachman-Diamond syndrome and Dyskeratosis Congenita was also negative. Approximately 30% of cells had loss of heterozygosity on chromosome 7q. Exome sequencing showed that he is heterozygous for a de novo gain of function variant, c.2471G>A (p.Arg824Gln), identified in the SAMD9 gene, confirmed by Sanger sequencing and consistent with

a diagnosis of MIRAGE syndrome. At 6 years of age, he developed pancytopenia requiring frequent transfusions with platelets and packed red blood cells. He underwent a successful bone marrow transplant at 7 years of age without significant complications, and remains transfusion independent without cytopenias greater than 18 months from bone marrow transplantation.

Conclusion: It is imperative to pursue work up for persistent congenital thrombocytopenia in a stepwise multidisciplinary manner. To the best of our knowledge, this is the first case of MIRAGE syndrome associated bone marrow failure treated with bone marrow transplant. Due to the individual rarity of MIRAGE syndrome and pediatric myelodysplastic syndrome, it is important to maintain an index of suspicion given their association and explore bone marrow transplant as a therapeutic option.

Poster # 032 | THE COMBINATION OF SORAFENIB AND CAPECITABINE IN RECURRENT FIBROLAMELLAR HEPATOCELLULAR CARCINOMA: A NOVEL ORAL CHEMOTHERAPY APPROACH

Jennifer Han, Jason McKee, Allyson Richards, Yehuda Patt, John Kuttesch

University of New Mexico, Albuquerque, New Mexico, United States

Background: Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare variant of hepatocellular carcinoma (HCC) that compromises less than 10% of all HCCs occurring predominately in the pediatric and young adult population and uncommonly associated with underlying liver disease. Currently, complete surgical resection with lymphadenectomy is the cornerstone treatment for long-term survival. Disease recurrence is unfortunately high, at 33% to 100%. There is no universal standard of care for FL-HCC patients with categorically unresectable disease. We present a case of a 13-year-old adolescent female patient with FL-HCC who had previously undergone multiple total resections for recurrent FL-HCC, but presented with unresectable disease two years after diagnosis.

Objectives: After the family refused intravenous chemotherapy, an oral chemotherapy approach combining Sorafenib and Capecitabine, based on an institutional study in adults (The Oncologist: 2017-0168. Epub 2017 Jul 7), was initiated. The primary objective was to achieve disease control.

Design/Method: The treatment schedule was based on a 28-day cycle that was continued until disease progression. The patient received Capecitabine 1300 mg/m2/day in divided BID doses on days 1–7 and 14–21, and Sorafenib 400 mg/m2/day in divided BID doses on days 1–28 for 24 cycles. In subsequent cycles, Capecitabine dosing was decreased to days 1–7, given continued stable disease. Close tumor surveillance with radiographic imaging and laboratory studies has occurred every three months.

Results: The patient demonstrated disease regression, initially, and continued without disease progression for 36 months. The regimen has been well tolerated with only minimal side effects of dry skin (CTCAE grade 1) and a transient episode of brief erythrodysesthesia (CTACAE grade 2) that resolved spontaneously.

Conclusion: The combination of Sorafenib and Capecitabine was effective and well tolerated in this adolescent patient with FL-HCC. Our observations, although in a single patient, lend support for further testing of this novel oral chemotherapy regimen in patients with FL-HCC, a disease for which there is no effective standard chemotherapy approach.

Poster # 033 | LONG TERM REMISSION WITH SIROLIMUS FOR A PEDIATRIC PATIENT WITH AN EBV-ASSOCIATED SMOOTH MUSCLE TUMOR AFTER BONE MARROW TRANSPLANTATION

Scott Penney, Della Howell, Bradie Bishop

Brooke Army Medical Center, San Antonio, Texas, United States

Background: Epstein-Barr virus (EBV) is a ubiquitous virus associated with a broad range of malignancies due to its oncogenic potential. History of organ or bone marrow transplantation, immunosuppressive therapy, and primary or acquired immunodeficiency syndromes increases the risk of EBV-associated tumors. Epstein-Barr virus associated smooth muscle tumors (EBV-SMT) are unique and rare neoplasms typically discovered in immunocompromised patients. Most information related to pathogenesis and therapeutic options is limited to case reports and case series of adult patients. There are several gene expression pathways that EBV utilizes, the most notable of which is the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway performs a key role through integrating various cell growth signals and factors to regulate protein synthesis and metabolism related to smooth muscle proliferation. Sirolimus is an immune modulating therapy that targets the mTOR pathway to block activation of lymphocytes.

Objectives: Several case reports have demonstrated short-term clinical remission of EBV-SMT in adult patients with the use of Sirolimus. We report the first case of long-term

clinical remission with Sirolimus in a pediatric patient with an EBV-SMT.

Design/Method: The design is a case report. This is the only case report that demonstrates long term remission with Sirolimus for pediatric patients with EBV-SMT.

Results: The patient, an 8-year old female with a history of acute lymphoblastic leukemia (ALL) with relapse, subsequent bone marrow transplantation (BMT) and resultant chronic graft-versus-host disease (GVDH), presented with multiple liver neoplasms three years post-transplant in the setting of immunosuppressive therapy. The liver neoplasms were consistent with EBV-SMT on pathologic evaluation. The patient was started on therapy with Sirolimus and has achieved long-term remission for over ten years.

Conclusion: Our case demonstrates the benefits and therapeutic implications of early detection and initiation of Sirolimus therapy for EBV-SMTs.

Poster # 034 | GENETIC CHARACTERIZATION OF BILATERAL NEUROBLASTOMA USING WHOLE EXOME SEQUENCING

Cristiana Hentea, Grzegorz Nalepa, Timothy Corson, Susanne Ragg

Indiana University, Indianapolis, Indiana, United States

Background: Bilateral neuroblastoma is characterized as neuroblastoma arising in both adrenal glands, a rare presentation with little data on its genetic make-up. A two-month-old patient was diagnosed with bilateral neuroblastoma in our clinic. Her risk assignment was based on biopsy of the left adrenal lesion, which showed MYCN amplification, an unfavorable genetic marker. Treatment regimen was intensified accordingly and after 5 courses of chemotherapy tumors were excised. Patient went on to receive a stem cell transplant and immunotherapy. With no knowledge of genetic similarity between the two tumors it is unclear whether biopsy of the right lesion would have yielded similar results or whether bilateral biopsies are needed for risk assessment of bilateral neuroblastoma.

Objectives: Utilize whole exome sequencing (WES) to characterize the genomic signature of bilateral adrenal neuroblastomas excised following chemotherapy treatment.

Design/Method: Paraffin-embedded samples from left (L) and right (R) tumors underwent WES at the Broad Institute. We analyzed resulting data including somatic variant calls, indel mutations, and copy number variants (CNVs) using Ingenuity software to evaluate and compare differences between the two tumor samples.

Results: Preliminary analysis of the data shows important descriptive information on the two tumor samples. Out of 29 somatic mutations in the R tumor cells and 25 mutations in the L tumor cells, only two common somatic mutations were present. Out of 40 CNV calls in the R tumor and 60 in the L tumor, 31 CNVs were common between the two tumors, or 73% of each tumor's CNV calls. There was a 14 fold higher frequency in gains versus losses. The median size of the common CNVs was 56,683 (range 220 to 3,323,064 bp). Cancer-related genes with increased copy numbers included transcription factors, receptors for signal transduction pathways, and histone methylation proteins.

Conclusion: Preliminary analysis of the WES results of the two adrenal tumors show some genomic divergence. Because the tumor tissue was exposed to chemotherapy prior to excision it is difficult to determine whether genomic divergence is a result of independently originated tumors or subsequent adaptation to chemotherapy of a clonal cell population. The high number of common CNVs in the two tumors points to a common cell of origin, however the low number of common somatic mutations does not fit that picture. A future study to help elucidate the question will be WES of the original biopsy tissue to provide information on tumor mutations prior to the effects of chemotherapy.

Poster # 035 | EXPLORING WHY PEDIATRIC CANCER PATIENTS ARE DYING IN THE INTENSIVE CARE UNIT WITH LONGSTANDING DO NOT RESUSCITATE ORDERS

Valeria Smith, Heidi Russell

Baylor College of Medicine, Houston, Texas, United States

Background: Although there has been significant improvement in the overall survival rates of children with cancer many children will still die from their illness or complications secondary to treatment. Research surrounding the deaths of children who succumb to their disease is warranted to ensure we are providing the best care possible for these patients.

Objectives: This case series aims to explore pediatric cancer deaths by focusing on perhaps the most extreme cases of high intensity end of life care. We explore those patients whom we know are dying or our very likely to die as evidence by their do not resuscitate (DNR) orders. In all of these cases despite the patients very grim prognosis, their great likelihood of death and limitations placed of resuscitation methods all patients

continued end of life care in the pediatric intensive care unit (PICU).

Design/Method: The primary medical records of all children with a cancer diagnosis who died between February 1, 2011 and January 31, 2017 in the PICU with a DNR order seven days or earlier prior to death. Each medical history included disease-directed treatment history and response with particular attention to the events surrounding the terminal admission.

Results: Eight patients met criteria for this study representing 1.9% of all cancer patients who died during this time period and 7.4% of those who died in the ICU. The average time between DNR and death is 19.6 days (7 days – 32 days). The average length of terminal admission was 43.5 days (1 day – 153 days). The average time between diagnosis and DNR is 10.75 months (0 months – 22 months). The average time between diagnosis and death is 11.25 months (0 months – 23 months).

Conclusion: These cases highlight the journey that patients, families and providers endure leading up to death. Medical care is complex, there are very few absolutes that are encountered when caring for patients and decisions around limiting or withdrawing medical care are made in a context of the prior journey. . These cases help to understand the complexity of death and how two seemingly opposite ideals can be congruent in the event of an anticipated death. Most of these cases show the need for improved anticipatory guidance surrounding death and greater consideration for de-escalation of care when death is expected.

Poster # 036 | EMBRYONAL RHABDOMYOSARCOMA SHOWING A NEW TRANSLOCATION (2:15): A CASE REPORT AND REVIEW OF THE LITERATURE

Samuele Renzi, Karin Langenberg-Ververgaert, Anne Ryan, Ted Gerstle, Sevan Hopyan, Mary Shago, Rose Chami, Abha Gupta

The Hospital for Sick Children, Toronto, Ontario, Canada

Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, with embryonal (ERMS) and alveolar (ARMS) representing the most common subtypes. ARMS tumors are associated with inferior outcome when compared to ERMS, and they are characterized in about 80% of the cases by a t (2;13) or t(1;13) chromosomal translocation with creation of a PAX3-FOXO1 or PAX7-FOXO1 fusion gene, respectively. It is increasingly clear that the PAX-FOXO1 fusion status is an important poor prognostic factor, thus the histological classification tends to be replaced by the fusion status, particularly in terms of risk stratification In contrast to ARMS, there are no recurrent chromosome alterations in ERMS; however, there are multiple numerical chromosome changes that are frequent in these tumours: gain of chromosome 2,8, 12 and 13 have been found in 25 to 50 % of EMRS karyotypes. Moreover, ERMS tumors show frequently allelic loss, the 11.p15.5 chromosomal region being the most frequently involved. Recently, novel gene fusions have been described also in ERMS tumours. These fusions involved mainly the NCOA2 and or the VGGL2 genes. The rearrangement partners are variable, and include, i.e. PAX 3 (2q35), SRF (8q11) and TEAD 1 (11p15).

Objectives: To present a patient who died as a consequence of brain metastases while on therapy in the setting of an FOXO1-negative RMS and the identification of a new translocation t(2;15)(q21;q22).

Design/Method: Case report and retrospective review of the literature.

Results: We report a case of pelvic embryonal rhabdomyosarcoma in a 3-month old boy. He was treated as per COG ARST 0531 intermediate risk group, but unfortunately was found to have a large cerebellar tumour during the course of his chemotherapy treatment and he subsequently passed away. A novel translocation between chromosomes 2 and 15 was observed in 11 of 20 metaphase cells by G-band analysis in the autopsy sample of the brain lesion. Breakpoints of the translocation were estimated to be at 2q21 and 15q22. There were no additional clonal chromosome abnormalities in the tumour cells.

Conclusion: ERMS tumors with fusion genes involved have been exclusively described in patients less than 12 months of age; they seem to be associated with spindle cell histology and, a favorable outcome. In our patient, a novel (2;15) translocation was found and clinically, the patient had a dismal outcome. Further studies are indicated to inquire whether this finding is of significance in term of prognosis for these patients.

Poster # 037 | IATROGENIC IMMUNODEFICIENCY-ASSOCIATED LYMPHOPROLIFERATIVE DISORDER IN A CHILD WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Sanam Shahid, Christopher Rossi, Catherine Bollard, Hema Dave

Children's National Medical Center, Washington, District of Columbia, United States

Background: Iatrogenic immunodeficiency-associated lymphoproliferative disorders (LPDs) are a group of lymphoid

proliferations or lymphomas that are well known to be associated with an immunosuppressed state. These disorders most commonly occur following hematopoietic or solid organ transplantation (called post-transplant lymphoproliferative disorders or PTLD), but cases have also been described during the treatment of autoimmune and rheumatologic disorders by immunosuppressive and immunomodulatory medications. These disorders are strongly associated with infection by the Epstein-Barr virus (EBV) as a result of impaired immune function in the immunosuppressed state. While this phenomenon has been well documented in autoimmune conditions, cases affecting pediatric patients while on anti-leukemia chemotherapy are lacking.

Objectives: To review the unique case of a pediatric patient on anti-leukemia therapy with iatrogenic PTLD.

Design/Method: Retrospective chart review and literature review.

Results: In this case report, we describe a 13-year-old patient with B-cell Acute Lymphoblastic Leukemia in maintenance therapy who presented with recurrent sinusitis. Imaging showed a large, destructive mass in the nasopharyngeal region and multiple liver lesions. Biopsy showed polymorphic, polyclonal, EBV-positive B-cells with extensive necrosis resembling a polymorphic PTLD. Primary immunodeficiency work-up was negative. The patient was successfully treated with rituximab without any cytotoxic chemotherapy. This is a novel case of a pediatric patient on anti-leukemia therapy with iatrogenic PTLD.

Conclusion: This case highlights the importance of recognizing iatrogenic PTLD in non-transplant patients with hematologic malignancies.

Poster # 038 | A CASE SERIES OF TWO UNIQUE CNS TUMOR DIAGNOSES PRESENTING AS LEPTOMENINGEAL DISEASE

Jenna Allison, Minnie Abromowitch, Stefanie Lowas, Terri Love, Peter Abasolo

Children's Hospital and Medical Center, Omaha, Nebraska, United States

Background: Atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system (CNS) in children younger than 3 years old has a prevalence of 1% to 2% and accounts for 1.6% of all pediatric CNS tumors. Only 15–30% of patients have leptomeningeal dissemination. Rhabdomyosarcoma is the most common soft tissue tumor in childhood, but represent only 3–4% of all pediatric cancers. Rarely, it can metastasize or even directly extend into the CNS, but typically, cases of CNS involvement arise either from parameningeal areas or other primary sites. Primary spinal or meningeal rhabdomyosarcoma is extremely rare.

Objectives: Our objective is to describe two unique CNS malignancies presenting as rare, primary leptomeningeal disease.

Design/Method: Case 1 A 19-month-old female presented with vomiting, fatigue and listlessness, despite a normal head CT and brain MRI. CSF showed hypoglycorrhachia and mild pleocytosis. Ceftriaxone was started, but she developed nuchal rigidity and cranial nerve VII palsy. Repeat brain MRI showed evolving leptomeningeal enhancement concerning for meningitis. She gradually developed worsening opisthotonus and ultimately a brain biopsy of the temporal lobe was consistent with AT/RT. Case 2 A 3-year-old male presented with new generalized tonic-clonic seizure activity and intermittent headaches with photophobia, phonophobia, and vomiting. Brain MRI was significant for enhancement of interpenducular and suprasellar cisterns extending to the optic nerves and chiasm most consistent with meningitis. Neurosurgery ultimately placed a lumbar drain for hydrocephalus, and a tissue biopsy demonstrated primary meningeal rhabdomyosacroma.

Results: In case 1, our patient's temporal lobe biopsy demonstrated grade IV malignant tumor cells consistent with atypical teratoid/rhabdoid tumor. FISH demonstrated a homozygous deletion of SMARCB1 (22q11.23). She was started on chemotherapy per the Dana Farber AT/RT protocol but ultimately was discharged home on hospice. In case 2, our patient's lumbar arachnoid biopsy demonstrated cellular tumor consistent with Group IIIA embryonal rhabdomyosarcoma. Immunostaining was positive for CD99, desmin, myogenin, and myo-D1 with neural markers EMA and GFAP highlighting the meninges but without a neural component to the tumor. He completed craniospinal radiation to 36Gy total with lumbar boost to 50.4Gy total. He is currently receiving chemotherapy per ARST0431 protocol.

Conclusion: These two cases are particularly instructive because of their similar initial presentations and neuroimaging, but with very different and unique diagnoses.

Poster # 039 | TWO CASES OF EBF1-PDGFRB FUSION B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA WITH SIMILAR CLINICAL PRESENTATIONS AND TREATMENT BUT DIFFERENT OUTCOMES AT THE UNIVERSITY OF IOWA

Jessica Zimmerman, Arunkumar Modi

University of Iowa, Iowa City, Iowa, United States

Background: EBF1-PDGFRB fusion causes Ph-like B-cell acute lymphoblastic leukemia (B-ALL), which has a Philadelphia positive phenotype without the BCR-ABL translocation. This is one of several mutations associated with Ph-like B-ALL and leads to downstream overexpression of tyrosine kinase. EBF1-PDGFRB fusion accounts for about 8% of children with Ph-like B-ALL. Patients with Ph-like B-ALL previously had poorer outcomes with conventional chemotherapy. The addition of tyrosine kinase inhibitors (TKI), like imatinib, has improved the outcome for many patients predicted to have TKI sensitive mutations.

Objectives: To review clinical characteristics and outcomes of two cases of Ph-like B-ALL at the University of Iowa Stead Family Children's Hospital and to compare these outcomes to similar cases reported in the literature.

Design/Method: A retrospective chart review was performed for two cases of Ph-like B-ALL diagnosed and treated at the University of Iowa Stead Family Children's Hospital.

Results: Both patients were males diagnosed at 8 years of age with high WBC count (110,700 and 347,200) and positive for EBF1-PDGFRB gene fusion. Patient 1 (Pt1) was CNS 2b at presentation while patient 2 (Pt2) was CNS negative; neither had testicular involvement. Both started treatment according to COG protocol AALL1131. Peripheral blasts cleared by induction day 22 for Pt1 and induction day 14 for Pt2. At end of induction, Pt1 had M3 bone marrow and Pt2 had M1 bone marrow but MRD 8%. Dasatinib was started induction day 13 for Pt1 and induction day 31 for Pt2. Pt1 was still not in remission at end of consolidation; bone marrow cell culture for TKI resistance showed best response to dasatinib. Pt1 proceeded to anti-CD19 CAR T-cell therapy followed by TBI-based matched unrelated donor bone marrow transplant. Pt2 had negative MRD at the end of consolidation and continues chemotherapy according to AALL1131, dasatinib arm. Both patients are currently clinically well.

Conclusion: Our patients had the same tyrosine kinase gene fusion and similar initial clinical courses. While both patients had persistent disease at end of induction, Pt1 had almost 80% blasts while Pt2 had significant reduction of disease burden before starting TKI. Pt2 showed good response with the addition of dasatinib while Pt1 did not. These findings suggest that response to conventional chemotherapy may potentiate the effect of TKI and may predict overall outcome. There are likely additional factors which must be taken into account when determining response to TKI for patients with Ph-like B-ALL which have not yet been identified.

Poster # 040 | PRIMARY LEPTOMENINGEAL MEDULLOBLASTOMA: A RARE PRESENTATION OF MEDULLOBLASTOMA IN A CHILD

Fiorella Iglesias, Sanjit Shah, Brent Orr, Matt Poppe, Lindsay Burt, John Kestle, Nicholas Whipple

University of Utah, Salt Lake City, Utah, United States

Background: Medulloblastoma is the most common malignant brain tumor of childhood. Classically, medulloblastoma presents as a well-defined mass lesion in the cerebellum, with a high rate of metastatic dissemination. Primary leptomeningeal medulloblastoma (PLMB) is an exceedingly rare type of medulloblastoma presentation with a dismal prognosis in which patients present with isolated leptomeningeal disease without an associated mass. To our knowledge, only three pediatric and three adult cases of PLMB (ages 5 – 30 years) have been reported, all of which died within 6 months of diagnosis. This is the first case of PLMB to report a molecular classification.

Objectives: To report the case of a pediatric patient with PLMB in which histopathologic and molecular characterization was performed and to describe the patient's treatment and clinical course.

Design/Method: Retrospective review of the patient's electronic medical record and review of the literature.

Results: A 9-year-old boy presented with headache, vomiting, diplopia, and fatigue. Physical examination revealed upward gaze palsy, left-sided extremity and facial weakness, and ataxia. Magnetic resonance imaging (MRI) of the brain revealed diffuse cerebellar leptomeningeal enhancement and edema without an identifiable mass and moderate hydrocephalus. MRI of the spine and cerebral spinal fluid analysis were normal. A diagnosis of cerebellitis was rendered, and the patient underwent placement of a ventriculoperitoneal shunt. An extensive infectious, neurologic, rheumatologic, and oncologic workup did not identify an etiology. Empiric antibiotics, high-dose steroids, and intravenous immunoglobulin therapy yielded minimal improvement. Two months later, repeat MRI of the brain performed for declining mental status demonstrated progressive thickening of cerebellar leptomeningeal disease. A suboccipital craniectomy with decompression and cerebellar biopsy were performed. Pathologic examination revealed a diagnosis of PLMB, classic histology, non-WNT/non-SHH, without gain/amplification of MYC/MYCN, and p53 wild type pattern. Craniospinal radiation to 4140 cGy with a 1440 cGy boost to the posterior fossa was delivered with concurrent carboplatin/vincristine over six weeks. Two months following chemoradiation, MRI of

the brain demonstrates significantly reduced pathological leptomeningeal enhancement of the cerebellum, and the patient is awaiting initiation of systemic chemotherapy while recovering from a surgical wound infection.

Conclusion: PLMB is extremely rare but should be considered in patients with cerebellitis and diffuse leptomeningeal involvement who are refractory to medical management or in whom an etiology has not been identified. Cerebellar biopsy is recommended early to enable timely treatment and improved outcomes. Molecular classification should be performed in cases of PLMB to further characterize this disease, inform treatment decisions, and improve clinical outcomes.

Poster # 041 | PRIMARY MULTIFOCAL INTRACEREBRAL EXTRAOSSEUS OSTEOSARCOMA WITH AGGRESSIVE CLINICAL COURSE IN A PATIENT WITH LOBAR HOLOPROSCENCEPHALY

Megan Paul, Jennifer Elster

University of California San Diego, La Jolla, California, United States

Background: Primary intracerebral osteosarcoma is extremely rare and limited to case reports. PTPN11 gain of function is associated with Noonan Syndrome, which has increased risk of multiple cancer types including brain tumors, but osteosarcoma has never been described. PTPN11 mutations have been reported in many cancers as both oncogenes and tumor suppressors, however no PTPN11 mutations have been described in osteosarcoma. PDGFR-a is a growth factor receptor whose activation is implicated in several malignancies. PDGFR-a and PTPN11 concurrent mutations are described in glioblastoma. There is no known link between holoprosencephaly, Noonan syndrome, and osteosarcoma.

Objectives: We report a case of multifocal intracerebral osteosarcoma in a child with lobar holoprosencephaly and chronic subdural hemorrhage and discuss the genetic changes found in the tumor.

Design/Method: A seven-year-old Caucasian female, with a known diagnosis of lobar holoprosencephaly, chronic subdural hemorrhage and well controlled seizure disorder presented with status epilepticus shortly after completing antibiotic therapy for infection of subdural hematoma. MRI showed diffuse dural thickening with mass lesions in the frontal lobe, temporal lobe, and the parasagittal region, the largest of which was contiguous with the subdural space but none of the lesions were associated with bone on MRI or by direct neurosurgical visualization. Tissue obtained for concern for recurrent infection resulted in a diagnosis of high grade osteosarcoma. DNA analysis was performed to help guide treatment choice.

Results: Standard metastatic work-up was negative for skeletal primary tumor or metastatic lesions outside of the brain. She was treated with high dose methotrexate for two cycles per modified AOST1331. Despite maximal supportive care, she quickly developed rapid tumor growth as well as intratumoral hemorrhage with resultant herniation and death from respiratory failure just three months after diagnosis. Tumor gene sequencing discovered three mutations with described roles in cancer: PDGFRA D842>VR, KDM6A loss of exons 1–4, and PTPN11 A72V.

Conclusion: To our knowledge, primary multifocal extraosseus intracerebral osteosarcoma has not been previously described. Despite known CNS penetration of high dose methotrexate, this tumor proved resistant and aggressive. Holoprosencephaly is associated with a multitude of known genetic drivers, but none are found in this case. Furthermore, the genetic changes in this tumor are not typical for osteosarcoma. PDGFR-a over-expression is described in osteosarcoma, but is not clearly correlated with worse overall survival. Further research is required to determine the role of PTPN11 in osteosarcoma.

Poster # 042 | DIFFUSE MIDLINE GLIOMA, H3K27M-MUTANT TUMOR WITH IMMUNOHISTOCHEMISTRY DIFFUSELY POSITIVE FOR SYNAPTOPHYSIN AND NEGATIVE FOR GFAP

Lincy Thomas, Abhishek Bavle, Rene McNall, Kar-Ming Fung, JoElle Peterson, Naina Gross, Spencer Thompson, Jason Chiang, David Ellison

University of Oklahoma, Oklahoma City, Oklahoma, United States

Background: Historically the diagnosis of pediatric tumors of the central nervous system (CNS) has relied on histology and immunohistochemistry, with glial tumors staining with glial fibrillary acidic protein (GFAP) and embryonal tumors with neuronal markers like synaptophysin. The 2016 WHO classification of tumors of the CNS, for the first time, incorporated pathognomonic molecular features in the diagnosis of tumors and defined new tumor entities like diffuse glioma, H3 K27M-mutant.

Objectives: We report the second case, in the literature, of a tumor staining diffusely for synaptophysin and being negative for GFAP, but harboring the mutant histone H3 p.K27M protein. This pathognomonic molecular finding established the diagnosis of a high-grade glioma, for a tumor that based on

immunohistochemistry, resembled an embryonal tumor. This case highlights the significant impact of the incorporation of molecular testing on the diagnosis, prognosis, and treatment of pediatric CNS tumors.

Design/Method: A 4 year old girl underwent gross total resection of a left thalamic hemorrhagic mass. Histopathologic evaluation, and immunohistochemistry for synaptophysin, GFAP, neurofilament, BAF47, Ki67 and TP53 were performed. Due to midline location and atypical morphology, immunostaining for the mutant histone H3 p.K27M protein and H3 K27Me3 were also performed. Fluorescent in situ hybridization (FISH) was performed for PDGFRA, EGFR, MET, MYCN and MYC genes.

Results: Histology revealed a hypercellular tumor with small blue cells, scant cytoplasm, nuclear pleomorphism, and increased mitotic activity. Tumor cells stained diffusely for the neuronal marker synaptophysin and were negative for the glial marker GFAP, suggesting an embryonal tumor. However, immunohistochemistry was positive for mutant histone H3K27M (H3K27M+ and H3K27me3-) establishing that the tumor was in fact a diffuse glioma, H3 K27M-mutant, an aggressive tumor with a reported median survival of 6 months. Nuclear staining for mutant TP53 was positive and FISH was positive for PDGFRA amplification, consistent with the diagnosis. The treatment plan was significantly altered, as the patient completed involved field radiation (declined oral chemotherapy), instead of cranio-spinal irradiation and multi-agent intravenous chemotherapy which would have been recommended for an embryonal tumor. Unfortunately, disease progression started six weeks into radiation therapy and she passed away 6.5 from diagnosis.

Conclusion: Diffuse midline glioma, H3K27M-mutant tumors can display aberrant diffuse staining with synaptophysin, and be negative for GFAP. The incorporation of molecular features can augment histopathological evaluation in the diagnostic process, and in some instances even alter the diagnosis, with a significant impact on prognosis and treatment.

Poster # 043 | AN ALK FUSION NOT PREVIOUSLY REPORTED IN REFRACTORY NEUROBLASTOMA

Michael Mowrer, Shanna White, Jaime Libes

Children's Hospital of Illinois, University of Illinois College of Medicine - Peoria, Peoria, Illinois, United States

Background: Anaplastic lymphoma kinase (ALK) encodes a receptor tyrosine kinase whose activation induces pathways associated with cell proliferation, angiogenesis, and cell survival. ALK rearrangements are rare in neuroblastoma, while ALK mutations and gene amplification occur more frequently. ALK mutations have been found to be associated with increased ALK protein expression that is associated with a worse prognosis. ALK is commonly mutated in neuroblastoma at three hotspots (F1174, R1275, and F1245). The EML4-ALK rearrangement has mostly been associated with lung adenocarcinomas, with only a few cases of non-lung cancers found. It has never been reported in neuroblastoma.

Objectives: To describe a case of EML4-ALK fusion (variant 5a/b) in a pediatric patient with relapsed neuroblastoma.

Design/Method: Case Report

Results: A 4-year old 9-month old boy initially presented with stage IV high-risk neuroblastoma. He underwent standard therapy with chemotherapy, hematopoietic stem cell transplant, radiation therapy, and immunotherapy, followed by a DFMO trial for maintenance. His 3-month follow-up scans while on DFMO demonstrated relapse and he was subsequently treated with ch 14.18, Irinotecan and Temozolamide per ANBL1221, Cyclophosphamide and Topotecan, surgical resection of CNS disease, and MIBG therapy. His initial ALK testing was negative, but Foundation One next-generation sequencing based assay identified multiple genomic alterations: ALK EML4-ALK fusion (variant 5a/b), ATRX loss exon 2–10, CDKN2A/B loss, and KEL splice site 1074-1G>T. Crizotinib therapy was started and initially showed improved disease control. However, he quickly developed resistance and passed away after receiving Ifosfamide, Carboplatin, Etoposide while awaiting a NANT Lorlatinib trial to open.

Conclusion: We present a unique case of an EML4-ALK fusion, not previously reported in neuroblastoma.

Poster # 044 | SUCCESSFUL TREATMENT OF SARCOMA ARISING WITHIN ANAPLASTIC WILMS TUMOR AND THERAPY-RELATED IRON OVERLOAD WITH PHLEBOTOMY

Jodi Muscal, Donald Mahoney, Murali Chintagumpala

Baylor College of Medicine, Texas Children's Cancer and Hematology Centers, Houston, TX, United States

Background: Sarcoma arising within Wilms tumor is rare. Multiple packed red cell transfusions leading to iron overload is a known but rare treatment-related complication of cancer therapy in children with solid tumors.

Objectives: To report a case of sarcoma arising within a stage 4 anaplastic Wilms tumor successfully treated with

multimodal therapy and to report the successful management of treatment related iron overload.

Design/Method: Case report

Results: A 10-year old male presented with abdominal swelling and CT showed a right kidney mass and bilateral lung nodules. He underwent right radical nephrectomy with lymph node sampling. Pathology was reviewed centrally and revealed Wilms tumor with diffuse anaplasia with rhabdomyosarcoma arising within the stromal component and 3 of 13 nodes positive. He received adjuvant intensive chemotherapy and radiation to the hemiabdomen and whole lungs. The 49-week chemotherapy regimen was vincristine, doxorubicin, cyclophosphamide (per COG ARST0431) alternating with carboplatin and etoposide (per COG AREN0321 revised UH-1). Treatment was complicated by multiple episodes of fever and neutropenia and anorexia requiring G-tube placement. Post-therapy, he had persistent neutropenia and thrombocytopenia without related complications. Every 6 months for 3 evaluations he underwent a bone marrow which revealed normocellular marrow with maturing trilineage hematopoiesis. Evaluation for a bone marrow failure syndrome was unrevealing. Starting at 6 months into therapy and all post-therapy imaging showed splenomegaly. He received 29 units of packed red blood cells through the duration of therapy. He was diagnosed with iron overload based on serum ferritin and imaging, including T2*MRI. He received therapeutic phlebotomy for 2 years with normalization of serum iron studies, T2* of the heart, and liver iron concentration. He is more than 6 years from completing therapy with no evidence of recurrent disease. Asymptomatic cytopenias persist and he has no evidence of iron overload.

Conclusion: Though a rare development, clonal sarcomatous transformation can occur in Wilms tumor. Our patient's tumor was successfully treated with intensive multimodal therapy targeting the diffusely anaplastic Wilms and the rhabdomyosarcomatous component. Treatment-related iron overload in a pediatric patient with a solid tumor was successfully treated with phlebotomy. Consideration should be given to screen patients with solid tumors who receive multiple packed red cell transfusions for iron overload at the completion of cancer therapy.

Poster # 045 | RECURRENT UNRESECTABLE CONGENITAL PARASPINAL PRIMITIVE MYXOID MESENCHYMAL TUMOR OF INFANCY: A CASE REPORT AND REVIEW OF THE LITERATURE

Erin Morales, Christopher Ours, Ana Ruano, Douglas Fair

Primary Children's Hospital, University of Utah, Salt Lake City, Utah, United States

Background: Malignant solid tumors are less frequently encountered in infants. Primitive Myxoid Mesenchymal Tumors of Infancy (PMMTI) are a myofibroblastic malignancy and cases are rarely reported in the literature. Cure is achieved in the majority of cases with surgical resection, however treatment for unresectable cases remains an enigma. Recently published literature postulates that the newly discovered BCOR duplication found in PMMTI is tumorigenic via an epigenetic pathway. This molecular signature resembles that of clear cell sarcoma of the kidney (CCSK) and the growing number of BCOR mutated sarcomas. A similar chemotherapeutic backbone and local control used for CCSK, has been proposed for the unresectable subset of PMMTI. Utilizing this approach a 19 month-old with relapsed disease has remained disease free for 12 months. However, given the rarity of this disease and the lack of published literature, there is no known standard of care treatment for unresectable and/or recurrent PPMTI.

Objectives: We report a case of unresectable recurrent PMMTI, a rare infant tumor, with less than 20 cases reported.

Design/Method: Medical record, radiological studies, pathology and literature was reviewed.

Results: Our patient is a now 12 month-old female who presented with constipation and lower extremity weakness in the first weeks of life. An MRI demonstrated a large lumbar epidural mass with spinal cord impingement. Given prolonged (>14 days) neurological symptoms and location, emergent chemotherapy was initiated. Biopsy showed a BCOR positive, primitive myxoid mesenchymal tumor of infancy (PMMTI). She was treated with Ifosfamide, Carboplatin and Etoposide, and demonstrated clinical and radiographic response. We gave two additional cycles of cyclophosphamide, carboplatin and etoposide until surgical resection was feasible followed by two post-surgical cycles of chemotherapy. Unfortunately, four month post-therapy MRI demonstrated two new lesions; an unresectable paraspinal soft tissue mass and a left iliopsoas groove mass. Given BCOR association and reported successful therapy with Vincristine, Doxorubicin, Cyclophosphamide alternating with Ifosfamide and Etoposide, we elected to incorporate vinca-alkaloid and anthracycline into her regimen. She is being treated with VDC/IE with plan for radiation consolidation.

Conclusion: PMMTI is a locally aggressive tumor, for which surgical resection is curative. For those not amendable to resection, best care practices are still being determined. We report a case of PMMTI initially responsive to chemotherapy, but not curative. This is the second case to conclusively demonstrate chemo-responsiveness. BCOR mutation seems

to be a common feature of this cancer; its role in the pathogenesis and as a target is an area of investigation.

Poster # 046 | RESOLUTION OF DIFFUSE LEPTOMENINGEAL ENHANCEMENT AFTER PRIMARY RESECTION OF ATYPICAL TERATOID/RHABDOID TUMOR

Kerri Becktell, Andrew Foy, Teresa Kelly, Tejaswini Deshmukh, Jeffrey Knipstein

Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Background: Atypical teratoid/rhabdoid tumors (ATRT) are central nervous system (CNS) tumors that most commonly occur in very young children. There is no widely accepted standard of care for ATRT patients, and while survival rates are improving they are historically poor. Patients with metastatic disease to the spine at diagnosis have a worse prognosis, and for patients >3 years old, the presence of metastatic disease often results in the use of craniospinal radiation. The importance of correctly identifying metastatic disease at diagnosis aids in decision making and can have both prognostic and therapeutic implications. MR imaging at diagnosis is used to identify metastatic disease; however, here we present a case of diffuse leptomeningeal enhancement that spontaneously resolved after resection of a primary supratentorial ATRT.

Objectives: To describe the resolution of diffuse leptomeningeal enhancement after resection of a primary ATRT tumor in a 12-month-old prior to any adjuvant therapy.

Design/Method: Case Report

Results: A 12-month-old male presented with a 2 month history of vomiting and weight loss, regression of gross motor developmental milestones, and left hemiparesis. A brain MRI demonstrated a $7 \times 5.8 \times 5.7$ cm solid and cystic right atrial mass with diffusion restriction and post-contrast enhancement. Smooth diffuse enhancement was noted along the surface of the brainstem and within the interpeduncular fossa. A spine MRI demonstrated diffuse circumferential post-contrast enhancement along the surface of the entire spinal cord. The patient underwent a successful near total surgical resection of the primary mass. Pathology confirmed the loss of INI-1 staining in tumor cells, consistent with a diagnosis of ATRT. No immediate adjuvant radiation or chemotherapy was given. Repeat imaging was completed 15 days after resection. Brain MR demonstrated expected post-operative changes within the surgical cavity without definitive residual mass or leptomeningeal enhancement. Spine MR demonstrated complete resolution of the previously seen circumferential enhancement along the entire spinal cord. CSF evaluation at that time was negative for tumor cells. After recovery from surgery, chemotherapy treatment was initiated.

Conclusion: Leptomeningeal enhancement at the time of diagnosis of ATRT has historically been considered clear evidence of metastatic disease. This case raises questions about the previously accepted etiology of these imaging changes and suggests that widespread leptomeningeal enhancement should be carefully interpreted in future patients with similar imaging findings. In this setting, clinicians should consider repeat imaging following primary surgical resection in order to provide appropriate prognostic information and inform therapeutic decisions.

Poster # 047 | PRIMARY EWINGS SARCOMA OF CERVICAL CORD MIMICKING CAUDA EQUINA SYNDROME

Sucharita Bhaumik, Joshua Chan

NYU Winthrop Hospital, Mineola, New York, United States

Background: Ewing's sarcoma (ES) is a malignant primary bone tumor usually involving long bones. Primary ES of spine is quite uncommon (0.9%) and its location in the cervical spine is even more rare. Cauda equina syndrome (CES) is symptoms due to damage to the bundle of nerves below the end of the spinal cord known as the cauda equina (low back pain, radiating shooting pain down the legs, paraplegia, and loss of bowel or bladder control). It often occurs with lesions of lumbosacral spine. Treatment with high-dose steroids may provide pain relief and improved neurologic function (by reducing edema) while awaiting diagnostic studies

Objectives: To demonstrate an unusual clinical presentation and emergent management of cervical ES presenting with CES like symptoms.

Design/Method: 15 year old male presented with a left sided posterior neck mass. Soon after, he developed weakness of left arm, urinary and stool retention and inability to walk or bear weight in both legs. On physical exam a left tempero-occipital 6×4cm fixed, non-tender, non-fluctuant mass was noted as well as motor and sensory impairment of left upper extremity, bilateral spastic paraplegia and loss of sphincter control. MRI cervical spine showed a left cervical tumor with moth eaten appearance involving the vertebral bodies of C2- C3, adjacent muscles, displacing vital structures of the neck and compressing the cervical spinal cord. The thoracic and lumbosacral spine had no disease involvement. Due to rapidly worsening spinal cord compression he was emergently treated with high dose steroids. He gained back all function in his extremities

and regained bowel and bladder control. This eliminated need for urgent neurosurgical intervention.

Results: Biopsy of the neck mass showed small blue round cells consistent with ES with EWSR1 gene rearrangement. Staging work up revealed no additional metastatic involvement. He then initiated treatment for localized ES with systemic chemotherapy and radiotherapy and has had excellent response to treatment so far.

Conclusion: This is the first known case of non metastatic primary cervical ES mimicking CES where an acutely enlarging mass presented with rapidly progressive neurologic deficits due to compression of anterior spinothalamic tract. In these unusual presentations of CES without lumbodorsal involvement it is important to consider cervical lesions. Early rapid steroid initiation should be considered while awaiting biopsy results to prevent worsening cord compression followed by ES focused treatments. This increases the chance of a successful outcome. The initial improvement with steroids may confuse the tumor with being a lymphoma

Poster # 048 | AN UNUSUAL ANAPHYLACTIC RESPONSE TO TREATMENT IN A PATIENT WITH SEVERE TYPE 1 VON WILLEBRAND DISEASE

Derrick Goubeaux, Shannon Carpenter

Children's Mercy Hospital, Kansas City, Missouri, United States

Background: von Willebrand disease (VWD) is a relatively common bleeding disorder with a high degree of genotypic and phenotypic variation. Bleeding is usually mucocutaneous but can be severe and include muscle and joint bleeds especially in type 3 VWD patients. Most common bleeding management consists of desmopressin, anti-fibrinolytics, and/or plasma-derived antihemophilic factor/von Willebrand factor (AHF/VWF) complex. A recombinant VWF has become available in the last few years. Anaphylaxis and inhibitor development in VWD are rare.

Objectives: To describe the rare clinical manifestation of anaphylaxis to factor concentrate in a patient with severe type 1 VWD.

Design/Method: Case report

Results: A 13-year-old female with severe type 1 VWD [baseline VWAg 10%, activity < 10%, factor VIII (FVIII) 26%] originally presented with heavy menstrual bleeding (HMB) leading to anemia requiring blood transfusion. She underwent placement of a levonorgestrel-releasing intrauterine device (LNgIUD) and began norethindrone. Her HMB continued despite the LNgIUD and an increase in norethindrone dosing. Plasma derived AHF/VWF complex was administered, which she had previously received. Following the infusion, the patient developed anaphylaxis with hives, wheezing, tachycardia, and itching requiring 2 doses of diphenhydramine and 1 dose of hydrocortisone with resolution of symptoms. Subsequently, she received recombinant VWF without incident. However, due to her low FVIII level, she also required treatment with a full length recombinant FVIII product. She again developed hives and itching after this infusion. She has since received recombinant VWF with recombinant FVIII/Fc fusion protein without further allergic reaction. There was no evidence of an inhibitor with her most recent post-infusion VWF level was 101%, factor VIII 199%.

Conclusion: Anaphylaxis to plasma derived factor products has been documented far less frequently within the VWD population compared to those with hemophilia and is typically seen in those with large gene deletions, usually with type 3 disease. Therefore, similar type 1 VWD patients with severe disease may benefit from gene sequencing. It is unclear in this patient's case to which aspect of her treatment she is allergic, as she reacted to plasma-derived AHF/VWF and full length recombinant FVIII, but not recombinant VWF or recombinant FVIII/Fc fusion protein. We hypothesize that she may be allergic to an epitope in the FVIII B domain, or that the presence of Fc fusion may have had a protective effect. Further investigation including genetic analysis is planned.

Poster # 049 | METASTATIC NEUROENDOCRINE CARCINOMA RESPONDING TO MEK INHIBITION

Debra Simon, Heather Bradeen, Jessica Heath, Steven DuBois, Katherine Janeway, Junne Kamihara, Alan Homans

University of Vermont Children's Hospital, Burlington, Vermont, United States

Background: Neuroendocrine carcinoma is rare in the pediatric age group and, when metastatic, has a very poor response rate to conventional therapy. Additional treatment options are needed.

Objectives: To describe a case of metastatic neuroendocrine carcinoma responding to MEK inhibition following the failure of conventional chemotherapy agents, and suggesting a role for targeted therapy in this type of tumor.

Design/Method: A previously healthy 14 year old male presented with a brief history of diffuse abdominal pain. Imaging demonstrated an extensive lower abdominal mass without a clear primary, but with metastatic disease to supradiaphragmatic and hilar nodes, ascites, and peritoneal

nodules. Biopsies were consistent with neuroendocrine carcinoma, large cell type (G3). Next generation sequencing revealed a KHDRBS2-BRAF fusion. He received conventional cytotoxic chemotherapy regimens both with cisplatin/doxorubicin, capecitabine/temozolomide, and doxorubicin/etoposide, but achieved a minimal response followed by rapid disease progression, massive ascites, and renal failure secondary to bilateral ureteral obstruction.

Results: Based on his prior genomic testing, therapy with single agent MEK inhibitor (Trametinib) was initiated. This produced a rapid, dramatic response with greatly reduced disease burden at all sites, resolution of ascites and return to completely normal activity within 2 months. This response lasted for approximately 6 months before the tumor again progressed. Further therapy with an ERK inhibitor was ineffective, and the patient expired from progressive disease. Located on the chromosome 7q34, the BRAF oncogene, as part of the RAS/MAPK pathway, is involved in cellular proliferation, differentiation, migration, and apoptosis. BRAF mutations are recognized in a wide range of adult malignancies: thyroid cancers, non-small cell lung cancer, cholangiocarcinoma, ovarian cancers, and multiple myeloma. BRAF mutations have also been described in adult neuroendocrine carcinoma of the colon. Trametinib is a highly specific inhibitor of MEK1/MEK2, a downstream mediator in the BRAF pathway. It has demonstrated activity in a number of tumors including advanced melanoma and gliomas. Trametinib was chosen for this patient based on his atypical BRAF fusion. We believe this is the first documented case of its successful use in neuroendocrine carcinoma in the pediatric population.

Conclusion: This case demonstrates the presence of BRAF fusion in a case of pediatric neuroendocrine carcinoma and significant response to single agent MEK inhibition in this context. This cases raises the question as to whether the combination of a targeted inhibitor, in addition to either conventional chemotherapy or other BRAF inhibitors, might offer a better approach to therapy than current treatment options.

Poster # 050 | USE OF ECULIZUMAB IN A PATIENT WITH REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA WITH HETEROZYGOUS NFKB1 MUTATION

Katharine Halligan, Lana Vasiljevic, Rachel Grace, Andrew Macginnitie, Sung-Yun Pai, Phillip Roehrs, Maria Boucher, Lauren Weintraub

Albany Medical Center, Albany, New York, United States

Background: Warm autoimmune hemolytic anemia (wAIHA) is characterized by autoantibody, and occasional complement binding of protein antigens, on the surface of red blood cells at temperatures ≥37 oC resulting in targeted destruction. We describe the case of a 17 year old male with a history of Evan's syndrome, poor immune response to vaccines and lymphoid hyperplasia, presenting with altered mental status and severe anemia, found to have a warm IgG pan agglutinin with evidence of both intra and extravascular hemolysis. His course was complicated by respiratory failure requiring intubation, pulmonary emboli, Enterococcus bacteremia and hypertension. He received multiple transfusions with only transient increases in hemoglobin. The AIHA was refractory to multiple rounds of treatment with high dose steroids, IVIG, rituximab, cyclophosphamide, bortezomib, plasma exchange and mycophenolate mofetil (MMF).

Objectives: Given the refractory nature of our patient's AIHA the decision was made to trial eculizumab, a monoclonal antibody targeting C5 complement, preventing its cleavage and activation, and shown to be effective in treatment of atypical hemolytic uremic syndrome and hemolysis due to an IgM cold agglutinin. Prior to eculizumab infusion, CH50 and Sc5b-9 assays were significantly elevated.

Design/Method: The patient was given two doses of eculizimab 6 days apart.

Results: His hemoglobin steadily rose independent of red cell transfusions with a corresponding decrease in reticulocyte count, LDH and CH50 levels. The patient has remained stable with a normal hemoglobin (12-14 g/dL) on maintenance steroids and MMF.

Conclusion: Although we cannot definitively conclude that Eculizumab directly caused his recovery, the clinical course post-Eculizumab suggests this may be an efficacious treatment for AIHA. Genetic testing showed monoallelic frameshift mutation of the NFKB1 gene and monoallelic missense mutation of the DOCK2 gene. Given the role of NFkB1 in both immunodeficiency and autoimmunity, it is thought that the patient's phenotype is due to NFkB1 haploinsufficiency and he is currently considering hematopoietic stem cell transplant.

Poster # 051 | RELAPSE OF T CELL ACUTE LYMPHOBLASTIC LEUKEMIA AFTER MORE THAN TEN YEARS: TRUE RELAPSE OR SECOND MALIGNANCY?

Shreya Agarwal, Burton Appel

Hackensack University Medical Center, Hackensack, New Jersey, United States

Background: T-Cell acute lymphoblastic leukemia (T-ALL) has a relapse rate approximating 25%, with most relapses occurring during treatment or within two years of therapy completion. Late relapses, however, have been described. It has been suggested that a proportion of late T-ALL relapses represent a second malignancy occurring years after initial T-ALL diagnosis.

Objectives: We describe a 19 year old male with T-ALL relapse eleven years after initial diagnosis, and present evidence that it represents a second T-ALL.

Design/Method: Case Report

Results: Our patient originally presented at 8 ½ years of age with extensive adenopathy, organomegaly and a mediastinal mass. CBC showed a WBC of 11.8, hemoglobin 12.6 and platelets 293,000. Bone marrow aspirate (BMA) was diagnostic of T-ALL (CD2+, CD7+, TdT+, CD34+ [40%], cytoplasmic CD3+). Cytogenetic test results were normal. There was no evidence of CNS leukemia. He was treated per Pediatric Oncology Group (POG) 9404 with high-dose methotrexate. He attained a morphologic remission and received planned 108 weeks of chemotherapy plus cranial XRT (1800 Gy). He was in a continuous remission for eleven years until he presented with adenopathy and hepatomegaly. BMA confirmed T-ALL with immunophenotype similar to his original T-ALL except CD34 was negative. CNS was negative. He received reinduction chemotherapy with vincristine, doxorubicin, prednisone and weekly PEG-asparaginase. At day 29 he was in remission with MRD <0.01% (University of Washington). He proceeded to bone marrow transplant from his HLA-matched sister. He remains in second remission, 19 months post-BMT. Bone marrow from his original diagnosis in 2004 had been cryopreserved per the POG 9900 protocol. We obtained a sample for next-generation sequencing (NGS) of T-cell receptor (TCR) loci and immunoglobulin heavy chain (IGHC) (Adaptive Biotechnologies, Seattle) to compare with a sample from relapse. No clonal abnormalities of TCRβ or IGHC were found at either time point. Sequencing of TCRγ from initial diagnosis revealed a "possible dominant sequence" at a frequency of 6.3% of total TCRγ sequences. Relapse marrow sequencing identified a different dominant TCR Gamma sequence (70.3%) that was not present at initial diagnosis.

Conclusion: Our patient experienced a T-ALL relapse later than most patients in the published literature and remains in a prolonged second remission. NGS of TCR loci provides evidence that this represents a second T-ALL which may have been more chemoresponsive than a true T-ALL relapse.

Poster # 052 | AN UNLIKELY PRESENTATION OF A RARE COMBINATION: A CASE SERIES OF ALPHA GLOBIN GENE TRIPLICATION ASSOCIATED WITH BETA THALASSEMIA TRAIT IN HISPANIC PATIENTS

Madiha Daud, Jill Menell, Alissa Kahn

St. Joseph's Regional Medical Center, Paterson, New Jersey, United States

Background: Heterozygous β -thalassemia typically manifests as thalassemia minor, characterized by mild microcytic hypochromic anemia with minimal clinical ramifications. Co-inheritance of α-globin gene triplication has been reported to exacerbate the clinical and hematological phenotype of β-thalassemia trait, due to increase in the alpha/non-alpha-chain imbalance. Reported phenotypes range from asymptomatic thalassemia minor to moderate thalassemia intermedia, usually diagnosed in adulthood without transfusion dependence. This combination has been described in Mediterranean, European and Asian populations, but rarely reported in Hispanics.

Objectives: To report two cases of unusually severe β-thalassemia intermedia in Hispanic patients with heterozygosity for triplicated α-globin gene and a $\beta(0)$-thalassemia allele.

Design/Method: Case series.

Results: Case 1: Sixteen-month-old male of Mexican descent presented with persistent microcytic anemia and jaundice. Peripheral smear showed nucleated rbcs with basophilic stippling and target cells. Hemoglobin electrophoresis revealed: HbA-79%, HbF-17%, HbA2-4.3%. β-globin gene testing revealed heterozygosity for $\beta(0)$ mutation (IVSI-I, G→A). Given the unusually severe anemia, α-gene testing was performed which showed α-globin gene(anti 3.7) triplication ($\alpha\alpha\alpha/\alpha\alpha$). At four years, he had splenomegaly and bilateral maxillary prominence. Head CT showed irregular contour of the parieto-occipital region due to medullary expansion. Due to significant persistent anemia (6-8g/dL) and progressive bony deformities of the skull, patient began chronic transfusions at age eight after family declined splenectomy.Case 2: Fifteen-year-old female, of Peruvian and Honduran descent, presented for evaluation prior to cholecystectomy for gallstones and recurrent RUQ pain. Father had known thalassemia trait. Her Hb was 9.2 g/dL with hypochromia, microcytosis, and target cells. Electrophoresis indicated β-thalassemia trait (HbA-94%, HbA2-4.7%, HbF-1.3%), confirmed by gene testing (heterozygous for a $\beta(0)$ mutation in codon 39 C>T). Given jaundice and gallstones, α-globin gene analysis was ordered showing triplication ($\alpha\alpha\alpha/\alpha\alpha$). RUQ pain resolved post-cholecystectomy, but she developed persistent painful splenomegaly. She began hydroxyurea to increase

gamma-globin production and decrease excess alpha chains, but it was discontinued due to hematological toxicity. Due to recurrent LUQ pain and progressive splenomegaly, she underwent laparoscopic splenectomy at age 22 with resolution of symptoms and improved hemoglobin.

Conclusion: α-globin gene testing should be considered in β-thalassemia carriers with an atypical clinical presentation including Hispanic patients. The wide variability in the phenotypic expression of $\alpha\alpha\alpha$(anti 3.7) mutation and β-thalassemia trait suggest interplay of other genetic factors which remain undefined. The clinically significant presentation amongst certain subjects, as in our two cases, makes it imperative to identify these factors to aid in phenotype prediction and genetic counseling.

Poster # 053 | A COMPLEX TRANSLOCATION INVOLVING CHROMOSOMES 2, 7, AND 12 IN A CASE OF PEDIATRIC WILMS TUMOR

Ashley Bonheur, Shivakumar Subramaniyam, Jogarao Vedula, Sucharita Bhaumik

NYU Winthrop Hospital, Mineola, New York, United States

Background: Wilms Tumor (WT) is one of the most common solid malignant neoplasms in children. A diverse range of genes and mechanisms are implicated in WT pathogenesis. Predisposing syndromes result from a disruption of WT1 gene, crucial for renal and gonadal embryogenesis. Another gene is WT2 gene locus at 11p15, an area of imprinting. The p53 tumor suppressor gene on chromosome 17p13.1 is seen in patients with anaplastic histology. In addition to these genes, whole and partial chromosome gains of 1q, 2, 7q, 8, 12, & 13 and losses of 1p, 7p, 16q, 22q, as well as loss of heterozygosity (LOH) are commonly seen. Some genetic markers appear to be predictive of outcome and are now incorporated into the assigning of risk-directed therapy. Patients with LOH at chromosome 1p and 16q are treated with more intensive chemotherapy, as they have been associated with increased risk of relapse and mortality.

Objectives: To describe a new complex translocation involving chromosome 2, 7, and 12 in a case of pediatric WT.

Design/Method: A four-year old female presented with abdominal pain and emesis. On exam, patient had a firm and large abdominal mass. Radiologic studies revealed a complex lobulated right renal mass. Right radical nephrectomy was performed. Histopathologic studies showed WT with triphasic histologic features with blastema predominance, invasion of the lymphovascular and perinephric adipose tissues, perinephric lymph node involvement and no anaplasia. Chest CT scan showed bilateral lung metastases.

Results: Tumor cytogenetics showed an abnormal karyotype, a complex translocation of 2, 7, and 12. The rearrangement occurred due to translocation between chromosomal bands 7q22 and 12q15, with an insertion of 7q22-32 on the 2q21 region. PCR based genotyping using microsatellite markers additionally identified LOH for chromosome 1p36 and 16q22. The patient was treated for High Risk Stage IV Wilms Tumor with favorable histology and received intensive chemotherapy and radiation therapy to the flank and the lungs. She is now in remission 8 months after, with no evidence of recurrence on surveillance scans.

Conclusion: Complex translocations associated with WT have not been rigorously studied. A question for further study is whether there is any relationship between recurrence potential with a complex translocation compared to common chromosomal abnormalities. Further knowledge of the molecular pathology and genetic changes in WT will help the development of new targeted therapies, as well as new biomarkers to aid diagnosis, risk stratification, and monitoring of treatment and relapse.

Poster # 054 | CLINICAL OUTCOME OF HB KHARTOUM/β THALASSEMIA COMPOUND HETEROZYGOSITY: A GLIMPSE INTO HOMOZYGOUS HB KHARTOUM

May Chien, Bertil Glader

Stanford University, Palo Alto, California, United States

Background: Hb Khartoum [β124(H)Pro→Arg] was first identified in 1969 during screening of hemoglobinopathies in Khartoum, Sudan. This mutation is predicted to interfere with β globin chain configuration by altering $\alpha 1\beta 1$ contact, resulting in an unstable hemoglobin. Based on previous clinical reports, patients with Hb Khartoum trait do not exhibit any clinical evidence of hemolysis. There has never been a reported case of homozygous Hb Khartoum. This suggests that either the condition is exceedingly rare, or that it is lethal disease state in utero.

Objectives: We report a patient with Hb Khartoum/β thalassemia compound heterozygosity, which may mimic the phenotype of homozygous Hb Khartoum.

Design/Method: A patient with Hb Khartoum/β thalassemia compound heterozygosity was followed clinically for two years

Results: A 4 week-old girl was referred for evaluation of an abnormal newborn screen. Mother was a known carrier of Hb Khartoum trait while father was a known carrier of β thalassemia trait. Patient's hemoglobin quantification performed by capillary zone electrophoresis showed HbF 92%, Hb variant 8%, and no detectable HbA. The Hb variant ran in the D zone, a pattern consistent with mother's Hb. Alkaline agarose gel electrophoresis banding pattern showed F/S. Acid agarose gel electrophoresis pattern showed V/F. Later testing revealed abnormal isopropanol stability with 3+ precipitation at 20 minutes. This electrophoresis pattern is consistent with the pattern previously reported of Hb Khartoum. Clinically, the patient is a healthy, active child whom we have followed for two years. She has not had any significant anemia outside of her physiologic nadir. She has not had any hemolytic episodes, and her bilirubin levels have always been within the normal range

Conclusion: To the best of our knowledge, this is the only reported case of Hb Khartoum/β thalassemia. The proline to arginine substitution of Hb Khartoum introduces a charged group on the β chain at the site of $\alpha 1\beta 1$ contact. The resulting unstable $\alpha 1\beta 1$ chains can dissociate into monomers and favor the formation of methemoglobin, leading to hemoglobin instability. We had wondered if this unstable hemoglobin might result in clinical hemolysis when challenged with oxidative stress, such as in periods of infection. However, in the two years we have followed this patient, she has never had a hemolytic episode. At two years of age, she has HbF 7.8%, Hb Khartoum 85.5%, and HbA2 6.7%. Whether HbF elevation is protective from oxidative stress remains to be determined as we continue to follow this child.

Poster # 055 | ACUTE LYMPHOBLASTIC LEUKEMIA IN PEDIATRIC GM1 GANGLIOSIDE TYPE 1

Jennifer Ruiz, Andrea Mejia, Nilka Barrios, Leslie Soto, Maria Echevarria

University of Puerto Rico - Medical Science Campus, San Juan, Puerto Rico, United States

Background: GM1 gangliosidosis is a lysosomal disorder caused by β-galactosidase deficiency due to mutations in the GLB1 gene. It is a rare autosomal recessive neurodegenerative disorder with an incidence of about 1:100,000-1:200,000 live births worldwide. This neurological disorder has three clinical forms. GM1 Type 1, or infantile form is characterized by psychomotor regression by the age of 6 months, visceromegaly (hepatosplenomegaly), macular cherry red spot, facial and skeletal abnormalities, seizures, and profound intellectual disability.

Objectives: We present a 4-year-old female with GM1 Type 1 and Acute Lymphocytic Leukemia (ALL).

Design/Method: She was diagnosed with GM 1 Type 1 at the 1st months of age and family history was remarkable for an older sister with GM 1 Type 1. Diagnostic studies reveal homozygous exon 7 of the GLB1 gene for a sequence variant defined as c.622C>T, predicted to an amino acid substitution p.Aarg208Cs.

Results: Patient presented to our hospital with petechiae in lower extremities, pallor and intermittent tracheal bleeding. Physical Examination shows a hemodynamically stable girl that is chronically ill dependent of mechanical ventilation, severe mental retardation and scatter petechiae at upper and lower extremities. Laboratory workup revealed severe normocytic anemia (Hgb: 5.7g/dL) with immature peripheral cells and thrombocytopenia (81 × 109/L). Serum chemistry revealed increase LDH (695U/L), increase hepatic enzymes (AST: 63U/L), normal uric acid level. There was no evidence coagulopathy. Chest X Ray was unremarkable except for evidence of chronic pulmonary illness. Abdominal Sonogram hepatosplenomegaly. During hospitalization, bone marrow aspirate and biopsy was performed which was diagnostic of B Cell Acute Lymphoblastic Leukemia (ALL) with 26.5% lymphoblast and orderly myeloid/erythroid maturation. Flow cytometry: 26% B lymphoblast with aberrant phenotype C/W B-acute lymphoblastic leukemia. Karyotype revealed hyperdiploid female of favorable prognosis. Cytogenetic by Fish: hyperdiploid ALL with extra copies of RUNX1 and IGH (no BCR-ABL Translocation).

Conclusion: Family was oriented about the new diagnosis and the dismal prognosis in conjunction to her primary condition. Parents agree on no chemotherapy treatment for ALL with only supportive treatment. To this date, there is no evidence in literature that has previously described association of GM1 and leukemia. Life expectancy of patient's primary condition is null therefore, correlation with leukemia might not be a coincidental finding. This patient opens the possibility of malignancy as part of GM1 type 1 thus, malignancy diagnosis should be considered as part of their medical lifetime course.

Poster # 056 | SUCCESSFUL USE OF ELTROMBOPAG IN A PEDIATRIC PATIENT WITH HIV-RELATED THROMBOCYTOPENIA

Elissa Engel, Mary Soliman, Juan Rico, Carina Rodriguez

University of South Florida, Tampa, Florida, United States

Background: Hematological manifestations related to HIV infection are not uncommon, with thrombocytopenia having an estimated prevalence of 5–15%. The pathophysiology is likely multifactorial. Studies suggest that the primary mechanism may be immunologic resulting in accelerated platelet destruction. Additional theories suggest that infection of megakaryocytes may also play a role causing inadequate platelet production. Treatment of HIV-related thrombocytopenia is challenging. First-line treatments include initiation and optimization of antiretroviral therapies, immunoglobulin (IVIG), and glucocorticoids. However, this approach is not effective in all patients and second line treatment options are less well studied, particularly in the pediatric population.

Objectives: We aim to present and discuss the case of a 13 year old patient with perinatally acquired HIV-1 infection and persistent thrombocytopenia who, after failing first line therapies, showed normalization of platelet count on the novel thrombopoietin receptor agonist, eltrombopag.

Design/Method: A retrospective chart review of the case patient's medical record was conducted. Additionally, a thorough literature review was performed on this topic including the pathophysiology of HIV related thrombocytopenia and its treatment modalities.

Results: The patient required monthly IVIG infusions for about 1 year, but did not show a sustained response, often with platelet count dropping to less than 10,000 in between infusions. After initiation of 50 mg eltrombopag daily the patient showed a sustained increase in platelet count (range 32,000-88,000). During a brief 2 week lapse in eltrombopag treatment his platelet count dropped to 17,000. Upon re-initiation of therapy his count increased to 84,000. The patient has remained asymptomatic, off of IVIG for over one year, with undetectable HIV viral load and greater than 500 CD4 T cell counts. No side effects or grade 2 laboratory abnormalities were reported.

Conclusion: Treatment of HIV-related thrombocytopenia can be challenging. First line therapies, including IVIG and glucocorticoids, are not effective in all patients. Several other treatment modalities have been utilized, including anti-D immunoglobulin, dapsone, danazol, interferon alfa, vincristine, thrombopoetic growth factors including romiplostim and eltrombopag, or splenectomy, but these are less well studied. This represents the first reported case of a pediatric patient with HIV who showed a positive response to eltrombopag with a sustained improvement in platelet count and no adverse effects from treatment. Eltrombopag may be a safe alternative to first line therapies in those patients with HIV and refractory thrombocytopenia, however additional studies are needed.

Poster # 057 | ACHROMOBACTER XYLOSOXIDANS SEPTIC SHOCK: RARE CASE IN A PEDIATRIC PATIENT WITH RELAPSED NEUROBLASTOMA

Jonathan Bardahl, Jaime Libes

University of Illinois College of Medicine at Peoria, Peoria, Illinois, United States

Background: Achromobacter Xylosoxidans is a gram negative rod with peritrichous flagella which causes rare opportunistic infections most commonly encountered by immunocompromised patients. It is primarily associated with uncomplicated bacteremia, cather-associated infections, and pneumonia. Most reports of bacteremia associated with A. Xylosoxidans are nosocomial, associated with neoplasm, and occurring mainly in adults. Most reported infections with A. xylosoxidans in children are associated with cystic fibrosis. There are very few reported cases of septic shock from A. xylosoxidans bacteremia and pneumonia in the pediatric oncology population.

Objectives: To describe a rare case of A. Xylosoxidans septic shock in a pediatric patient with relapsed neuroblastoma

Design/Method: Case Report

Results: A 4-year old boy with history of stage IV high-risk neuroblastoma underwent standard frontline therapy with chemotherapy, hematopoietic stem cell transplant, radiation therapy, and immunotherapy, followed by a DFMO trial for maintenance. His 3-month follow-up scans demonstrated relapse and he was subsequently treated with additional chemotherapy, surgical resection, and MIBG therapy, Crizotinib for an EML4-ALK fusion and finally Ifosfamide, Carboplatin and Etoposide (ICE). He developed neutropenic fevers and was started on Cefepime, Vancomycin and Fluconazole. Blood cultures were initially negative. On the 4th day of fever, his previously scheduled PET scan was performed during hospitalization and showed new pulmonary opacities. He did not have respiratory symptoms, but therapy was escalated to Meropenem, Vancomycin and Amphotericin. Emergent bronchoscopy was performed the same day, with all bacterial and fungal cultures remaining negative. Overnight, he developed tachypnea and saturations in the upper 80s, requiring nasal cannula. IR-guided lung biopsy was performed the next day, a flexible bronchoscopy was done to remove blood clots in the airway, the patient was placed on a ventilator, femoral lines were placed, granulocytes ordered and pressors were started for deterioration to presumed septic shock. Arterial and femoral lines were placed but patient continued to have hemodynamic instability on multiple pressors. The following day, blood and respiratory cultures returned positive for

gram negative rods, later found to be A. Xylosoxidans that should have been susceptible to Meropenem. Unfortunately, our patient passed away that day.

Conclusion: We present a rare case of septic shock by A. Xylosoxidans in a pediatric patient with relapsed neuroblastoma in hopes to increase awareness of this rare pathogen in our immunocompromised pediatric cancer patients.

Poster # 058 | SUCCESSFUL SUPPRESSION OF FACTOR VIII INHIBITOR TITERS WITH IMMUNE TOLERANCE INDUCTION IN AN INFANT WITH SEVERE HEMOPHILIA A DUE TO EXON DUPLICATION

Majd Ghanim, Mayra Robinson, Shayla Bergmann

Medical University Of South Carolina, Charleston, South Carolina, United States

Background: Inhibitor development is a major problem in hemophilia patients. Inhibitors are antibodies that the immune system produces against specific epitopes on the factor VIII molecule. Inhibitor activity is measured with Bethesda units. The incidence of inhibitor formation in patients with hemophilia A is estimated to be as high as 25–30%. Even for patients who are started on prophylactic plasma derived factor VIII, the incidence is still 11–26%. Patients with hemophilia who develop inhibitors often undergo time- and resource-intensive immune tolerance induction (ITI) protocols.

Objectives: To describe successful treatment of inhibitor in a severe hemophilia A patient with a rare mutation

Design/Method: We report the case of an 8-month-old male with severe hemophilia A and a high-titer inhibitor that occurred while receiving prophylactic treatment with human plasma-derived factor VIII and von Willebrand factor (VWF) complex (Alphanate) twice weekly. The patient developed an inhibitor after 14 exposure days. The inhibitor was discovered after the patient was admitted for a major bleeding, one month following a port placement, with a Bethesda unit of 26.8 peak. Significant inhibitor titer reduction was achieved with high-dose human plasma-derived factor VIII and von Willebrand factor (VWF) complex (Alphanate) 200 IU/kg daily bridging with Factor VII 3 times a week for severe bleeding.

Results: At 33 days after the start of ITI, the inhibitor was <0.1 BU and continued undetectable 6 months after initiation of ITI therapy. In this patient, ITI with high-dose plasma-derived factor VIII and von Willebrand factor (VWF) complex was well tolerated and effective. Genetic analysis confirmed a large factor VIII gene duplication of exons 7 to 22. We believe our patient developed inhibitor so quickly (14 exposure days) due to the possibility of this mutation causing a frameshift that introduces a premature termination codon. This might be functionally similar to a deletion in the factor VIII gene which poses the highest risk for inhibitor development in patients with severe hemophilia A. This variant has only been identified previously in two unrelated patients diagnosed with severe hemophilia A. This duplication is not listed in dbSNP variant database, nor observed in the general population database.

Conclusion: Our case proves the effectiveness of this method for patients with severe hemophilia A and an inhibitor. It also shows that more research is needed to identify patients at risk for inhibitor development.

Poster # 059 | ALLOPURINOL USE WITH 6-MERCAPTOPURINE IN MAINTENANCE THERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE SERIES

Lia Phillips, Katherine Minson, Sharon Castellino, John Bergsagel, Glen Lew, Himalee Sabnis, Melinda Pauly, Frank Keller

Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, Georgia, United States

Background: Mercaptopurine (6-MP) is a prodrug that is a core component of maintenance chemotherapy for patients with a diagnosis of acute lymphoblastic leukemia (ALL). Suppression of the neutrophil count is used to demonstrate adequate dosing of 6-MP during this phase of therapy. Bone marrow suppression is mediated by the active metabolite 6-thioguanine (6-TGN), whereas the metabolite 6-methylmercaptopurine nucleotides (6-MMPN) has been shown to cause hepatotoxicity. Allopurinol has been used infrequently in ALL maintenance therapy in the setting of skewed metabolism when adequate myelosuppression is difficult to achieve due to excessive hepatic toxicity. When given in combination with allopurinol a reduced dose of 6-MP may result in both increased 6-TGN levels and decreased 6-MMPN levels.

Objectives: Describe the characteristics and clinical course of patients treated with allopurinol and reduced dose 6-MP during maintenance chemotherapy for ALL.

Design/Method: We performed a retrospective chart review of patients at Aflac Cancer and Blood Disorders Center of

Children's Healthcare of Atlanta with new diagnoses of B or T-cell ALL who received allopurinol during maintenance chemotherapy.

Results: We identified eleven patients with B-cell or T-cell ALL who received allopurinol adjunctive therapy during maintenance chemotherapy at a single institution between 2014–2017. These 11 patients received adjunctive allopurinol for 2–120 weeks (median 52 weeks) with reduced 6-MP (25-65% of full dose). All ten patients with genetic testing for thiopurine S-methyltransferase (TPMT) had wildtype genotype associated with normal enzyme levels. Indications for allopurinol use were most commonly unfavorable 6-MP metabolite levels, transaminitis (n = 8), pancreatitis (n = 3) and hyperbilirubinemia (n = 3). Favorable metabolite shift was achieved in all patients. Liver enzymes improved in 6 of 10 patients with transaminitis after initiation of allopurinol/reduced 6-MP. Three patients who experienced pancreatitis during maintenance did not have recurrence after initiation of allopurinol (2 of these patients previously reported). Six patients developed pancytopenia while on allopurinol, and two of those patients developed pancytopenia severe enough to require allopurinol cessation. Four patients developed isolated anemia (Hgb <11.0 g/dL) without thrombocytopenia or severe neutropenia. No patient has experienced a recurrence of leukemia.

Conclusion: Overall, treatment with allopurinol and reduced dose 6-MP was successful in producing a favorable 6-MP metabolite distribution and reducing toxicity. Therapy was generally tolerated; however a major and notable side effect was pancytopenia, in two cases severe enough to stop allopurinol treatment. Anemia may be more prominent with allopurinol usage. Allopurinol effect is variable among individual patients despite normal TPMT genotypes.

Poster # 060 | CONGENITAL SIDEROBLASTIC ANEMIA, IMMUNODEFICIENCY, PERIODIC FEVERS, AND DEVELOPMENTAL DELAY SYNDROME MASQUERADING AS ALPHA THALASSEMIA VARIANT

Kayla Foster, Katie Bergstrom, Ashley Holloman, Andrea Marcogliese, Amber Yates

Baylor College of Medicine, Houston, Texas, United States

Background: Congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers and developmental delay syndrome (SIFD) is a rare inherited sideroblastic anemia syndrome, first described in 2013 with 12 clinically similar cases. Genetic variations of TRNT1 were identified as causative.

Objectives: To present an unusual presentation of a patient with SIFD complicated by diagnosis of concomitant alpha thalassemia trait.

Design/Method: Retrospective chart review.

Results: A five month old male infant was referred to our hematology center for evaluation of elevated hemoglobin Barts identified on newborn screen. Despite numerous attempts, blood work was unable to be collected. At seven months of age he had microcytic anemia (hemoglobin 7.5 g/dL, mean corpuscular volume 44 fL) more severe than what would be expected with alpha thalassemia trait. No variant hemoglobin was identified with isoelectric focusing or high performance liquid chromatography. By nine months of age he developed growth failure, intermittent emesis with fevers, developmental delays (predominantly gross motor), hearing loss, a disproportionally large head and coarse, thinning hair. Over the next ten months, he was seen by numerous specialists for seemingly unconnected problems including sensorineural hearing loss, elevated liver enzymes and growth hormone deficiency. Alpha globin analysis revealed deletion of two alpha globin genes. At 20 months of age, he was admitted with one week of fevers, jaundice, and emesis. Peripheral blood smear showed microcytic hypochromic anemia with marked anisopoikilocytosis including target cells, elliptocytes, tear drops, spherocytes, poikilocytes, marked polychromasia, and coarse basophilic stippling. Given the inconsistency of his laboratory findings with the diagnosis of alpha thalassemia trait and clinical syndromic findings, bone marrow biopsy was performed which revealed rare ringed sideroblasts. One month later whole exome sequencing revealed TRNT1 splicing variant c.1057-7C>G and novel missense variant c.1092A>T consistent with SIFD.

Conclusion: Hemoglobin Barts on newborn screen with moderate to severe microcytic anemia directed initial diagnostic work-up towards variant alpha thalassemia. As additional medical conditions developed the focus shifted to a unifying syndrome. Compared to previously described cases, our patient was diagnosed at an older age, presented with anemia rather than episodes of febrile illnesses, and had rare sideroblasts on bone marrow examination. Diagnosis in this case led to identification of the novel c.1092A>T variant in his sister who had similar, but milder, features. SIFD is a rare disease with variable phenotypic severity making diagnosis challenging without high index of suspicion which is crucial for appropriate management. Wiseman, Blood, 2013. Chakraborty, Blood, 2014.

Poster # 061 | CHOLELITHIASIS IN PATIENTS WITH CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE SERIES

Soohee Cho, Frank Keller

Emory University, Atlanta, Georgia, United States

Background: Cholelithiasis is uncommon in childhood. Cholelithiasis is known to occur more frequently in children with predispositions, including female sex, obesity, parenteral nutrition, previous abdominal surgery, use of oral contraceptives, family history of gallstones, chronic hemolytic anemias, hepatobiliary disease, or exposure to specific drugs. Although there have been occasional case reports linking cholelithiasis to childhood leukemia or leukemia therapy, the prevalence and risk factors of cholelithiasis in patients with childhood leukemia remain unclear.

Objectives: To estimate the prevalence of cholelithiasis in patients diagnosed with childhood acute lymphoblastic leukemia (ALL), and to evaluate possible risk factors for the development of cholelithiasis in patients with childhood ALL.

Design/Method: We performed a computer-assisted review of the electronic medical records of 503 patients diagnosed for B or T-cell ALL at Children's Healthcare of Atlanta in the period from 2010 to 2016. Patients with diagnoses of cholelithiasis, cholecystitis or who had a cholecystectomy were identified. Possible risk factors of age, sex, BMI, history of abdominal surgery and parenteral nutrition use were abstracted. Patients with underlying chronic hemolytic anemia or pre-existing gallbladder disease were excluded.

Results: Seventeen cases of cholelithiasis and 2 cases of cholecystitis without documented cholelithiasis were identified. Among patients with cholelithiasis, 8 were female. Median age at diagnosis of cholelithiasis was 14.0 (range 2.7 – 21.6) years. Seven patients had no symptoms referable to cholelithiasis at the time of diagnosis. The median age of leukemia diagnosis among these patients was 12.1 (range 0.9 - 18.8) years. The median interval from diagnosis of leukemia to gallbladder disease was 1.0 years. Four patients had BMI over the 95th percentile for age. Two patients had a prior history of intraabdominal surgery. No patient received oral contraceptive pills. Six patients received parenteral nutrition for more than 30 days. There was no documented family history of cholelithiasis. Seven patients did not receive any cholelithiasis directed therapy. Two patients were managed with medical management only, 1 with endoscopic retrograde cholangiopancreatogram with stone extraction, and 7 with cholecystectomy.

Conclusion: Our study estimates the prevalence of cholelithiasis in childhood lymphoblastic leukemia to be 3.3%, higher than the reported prevalence in the general pediatric population of 0.13-0.22%. Although our cohort size is small, it appears that ALL therapy and supportive care modalities associated with ALL are likely to play a larger role in the development of cholelithiasis than known predisposing factors in the general population. Further studies are warranted.

Poster # 062 | CRITICALLY ILL 16-YEAR-OLD MALE WITH SEVERE IVIG-INDUCED COOMBS-POSITIVE HEMOLYTIC ANEMIA

Clare Zimmerman, Casey Mehrhoff, Astha Sharma

Loyola University Chicago, Maywood, Illinois, United States

Background: An uncommon side effect of intravenous immunoglobulin (IVIG) administration is clinically apparent, sometimes severe hemolysis. We describe a severe case of Coombs-positive hemolytic anemia secondary to IVIG administration. IVIG is a blood derivative manufactured from pools of 5,000 to 10,000 individual plasma donations. IVIG is not ABO-type restricted, so anti-A, anti-B and anti-A,B isoagglutinins are detectable.

Objectives: To describe a rare but serious type of transfusion reaction leading to gross hemolysis after IVIG administration.

Design/Method: Case Report

Results: A 16-year-old male with a past medical history of obstructive sleep apnea and obesity was admitted to the pediatric intensive care unit for adenoviral pneumonia and subsequent respiratory failure requiring mechanical ventilation. He had a complex hospital course with many complications including acute respiratory distress syndrome (ARDS), septic-shock, and Coombs-positive hemolytic anemia. The patient was treated with commercial IVIG (Baxter/Baxalta) 400-mg/kg daily for five days. He had two isolated episodes of severe hemolysis in relation to IVIG administration requiring multiple transfusions of packed red blood cells (pRBC). Examination of pre-transfusion peripheral blood smear showed spherocytosis with rouleaux formation and large clumped RBC aggregates. The patient's blood type was classified as Blood Group A, Rh-negative and his initial pRBC transfusions were of this type. Subsequently, the patient's Coombs test was found to be positive using polyspecific and anti-IgG typing sera. The patient's antibody screen against reagent Group O screening cells was negative ruling out autoimmune hemolytic anemia. However, type specific Anti-A antibodies were detected in his plasma as well as the acid eludate prepared from the Coombs-positive red blood cells. It was concluded that the patient's hemolysis was due to anti-A antibodies presumed to arise from IVIG. The patient's

RBC transfusions were changed to O-negative blood and the hemolytic process resolved. The patient ultimately died due to complications of ARDS.

Conclusion: Although hemolysis is a known side effect of IVIG, it is rarely considered when deciding to administer IVIG. In addition, it has rarely been described in the pediatric population. IVIG is used in the treatment of a growing number of medical conditions. Due to the critical nature of many of these patients, hemolysis secondary to IVIG may not be considered and continued blood transfusions with the patient's specific blood type may be used. It is crucial to remember that severe hemolysis can occur from IVIG, and the importance of transfusing with Blood Group O, Rh-negative blood when applicable.

Poster # 063 | USE OF EXTRACORPOREAL MEMBRANE OXYGENATION IN A PATIENT WITH NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA DESPITE COAGULOPATHY AND HEMORRHAGE

Matthew Grant, Regina Macatangay, Adrian Holloway

University of Maryland Medical Center, Children's Hospital, Baltimore, Maryland, United States

Background: Coagulopathy is a well-described complication of acute promyelocytic leukemia (APML), and remains a leading cause in induction failure. With treatment, coagulopathy associated with APML has been shown to rapidly improve. Multiple organ dysfunction syndrome (MODS) in APML, including acute respiratory distress syndrome (ARDS), has been associated with infection, traumatic injury, malignant infiltration, and cytokine release syndrome. When mechanical ventilation is no longer sufficient, extracorporeal membrane oxygenation (ECMO) can be considered; however, coagulopathy, severe end-organ damage, and malignancy are all relative contraindications to initiation of treatment.

Objectives: We report the case of a 17-year-old female presenting in respiratory failure, disseminated intravascular coagulopathy (DIC), with intracranial hemorrhage, and MODS, diagnosed with APML, successfully treated with ECMO therapy.

Design/Method: Retrospective case analysis and literature review.

Results: Our patient, a 17-year-old female was admitted in respiratory failure and altered mental status, following a fall shortly prior to presentation. Initial laboratory values were notable for pancytopenia, DIC, and acute renal failure. A non-contrast head CT showed left temporal lobe intraparenchymal hemorrhage. She was diagnosed with APML by peripheral smear, later confirmed by FISH for t(15:17), and was started immediately on high-risk induction chemotherapy as per COG Protocol AAML1331, including all-trans retinoic acid, arsenic trioxide, Idarubicin, and dexamethasone. CVVHD was required for acute renal failure. Despite maximal respiratory support, she remained hypoxemic, with oxygenation index of 46, PaO2/FiO2 ratio of 70. ECMO was initiated 24 hours after start of induction, 48 hours after admission. Coagulopathy resolved on day 6 of induction, ECMO was discontinued after 9 days, mechanical ventilation and CVVHD were stopped after 15 days and she continued to improve, eventually achieving remission with few neurologic side effects.

Conclusion: Despite relative contraindications to ECMO, this patient was successfully treated with ECMO without significant neurologic side effects. The correction of her coagulopathy was multifactorial: 1) restoration of adequate oxygen delivery via ECMO improving endothelial function; 2) successful organ support to allow sufficient response to induction chemotherapy with ATRA leading to the terminal differentiation of leukemic blasts; 3) complement and contact system activation through contact with ECMO circuitry. This case illustrates that ECMO can still be considered in patients despite coagulopathy and end organ damage.

Poster # 064 | A RARE CASE OF PRIMARY POLYCYTHEMIA VERA IN A PEDIATRIC PATIENT

Katherine Ryan, Kaydee Kaiser, Aziza Shad

Sinai Hospital of Baltimore, Baltimore, Maryland, United States

Background: Primary polycythemia vera is an extremely rare diagnosis in the pediatric patient and is defined by a marked elevation of red blood cells due to erythropoietin-independent mechanisms. Presentations of this disorder range from the asymptomatic person to severe thrombotic events, such as Budd-Chiari syndrome or cerebrovascular stroke. Mutations in the JAK2 gene are found in adult and pediatric patients with polycythemia vera; however, the JAK2 V617F mutation is less commonly identified in pediatric patients.

Objectives: We describe an otherwise healthy 16-year-old female who presented with a significantly elevated total erythrocyte count, hemoglobin, and platelets, incidentally discovered upon routine annual blood work obtained by her pediatrician.

Design/Method: This is a report and discussion of a rare case.

Results: Polycythemia Vera was suspected based upon a hemoglobin of 17 g/dL, total erythrocyte count of 7.79 million/mm^3, and a platelet count over 400,000 per mm^3 and a low erythropoietin level. Furthermore, bone marrow analysis revealed trilineage hyperplasia with predominance of erythroid precursors and cytogenetic panels were negative for malignancy. An evaluation for secondary causes of polycythemia were investigated and excluded. The JAK2 V617F mutation was identified on this patient's genetic testing, thus confirming the diagnosis.

Conclusion: The patient described has done well since diagnosis and is continuing treatment with daily aspirin and frequent phlebotomy, as is the standard first-line therapy for adults with polycythemia vera. This case illustrates an important, but rare entity in pediatrics that benefits from prompt diagnosis in order to limit life-threatening complications of the disease. Further studies are needed to determine standardization of optimal therapy for pediatric patients with PV.

Poster # 065 | SYNCHRONOUS HEMATOLOGIC MALIGNANCIES: CONCURRENT SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA AND B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA IN A PEDIATRIC PATIENT

Robert Galvin, Daniel Miller, Sheilagh Maguiness, Lucie Turcotte

University of Minnesota, Minneapolis, Minnesota, United States

Background: Subcutaneous panniculitis-like T-cell Lymphoma (SPTCL) is a rare (<1%) subtype of non-Hodgkin lymphoma that affects both children and adults. It is derived from cytotoxic T-cells of $\alpha\beta$ phenotype. A related lymphoma with a $\gamma\delta$ phenotype has a more severe clinical course. Hemophagocytic lymphohistiocytosis (HLH) is a feared complication of SPTCL and occurs in 15–20% of cases. SPTCL is also associated with autoimmune disease in 20% of cases across the age spectrum, but the lymphoma has low malignant potential and has not been associated with second malignancies. Synchronous multiple primary cancer is exceedingly rare in children outside of cancer predisposition syndromes.

Objectives: To report a case of synchronous hematopoietic malignancies in a pediatric patient.

Design/Method: Case report and literature review.

Results: A previously healthy 3-year-old boy presented with fevers and pancytopenia. A bone marrow sample at this time demonstrated cellular marrow with trilineage hematopoiesis and no dysplasia. Cytogenetics were not assessed. His hemoglobin and platelet count recovered but leukopenia and neutropenia persisted. Follow-up evaluation at three months revealed fevers, ongoing cytopenias, a one-month of a nodular skin rash on the trunk and extremities resembling erythema nodosum, and hepatitis (peak ALT and AST of 1,176 and 1,008, respectively). Following clinical evaluation, a skin biopsy was performed and was remarkable for atypical lymphocytes within the subcutis with T-cell markers, a high Ki-67, and positive TIA-1, perforin, and β-F1 immunoperoxidase stains. Negative stains for CD56, CD30, and EBV were noted. These results are consistent with SPTCL. Additional evaluation did not support a diagnosis of HLH. A staging evaluation was performed. PET-CT showed widespread hypermetabolic subcutaneous activity in the legs, trunk and skull and diffuse marrow hyperplasia. Bone marrow demonstrated involvement with precursor B-cell acute lymphoblastic leukemia, with a MLL gene rearranagement. His skin biopsy was retrospectively stained with TDT, CD34, PAX-5, CD79a, and CD20 with negative results, and a blood smear taken at the time of the skin biopsy did not demonstrate leukemic cells.

Conclusion: This is the first report of a patient with SPTCL having a synchronous malignancy. The patient is doing well, currently in the Maintenance phase of treatment for his ALL, and his skin disease has resolved on PET-CT. While it is possible that his presentation was a function of chance, the possibility of an underlying immune dysfunction or cancer predisposition warrants further investigation.

Poster # 066 | HEREDITARY XEROCYTOSIS MISDIAGNOSED AS HEREDITARY SPHEROCYTOSIS

Allison Bartlett, Omar Niss

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Hereditary xerocytosis (HX) is a rare red blood cell (RBC) dehydration disorder, characterized by variable hemolysis and propensity to iron overload. HX is often misdiagnosed as hereditary spherocytosis (HS). While splenectomy is curative for HS, it is relatively contraindicated in HX due to a substantial thromboembolism risk, signifying the importance of delineating these diseases. Blood smear abnormalities are variable and often insufficient to make an accurate diagnosis. Osmotic-gradient ektacytometry and genetic confirmation are critical in distinguishing these overlapping disorders.

Objectives: Describe a family with HX, initially misdiagnosed as HS. Discuss the importance of distinguishing these disorders and the utility of ektacytometry in making this distinction.

Design/Method: A 13-year-old Caucasian male was diagnosed with HS after presenting with prolonged neonatal jaundice starting on the first day of life. He described mild scleral icterus and history of intermittent jaundice and dark urine, without need for transfusions. His father, paternal uncle and paternal grandmother were all diagnosed with HS during childhood and underwent cholecystectomy. Additionally, his father underwent splenectomy for abdominal pain. The child's blood counts revealed compensated anemia (Hb 12.9 gm/dL) and reticulocytosis (ARC 347 × 103/mcL) with increased MCV (96.6 fL) and MCHC (38.2 gm/dL). Blood smear showed increased polychromasia and poikilocytosis with rare spherocytes and few stomatocytes. While the child had normal ferritin, his father had iron overload (ferritin 800 ng/mL) despite no prior transfusions. Osmotic-gradient ektacytometry profile of the child and father's RBCs showed a characteristic left-shifted, bell-shaped curve with decreased Omin and Ohyp, diagnostic of HX. The family is currently undergoing genetic studies.

Results: Despite clinical similarities between HS and HX, distinguishing these diseases has significant management implications. HX is a disorder of RBC permeability, causing shortened RBC survival. Stomatocytes on blood smear can raise suspicion for HX, but are insufficient to make an accurate diagnosis. Identifying characteristic biomechanical membrane properties using osmotic-gradient ektacytometry is the gold standard for clinical diagnosis, which can then be confirmed by molecular studies. HS and HX can be easily and reliably distinguished using ektacytometry, as both disorders have very distinctive curves representing different RBC deformability patterns. After HX diagnosis was made, we counseled the family against splenectomy, as the risk of thromboembolism is significantly increased in HX compared to HS, and the father was diagnosed with iron overload.

Conclusion: HX is commonly misdiagnosed as HS. This case highlights the importance of making this distinction, and the utility of osmotic-gradient ektacytometry in reliably distinguishing these conditions.

Poster # 067 | TREATMENT OF RELAPSED ACUTE MYELOID LEUKEMIA PRESENTING AS INTRACRANIAL MYELOID SARCOMA: A CASE SERIES

Kenneth Bujold, Smita Dandekar, Mustafa Barbour

Penn State Health Children's Hospital, Hershey, Pennsylvania, United States

Background: Relapsed acute myeloid leukemia (AML) presenting as an isolated central nervous system myeloid sarcoma (CNS MS) is very rare and its treatment is not well-defined. Thiotepa, vinorelbine, topotecan and clofarabine (TVTC) has been successful for re-induction therapy to induce remission prior to hematopoietic stem cell transplant (HSCT).

Objectives: To describe our experience in utilizing TVTC therapy in two children with no extramedullary disease at initial diagnosis who presented with relapsed AML as intracranial myeloid sarcomas.

Design/Method: Retrospective chart review.

Results: Case 1: 34 month-old female was diagnosed with FLT3 negative AML and completed treatment per the Children's Oncology Group (COG) AAML1031 study on the low risk arm without Bortezomib. Cerebral spinal fluid (CSF) negative at diagnosis. FISH testing positive for TCF3 gene deletion of unknown significance. MRD was undetectable after Induction I and remained undetectable after each cycle. Nine months off therapy, recurrent headaches prompted MRI imaging which revealed two posterior fossa masses. CSF and bone marrow testing were negative. Stereotactic biopsy of the larger mass confirmed recurrence of AML. Patient underwent two cycles of TVTC with a total of seven doses of intrathecal cytarabine with almost near resolution of the CNS MS. Completed cranial radiation and proceeded to allogeneic stem cell transplant with unrelated cord marrow donor and is disease free at approximately day +200.Case 2: 5 year-old female diagnosed with FLT3 and MLL negative AML and completed treatment per COG AAML1031 study on the low risk arm without Bortezomib. CSF negative at diagnosis. MRD was undetectable after Induction I and completed therapy without complications. Two months off therapy, a retrospective analysis of her diagnostic bone marrow by the cytogenetic laboratory to test a new panel identifying novel 11q partners revealed a cryptic insertional 10:11(MLLT10/MLL(KMT2A) translocation. At four months off therapy, acute mental status changes prompted MRI imaging which revealed two intracranial MS and lumbar spine involvement. Resection of the larger lesion for symptomatic relief confirmed the MLLT10/MLL(KMT2A) fusion. CSF positive for blasts and marrow negative for relapsed disease. Patient completed two cycles of TVTC with a total of seven doses of IT cytarabine with near resolution of CNS disease (only 3 mm contrast enhancement in the medulla). She received craniospinal radiation and is awaiting improvement in her cardiac function before proceeding to HSCT.

Conclusion: TVTC is a successful reinduction regimen for relapsed AML with CNS MS prior to HSCT.

Poster # 068 | DIFFERENTIATING ATYPICAL HEMOLYTIC UREMIC SYNDROME VERSUS AUTOIMMUNE HEMOLYTIC ANEMIA: MANAGEMENT OF PATIENTS IN EXTREMIS

Nidhi Shah, Jonathan Powell

Nemours/AI DuPont Hospital for Children, Wilmington, Delaware, United States

Background: Acute severe anemia can be a life-threatening medical condition. The differential is quite broad for possible etiologies of acute severe anemia, including autoimmune hemolytic anemia (AIHA) and atypical hemolytic uremic syndrome (aHUS). Autoimmune hemolytic anemia is an antibody-mediated process that targets the protein antigens located on the surface of red blood cells. Treatment options for AIHA include corticosteroids, with up to 80% of patients being responsive, with some requiring splenectomy. Atypical hemolytic uremic syndrome is a medical urgency, defined as the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. The etiology is usually due to genetic causes, or less commonly, due to autoantibodies or idiopathic reasons. Prognosis is very poor.

Objectives: Differentiating between autoimmune hemolytic anemia and atypical hemolytic uremic syndrome can be a time-sensitive diagnostic dilemma while the patient is in critical condition, but this important delineation can vastly alter therapeutic options.

Design/Method: Here we discuss two cases highlighting the diagnostic workup involved in differentiating between atypical hemolytic uremic syndrome and autoimmune hemolytic anemia. Patient A is a 3-year-old male who presented in extremis with severe anemia, uremic encephalopathy, and severe acute renal injury requiring hemodialysis and multiple blood transfusions. Patient B is a 10-month-old male, who also presented in extremis with respiratory failure secondary to Adenovirus/Rhinovirus/Enterovirus, with acute progressive renal failure and microangiopathic hemolytic anemia, requiring hemodialysis and cardiorespiratory support.

Results: Patient A underwent a full hematologic and infectious disease workup. Subsequent laboratory studies confirmed enteropathogenic E.coli (EPEC) in the patient's stool; blood cultures remained negative. Renal biopsy results were consistent pigment nephropathy. Bloodwork indicated positive direct coombs. Patient A was ultimately treated with steroids 2mg/kg/day, with significant improvement. Patient B also included a full hematologic work-up, including ADAMTS13 activity and aHUS genetic panel, as well as full infectious disease work-up. Subsequent laboratory testing revealed blood cultures growing streptococcus pneumoniae, with ADAMTS13 activity at 41% (Adult ref range: >/ = 70%), and normal complement levels. Imaging findings also supported diagnosis of aHUS.

Conclusion: The management of a critically ill patient with acute severe anemia requires a thorough hematologic and infectious disease work-up. While molecular and genetic are helpful in definitive diagnosis of aHUS, the utility of such results is limited by time. Overlapping clinical presentation of a patient in extremis due to acute severe hemolytic anemia with progressive renal failure presents a rather broad differential, with time-sensitive treatment and prognostic implications. The favorable response to steroids delineates AIHA from HUS.

Poster # 069 | IDH1 MUTATED ACUTE MYELOID LEUKEMIA IN A CHILD WITH METAPHYSEAL CHONDROMATOSIS WITH D-2-HYDROXYGLUTARIC ACIDURIA

Anand Srinivasan, Yaolin Zhou, Joel Thompson, Klaas Wierenga, Teresa Scordino, Andrea Weirenga, Sandeep Prabhu, Arpan Sinha

University of Oklahoma, Oklahoma City, Oklahoma, United States

Background: D-2-hydroxyglutaric aciduria (D-2-HGA) is a rare metabolic disorder characterized by developmental delay, hypotonia, and bi-allelic mutations in D-2-hydroxyglutarate dehydrogenase (D2HGDH) or isocitrate dehydrogenase 2 (IDH2). Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria (MC-HGA) is a type of D-2-HGA that has been previously reported in seven patients (OMIM 614875; PMID 24049096), three of whom had somatic mosaicism for R132 variants in isocitrate dehydrogenase 1 (IDH1).

Objectives: We describe a 3-year-old boy with MC-HGA who subsequently developed acute myeloid leukemia (AML) and was found to have a R132 variant in IDH1 in a leukemic bone marrow sample. We report the first case of AML with this metabolic disorder.

Design/Method: A 1-year-old Hispanic boy presented with short stature, developmental delay, abnormal skin pigmentation, and unilateral congenital cataract. Workup revealed multiple skeletal enchondromatosis and elevated urine D-2-hydroxyglutaric acid levels. He was diagnosed with MC-HGA. No pathogenic variants in D2HGDH, IDH1 and IDH2 were identified in peripheral blood. Germline testing with

biopsies of skin lesions was declined by the family. Two years later, he presented with streptococcal sepsis and pancytopenia. Blasts were noted on peripheral smear. Bone marrow morphology was consistent with acute myelomonocytic leukemia (~23% blasts). Chromosome analysis showed normal 46 XY, and molecular testing by pyrosequencing IDH1 and IDH2 revealed a R132C variant in IDH1 (25% mosaicism).

Results: The patient is being treated as per the COG study AAML1031. End of Induction I bone marrow aspirate was hemodiluted, but there was no obvious residual disease by flow cytometry (0.01-0.01% sensitivity) or morphology. The previously identified IDH1 variant was no longer detectable (limit of detection <10%). Although targeted therapy for AML with IDH1 mutation is currently in Phase I clinical trials in adults, there is no safety or efficacy data for using IDH1 inhibitors in children. Treatment with ivosidenib is therefore not currently an option for our patient.

Conclusion: This is the first case of AML reported with this rare metabolic disorder. Somatic R132 variants in IDH1 have been identified in three other MC-HGA cases. This same mutation leads to the accumulation of D-2-hydroxyglutarate in gliomas and AML. Without any confirmed germline mutation or somatic mosaicism testing of multiple specimen sources, we can only speculate that the patient has an underlying somatic IDH1 mutation associated with MC-HGA which subsequently led to leukemogenesis. We present the first case of this association, to increase index of suspicion for development of AML in children with metabolic disorders associated with variants in IDH1.

Poster # 070 | CONGENITAL COMBINED DEFICIENCY OF THE VITAMIN K-DEPENDENT CLOTTING FACTORS (VKCFD): A NOVEL HOMOZYGOUS MISSENSE GAMMA-GLUTAMYL CARBOXYLASE (GGCX) MUTATION

Hebah Al Absi, Mohammad Abdullah

Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates

Background: Congenital combined deficiency of the vitamin K-dependent coagulating factors (VKCFD) is a rare heterogeneous autosomal recessive bleeding disorder. VKCFD is caused by mutations in the genes of either gamma-glutamyl carboxylase (GGCX) or vitamin K epoxide reductase complex (VKORC), which are responsible for the gamma-carboxylation of vitamin K dependent proteins (VKDPs) allowing for their activation. The clinical presentation ranges from no bleeding to intracranial hemorrhage. To date, VKCFD has been reported in few patients worldwide.

Objectives: We report a case of a girl with novel homozygous mutation of the GGCX gene, highlighting her clinical and biochemical characteristics with a review of the literature.

Design/Method: A 3-month-old girl of consanguineous Emirati parents, presented to our hospital with a history of bleeding from puncture site after receiving her second-month vaccine. That was associated with episodes of mild mucosal bleeding. Review of systems was negative for jaundice, steatorrhea and failure to thrive and physical exam was unremarkable. Investigations revealed markedly prolonged PT and aPTT with high INR. Fibrinogen, hemoglobin and platelets were always normal. Activities of vitamin K-dependent factors including FII, FVII, FIX, FX, protein C and S were all low. A measurement of Proteins Induced by Vitamin K Absence (PIVKA-II) was done and came very high. This was associated with a mild elevation in liver enzymes but normal liver function test. The picture was supporting vitamin K deficiency, and as a result, she was started on oral vitamin K supplements of 1 mg/day. She responded partially to vitamin K and required higher doses to stabilize her INR. After excluding acquired causes and due to her requirement of high doses of vitamin K, a mutation in either GGCX or VKORC genes was suspected. Genetic analysis was conducted for her which revealed a novel missense homozygous mutation in the GGCX gene (c.548A>T) confirming the diagnosis of Combined Deficiency of Vitamin K-Dependent Clotting Factors type 1. The asymptomatic parents were both heterozygous for the same mutation.

Results: She is currently stable on 10 mg/day of vitamin K supplements.

Conclusion: VKCFD is a rare bleeding disorder with an overall good prognosis due to the availability of several effective therapeutic options. The function of the mutated gene is unknown. Our patient demonstrated a partial response to vitamin K supplements suggesting presence of a residual carboxylation capacity and a possible role of this gene in the enzyme-substrate interactions.

Poster # 071 | A UNIQUE PHENOTYPE OF T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA IN A PATIENT WITH GATA2 DEFICIENCY

Orlando Esparza, Ana Xavier, Kimberly Whelan

University of Alabama at Birmingham, Birmingham, Alabama, United States

Background: GATA2 is a zinc finger transcription factor that plays a critical role in the regulation of hematopoiesis and lymphatic angiogenesis. Mutations leading to GATA2 deficiency (GD) have been linked to a variety of clinical conditions. Patients with GD have a striking predisposition to develop myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), or chronic myelomonocytic leukemia (CMML). Acute lymphoblastic leukemia (ALL) has not been associated with GD, although the association of B-cell ALL and GD has been previously reported.

Objectives: To describe a unique association of GATA2 deficiency and T-cell ALL in a young child.

Design/Method: Case report.

Results: An 8-year-old female presented with a one-week history of fever and malaise. She had a significant past medical history of verruca plantaris and self-resolving leukopenia associated with febrile illnesses. Significant family history included sister with neutropenia and human papilloma virus (HPV) infection, and mother with neutropenia, monocytopenia, atypical mycobacterial infections, and HPV infection. Peripheral blood revealed hemoglobin 9.3 g/dL, hematocrit 26.7%, platelets 176,000/uL, and white blood cell 1,740/uL (neutrophils 122/uL, lymphocytes 1601/uL, monocytes 17/uL). Patient underwent a bone marrow biopsy demonstrating lymphoblast infiltration. Flow cytometry analysis demonstrated monoclonal lymphoid blast population that co-expressed CD117, CD34, CD13, nuclear TdT, CD2, however, lacked expression of CD33, CD10, CD3, CD19, HLA-DR, or myeloperoxidase. Findings were consistent with T-cell ALL with aberrant myeloid markers. Cytogenetics analysis revealed 45,XX,dic(21;22)(p11.2;p11.2). Patient began treatment as per Children's Oncology Group AALL0434 and achieved remission at the end of induction. Course of therapy was complicated by episodes of fever, reciprocating junctional tachycardia, asparaginase-associated thrombosis, viral meningitis, recurrent episodes of verruca plantaris, and resistant Streptococcus pneumoniae or Haemophilus parainfluenza infections causing chronic cough. Later, she was also found to have low IgM levels; after completion of therapy, she developed monocytopenia. Lymphocyte subset panel revealed absent B cells, decreased number of natural killer (NK) cells, and CD4/CD8 inversion. Further work-up included GATA2 sequence analysis that showed heterozygous nonsense mutation (c.58C > T/C; reference NM_001145661) likely resulting in GATA2 haploinsufficiency. Patient continues to be in remission, is receiving monthly immunoglobulin replacement and is on azithromycin for atypical mycobacterial prophylaxis. Surveillance bone marrow biopsies have shown no evidence of MDS or leukemia, however, have demonstrated persistent hypocellularity. The possibility of undergoing an allogeneic bone marrow transplant is actively being discussed given its curative potential.

Conclusion: Clinicians should be aware that T-cell ALL may be associated with GATA2 deficiency.

Poster # 072 | SUCCESSFUL TREATMENT WITH MYCOPHENOLATE MOFETIL IN SEVERE HEMOPHILIA A COMPLICATED BY HIGH TITER INHIBITOR: A CASE REPORT

Allison Remiker, Eric Mullins

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Treatment for severe hemophilia A is centered on Factor VIII (FVIII) replacement therapy. Development of an alloantibody (inhibitor) against FVIII is a significant treatment complication occurring in as many as 25–30% of patients. High titer inhibitors render treatment with factor VIII ineffective, necessitating the use of bypass agents that may not achieve hemostasis with the same efficacy. Considering the substantial ramifications of inhibitor development on treatment, eradication of inhibitors is of great importance to achieve adequate hemostasis in this patient population. Desensitization by immune tolerance induction (ITI) is the primary method of inhibitor elimination. However, not all patients respond to ITI. Immunomodulation may be considered as the next line of therapy, although controversy remains in regards to agent selection and use.

Objectives: There is incomplete data on the use of immunomodulation therapy for inhibitor eradication in severe hemophilia A. We present a case of a pediatric patient with severe hemophilia A and high titer inhibitor who failed initial ITI therapy to better illustrate potential treatment options for the future.

Design/Method: A retrospective chart review was performed on a patient with severe hemophilia A at Cincinnati Children's Hospital Medical Center.

Results: An 8-year-old Caucasian male with severe hemophilia A secondary to intron 22 inversion, was initially diagnosed following extensive bleeding after circumcision at birth. He was identified as having an inhibitor (312 Bethesda units (BU)) at 12 months of age after 15 exposure days of treatment. He failed multiple attempts of ITI, with recombinant and plasma-derived (pd) FVIII. He was advanced to immunomodulation therapy in combination with pdFVIII, however demonstrated anaphylaxis to rituximab and ofatumumab. He underwent tolerization to rituximab, and received a six month course with a partial response (nadir of 0.56 BU). 12 months following last dose of rituximab, a rising inhibitor

titer (7.44 BU) was found. Mycophenolate mofetil (MMF) was initiated with subsequent inhibitor stabilization and a decreasing titer (1.48 BU) over the course of the following year. MMF has been well tolerated without major side effects or infection throughout therapy.

Conclusion: Development of an inhibitor against FVIII is a considerable complication in patients with severe hemophilia A. Use of immunomodulatory therapies following ITI failure remains controversial. MMF has not been well studied in this patient population. We report a case of a patient who is being successfully treated with MMF with minimal side effects. Further prospective studies should be considered to further define the role of MMF immunomodulation therapy.

Poster # 073 | VERY EARLY RELAPSE IN DS AML PATIENTS TREATED WITH A REDUCED DOSE ARA-C REGIMEN: A REPORT OF 2 CASES

Colleen Mathews, Michael Huang

University of Louisville School of Medicine, Louisville, Kentucky, United States

Background: Down syndrome (DS) children with AML (DS AML) have higher cure rates than their non-DS counterparts. Outcomes for refractory/relapsed cases, however, remain dismal. Somatic mutations of the gene encoding the transcription factor GATA1 in DS AML patients are responsible for the observed hypersensitivity of DS AML blasts to cytosine arabinoside (ara-C). In view of excellent survival rates (approaching 90%) of DS AML patients, the ongoing Children's Oncology Group (COG) AAML1531 study seeks to determine the feasibility of treating standard risk (minimal residual disease/MRD negative) DS AML patients using a reduced dose (7-fold decrease) ara-C backbone. Although results from Japanese trials with this approach are promising, North American and European data are conflicting. Although chromosome 7 rearrangements in DS AML do not appear to carry the same adverse prognostic significance as in non-DS AML, monosomy 7 in DS AML patients has been associated with a moderately worse outcome. Isochromosome 7q, however, is rare and has only been reported in 3 previous cases of DS AML.

Objectives: To report our institutional experience of very early relapse involving 2 cases of DS AML patients treated per the reduced dose ara-C arm (3.8 g/m2) of the AAML1531 study.

Design/Method: We hereby report the disease course and cytogenetics of the above 2 DS AML patients.

Results: Patient 1 is a 20 month old Caucasian female who had GATA1 mutation negative AML. Patient 2 is a 3-year old Caucasian male whose chromosomal analysis revealed isochromosome 7q (3 copies of the long arm of chromosome 7). Both patients achieved negative MRD (<0.05%) after induction I chemotherapy with thioguanine, low-dose ara-C and daunorubicin and proceeded per the reduced dose ara-C arm of AAML1531. Patient 1 relapsed immediately after completion of chemotherapy. Salvage chemotherapy with mitoxantrone/high dose ara-C (HiDAC) failed to induce a second remission and the patient subsequently died of disease. Patient 2 relapsed within 4 months from end of therapy. The patient underwent salvage chemotherapy utilizing a HiDAC backbone and remains in disease remission.

Conclusion: The noted very early relapse following a reduced dose ara-C regimen in our 2 above DS AML children suggests that testing for GATA 1 mutation and chromosome 7 rearrangements may play a useful role in the development of future risk-stratified treatment strategies for DS AML.

Poster # 074 | WHEN THE HISTORY TELLS THE STORY: A CASE OF VITAMIN B12 DEFICIENCY DISCOVERED IN AN EXCLUSIVELY BREASTFED INFANT WITH PALLOR AND FAILURE TO THRIVE

Carol Fries Simpson, Angela Girvin

University of Rochester, Rochester, New York, United States

Background: In developed countries in the 21st century, severe nutritional deficiency is not an often considered differential diagnosis of unexplained childhood anemia. Aside from iron deficiency anemia, vitamin deficiency severe enough to impact hematopoiesis is uncommon in the general pediatric population. Here we present the unique case of a 10-month-old infant who presented with intermittent emesis, failure to thrive (FTT), developmental delay, macrocytic anemia, and neutropenia which was initially concerning for a congenital bone marrow failure syndrome. Instead, she was discovered to have an underlying, potentially familial deficiency of B12.

Objectives: 1. To describe the unique case of an infant with B12 deficiency. 2. To outline the importance of including B12 deficiency in the differential diagnosis of unexplained megaloblastic anemia in children.

Design/Method: A 10-month-old exclusively breastfed infant presented for gastroenterology evaluation due to persistent emesis and poor weight gain over the course of 2 months. Her history was notable for delayed developmental

milestones and hypoactivity. Marked pallor prompted hematologic evaluation, which revealed concern for macrocytic anemia (hemoglobin 7.1 g/dL, MCV 107), reticulocytopenia (48.1 × 10^3/μl), and neutropenia (ANC 0.4 × 10^9/l). An otherwise reassuring physical examination and laboratory evaluation was notable only for the discovery of an undetectable B12 level and marked hyperhomocysteinemia (162 μmol/L). Her hemoglobin (Hgb) continued to decline (to 5.9 g/dL) over the first few days after presentation, and she required red blood cell (RBC) transfusion.

Results: Within only a few days of initiation, daily cyanocobalamin injections resulted in a robust reticulocytosis response, improved Hgb, immediate normalization in the neutrophil count, and resolution of hyperhomocysteinemia. Additional history and laboratory evaluation from the patient's mother revealed a concurrent, asymptomatic maternal B12 deficiency as well as a history of a need for B12 supplementation in the maternal grandfather, raising concern for an inherited etiology.

Conclusion: Despite the rarity of vitamin-deficient hematologic abnormalities in the general pediatric population, B12 deficiency should be considered as a potential cause of an otherwise unexplained megaloblastic anemia, especially in the setting of concurrent FTT and neurodevelopmental delay. A detailed family history should be obtained in such cases and may have helped to prevent this patient's clinical sequelae had the deficiency been discovered sooner. Our patient has experienced a favorable clinical response to B12 supplementation, attesting to the importance of vitamin B12 in early childhood growth and development.

Poster # 075 | PROTRACTED ANAPHYLAXIS AFTER PEG-ASPARAGINASE: ACUTE MANAGEMENT AND SUBSEQUENT ASPARAGINASE TOLERANCE

Jessica Heath, Alan Homans, Heather Bradeen

University of Vermont, Burlington, Vermont, United States

Background: PEG-asparaginase is universally utilized in the treatment of pediatric acute lymphoblastic leukemia (ALL). Despite its high efficacy in this disease, it is associated with hypersensitivity and allergy in 10 - 20% of patients. Protracted anaphylaxis has been described in circumstances such as severe food allergy with ongoing allergen exposure; however, it has not yet been described in relation to PEG-asparaginase. We describe the first reported case of protracted anaphylaxis after PEG-asparaginase administration, provide guidance as to time course and management of protracted anaphylaxis, as well as evidence that Erwinia asparaginase may be safely administered even in this high risk population.

Objectives: To provide guidance regarding the duration, course and management of protracted, severe anaphylaxis after PEG-asparaginase therapy.

Design/Method: A 15 year old male with very high risk ALL presented for Consolidation therapy with PEG-asparaginase (intramuscular) and vincristine. One hour after administration, he developed generalized hives and angioedema, for which he was given diphenhydramine. He then quickly developed progressive hives, angioedema, subjective throat and chest tightness, and wheezing. He was treated with diphenhydramine, epinephrine, albuterol, and methylprednisolone with resolution of symptoms. One hour later, symptoms recurred and the patient became hypotensive; he was retreated with methylprednisolone and epinephrine, and was transferred to the pediatric intensive care unit (PICU). In the PICU, he was placed on an epinephrine drip, and continued on methylprednisolone, diphenhydramine, cetirizine, albuterol, and ranitidine. The epinephrine drip was successfully discontinued after 48 hours, and his other medications were gradually weaned over the course of two weeks. Of note, the patient did have ST segment changes in his electrocardiogram during the first 48 hours of anaphylaxis. These were associated with normal ventricular function as per echocardiogram, and resolved within one week. This patient has subsequently tolerated multiple doses of Erwinia asparaginase (intramuscular) without premedication.

Results: This patient was acutely managed in the pediatric intensive care unit with steroids, anti-histamines, and continuous infusion epinephrine. Symptoms consistent with severe anaphylaxis including hives, angioedema, throat and chest tightness, wheezing, and hypotension persisted for a total of four days before finally resolving. He has thus far tolerated multiple doses of Erwinia asparaginase without any symptoms of allergy, hypersensitivity, or anaphylaxis.

Conclusion: Protracted severe anaphylaxis after PEG-Asparaginase therapy can be successfully managed with multi-agent therapy, including antihistamines, steroids, and continuous infusion epinephrine. Re-challenge with an alternate form of asparaginase may be tolerated, even in a patient with protracted anaphylaxis to PEG-Asparaginase.

Poster # 076 | VINCRISTINE-INDUCED ANEMIA IN HEREDITARY SPHEROCYTOSIS

Jennifer Michlitsch, Elliott Vichinsky, Sandra Larkin, Frans Kuypers

UCSF Benioff Children's Hospital Oakland, Oakland, California, United States

Background: Vincristine (VCR) is widely used in pediatric cancers. Unlike most cytotoxic agents, hematopoietic toxicity is uncommon. VCR-induced anemia has been observed but its mechanism has not been well studied. Vinca alkaloid-induced membrane changes were seen in early studies of hereditary spherocytosis (HS) and anecdotal cases suggest VCR may increase hemolysis in such patients. Here we describe a case involving severe VCR-induced anemia in a patient with HS and an explanation as to the mechanism.

Objectives: To describe the mechanism of VCR-induced anemia in HS.

Design/Method: Case report.

Results: A 6 year-old female with HS was diagnosed with T-lymphoblastic lymphoma. She had required 2 packed red blood cell (PRBC) transfusions as a neonate and thereafter had done well without episodes of acute hemolysis or aplasia. Complete blood counts (CBC's) demonstrated a compensated hemolysis, and she did not require further transfusions until she commenced chemotherapy. By the start of maintenance she had received many more PRBC transfusions than the average patient. Intermittent drops in hemoglobin (Hb) did not correlate with any particular agent, and she had stable, mild splenomegaly. A clear pattern emerged during maintenance. Her Hb was 8–9 g/dL at monthly clinic visits, when she received VCR, intermittent intrathecal methotrexate, and corticosteroids. Within 3–4 days, her Hb dropped to 5.8±0.6 g/dL, and reticulocyte count decreased from 13.4 to 4.3±0.7%. Transfusion at day 4 corrected Hb, and the reticulocytes and Hb returned to baseline. White blood cell and platelet counts did not change after VCR. Blood samples from pre, immediately post, and 4 days post VCR were analyzed and RBC characteristics and markers of hemolysis were not significantly different. Ektacytometry showed identical curves, indicating no change in RBC deformability. In vitro incubation of patient blood samples with VCR also did not affect the osmotic deformability, confirming that a change in RBC rigidity was unlikely the reason for the drop in Hb.

Conclusion: These data indicate that a dysregulation of erythropoiesis was responsible for the anemia after VCR, rather than damage of peripheral RBC's. In most patients, maintenance therapy for lymphoblastic lymphoma does not cause severe anemia, likely because a temporary reduction in erythropoiesis in patients with a normal RBC survival and low reticulocyte count is not noticed. However, in a patient with decreased RBC survival and a brisk reticulocytosis, a disruption in RBC generation is more apparent. In conclusion, VCR administration to patients with an RBC disorder warrants close observation for potentially severe VCR-induced anemia.

Poster # 077 | CLONE WARS: THE EMERGENCE OF A PHILADELPHIA-NEGATIVE CLONE IN A PHILADELPHIA-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA RELAPSE

Casey Mehrhoff, Charles Hemenway, Eugene Suh

Loyola University Medical Center, Maywood, Illinois, United States

Background: The addition of tyrosine kinase inhibitors (TKI) to conventional chemotherapy has improved outcomes for pediatric patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), however there remains an increased risk of relapse compared to other types of childhood ALL. Typically, in relapsed disease the Philadelphia chromosome persists and several mechanisms of resistance involving acquired mutations of the BCR-ABL1 chimeric oncoprotein have been reported.

Objectives: Describe a unique case of a pediatric patient with Ph+ B-precursor ALL relapsing with B-precursor ALL without the Philadelphia chromosome.

Design/Method: Case report

Results: An 8-year-old boy was diagnosed with Ph+ B-precursor ALL with the presence of the t(9;22)/BCR-ABL1 translocation by cytogenetics and fluorescence in situ hybridization (FISH), respectively. Additional abnormalities included gains of RUNX1 and loss of one copy of ETV6. A remission bone marrow with negative minimal residual disease (MRD) was achieved at the end of induction with dasatinib and the EsPhALL chemotherapy backbone. Duration of TKI therapy was two years post diagnosis. Nearly one year after the completion of therapy, cytopenias prompted a bone marrow investigation. Relapsed B-precursor ALL was established by immunophenotyping, however FISH analysis did not identify the BCR-ABL1 rearrangement. Moreover, quantitative reverse transcriptase PCR was negative for the BCR-ABL1 fusion transcript. Again FISH analysis of the bone marrow revealed multiple additional copies of RUNX1 and mono-allelic loss of ETV6, similar to the initial diagnostic sample. The patient was re-induced per AALL0232 anticipating a Ph+ ALL relapse. However, with confirmation of the loss of the Ph+ clone, TKI therapy was not re-initiated. Due to positive MRD of 3.5% at the end of re-induction therapy, the patient was salvaged with blinatumomab therapy and subsequently underwent an allogenic stem cell transplant with a sibling donor.

Conclusion: This is the first known report of a pediatric patient with Ph+ B-precursor ALL who developed recurrent B-precursor ALL without the Philadelphia chromosome. The persistent findings of gain of RUNX1 and loss of ETV6 makes

it unlikely that a second unrelated B-precursor ALL developed following successful treatment of the original disease. This case highlights the possibility of a genetically distinct subclone present at the onset of disease that shared abnormalities of RUNX1 and ETV6 but did not contain the Philadelphia chromosome. Nevertheless, the subclone harbored leukemogenic potential in the absence BCR-ABL1 expression. It is plausible that the predominant clone present at diagnosis was effectively treated with dasatinib and extinguished, but the BCR-ABL1-negative clone persisted in the face of TKI therapy.

Poster # 078 | FRESH-FROZEN PLASMA TRANSFUSION FOR REPLACEMENT THERAPY IN A CHILD WITH HYPOPLASMINOGENEMIA AND LIGNEOUS CONJUNCTIVITIS: AN ALTERNATIVE OPTION TO DELAY RECURRENCE

Hanan Nazir, Maha Mameesh, Anil Pathare

Alexandria Faculty of Medicine, Alexandria, Alexandria, Egypt

Background: Ligneous conjunctivitis is a rare form of pseudomembranous conjunctivitis that develops specifically in patients with type 1 plasminogen deficiency. Lack of plasmin activity in those patients result in defective fibrinolysis and formation of fibrin- rich membranous material/ masses that develops on the palpebral conjunctiva as well as other sites in the body.Current management involve surgical excision of the masses that is usually complicated by multiple recurrences. Recently, use of topical plasminogen concentrates helped delaying recurrence, but currently, those concentrates are not commercially available. We report on a 7-year-old Omani girl, with hypoplasminogenemia who required optimization of plasminogen level at the time of surgery to delay/ prevent recurrence.

Objectives: Case report on the peri-operative use of FFP versus cryopricipitate transfusion as an alternative replacement of plasminogen during surgical excision of ligneous conjunctivitis.

Design/Method: Pharmacokinetic study was performed to assess plasminogen recovery after FFP (15 ml/kg) and precipitate (1 bag/5kg) transfusion

Results: Plasminogen levels remained subnormal after either FFP or cryoprecipitate administration. With FFP, the maximum concentration reached was almost 50% of normal. Although half- life of plasminogen is known to be 2-2.5 days, the patient seemed to have a high catabolic rate after receiving cryoprecipitate, with plasminogen levels reaching basal levels within 4 hours. Because of the better recovery profile with FFP, we opted to give FFP before and after surgery. Peri-operative management included FFP transfusion at 20 ml/kg/12 hours one day before and for 3 days post operatively, followed by 10 ml/kg once daily from day 4–6, then 20 ml/kg on 7th post- operative day. Topical treatment was initiated using antibiotic and steroids ED on the day of surgery, followed by Heparin ED on the second day. On follow up, she used topical heparin, cyclosporine, prednisolone, and topical lubricant eye drops for variable duration. Clinical picture remained stable for almost 1 year post operatively, when she started to develop recurrence of ligneous lesions again.

Conclusion: Until topical and plasminogen concentrates are widely available, systemic use of FFP transfusion around the time of surgical excision of ligneous conjunctivitis can delay but not totally prevent recurrence.

Poster # 079 | PONATINIB USE IN PEDIATRIC/ADOLESCENT AND YOUNG ADULT PATIENTS WITH RELAPSED PH+ ALL: A CASE SERIES AND REVIEW OF THE LITERATURE

Stephanie Gruner, Hadi Sayeed, Lizmery Suarez-Ferguson, Kevin Fisher, Matthew Miller, Rayne Rouce, Rachel Rau

Baylor College of Medicine, Houston, Texas, United States

Background: Ponatinib (Inclusig®, ARIAD pharmaceutical) is a 3rd generation multi-targeted tyrosine kinase inhibitor (TKI) approved for treatment of adults with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant to or intolerant of other TKIs. Ponatinib has numerous drug-drug interactions and a black box warning for associated serious adverse vascular events and hepatotoxicity. For this reason, ponatinib use has been confined to specific high-risk populations. However, in patients who prove refractory to other therapies, the potential benefits of ponatinib may outweigh risks. To date, ponatinib has not been studied in the pediatric/adolescent and young adult (AYA) population. Furthermore, literature describing the use of ponatinib alone or in combination with other agents in pediatric oncology patients is scarce.

Objectives: To describe a single institutional experience using ponatinib in the pediatric patients with Ph+ ALL.

Design/Method: Two cases of ponatinib use in pediatric Ph+ patients resistant to other TKIs were identified at our institution and are described. Peripheral blood samples obtained from both patients identified BCR-ABL1 p190 fusion

transcripts and Sanger sequencing was used to identify resistant mutations.

Results: Our first case is a 15-year-old female who received upfront multi-agent chemotherapy plus dasatinib for Ph+ ALL. Relapse was confirmed on end-of-therapy bone marrow evaluation, thus BCR-ABL mutation testing was performed and revealed a T315I mutation. Ponatinib was initiated then discontinued after one week due to clinically significant fluid retention with peripheral edema and bilateral pleural/pericardial effusions. The second case is a late-adolescent female with Ph+ ALL who relapsed 4-years after stem cell transplant (SCT). Following relapse, TKI therapy included both imatinib and dasatinib. Due to persistence of BCR-ABL fusion transcript despite TKI therapy she was switched to ponatinib. Shortly following initiation of ponatinib she developed a diffuse, maculopapular rash, which persisted despite dose reduction, resulting in ultimate discontinuation of the drug. BCR-ABL mutation testing identified F317L and F357V resistance-conferring mutations.

Conclusion: To date, there is scant existing literature detailing the use of ponatinib in pediatric patients. Appropriate dosing is undefined and side effect profile not well described, particularly when used concurrently with other chemotherapeutic agents. Thus, this case series reporting the response to and toxicity of ponatinib in pediatric Ph+ ALL patients has important clinical implications. Additionally, this is the first report of a pediatric Ph+ ALL patient with documented T315I mutation underscoring the importance of BCR-ABL mutational testing, particularly at the time of relapse.

Poster # 080 | COMPLEXITY IN THE DIAGNOSIS OF MYOSIN HEAVY CHAIN 9-RELATED PLATELET DISORDER IN A PEDIATRIC PATIENT WITH ASYMPTOMATIC THROMBOCYTOPENIA

Dilruba Khanam, Ka Li, Rafat Ahmed, Jaya Ganesh

Cooper University Hospital, Camden, New Jersey, United States

Background: MYH9-related disorder is a rare autosomal dominant disease, encompassing several subtypes: May Hegglin anomaly, Epstein syndrome, Fechtner's syndrome, and Sebastian syndrome. Heterozygous mutations are seen in the gene encoding non-muscle myosin heavy chain IIA (NMMHC-IIA) which is involved in cell motility as well as functions to maintain cellular shape and integrity. The presentation of MYH9-RD is mainly characterized by macrothrombocytopenia, but various related expressions exist: nephritis often leading to renal failure, cataracts and sensorineural deafness (1). A 4-year-old girl with history of extensive dental caries, hyperactivity, and speech delay due to suspected hearing loss was incidentally found to have thrombocytopenia at the time of genetic evaluation. She did not have any bruising or excessive bleeding. She did not respond to observation, immunoglobulins, or steroid therapy. Her platelet count remained persistently low (4-23 K/uL). She underwent extensive evaluation to rule out platelet disorder vs. coagulation defect. Her peripheral smear showed enlarged platelets by Giemsa stain but no inclusion bodies were noted in granulocytes. Her platelet aggregation and platelet surface glycoprotein by flow cytometry were negative. Her coagulation profile was also normal.

Objectives: This case report summarizes the complexity in diagnosing MYH9-RD in a pediatric patient.

Design/Method: Since a unifying diagnosis for her clinical presentation was not apparent, whole exome sequencing (WES) was undertaken.

Results: WES revealed the R702C heterozygous pathogenic variant, located in exon 17 in the MYH9 gene. MYH9 gene alteration explained the patient's clinical features of macrothrombocytopenia and hearing loss. This mutation was paternally inherited, and her father demonstrates mosaicism. He was asymptomatic with normal platelet count but his morphology showed enlarged platelets with no inclusion bodies in granulocytes.

Conclusion: When dealing with patients who have mild or no symptoms of bleeding diathesis but evidence of persistent macrothrombocytopenia, considering a platelet disorder belonging to MYH9-RD can help delineate certain predisposing syndromes and guide clinical management. Patients are likely to benefit from early genetic testing while receiving supportive therapy. WES can highlight syndromes and provide information on recurrence risk for families. The renal and hearing abnormalities are indistinguishable between Epstein and Fechtner's syndromes, but the pathogenic variants differ (2). The genotype-phenotype correlation implies that our patient may have either syndrome, although clinical features compatible with nephritis have yet to manifest. Patients should be monitored closely for long-term progression of MYH9 disease, and treatments should be initiated accordingly. References: 1. Althaus, Transfus Med Hemother, 2010 2. Seri, Marco et al., Hum Genet, 2002

Poster # 081 | A NOVEL DE NOVO HETEROZYGOUS MUTATION IN THE PCDH17 GENE WITH MICROCEPHALY, DEVELOPMENTAL DELAY AND HISTORY OF ACUTE LYMPHOBLASTIC LEUKEMIA

Katrina Gleditsch, Renee Gardner, Yves Lacassie

Louisiana State University Health Sciences Center, Children's Hospital New Orleans, New Orleans, Louisiana, United States

Background: We present an 11-year old female evaluated by genetics at birth due to prenatal microcephaly. Chromosomes and microarray were normal. At age 3 she developed standard risk pre-B-cell acute lymphoblastic leukemia (ALL). She completed treatment in 2012 and has been doing well in the interim, remaining in complete clinical remission. During and after treatment she exhibited developmental delay and neurocognitive deficits. At age 11 her height and weight were at or below the 5th centile and head circumference was below the 2nd centile (approximately 6 standard deviations below the mean and corresponding to the 50th centile for a 9-month-old girl). Bone age was appropriate. She had a distinctive triangular face with micrognathia and a pointed nose resembling a Seckel-like syndrome. The patient also had clinodactyly of the 4th toes, zygodactylous triradius involving the 2nd and 3rd left toes, tendency to Sydney line in the right palm and a radial loop in the left middle finger.

Objectives: The patient's unique clinical presentation prompted a more thorough genetic evaluation, which led to a novel finding we feel is clinically significant with regard to the development of malignancy.

Design/Method: Whole Exome Sequencing (WES) was performed on the patient as well as her biological parents (trio).

Results: A de novo heterozygous mutation in the gene PCDH17 with potential relation to the phenotype was discovered. This c.716dupA variant causes a frameshift starting with codon Asparagine239, changing this amino acid to a Lysine residue and creating a premature stop codon at position 34 of the new reading frame denoted p.Asn239LysfsX34. This variant is predicted to cause loss of normal protein function via protein truncation or nonsense-mediated mRNA decay.

Conclusion: PCDH17 is a member of the protocadherins family which is important in cell-to-cell adhesion and synaptic function in the central nervous system and is highly expressed in areas of the brain involved in higher cortical function and speech. Aberrant expression of protocadherins has been associated with the development of malignancies in many organ systems. With regards to leukemia, the methylation status of this gene at diagnosis has been implicated in the prognosis of ALL and could be used as a biomarker to predict relapse. This patient's de novo mutation and clinical presentation are unique to what has been previously presented in the literature. We feel that this mutation is a clinically significant finding that may shed light on the role of this gene in the development of hematopoeitic malignancies.

Poster # 082 | TEENAGER WITH ATRAUMATIC COMPARTMENT SYNDROME: A RARE CASE OF ACQUIRED HEMOPHILIA A

Shreya Agarwal, Frances Flug, Burton Appel, Krupesh Patel, Fatima Elgammal

Hackensack University Medical Center, Hackensack, New Jersey, United States

Background: Acquired Hemophilia A (AHA) is an uncommon and potentially life-threatening hemorrhagic disease characterized by sudden onset of bleeding in patients with neither personal nor family history of bleeding dyscrasia. It is usually seen in adults with autoimmune diseases, solid tumors, lymphoproliferative diseases, pregnancy or during the postpartum period; occurrence in the pediatric population has rarely been reported.

Objectives: We report a case of an otherwise healthy teenager who was found to have AHA when he presented with acute onset of atraumatic soft tissue hematoma.

Design/Method: Case report and review of literature

Results: A 13-year old male of Middle Eastern descent with history of congenital absence of the right external ear, but otherwise in good general health, presented to our emergency department with a three day history of progressive worsening of right lower leg pain, swelling, and paresthesia, without preceding history of trauma. Evaluation by the pediatric orthopedics service documented significantly elevated compartment pressures, necessitating immediate four-compartment fasciotomy. Pre-operative labs were significant for prolonged activated partial thromboplastin time (APTT) of 67.7 (23.4-38.9) seconds with normal prothrombin time (PT) and international normalized ratio (INR). PTT did not correct on mixing studies, suggesting the presence of a circulating anticoagulant. Factors XII and XI were in the normal range; Factor IX was elevated, 247 (60-150). Factor VIII level was 4% and FVIII inhibitor level was 5.3 Bethesda Units (<0.8), confirming the diagnosis of AHA. Work up for autoimmune disease was negative. His bleeding and surgical hemostasis were managed with recombinant factor VII (NovoSeven) 90 mcg/kg every 3 hours for 24 hours post operatively, with gradual interval prolongation. Factor VIII antibody eradication was managed with prednisone 1 mg/kg/day. Factor VIII and inhibitor levels normalized by day 5 of hospitalization. Recombinant Factor VII was discontinued; steroids were gradually tapered and discontinued at discharge (hospital day 15).

Conclusion: Acquired hemophilia is likely an underdiagnosed condition in pediatrics. While it is typically seen in adults with underlying autoimmune disease, solid tumors, lymphoproliferative disease, or during pregnancy or the

postpartum period, pediatric cases may have no identifiable etiology. This case highlights the importance of considering this diagnosis in any patient with unexplained bleeding regardless of their age, so as to intervene early and prevent adverse consequences.

Poster # 083 | MYELOID NEOPLASMS ASSOCIATED WITH EOSINOPHILIA: A RARE PEDIATRIC ENTITY

Anand Srinivasan, Ashley Baker

University of Oklahoma, Oklahoma City, Oklahoma, United States

Background: Myeloid neoplasms associated with eosinophilia is a rare subtype of chronic leukemia characterized by clonal eosinophilia. The true incidence is unknown due to its rarity and possible classification as idiopathic hypereosinophilia syndrome. The most common chromosomal aberrations involve platelet-derived growth factor receptors (PDGFRs). We report one such rare case in a pediatric patient. Most of the pediatric management of this entity is derived from adult case reports and case series.

Objectives: To describe a case of chronic leukemia presenting as eosinophilia

Design/Method: Case report

Results: A previously healthy 15 year old Caucasian male presented with a several week history of migrating joint pain, splenomegaly, and abnormal blood counts with leukocytosis, thrombocytopenia and absolute eosinophilia. White blood cell differential showed myeloid precursors suggestive of chronic myeloid leukemia. Bone marrow evaluation showed 10% blasts and 18% eosinophils. BCR-ABL testing was negative, ruling out CML. FISH analysis for eosinophilic clonality revealed deletion of CHIC2 gene, resulting in FIP1L1/PDGFRA fusion gene, diagnostic for myeloid neoplasm with eosinophilia associated with PDGFR abnormalities. Treatment was started with tyrosine kinase inhibitor (TKI), Imatinib 100mg daily. Within 3 months, FISH analysis for fusion gene was negative. After approximately 18 months of daily Imatinib, he was switched to maintenance dose of 200mg weekly. He is approximately 36 months since diagnosis and doing well on maintenance Imatinib.

Conclusion: In 2008, the WHO revised its classification of some chronic eosinophilic leukemias to Myeloid and lymphoid neoplasms associated with eosinophilia and rearrangement of PDGFRA, PDGFRB, FGFR1. The most common abnormality is the FIP1L1/PDGFRA fusion gene. Other less common abnormalities include fusion genes KIF5B-PDGFRA and ETV6-PDGFRB and point mutations in PDGFRA22. Some features of chronic eosinophilic leukemia include absolute eosinophilia, splenomegaly, elevated Vitamin B12 and tryptase levels, and organ damage from eosinophil infiltrates and cytokine release. Patients with rearrangements or mutations involving PDGFRA are usually very responsive to Imatinib. Starting doses have not been well studied or established. Experts recommend co-administration of corticosteroids during the first few days of Imatinib therapy in patients with a history of cardiac involvement and/or elevated serum troponin levels to prevent myocardial necrosis, a rare complication of Imatinib therapy in eosinophilic patients. Fortunately our patient did not have cardiac involvement and to date has not exhibited signs of chronic TKI toxicity. Conclusion: Myeloid neoplasms with eosinophilia constitute a rare form of chronic leukemias. They are often associated with PDGFR abnormalities and are usually very responsive to tyrosine kinase inhibitor therapy.

Poster # 084 | NOVEL SAMD9L MUTATION IN A PATIENT WITH PANCYTOPENIA, IMMUNE DYSFUNCTION, AND MONOSOMY 7 MYELODYSPLASTIC SYNDROME

Rebecca Ortolano, Kenneth Lieuw

Walter Reed National Military Medical Center, Bethesda, Maryland, United States

Background: Germline SAMD9L mutation is a rare cause of constitutional bone marrow failure with a unique propensity for clonal evolution to monosomy 7 and MDS.

Objectives: Previous case series have demonstrated diverse clinical outcomes in patients with a germline SAMD9L mutation. Our case presents a novel SAMD9L mutation (p.Val1551Leu). Additionally, the case highlights the challenges in clinical decision making for a patient with a gene mutation that is known for clonal evolution towards monosomy 7 with risk of progression to myeloid malignancy, but also known for self-correction through uniparental disomy or inactivating mutations which results in disease remission.

Design/Method: A retrospective chart review and review of the literature was performed. DNA was isolated from peripheral blood and used for whole exome sequencing. A peripheral blood sample from the patient's mother and father showed no SAMD9L mutation. Skin biopsies of the patient and parents were evaluated for uniparental disomy or new mutations. To determine the pathogenicity of this novel mutation, the specific SAMD9L mutant DNA was transfected into the 293human embryonic kidney cell line to assess its role in inhibiting cell proliferation.

Results: Our patient presented at 8 months of age with pancytopenia and hypocellular bone marrow in the setting of

sepsis. He had evidence of dysfunctional immune activation with hemophagocytosis and elevated soluble IL2 with simultaneous severe hypogammaglobulinemia. Analysis of the peripheral blood showed no increase in chromosomal breakage, normal telomere length, and normal flow cytometry. Gene testing for primary hemophagocytic lymphohistiocytosis and inherited bone marrow failure were negative. After the patient recovered from his presenting illness, a repeat bone marrow biopsy demonstrated improved cellularity with myelodysplasia and cytogenetics significant for monsomy 7.Whole exome testing demonstrated a novel SAMD9L mutation. The patient continued to require intermittent IVIG and failed to demonstrate appropriate leukocytosis with intermittent infections. On repeat bone marrow evaluation over the course of 9 months, the patient demonstrated no evidence of evolution towards self-correction and had a persistent monosomy 7 clone. The patient is scheduled to undergo a matched unrelated donor bone marrow transplant.

Conclusion: Our case highlights the unique clinical picture associated with constitutional marrow failure and clonal evolution secondary to a novel SAMD9L mutation which is thought to cause pancytopenia by inhibiting cellular proliferation and often results in the development of monosomy 7 which rescues hematopoiesis but with a risk for malignancy.

Poster # 085 | SUCCESSFUL TREATMENT WITH BORTEZOMIB, PANOBINOSTAT, AND DEXAMETHASONE OF ACUTE MYELOID LEUKEMIA (AML) IN 2ND RELAPSE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (SCT): THERAPY SELECTED BASED UPON RESULTS OF A PERSONALIZED FLOW CYTOMETRIC SCREEN FOR DRUG SENSITIVITY

Deborah Schiff, Eric Anderson, William Roberts, Peter Quinzio, Sacha Prashad, Diane Heiser, Stephen Western

University of California San Diego, San Diego, California, United States

Background: Notable Labs developed a flow cytometric-based assay with a custom robotic platform to test FDA-approved drugs for anti-cancer activity against individual patient's tumor cells. This personalized assay is a potential method for identifying novel agents and drug combinations to treat AML patients who have failed standard therapies.

Objectives: To present the case of a teen who underwent successful treatment of relapsed AML post-SCT with bortezomib, panobinostat, and dexamethasone—a regimen selected based upon results of Notable Lab testing.

Design/Method: Case report.

Results: A 15-year-old male with M4-AML had an isolated bone marrow relapse 8 months after completion of scheduled therapy. At relapse, his AML was FLT3-ITD positive. He achieved a second remission with negative MRD and underwent matched sibling donor BMT after busulfan/cyclophosphamide conditioning. BMA performed on day +180 was MRD positive (0.13%). Repeat BMA done on day +204 showed 5.7% MRD. He started sorafenib on day +212. He received donor lymphocyte infusion (DLI) on day +246, then received 2 cycles of azacitadine (AZA) followed by DLI. Marrow MRD by flow after sorafenib alone, sorafenib with DLI, and sorafenib with AZA/DLI were 16%, 15.7%, and 0.16%, respectively. Treatment was complicated by varicella meningitis, grade I skin aGVHD, febrile neutropenia and C. difficile colitis, and metapneumovirus pneumonia. Despite extremely low levels of leukemia (marrow MRD 0.16%), Notable Lab testing performed on the patient's leukemia cells from marrow collected after AZA/DLI/sorafenib revealed sensitivity of his leukemic blasts to a combination of bortezomib, panobinostat, and dexamethasone. Because of prolonged cytopenias, multiple infectious complications, and persistently positive MRD, he discontinued AZA/DLI/sorafenib and on day +368 started bortezomib 1.3 mg/m2 IV on days 1, 4, 8, and 9; panobinostat 20 mg po on days 1, 3, 5, 8, 10, 12; and dexamethasone 20 mg po on days 1, 2, 4, 5, 8, 9, 11, and 12. Chemotherapy cycle 2 started 21 days later. He tolerated treatment without side effects and with resolution of rash and cytopenias. He achieved full donor chimerism, negative FLT3-ITD, and complete remission by morphology and flow after two cycles.

Conclusion: Notable Lab testing is a powerful tool for evaluating the sensitivity of small populations of leukemic blasts to novel drug therapy. Results from Notable Lab testing may serve as a useful guide for treatment selection after failure of standard AML therapy. This patient achieved morphologic and MRD remission post-SCT with bortezomib, panobinostat, and dexamethasone—a regimen predicted to be efficacious based upon Notable Lab results.

Poster # 086 | SUCCESSFUL IMMUNE TOLERANCE IN FACTOR IX DEFICIENCY PATIENTS WITH CYCLOPHOSPHAMIDE AND RITUXIMAB

Maria Ahmad-Nabi, Christine Knoll, Sanjay Shah, Esteban Gomez, Lori Wagner

Phoenix Children's Hospital, Phoenix, Arizona, United States

Background: Development of inhibitors in patients with factor IX deficiency (FIXD) is a well-recognized complication occurring in 1–3% of patients. Within this subset a small percentage can develop anaphylaxis to factor. Desensitization with cyclophosphamide, an alkylating agent used in the management of various oncologic malignancies, and reported for use in factor VIII desensitization has been previously unreported for use in desensitization in patients with FIXD. Rituximab, an anti-CD 20 antibody, however has been used.

Objectives: To induce immune tolerance (IT) in patients with inhibitors to factor IX with either novel or under reported methods using cyclophosphamide and/or rituximab.

Design/Method: We report a case series of 2 patients at Phoenix Children's Hospital with FIXD who achieved IT with cyclophosphamide and/or rituximab.

Results: Patient one was a 14 year old male with severe FIXD, who at the time of desensitization had inhibitor levels of 12 BU. He was desensitized with cyclophosphamide, then admitted for infusion of recombinant factor IX. He experienced a few minor symptoms of intolerance including an urticarial rash which was self-limited, and hemarthrosis of the right elbow on day 1 which responded to novo 7. He tolerated the remainder of his infusion without issues. He continued recombinant factor IX daily, and returned to clinic for monthly cyclophosphamide for 6 months. He did develop urticaria with hemarthrosis and spontaneous muscle bleeds which were tempered with zantac, zyrtec, solumedrol, and benadryl. He remained without a recurrence of inhibitors, however did have intermittent hemarthrosis of his ankles thereafter requiring prophylactic twice daily dosing recombinant factor IX. Patient two was a 10 year old male with severe FIXD and a family history of anaphylaxis to factor causing early death in all male relatives with the disease. He had never received Factor IX and did not have a detectable inhibitor prior to desensitization. He successfully underwent desensitization to recombinant factor IX with rituximab in the ICU, and returned to clinic for weekly infusions x 4. He experienced no adverse reactions concerning for anaphylaxis. He continued to tolerate factor IX products without evidence of intolerance, development of inhibitors, and continues on as prophylactic dosing of recombinant factor IX every other day.

Conclusion: Our experience at a single institution proves cyclophosphamide as a novel agent for inducing IT in those with FIXD and anaphylaxis. It also provides further evidence that rituximab can desensitize patients with severe FIXD. Differences include longer duration for cyclophosphamide therapy (6 months vs 1 month).

Poster # 087 | RITUXIMAB FOR ADVANCED BURKITT LYMPHOMA IN A PATIENT WITH DEFECTIVE CELL MEDIATED IMMUNITY DUE TO CARTILAGE-HAIR HYPOPLASIA (CHH)

Reuben Antony, Josue Flores, Beth Speckhart, Eric Bugaieski, Karen Fernandez

Valley Children's Healthcare, Madera, California, United States

Background: Cartilage-hair hypoplasia (CHH) is an autosomal recessive chondrodysplasia associated with defective cell-mediated immunity caused by mutations in the ribonuclease mitochondrial RNA processing (RMRP) gene. Cancer incidence is 7-fold higher in patients with CHH than in the general population, especially non-Hodgkin lymphoma. The use of Rituximab, an anti CD20 antibody, results in decreased host B-cell number and impaired humoral function for 6–9 months. The safety of Rituximab in pediatric patients with cancer and immunodeficiency is not well documented. A diagnosis of underlying immunodeficiency may discourage physicians from using Rituximab due to the risk of severe bacterial infection or viral re-activation.

Objectives: To report a case of Burkitt lymphoma in a young adult female with CHH and defective cellular immunity successfully treated with Rituximab.

Design/Method: Case Report

Results: An 18-year old Amish female with disproportionate short stature presented to our center for management of stage IV biopsy proven Burkitt lymphoma with Myc rearrangement. She had presented a week earlier with cervical, occipital, and submandibular lymphadenopathy, splenomegaly; fevers, night sweats, and weight loss for 2–4 weeks. On exam, her height was three feet associated with brachydactyly, mild bowing of the legs, normal size head without frontal bossing, fine and sparse hair. She had normal intelligence. Her pattern of dysmorphisms was suggestive of CHH (genetic testing not performed at time of diagnosis). PET-CT scan showed stage IV disease with involvement of cervical lymph nodes, spleen, iliac bone and bone marrow. Treatment with standard-intensity FAB/LMB therapy (group C) with the addition of Rituximab was initiated. She had an incomplete response to COP (~80% reduction of tumoral masses) but achieved complete remission after COPADAM1. Her course was complicated with severe varicella zoster but she completed therapy and remains in complete disease remission for 24 months after treatment completion. Genetic testing subsequently performed proved homozygosity for CHH with a n.71A>G variant. She had no other opportunistic infections during or after therapy.

Conclusion: The use of Rituximab was both safe and beneficial in our patient despite defective cell mediated immunity secondary to CHH suggesting that Rituximab may be safe to use in patients with cellular immune deficiencies.

Poster # 088 | CONCURRENT LYME DISEASE SIGNIFICALLY IMPAIRS HEALING IN HEMOPHILIA HEMARTHROSIS

Lisa Maurer, Jillian Lapinski, James Cooper, Cheryl McShea, Frederico Xavier

Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, United States

Background: Hemophilia A and B are bleeding disorders characterized by deficiency in factor VIII or IX, respectively. Spontaneous or provoked hemarthrosis is a known complication of hemophilia. Repetitive episodes of hemarthrosis can lead to debilitating hemophilic arthropathy. Lyme disease is a tick-born infection which is endemic to increasing parts of the United States. Chronic Lyme disease, the phase in which Lyme arthritis typically develops, occurs months to years after initial infection and is characterized by swelling of one or more large joints generally in the absence of systemic symptoms.

Objectives: Review cases of hemophilia A and B patients with episodes of provoked hemarthrosis refractory to intensive recombinant factor replacement therapy found to have concurrent Lyme arthritis.

Design/Method: We report two clinical cases and review relevant literature.

Results: First, we report a 12 year-old male with moderate hemophilia A with a provoked knee hemarthrosis which failed to improve despite 3 months of intense factor replacement therapy requiring multiple hospitalizations. Factor replacement regimens included twice daily standard half-life recombinant factor VIII products or daily to every other day extended half-life recombinant factor VIII products with trough levels aimed as high as 50–80%. Factor VIII PK studies were obtained for dosing, to confirm adherence, and to evaluate for subclinical inhibitors (inhibitor testing was negative). Given protracted symptoms additional work-up for hemarthrosis was pursed. Lyme titers were positive for (8)IgG, though negative for IgM. He was treated with 28 days of doxycycline during which time hemarthrosis greatly improved on examination and imaging, and he was able to recover function through physical therapy. Second, we report a 6 year-old male with moderate hemophilia B who required multiple hospital admissions for a provoked knee hemarthrosis with no improvement in symptoms despite weeks of daily or twice daily factor replacement with standard half-life recombinant factor IX products aiming for 100% correction. We performed inhibitor testing (which was negative) and PK studies to assess for non-detectable inhibitors, dosing and adherence. Lyme testing was positive for (6)IgG, though negative for IgM. He was treated with amoxicillin for 28 days during which time hemarthrosis significantly improved on examination and imaging. Diagnosis and follow-up imaging studies for both patients included MRI and serial bedside ultrasounds performed as per UC San Diego School of Medicine MSKUS guidelines.

Conclusion: Concurrent Lyme arthritis should be considered for patients with hemophilia A or B who live in Lyme endemic areas with refractory hemarthrosis despite intensive medical management.

Poster # 089 | LONG TERM REMISSION WITH TOPOTECAN, VINORELBINE, THIOTEPA, AND CLOFARABINE (TVTC) FOR RE-INDUCTION FOLLOWED BY MAINTENANCE THERAPY WITH VENETOCLAX IN A YOUNG ADULT PATIENT WITH AML THAT RELAPSED POST TRANSPLANT

Mark Shamoun, Sung Choi, Julia Brown, Qing Li, Rama Jasty Rao

University of Michigan, Ann Arbor, Michigan, United States

Background: Relapse/refractory AML following allogeneic hematopoietic stem cell transplant (HSCT) holds a high mortality rate. Current relapse/refractory therapy modalities for younger patients may include re-induction with a clofarabine-based regimen followed by second allogeneic HSCT. Even for patients who undergo second HSCT, the five-year survival rate is dismal. New therapies, including small molecule inhibitors, are being studied in the post-HSCT relapse setting or those unfit for HSCT with promising results. Venetoclax is a small molecule inhibitor that has received breakthrough designation for AML treatment in elderly patients

Objectives: To report a young adult AML patient with relapse post HSCT who was successfully re-induced with topotecan, vinorelbine, thiotepa, clofarabine (TVTC) and has sustained remission with venetoclax maintenance therapy. This approach appears to be unique in terms of reported literature.

Design/Method: Case Report

Results: Our patient is now a 23-year-old female noted to have MLL rearranged AML at initial diagnosis when she was 21 years old. She underwent chemotherapy consisting of cytarabine/daunorubicin according to standard 7+3. Due to persistent disease, she was re-induced with G-CSF, clofarabine, and high-dose cytarabine (GCLAC) which put her in CR. Her course was complicated by sepsis, colitis, gastrointestinal bleed, deep venous thrombosis, and transfusion-associated circulatory overload. Given her co-morbidities, she received another cycle of clofarabine/cytarabine, and then proceeded to reduced intensity allogeneic HSCT, according to BMT CTN 1101. The patient tolerated HSCT well and experienced no transplant-related complications, including no acute or chronic GVHD. Unfortunately, she relapsed about 10 month's post-HSCT. Initial salvage therapy consisted of another course of G-CLAC, but due to persistent disease the decision was made to re-induce her with topotecan, vinorelbine, thiotepa, and clofarabine (TVTC). During this time however, she was found to have extensive infection with a fusarium species requiring a course of anti-fungal therapy. Bone marrow evaluation showed no residual disease with an MRD of <0.1%. Once the absolute neutrophil count recovered, the patient was started on single-agent venetoclax for maintenance therapy, which has been well-tolerated. She remains in morphologic remission for over 8 months.

Conclusion: We describe herein a young adult with multiply relapsed AML wherein TVTC re-induction, followed by maintenance with venetoclax were safely used in the post-HSCT setting. Venetoclax therapy in the relapsed AML setting warrants further study.

Poster # 090 | DIAGNOSING VITAMIN B12 DEFICIENCY ANEMIA IN A CHILD WITH A COMPLEX HEMATOLOGICAL PRESENTATION

Kari Galipp, Anand Srinivasan, William Kern, Arpan Sinha

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States

Background: Vitamin B12 deficiency is uncommon in children in developed countries, especially in the absence of risk factors like malabsorption or inadequate dietary intake. It often presents with non-specific symptoms and signs and can elude diagnosis. The recognition and treatment of vitamin B12 deficiency is critical as it can lead to bone marrow failure as well as severe neurological and developmental problems in children.

Objectives: To increase index of suspicion of Vitamin B12 deficiency anemia in children. We report a rare case of Vitamin B12 deficiency anemia in a child who presented with a severe macrocytic anemia, with signs of hemolysis and concern of malignancy.

Design/Method: An almost three-year-old previously healthy girl presented with a few day history of fever, emesis, fatigue and pallor. She had no dysmorphic features, hepatosplenomegaly or lymphadenopathy on exam, growth and development were normal. Laboratory findings showed severe macrocytic anemia (hemoglobin 4.4 grams/dL; MCV 104.1 fL) with reticulocytopenia. Signs of intravascular hemolysis were present with elevated lactate dehydrogenase (3,842 units/L) and haptoglobin below assay limit. Immune-mediated hemolysis was ruled out. Initial picture of a hemolytic anemia was compounded by other findings of moderate neutropenia, mild thrombocytopenia and peripheral smear showing occasional blasts. Further workup was done with a broad differential diagnosis that included leukemias, hemolytic anemias, bone marrow failure syndromes, and specific deficiencies.

Results: Workup revealed abnormally low Vitamin B12 levels along with significantly elevated homocysteine and methylmalonic acid levels indicating functional Vitamin B12 deficiency. Bone marrow evaluation showed megaloblastic anemia and dyserythropoiesis consistent with Vitamin B12 deficiency, and ruled out leukemia. Vitamin B12 deficiency can cause a hemolytic anemia like picture secondary to intramedullary hemolysis due to ineffective erythropoiesis. Myeloid precursors are also affected which can lead to neutropenia, thrombocytopenia, and abnormal peripheral blood cells. In our patient, initial symptomatic anemia was treated with blood transfusion, followed by intramuscular Vitamin B12 injections with normalizing lab values. So far, workup for an etiology for Vitamin B12 deficiency is negative except for an equivocal range of anti-parietal cell antibodies raising concerns for pernicious anemia; however it is rare in this age group. Another rare condition is an inborn error of the cobalamin transporter. She is currently on oral Vitamin B12 supplementation and further workup will be planned based on response.

Conclusion: This case highlights the importance of early consideration and thorough evaluation of Vitamin B12 deficiency in children with unclear etiology of anemia, so that prompt treatment can be initiated.

Poster # 091 | MULTIPLE SITES OF EXTRAMEDULLARY RELAPSE ON BLINATUMOMAB: A PEDIATRIC CASE REPORT

Simone Chang, Daniel Ortiz, Julio Barredo

Jackson Memorial Hospital/ University of Miami, Miami, Florida, United States

Background: Despite great success in the treatment of Acute Lymphoblastic Leukemia (ALL), the outcomes for patients with relapsed ALL remain poor. Prognostic indicators include timing and site of relapse. Blinatumomab, is the first agent in its class that simultaneously binds CD3- positive cytotoxic T cells to CD19- positive B cells resulting in lysis of malignant cells. However, mechanisms of leukemia resistance to blinatumomab are unclear.

Objectives: To describe a case with multiple sites of extramedullary (EM) relapse during Blinatumomab therapy.

Design/Method: Case Report

Results: A 9-year-old Hispanic male with Philadelphia positive, CD19-positive B-precursor cell ALL refractory to chemotherapy, had failed a bone marrow (BM) and was placed on blinatumomab and imatinib. He achieved minimal residual disease (MRD)-negative systemic remission, but during his fifth cycle developed bilateral periorbital masses. Biopsies confirmed CD19-negative isolated EM relapsed disease, which was treated with radiation therapy (RT). There was notable resolution of EM disease and he continued systemic therapy. Subsequently, he presented with a painful left scapular swelling. Imaging showed muscle and lung parenchymal EM relapse with CD19-positivity confirmed on histology. He continued on blinatumomab with localized RT while awaiting CAR-T cell therapy. His BM MRD remained negative until he developed systemic MRD-positivity with CD19-positive blasts following the sixth cycle. Primary resistance to blinatumomab is poorly understood. It is proposed that expansion of CD19-negative clones or downregulation of CD19 following blinatumomab may play a role. This was observed in our patient's periorbital relapse; but subsequent EM and systemic relapses were CD19-positive, consistent with the co-existence of multiple clones in relapsed ALL. It has also been postulated that EM relapse could be linked to the failure of blinatumomab or T cells to migrate to EM sites of disease or drug inactivation by the microenvironment. The second EM relapse in our patient, with CD19-positive disease suggests this as a possible mechanism of relapse. This was reported in patients with CD19 positive Non-Hodgkin Lymphoma (NHL), and higher doses of blinatumomab however, have shown promising results in this population.

Conclusion: Despite blinatumomab's effectiveness in inducing remissions in patients with refractory/relapsed ALL, it appears to have limitations in patients with EM disease. These may arise either from the multiclonality associated with relapsed ALL or due to the emergence of resistance to blinatumomab, including failure to migrate to EM sites.

Poster # 092 | CASE REPORT: CYCLIC NEUTROPENIA AND ASSOCIATED AMYLOIDOSIS

Kari Galipp, Chibuzo Ilonze, Kruti Shah, Ankur Rughani, Stephen Travis, Anjali Nayak, Teresa Scordino, William Kern, Klaas Wierenga, William Meyer

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States

Background: Cyclic neutropenia is a rare hereditary disorder, characterized by recurrent neutropenia, cycling at about 3 week intervals, with variable associated symptoms including oral ulcers and fever. There are 4 reported cases of cyclic neutropenia associated with chronic inflammation leading to development of reactive AA amyloidosis. One patient also presented with amyloid goiter.

Objectives: We report a new case of cyclic neutropenia with associated renal and thyroid amyloid.

Design/Method: A 12-year-old female presented with a 1 month history of thyromegaly, and recurrent aphthous ulcers associated with fevers. Laboratory workup showed severe neutropenia, anemia, azotemia, and abnormal thyroid function, with an absolute neutrophil count - 0/μL, hemoglobin - 9.0 g/dL, serum creatinine - 1.89 mg/dL, and uric acid - 9.0 mg/dL. Thyroid stimulating hormone was elevated - 12.5 μIU/mL, and normal free T4. Urinalysis showed 2+ protein, 2+ blood, and 5–10 urine red blood cells/hpf. Chest radiograph showed mild narrowing of the trachea from thyroid compression. Bone marrow biopsy showed a hypocellular marrow, with tri-lineage hematopoiesis, left shifted myeloid maturation with very rare mature neutrophils. Both renal biopsy and thyroid fine needle aspiration revealed abundant amyloid. Of note, her father had AA amyloidosis, resulting in end-stage renal disease (ESRD) requiring hemodialysis, and recurrent aphthous ulcers. The family history suggested a familial predisposition. Genetic testing revealed a pathogenic ELANE c.358 A>T gene mutation with autosomal dominant inheritance confirming the diagnosis of cyclic neutropenia. We treated our patient with daily granulocyte colony stimulating factor to reduce the burden of chronic inflammation induced by cyclic neutropenia, and to preserve renal and other end organ function affected by further amyloid deposition.

Results: Proband with ELANE gene mutation positive cyclic neutropenia, amyloidosis of thyroid and kidney, with a positive paternal history of AA amyloidosis resulting in ESRD.

Conclusion: Cyclic neutropenia may result in chronic inflammatory states leading to secondary amyloidosis.

Poster # 093 | COMMON VIRUS OR RETURN OF MALIGNANCY? ADENOVIRUS IN A PATIENT WITH BURKITT LYMPHOMA

Samantha Wilson, Dava Piecoro, Caryn Sorge

University of Kentucky, Lexington, Kentucky, United States

Background: Overall survival of Burkitt Lymphoma (BL), regardless of stage, is greater than 85% in the pediatric population when treated with multi-agent chemotherapy. Adenovirus is a common, usually self-limited infection within the pediatric population; however, findings can vary within an immunocompromised host. Hepatitis is a rare complication, with very few reports of radiologic findings in this patient population.

Objectives: We discuss a three year old male with history of BL who presented with clinical and radiographic evidence of relapse but was found to have adenovirus hepatitis.

Design/Method: A case report of a patient with BL in complete remission after completion of standard of care chemotherapy, who presented with return of high fever, elevated LDH, transaminitis and hepatic lesions. We describe the hepatic imaging and pathology consistent with adenovirus hepatitis in this immunocompromised host.

Results: Our patient presented at three years old with a six week history of worsening abdominal pain and fevers. He was found to have a right sided pleural effusion, multiple lesions of the liver, and diffuse abdominal lymphadenopathy; biopsy of lymph tissue was consistent with BL. He completed therapy per ANHL1131 arm B and was in a complete remission at the end of planned therapy. One month after completion of therapy, he returned with high fever, abdominal pain and transaminitis, similar to his initial presentation. CT scan showed multiple hypodense discrete lesions throughout the liver and re-accumulation of right sided pleural effusion. LDH peaked at 3580 U/L (ULN 370 U/L). Uric acid remained within normal limits. Bilirubin peaked at 4.0 mg/dL, conjugated 3.2mg/dL. Liver biopsy was performed, showing smudgy nuclei with immunohistochemical staining positive for adenovirus. There was no evidence of lymphomatous involvement. Resolution of hepatic lesions and transaminitis, with normalization of LDH and fever, occurred with symptomatic treatment alone.

Conclusion: Adenovirus is known to cause systemic disease in immunocompromised patients and rarely hepatitis. No pediatric patients with discrete hepatic lesions secondary to adenovirus have been reported in the literature. Three cases of discrete hepatic lesions have been reported in adult immunocompromised patients, two with fatal fulminant liver failure and one who required cidofovir. This case demonstrates that a common pediatric viral infection can present with lesions concerning for metastatic disease in a pediatric lymphoma patient. Prompt diagnosis is vital in the management of these patients when recurrent lymphoma is in the differential.

Poster # 094 | A CHALLENGING CASE OF HEPARIN INDUCED THROMBOCYTOPENIA IN A CRITICALLY ILL PEDIATRIC PATIENT AND NEED FOR ALTERNATIVE ANTI-COAGULATION

Manuel Izquierdo, Sruthipriya Sridhar, Hunter Johnson, Andrea Whitfield

Brody School of Medicine at East Carolina University / Vidant Medical Center, Greenville, North Carolina, United States

Background: Heparin induced thrombocytopenia (HIT) is an immunologic process in which antibodies bind a heparin complex and cause a paradoxical hypercoagulable state. Ramifications of this process may include a multitude of thrombotic events and bleeding complications secondary to platelet consumption. In our patient, HIT manifested as increased bruising, an acute decrease in platelet count, and continual clotting of her CRRT circuit. HIT, although rare in pediatrics, should be included in the differential for children with thrombocytopenia who have received heparin products.

Objectives: To present a unique case report of a critically ill pediatric patient who developed HIT in the presence of multiorgan system failure and to discuss the challenges encountered with identification of an alternative anti-coagulant.

Design/Method: Chart review and case presentation.

Results: A 12yo obese, Caucasian female child presented to our facility with bilateral pulmonary emboli (of unclear etiology). Initially, she was started on a continuous heparin infusion, but was transitioned to enoxaparin within 3 days without issue. Five days after enoxaparin was initiated, the patient developed acute kidney injury (evidenced by increasing creatinine) attributable to her biventricular heart failure. Due to her need for continuous renal replacement therapy (CRRT), she was transitioned back to a continuous heparin infusion. Whereas her initial platelet count on transition was normal, she developed severe thrombocytopenia (15,000uL) within 48 hours. Due to intermediate risk but low suspicion for HIT, PF4 antibodies were sent which were positive. After much discussion, she was transitioned to an argatroban infusion which was titrated according to PTT levels. Within 48 hours, her platelet count normalized. At discharge, she was prescribed apixaban for anti-coagulant management.

Conclusion: HIT is an uncommon presentation in the pediatric population. Given its rarity, there is often a delay in diagnosis which increases risk of complications such as bleeding, stroke, and limb ischemia. Even if the diagnosis is suspected or proven, there may be challenges in initiating alternative agents as limited data exists on pediatric options. As argatroban remains the treatment of choice for patients with HIT, experience in pediatric patients is limited, and dosing recommendations have been extrapolated from adult studies. Anecdotal data exists for use of bivalirudin in children, although studies, primarily, focus on use in specific cardiac cases. In our patient's case, choice was further complicated by renal failure. This case study highlights the need for further research regarding the identification of a secondary anti-coagulant agent for use in pediatric patients with HIT.

Poster # 095 | CYTOKINE RELEASE SYNDROME AS A COMPLICATION OF SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA THERAPY

Hannah Lust, Gina Ney, Mark Shamoun, Rajen Mody, Rama Jasty Rao

University of Michigan, Ann Arbor, Michigan, United States

Background: Subcutaneous panniculitis-like T-cell lymphoma (SPTL) is a rare form of non-Hodgkin's lymphoma characterized by infiltration of cytotoxic T-cells into subcutaneous tissue. SPTL occurs in both adults and children and can present in both patient populations as either alpha/beta or gamma/delta subtypes. Patients with the gamma-delta phenotype have an overall poorer survival, although the exact etiology is unclear. Interestingly, both subtypes of SPTL can present with secondary hemophagocytic lymphohistiocytosis (HLH), and this is associated with a worse prognosis. Currently, there are no standardized treatment protocols for SPTL, and clinical management includes watchful waiting, corticosteroids/immunosuppression, chemotherapy, and stem cell transplant.

Objectives: The primary objective was to compare how two patients with the same diagnosis responded acutely to therapy.

Design/Method: We performed a retrospective chart review of two pediatric patients at our institution who were diagnosed with alpha/beta SPTL and secondary HLH. We examined each presentation, treatment course, and outcome. We then completed a brief review of the current literature describing treatment of and outcomes for SPTL with secondary HLH.

Results: These two patients presented in a similar manner with signs and symptoms of HLH. Each was then subsequently diagnosed with alpha/beta SPTL after biopsy of cutaneous nodules and each had diffuse disease, as measured by PET. However, they demonstrated vastly different acute responses to therapy. One patient was pre-treated with systemic glucocorticoids before receiving definitive chemotherapy and tolerated therapy well as an outpatient. The other patient started systemic chemotherapy without steroid pretreatment and developed severe cytokine storm characterized by hypotension, cardiac dysfunction, multi-organ failure and cytokine elevation. Both patients achieved complete remission (CR) after treatment with CHOP chemotherapy and remain disease-free 12–24 months off therapy.

Conclusion: In patients presenting with SPTL and secondary HLH, we propose that initial treatment with anti-inflammatory or anti-cytokine therapy can decrease, or even prevent, the possibility of life threatening cytokine release as a result of cytotoxic chemotherapy.

Poster # 096 | THE NOVEL USE OF DEFEROXAMINE IN A NEONATE WITH CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE II

Heather Bernard, Allison Close, Sarita Joshi, Kelly Bailey, Karin Potoka, Randy Windreich

Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, United States

Background: Congenital Dyserythropoietic Anemia Type II (CDA II) is a rare autosomal recessive disorder, rarely presenting in the neonatal period. Iron overload often occurs as a late sequela of ineffective erythropoiesis and intramedullary hemolysis.

Objectives: To report the novel use of iron chelation in an infant with CDA II associated with severe iron overload.

Design/Method: The patient is a 3-month-old, former 27-week infant with prenatal non-immune hydrops and transfusion-dependent fetal anemia who presented with persistent anemia, reticulocytopenia, hyperbilirubinemia, liver dysfunction, and hyperferritinemia. His initial ferritin was 4822.3 ng/ml, TIBC 185 ug/dL, and transferrin 116 mg/dL. His bone marrow biopsy showed trilineage hematopoiesis and erythroid dyspoiesis characterized by binucleation of late-stage precursors. Genetic testing revealed a compound heterozygous missense mutation and splice site mutation in the SEC23B gene, confirming the diagnosis of CDA II. Initial liver biopsy revealed mild portal fibrous expansion, and abundant hepatic iron deposition. His ferritin continued to increase, peaking at 21,114 ng/ml, along with liver

enzymes peaking at an alanine aminotransferase (ALT) of 505 U/L and aspartate aminotransferase (AST) of 776 U/L. FerriScan showed an elevated estimated liver concentration of 2.8 mg/g dry tissue. Repeat liver biopsy 3 months later showed giant cell hepatitis with worsening mild portal fibrosis and hemosiderosis. Additionally, tissue liver iron concentration was 4755 mcg/g dry weight. Cardiac T2* MRI revealed mild cardiac iron deposition. Given his significant degree of iron overload, Deferoxamine was used to reduce hemosiderosis and liver morbidity in preparation for bone marrow transplantation.

Results: The patient received Deferoxamine 15 mg/kg/day IV x 5 days/week for three months, without any clinically significant adverse events. Blood counts and hepatic and renal function were monitored weekly without any abnormalities. Growth parameters and liver enzymes significantly improved while receiving chelation therapy. As a non-invasive, cost-effective method, serum ferritin levels were monitored monthly to gauge response to treatment. Despite receiving blood transfusions every 3–4 weeks, serum ferritin decreased to 344 ng/ml and liver enzymes decreased to ALT 29 U/L and AST 26 U/L prior to bone marrow transplantation.

Conclusion: We report the use of Deferoxamine in a patient with CDA II less than 2 years of age, for treatment of iron overload. Our patient tolerated Deferoxamine well without significant adverse events or organ toxicity. Deferoxamine may be a well-tolerated method of reducing iron burden in young patients with iron-loading pathologies.

Poster # 097 | PERITONEAL DISSEMINATION OF BRAF FUSION POSITIVE HIGH GRADE NEUROEPITHELIAL TUMORS IN A CHILD WITH A VENTRICULO-PERITONEAL SHUNT PLACED FOR A BRAF-FUSION POSITIVE LOW GRADE GLIOMA

Shanna White, Sarah Bach, Jason Chiang, Julian Lin, John Lucas, Jr, Ibrahim Qaddoumi, Charles Aprahamian, Chibuzo O'Suoji, Jaime Libes

University of Illinois College of Medicine at Peoria, Peoria, Illinois, United States

Background: Low grade gliomas with KIAA-1549-BRAF fusions typically have a favorable prognosis with infrequent rates of high grade transformation, low rates of metastasis and even lower rates of extra CNS metastasis. While high-grade transformation has been reported for tumors with BRAF V600E mutations and CDKN2A deletions, it has not been previously reported in gliomas with KIAA-1549-BRAF fusions. While there are case reports of high-grade CNS malignancies metastasizing through a ventriculo-peritoneal (VP) shunt, low-grade gliomas metastasizing in this manner are extremely rare.

Objectives: To describe a unique case of peritoneal tumor dissemination of a BRAF fusion positive high grade neuroepithelial tumor in a child with a VP shunt placed for multifocal BRAF fusion positive low grade astrocytomas

Design/Method: Case Report

Results: An eight-year-old male was initially diagnosed with multifocal low-grade astrocytomas of the hypothalamus and C2-C4 spinal cord. Initial testing revealed the KIAA-1549-BRAF fusion, but no CDKN2A or BRAF V600E mutation. Initial surgical management included a VP shunt and resection of the cervical spinal lesion. He received Vincristine and Carboplatin, followed by transition to Vinblastine given new thoracic metastatic lesions after 10 months of therapy. At 15 months after diagnosis, scans were concerning for diffuse leptomeningeal progressive disease and new intracranial lesions, necessitating craniospinal radiation. Following a near CR, he presented 13 months later with acute onset of abdominal pain. A CT scan revealed peri-renal and perirectal soft tissue masses, confirmed by exploratory laparotomy to be peritoneal tumor dissemination of high grade neuroepithelial tumor. A KIAA1549-BRAF fusion was noted and confirmed by RT-PCR, identical to that seen in the original CNS tumors. Additional findings included deletion of chromosome 1p (without 19q loss) and heterozygous and homozygous deletion of CDKN2A found by FISH. Brisk mitotic activity justified a high-grade designation. Salvage chemotherapy consisted of 4 cycles of ICE with subsequent resolution of PET-avid disease and only minimal peri-nephric tissue remaining. Given the favorable response, surgical resection and multiple tissue biopsies were performed which documented no residual active disease. The shunt was revised and he started Trametinib for maintenance.

Conclusion: We present a unique case of peritoneal dissemination of high grade neuroepitheial tumors with the same KIAA-1549-BRAF fusion as multifocal low grade astrocytomas in a child with a VP shunt. This raises suspicion for tumor metastasis and transformation to a higher grade malignancy versus two distinct diseases, which may be indicative of an underlying cancer predisposition.

Poster # 098 | 17 YEAR OLD FEMALE WITH POLYCYTHEMIA SECONDARY TO A HIGH OXYGEN AFFINITY HEMOGLOBINOPATHY

Kiranmye Reddy, Jennifer Tran

Texas Children's Hospital, Houston, Texas, United States

Background: Polycythemia is a common referral to hematology. It is important to evaluate for a high oxygen affinity hemoglobinopathy, ensuring appropriate testing is performed for early diagnosis and avoidance of additional tests and procedures. A 17 year old Mexican female presented with an elevated hemoglobin and hematocrit, symptoms of plethora of her hands and feet, chest pain, palpitations, and fatigue. Further confounding the picture, she also had significant menorrhagia and iron deficiency. She was diagnosed with the rare high oxygen affinity Hemoglobin New Mexico variant, only previously described once in the literature in a 4 year old black boy.

Objectives: The patient initially presented at age 14 with a hemoglobin of 16.7g/dL and a hematocrit of 52.4%. Initial work up consisted of a hemoglobin electrophoresis which diagnosed sickle cell trait, a co-oximetry panel which was normal, and erythropoietin level of 7mU/mL, also normal. She was then lost to follow up and re-referred at age 17. She is a competitive basketball athlete, and at that time, she presented with a hemoglobin of 17.1g/dL, and hematocrit of 50%. Erythropoietin level continued to be normal at 13mU/mL.

Design/Method: Cardiology was consulted regarding chest pain and palpitations with a normal evaluation. Chest X-Ray was also normal. A bone marrow aspirate and biopsy was performed with results significant for mild erythroid hyperplasia and mild reticulin fibrosis. JAK 2 mutation, Von Hippel Lindau, BPGM, and hereditary erythrocytosis mutations including PHD2, HIF2A, and EPOR mutation analysis were sent, all of which were normal. Testing to Mayo clinic for p50 RBC oxygen dissociation returned low at 19mmHg (24-30mmHg normal range) and subsequently a hemoglobin electrophoresis identified a hemoglobin variant leading to Beta Globin gene sequencing.

Results: Patient found to be heterozygous for hemoglobin New Mexico, with 41.9% Hb New Mexico and 54.5% HbA, and 3.6% HbA2. There was no evidence of HbS.

Conclusion: When evaluating patients with polycythemia, maintaining a high index of suspicion for high affinity hemoglobinopathies may eliminate further unnecessary and invasive testing for patients. Caution should be used when using hemoglobin electrophoresis testing since Hb New Mexico is known to migrate similarly to HbS on HPLC with minimal change that may not be detected in regular laboratories. Most high affinity hemoglobinopathies are reported to not have significant symptoms. In this case, our patient complains of fatigue, occasional palpitations and plethora of hands and feet. We will need to further follow this patient for possible attributable symptomatology.

Poster # 099 | A UNIQUE CASE OF BCOR+ UNDIFFERENTIATED SARCOMA- A NEW SUBTYPE OF SARCOMA

Divya Keerthy, Simone Chang, Warren Alperstein, Patricia Delgado, Claudia Rojas, Ofelia Alvarez, Matteo Trucco

University of Miami Jackson Memorial Hospital, Miami, Florida, United States

Background: Improved technology is enabling detection of previously unidentified translocations and mutations in otherwise unclassified sarcomas. One such mutation is the BCL-6 co-repressor - internal tandem duplication (BCOR-ITD) allowing for the new classification of BCOR positive undifferentiated round cell sarcomas (URCS). This sarcoma has a similar appearance to clear cell sarcoma of the Kidney (CCSK), potentially representing an extra-renal manifestation of this tumor, but their clinical pathologic features are not identical.

Objectives: This case highlights how recombinant polymerase chain reaction (RT-PCR) and BCOR immunohistochemical staining can ease the diagnosis of this rare sarcoma.

Design/Method: Case report

Results: A 5 month-old female presented for right sided pre-septal cellulitis and a temporal subcutaneous mass. The detection of multiple other subcutaneous nodules on exam raised the concern for malignancy and she was admitted for evaluation. She had two subcutaneous masses on her abdomen, with more cutaneous masses on her legs, back, shoulder, cheek and submandibular areas. She lacked spontaneous lower limb movement and had bilateral clonus. Imaging confirmed multiple masses throughout the body including paravertebral area from T3 to L2, bilateral adrenal glands, left kidney and muscles of upper and lower extremities. Initial differential included neuroblastoma, infantile myofibromatosis, rhabdomyosarcoma or atypical presentation of a renal tumor. However, synaptophysin and chromogranin stains were negative. With standard immunohistochemistry, the tumor could be only broadly classified as "undifferentiated sarcoma" maintaining the diagnostic challenge. Using RT-PCR in the setting of a morphologically primitive round cell neoplasm with strong BCOR expression, two external institutes simultaneously diagnosed the tumor as BCOR-URCS. The primary lesion is unknown but potentially may have arose from the kidney. BCOR-URCS has a heterogeneous histology with tumor cells appearing monomorphic in nests of 6–10 cells separated by septa with uniform nuclei. There is frequently an "orphan Annie eye" appearance and sparse cytoplasm to the cells. Diagnosis cannot be made solely on evaluation of this nonspecific histology. RT-PCR uses the genetic abnormality in undifferentiated sarcomas to narrow the differential and BCOR immunohistochemical staining provides further

context. BCOR has significant diagnostic value given its sensitivity and specificity in URCS. Another potential marker includes YWHAE-NUTM2B fusions, which occur in smaller subset of cases, but requires further study.

Conclusion: RT-PCR has helped further classify tumors leading to the diagnosis of a rare undifferentiated sarcoma with BCOR overexpression. While this technology is beneficial, its availability is limited. If accessibility improves, earlier identification and treatment may be possible maximizing the chance for a positive outcome.

Poster # 100 | A CONDITION OF MULTIPLE ORIFICE BLEEDING IN ABSENCE OF COAGULATION OR PLATELETS DEFECTS

Yasmin Saied, Walaa Abdel Fattah Attia, Ilham Youssry

Pediatric Department Abu Elreesh Hospital, Cairo, Masr Elkadema, Egypt

Background: Hematohidrosis is a rare condition that mimics bleeding disorders. Cases present with oozing blood tinged fluid from various sites like eyes, ears, nose, skin, etc. Reported causes of this condition were stress or fear, physical activity, psychological disorders. The condition is self-limited and don't affect the general condition of the patients, but it may contributes to psychosocial problems and may increases their stress and anxiety. So this condition needs to be promptly treated.

Objectives: To test the response of this disease and the associated headache to Propranolol treatment.

Design/Method: Our case female patient 11 years old 1st offspring of non consanguineous marriage, was admitted with recurrent episodes of oozing blood tinged fluid from eyes, ears and nose 2 months before admission, about 0.5-1 ml from each orifice, lasted 5–10 minutes and subsided spontaneously. It could involve the 3 sites simultaneously or 1-2 sites. The number of attacks was 3–4 times per day then gradually increased to 15–20 times per day. Later on the patient developed a bleeding attack from umbilicus. These attacks were aggravated by stress and physical activity and decreased with rest and sleep. The condition was associated with severe headache involving the whole head, throbbing in nature of gradual onset, increased by physical activity and relieved by analgesics. The condition was not associated with vomiting, blurring or diminution of vision, ocular pain, eye discoloration. No earache, tinnitus or diminution of hearing. There was no other form of discharge from eyes, ears or nose. No history of ecchymotic patches, bleeding from other orifices or blood product transfusion. No history of trauma, drug intake, fever or rash. No symptoms of other system affection. Past history of recurrent attacks of epistaxis and two operations were done that passed without remarkable bleeding. No similar condition in the family Physical examination was free, no evidence of psychological problems. Complete blood count, coagulation profile, platelets function, factor 13 and C.T brain were normal. Oozing Fluid from the patient was analyzed showed the same components as blood.

Results: Our case started oral propranolol 0.5mg/kg/day based on its use in similar cases in literature. The frequency of attacks and headache reduced then stopped after 2 months of treatment and didn't recur after stoppage of propranolol.

Conclusion: Propranolol can treat this condition successfully. Further investigations are needed to determine the link between this condition and severe headache our case was suffering from.

Poster # 101 | PRIMARY EXTRARENAL WILMS TUMOR OF THE TESTIS

Lauren Pommert, Nathan Schloemer, Paul Harker-Murray

Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, Wisconsin, United States

Background: Wilms tumor is the most common renal solid tumors of childhood and is derived from primitive metanephric cells located in the kidney. Primary extra-renal Wilms tumors (ERWT) are extremely rare, estimated to comprise 0.5-1% of all Wilms tumors. Despite similar histologic appearance intrarenal and ERWTs differ in embryologic tissues of origin. ERWTs arise from the more primitive mesonephric or pronephric origin and, therefore, can develop anywhere along the craniocaudal migration pathway of these primitive tissues, most often retroperitoneal, inguinal/genital, lumbosacral/pelvic and mediastinal. These tumors are typically staged and treated per National Wilms Tumor Study (NWTS) guidelines, and, by definition, are stage II or greater due to location beyond the kidney borders. Based on the cases reported in the literature, outcomes for ERWT are comparable to renal Wilms tumors with an 11% local recurrence rate and an 85% two-year event-free survival.

Objectives: We report the first case of a stage III testicular extrarenal Wilms tumor in an 8-month-old male with an intrabdominal undescended testis who underwent complete surgical excision followed by chemotherapy and inguinal radiation.

Design/Method: Case report

Results: A full term 8-month old male underwent orchipexy for an undescended left testicle. The testicle was noted to be grossly abnormal with a pea-sized thickened tissue adherent to the upper pole and a separate mass outside of the scrotum on the superior epididymis. Both masses were removed, and

pathology demonstrated Wilms tumor with favorable histology and negative margins. CT imaging of the chest, abdomen and pelvis were negative for a primary renal tumor, local residual disease, pathologic lymph node enlargement or distant metastases. The tumor was classified per NWTS as stage III due to tumor removal in multiple pieces. The patient completed DD-4A treatment with vincristine, doxorubicin and dactinomycin per AREN0534 with 10 cGy left inguinal radiation. He is currently 15 months off therapy without clinical or radiographic evidence of recurrent disease.

Conclusion: Primary ERWT is an extremely rare malignant neoplasm associated with challenges in diagnosis, staging and treatment. Based on the 80 cases reported in the literature, outcomes are similar to that of intrarenal Wilms tumor. There are four pediatric paratesticular Wilms tumors reported in the literature and, to the best of our knowledge, this is the first case of stage III testicular Wilms tumor successfully treated with DD-4A chemotherapy and radiation. In ERWT, NWTS guidelines for staging and treatment should be applied with evaluation of both kidneys to exclude an intrarenal primary tumor.

Poster # 102 | A CASE OF ATYPICAL HUS IN THE ABSENCE OF SCHISTOCYTES

Leah Bruno

Tulane University, New Orleans, Louisiana, United States

Background: Patient is a 20 YO F, with ESRD secondary to atypical HUS versus TTP, who presented with thrombotic microangiopathy, AKI, thrombocytopenia and anemia after a living unrelated donor kidney transplant. Patient initially had downtrending creatinine. On post-op day 2, hematology was consulted for an increasing LDH and drop in platelets. Peripheral smear was notable for an absence of schistocytes. Yet, biopsy of the kidney revealed microthrombi. The patient was diagnosed with a thrombotic microangiopathy. Plasmapharesis was initiated on day #3, at which time Ms R was noted to have significantly elevated creatinine. Plasmapharesis did not yield any correction in labs and significant bruising developed. Patient was started on eculizimab; plasmapharesis was stopped. Shortly after, creatinine, anemia and thrombocytopenia corrected to levels at which she was discharged. Overall, patient was found to have progressive anemia, thrombocytopenia, an increasing creatinine and LDH (600s) concerning for atypical HUS, despite absence of schistocytes on peripheral smear. She responded well to eculizimab, with correction of hematologic changes during induction. She was discharged on eculizimab and continued to respond with normalizing platelet counts and hemoglobin. The differential in light of patient's thrombotic microangiopathy and thrombocytopenia also included TTP. Yet, ADAMTS13 remained normal. DIC was unlikely given normal fibrinogen level and d-dimer.

Objectives: Presentations of atypical HUS vs TTP. Discuss eculizumab as a treatment of atypical HUS. Highlight atypical presentations of illness in transplant patients.

Design/Method: Patient was an individual case.

Results: Despite absence of schistocytes by smear, pt was diagnosed with atypical HUS based on presentation and after failing plasmapharesis, she responded well to eculizumab. Though her presentation was abnormal, her response to this antibody that blocks the complement cascade suggests that she was experiencing a complement-mediated process. There are rare documented cases in the literature of atypical HUS without schistocytes.

Conclusion: Hemolytic Uremic Syndrome (HUS) is characterized by hemolytic anemia, thrombocytopenia and acute kidney injury. Atypical HUS is a diagnosis of exclusion, not due common etiologies such as shiga toxin. Among atypical causes are complement-mediated forms, caused by an antibody to complement factor. In addition to plasmapharesis, renal transplant and supportive care, the mainstay of treatment for atypical HUS is eculizumab (an antibody that blocks the complement terminal cascade). This case describes a patient unique in that, she was diagnosed with atypical HUS without any schistocytes by smear. Secondly, she responded to eculizumab, with unremarkable gene studies. Finally, this case highlights that transplant patients often have unique presentations.

Poster # 103 | TRABECTEDIN RESPONSE IN REFRACTORY METASTATIC SYNOVIAL SARCOMA

Adriana Trabal, Guillermo De Angulo, Michell Lozano, Diego Jaramillo

Nicklaus Children's Hospital, Miami, Florida, United States

Background: Synovial sarcoma is a spindle cell tumor categorized as a soft tissue sarcoma. The chromosomal translocation t(X;18) leading to the SS18-SSX fusion protein is unique to this sarcoma. It is a slow growing tumor with common recurrences and often, at presentation, with evidence of metastatic disease. If resection is not feasible, then neoadjuvant with adjuvant chemotherapy is recommended. Metastasis carries an unfavorable prognosis given synovial sarcoma historically does not respond well to chemotherapy. Trabectedin is a well-tolerated alkylating agent currently indicated for the treatment of liposarcoma and leiomyosarcoma.

Objectives: We present a 17-year-old male with metastatic synovial sarcoma to the lungs that progressed and was refractory to chemotherapy. He was administered Trabectedin as a

form of palliative chemotherapy, with significant clinical and radiographic response.

Design/Method: PubMed search was done with search for terminology including "Synovial Sarcoma" and "Trabectedin". Papers relevant to our case were selected for literature review.

Results: A 17-year-old male patient presented with a large right axillary mass. Initial imaging showed a heterogeneous multiseptated mass invading the Subscapularis and Teres Major muscles along with innumerable lung nodules. Biopsy confirmed diagnosis of monophasic synovial sarcoma. The patient was started on protocol ARST 0332 with Ifosfomide, Mesna, Doxorubicin. He completed 4 cycles followed by radical resection and 33 sessions of radiation. Due to progression of disease multiple chemotherapy regimens were tried including Topotecan and Cyclophosphamide, protocol ADVL 1522 with Lorvotuzumab, and Pazopanib. Imaging of the chest continued to show significant progression of metastasis. The patient's clinical status deteriorated with worsening respiratory status, requiring 10L of oxygen therapy, and inability to ambulate. He was started on Trabectedin 1.2mg/m2 for palliative care. After 2 cycles of treatment patient was no longer requiring oxygen and was ambulating without assistance. Radiological imaging showed significant reduction in number and size of lung nodules.

Conclusion: Trabectedin is a recently approved alkylating agent for the management of sarcomas resistant to first line treatment. Response in synovial sarcoma is scarcely documented in the pediatric population. Epidemiology places the most common age group in the young adults and children. Our case opens the doors to further consideration of the use of Trabectedin in the pediatric patient with metastatic synovial sarcoma.

Poster # 104 | A PATIENT WITH MACROCYTIC ANEMIA AND PLATELET DYSFUNCTION ASSOCIATED WITH A NOVEL VARIANT OF GATA1 MUTATION

Yixian Li, Michelle Manalang, Michael McManus

Marshfield Clinic Health System, Marshfield, Wisconsin, United States

Background: GATA1 is an X-linked gene that plays critical role in hematopoiesis. Mutations of GATA1 gene can be associated to various blood disorders including Diamond Blackfan Anemia, cytopenia, congenital dyserythropoietc anemia and acute megakaryoblastic leukemia.

Objectives: We report a patient with macrocytic anemia and platelet dysfunction who carries a novel GATA1 mutation that has not been reported.

Design/Method: Case report.

Results: A now 28-month-old male with complex medical history including prematurity at 33 weeks, dysmorphic features, global developmental delay, hyperinsulinism, hypogonadotropic hypogonadism, growth hormone deficiency, micropenis, failure to thrive, patent ductus arteriosus status post ligation, and severe hypotonia, was referred to hematology at 16 months old for resolved, transient thrombocytopenia and macrocytic anemia since 1 month of age. Chromosomal microarray showed chromosome deletion of 14q21.3, which is the RPS29 gene. He doesn't have a family history of Diamond Blackfan Anemia (DBA), despite mom having the same RPS29 mutation. He was then diagnosed with DBA. His lab workup showed mild macrocytic anemia (Hgb 9.1 g/dL, MCV 95fL), normal to inappropriately low reticulocyte count, normal white blood cell and platelet counts, HgF 0%, erythroid ADA 1.39 EU/gm Hgb (elevated). He has abnormal PFA-100, with prolonged closure time of both ADP and epinephrine. He had low von Willebrand antigen and Ristocetin cofactor activity. He has severe pancreatic insufficiency. Bone marrow biopsy showed normocellular marrow with trilineage hematopoietic maturation, without ringed sideroblasts. Since mother has the same RPS29 gene mutation, maternal labs were done and showed no evidence of macroytosis or anemia. The diagnosis of DBA was questioned. Whole exome sequencing did not identify any pathogenic sequence changes in the coding regions of RPS29 gene, but detected a GATA1 mutation R140W, which was reported variant of uncertain significance. His mother shares the same mutation and is asymptomatic, but she may not be affected since GATA1 iIs X-linked. His father doesn't harbor the GATA1 mutation.

Conclusion: GATA1 gene encodes zinc finger DNA binding hematopoietic transcription factor, which is important during erythroid differentiation. GATA1 mutation R140W has not been reported in literature and is a novel variant of GATA1 mutation, which might be contributing to this patient's clinical picture. Further studies are warranted to confirm GATA1 mutation R140W to be a pathogenic sequence change.

Poster # 105 | DOSE MODIFICATIONS AND PHARMACOKINETICS OF CISPLATIN MONOTHERAPY FOR THREE PATIENTS WITH LOW-RISK HEPATOBLASTOMA AND DIALYSIS-DEPENDENT END-STAGE RENAL DISEASE

Alexander Boucher, Tomoyuki Mizuno, Alexander Vinks, Greg Tiao, Stuart Goldstein, James Geller

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Hepatoblastoma (HB), the most common pediatric primary hepatic malignancy, can be associated with specific congenital syndromes. Recently, chronic kidney disease and genitourinary anomalies have been linked to HB. Cisplatin is a key chemotherapeutic agent in treating HB but its renal clearance and toxicity profile can limit its use for those with end-stage renal disease (ESRD).

Objectives: Using an institutional case series, we present data using cisplatin for HB in dialysis-dependent ESRD and define recommended dosing for future use.

Design/Method: A chart review of patients with concurrent HB and ESRD on dialysis treated with cisplatin at our institution was undertaken. Demographic data, diagnostic history, tumor pathology, alpha fetoprotein (AFP), hearing assessments, dosing schema, treatment outcomes, and therapy-related toxicities were reviewed. Total cisplatin levels were collected at 5 time points within 10 days after each infusion. Free cisplatin levels were also collected for 2 infusions, as were dialysate cisplatin levels. PK parameters were generated using Bayesian estimation with a published population PK model as a priori information.

Results: Three patients meeting these criteria were identified. Each had "low risk" (non-metastatic resectable) disease at presentation and underwent upfront resections. All had congenital renal anomalies with ESRD prior to their HB diagnosis. All cisplatin infusions were given over 3 hours, followed 3 hours later by hemodialysis. Patients 1 and 3 received cisplatin at 50% of Children's Oncology Group's AHEP0731 weight-based dosing (1.67 mg/kg). Patient 2 received 50% of AHEP0731 body surface area-based dosing (50 mg/m2) during cycle 1 but required a second dose reduction (25 mg/m2) for cycle 2 due to prolonged cisplatin exposure (total area under the curve 342 mg·h/L; average for all seven evaluable cycles 238 mg·h/L) and early sensorineural hearing loss at 2000–4000 Hz. No other hearing loss in any patient was identified; mild toxicities also included grade 1–2 emesis and grade 1 neutropenia and thrombocytopenia. The median (range) of clearance, volume of distribution at steady-state, and elimination half-life at terminal phase for total platinum were 0.19 (0.15-0.31) L/hour/70 kg, 69.1 (59.0-105.7) L/70 kg and 155 (102-185) hours, respectively. Patients 1 and 2 received 2 cycles with rapid AFP normalization. Patient 3 required an additional 2 cycles, for a likely second primary HB 1 year after initial therapy.

Conclusion: Cisplatin can be used successfully in pediatric patients with ESRD on hemodialysis to treat HB with minimal morbidity using 50% standard mg/kg-based dosing (1.67 mg/kg), achieving pharmacologically appropriate cisplatin exposures.

Poster # 106 | MANAGEMENT OF BLEEDING IN A PATIENT WITH JUVENILE DERMATOMYOSITIS AND UNRESPONSIVE IMMUNE THROMBOCYTOPENIA

Erin Wright, Matthew Henderson, Stephanie Savelli, Donna Patton

Akron Children's Medical Center, Akron, Ohio, United States

Background: Treatment for immune thrombocytopenia (ITP) has been grouped into rescue and maintenance therapy and often is reserved for patients with bleeding, severe thrombocytopenia, or for improvement in quality of life. Splenectomy is considered one of the more invasive but definitive treatments with success rates of 70–80%. Treatment of ITP can be more difficult in the setting of previous treatment with immune modulation or when the patient is immunocompromised and not a candidate for splenectomy.

Objectives: Present an interesting case of a patient with an autoimmune disease that presented with severe thrombocytopenia, un-responsive to rescue therapy, and requiring emergent splenectomy in the setting of acute intracranial hemorrhage (ICH).

Design/Method: A 13 year old female with a history of Juvenile Dermatomyositis presented with a fine purpuric rash on her extremities, wet purpura, and a platelet count of 1K/μL. Bone marrow evaluation at that time was consistent with ITP. She was on Cyclosporine and Plaquenil for dermatomyositis. Platelets failed to increase after three doses of Intravenous Immunoglobulin and high dose steroids. Following a two week course of oral prednisone and Eltrombopag, she presented with persistent severe thrombocytopenia of 1K/μL, anemia of 6.4 g/dL, and a lower GI bleed. She was started on Amicar, Novo-Seven, Rituximab, and given platelet transfusions with no improvement in bleeding. Subsequently, she developed a subdural hematoma with midline shift. Surgery performed an emergent open splenectomy with concurrent continuous platelet transfusion.

Results: She was monitored closely post operatively and, due to ICH, transfused to maintain platelets greater than 100K/μL. By 1 week post-op she had normal platelet counts off transfusions. All medications were stopped within three days of discharge. She represented eight days later with abdominal pain and thrombocytosis and was found to have a portal vein, splenic vein and mesenteric vein thrombosis. She was started on Lovenox therapy and admitted for monitoring due to her history of ICH.

Conclusion: It is unknown whether our patient's underlying immune dysregulation and history of treatment with immunosuppressive medications may have contributed to her

unresponsiveness to multiple therapeutic agents. In addition, her significant bleeding did not allow us to fully evaluate her response to second tier therapy. This adds to the scarcity of literature of ITP response in pediatric patients with autoimmune disease, and may support more aggressive therapy upfront in these patients.

Poster # 107 | MULTIVISCERAL ORGAN TRANSPLANTATION IN A 16-YEAR-OLD MALE WTH FIBROLAMELLAR HEPATOCELLULAR CARCINOMA

Shane Rainey, Nada Yazigi, Stuart Kaufman, Khalid Khan, Cal Matsumoto, Robert Kanard, Jaime Libes

Medstar Georgetown Transplant Institute, Washington, District of Columbia, United States

Background: Multivisceral organ transplantation involves concurrent transplantation of the stomach, pancreas, liver, and intestine with splenectomy, and has been classically used in the pediatric population for infants with intestinal failure from disorders affecting foregut integrity. While there is some data demonstrating its efficacy in adults with low-grade abdominal malignancies, it has not been traditionally used for hepatocellular carcinoma treatment.

Objectives: To describe a unique pediatric case of multivisceral organ transplantation as definitive therapy for refractory fibrolamellar hepatocellular carcinoma in an adolescent male.

Design/Method: Case Report

Results: A 16 year old male presents with a history of fibrolamellar hepatocellular carcinoma, tumor invasion of the portal vein, severe portal hypertension complicated by bleeding esophageal varices and hypersplenism. He had two treatments with Yttrium-90 radioembolization, without significant response. He completed six cycles of traditional chemotherapy in combination with Sorafenib with resolution of PET-avidity, but minimal decrease in tumor size and continued portal hypertension. Since his disease remained relatively stable for over 2 years, he was evaluated and listed for multivisceral organ transplantation. At approximately 2 years and 7 months after diagnosis, he underwent en bloc liver, pancreas, stomach, small bowel, and colon transplant with splenectomy. A single lymph node was positive for malignancy at the time of resection. In addition to expected post-transplant complications, he also developed skin only acute graft versus host disease at 2 weeks after transplant, treated successfully with a thymoglobulin course. He clinically improved and was back to his baseline activity level, on full oral feedings within 3 months post-transplantation. At three and six month post-transplantation, there is no concern for relapsed hepatocellular carcinoma on comprehensive imaging and evaluation. He is maintained on protocol immunosuppression and post-transplant support.

Conclusion: We present the first known case of successful multivisceral organ transplantation in the treatment of refractory pediatric fibrolamellar hepatocellular carcinoma.

Poster # 108 | SWEATING BLOOD: A CASE SERIES OF TWO SIBLINGS WITH HEMATOHIDROSIS

Alex Hoover, Christopher Rokes, Nicholas Fustino, Andrea Olivares Sparks

Blank Children's Hospital, Des Moines, Iowa, United States

Background: Hematohidrosis is a rare disorder that presents with spontaneous excretion of whole blood from intact skin or mucosa. Diagnosis is based on clinical observation of the occurrence with the proven presence of erythrocytes and other blood components, without other abnormalities to account for the phenomenon. The existing literature is scarce and consists of primarily case studies. Most reports describe bleeding from facial sites around the eyes, ears, and nose. The available literature suggests anxiety and physical or emotional stress reactions as the most common inciting events. Little evidence exists regarding the ideal therapeutic approach, however propranolol has been used successfully to reduce bleeding frequency and severity in multiple case reports. A specific genetic etiology has not been elucidated, and no familial cases have previously been reported.

Objectives: We present a pair of half-siblings, both of whom presented with spontaneous cutaneous and mucosal bleeding before two years of age, and report on preliminary results of propranolol therapy.

Design/Method: Patient A is a 9-year-old male born in Tanzania. At 20 months of age, he became ill and developed spontaneous bleeding from his ears, nose, and scalp. He continued to have frequent bleeding episodes, usually related to illness or physical distress. A bleeding diathesis work-up was unremarkable, however some episodes were severe enough to require transfusions. The patient was subsequently diagnosed with HIV and Hepatitis B, presumably acquired via unscreened blood product transfusions. Patient B is an infant female born to the same mother as Patient A, with a different father. She was healthy until two months of age when she developed spontaneous bleeding from the hairline, eyelids, ears and genital/rectal area. Bleeding episodes were nearly always associated with irritability and crying. Extensive coagulation workup was unremarkable.

Results: Propranolol therapy was started in both patients, titrated to a goal of 2 mg/kg/day. In both patients, the frequency and duration of bleeding episodes significantly improved. Patient B continues to have milder occasional bleeding episodes from her eyes, ears and scalp but has significantly less discomfort and irritability during the episodes.

Conclusion: To our knowledge, there are no prior reports involving two related patients with hematohidrosis. This case series suggests that there may be a genetic predisposition which has yet to be identified. Propranolol has shown effectiveness in reducing symptom frequency and severity.

Poster # 109 | A CASE FOR EARLY DABRAFENIB USE IN PATIENTS WITH BRAF V600E POSITIVE LOW GRADE GLIOMAS

Krupesh Patel, Derek Hanson, Shreya Agarwal

Hackensack University Medical Center, Hackensack, New Jersey, United States

Background: Gliomas are the most common central nervous system tumors in children. They are classified into different grades based on genotype (IDH, BRAF, TSC, etc.). Low-grade gliomas such as oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas are classified as grades I and II. Of the molecular level alterations this case report focuses on the BRAF V600E mutation. BRAF is a member of the RAF family of serine/threonine protein kinases and it plays an important role in cell survival, proliferation and terminal differentiation.

Objectives: Here we discuss two cases where Dabrafenib, a BRAF kinase inhibitor, was utilized in the management of gliomas. The cases focus on the use of Dabrafenib late versus early in disease course.

Design/Method: Patient JL is a 20 year old female who was diagnosed with a low-grade glioneuronal tumor (C7-T1 with a metastatic lesion to the brain) in 2007. JL was treated with chemotherapy, radiation, and surgical resection. Despite treatment, the patient's disease progressed. She developed lower extremity dysfunction, urinary incontinence, poor truncal control, and hydrocephalus. Dabrafenib was started after the BRAF V600E mutation was confirmed. Patient LG is a 12 year old female who presented in November 2016 with left facial and upper extremity weakness. CT and MRI scans demonstrated a mixed solid and cystic lesion extending from the optic chiasm and hypothalamus to the right thalamus and posterior basal ganglia with additional involvement of the right cerebral peduncle. Neurosurgical intervention was undertaken and Dabrafenib was started after the BRAF V600E mutation was confirmed.

Results: Patient JL's MRI scans have demonstrated improvement of the spine with diminished areas of enhancement along thecal margins, decreased volume and enhancement within the trigeminal plate cistern and resolution of ependymal enhancement within the right ventricle. The patient's most recent MRI exhibits no disease progression in head or spine. JL has shown improvement clinically since starting Dabrafenib. Patient LG has shown improvement in strength and recent MRI of the brain has shown resolution of enhancement along surgical resection margins, decreased hyperintensity along the inferomedial aspect of the right basal ganglia and no new enhancements.

Conclusion: Low grade gliomas can alter a person's quality of life and even lead to life threatening complications. Often the standard chemotherapy, radiation and surgery don't prevent these complications. Genetic analysis can help clinicians target therapy towards certain mutations such as BRAF V600E. Dabrafenib has shown to decrease tumor burden, early utilization as therapy can help prevent morbidity and mortality.

Poster # 110 | THE PROOF IS IN THE PUDDING: A CASE OF COPPER DEFICIENCY CAUSING CYTOPENIAS IN A FOOD RESTRICTED CHILD

Allison Close, Lynn Malec

Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, United States

Background: Copper is an essential cofactor in enzymatic reactions essential to proper hematologic, skeletal, neurologic and vascular function. Copper requirements in children over the age of 4 are 15 mg/day, which is readily acquired in a typical diet. Copper deficiency is known to occur in patients with the rare X-linked mutation and in older individuals with gastrointestinal bypass surgery; however, it is rarely reported in other conditions.

Objectives: To highlight individuals with autism spectrum disorders or developmental delay with a limited dietary repertoire are at risk for copper deficiency, thus a high index of suspicion must exist in order to diagnose the disorder.

Design/Method: A 15 y/o boy with a prior diagnosis of global developmental delay and oral aversion presented with slowly progressive fatigue, weakness, gait instability, and weight loss. His longstanding feeding difficulties were refractory to intensive feeding programs. His daily diet consisted of 50–60oz of milk and 25–30 individual servings of butterscotch pudding (1680-1880calories/day, 0.7mg iron/day). Initial complete blood count demonstrated white blood cell count

of 3.3, absolute neutrophil count of 760, hemoglobin of 4.4, mean corpuscular volume of <50, reticulocyte count of 0.5, platelet count of 392. Review of his peripheral blood smear revealed microcytic, hypochromic red cells without marked fragmentation, anisopoikilocytosis and ringed sideroblasts; there were no morphologic abnormalities of his leukocytes or platelets. Iron studies demonstrated ferritin of 45, total iron binding capacity of 514, and 2% iron saturation. He had no evidence of B12, folate deficiency or blood loss. Additional evaluation revealed a serum copper level of 6 (range 60–190), and cerulosplasmin of 2.1 (range 22–58).

Results: Once a diagnosis of copper deficiency was made, the patient promptly began a course of parenteral copper repletion. He received IV copper 35mcg/kg/day x 3 days then weekly intravenous infusions. Given his malnutrition, a G-tube was placed to begin oral copper repletion and enteral nutrition. Within 3 weeks his copper level improved as well as his blood counts. Unfortunately, although his blood counts and copper levels normalized, his neurologic status remains below his old baseline although, he has made gains in his gross and fine motor abilities.

Conclusion: Acquired copper deficiency in the pediatric population is a rare event but given the hematologic and neurologic consequences, prompt recognition and treatment is important. This patient's clinical course demonstrates the need to have a high index of suspicion of concomitant nutritional deficiencies other than those routinely evaluated such as iron, B12 and folate.

Poster # 111 | EXCEPTIONAL CLINICAL RESPONSE TO MOLECULAR GUIDED THERAPY IN A PATIENT WITH PROGRESSIVE LYMPHOEPITHELIOMA-LIKE THYMIC CARCINOMA

Majd Ghanim, Giselle Saulnier Sholler, Michelle Hudspeth, Lori Donahoo, William Rieter, Genevieve Bergendahl, Gina Hanna, William Hendricks, Sarah Byron, Abhinav Nagulapally, Jeffrey Bond, Jeffrey Trent, Jacqueline M Kraveka

Medical University of South Carolina, Charleston, South Carolina, United States

Background: Lymphoepithelioma-like thymic carcinoma (LELC) is a rare, aggressive neoplasm with a high rate of invasion, metastasis and recurrence. There are no known curative therapies for metastatic LELC. We report the case of a 16-year-old male who presented with metastatic EBV positive LELC. Sites of disease included a large primary anterior mediastinal mass and metastases to hilar lymph nodes, lungs and liver. He was initially treated with cisplatin and 5-fluorouracil followed by mediastinal radiation. He had a partial response to therapy but his end of therapy scans showed disease progression in lungs, liver, and hilar, supraclavicular and axillary lymph nodes.

Objectives: Molecularly targeted therapies tailored to the patient's genetic profile offer a novel approach to obtain improved survival outcomes.

Design/Method: The patient enrolled on a precision medicine trial, NMTRC009: Molecular-Guided Therapy for the Treatment of Patients with Relapsed and Refractory Childhood Cancer (NCT02162732). In this study, tumor/normal whole exome sequencing and tumor RNA sequencing were performed and a molecular report detailing the results of genomic and gene expression analysis was generated. A treatment plan was designed within a molecular tumor board comprising oncologists, pharmacists, genomicists, and molecular biologists with domain expertise.

Results: Exome sequencing revealed 26 somatic coding point mutations and no structural mutations (focal copy number changes or translocations). Candidate somatic driver mutations included TP53 S94X and R248W as well as KIT N655K. Both genes have been previously implicated in thymic carcinoma. RNA expression analysis demonstrated aberrant activation of biological pathways, including overexpression of KIT, HDAC1, 2 and 9, TYMS, and DHFR. The molecular tumor board selected the combination of pemetrexed (500 mg/m2) on Day 1 of a 21 day cycle, imatinib (400 mg daily), and vorinostat (400 mg days 1–5, 8–12, and 15–19). On Day 8 of Cycle 1, he was admitted with a herpes zoster infection and imatinib was discontinued in order to reduce risk of herpes zoster recurrence. Imaging after 2 cycles showed a complete metabolic response on F-18 FDG PET and a partial response by CT size criteria. As of December 2017, the patient had received 15 cycles of pemetrexed and vorinostat. Scans in December 2017 showed an increase in the size and metabolic activity of two right lower lobe pulmonary nodules. There were no new sites of disease and imatinib was re-started.

Conclusion: Aside from the episode of herpes zoster, there have been no serious adverse events, no hospitalizations and excellent quality of life and prolonged disease stabilization.

Poster # 112 | EVANS SYNDROME, SYSTEMIC LUPUS ERYTHEMATOSUS, AND NEUROFIBROMATOSIS: AN UNUSUAL COMBINATION IN PEDIATRIC PATIENT

Amy Moskop, Leili Dolatshahi, Austin Dalrymple

Saint Louis University School of Medicine, SSM Health Cardinal Glennon Children's Hospital, St. Louis, Missouri, United States

Background: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects multiple organ systems and is associated with many different autoantibodies. Patients can present with vague constitutional symptoms including fever, rash, fatigue, and weight loss. Some of the various hematologic manifestations of SLE include anemia of chronic disease, leukopenia, autoimmune hemolytic anemia (AIHA), and idiopathic thrombocytopenic purpura (ITP). These can be the presenting signs of SLE. Evans syndrome (ES), a disease characterized by ITP and AIHA, is a rare hematologic manifestation of SLE. Neurofibromatosis 1 (NF1) is a relatively common neurocutaneous disorder. These patients are at risk of developing benign and malignant tumors. Its association with autoimmune disorders, including SLE, remains rare.

Objectives: There are few cases in the literature that have patients with the combination of SLE and NF1. This is the only case that has a patient with SLE, NF1, and ES.

Design/Method: Case report and literature review

Results: A 16-year-old Caucasian female presents with two months of vaginal bleeding, weight loss and petechiae. Her exam is remarkable for petechiae and café au lait macules. Laboratory findings show severe anemia and thrombocytopenia. She receives blood and platelet transfusions during stabilization, and a bone marrow aspirate is performed to rule out a malignancy which is negative. Based on the presence of thrombocytopenia and a positive Coombs test, an autoimmune process such as ES is considered. Screening tests for SLE reveal positive antinuclear and anti-double stranded DNA antibodies as well as low complement. She receives intravenous immunoglobulin and methylprednisolone and eventually her vaginal bleeding slows and her counts recover. She begins SLE therapy with hydroxychloroquine and azathioprine. Due to the presence of café au lait macules on her exam, a genetics evaluation is performed and the patient is also diagnosed with NF1. To date, there are seven cases of SLE with NF1 reported in the literature, only two of which are pediatric cases. There are no reports of the combination of SLE, NF1, and ES.

Conclusion: ES is a rare hematologic manifestation of SLE but can be the initial presentation of this disease. One large study estimates 2% of childhood-onset SLE cases are observed to have ES. Screening for SLE should be considered in all ES patients even in the absence of typical clinical findings. Association of NF1 and SLE has been rarely described. Whether this association reflects a causal relationship or is coincidental needs more investigation. (Lube, Ped Blood & Cancer, 2016).

Poster # 113 | BONE METASTASES IN PEDIATRIC HIGH GRADE GLIOMA: A CASE SERIES AND REVIEW OF THE LITERATURE

Megan Paul, John Crawford, Jennifer Elster

University of California San Diego, La Jolla, California, United States

Background: High grade glioma (HGG) has poor outcomes in adults and children. Extraneural metastases are very rare in HGG, and poorly characterized with only a few small case series in adults and only isolated case reports in pediatrics. No genomic data has previously been published for any children with HGG who develop extraneural metastases.

Objectives: Our objective is to describe the natural history of two children with HGG and bony extraneural metastases, comparing their clinical characteristics as well as whole exome sequencing data for both tumors. This information would suggest similar patients should be monitored closely for extraneural metastasis and may benefit from more systemic therapy.

Design/Method: We present a case series of two patients who presented with HGG and had development of bony metastases less than six months after initial diagnosis. Both patients had molecular profiling with whole exome sequencing (WES).

Results: The first patient was an 11-year-old male with a tumor found in the left lateral ventricle invading into the fornices, hypothalamus, and left midbrain, who had subtotal resection. Bony metastasis were found at 3.5 months after diagnosis, and he died 9 months after diagnosis. He initially received radiation, followed by nivolimuab. The second was a 12-year-old female with a tectal/pineal tumor and multiple spinal cord metastases, who had subtotal resection. She developed bony metastasis at 5.5 months after diagnosis and died 13 months after diagnosis. Her histologic diagnosis was pineoblastoma, revised to HGG after whole exome sequencing. She received craniospinal radiation followed by chemotherapy per ACNS0332 (cisplatin, vincristine, and cyclophosphamide) for 2 cycles. When she failed to respond satisfactorily to this therapy, WES of tumor was performed and the findings were consistent with HGG. Treatment was transitioned to temodar and lomustine after HGG diagnosis was given. She had ongoing progressive disease despite this therapy as well as trials of nivolumab, everolimus, and vorinostat. Neither patient had extraneural metastasis at presentation. In both tumors, whole exome sequencing identified the H3F3A K27M mutation. Both tumors also had additional known mutations associated with HGG but no other overlapping mutations.

Conclusion: This case series represents the first description of the genetic alterations of pediatric HGG patients who

developed extraneural metastases. While H3F3A K27M is a common mutation in pediatric midline HGG, especially DIPG, and is associated with more aggressive disease, there has not been an association with extraneural metastasis prior to this series.

Poster # 201 | NEUTROPENIA AND LIFE THREATENING AGRANULOCYTOSIS AMONG CHILDREN WITH B THALASSEMIA TREATED WITH ORAL IRON CHELATORS IN A COMMUNITY WITH BACKGROUND OF ETHNIC NEUTROPENIA

Hanan Nazir, Maryam Alshizawy

Sultan Qaboos University Hospital, Muscat, Muscat, Oman

Background: Deferiprone- induced agranulocytosis is a well -known albeit rare side effect of the drug. Incidence of agranulocytosis varies from 0.5-3.6%, while milder neutropenia is reported in 8.5% of patients treated with deferiprone. Deferasirox is unknown to cause such a complication. Clinical trials and post marketing side effect monitoring studied possible correlations between different risk factors and development of agranulocytosis. Unfortunately, no studies directly addressed a special risk in a community with background of ethnic neutropenia, like Oman.

Objectives: To report on the incidence of neutropenia among Omani children with B thalassemia using different iron chelators

Design/Method: A retrospective study conducted on patients < 21 year-old with B thalassemia treated with different iron chelators. Electronic Patients Records were reviewed to detect episodes of neutropenia either mild (ANC 1.0- <1.5/cmm), moderate (ANC 0.5-<1), severe < 0.5, or agranulocytosis ANC = 0). Data were collected including sex, age, personal or family history of ethnic neutropenia, iron chelating agent, infective complications, management and outcome. Detailed clinical, laboratory ± radiological information were reported for patients who developed life-threatening agranulocytosis.

Results: Among 179 young patients with B thalassemia, treated between 2007–2017 in SQUH, neutropenia, was reported in 78 patients (43.6%).Severe neutropenia was encountered on 14 occasions in 11 patients (11/179: 6.1%) (8 on deferiprone including 5 episodes of agranulocytosis, 1 on defersirox, 1 on combined chelation, and 5 off chelation). Moderate neutropenia was encountered in 29 patients (29/179: 16.2%), on 36 occasions: Deferiprone (15), Deferasirox (8), combined chelation (4), and 9 episodes off chelation. Mild neutropenia was more prevalent, encountered in 59 patients (32.9%) on 124 occasions (30 on deferiprone, 44 on defersirox, 19 on combined chelation, and 31 off chelation) Of 85 patients exposed to deferiprone, 35 patients had neutropenia (41%), higher than previously reported. Deferiprone-induced agranulocytosis was encountered in 4 patients (4/85 = 4.7%). Three of them had life threatening complications. One patient developed pneumonia complicated by rupture of pulmonary artery aneurysm- massive hemoptysis, who recovered fully after catheter embolization. The second had facial cellulitis and treatment with GCSF was complicated by frequent ventricular extrasystoles. The third had sepsis, disseminated herpes simplex and required admission to ICU for inotropic support.

Conclusion: In a community with background ethnic neutropenia, neutropenia is more common to be encountered among thalassemic patients, both on and off chelation therapy. Careful monitoring of ANC and rational choice/modification of chelating agents is required for optimal management of iron overload and to avoid life threatening complications.

Poster # 202 | DIASTOLIC DYSFUNCTION IN NON TRASNFUSED β THALASSAEMIA INTERMEDIA: CASE CONTROL STUDY

Khalfan Al Senaidi, Hanan Nazir, Surekha Tony, Shoaib AL Zadjali, Yasser Wali

Sultan Qaboos University Hospital, Muscat, Oman

Background: Serious cardiac complication can occur in patients with β thalassaemia intermedia (TI).

Objectives: This case control study aimed to evaluate the systolic and diastolic cardiac function in 2 groups of children with TI: non transfused group and a group that received early regular blood transfusion comparing them to healthy controls.

Design/Method: Thirteen regularly transfused patients with TI with a mean age of 11.8+5.6 years were compared with eight patients who are non-transfused or minimally transfused (< 3 RBCs transfusion/year); mean age 11.8+9.4 years and 18 healthy controls with a mean age of 8.8 ± 3.9 years. Clinical parameters and standard echocardiographic and Tissue Doppler Imaging (TDI) were compared.

Results: Young non-transfused TI patients had a statistically significant higher peak late diastolic velocity of the left ventricular inflow Doppler, a mitral valve A wave duration over the pulmonary vein A wave duration ratio and the pulmonary

vein S/D velocities ratio compared to the transfused group with p values of 0.028, 0.01, 0.01 respectively. In addition, they have a lower E/A ratio of the mitral valve inflow and a larger left atrial to aortic diameter ratio compared to the control group with p values of 0.025 and 0.01 respectively. The diameters of the right and left outflow tract were significantly larger in the non transfused group with a trend to have a higher cardiac index compare to the transfused group. Systolic function was similar in the 3 studied groups and none of the patients had evidence of pulmonary hypertension.

Conclusion: Young patients with TI who are receiving early regular blood transfusion have normal systolic function. Diastolic function assessment revealed indicators of an abnormal relaxation of the left ventricle in the non transfused group which indicate diastolic dysfunction. The abnormalities affected multiple diastolic function parameters which give an indication that the changes are clinically significant. A statistically significant increase in the diameters of the outflow tracts are likely attributed to high cardiac output status in non-transfused TI patients as they had a trend to have a higher cardiac index. These findings support the early commencing of regular blood transfusion therapy for TI patients to prevent serious cardiac complications in adult life.

Poster # 203 | CRIZANLIZUMAB 5.0 MG/KG INCREASED THE TIME TO FIRST ON-TREATMENT SICKLE CELL PAIN CRISIS (SCPC) AND THE LIKELIHOOD OF NOT EXPERIENCING SCPC WHILE ON TREATMENT: SUBGROUP ANALYSES OF THE PHASE 2 SUSTAIN STUDY

Julie Kanter Washko, Abdullah Kutlar, Darla Liles, Rodolfo Cançado, Michael Shi, Zewen Zhu, Kenneth Ataga

Medical University of South Carolina, Charleston, South Carolina, United States

Background: In the 52-week SUSTAIN study, crizanlizumab 5.0 mg/kg significantly reduced the frequency of SCPCs versus placebo (1.6 vs 3.0, P = 0.01) and increased the time to first on-treatment SCPC (4.1 vs 1.4 months, P = 0.001) in patients with sickle cell disease (SCD).

Objectives: To evaluate time to first SCPC in SUSTAIN study subgroups and the likelihood of not experiencing SCPC for the duration of the trial using post hoc analyses.

Design/Method: SUSTAIN was a randomized, double-blind, placebo-controlled, phase 2 study (NCT01895361). Inclusion criteria were: SCD patients aged 16–65 years; 2–10 SCPCs in previous 12 months; concomitant hydroxyurea use permitted if ≥6 months and stable dose for ≥3 months. Patients were randomized 1:1:1 to receive intravenous crizanlizumab 5.0 mg/kg, 2.5 mg/kg, or placebo. Study treatments were administered on days 1 and 15, then every 4 weeks to week 50, with the final assessment at week 52. Median time to first SCPC after first dose was summarized for crizanlizumab 5.0 mg/kg or placebo in these subgroups: 2–4 or 5–10 SCPCs in previous 12 months; SCD genotype; and hydroxyurea use at baseline. Hazard ratios (HRs) for crizanlizumab 5.0 mg/kg versus placebo were calculated based on Cox regression analysis, with treatment as a covariate. Descriptive statistics were used to summarize the frequency of patients who were SCPC event-free for the duration of the study by prior SCPC events, SCD genotype, and hydroxyurea use at baseline.

Results: 67 patients received crizanlizumab 5.0 mg/kg and 65 received placebo. There was a meaningful delay in time to first SCPC with crizanlizumab 5.0 mg/kg versus placebo observed in the entire study population. The effect was present in both SCPC subgroups, and the largest treatment difference was observed in HbSS SCD versus other genotypes (4.1 vs 1.1 months; HR: 0.50). In patients taking hydroxyurea who experienced 2–10 SCPCs in the previous year, time to first on-study SCPC was longer with crizanlizumab 5.0 mg/kg versus placebo (2.4 vs 1.2 months; HR: 0.58). A greater proportion of patients treated with crizanlizumab 5.0 mg/kg were SCPC event-free versus placebo in each of the analyzed subgroups. One third of patients who were taking hydroxyurea and treated with crizanlizumab 5.0 mg/kg were SCPC event-free during the study versus 17.5% with placebo, possibly suggesting an additive effect.

Conclusion: With crizanlizumab 5.0 mg/kg, there was a clinically meaningful delay in time to first SCPC and an increased likelihood of being SCPC-free versus placebo in all subgroups investigated.

Poster # 204 | MDS AND AML IN SHWACHMAN DIAMOND SYNDROME: CLINICAL FEATURES AND OUTCOMES

Kasiani Myers, Elissa Furutani, Bradford Siegele, Mark Fleming, M. Tarek Elghetany, Valerie Arsenault, Blanche Alter, Farid Boulad, Carlos Bueso-Ramos, Lauri Burroughs, Paul Castillo, James Connelly, Stella Davies, Marie Desierto, Courtney DiNardo, Iftikhar Hanif, Richard Ho, Nicole Karras, Sioban Keel, Michelle Manalang, Lisa McReynolds, Taizo Nakano, Grzegorz Nalepa, Maxim Norkin, Matthew Oberley, Etan Orgel, Yves Pastore, Joseph Rosenthal, Kelly Walkovich, Akiko Shimamura

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Shwachman-Diamond syndrome (SDS) is an inherited marrow failure syndrome associated with increased risk of myelodysplasia (MDS) and acute myeloid leukemia (AML).

Objectives: This multi- institutional retrospective study investigated clinical features, treatment, and outcomes of 38 SDS patients who developed MDS or AML by central pathology review.

Design/Method: Nine individuals presented with AML (4 male, 5 female), 5 MDS-EB1/2 (3 males, 2 females, 23 with MDS (11 male and 12 female), and one male with isolated persistent somatic TP53 mutation. One MDS-EB1 and 1 MDS patient progressed to AML. Median age (years) at diagnosis of MDS was 16 (range 0.5-30), MDS-EB1/2 was 9 (range 0.7-20) and AML was 28.8 (range 5.5-47).

Results: Complex cytogenetics were noted in 10/11 AML cases, with one having normal cytogenetics. Complex clonal cytogenetic abnormalities were noted in 4 of 5 MDS-EB1/EB2 patients and clonal abnormalities in 17 of 18 MDS patients. Follow up was available for 10 AML patients; 9 are deceased. 9 received chemotherapy with intent to proceed to hematopoietic stem cell transplant (HSCT). Four failed to achieve remission and died with disease without proceeding to transplant. One patient proceeded to HSCT without prior chemotherapy. Four of six transplanted subjects died with relapsed disease. Treatment related mortality was largely infectious or GVHD. The sole surviving AML patient had normal cytogenetics, achieved remission with chemotherapy and underwent HSCTs with 3 separate stem cell infusions due to two primary graft failures. He remains alive in remission more than 4 years after diagnosis. Of the 5 MDS-EB1/2 patients, 4 underwent RIC HSCT, three of whom are alive, one died of infection. The fifth patient has stable disease on continued decitabine monotherapy for 4.75 years. Of 19 MDS patients with treatment data, 13 had upfront HSCT therapy, 2 upfront chemotherapy and 4 had no therapy. Three patients required ≥2 HSCTs all due to graft failure. Follow up is available for 18, 11 of whom are deceased, 6 with relapsed disease. Treatment related mortality was largely infectious or graft failure. One individual died of hepatic failure unrelated to MDS. Seven MDS patients are alive in remission.

Conclusion: In summary, prognosis is poor for patients with SDS who develop AML due to resistant disease and treatment-related complications. Better markers for risk stratification are needed to identify patients who would benefit from early transplant. Novel therapeutic strategies are urgently needed to improve outcomes of SDS patients with MDS or AML.

Poster # 205 | CONGENITAL THROMBOCYTOPENIA AND MYELOFIBROSIS DUE TO GERMLINE MUTATIONS IN G6B-B

Inga Hofmann, Andrew Crispin, Dean Campagna, Monica Calicchio, Klaus Schmitz-Abe, Esther Obeng, Kyriacos Markianos, Yotis Senis, Mark Fleming

University of Wisconsin - Madison, Madison, Wisconsin, United States

Background: Unlike primary myelofibrosis (PMF) in adults, which is associated with somatic mutations in JAK2, MPL, or CALR, myelofibrosis in children is rare and the underlying genetic mechanisms remain elusive. Here we describe 3 families with autosomal recessive congenital macrothrombocytopenia with focal myelofibrosis (cMTFM) due to germline mutations in the megakaryocyte-specific immune receptor tyrosine-based inhibitory motif (ITIM) receptor G6b-B.

Objectives: To characterize the clinical phenotype, histological features and identify the causative gene for cMTFM.

Design/Method: We performed Affymetrix SNP 6.0 genotyping on the index family to identify shared regions of homozygosity by descent. Whole exome sequencing (WS) was performed on all three pedigrees to identify potentially causative mutations.

Results: We studied 6 affected children from 3 families, with macrothrombocytopenia, anemia, mild leukocytosis and a distinctive pattern of bone marrow (BM) fibrosis centered around clusters of atypical megakaryocytes. Affected children had mild to moderate bleeding symptoms and required platelet and red cell transfusions. None showed evidence of extramedullary hematopoiesis, and all were negative for mutations in JAK2, MPL, and CALR. SNP genotyping identified multiple statistically non-significant genomic loci, including the region of the major histocompatibility locus (MHC) on chromosome 6p (LOD = 2.01). We focused on this region because affected individuals in two families shared a common homozygous human leukocyte antigen (HLA) type and had congenital adrenal hyperplasia (CAH) due to 21-hydroxylase (CYP21A2) mutation; the CYP21A2 and HLA loci are located at 6p21.33 and 6p21.32-6p22.1. WES revealed homozygous frameshift mutations in the megakaryocyte and platelet inhibitory receptor G6b-B, encoded within the candidate linkage region. We identified two distinct G6b-B frameshift mutations (c.61_61+1dup; p.20fs and c.147insT; p.49fs) in 7 individuals within these three families. No other mutations that segregated with the phenotype were identified. To validate G6b-B as a potential disease-causing gene, we evaluated G6b-B expression in BM biopsy specimens from affected patient and control samples by immunohistochemical staining using a monoclonal antibody. G6b-B was strongly

and selectively expressed in megakaryocytes of control samples, but completely absent in clinically affected individuals. A murine knockout that lacks G6b-B has a strikingly similar phenotype with macrothrombocytopenia, myelofibrosis and aberrant platelet production and function, further affirming the causality of G6b-B mutations.

Conclusion: We showed that autosomal recessive loss-of-function mutations in G6b-B cause cMTFM, uncovering the molecular basis of this rare disease. Loss of G6b-B-dependent inhibition of megakaryocyte activation likely underlies the distinctive focal myelofibrotic phenotype and might be important in other forms of marrow fibrosis.

Poster # 206 | CLINICAL OUTCOME OF FETUSES AND NEWBORNS WITH ALLOIMMUNIZATION WHO RECEIVED INTRAUTERINE TRANSFUSION

Marie Laurence Noisette, Leili Dolatshahi

Cardinal Glennon, Saint Louis, Missouri, United States

Background: Intrauterine transfusion is the method of choice for management of fetal anemia due to red blood cell alloimmunization. Despite the decrease in prevalence of anemia due to Rhesus D alloimmunization with prophylactic administration of anti-RhD immunoglobulin in Rh D negative patients, maternal red red blood cell alloimmunization with other type of red blood cell antigens remains an important cause of fetal anemia. Newborn who received intrauterine transfusion for hemolytic disease may have prolonged postnatal transfusion requirement.

Objectives: 1- To evaluate clinical outcome of fetuses and newborns who received intrauterine transfusions. 2- To determine the need of packed red blood cell transfusions until 6 months of age.

Design/Method: We conducted a retrospective case series study of all intrauterine transfusions due to anemia secondary to red blood cell alloimmunization performed in our regional center SSM in St Louis Missouri, between April 2011 and January 2016. We evaluated the indications, diagnosis, gestational age, and frequency of intrauterine transfusions, along with the infant's gestational age at birth, duration of admission, timing of blood transfusion and monitoring of hemoglobin.

Results: 37 Intrauterine transfusions were performed in 14 patients. The most common causes of alloimmunization were due to D antibodies (n = 7, 50%) and Kell antibodies (n = 5, 35.7%). The median gestational age of the first intrauterine transfusion was 28.1 weeks, and the median pre-transfusion hemoglobin was 8.9 g/dl. The gestational age at the first intrauterine transfusions was found to be significantly correlated with the number of postnatal transfusions (r = 0.8. p = 0.001). The median gestational age at birth was found to be 35 weeks (28.6-36.9 weeks), with a hemoglobin of 13.1 (10.8-14.1). In our population, 6 patients (42%) received postnatal transfusions, of which 4 were during the first 3 weeks of life, and close monitoring follow up with a Hematologist was established in 6 patients at their discharge from the Nursery/NICU. One neonatal death occurred and severe morbidity due to severe anemia occurred in one infant. Despite the continuing risk factor for persistent anemia, only 8 patients had follow up hemoglobin monitored by their primary care provider.

Conclusion: Infants with anemia due to red blood cell alloimmunization treated with intrauterine transfusion should be monitored closely via regular complete blood count for persistent anemia due to suppression of fetal erythropoiesis.

Poster # 207 | INTERROGATING THE HUMAN NEUTROPHIL GRANULOCYTE IN MONOGENIC DISEASE BY NEXT GENERATION PROTEOMICS

Sebastian Hesse, Piotr Grabowski, Juri Rappsilber, Christoph Klein

Dr. von Hauner Childen's Hospital, LMU University Hospital, Munich, Munich, Germany

Background: Neutrophil granulocytes are the most abundant leukocytes in the peripheral blood. Validated diagnostic options for these cells are limited, leaving many patients with functional neutrophil defects without a defined diagnosis.

Objectives: Here we evaluate proteomics as a new diagnostic tool to investigate defects of neutrophil granulocytes.

Design/Method: We analyzed neutrophil granulocytes from 6 children with severe congenital neutropenia (SCN) associated with ELANE mutations, 4 children with chronic granulomatous disease (CGD) with CYBA (2) or CYBB (2) mutations and 2 children with leukocyte adhesion deficiency (LAD) due to ITGB2 mutations. In addition we collected samples of children with genetically undetermined neutrophil defects. Neutrophils from 68 healthy individuals served as controls. Cells were isolated from fresh venous blood using negative selection (purity >99%). Whole cell proteome analysis was done by data-independent acquisition.

Results: We quantified ~4300 proteins in each sample. Reproducibility for one donor at 3 different time points

showed a correlation coefficient of ~0.9. Principal component analysis demonstrated unequivocal separation of the proteome of healthy and diseased cells. Differential expression analysis showed minimal proteome aberrations in LAD with deficiency in cell surface receptors and upregulation of ALPL (total downregulated proteins: 7/ total upregulated proteins: 5). Analysis of neutrophils from CGD patients also showed limited proteome aberration. CYBA and CYBB were both diminished independent of genotype, whereas protein clusters around a STAT1/2 centered network were increased (total down: 11/ up: 23). Neutrophils with ELANE mutations showed the gravest proteome disturbance (total down: 47/ up: 93) with an upregulated translational apparatus (SRP-dependent ribosomes and protein folding complexes) and increased mitochondrial proteins. Proteins of each granule subset were dysregulated and metabolic pathways upregulated. A detailed analysis of the proteome from patients with genetically undefined diseases is currently ongoing. One patient with clinical phenotype of CGD was found to have no mutations of NADPH oxidase members in whole exome sequencing but critically low levels of NCF1 on protein level. Heterozygosity mapping showed autozytocity in the NCF1 region warranting current efforts to sequence promoters and intronic regions of the gene.

Conclusion: Mass spectrometry based proteomics promises exciting new insights into monogenic disease of neutrophil granulocytes and may offer new diagnostic options, in particular in synergy with genome sequencing. By virtue of our international care-for-rare alliance, open to new partners, we hope that our proteome focus may lead to better delineation of as yet unknown disease of neutrophil granulocytes.

Poster # 208 | ABATACEPT FOR MANAGEMENT OF REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA

Michelina de la Maza, Sanjay Shah, Maria Ahmad-Nabi

Phoenix Children's Hospital, Phoenix, Arizona, United States

Background: Warm autoimmune hemolytic anemia (AIHA) is an IgG mediated disease. Although it can be post-viral, it is often idiopathic and can also be a forme fruste for malignancy or an autoimmune disease. Initial management includes steroids. It often relapses on steroid wean and can be refractory to the use of second line treatment such as rituximab.

Objectives: Abatacept (CTLA-4-Ig fusion protein, CTLA-4 mimetic) has been used to ameliorate autoimmune manifestation associated with CTLA-4 haploinsufficiency. We used abatacept as a novel therapeutic agent to manage patients with refractory AIHA.

Design/Method: A retrospective case series of two patients at Phoenix Children's Hospital with severe refractory AIHA.

Results: Patient 1, a previously healthy 12 year old female, presented with 8 weeks of icterus, fatigue, and hemoglobinuria. Spleen was enlarged 8cm below the costal margin. Laboratory evaluation demonstrated: hemoglobin 3.8 g/dL, mild leukopenia 3200/microliter, platelets 99,000/microliter, reticulocytosis 14.3%, positive direct Coombs' test, mycoplasma IgM and IgG positive. Bone marrow evaluation showed a hypercellular marrow. She continued to need packed red blood cell (pRBC) transfusions despite receiving high dose steroids, IVIg and rituximab from May-July 2017. In August, she started sirolimus decreasing her transfusion requirement. After starting Abatacept (10mg/kg/dose bi-monthly for three doses and then monthly) in October, she maintained hemoglobin of 9–10 g/dL without transfusion. Patient 2, a previously healthy 2 month old male, presented with one week of progressive fatigue, jaundice, and poor feeding. Splenomegaly was absent. Laboratory evaluation revealed hemoglobin 3.8g/dL, leukocytosis 20,200/microliter, platelets 324,000/microliter, reticulocytosis 16.1%, negative direct Coombs' test, and non-specific reactivity on antibody screen. Evaluation for inherited hemolytic anemia including a next generation sequencing panel was negative. Further evaluation by blood bank showed 2+ positive Coombs' for C3d due to a warm antibody. Cold agglutinin disease was ruled out. Bone marrow evaluation was normal. He received high dose IVIG as a steroid sparing agent but continued to require pRBC transfusions weekly. When prednisone did not seem to slow down hemolysis, treatment with abatacept was initiated and he has not required transfusions for two months. Steroids are being weaned.

Conclusion: We present successful treatment of two refractory AIHA cases with abatacept. Patient 1 is steroid and transfusion free and continues on monthly abatacept and sirolimus. Patient 2 is also transfusion free and continues on a steroid taper. CTLA-4 is crucial for suppressive function of Treg cells. Abatacept by binding to CD80/86 seems to enhance Treg activity ameliorating autoimmune hemolysis.

Poster # 209 | SHORT-TERM HIGH-DOSE INTRAVENOUS DEFEROXAMINE AS COMBINATION THERAPY FOR REDUCTION OF IRON IN PATIENTS WITH PERSISTENT IRON OVERLOAD

Stephanie Fritch Lilla, Nicole Hart, Kristen Appert

Children's Minnesota, Minneapolis, Minnesota, United States

Background: Transfusional iron overload is common in patients receiving chronic red cell transfusions. As a result, iron chelation is required to minimize toxicity from iron overload. Chelation with a single agent can be inadequate at controlling or reducing iron burden. When combination therapy is required deferoxamine may be added to oral chelation. Deferoxamine is generally given subcutaneous over 8–12 hours for 5–6 days a week at 25–60mg/kg/day. Many patients struggle to remain compliant with this schedule which has prompted trials of intravenous high-dose (HD) deferoxamine. Prior reports of short-term HD deferoxamine have shown minimal side effects however, prolonged use of HD deferoxamine has known toxicity. When compliance is a concern, our center has used HD deferoxamine infusions at 15mg/kg/hr x 48hours every 2 to 4 weeks.

Objectives: Evaluate the safety and efficacy of HD deferoxamine at our institution to help guide future therapy.

Design/Method: A retrospective review was completed of patients previously treated with HD deferoxamine between April 2011 and September 2017 at Children's Minnesota. Final sample included 8 patients ages 3 to 14 years with underlying diagnosis of thalassemia (7) and diamond-blackfan anemia (1). Deferoxamine infusions were given for 48 hours every 24–35 days with a mean length of treatment of 279 days.

Results: All patients were on combination therapy with deferasirox, however deferasirox was held during deferoxamine infusion. Mean pre-deferoxamine liver iron concentration (LIC) was 31.75mg/g and mean post LIC was 12.11mg/g ($p = 0.0008$). Ferritin mean pre-deferoxamine was 2677ng/mL compared with mean post 1594ng/mL ($p = 0.0107$). Two patients had possible allergy, leading to deferoxamine discontinuation. One patient developed hives, eye swelling and cough while the other had emesis and cough. Another patient experienced facial nerve palsy of unclear etiology, which did not recur with resumption of deferoxamine. No respiratory complications were seen.

Conclusion: Results showed significant decrease in iron burden following combination therapy with high dose deferoxamine and deferasirox. No significant pulmonary, liver, renal, vision, or hearing toxicities were observed. Three patients reported reactions to deferoxamine infusions. However, one of these was able to successfully continue deferoxamine without further incident. Short-term, HD deferoxamine was effective at reducing LIC in combination with oral chelation but requires further evaluation to assess for potential increased risk of toxicity. Short-term HD deferoxamine may be considered in the setting of poor compliance of subcutaneous administration or inadequate chelation with single agent therapy. Further studies are needed to clarify ideal dosing, timing and risk of toxicity.

Poster # 210 | TWO CASES OF NEWLY DIAGNOSED MUSCULAR DYSTROPHY DISCOVERED IN CHILDREN WITH IMMUNE THROMBOCYTOPENIA

Jonathan Miller, Latika Puri, Akram Mesleh Shayeb, Vanessa Howard

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: Immune thrombocytopenia (ITP) is the most common cause of symptomatic thrombocytopenia in childhood but remains a diagnosis of exclusion warranting further evaluation if atypical findings are present. Two male children (15 months and 3 years old) with newly diagnosed immune thrombocytopenia (ITP) were found on initial evaluation to have persistent elevations of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). These serum enzyme abnormalities cannot be attributed to ITP. In the setting of thrombocytopenia, elevated transaminases and LDH create diagnostic complexity for the hematology/oncology provider as their elevation raises concern for malignancy, hemolytic disease, and other systemic diseases.

Objectives: To raise awareness about an unexpected pattern of Duchenne Muscular Dystrophy in patients undergoing evaluation for ITP. To expand the differential of a hematologist/oncologist when abnormal labs support a non-hematologic diagnosis

Design/Method: This case-series of two patients with their clinical and laboratory findings were discovered with retrospective chart review.

Results: After a thorough evaluation for hemolytic anemias, liver disease and infectious etiologies was negative, bone marrow and liver biopsies were considered. Eventually, both children were found to have severely elevated serum creatine kinase (CK). Skeletal muscle has the highest concentration of CK of any tissue. Thus, significant CK elevation is almost exclusively attributable to muscle injury and is the most sensitive and specific enzyme for diagnosis of muscle disease. Referral to a neuromuscular specialist and further genetic testing confirmed the diagnosis of Duchenne muscular dystrophy in both children allowing initiation of appropriate interventions. To date, there is no clear genetic predisposition to ITP in patients with muscular dystrophy although further investigation may be needed.

Conclusion: Hematology/oncology providers should consider obtaining a serum CK to rule out muscle disease in any male child with unexplained elevations of serum LDH and/or aminotransferases, as it provides an easy and inexpensive, non-invasive approach to screening. Additionally,

clinical history and physical examination can aid in the diagnosis of muscular dystrophy, with gross motor delay, abnormal muscle bulk, Gower's sign, and proximal muscle weakness all possible findings.

Poster # 211 | ESTABLISHING REFERENCE RANGES FOR COMPLETE BLOOD COUNTS IN CHILDREN WITH DOWN SYNDROME

Susan Harvey, Daniel Ambruso, Kristine Wolter-Warmerdam, Francis Hickey, Christopher McKinney, Dee Daniels

Children's Hospital of Colorado, Aurora, Colorado, United States

Background: Children with Down syndrome (DS) are more likely to have hematologic and immunologic abnormalities compared to their typically developing peers; yet the actual normal range values and nature of complete blood counts (CBC) in the DS population are lacking.

Objectives: To identify the range of CBCs in patients with DS without infections, hematologic or immune disorders and to create more accurate reference ranges for total white blood count; hemoglobin; hematocrit; MCV; platelet count and absolute neutrophils (ANC), lymphocytes, monocytes, eosinophils, and basophils.

Design/Method: A retrospective investigation of healthy pediatric patients with DS who received a CBC between 2011 and 2017 as part of their medical care at a single, large, pediatric teaching hospital. The study group consisted of 562 children with DS (male = 310, 55.2%; mean age = 2.10 years, SD = 3.17) at time of blood draw. Initially 692 children were reviewed for possible participation in the study; however, 130 patients were excluded due to not meeting the study's inclusion criteria. Descriptive statistics were performed on demographic and clinical characteristics. Kruskal-Wallis H tests, ANOVA, and T-tests were run to determine the significant associations between independent means.

Results: A significant difference in absolute neutrophils between racial groups, $F(2, 183.553) = 3.990$, $p = 0.020$, was observed. There was an increase in ANC from 2.5 +/- 1.1 with African Americans to 3.0 +/- 1.6 in the other racial groups and to 2.9 +/- 2.0 with caucasians. Differences were also found in ANC in Hispanics/Latinos versus non-Hispanic/Latinos. The results were higher in non-Hispanics and Latinos, a significant difference of -.584 (95% CI, -.791 to -.376), $t(1255) = 2.572$, $p = 0.001$. Preliminary Kruskal-Wallis H tests run determined that there were significant differences between age groups for total white blood cell, hemoglobin, hematocrit, platelets, lymphocytes and ANC. Further studies are being run to evaluate in which age groups these differences lie and create reference ranges by age, race and sex.

Conclusion: Among patients with DS, there are differences between racial groups and age groups. This data has been compared to previously established reference ranges for CBCs, but we are currently establishing healthy CBC controls which we will use to validate the reference ranges. These ranges will be published to help guide providers in workup and management of patients with DS.

Poster # 212 | PREDICTORS OF RED BLOOD CELL TRANSFUSION, UNITS REQUIRED AND DONOR EXPOSURE IN LOW BIRTH WEIGHT INFANTS

Peter McCarthy, Patricia O'Leary, Eugene Dempsey

Cork University Maternity Hospital, Cork, Ireland

Background: Transfusion is a critical part of the care provided in the neonatal intensive care unit, but it is not without risks. Low birth weight and premature infants can become anaemic from an immature haematopoietic system and frequent phlebotomy. These infants often receive multiple red blood cell transfusions. Identifying infants more likely to require such intervention is important in ensuring the appropriate usage of this scarce resource.

Objectives: To determine whether birth weight, gestational age, gender, length of stay and mode of delivery can predict red cell concentrate (RCC) transfusion, units required, donor exposure and time to exposure.

Design/Method: A retrospective chart review of all infants born below 32 weeks gestation and/or birth weight less than 1,500g who received a red blood cell transfusion between July 2009 and July 2012 in the Cork University Maternity Hospital Neonatal Unit.

Results: 224 infants met the inclusion criteria, 105 (46.87%) received a RCC transfusion. Our study showed lower gestational age ($p<0.01$) and lower birth weight ($p<0.01$) infants are more likely to be transfused. Donor exposure increases with a lower birth weight ($p = 0.016$). Multivariate analysis showed infants with a lower gestational age (OR -0.019 per day; $p<0.05$); lower birth weight (OR -0.002 per 1g; $p<0.01$) and a longer length of stay (OR 0.016 per day; $p<0.05$) are more likely to receive a higher number of RCC transfusions. The time to first RCC transfusion is shorter in those with lower birth weight (OR 0.013 per 1g; $p<0.05$) and lower gestational age (OR 0.356 per day; $p<0.01$). Gender and mode of delivery were not found to be predictors of red blood cell transfusion in this study.

Conclusion: Low birth weight and premature infants are more likely to receive a RCC transfusion during admission to the neonatal unit. Our study highlights predictors of RCC transfusion, donor exposure and time to transfusion. These can be used in identifying at risk infants, counselling parents and in anticipating transfusion requirements.

Poster # 213 | THE EMERGING ROLE OF MECOM MUTATIONS IN PEDIATRIC BONE MARROW FAILURE: A CASE SERIES

Emily Southard, R. Grant Rowe, David Williams, Akiko Shimamura, Taizo Nakano

Children's Hospital Colorado, Aurora, Colorado, United States

Background: The MECOM locus encodes transcription factors that regulate hematopoietic stem cell self-renewal and maintenance. Overexpression of MECOM has been noted in 5–10% of acute myeloid leukemia, several solid tumors, and denotes a poor prognosis. Mutations that reduce MECOM expression or that disrupt protein function, however, have been implicated in the development of bone marrow failure (BMF) through undefined pathways. An association between MECOM mutations and Radioulnar Synostosis with Amegakaryocytic Thrombocytopenia (RUSAT) syndrome has been reported, however further characterization of this phenotype has yet to be explored.

Objectives: To characterize the phenotypic spectrum of a cohort of pediatric patients with novel MECOM mutations.

Design/Method: We performed a retrospective review of five patients with MECOM mutations who were referred to hematology at Children's Hospital Colorado or Boston Children's Hospital. Clinical, laboratory, and genetic data was collected on subjects and available family members.

Results: Four of 5 subjects were identified in infancy presenting with congenital cytopenias or physical dysmorphisms that prompted broad genetic screening. Platforms for genetic detection included microarray, targeted genetic panels, and whole exome sequencing. Three of 4 subjects with cytopenias presented with congenital thrombocytopenia, 1 of whom rapidly progressed to severe aplastic anemia. Four of 5 subjects presented with congenital anomalies, 3 of whom demonstrated radioulnar synostosis. Additional dysmorphic features identified include craniofacial (low set ears x1), cardiac (PDA x1, VSD x1, aortic root dilation x1), pulmonary (pulmonary hypertension x1, arteriovenous malformations x1), and developmental delay. One subject presented at age 13 years with acute pancytopenia, hypocellular marrow, no dysmorphisms, and a MECOM variant of unknown significance. The identified MECOM mutations include one 4.1 Mb deletion involving several genes including MECOM, one variant affecting a splice acceptor consensus sequence predicted to disrupt splicing, and three novel missense mutations, Tyr949Cys, Arg950Thr, and Tyr1118Cys, all of which were absent from public databases and were predicted in silico to be deleterious.

Conclusion: We describe the phenotypic spectrum of 5 patients with novel MECOM variants. A subset of patients lacked radio-ulnar synostosis and had presence of additional systemic anomalies, demonstrating a varied clinical phenotype that is not isolated to RUSAT syndrome. A centralized publically accessible database to share clinically annotated MECOM variants, together with analysis by experts in MECOM function would advance our understanding of the clinical interpretation of MECOM variants. MECOM should be considered in the differential diagnosis of bone marrow failure and we advocate for the inclusion of MECOM in targeted sequencing panels.

Poster # 214 | ASSESSMENT OF QUALITY OF LIFE AMONG B -THALASSEMIA MAJOR PATIENTS AT A TERTIARY CARE HOSPITAL IN EGYPT

Mona Mohamed Hamdy Mahmoud, Marwa Rashad, Iman Draz, Azza Ayad

Cairo University, Cairo, Egypt

Background: Beta thalassemia is regarded as a serious public health problem in the Mediterranean region, Southeast Asia, and the Middle East. However, very few studies have been conducted to assess the quality of life (QoL) among thalassemia major patients.

Objectives: to assess the quality of life among B-thalassemia major patients using Short Form (SF)-36 questionnaire and to determine the factors associated with their quality of life.

Design/Method: A cross-sectional study was conducted among thalassemia major patients who were attending the hematology outpatient clinic at Cairo University Hospital, during the study period. Data were collected between October 2016 and March 2017. The quality of life was assessed for patients aged $\geq$17 years.

Results: The mean age of the studied group was 18.32$\pm$ 1.33 years. The majority (93.63%) had one monthly blood transfusion. The mean total score of SF-36 was 44.90$\pm$7.54. General health perception domain was the most affected domain with mean score, while vitality was the least affected one. There was no statistically significant difference between males and

females regarding different quality domains except for vitality where the mean score was significantly higher in males than females ($p = 0.05$). Age at onset of disease, and at first blood transfusion were the most documented factors positively correlated with the quality of life among the enrolled thalassemia patients.

Conclusion: the quality of life in thalassemia major patient was found to be compromised. All thalassemia patients should undergo assessment of the quality of life so that interventions focusing on the affected domains can be implemented.

Poster # 215 | THE FAMILIES WITH ADOPTED CHILDREN WITH THALASSEMIA STUDY (FACT STUDY)

Ashley Cronkright, Jennifer Eile, Diane Calamaras, Janice Beatty, Wendy Murphy, Danielle Massey-Hill, Sandy Gilbert, Susan Carson

Boston Children's Hospital, Boston, Massachusetts, United States

Background: International adoption of children with special needs has become more prevalent in recent years leading to tremendous growth in the number of U.S. thalassemia patients adopted from foreign countries. Currently 13% of the 1,119 thalassemia patients registered in the Cooley's Anemia Foundation (CAF) Patient Database have been adopted from foreign countries, primarily China. As this population continues to grow, further information is needed in order to provide these families with best supportive care.

Objectives: The primary goal of this study is to characterize the socio-demographics and health statuses of adopted children with Thalassemia and their families. A secondary goal is to describe adoptive families' motivations, experiences, challenges, and support resources.

Design/Method: A REDCap survey was accessed by families of adopted children with thalassemia through the CAF website and CAF social media from January to August 2017. Following a four-question screen, eligible subjects were directed to complete an adoption questionnaire. Families who had at least one adopted child with thalassemia receiving care at a participating Thalassemia Treatment Center or Hematology Office in the U.S. were considered eligible. Descriptive statistics were analyzed using SAS 9.4. Respondents who were ineligible or who provided incomplete data were removed from the dataset prior to analysis.

Results: Of 78 survey respondents, 67 qualified and completed the survey. These households had adopted a total of 74 children with thalassemia (33.8% male), most from China (93.2%), where they had been living in orphanages (73.0%). Legal guardians identified primarily as Christian (87.3%). The majority had completed post-secondary education (76.9%) with reported household incomes greater than $80,000 (76.1%). Most adoptive families were connected to an adoption group or community including online groups, local support groups, and adoption networks (98.5%). Commonly cited challenges were: 1) volume of frequent medical appointments, 2) Insufficient support from their local care centers, and 3) Financial burdens. The reality of care for the population of adopted patients with thalassemia in the U.S does not seem to match the expectations set by their providers.

Conclusion: We are hopeful this data will be used to assist adoptive families navigating the complexities of thalassemia care. The findings suggest that this population would benefit from additional outreach, education, guidance, and advocacy resources – especially in the early stages of adoption and during initiation of post-adoption medical care.

We would like to acknowledge the National Thalassemia Nurses and Social Workers Committee and The Cooley's Anemia Foundation for their work and support with this project.

Poster # 216 | EVALUATION OF QUALITY OF LIFE IN SRI LANKAN PATIENTS WITH THALASSEMIA

Nancy Olivieri, Helen Chan, Eymard dela Rea, Amir Sabouhanian, Sandara Wadanamby, Dulanjalee Senadeera, Malsha Walgamage, Thilini Walgamage, Prarthana Seneviratne, Anuja Premawardhena, Angela Allen, David Rees, David Weatherall, Robert Yamashita

National Thalassemia Centre, Kurunegala, Sri Lanka

Background: In many higher-income countries, thalassemia major has become a chronic disorder; many outcomes are different in emerging countries with more limited resources. Most analyzes of health-related quality of life (QofL) in thalassemia have been conducted in high-income settings.

Objectives: To assess the impact of health status on QofL in thalassemia patients in an emerging country.

Design/Method: We assessed QofL in 110 randomly-selected patients (72 thalassemia major; 33 with Hemoglobin E thalassemia; five thalassemia intermedia) at The National Thalassemia Center in Kurunegala, Sri Lanka where approximately 800 patients are managed. Treatment is free, but compared to North America/Europe, access to tertiary staff and other resources are limited. Overall, control of body iron as estimated by serum ferritin concentration (mean± SEM, 2906±267 μg/L) was not optimal in many patients. To understand the impact of health status on QofL, we used the SF36v2 health survey, analyzing scores of physical function,

pain, general health, social functioning, emotional and mental health, to generate overall physical and mental component scores.

Results: Compared to reports from higher-income countries (American Journal of Hematology 2011; 86:92–5), physical function scores (mean±SD, 48.16±10.72) were similar in Sri Lankan patients; indeed, in three categories (physical role, social function, emotional role), Sri Lankan scores were slightly higher. By contrast, compared to scores from higher-income settings, those estimating bodily pain, general health, and mental health were significantly lower, resulting overall in a significantly lower physical component score in Sri Lankan patients. Male Sri Lankan patients reported higher scores than females, and somewhat surprisingly, in four categories (physical function, physical role, social function and emotional role) reported higher scores than those obtained in higher-income settings. Lower scores in physical functioning, leading to an overall lower physical component score, were recorded by females. Patients with Hemoglobin E thalassemia reported generally poorer QofL than those with thalassemia major. The lack of differences in QofL in patients with "high" and "low" hemoglobins was likely related to low pre-transfusion Hbs (mean±SEM, 8.31 ± 0.14 g/dL) in nearly all patients.

Conclusion: These early data in a small cohort of thalassemia patients in an emerging setting suggest that in many patients bodily pain, reduced mental health, and poorer views of general health affect overall QofL. Prospective studies in larger cohorts including evaluation of adequacy of transfusions and chelation therapy, complications, and overall accessibility of care may guide approaches to improve QofL in lower-income settings of thalassemia care.

Poster # 217 | FACTORS AFFECTING BONE MINERAL DENSITY IN YOUNG CHILDREN AND ADOLESCENTS WITH TRANSFUSION DEPENDENT THALASSEMIA

Geetanjali Bora, Anand Prakash Dubey, Tarun Sekhri, Mammen Puliyel, Aparna Roy

Maulana Azad Medical College, New Delhi, Delhi, India

Background: In the last two decades, the presence of osteopenia has been described in optimally treated patients with transfusion dependent Thalassemia, the pathogenesis of which seems to differ from osteopenia in non-transfused patients. The prevalence rate of low bone mineral density (BMD) in pediatric population is highly variable amongst studies done worldwide. Furthermore, the role of metabolic and endocrine factors in determining bone mass in this population is not well understood.

Objectives: To assess BMD in subjects with transfusion dependent Beta Thalassemia by Dual-energy-x ray-absorptiometry and find its co-relation with clinical, biochemical and hematological parameters.

Design/Method: This is a comparative cross-sectional study and includes patients with transfusion dependent Beta Thalassemia between ages 6 to 16 years enrolled from a Thalassemia day care center in the year 2012 -2013. At the time of enrollment age, sex, BMI z scores, pubertal staging, duration and type of chelation therapy were noted. Enrolled subjects were scanned for BMD at lumbar spine L2-3 and left femoral neck using DEXA scan. The BMD was expressed in mean values and z scores. Age, BMI, ethnicity and gender matched historic controls were used to generate z scores. 5 ml of pre transfusion fasting venous blood samples were obtained to test for serum calcium, phosphate, alkaline phosphatase, PTH, thyroid function panel, serum ferritin and serum IGF-1 levels. Mean values for pretransfusion hemoglobin and serum ferritin over last 12 months were calculated.

Results: Total no of subjects 50, Median age 11.6 years, Male 32 (64%), Female 18 (36%), ethnicity 100 % Asian, BMI < 3rd centile 13 (26%), pre pubertal 50%, all receiving transfusion and chelation therapy. Prevalence of low (z score < -1 SD) and very low (< -2.5 SD) BMD was 74%, 52 % at L1-L2 respectively and 66 %, 24% at left femoral neck respectively. There was trend of lower BMD z scores with advancing age. Statistically significant co-relation (p value < 0.05) was found between low BMD and low mean pretransfusion hemoglobin, serum phosphate, IGF -1 and vitamin D levels

Conclusion: A sizable proportion of children and adolescents with transfusion dependent Thalassemia have suboptimal bone mineral density and this decline may start as early as 6–7 years of age despite being on transfusion regimen highlighting the importance of yearly DEXA screening and optimization of pre- transfusion hemoglobin, vitamin D and IGF 1 levels.

Poster # 218 | THROMBOCYTOPENIA IN THE SETTING OF MENORRHAGIA-INDUCED IRON DEFICIENCY ANEMIA: A SERIES OF THREE CASES

Christine Smith, Heather McDaniel

Vanderbilt University Medical Center, Nashville, Tennessee, United States

Background: It is well described that iron deficiency anemia (IDA) can co-present with thrombocytosis or thrombocytopenia, though cases of thrombocytopenia are less frequent than thrombocytosis. Prior reports of thrombocytopenia have included adult and pediatric patients with menorrhagia (1-2), menorrhagia due to uterine fibroids (3), or other gynecologic abnormalities (4). Our cases highlight the pattern of IDA, thrombocytopenia, and menorrhagia in the setting of significant menstrual clotting without observed gynecologic abnormalities in African-American adolescents.

Objectives: To describe the clinical course of three adolescent females with severe IDA, menorrhagia, and thrombocytopenia.

Design/Method: Retrospective case series.

Results: Our cases included three female African-American patients ages 12–17 who presented with severe anemia and concurrent thrombocytopenia in the setting of menorrhagia. All three patients reported heavy and prolonged menstrual cycle bleeding with significant clots. Two of the three were admitted for transfusions at presentation and noted to have significant menstrual bleeding with continued blood loss requiring additional transfusions until bleeding was controlled with estrogen therapy. These two patients were evaluated with pelvic ultrasounds revealing a prominent endometrium in both patients and hyperechoic material consistent with a clot in one patient. Average hemoglobin on presentation was 4.3 gm/dL (2.8-6.5), average platelet count was 70,000/mcL (18,000-99,000), and average MCV was 63 (54-68). All had severe iron deficiency with an average ferritin of 4 ng/mL (2-7) subsequently treated with oral iron. One patient had a prior history of IDA that required transfusion and had subsequent normalization of her complete blood count. Two patients had subsequent thrombocytosis before normalization of their platelet counts. Two patients received platelet transfusions: one due to recent neurosurgical intervention with a higher goal platelet count and the other to help control menstrual bleeding after a nadir platelet count of 9,000.

Conclusion: A review of the clinical history and red cell indices pointed to IDA and ongoing blood loss from menorrhagia as the reason for the bicytopenias. The thrombocytopenia in these cases may have been exacerbated by consumption of platelets in the significant clots all three patients reported. It is reasonable to treat with iron supplementation and supportive care which may include transfusions or management of menorrhagia with oral contraceptives or other hormonal methods. 1. Berger M, et al, American Journal of Hematology, 1987. 2. Morris VK, et al, Pediatr Hematol Oncol, 2010. 3. Verma V, et al, Ann Hematology, 2014. 4. Ibrahim R, et al, Clinical Medicine Insights: Case Reports, 2012.

Poster # 219 | DIFFERING PRENATAL HEMOGLOBINOPATHY SCREENING PRACTICES: HOW CAN THE PEDIATRIC HEMATOLOGIST INTERVENE?

Scott Moerdler, Kerry Morrone, Michael Roth, Ellen Silver, Melissa McKee, Siobhan Dolan, Kafui Demasio

Children's Hospital at Montefiore, Bronx, New York, United States

Background: Sickle cell disease is one of the most common inherited red blood cell disorders, yet many are not aware of their carrier status. The American College of Obstetricians and Gynecologists' guidelines recommend that pregnant women of African, Mediterranean and Southeast Asian descent be screened for hemoglobinopathies with a CBC and hemoglobin electrophoresis1. However, adherence to this practice and frequency of improper screening with Sickledex is unknown. Proper screening and counseling can impact families' knowledge, allowing for establishing relationships with pediatric hematology providers earlier.

Objectives: We sought to assess prenatal hemoglobinopathy screening practice patterns and methods of Obstetrics & Gynecology (OBGYN) and Family Medicine providers in the NYC regional area.

Design/Method: A cross-sectional electronic survey was administered to OBGYN and Family Medicine practitioners from four NYC institutions. Questions focused on prenatal hemoglobinopathy screening practices using case scenarios with variations on parental trait status and ethnicities. Chi-square analyses were used to compare the two provider groups on categorical variables.

Results: There were 98 total responses; 71 surveys were complete, of which 48 were OBGYN and 23 Family Medicine providers. Respondents were mainly from academic medical centers, with the majority being faculty (68% of the OBGYNs and 41% of Family Medicine). No significant difference was found in frequencies of screening patients with a positive family history of a hemoglobinopathy. When asked about screening practices for patients without a personal/family history of a hemoglobinopathy, 92% of OBGYNs versus 70% of Family Medicine providers "always" screened for hemoglobinpathies ($p = 0.03$). When analyzed by ethnic background, there were significant differences by group in screening patients of White (92% vs 70%), Black (94% vs 74%), Mediterranean (94% vs 74%), and Asian descent (94% vs 70%) ($p \leq 0.05$ for all). However, in cases where the hemoglobinopathy carrier status of both parents was known, there was no difference in screening with a hemoglobin electrophoresis. Furthermore, >20% of all respondents use Sickledex for screening in the case scenarios.

Conclusion: This pilot survey highlights a difference in the methods and likelihood of prenatal hemoglobinopathy screening based on the type of prenatal care provider. Screening differences can lead to variations in prenatal guidance, diagnostic procedures, informed decision-making and knowledge of families referred to pediatric hematology clinics. This is the first study analyzing prenatal screening for hemoglobinopathies in OBGYN and Family Medicine. Improving prenatal screening practices by collaborating with hematologists may decrease health care disparities and allow for earlier relationship building with pediatric hematology. 1. ACOG, Opinion#691, 2017

Poster # 220 | HERMANSKY- PUDLAK SYNDROME: SPECTRUM IN OMAN

Hanan Nazir, Nashat Alsukaiti, Yasser Wali

Sultan Qaboos University Hospital, Muscat, Muscat, Oman

Background: Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder, characterized by the triad of oculocutaneous albinism, a hemorrhagic diathesis resulting from storage pool-deficient platelets, and accumulation of ceroid/lipofuscin-like material in various tissues. Before 2016, nine different types of Hermansky-Pudlak syndrome were identified, which can be distinguished by their signs and symptoms and underlying genetic cause. In 2016, a tenth type was defined based on mutations in the AP3D1 gene. HPS type 2 is characterized in addition by severe neutropenia and recurrent sinopulmonary infection. The disease is more common in Puerto Rico, and this is the first report from Oman.

Objectives: To describe the clinical, laboratory and genetic characteristics of HPS sub-types in Oman, including the first 2 cases of HPS type 2.

Design/Method: This is a retrospective study, including 7 cases with HPS that had been suspected clinically and confirmed through genetic mutation analysis. Clinical data included sex, age at presentation, initial clinical presentation (skin, eyes, development, neurological involvement, bleeding tendency, recurrent infections) and course of disease. Laboratory data (complete blood counts, platelet and absolute neutrophil counts, coagulation screening, platelet function tests by platelet function analyzer, and platelet aggregation studies using different agonist had been recorded. PCR and next generation sequencing for genetic confirmation by testing mutations in HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBP1,, BLOC1S3, BLOC1S6 genes had been done.

Results: Seven Omani cases with HPS have been identified (4 males and 3 females). Their age ranged between 0 (at birth) to 10 years. Two patients had HPS type 2, 1 patient had type 6, while the other 4 cases had HPS type 3. No other sub-types were encountered in Oman. All patients were products of consanguineous marriage. One patient had adrenal Hge, while the others had mild hemorrhagic phenotype, characterized by recurrent bruising and mild epistaxis. Laboratory testing confirmed variable platelet aggregation defects with different platelet agonists. All patients had characteristic hypopigmentation, iris transillumination, nystagmus, and foveal hypoplasia. Both patients with HPS type 2 had the same homozygous mutation in the AP3B1 gene (c.12_13delTA), and presented with severe neutropenia. Early diagnosis and initiation of GCSF on one of them improved outcome and prevented the development of complications. Late diagnosis in the other patient resulted in the development of bronchiectasis as a result of recurrent sinopulmonary infections.

Conclusion: Increased clinician awareness on HPS is needed. High index of suspicion and early referral for diagnosis/initiation of proper treatment might help to improve outcome.

Poster # 301 | INITIAL RESULTS FROM A COHORT IN A PHASE 2A STUDY (GBT440-007) EVALUATING ADOLESCENTS WITH SICKLE CELL DISEASE TREATED WITH MULTIPLE DOSES OF VOXELOTOR, A SICKLE HEMOGLOBIN POLYMERIZATION INHIBITOR

Carolyn Hoppe, Adlette Inati, Clark Brown, Winfred Wang, Lewis Hsu, Victor Gordeuk, Robert Liem, Gerald Woods, Connie Piccone, Erica Fong, Ganesh Balaratnam, Sandra Dixon, Margaret Tonda, Carla Washington, Yifah Yaron, Josh Lehrer

UCSF Benioff Children's Hospital Oakland, Oakland, California, United States

Background: Sickle cell disease (SCD), a genetic disorder characterized by defective sickle hemoglobin (HbS), triggers red blood cell sickling, hemolysis, vaso-occlusion, and inflammation. Ischemic injury from SCD starts in infancy and accumulates over a lifetime, causing pain, fatigue, and progressive end-organ damage that culminates in early mortality. Voxelotor (GBT440) is an oral, once-daily therapy that modulates hemoglobin's oxygen affinity, thereby inhibiting hemoglobin polymerization.

Objectives: To assess the safety, pharmacokinetics, and efficacy of voxelotor in pediatric patients with SCD.

Design/Method: This ongoing study is being conducted in 2 parts: Part A: a single dose of voxelotor 600 mg in

pediatric and adolescent patients; Part B: multiple doses of voxelotor 900 mg/d or 1500 mg/d for 24 weeks in adolescents. Part B's primary objective is to assess the effect of voxelotor on modifying anemia. Secondary objectives include measuring other markers of disease modification, such as hemolysis; daily SCD symptoms, using a patient-reported outcome (PRO) measure; and safety.

Results: As of November 6, 2017, 24 patients (10 females) had received voxelotor 900 mg and 12 patients (6 females) had received voxelotor for ≥16 weeks. The median age for the 12 patients was 13 years, 92% were receiving hydroxyurea (HU), and 41% had ≥1 painful crises in the past year. Data for hemolysis measures are available for 11 patients who received voxelotor for 16 weeks. Six of the 11 patients achieved a hemoglobin (Hb) response of >1 g/dL increase. Laboratory markers of hemolysis improved concordantly; the median reductions in reticulocytes and indirect bilirubin were 11% and 40%, respectively. Ten of 12 patients showed reduction in total symptom scores (TSS) at week 16, with a 94% median reduction in TSS from baseline. There were no treatment-related serious adverse events (AEs) or drug discontinuations due to AEs.

Conclusion: Voxelotor 900 mg for 16 weeks in adolescents with SCD, the majority receiving HU, demonstrated consistent, sustained efficacy on Hb levels and measures of hemolysis; >50% of patients showed a >1 g/dL improvement in Hb. Improvement in TSS in mildly symptomatic patients suggests that the PRO is sensitive to treatment effect and supports use in the ongoing HOPE phase 3 study. Voxelotor's reassuring safety profile is consistent with results in adults. These interim results support ongoing clinical evaluation of voxelotor as a potential disease-modifying therapy for adults and children with SCD. Supported by Global Blood Therapeutics.

Poster # 302 | ACUTE KIDNEY INJURY DURING PARVOVIRUS B19-INDUCED TRANSIENT APLASTIC CRISIS IN SICKLE CELL DISEASE

Jamie Oakley, Rima Zahr, Rakesh Patel, Varsha Kulkarni, Rhiannon Penkert, Julia Hurwitz, Jane Hankins, Jeffrey Lebensburger

University of Alabama at Birmingham, Birmingham, Alabama, United States

Background: Acute kidney injury (AKI) is a common complication in sickle cell disease (SCD), and a potential risk factor for sickle nephropathy. AKI is associated with acute decline in hemoglobin (Hb) during vaso-occlusive pain crisis and acute chest syndrome (ACS). It is unclear which pathologic factor plays a stronger role in AKI development during Hb drop: increase in free heme during vaso-occlusive events secondary to hemolysis or Hb decline itself.

Objectives: To investigate if Hb decline alone is associated with AKI, we tested if the renal function of patients with SCD worsened during parvovirus B19-induced transient aplastic crisis (TAC), in the absence of accentuated hemolysis.

Design/Method: With IRB approval, a retrospective study of patients who had laboratory confirmed parvovirus-B19 was conducted. Serum creatinine (SCr), both during and within 12 months from the TAC event, was collected. Comparisons of the clinical and laboratory characteristics were analyzed using the Wilcoxon test for continuous variables. AKI was defined as an increase in SCr by ≥0.3 mg/dL or a 50% increase in SCr from baseline. To evaluate differences in change in Hb on AKI risk, changes in SCr during TAC were compared to those during pain crisis or ACS admissions by fitting a generalized linear mixed model for binary outcome. A comparative sample of 149 ACS events and 197 vaso-occlusive pain crisis were used to estimate rates of AKI according to Hb levels.

Results: Three (9%) of the 34 patients with SCD developed AKI during TAC. No association was identified between change in Hb from baseline to TAC event ($p = 0.08$). No cases of AKI were identified until Hb decreased <5.0 g/dL or the change in Hb was ≥4.5 g/dL from baseline. Next, we developed a model to evaluate the impact of change in Hb from baseline for patients admitted with TAC, pain crisis or ACS on AKI. With a 2 g/dL decrease in admission Hb from baseline, patients with TAC had a 3% probability of developing AKI, while acute chest syndrome and pain crisis would have a 9% and 27% probability, respectively.

Conclusion: Our data suggest that AKI is still prevalent during parvovirus B19-induced TAC. However, the risk of AKI during a TAC event is 3 and 9 times lower than that from severe anemia induced by acute chest syndrome and vaso-occlusive pain events, respectively. Hemolysis-induced anemia during SCD crisis appears to have a more significant role in the development of AKI as compared to agenerative anemia.

Poster # 303 | TWENTY-YEAR FOLLOW-UP OF PATIENTS WITH HEMOGLOBIN E THALASSEMIA IN SRI LANKA

Nancy Olivieri, Anuja Premawardhena, Angela Allen, Amir Sabouhanian, Sachith Mettananda, Helen Chan, Sandara Wadanamby, Dulanjalee Senadeera, Malsha Walgamage, Thilini Walgamage, Prarthana Seneviratne, Saambavy Shanmugananatham, Saranyau Uthayakumaran, Bhumika

Deb, Dayananda Bandara, Robert Yamashita, David Rees, David Weatherall

National Thalassemia Centre, Kurunegala, Sri Lanka

Background: The natural history of Hemoglobin E beta thalassemia (HbEthal), the commonest form of severe beta thalassemia worldwide, has been examined in very few long-term studies. Previously, we reported findings in 109 HbEthal patients in Sri Lanka.1

Objectives: To evaluate longterm requirements for transfusion and splenectomy, complications and death in HbEthal patients.

Design/Method: All available patients were reviewed 1-4 times annually over 12 years.

Results: 33 patients (30%) died, aged (mean ± SEM) 29.3 ± 4.2 years; the (known) causes commonly included iron overload (9) and infection (12); 76 patients surviving patients are aged 33.4 ± 1.2 years. Of 109 patients originally classified by severity (Group 1 the mildest, and Group 5 the most severe, phenotypes), 62 (57%) were assessed as mild (Groups 1 and 2), of whom transfusions had been discontinued in 46. Ultimately, 23/46 (50%) resumed transfusions, often following shifts to increasingly severe phenotypes including increasing intolerance to anemia. Age at resumption of transfusions (following a transfusion-free interval of 14.9 ± 1.6 years) was 32.8 ± 2.7 years; in the more severe Groups 4 and 5, regular transfusions were stopped in 27/33 patients and resumed in 22/27 (81%), at younger ages (19.9±1.8 years) and after shorter transfusion-free periods (10.1±1.4 years) than in "milder" patients. Mid-parental height (MPH) was ultimately achieved in 53%. 84 patients (77%) were splenectomized; updated analysis of responses to splenectomy (originally "Group 3" patients), showed that splenectomy (at 9.0 ± 0.9 years) was followed by an extended, but impermanent, transfusion-free interval (11.1 ± 1.4 years); 50% patients resumed transfusions, usually related to exercise intolerance or poor growth. In Groups 1 and 2, complications of anemia and ineffective erythropoiesis, including leg ulcers (in 38% and 50%) and gallstones (44% and 54%), were more frequent than in Groups 4 and 5; fractures were observed (25-48%) across all groups, except for regularly-transfused Group 5 patients (0%). Pulmonary artery pressures >30 mm were recorded in 39% patients.

Conclusion: Evaluation of patients with HbEthal requires observations over years, without which definition of patients as "mild" or "severe" may be misleading. While in many patients transfusions may be withheld or reduced in frequency, troublesome complications may surface with advancing age even in "milder" patients. Although individual consideration of transfusion requirements is critical, the availability of effective chelation, where this can be provided without prohibitive cost, may alter the balance of risks and benefits of regular transfusions in HbEthal. 1(Premawardhena A. Lancet 2005).

Poster # 304 | SCREENING FOR SOCIAL DETERMINANTS OF HEALTH IN AN URBAN PEDIATRIC SICKLE CELL DISEASE CLINIC: A QUALITY IMPROVEMENT INITIATIVE

Alexandra Power-Hays, Akosua Mensah, Amy Sobota

Boston Medical Center, Boston, Massachusetts, United States

Background: Social determinants of health (SDH) are environmental and socioeconomic factors, such as access to food and housing that affect health outcomes. Pediatricians are increasingly screening for SDH as part of primary care visits, however less is known about screening for SDH in pediatric hematology. Evidence suggests that SDH play a role in disease severity for children with SCD, who face significant socio-economic and racial disparities.

Objectives: The goal of our quality improvement (QI) project was to increase the percentage of patients with SCD who were connected to community resources for unmet social needs.

Design/Method: We based our intervention on the successful implementation of WeCare in our institution's pediatric primary care clinic. Eligible patients were identified at the start of each clinic session. On arrival the parent was given a self-reported screening tool for six SDH (childcare, education, employment, food, utilities and housing). Results were entered in the electronic health record by the physician or social worker who then printed a pre-existing resource list for patients with a positive screen. We used a series of Plan-Do-Study-Act (PDSA) cycles to study tests of change. We tracked process measures (percentage of patients screened, percentage of patients with an unmet social need who received a resource sheet), outcome measures (percentage of patients with an unmet social need who connected with a community resource) and balancing measures (staff, patient and provider satisfaction). Run charts were reviewed weekly and then monthly to inform further tests of change. Examples of PDSA cycles include who gave the paper survey to patients (social worker or physician versus medical assistant) and length of time between surveys (3 to 6 months).

Results: Between August and December 2017 screening rates improved from 57% to 88%. Of the patients screened, 67% report at least one unmet social need; of those 33% received a targeted list of community resources in the first month of the project, and 92% in the fifth month. Finally, 44% of patients

reached by phone had connected with a community resource within 2 weeks of the clinic visit.

Conclusion: We have successfully implemented universal screening for SDH for patients with SCD in our urban pediatric hematology clinic without requiring extra staff. Next steps include further PDSA cycles to connect more patients to appropriate resources, and tracking improvement in health care utilization outcomes from addressing SDH in this vulnerable patient population.

Poster # 305 | THE PHARMACOKINETICS OF VOXELOTOR FOLLOWING SINGLE DOSES IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

Carla Washington, Rada Savic, Michelle Green, Adlette Inati, Jeremie Estepp, Clark Brown, Carolyn Hoppe, Winfred Wang, Gerald Woods, Ganesh Balaratnam, Sandra Dixon, Erica Fong, Athiwat Hutchaleelaha, Margaret Tonda, Josh Lehrer

Global Blood Therapeutics, South San Francisco, California, United States

Background: The clinical manifestations of sickle cell disease (SCD), chronic hemolytic anemia, and vaso-occlusion occur as a direct result of sickle hemoglobin (HbS) polymerization. Voxelotor (GBT440) is a first-in-class, oral, once-daily investigational agent designed to modulate hemoglobin's oxygen affinity in a targeted approach to inhibit HbS polymerization.

Objectives: To examine the pharmacokinetics (PK), safety, and dosing of voxelotor in children (aged 6–11 years) and adolescents (aged 12–17 years) with SCD from Part A of the GBT440-007 study.

Design/Method: GBT440-007 is an ongoing, open-label, phase 2a study in patients aged 6–17 years with SCD (sickle cell anemia or sickle beta zero thalassemia). Part A of this study (the focus of this abstract) is examining PK of single-dose (600 mg) voxelotor. PK samples to measure whole blood and plasma voxelotor concentrations were collected up to 15 days following single-dose administration. Separate population PK (PPK) models were developed to describe the concentration versus time profiles of voxelotor in whole blood and plasma using nonlinear mixed effects modeling (NONMEM, version 7.3). PPK modeling and physiologically based PK (PBPK) modeling were used to simulate voxelotor PK parameters and support dose selection for future evaluation in younger children.

Results: Part A included 7 adolescents (4 females; median age 16 years [range 14-16]) and 6 children (3 females; median age 8.5 years [range 6-10]). Mean weight was 52.8 kg (range 45–66 kg) and 21.1 kg (range 16–38 kg) in adolescents and children, respectively. Voxelotor was well tolerated with no drug-related grade ≥3 adverse events (AE) or serious AEs. A 2-compartment model with first-order absorption best described the PK of voxelotor (and was the same model structure used for adults with SCD). Voxelotor PK exposures in adolescents were comparable to those observed in adults, but higher exposures were observed in children. PPK and PBPK modeling support the use of a weight-based dosing strategy in younger children (aged <12 years) in future trials.

Conclusion: Adult voxelotor doses can be used in adolescents. However, based on higher PK exposures, a lower weight-based dosing strategy is recommended in children. PPK and PBPK modeling provides an innovative approach to minimize experimental dosing in children and accelerate dose selection of voxelotor in ongoing and future clinical studies. This abstract is supported by Global Blood Therapeutics.

Poster # 306 | DISPENSING LIQUID HYDROXYUREA TO PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE: A NOVEL INSTITUTIONAL APPROACH TO REDUCING BARRIERS TO ADHERANCE

Puja Umaretiya, Amanuel Kehasse, Myrdine Sinous, Amy Sobota

Boston Medical Center, Boston, Massachusetts, United States

Background: Hydroxyurea (HU) reduces rates of acute complications, and improves long term outcomes in patients with sickle cell disease (SCD) and is now FDA approved for children. Through previous work we have increased the number of eligible patients on HU in our clinic, however accessing a compounding pharmacy remained a significant barrier to HU adherence for infants and children who cannot swallow capsules.

Objectives: The objective of our quality improvement project was to improve adherence to HU among pediatric patients with SCD at our urban safety net hospital by addressing barriers to obtaining liquid HU.

Design/Method: To begin we met with the leadership of our outpatient pharmacy which offers mail order delivery. However, like most retail pharmacies, they do not have the necessary protective equipment to compound liquid HU. Through a series of discussions, we began a unique partnership with our institution's inpatient chemotherapy pharmacy who compounds the liquid HU and delivers it to the outpatient

pharmacy, who then dispenses liquid HU to families. Using a series of Plan-Do-Study-Act (PDSA) cycles we tracked adherence by calculating the medication possession ratio (MPR), defined as the percentage of days in a given period of time that each patient had their medication on hand. The MPR for liquid HU MPR among enrolled patients was tracked by pharmacy staff and reviewed monthly. Additional PDSA cycles included adding automatic refills and reminder calls by pharmacy staff and improving communication about delivery. We also tracked patient satisfaction.

Results: Between March 2016 and December 2017, a total of thirty pediatric patients were enrolled in our program for on-site compounding and free mail order delivery of liquid HU. MPR for liquid HU is currently 93.8% among enrolled patients, significantly higher than the MPR of 60% reported in the literature, and has risen steadily since the beginning of the project. Families are highly satisfied with the program, specifically appreciating the convenience of mail order delivery, saving on delivery fees, and reminder calls when refills were due.

Conclusion: By compounding and dispensing liquid HU directly from our institution's outpatient pharmacy we have significantly improved adherence to this HU therapy in our high-risk population. Next steps include analysis of change in clinical outcomes for patients enrolled in this program. As adherence to hydroxyurea is associated with decreased acute care utilization and cost, programs such as ours could play a crucial role in reducing the excessive costs and ED utilization among this patient population.

Poster # 307 | EXPERIENCE WITH THE IRON-CHELATOR DEFERASIROX IN SRI LANKAN PATIENTS WITH THALASSEMIA

Nancy Olivieri, Priya Chandrakumaran, Sanasi Jayawardena, Amir Sabouhanian, Anuja Premawardhena, Sachith Mettananda, Dulanjalee Senadeera, Sandara Wadanamby, Malsha Walgamage, Thilini Walgamage, Prarthana Seneviratne, I Silva, N Hameed, Dayananda Bandara, JM Nimal, Helen Chan, saambavy Shanmugananatham, Bhumika Deb, Robert Yamashita, David Rees, Angela Allen, David Weatherall

National Thalassemia Center, Kurunegala, Sri Lanka

Background: Experience with the iron-chelator deferasirox is reported widely in higher-income settings. By contrast, real-life experiences in emerging countries are infrequently reported.

Objectives: To evaluate, in a non-trial setting, the real-life response to deferasirox in an emerging country.

Design/Method: In Sri Lanka's National Thalassemia Center which manages 800 patients without tertiary staff, quantitative evaluations of body iron or estimates of extra-hepatic iron, the records of 328 patients who began deferasirox in 2010/11 were retrospectively reviewed.

Results: Baseline assessments (mean±SEM) indicated substantial iron loading [serum ferritin (SF) 4,529±125 ug/L; serum ALT 111±3.5 U/L (normal ≤ 40 U/L)]. Deferasirox was introduced at low doses (21.2 ± 0.3 mg/kg/day); many patients started at <20 mg/kg and, after 12 months, doses remained ≤30 mg/kg/day in 60% patients. After 24 months, SF in 50% patients remained >2,500 ug/L; only by 48 months had (mean) SF declined to <2,500 ug/L (2475±344; P<0.001). Similarly, mean ALT normalized (to 35 ± 5 U/L) only by 60 months. Death and complications were not systematically recorded by staff who had been charged, without provision of additional resources, with the introduction of this new drug in hundreds of patients. These results contrast to those in Sri Lanka's tertiary thalassemia center where, in 107 patients following the introduction of deferasirox 32 ± 0.1mg/kg/day, SF declined rapidly, even in relatively less iron-loaded patients (from 3,231±278 to 2,153±218 μg/L after 24 months; P = 0.0002).

Conclusion: These findings underscore the importance, during the implementation of new drug regimens in lower-income centers with marginal resources, for investments in methods to quantitate body iron burden, hands-on educational initiatives to guide day-to-day management by competent but non-expert staff, and data systems to record efficacy, effectiveness, toxicity and compliance. Such investment is critical to optimising therapy and improving complications in thalassemia patients worldwide: even in Sri Lanka, where resources directed to thalassemia management are greater than in most of Asia, results in the oldest living cohort (born 1980–1990) indicate under-treatment [elevated iron burdens (SF 3,565±323 ug/L) and high prevalences of diabetes (27%) and hypothyroidism (29%)]. Even in a younger cohort (born 1990–2000) which has benefitted from improved treatments, the prevalence of many complications exceeds those reported from high-income settings. Over the next decade, and two decades after the 2006 WHO declaration that the impact of thalassemia on global mortality and morbidity is under-recognized, increased investments by governmental and non-governmental sources will be necessary to improve outcomes for Asian patients with thalassemia.

Poster # 308 | QUALITY IMPROVEMENT FOR UREA ADHERENCE IN KIDS WITH SICKLE CELL DISEASE (QUAKS)

Kay Saving, Nicole Alwan, Diana Simmons, Robert Lucia, Linda Drawhorn

OSF St. Francis Medical Center, Peoria, Illinois, United States

Background: A major barrier to success in Hydroxyurea (HU) treatment of patients with sickle cell disease (SCD) is non-adherence.

Objectives: To optimize HU adherence in patients with SCD.

Design/Method: A care model was designed by the Sickle Cell (QI) team at Children's Hospital to improve HU adherence among SCD patients. The original model included bimonthly family phone contact, monthly dispensing pharmacy phone contact and lab monitoring. Adherence measures included obtaining HU from pharmacy monthly, completion of monthly labs, Hb F percentage and MCV, and MTD achievement. From 6/2016 - 6/2017, several PDSA Cycles refined our care model. A one-year follow-up survey gathered feedback on the care model.

Results: The first-year data involved ~ 30 patients. The biggest improvements resulted from making pharmacy calls before patient/family calls, shipping liquid HU to outlying patients, and tracking call time/content. The QI goal was 75 % HU adherence by 12/2017. The 33% baseline adherence rate increased to 80% by 12/2016, and has remained in that range. The completion rate of patient/parent phone calls increased from 33% the first month to 77% at six months. Pharmacy prescription pick-up has increased from 50 % to 77% per month. Lack of liquid HU availability was overcome by shipping the medication to the patient's home. Parental hesitance to share information by phone, especially with QI team members with whom they had no established relationship, was overcome by having the longtime sickle cell nurse do many of the early calls. However, survey feedback showed families became comfortable with several clinic personnel calling. The calls gave families the opportunity to ask questions about their child and/or get additional information about SCD. The calls also provided an opportunity for seasonal flu shot or TCD testing reminders. The surveys gave information on the optimal time of day to reach each family, providing individualization and further increasing the percentage of completed calls. Two families surveyed said they no longer needed two calls a month because they were now able to remember to pick up HU, administer it, and get labs on their own.

Conclusion: This QI project has not only improved HU adherence, but also fostered health education/counseling, increased patient/parent satisfaction, and enhanced service utilization. Medical team member and patient/family comments demonstrate that it has helped build relationships and trust between families and the medical care system. Based on survey feedback, we will further individualize care to increase adherence rate and sustain improvements.

Poster # 309 | DELAYED OR INCORRECT DIAGNOSIS OF β-THALASSEMIA: α-GLOBIN GENE TRIPLICATION AS A COVERT GENETIC MODIFIER

Arun Gurunathan, Cristina Tarango, Patrick McGann, Charles Quinn

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: The thalassemias are a heterogeneous group of genetic blood disorders caused by mutations that decrease or eliminate the synthesis of the α- and/or β-globin subunits of hemoglobin. The phenotype of thalassemia depends on the interaction of the α- and β-globin gene clusters, because both loci determine the α-/β-chain balance. For example, a β-thalassemia phenotype can be more severe than expected when coinherited with α-globin gene triplication (copy number gain), which exacerbates the α-/β-globin imbalance.

Objectives: Describe four individuals with an incorrect diagnosis of β-thalassemia trait who were later properly diagnosed by comprehensive genetic testing to have β-thalassemia intermedia caused by heterozygous β-thalassemia mutations coinherited with triplicated α-globin loci.

Design/Method: Sequence analysis of the α-globin (HBA1/HBA2) and β-globin (HBB) genes, and copy number variation analysis of the α- and β-globin gene clusters by multiplex ligand-dependent probe amplification.

Results: Four unrelated individuals of northern European ancestry were evaluated for signs and symptoms not explained by a diagnosis of β-thalassemia trait (previously made by a pediatric hematologist), including growth delay, splenomegaly, moderate anemia, marked elevation of hemoglobin F, thalassemic facies, reticulocytosis, and/or indirect hyperbilirubinemia. Genetic testing revealed that all were heterozygous ($\beta/\beta 0$) for the same, single β-globin mutation [HBB.c.118C>T (p.Q40*)] and also heterozygous for an α-globin triplication ($\alpha\alpha/\alpha\alpha\alpha$anti-3.7). Their previous diagnoses of thalassemia trait had been made by complete blood counts, hemoglobin electrophoresis, and/or sequence analysis of the β-globin genes only. These individuals' phenotypes ranged from moderate anemia only to multiple stigmata of thalassemia, demonstrating the phenotypic variation of a thalassemia genotype. Correct diagnosis was made at an average age of 8.9 years. A trial of chronic transfusions was initiated for one patient for growth failure. All were educated about the potential for exacerbations of anemia, gallstones, osteoporosis, and iron overload (even without transfusions). Parental genetic testing was recommended to assess reproductive risk, because inheritance of this complex genotype can be apparently autosomal dominant.

Conclusion: Heterozygosity for a β-thalassemia mutation does not necessarily indicate β-thalassemia minor or "trait". When coinherited with α-globin gene triplication, a symptomatic form of β-thalassemia can occur. Correct and timely diagnosis of thalassemia requires careful consideration of the degree of anemia and examination for organomegaly, bony changes, and jaundice. Sequence analysis and copy number variation analysis of both the α- and β-globin gene clusters is key. Hematologists need to be aware of this diagnostic possibility and how to test for it to prevent inaccurate or delayed diagnosis.

Poster # 310 | IDENTIFICATION OF SICKLE CELL SUPER-UTILIZATION, A SINGLE INSTITUTION EXPERIENCE

Titilope Fasipe, Christine Youngblood, Precious Uwaezuoke, Devin Olivares-Reed, Heidi Russell

Baylor College of Medicine, Houston, Texas, United States

Background: The burden of healthcare costs for sickle cell disease (SCD) is nationally estimated at over $488 billion. The major components of these costs are inpatient and emergency center (EC) visits, many of which are potentially avoidable. In several chronic conditions, a subset of patients account for most of the avoidable encounters. Identifying these patients is the first step in targeted care delivery.

Objectives: To measure and analyze SCD patient utilization patterns in the EC and inpatient at Texas Children's Hospital (TCH).

Design/Method: We identified all individuals under 21 years old with any encounter at TCH associated with an International Classification of Disease (ICD)-9 or 10 code for SCD, including Hgb SS, Hgb SC, and Hgb S/beta thalassemia. For each patient, we identified all inpatient and EC encounters in the 365 days prior to their most recent encounter. Finally, each encounter was classified as associated with pain, acute chest syndrome (ACS), or "other" using an algorithm of discharge diagnosis codes and pharmaceutical delivery. The total number of SCD-associated EC and inpatient encounters over the prior year was calculated for each patient. We stratified each patient according to their utilization patterns: low (0-1 encounters), intermediate (2-3 encounters), and high ($\geq$4 encounters).

Results: We identified 952 unique patients with SCD that had at least one encounter from July 2016 until June 2017. There were 1,100 SCD-related encounters in the 365 days prior to their most recent encounter. Most (74%, n = 701) patients exhibited low-utilization patterns and 18% (n = 174) were intermediate. Finally, a small subset (8%, n = 77) demonstrated high-utilization patterns and accounted for 41% of all encounters. High-utilization was associated with older age and public payment mechanisms. Pain encounters were predominantly in pre-adolescents and teenagers with high- and intermediate-utilization patterns. ACS was most frequent in pre-teens and younger teens in the intermediate-utilization group. Finally, the youngest-aged high and intermediate users presented for other reasons such as febrile episodes and splenic sequestration.

Conclusion: Our findings reflect national trends in that a significant portion of encounters are attributed to a small subset of patients exhibiting a high- or "super-" utilization pattern. At our institution, SCD super-utilization is associated with older age and pain. We also identified a group of infants and toddlers with frequent encounters for fever. To comprehensively address this burden, it will be important to design interventions targeted toward age and specific medical needs.

Poster # 311 | CHARACTERIZATION, TREATMENT, AND TOXICITIES IN A PEDIATRIC DIAMOND BLACKFAN ANEMIA COHORT

David Claassen, Chen Li, Guolian Kang, Ulrike Reiss

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: Background: The rarity of Diamond Blackfan Anemia (DBA) has hindered describing the spectrum of disease, identifying predictive correlations, and guiding data-driven recommendations. Long-term toxicities from steroid or transfusion therapy that start in childhood remain the major clinical problems in patients with DBA who do not receive stem cell transplant.

Objectives: Objective: To define the DBA patient population at St. Jude Children's Research Hospital including treatment responses and toxicities to help inform recommendations on treatment and monitoring.

Design/Method: Method: Medical records were reviewed for all patients with DBA treated at St. Jude between 1997 and 2017 for diagnostic testing, treatment types and regimens, and outcomes. Two-sample t-test or Wilcoxon rank sum test was used to compare continuous variables in two groups depending on the normality of the data tested by Shapiro-Wilk test.

Results: Results: A total of 22 patients with DBA were identified with a median age of 8.29 years (range 3 months - 35 years) at last follow up. A ribosomal protein gene mutation was identified in 15/22 patients (68%) with an RPS19 mutation 8/22 (36%). Thirteen different congenital

malformations were described in 9/22 patients (41%). Fourteen of twenty (70%) patients treated with corticosteroids had an initial response and 3 of those achieved full remission. Three patients became steroid-refractory and 2 were unable to wean to an acceptable dose. Five of twenty patients continue on lower-dose steroids. Five patients currently require no therapy. Univariate analysis revealed no statistically significant genetic predictors of response or remission, however, 3/3 RPL11 patients responded to steroids with 2/3 (66%) in long-term remission. Ten patients are maintained on chronic transfusions and 2 have undergone successful hematopoietic stem cell transplant. Nineteen of 20 treated patients (95%) had a treatment-related toxicity. Patients on steroids were more likely to have short stature than patients on transfusions or in remission ($p = 0.005$). Severe bone mineral density deficit occurred in 4/20 (20%) patients, in 2 before age 7 years. Eight patients had hepatic iron overload, in one documented by age 2 years. Other severe toxicities included restrictive cardiomyopathy from iron overload, pathologic fracture, diabetes mellitus, and premature ovarian failure in one patient each.

Conclusion: This genotypically and phenotypically heterogeneous DBA cohort had a high rate of treatment-related toxicities, notably growth retardation, bone density loss, and hepatic iron overload even in very young children. These findings underscore the need for early standardized monitoring.

Poster # 312 | ADDRESSING THE EDUCATIONAL NEEDS OF ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE AS THEY TRANSITION TO THE ADULT HEALTHCARE SYSTEM: A PILOT STUDY

Ariel Reinish, Jeffrey Andolina, Tiffany Pulcino, Heather Busick, Lauren Bruckner, Akua Asante, Carol Fries, Suzie Noronha

University of Rochester Medical Center, Rochester, New York, United States

Background: Patients with sickle cell disease (SCD) face worsening morbidity and mortality between ages 18 and 30, when they must transition from pediatric to adult healthcare.(1) An effective curriculum addressing disease knowledge, educational and vocational skills, self-efficacy, and social supports is critical to a successful transition. Traditional didactic approaches have not led to durable knowledge retention.(2) Technology-based methods have been attempted, but the best educational approach remains unknown.

Objectives: 1. To understand how adolescent and young adult (AYA) patients with SCD view existing transition education. 2. To include patient preferences in improving our transition curriculum.

Design/Method: We developed a qualitative survey to assess patient views of existing approaches for learning about SCD and their opinions about preferred transition topics. Thirty patients with SCD aged 12 to 24 years old were recruited between January and December 2017. Responses were managed using REDCap electronic data tools hosted at the University of Rochester.(3,4) Qualitative and quantitative data analyses were performed, including independent t-testing to compare responses between age groups.

Results: Approximately 68% of subjects were under 18 years of age, while 32% were 18 or older. Seventy-one percent had a computer, and 93.5% had a cell phone, with most reporting daily use. Subjects reported greatest satisfaction with learning from their doctor during clinic visits (83.9% agree or strongly agree) and websites on a cell phone (77.4% agree or strongly agree); the least popular methods were online chat rooms and Microsoft® PowerPoint presentations. Satisfaction was similar across age groups. Recommended transition topics were viewed positively, with subjects ranking highest understanding their bloodwork (87.1% agree or strongly agree) and understanding laws protecting students with chronic disease (93.6% agree or strongly agree). Older subjects (18-24 years old) agreed more strongly with learning about opioid addiction and understanding differences between adult and pediatric doctors than did younger subjects (12-17 years old) ($p < 0.05$).

Conclusion: This pilot study was successful in helping us to understand the educational needs of AYA patients with SCD. Preliminary data underscore the importance of education provided by the pediatric hematologist. Our results also suggest that the optimal use of technology-based methods requires further investigation and that tailoring transition education by age group may be useful. 1. DeBaun MR, Telfair, J Pediatrics, 2012. 2. Williams CP et al, J Pediatr Hematol Oncol, 2015. 3. Supported by Grant # UL1 TR002001 from the NIH. 4. Harris P et al, J Biomed Inform, 2009.

Poster # 313 | OPTIMIZING TRANSFUSION THERAPY FOR SURVIVORS OF HEMOGLOBIN BARTS HYDROPS FETALIS: DEFINING THE OPTIMAL TARGETS FOR HEMOGLOBIN H AND "FUNCTIONAL" HEMOGLOBIN LEVELS

Catherine Tucker, Shiyi Chen, Isaac Odame, Melanie Kirby-Allen, Ali Amid

Hospital for Sick Children, Toronto, Ontario, Canada

Background: Similar to patients with transfusion-dependent beta-thalassemias (TDT-beta), survivors of hemoglobin Barts hydrops fetalis (homozygous alpha-0-thalassemia, TDT-alpha) will require lifelong transfusions of erythrocytes. We have previously shown that a transfusion strategy that is based on the guidelines developed for TDT-beta (conventional transfusion) is suboptimal for these patients owing to the differences in the pathophysiology of anemia in the two conditions: in TDT-alpha, conventional transfusion strategy will lead to a gradual increase in non-functional HbH with subsequent tissue hypoxia and hemolysis. An aggressive transfusion strategy that was based on reduction of HbH and increase in "functional" hemoglobin level resulted in improvement of tissue oxygenation and reduction of hemolysis but was associated with significant increase in transfusional iron burden [Amid et al, Blood 2016].

Objectives: To define the optimal chronic blood transfusion targets for HbH% and functional hemoglobin in patients with TDT-alpha.

Design/Method: Following Research Ethics Board approval, longitudinal data of 6 patients with TDT-alpha (2 males, median age 11.5 (2.1-18.0) were retrospectively collected. Variables of interest included total pre-transfusion hemoglobin, HbH%, and "functional" hemoglobin [measured as total hemoglobin x (1-HbH/100)]. Outcome variables were lactate dehydrogenase (LDH, marker of hemolysis), and soluble transferrin receptor (STR, marker of erythropoiesis). Hemoglobin analysis was done using high-performance liquid chromatography and capillary zone electrophoresis. We examined the association of "functional" hemoglobin with STR, and HbH% with LDH, using repeated-measures ANOVA to adjust for the effect of multiple testing. We constructed Receiver Operating Characteristic curve and calculated the Area under the Curve to define the best cut-off values for variables of interests.

Results: There was a strong association between functional Hb and STR, as well as HbH and LDH. The optimal cut-off for "functional" hemoglobin that was associated with STR <2.0 mg/L was 98 g/L (AUC = 0.94, sensitivity and specificity of 82.76% and 100% respectively). The optimal cut-off for HbH to supress LDH to <1000 U/L was 18% (AUC = 0.94, sensitivity and specificity of 87.5% and 87% respectively).

Conclusion: The optimal pre-transfusion HbH% for reduction of hemolysis was 18% and the optimal "functional" hemoglobin to adequately supress erythropoiesis was 98 g/L. To meet these HbH% and functional Hb targets by simple blood transfusions, patients with TDT-alpha would require a hypertransfusion regimen with a minimum pre-transfusion total Hb of 116 g/L and consequently high transfusional iron burden. An alternative approach using exchange transfusion to reduce HbH% and improve functional hemoglobin would be associated with less volume of transfusion and potentially better long-term outcome.

Poster # 314 | THE CLINICAL COURSE OF CHILDREN AND YOUNG ADULTS WITH SICKLE CELL DISEASE IN NORTHERN HAITI TREATED WITH PENICILLIN AND HYDROXYUREA

Philippa Sprinz, Michael Canarie, Emanise Muscadin

Hospital Sacre Coeur, Milot, Haiti

Background: Initial results of work developing a pediatric sickle cell disease (SCD) clinic at the Hôpital Sacré Coeur (HSC) in Milot, Northern Haiti were presented at ASPHO 2017. The purpose of this clinic is for a pediatrician with a special interest in SCD to provide SCD care, advising on trait and managing disease with penicillin prophylaxis (PCN) and hydroxyurea therapy (HU) for select patients. This clinic was started in collaboration with a US based hematologist and support from Yale-New Haven Hospital.

Objectives: To describe the success and challenges of providing PCN and HU in the SCD clinic at HSC through a review of patient records.

Design/Method: Since this clinic's inception, a database of patients, with basic clinical information has been kept and made accessible, through 'Drop-Box', to the US hematologist. The records of those that presented to the clinic were reviewed. The hemoglobin diagnosis was made either by clinical history and Sickle Cell Prep or by hemoglobin electrophoresis through Alpha Laboratory, Port-au-Prince, Haiti.

Results: Ninety-nine individuals were seen in the first 2 years of the program. Fifty-six underwent a hemoglobin electrophoresis. Of these 99, 49 are ≤ 6 years old. Thirty-two were started on PCN VK, of which 10/32 (31%) were ≤ 3 years old. Eleven patients were started HU therapy. All patients on HU have shown progressive increases in hemoglobin. There have been no clinical complications of HU therapy. None of the patients taking HU have required hospitalization or transfusion in 2017. Three patients (not on HU) were hospitalized in 2017 for complications of SCD (osteomyelitis, pain). In 2016, with less than half the numbers in the program, there were 7 admissions for severe anemia, pain, stroke and splenic sequestration.

Conclusion: With ongoing external support and a local reputation for excellence in sickle cell care, the clinic at HSC has

been able to expand services and improve the health of a growing number of patients with SCD. Early data suggests that PCN and HU therapies are helping to reduce complications and improve quality of life. Challenges to date have included lack of funding for transportation to clinics, for hospitalizations and to cover the cost of electrophoreses. At the same time as continuing providing excellent care and gathering data, it is crucial to explore opportunities for collaboration and cooperation in ways that will assure that the clinic can become independently sustainable while continuing to improve the quality of life for the individuals it serves.

Poster # 315 | SERUM YKL-40 LEVEL IN PATIENTS WITH B-THALASSEMIA: RELATION TO VIRAL HEPATITIS, LIVER STIFFNESS AND HEPATIC IRON CONCENTRATION

Mona Mohamed Hamdy Mahmoud, Amina Abd El Salam, Hadeel Seif El Dien, Nermin Magdi, Samah Ahmed Mostafa

Cairo University, Cairo, Cairo, Egypt

Background: YKL-40 is an inflammatory glycoprotein expressed by infiltrating macrophages in various inflammatory conditions. It has been found to be elevated in patients with different pathological conditions like acute and chronic inflammations, increased remodeling of the extracellular matrix (ECM), development of fibrosis and cancer. Several studies have found elevated YKL-40 concentrations in sera of patients with liver diseases such as hepatic fibrosis by hepatitis C virus. It has been suggested that YKL-40 concentrations reflect the degree of liver fibrosis.

Objectives: To evaluate serum YKL-40 Levels in patients with β-thalassemia and its relation to viral hepatitis, liver stiffness as assessed by Transient elastography (FibroScan, FS) and Hepatic Iron Concentration.

Design/Method: A prospective study included 100 patients with β- TM (43 males and 57 females) with mean age 13.8 $\pm$ 2.7 years (range: 5–18 years). Serum ferritin level, Liver enzymes (ALT and AST), HBs Ag, Anti HCV Ab and Serum YKL-40 using ELISA kit were evaluated. All patients were subjected to Liver MRI T2* to detect liver iron content by the sequence and Transient elastography (FibroScan, FS) to assess degree of liver stiffness.

Results: Mean fibroscan value was (10.99$\pm$11.5) kPa with a median 6.7 (range 1.3 to 47) kPa. 64 (64%) patients were categorized as F0-1 and 17 (17%) were stage F2-3, 19 (19%) patients had severe fibrosis. Their median serum ferritin was 3100 ng\ml, with 61 (61%) patients had values exceeding 2500μg/L. Median cardiac T2* was 24.2 with 30 patients had values below 20 ms, and the median LIC was 16.21 mg/g DW with 68 patients showed readings above 7 mg/g dw. NYL-40 was evaluated as a marker of inflammation and liver fibrosis and showed mean value 1505.1 ($\pm$960.9) pg/ml, and range from 500 to 3529 pg/ml. Mean YKL-40 was significantly higher among males ($p = 0.03$), patients on chelation therapy ($p = 0.002$), patients on DFS ($p \leq 0.001$), in those with abnormal liver enzymes, splenectomised patients, patients with HBV sero-positivity, those with moderate elevation of T2* and patients with high grades of liver fibrosis ($p<0.05$). YKL-40 showed positive correlation with the rate of transfusion, LIC, ferritin, ALT and AST but negative correlation with weight, height and T2*. ROC curve analysis revealed that the cutoff value of YKL-40 at 1500 pg/mL could differentiate β-TM patients with and without viral hepatitis with 86.7% sensitivity and specificity of 91.4%, area under the curve (AUC) 0.933, positive predictive value 81.2 and negative predictive value 94.1 ($p<0.001$). ROC curve analysis revealed that the cutoff value of YKL-40 at 1600 pg/mL could detect β-TM patients with liver cirrhosis with 93.4% sensitivity and specificity of 97.1%, area under the curve (AUC) 0.972, positive predictive value 93.7 and negative predictive value 97.1 ($p<0.001$).

Conclusion: Serum YKL-40 Levels are elevated in patients with β-thalassemia and can detect patients with active viral hepatitis and liver stiffness.

Poster # 316 | EFFECTS OF HYDROXYUREA ON PULMONARY HYPERTENSION IN SPLENECTOMIZED CHILDREN WITH SCD

Joseph Abdul-Malak, Nataly Apollonsky, Bruce Bernstein

Marian Anderson Center at St. Christopher's Hospital for Children, Philadelphia, Pennsylvania, United States

Background: The most common splenic complication in pediatric patients with sickle cell disease (SCD) is acute splenic sequestration (ASS), which has often been managed with splenectomy. Although splenectomy has been a treatment of choice for years, long-term vascular complications have not been thoroughly evaluated. Pulmonary hypertension (PHTN) is a severe complication of SCD. In adults with SCD, PHTN has been associated with a 40-month mortality rate of approximately 40%. It has been reported that splenectomized patients with hemolytic disorders are at even greater risk of PHTN. Several medications exist to treat PHTN, but

with few studies of their efficacy or toxicities in patients with SCD. Additionally, these patients are often treated with either chronic pRBC transfusions or Hydroxyurea (HU) to raise hemoglobin, reduce hemolysis, and prevent vaso-occlusive events.

Objectives: To evaluate effect of chronic pRBC or HU vs. no intervention, on tricuspid regurgitant jet velocities (TRV) in pediatric patients with SCD and history of splenectomy.

Design/Method: Retrospective chart review of splenectomized patients with HbSS followed at Marian Anderson Center at St. Christopher's Hospital for Children, Philadelphia, between 1999 and 2017. We analyzed 73 TRVs (16 HU, 40 pRBC, and 17 from control group receiving neither treatment) from 35 patients (10 HU, 13 pRBC, 12 neither). Mean age at echo was 13.31 +/- 5.1. Data was analyzed with linear correlations and analysis of variance (ANOVA), including the post hoc test of least significant difference (LSD) for all pairs of treatment groups.

Results: TRV was not significantly correlated with age at time of assessment or with time between splenectomy and TRV. Univariate ANOVA among groups yielded TRV means of: 214.0 +/- 36.0 cm/s (HU), 231.3 +/- 28.1 (pRBC), 231.3 +/- 25.4 (neither). We found a notable difference as the mean of the HU group was almost 18 cm/s lower than the others, but no overall statistically significant association for any of the groups exists. However, when we performed post hoc tests to adjust for multiple comparisons and looked at all 3 pairings within the ANOVA, we found that the LSD between the HU and the pRBC groups was statistically significant (P = .051), and that a trend exists between the HU group and the neither treatment group (P = .095).

Conclusion: Our data suggests that treatment with HU is correlated with a reduction in TRV in pediatric patients with SCD who underwent splenectomy. Given these promising results, we believe our data warrants further study with larger treatment groups.

Poster # 317 | EVALUATION OF CLINICAL AND LABORATORY FINDINGS IN PATIENTS WITH HEMOGLOBIN E BETA THALASSEMIA IN A SINGLE CENTER IN KOLKATA, INDIA

Nancy Olivieri, Gaurav Sharma, Susmita Nath, Rajib De, Tuphan Kanti Dolai, Prakas Kumar Mandal, Abhijit Phukan, Amir Sabouhanian, Robert Yamashita, Angela Allen, David Weatherall, Prantar Chakrabarti

Nil Ratan Sircar Medical College (NRS), Kolkata, West Bengal, India

Background: Hemoglobin E thalassemia (HbEthal), which accounts for 50% of all severe beta thalassemia worldwide, has an estimated prevalence of 1.4/10,000 in West Bengal, from which little information about clinical findings has been reported.

Objectives: To document clinical and laboratory findings in patients with HbEthal, ultimately to improve resources for clinical management.

Design/Method: We reviewed records from: a database recording patient names; clinic charts; "special" charts containing additional details; and, in transfused patients, transfusion day-care records. Additionally, because in India's public hospitals original lab/imaging reports are commonly retained at home, 20% of families were interviewed to provide additional information. We excluded records of patients aged <5 years and patients aged <30 years who had not been reviewed since 2014.

Results: While at least one visit had been recorded in 1,398 HbEthal patients at NRS Hospital, most patients are not regularly reviewed there. We examined 219 charts [84 (38%) aged ≥30 years; 135 (62%) aged 5–29 years; 61% male], representing approximately 70% of regularly-reviewed patients. Most families (84.9%) reported monthly incomes (<5,000 Indian rupees), below the monthly cost of living (70,000 rupees) in Kolkata. Mean (±SEM) hemoglobin was 6.9±1.1 g/dL. 43% patients were receiving eight or more transfusions per year; from 2013, 40% had been treated with deferasirox, 26.5±8.5 mg/kg/day. Iron control estimated by serum ferritin concentration (1357.2±1187 μg/L) was highly variable. A total of 24% patients were splenectomized. A substantial obstacle to documenting complications was the lack of recording, in any of the five sources, of many relevant parameters: for example, the status of sexual maturation (normal, delayed, or absent) was documented in less than 60%, and measurements of fasting blood glucose in less than 50%, of records. Where recorded, complication rates were high: delayed/abnormal sexual maturation was recorded in 15% patients aged >30 years; in the patients aged >30 years and those aged 5–29 years, respectively, hypothyroidism was recorded in 31% and 44%, and elevated serum ALT in 30% and 35%. In most evaluable patients >30 years, height was measured between the 3rd-10th percentiles. Cardiac findings, rarely documented, included pulmonary hypertension and reduced left ventricular ejection fractions in a few patients.

Conclusion: Despite dedicated attention to many aspects of thalassemia care, insufficient documentation limited a clear understanding of the current morbidity in HbEthal patients. Investment in personnel and technology will be critical to record relevant information, ultimately to improve clinical management, over the next decade.

Poster # 318 | IMPACT OF PCR-BASED VIRAL PANELS ON CARE FOR FEBRILE CHILDREN WITH SICKLE CELL DISEASE

Matthew Schefft, Adam Rossi, Megan Lyle

Children's Hospital of Richmond at VCU Health, Richmond, Virginia, United States

Background: Sepsis is a common cause of death in children with sickle cell disease (SCD). Recommendations for care of fever in children with SCD include immediate medical evaluation including blood culture and initiation of broad-spectrum antibiotic therapy. The increasing availability of PCR-based respiratory pathogen panels (RPP) provide the opportunity to rapidly identify viral causes of fever. The role for RPPs in identifying the source of fever in children with SCD and how it affects provider practice is not well studied.

Objectives: (1) to determine the epidemiology of respiratory virus-associated fever in children with SCD and (2) to determine whether a positive RPP is associated with reduced risk of bacteremia in this population.

Design/Method: This was a single-center, retrospective cohort study. We identified and reviewed the medical records of all children with SCD seen in our emergency department (ED) with temperature ≥38.3oC at home or in the ED from January 1, 2016, through September 30, 2017, as well as, all febrile children for whom RPPs were sent since the introduction of RPPs April 2014. We reviewed the results of blood cultures, RPPs, chest radiographs, and ED notes and discharge summaries to identify sources of infections. Independent T test and Chi-square analysis were used as appropriate to compare results using SPSS©.

Results: Overall, the rate of bacteremia was 1%. There were no cases of bacteremia among children with positive RPPs. 4% of children with negative RPPs had true bacteremia. A positive RPP did not reduce the likelihood of bacteremia (p 0.11). Patients with bacteremia had higher presenting temperatures than those without bacteremia (39.5oC vs 37.9oC, p 0.017). The most common RPP findings were rhinovirus/enterovirus (38%), human metapneumovirus (13%), and influenza A (10%). Sending an RPP did not affect admission rate (29% and 26% respectively, p 0.70); however, likelihood of admission was lower in patients with positive RPPs (21% vs 49%, OR 0.27 [0.13-0.56], p 0.004). Length of stay (LOS) was shorter in patients for whom an RPP was not sent (3.1 vs 4.5 days, p 0.036).

Conclusion: As previously reported, bacteremia in febrile children with SCD is very low, but remains a serious concern, particularly in the setting of high fever (>39oC). A positive RPP did not reduce the odds of bacteremia, but did have a statistically significant impact on both admission rate and LOS. More work is needed to understand how RPP results impact provider decision-making and care for children with SCD.

Poster # 319 | EARLY INITIATION OF DISEASE-MODIFYING THERAPY PREVENTS DIFFUSE MYOCARDIAL FIBROSIS IN SICKLE CELL ANEMIA

Charles Quinn, Omar Niss, John Wood, Thomas Coates, Punam Malik, Michael Taylor

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Diffuse myocardial fibrosis is a common, if not defining, feature of the heart in sickle cell anemia (SCA) that is strongly associated with diastolic dysfunction. We found diffuse myocardial fibrosis in every patient in a SCA cohort (N = 25) ranging in age from 6 to 61 years (Niss 2017). The treatment and prevention of this complication of SCA has not been studied before.

Objectives: Because diffuse myocardial fibrosis must begin in early childhood, we hypothesized that early initiation and uninterrupted use of disease-modifying therapy for SCA can prevent it.

Design/Method: We use cardiac magnetic resonance imaging (CMR) to measure the myocardial extracellular volume fraction (ECV) to quantify diffuse myocardial fibrosis in individuals with SCA who have been treated, uninterrupted, with hydroxyurea or chronic transfusion therapy since ≤4 years of age. Two comparison groups were used: individuals with SCA who have not been treated with disease-modifying therapy since ≤4 years of age (N = 25) and controls without SCA (N = 16).

Results: We studied 7 individuals (3M/4F) with a mean age of 13.4 years (range 7 - 24). Mean age at the start of disease-modifying therapy was 2.5 ± 0.4 years (range 1–4). Only 1 had evidence of mild diffuse myocardial fibrosis (ECV 0.339); the other 6 had no detectable diffuse fibrosis (all had ECV <0.304, the upper limit of normal). Mean ECV was 0.283 ± 0.012, which was significantly lower than the ECV of individuals with SCA who have not received early uninterrupted therapy (0.441 ± 0.016; P = 0.009) and not statistically different from normal controls (0.257 ± 0.004; P = 0.898). None had macroscopic fibrosis by late gadolinium enhancement or evidence of myocardial hemosiderosis by T2* imaging. No patient had diastolic dysfunction by echocardiographic classification, right heart catheterization, or both.

Conclusion: Disease-modifying therapy for SCA can prevent diffuse myocardial fibrosis, and possibly diastolic

dysfunction, if started in early childhood. Prospective trials of disease-modifying and anti-fibrotic therapy are planned to prevent diffuse myocardial fibrosis, which can be monitored noninvasively by CMR, and improve outcomes in SCA. (Niss, Blood, 2017).

Poster # 320 | VACCINATION STATUS IS NOT CORRELATED WITH MORTALITY IN ADULTS WITH SICKLE CELL DISEASE

Rhea Thukral, Brandy Kimani, Brandon Hardesty, Chrisopher Roberson, Emily Meier

Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana, United States

Background: A statewide sickle cell surveillance system (SSCSS) was developed with the goal of determining the prevalence of sickle cell disease (SCD) in Indiana and the level of care that patients receive throughout the state. Persons with SCD are at high risk of infection, especially with encapsulated organisms, as well as at increased complications from influenza. Utilizing SSCSS data, the relationship between vaccination status and mortality was explored.

Objectives: To determine if vaccination status is associated with mortality in persons with SCD.

Design/Method: The project was granted a waiver of consent by the St. Vincent IRB. Death certificates were obtained to identify cause of death. Deceased patients (cases) were matched by age, gender, and sickle genotype to living patients (controls). Vaccination data were collected from the medical record and the Children and Hoosier Immunization Registry Program (CHIRP) through the date of death for each case. Cases and controls were assigned a point for completion of the pneumococcus, meningococcus and haemophilus influenza type B (HiB) vaccine series and one point if the influenza vaccine was given within a year prior to death of the cases [max vaccine status score (VSS): 4]. Total points were compared between the cases and controls. Two tailed t-tests to compare means of continuous data and Wilcoxon Signed-Rank test to compare ordinal data.

Results: One thousand forty-eight individuals were included in the SSCSS. Six hundred and seven (48.6%) were seen at one institution and included in this analysis (mean age = 21 years). Thirty-three of the 607 (5.4%) were deceased at the time of analysis. Six point one (6.1)% of controls and 12.1% of cases received a VSS of 4. The mean VSS for cases was 0.7±1.3 and 0.6±1.1 for controls. Thirty point three (30.3) % of controls had a VSS of one or more, compared to 27% of cases ($p = 0.41$). Patients who died of infection [streptococcus (n = 1), pseudomonas (n = 1) and unidentified organisms (n = 4)] were not up to date on vaccination against encapsulated organisms, but two had received the influenza vaccine in the year prior to death.

Conclusion: In this sample, mortality occurred exclusively among adult patients, which is consistent with current patterns in developed countries. Among these adults, VSS and mortality rates were not related. Limitations to the study include small sample size and potential incompleteness of vaccine records. Vaccination rates and other standard of care indicators should be explored in a larger cohort of patients to determine associations with mortality.

Poster # 321 | PUBERTAL CHANGES IN CHILDREN WITH SICKLE CELL DISEASE AT KORLE BU TEACHING HOSPITAL, ACCRA, GHANA

Catherine Segbefia, Yvonne Dei-Adomakoh, Diana Dwuma-Badu

Korle Bu Teaching Hospital, Accra, Ghana

Background: Sickle cell disease (SCD) is a genetic disorder resulting in acute and chronic complications, including delayed puberty. Delayed puberty can have adverse physical and psychosocial effects on affected children and families. There are no published reports from Ghana on pubertal timing in children with SCD.

Objectives: The aim of this cross-sectional study was to describe pubertal changes in children with SCD at Korle Bu Teaching Hospital (KBTH), Accra, and compare these findings to those in a control group without SCD.

Design/Method: 178 children with SCD and 174 children with Hb AA, ages 8–19 years, were consecutively recruited and matched for age, sex and socioeconomic status. Investigator-administered questionnaires were used to obtain demographic data for all participants and information on menarche (girls only). Pubertal status was assessed by physical examination using Tanner staging. Testicular volumes were determined in boys using a Prader orchidometer. Body mass index (BMI) and socioeconomic status (SES) of participants were analyzed to determine if there were any associations with Tanner stage.

Results: Of the 178 with SCD, 133 (74.7%) were Hb SS and 45 (25.3%) Hb SC. Females comprised 51.1% (cases and controls). Mean age at onset of breast development was significantly delayed in girls with SCD (13.1 ± 1.9 years) compared to controls (10.8 ± 1.9 years) but there was no significant age difference at onset of pubic hair development. Mean age at menarche was significantly delayed in girls with

Hb SS (14.0 ± 1.8 years) and Hb SC (13.5 ± 1.5 years), compared to those with Hb AA (12.5 ± 1.3 years). In boys, the mean ages at onset of puberty were significantly delayed in those with SCD (13.6 ± 2.7 years, for genital development and 15.1 ± 2.2 years, for pubic hair development), compared to those without SCD (11.3 ± 1.9 years and 11.4 ± 1.9 years, respectively). Mean testicular volumes were significantly lower in cases compared to controls, across all age ranges ($p<0.001$). Mean BMI in both cases and controls were similar at onset of breast development in girls. However, in boys with and without SCD, mean BMI values were significantly different at pubertal onset. In univariate analysis, SES was not associated with Tanner stage for both genital and breast development.

Conclusion: Mean ages at pubertal onset were significantly delayed in children with SCD. Longitudinal studies are needed to further characterize any associations with BMI and determine potentially modifiable risk factors affecting pubertal onset in SCD.

Poster # 322 | CLINICAL BURDEN AND MANAGEMENT OF SICKLE CELL DISEASE AMONG PEDIATRIC PATIENTS

Menaka Bhor, Yuexi Wang, Lin Xie, Rashid Halloway, Steve Arcona, Jincy Paulose, Adesuwa Ogbomo, Ying Shen, Huseyin Yuce, Nirmish Shah

STATinMED Research, Ann Arbor, Michigan, United States

Background: Sickle-cell disease (SCD) is a life-threatening genetic disorder associated with multiple chronic and acute complications. Specific monitoring and treatment for children is a major part of the medical focus, but there remains a lack of real-world evidence of the disease burden and practice patterns among the pediatric SCD population.

Objectives: To examine the clinical burden and management of SCD among pediatric patients.

Design/Method: A retrospective claims study was conducted using the Medicaid Analytic Extracts Database from 01JAN2009-31DEC2013. Pediatric patients (aged <18 years) with SCD were identified using ICD-9-CM diagnosis codes (282.41-282.42, 282.60-282.69). The first observed SCD diagnosis during the identification period was designated as the index date. Patients were required to have continuous medical and pharmacy benefits for at least 6 months pre- and 12 months post-index period. Patient data were assessed until the earliest occurrence of the following events: disenrollment, death, or the end of the study period. Patient demographic and baseline clinical characteristics, clinical outcomes (mortality, incidence of pain crisis, complications), SCD management, and healthcare utilization were examined. All variables were analyzed descriptively.

Results: A total of 12,388 patients met the study inclusion criteria, with a mean age of 7.7 years. Most patients were black (59.9%) and had a Charlson Comorbidity Index score of 0 (80.9%). Mortality during follow-up was 0.1 in 100 person-years, and the event rate of pain crisis in the inpatient setting was 54.0 in 100 person-years. The three most common complications after pain crisis (highest rates in 100 person-years) were fever (31.9), infectious and parasitic diseases (27.7), and asthma (14.5). Rates of life-threatening complications were also examined in 100 person-years, including acute chest syndrome (7.0), stroke (1.8), splenic sequestration (1.1), pulmonary hypertension (0.3), and pulmonary embolism (0.1). 83.9% of patients were prescribed antibiotics during the one-year post-index period. Other frequent medications utilized among children were folic acid (39.2%), nonsteroidal anti-inflammatory drugs (37.4%), opioids (11.2%), and hydroxyurea (11.5%). 16.0% of patients had a blood transfusion within one year post-index date. Patients had frequent health care utilizations in the inpatient (1 visit), emergency room (2 visits), office (7 visits), and pharmacy (11 visits) settings during the one-year follow-up period.

Conclusion: Pediatric SCD patients are burdened with a high rate of complications including pain crisis. In addition, patients utilized a substantial amount of health care resources including outpatient office care and acute care visits.

Poster # 323 | NOVEL USE OF HYDROXYUREA IN AN AFRICAN REGION WITH MALARIA (NOHARM): YEAR 2 FINAL RESULTS

Robert Opoka, Christopher Ndugwa, Teresa Latham, Adam Lane, Heather Hume, Phillip Kasirye, James Hodges, Russell Ware, Chandy John

Mulago Hospital Sickle Cell Clinic, Kampala, Uganda

Background: Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM, NCT01976416) is a randomized controlled trial of hydroxyurea for very young children with sickle cell anemia living in Uganda. During Year 1, study participants received blinded study treatment of hydroxyurea or placebo; those receiving hydroxyurea had no increased risk of malaria, but had both laboratory and clinical benefits. During Year 2, all study participants received open-label hydroxyurea treatment.

Objectives: To assess the effects of open-label hydroxyurea treatment in a very young population of children with sickle

cell anemia living in Uganda. Study endpoints included the rates and severity of malaria infections, clinical sickle-related events, and laboratory effects.

Design/Method: All children in the NOHARM trial were enrolled at Mulago Hospital Sickle Cell Clinic in Kampala Uganda. During Year 2, all children received open-label fixed-dose hydroxyurea (20 mg/kg/day) for 12 months, after previously receiving either hydroxyurea or placebo for 12 months.

Results: A total of 198 children entered Year 2 of the NOHARM trial and received fixed-dose hydroxyurea, including 107 males and 91 females, at an average age of 3.3 ± 0.9 years. Among 99 children previously on placebo, there were 6 malaria events in 6 children, including 3 with severity grade ≥3, and three deaths (two acute chest syndrome, one sepsis). Clinical adverse event rates dropped from 3.0 to 1.6 per patient year, and hospitalizations were reduced from 35 to 7. Expected hematological benefits of increased hemoglobin, MCV, and fetal hemoglobin, along with decreased neutrophils and reticulocytes, were rapidly achieved. Laboratory adverse events were infrequent at 0.2 events per patient-year, and only half of those were dose-limiting hematological toxicities. Among 99 children previously on hydroxyurea, there were 7 malaria events in 5 children, including 2 with severity grade ≥3, and two deaths (one acute chest syndrome, one sepsis). Clinical adverse event rates and hospitalizations were maintained at low rates, the hematological benefits of hydroxyurea continued throughout the extended treatment period, and dose-limiting toxicities remained infrequent.

Conclusion: Fixed-dose hydroxyurea treatment of young children with sickle cell anemia living in Uganda is associated with no increased risk for malaria. Clinical and laboratory benefits occur, including children previously on placebo who crossed-over to hydroxyurea treatment. Future studies should focus on the optimal dosing and monitoring strategies, in an effort to determine the overall feasibility and safety of introducing hydroxyurea therapy across sub-Saharan Africa.

Poster # 324 | THE SIGNIFICANCE OF EARLY TRANSFUSION IN THE MANAGEMENT OF ACUTE CHEST SYNDROME IN PATIENTS WITH SICKLE CELL DISEASE

Christina Caruso, Abena Appiah-Kubi, Banu Aygun, Lawrence Wolfe, Seungjun Ahn, Cristina Sison

Cohen Children's Medical Center at Northwell Health, New Hyde Park, New York, United States

Background: Acute chest syndrome (ACS) is the second most common cause of hospitalization in patients with sickle cell disease and is a leading cause of morbidity and mortality. In mid-2009, an algorithm was implemented at Cohen Children's Medical Center to initiate transfusions within four hours of diagnosis of ACS in order to improve patient outcomes.

Objectives: The aim of this project was to analyze the effect of early blood transfusion on the outcomes of patients with ACS. We focused on the number of total transfusions, need for exchange transfusion, need for intensive care unit (ICU) stay, and length of hospitalization.

Design/Method: A retrospective chart review was completed on patients admitted to CCMC with a primary diagnosis of sickle cell disease and a secondary diagnosis of either ACS or pneumonia during the years of 2006–2012. Data from the three years directly prior to implementation of the algorithm was compared to data from the three years directly after implementation of the algorithm.

Results: A total of 118 patients were analyzed, of which 45 belonged to the pre-algorithm group and 73 to the post-algorithm group. Patients from the post-algorithm group had a higher incidence of transfusions (78% with a mean transfusion number of 1.49 pre versus 86% with a mean of 1.83 post) as well as exchange transfusion (17% pre versus 27% post). The post-algorithm group had a shorter overall length of stay (mean of 6.0 days pre versus 5.0 days post). While the overall percentage of patients requiring an ICU admission was similar in each group (27% pre versus 29% post), the post-protocol group had a lower likelihood of requiring an ICU admission for reasons outside of line placement for exchange transfusion, most commonly for ICU-level respiratory support (13% pre versus 4% post).

Conclusion: Despite a higher total number of transfusions, early recognition and transfusion for ACS can lead to decreased lengths of hospitalization as well as decreased need for ICU-level respiratory support. Further studies comparing different center's clinical practice guidelines are necessary to improve the standard of care.

Poster # 325 | NOVEL USE OF HYDROXYUREA IN AN AFRICAN REGION WITH MALARIA: EFFECTS OF HYDROXYUREA TREATMENT ON TRANSCRANIAL DOPPLER (TCD) VELOCITIES

Jennifer Tymon, Maria Nakafeero, Robert Opoka, Adam Lane, Teresa Latham, Chandy John, Russell Ware

Mulago Hospital Sickle Cell Clinic, Kampala, Uganda

Background: Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM) was the first placebo-controlled randomized clinical trial of hydroxyurea in sub-Saharan Africa. In NOHARM, young children with SCA received either hydroxyurea or placebo during Year 1, followed by open-label hydroxyurea for all study participants during Year 2. An ancillary NOHARM project was designed to determine if hydroxyurea treatment lowers transcranial Doppler (TCD) velocities and possibly reduces stroke risk in this very young cohort.

Objectives: To perform TCD screening on the NOHARM cohort, measuring the time-averaged mean velocity (TAMV) at the end of both Year 1 and Year 2. We hypothesized that the maximum TAMV would be lower for NOHARM study participants receiving hydroxyurea compared to those receiving placebo, and that key clinical and laboratory parameters would also influence TCD velocities.

Design/Method: All children enrolled in NOHARM were eligible to undergo TCD examination at two study time points: Month 10–12 when they were completing the blinded treatment phase, and again at Month 22–24 at the end of the open-label treatment phase. TCD measurements included TAMV readings from the main intracranial arteries: middle cerebral artery, distal internal carotid artery, and bifurcation on TCD. All TCD examinations were scored and classified as normal (less than 170 cm/sec), conditional (170-199 cm/sec) or abnormal (greater than or equal to 200 cm/sec), with higher scores correlating to greater risk of stroke.

Results: At the end of Year 1, 185 TCD exams were conducted of which 164 were suitable for analysis (81 hydroxyurea, 83 placebo). Based on the maximum TAMV, the median velocity was 138 cm/sec (IQR 120 – 159) for children on hydroxyurea and 150 cm/sec (IQR 134 – 168) on placebo, $p = 0.0509$. Maximum TAMV values had negative correlations with hemoglobin concentration (-0.47), fetal hemoglobin (-0.32), and oxygen saturation (-0.27); positive correlations were noted with age (0.27) and absolute neutrophil count (0.27). At the end of Year 2, 187 TCD exams were conducted and all were suitable for analysis; the median velocity was 137 cm/sec on open-label hydroxyurea treatment, regardless of previous blinded treatment. All correlations with TAMV were maintained except for age.

Conclusion: Compared to placebo, hydroxyurea treatment for young children with SCA living in Uganda was associated with lower TCD velocities, which have been correlated in other studies with lower risk of primary stroke. TCD velocities were correlated with hematological and clinical parameters that can be improved by hydroxyurea therapy.

Poster # 326 | QUALITY IMPROVEMENT INITIATIVE TO INCREASE INCENTIVE SPIROMETRY USE IN HOSPITALIZED CHILDREN WITH SICKLE CELL DISEASE

Megan Lyle, Kelsi Baughan, Jessica Cohen, India Sisler

Children's Hospital of Richmond at Virginia Commonwealth University, Richmond, Virginia, United States

Background: Acute chest syndrome (ACS), defined by respiratory symptoms and a new pulmonary infiltrate, is a serious complication of sickle cell disease (SCD). ACS can occur during hospitalization for non-pulmonary conditions, such as a vaso-occlusive crisis or after surgery. NIH clinical practice guidelines encourage incentive spirometry (IS) which decreases the incidence of ACS. It is additionally widely accepted that early, frequent ambulation in post-operative and pneumonia patients decreases the length of stay (LOS).

Objectives: To decrease ACS events in children with SCD at our children's hospital, we aimed for IS use in 100% of age-appropriate pediatric sickle cell admissions.

Design/Method: A multidisciplinary team examined inpatient ACS prevention practices, including IS, at Children's Hospital of Richmond. Key drivers were identified, including educational awareness of patients and healthcare staff, order placement, and documentation. We aimed for all SCD patients $\geq$ 15 months of age hospitalized with any admission diagnosis to participate in IS with the use of a traditional incentive spirometer or similar age- and ability-appropriate devices (e.g. positive expiratory pressure devices, bubbles, and pinwheels). We secondarily aimed to increase activity events, specifically ambulation and out of bed time. Educational and outreach tools included patient informational brochure and incentive program, and staff informational sessions and reference materials at workstations. A disease-specific order set was implemented including desired IS and activity orders. Data were collected prospectively May through November 2017, during which 3 PDSA cycles were conducted. Admissions during the corresponding months of the previous year were reviewed for comparison. Independent t-test analysis was performed using GraftPad Prism 6 statistical analysis software.

Results: Improvements reaching statistical significance included increase in IS order placement from 44% to 89% of admissions ($p < 0.01$), and admissions with documented IS use increased from 32% to 59% ($p < 0.01$). LOS decreased from a mean of 3.7 days to 2.7 days (p 0.02). Post-admission development of ACS also decreased from 12% to 4% of admissions, but did not reach statistical significance (p 0.18).

There was an additional increase in appropriate activity order placement and documentation of activity events.

Conclusion: Improving education and outreach to patients and staff, including implementation of a disease-specific order set, can improve IS use and activity events. The decline seen in incidence of ACS development during hospitalization, though not statistically significant, and the decreased LOS are encouraging, and efforts continue to improve on these trends.

Poster # 327 | COLD PAIN CAUSES GREATER VASOCONSTRICTION IN SICKLE CELL DISEASE SUBJECTS AND NORMAL CONTROLS EXPOSED TO GRADED THERMAL STIMULI

Saranya Veluswamy, Payal Shah, Maha Khaleel, Mammen Puliyel, Wanwara Thuptimdang, Patjanaporn Chalacheva, John Sunwoo, Roberta Kato, Lonnie Zeltzer, John Wood, Michael Khoo, Thomas Coates

Children's Hospital Los Angeles, Los Angeles, California, United States

Background: Painful vaso-occlusive crises (VOC) are a frequent and debilitating complication of sickle cell disease (SCD) and are thought to occur due to progressive blockage of the microvasculature with rigid sickle shaped red blood cells. Any trigger that decreases the microvascular blood flow (MBF) can promote entrapment of sickled cells in the microvasculature and progression to VOC. Exposure to cold wind and changes in weather are common triggers of VOC and are associated with increased frequency of hospitalizations for pain in patients with SCD. There is limited experimental data on the physiologic effects of these factors on peripheral perfusion in SCD.

Objectives: To study the effect of graded thermal stimuli on the peripheral MBF in SCD.

Design/Method: 17 SCD and 16 control (healthy or sickle trait) subjects aging 13 to 39 years were exposed to their individual threshold temperatures for heat and cold detection, heat and cold pain via TSA- II thermode that was placed on the thenar eminence. MBF was measured on the contralateral thumb using photo-plethysmography (PPG). The vasoconstriction response within the complex PPG signal was detected using cross-correlation technique. Mean MBF was derived from the PPG amplitude during each of these stimuli and compared to baseline MBF.

Results: Cross correlation analysis showed that cold pain caused significant vasoconstriction response in 67% of the subjects, followed by heat pain (58%), cold detection (36%) and heat detection (18%).There was a significant drop in the MBF during cold pain ($p < 0.0001$), heat pain ($p < 0.0001$), heat detection ($p = 0.0005$) and cold detection ($p = 0.02$) when compared to baseline MBF, with cold pain causing the greatest drop in MBF. Thermal sensitivity and MBF responses were comparable between SCD and controls.

Conclusion: Exposure to graded thermal stimuli causes a progressive drop in MBF with exposure to cold pain eliciting the strongest vasoconstriction response. Vasoconstriction occurred in the contralateral hand at an average of 11 seconds after the stimuli, suggesting a neurally mediated mechanism. Although there was no significant difference in vasoconstriction responses between SCD and controls, the drop in MBF in patients with Sickle Cell Disease can increase the likelihood of entrapment of the sickled red blood cells, leading to vaso-occlusion. These findings are consistent with extensive reports in literature that exposure to cold weather is associated with a higher frequency of VOC. This suggests that neurally mediated vasoconstriction is likely an important factor in the pathophysiology behind cold exposure leading to VOC in SCD.

Poster # 328 | BIOMARKERS TO PREDICT SEVERITY OF SICKLE CELL VASO-OCCLUSIVE CRISIS IN THE PEDIATRIC AGE GROUP

Sairam Kumar, Fernanda Kupferman, Kusum Viswanathan, Sharef Al-Mulaab, Mario Peichev

Brookdale University Hospital and Medical Center, Brooklyn, New York, United States

Background: Vaso-occlusive crisis (VOC) is a major cause of hospital admissions in children with Sickle Cell Disease (SCD). Although the use of clinical biomarkers in VOC has been studied, especially with regards to Acute Chest Syndrome (ACS), there is less data regarding overall VOC severity prediction. In addition new biomarkers such as platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and lymphocyte to monocyte ratio (LMR) have been little studied with regards to SCD.

Objectives: To identify whether admission laboratory values, changes from well baseline laboratory values, and new biomarkers such as PLR, NLR, and LMR could predict severity of Vaso-occlusive crisis in children with Sickle Cell Disease admitted with VOC.

Design/Method: This was a retrospective single center observational study of admissions of VOC in children aged 1 - 21 years with HbSS or HbS-b0thal from September 2014 to November 2017 excluding those on hyper-transfusion

protocol or having an admission diagnosis of ACS. Univariate analysis was done using Student's T-test, Mann-Whitney non parametric test, or Fischer's exact test as appropriate depending on the distribution between admission laboratory data of complete blood count (CBC), reticulocyte count, comprehensive metabolic panel, lactate dehydrogenase (LDH), change from well baseline CBC values within 6 months previously, PLR, NLR, LMR, and the development of complicated VOC. Complicated VOC was defined as the development of secondary acute chest syndrome, prolonged admission duration > 5 days (120 hours), requirement of blood transfusion, and readmission within 30 days.

Results: A total of 109 admissions were studied. Fifty-nine (54.1%) were female. Of the 109, 50 (45.9%) were complicated with no significant differences in sex (p 0.447) or age (p 0.435). Univariate analysis revealed significant elevations in total bilirubin (p 0.017), LDH (p 0.010), and platelet count (p 0.019) in those with complicated VOC. There is also significant difference in the percentage change of platelet count from baseline with greater decline in uncomplicated VOC (p 0.014). There were no significant differences in PLR (p 0.186), NLR (p 0.775), or LMR (p 0.445).

Conclusion: Elevations in total bilirubin, LDH, and platelet count in admission laboratory values are associated with developing complicated VOC. In addition, those with complicated VOC present with significantly less decline in platelet count from baseline well CBC. PLR, NLR, and LMR do not seem to be useful predictive biomarkers for severity of VOC.

Poster # 329 | PSYCHOSOCIAL RISK FACTORS OF SEVERITY OF SICKLE CELL DISEASE IN YOUNG CHILDREN

Ellen Bloom, Kisha Hampton, Natalie Duncan, William Kronenberger, Emily Riehm Meier

Indiana Hemophilia and Thrombosis Center, Inc., Indianapolis, Indiana, United States

Background: Sickle cell disease (SCD) causes health problems of varying frequency and severity. The only validated biomarker for children with SCD is transcranial Doppler. If reliable predictors existed for SCD severity, children with SCD could be treated according to risk category. Many patients with SCD face psychosocial or economic hardships, but these factors have not been evaluated as risk markers for medical or functional severity of SCD.

Objectives: The goal of this project was to develop and stratify a preliminary list of psychosocial risk factors for health outcomes that could be used as SCD severity predictors.

Design/Method: A waiver of consent was obtained from St. Vincent Institutional Review Board. A list of potential psychosocial risk factors for adverse health outcomes was compiled based on assessment materials utilized by the Sickle SAFE program (Indiana's hemoglobinopathy newborn screening follow-up program). This list of 39 items was distributed to child abuse prevention (12) and SCD (17) experts, who ranked each item on a Likert scale of 1 (least important) to 5 (most important). Mean scores were calculated using SPSS Version 24; 163 assessments were retrospectively analyzed to determine psychosocial risk factor frequency. Risk factors occurring in ≥15% of homes were considered high frequency events.

Results: Overall, there was high agreement among experts on the risk factors that were considered the most important predictors of severe SCD outcomes. The risk factor with the highest frequency (92%) was eligibility for public assistance programs. Fifteen risk factors were rated ≥4 by the experts. Four (26.7%) were high frequency events occurring in ≥15% of homes: A child with HbSS or HbSβ0thalassemia not taking hydroxyurea (15%); parent report that they had treated a fever (>101®F) at home in the past 6 months (25%); tobacco use by someone in the household (23%); and the family reporting significant psychosocial stressors in the past year (30%). Tobacco use in the home was significantly correlated with several other risk factors (smoking during pregnancy [r = 0.503], other health concerns in the child [r = 0.459], and child having health insurance [r = -0.459]), suggesting that it is part of a constellation of health risk. In general, the risk factors that were rated as most important for health outcomes occurred less frequently in the sample.

Conclusion: This study represents important progress toward identifying a group of psychosocial risk factors for SCD severity, which is a necessary first step for future investigation of empirical relationships between candidate risk factors and SCD outcomes.

Poster # 330 | STANDARDIZATION OF A NEW PARTIAL EXCHANGE TRANSFUSION PROTOCOL IN A PEDIATRIC POPULATION WITH SICKLE CELL DISEASE IN CARTAGENA, COLOMBIA

Angel Castro Dager, Victor Rodriguez Balseca, Stephanie Casadiego Payares, Soraya Paternina Palomo

Unitversity of Cartagena, Cartagena, Bolivar, Colombia

Background: Sickle cell disease is an autosomal recessive disorder characterized by a mutation in the β-globin chain, which produces HbS. Acute and chronic complications as aplastic crisis, acute chest syndrome, priapism, stroke, leg ulcers and primary/secondary prevention of stroke can be treated with simple transfusion or exchange transfusion. The latter offers advantages as lower iron overload, post-treatment HbS goal control, lower viscosity and improved microvascular circulation. But it is not a widely-used option because is associated with technical difficulties.

Objectives: Standardization of a new partial exchange transfusion protocol in a group of patients with sickle cell disease, within the framework of a chronic transfusion program.

Design/Method: This is a prospective descriptive study, which included 25 patients under 18 years with sickle cell disease (20 HbSS, 5 HbS-tal), with indication of partial exchange transfusion in a chronic transfusion program, according to the institutional protocol; patients who fulfilled the inclusion criteria were enrolled in the study between February 2016 and December 2017. A registry of the medical and technical complications was made in each of the procedures. A database was constructed in Excel, and the GraphPad PRISM® Version 6 Oc software was used for statistical analysis. The sequence is as follows: isovolemic phlebotomy and transfusion of packed red cells. Depending of the recent hemoglobin level (48 hrs), we do the phlebotomy there: Hb:7–7.9: 10 cc/kg, Hb: 8-8.9: 15 cc/kg, Hb>9: 15 cc/kg; isovolemic solution (NS 0,9%) there: Hb:7–7.9: 10 cc/kg, Hb: 8-8.9: 15 cc/kg, Hb>9: 15 cc/kg and packed red cell transfusion there: Hb:7–7.9: 15 cc/kg, Hb: 8-8.9: 15 cc/kg, Hb>9: 10 cc/kg.

Results: The safety of this exchange transfusion protocol was analyzed in 25 patients with sickle cell disease (176 procedures). There were no differences in the sex distribution, and the median age was 8 years. 80% of the population was homozygous. The indication of transfusion was 52.27%(92/176) primary stroke prevention, 44.31%(78/176) secondary stroke prevention and 2.84%(5/176) was other reason. A low percentage of complications was found (7.3%); of which, those of medical origin (hypotension and nausea/vomiting) were only presented in 2.2% of the total procedures.

Conclusion: The standardization of this protocol was safe and its use could be extended to other low-income centers that treat patients with sickle cell disease that need chronic transfusion program including patient with hemoglobin level until 7gr/dL. We suggest do studies for measure the security and efficacy of this protocol in patients with acute complications.

Poster # 331 | IDENTIFYING AND ASSESSING AT-HOME VASO-OCCLUSIVE CRISES (VOC) IN PATIENTS WITH SICKLE CELL DISEASE (SCD) LONGITUDINALLY USING ELECTRONIC PATIENT-REPORTED OUTCOMES (PRO), ACTIGRAPHY AND BIOMARKERS (ELIPSIS)

Ahmar Zaidi, Michael Callaghan, Jennell White, Patrick Hines, Bryan Hannan, Debra Pittman, David Beidler, Denis Rybin, Ke Liu, Xiufeng Gao, Andreas Pleil, Alexandra Barsdorf, Martin David, Melanie Simmons, Andrew Frelinger III, Alan Michelson, Nick Clarke, Robert Charnigo

Children's Hospital of Michigan, Detroit, Michigan, United States

Background: Clinical trials that aim to achieve pain reduction have challenges achieving clinical endpoints as pain has no quantifiable biomarkers and may be unrelated to SCD. Furthermore, the threshold of seeking medical care differs between patients and VOCs that occur at home are missed. We present a non-interventional, longitudinal study to identify VOCs in patients with SCD.

Objectives: To examine the longitudinal relationship between PROs and biomarkers in subjects with SCD before, during, and after a self-reported VOC event, in order to build a model of in-home and clinical VOC and to collect longitudinal PROs and biomarker data from subjects that span VOC events in the home, clinic and the hospital.

Design/Method: Longitudinal measures of pain, fatigue, function, activity, and biomarkers from SCD patients in steady state and VOC were studied over a six month period. Patients self-reported pain, fatigue, function, and medication use using a novel ePRO tool. VOC was reported in real-time, triggering a mobile phlebotomy team. Blood was collected sequentially after self-reported VOC (at home or hospital). Blood samples were drawn two days after resolution of VOC, as reported by the patient. During non-VOC periods, blood was drawn every 3 weeks to establish a baseline. Biomarkers included leukocyte-platelet aggregates and circulating microparticles, cell and soluble adhesion molecules, cytokines, inflammatory mediators and coagulation factors. Patients wore an actigraphy device to track sleep and activity and rest.

Results: Twenty-seven of thirty-five patients experienced a total of 286 days with VOC >4 hr, of which only 58 days resulted in healthcare utilization. VOC days had significantly higher pain and fatigue scores. VOC days were associated with significantly decreased functional scores, with

significantly greater decreases during VOCs requiring medical contact compared to at-home VOCs. Different activity profiles were identified for non-VOC, at-home VOC and medical contact VOC days by actigraphy monitoring. At-home VOC days exhibited increased daytime resting compared to non-VOC days. Medical contact VOCs had decreased average and peak activity, and increased daytime resting compared to non-VOC days. A sleep fragmentation index trended up for both at-home (16%) and medical contact VOC days (18%). Significant changes during VOC days were observed in: C-reactive protein (54% increase), nucleated RBC (34% increase), monocyte-platelet aggregates (25% increase) and neutrophil-platelet aggregates (35% increase), interleukin-6 (112% increase), interleukin-10 (19% increase) and TNF-alpha (14% increase).

Conclusion: The identification and assessment of at-home VOCs through use of ePROs, actigraphy and biomarkers is feasible as demonstrated by this innovative at-home study design.

Poster # 332 | VON WILLEBRAND FACTOR ANTIGEN AND MULTIMERS AS BIOMARKERS IN YOUNG PATIENTS WITH SICKLE CELL DISEASE

Liron Grossmann, Karen Mittermeier, Megan Reynolds, Punam Malik, Lori Luchtman-Jones

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Risk-stratifying sickle cell disease (SCD) patients and demonstrating response to disease-modifying therapies is challenging due to the phenotypical heterogeneity of SCD. A pathogenic role for procoagulant von Willebrand factor (VWF) via excess VWF high molecular weight multimers (HMWM) has been proposed, with variable reports of increased VWF and HMWM in crisis vs. steady-state in adults, but less so for VWF in children with SCD. Moreover, VWF and multimers have not been studied in sickle trait.

Objectives: Our pilot study evaluated the potential for VWF antigen (VWF:Ag) and HMWM on densitometric tracings to serve as biomarkers for disease severity or treatment response in children and young adults with SCD compared to sickle trait (HbAS) siblings.

Design/Method: We evaluated VWF:Ag, VWF multimers and retrospective clinical data from 10 HbSS, 3 HbSC and 5 HbAS subjects at steady state. One HbSC subject also had a crisis sample. Median SCD age was 17 years (8.0-20.1 years). 46% were female. SCD severity was judged by annual vaso-occlusive and acute chest events, or stroke/elevated TCD. Eight of 13 (6 HbSS and 2 HbSC) took hydroxyurea. Four HbSS subjects had severe SCD, all of whom were chronically transfused.

Results: Mean VWF:Ag (normal 50–160 IU/dl) was higher for HbSS (175+/-17.4) and severe HbSS (195+/-33.5) compared to HbSC (103+/-3.2, $p = 0.049$ and 0.044, respectively); however, lacked statistical significance when compared to HbAS (152+/-34.5, $p = 0.52$ and 0.41, respectively). VWF:Ag was elevated in 7/10 (70%) steady-state, including 3/4 (75%) with "severe" disease on chronic transfusion and 4/6 (67%) taking hydroxyurea, in 1 HbSC crisis but no HbSC 3/3 (100%) at baseline. VWF:Ag was high in 2/5 (40%) HbAS siblings. Four (31%) had increased HMWM at baseline: 1 HbSS/severe disease/chronic transfusion, 2 HbSS/hydroxyurea and 1 HbSC untreated. HMWM were increased only during vaso-occlusive crisis in 1 hydroxyurea-treated HbSC subject. No ultra-large HMWM were observed.

Conclusion: In this preliminary study, in young SCD subjects, VWF:Ag trended higher in HbSS vs. HbSC and in severe HbSS participants at a single time-point, but serial evaluations at baseline, in crisis and with optimized disease-modifying therapy are needed to determine the potential of VWF:Ag and HMWM as biomarkers for severity or treatment response. Surprisingly, vWF:Ag was high in some sickle trait subjects. Since HbAS is associated with some health challenges such as increased thrombosis risk, further examination of VWF and endothelial dysfunction in sickle trait may provide novel insights into its role as a biomarker.

Poster # 333 | UNANTICIPATED CONSEQUENCES IDENTIFIED AFTER IMPLEMENTATION OF A PEDIATRIC EMERGENCY DEPARTMENT (PED)-BASED INTRANASAL FENTANYL (INF) PROTOCOL FOR THE TREATMENT OF VASO-OCCLUSIVE PAIN EPISODES (VOE) IN CHILDREN WITH SICKLE CELL DISEASE (SCD)

Kirshma Khemani, Lankala Reddy, Shabnam Jain, Amanda Mallino, Leah Bryan, Courtney McCracken, April Zmitrovich, Bolanle Akinsola, Lakshmanan Krishnamurti, Claudia Morris

Emory University School of Medicine/Children's Healthcare of Atlanta, Atlanta, Georgia, United States

Background: The 2014 National Heart Lung & Blood Institute(NHLBI) guidelines for acute management of VOE recommends rapid evaluation and treatment of pain, including administration of a parenteral opioid within 30-minutes of triage or 60-minutes from registration, pain reassessment & repeat opioid delivery within 15-30-minutes. INF use has been increasing in PEDs due to its rapid onset and ease of administration.

Objectives: To evaluate PED utilization of INF & its effect on intravenous (IV) opioid administration and pain control for the treatment of VOE.

Design/Method: A retrospective review of 250 EMR was performed on children with SCD±2years presenting to a PED with VOE (pain scores 6 on a 0–10 scale) from Jan-June 2017. Variables studied were median time (IQR,95%CI) from PED arrival to first-parenteral-opioid-administration, time-to-first-IV-opioid, first & final pain score, disposition and readmission rate. Time-to-first-IV-opioid was also compared to historical data (Jan-Dec2012,n = 231) prior to INF protocol initiation.

Results: Mean age was 13±4years, 48% male and majority had HbSS (66%). Admission rate was 60%. Of 250 VOE episodes, 183(73%) received INF & 204 (82%) received an IV opioid. Both INF+IV opioid were given to 141 patients, while 42 (17%) patients received INF only. Time-to-first-parenteral-opioid administration for those treated with INF vs. IV opioid alone was 26 minutes (19-33) versus 74 minutes (46-10), p<0.01. Pain scores at disposition were lower in patients who received INF. Time-to-IV-opioid was longer in patients receiving INF vs. IV opioid alone (115 vs 83 minutes,p<0.01) & compared to historical date (35±18minutes). Additionally, 15% patients received IV opioids within 60 minutes of ED arrival in the INF+IV opioid vs. 40% in the IV opioids alone group (p<0.01). No differences in 72-hour-return-rates were found in any of the groups, including INF alone group.

Conclusion: Use of INF in the PED for VOE is an excellent strategy to shorten time-to-first-parenteral-opioid-administration, improve pain scores & improve adherence to the NHLBI guidelines. However we had 2 distinct unexpected findings: (1) Delays in IV opioid delivery after INF use & (2) INF alone appeared to provide sufficient pain control without IV opioids for disposition home in 17% of VOE patients. Whether the latter reflects insufficient pain management or that there is a milder subgroup for whom INF alone is sufficient, requires further investigation. This study illustrates our experience with a PED-based INF protocol in terms of unanticipated delays in IV opioids and also discharges after INF alone. Efforts are underway to further improve use of INF in VOE management.

Poster # 334 | THE ROLE OF FOLATE SUPPLEMENTATION IN IMPROVING CLINICAL OUTCOMES IN CHILDREN WITH SICKLE CELL DISEASE

Neena Alex, Bruce Bernstein, Deepti Raybagkar

St. Christopher's Hospital for Children, Philadelphia, Pennsylvania, United States

Background: Folate supplementation is commonly included as standard management in patients with sickle cell disease. However, clear evidence supporting the clinical benefits of this practice is lacking. A single study demonstrated improvement on the occurrence of repeat dactylitis at a higher dose of folic acid.

Objectives: To compare clinical outcomes in pediatric patients with sickle cell disease treated with folate supplementation versus those who were not.

Design/Method: This study was a retrospective chart review that included patients 3 to 23 years old with sickle cell disease type SS and Sβ0 followed at St. Christopher's Hospital for Children. Data collected included information about folate supplementation, red cell indices and the presence or absence of clinical outcomes including vaso-occlusive crisis requiring hospitalization in the last six months, acute chest syndrome, infections, asthma, sleep apnea, nephropathy, cerebral vascular disease, stroke and avascular necrosis. Analysis of variance (ANOVA) was used to evaluate mean differences between age, number of infections, number of VOC events, hemoglobin, reticulocyte count, and mean corpuscular volumes. Additionally, chi square analysis was implemented to evaluate differences in folate and non-folate groups for left ventricular remodeling (LVR), sickle cell nephropathy, asthma, obstructive sleep apnea (OSA), nocturnal hypoxia, and avascular necrosis (AVN). Mean differences between the folate and non-folate groups were compared for patients on and off hydroxyurea therapy.

Results: One hundred and seven patients met inclusion criteria following review of clinical data. Of the patients included in the study, 45 patients were found to be taking folate (42%), while 62 patients were not (58%). Statistical analysis showed that there were no significant differences in the incidence of clinical outcomes between patients on folate versus those who were not on folate. Of the patients who were not on hydroxyurea, hemoglobin levels were significantly higher in patients on folate versus those who were not (p = 0.053), but not significantly different for the patients on hydroxyurea.

Conclusion: This study suggests that folate supplementation makes no significant impact on the red blood cell indices of

anemia nor on the incidence of adverse clinical outcomes in children with sickle cell disease. However, a larger prospective study is needed to guide future considerations for folate supplementation in sickle cell patients in the clinical setting.

Poster # 335/Early Career Travel Stipend Award Recipient | GEOSPATIAL MAPPING OF SICKLE CELL DISEASE IN NORTHWESTERN TANZANIA

Luke Smart, Emmanuela Ambrose, Adolfine Hokororo, Mwesige Charles, Medard Beyanga, Erasmus Kamugisha, Erius Tebuka, Arielle Hernandez, Thad Howard, Russell Ware

Bugando Medical Centre, Mwanza, Tanzania, United Republic of Tanzania

Background: Tanzania ranks 3rd globally for the number of infants born annually with sickle cell disease (SCD) but lacks a national newborn screening program. The prevalence of sickle cell trait (SCT) and SCD is highest in the Northwestern regions around Lake Victoria served by Bugando Medical Centre (BMC) a teaching and consultancy hospital in Mwanza. BMC also houses the HIV early infant diagnosis (EID) laboratory that tests dried blood spots (DBS) from HIV-exposed infants. DBS can be tested for HIV and then retested for sickle cell trait and disease.

Objectives: To determine the prevalence of sickle trait and disease by region and district in Northwestern Tanzania using existing public health infrastructure. Secondary objectives explored associations between SCT, SCD, malaria and HIV.

Design/Method: The Tanzania Sickle Surveillance Study (TS3) is a prospective year-long cross-sectional study of HIV-exposed infants born in northwestern Tanzania, whose DBS collected by the EID program are tested at BMC and available for further testing of SCT and SCD. Samples from children ≤24 months of age were tested by isoelectric focusing (IEF) and scored independently by two Tanzanian staff as normal, SCT, SCD, variant, or uninterpretable. DBS samples scored as disease or variant were repeated.

Results: Over the course of 9 months, 157 IEF gels have been run. A total of 10,019 DBS samples have been scored, including 9,567 from children less than 24-months old. The overall prevalence of SCT is 20.65% and the prevalence of SCD is 0.99%, along with 0.10% hemoglobin variants. Quality of the laboratory results is extremely high, with only 0.15% DBS samples yielding an uninterpretable result. Geospatial mapping of the first 5,900 samples revealed a regional SCD prevalence ranging from 0.3% up to 2.0% among the 9 regions served by BMC.

Conclusion: The prevalence of SCT and SCD is very high in Northwestern Tanzania. Geospatial mapping will identify high prevalence areas where targeted newborn screening can be started using existing public health infrastructure with minimal start-up cost and training. Further data will enhance the accuracy of the map to the district level.

Poster # 336 | EFFECT OF HYDROXYUREA AND CHRONIC PRBC TRANSFUSIONS ON PULMONARY FUNCTION DECLINE IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

Melissa Knudson, Seema Rani, Bruce Bernstein, Nataly Apollonsky

St. Christopher's Hospital for Children, Philadelphia, Pennsylvania, United States

Background: Pediatric patients with sickle cell disease (SCD) could develop obstructive, restrictive or mixed abnormalities of pulmonary function (PF). Several publications report progressive worsening of PF over time, which could lead to severe morbidity in adult patients with sickle cell disease. In adults with sickle cell anemia up to 20-30 % of mortality is related to lung disease. Early intervention aimed at improvement of lung function could significantly decrease morbidity and possibly improve life expectancy. Among disease modifying approaches commonly used in SCD are Hydroxyurea (HU) and chronic pRBC transfusions. Both interventions lead to increase of hemoglobin, decrease of HbS fraction, leading to decreased hemolysis. Reports of effect of HU on pulmonary function are conflicting with some suggesting no effect and others proposing a slower decline of pulmonary function.

Objectives: The goal of our study is to evaluate effect of disease modifying therapies, like HU and chronic pRBC on change of pulmonary function in pediatric patients with sickle cell disease.

Design/Method: This study utilized a retrospective chart review of children with SCD who had multiple PFTs. We analyzed 286 PFTs from 80 patients done during clinic visits. SCD patients were divided into three treatment groups: hydroxyurea, chronic transfusions or neither. Data was analyzed with linear correlations and analysis of variance (ANOVA). Comparison were made between the three groups specifically observing the changes in absolute numbers on PFTs over time using the first and last PFT the patient had.

Results: There were a total of 80 patients with multiple PFTs (ranging from 2-7); control (40), hydroxyurea (23) and chronic transfusion (10). The mean changes of the control, and hydroxyurea for the PFT parameters FEV1 (-5.53

vs. -4.30), FVC (-3.99 vs. -3.96), FEV1/FVC (-0.0079 vs. -0.023) and FEF25-75 (-1.021 vs. -4.96) all demonstrated a decline in PFT over time. The chronic transfusion group demonstrated a small improvement in PFTs over time for FEV1 (0.300), FVC (1.300), FEF25-75 (0.400), however there was a decline in FEV1/FVC (-0.013). However, there was no statistically significant (p-value <0.005) in the difference in any PFTs parameters between any of the groups.

Conclusion: In children with SCD there is a decline of PF parameters over time. Although no significant differences were seen between the three groups it appears chronic transfusion may improve or limit the decline in PFTs. Larger studies need to be done to evaluate difference in PF decline in patients with SCD patients.

Poster # 337 | VALIDITY AND FEASIBILITY OF USING A MOBILE APPLICATION AND WEARABLE TECHNOLOGY FOR PATIENTS WITH SICKLE CELL DISEASE HOSPITALIZED FOR PAIN

Kalindi Narine, Fan Yang, Tanvi Banerjee, Nirmish Shah

Duke University Medical Center, Durham, North Carolina, United States

Background: The use of mobile technology in health care has been a growing trend. Patients with chronic diseases such as sickle cell disease (SCD) require close monitoring to provide appropriate treatment recommendations and avoid complications. We conducted a feasibility study for patients with SCD hospitalized for pain using our self-developed mobile application (TRU-pain: Technology Resources to better Understand Pain) and a wearable activity tracker. Subjective symptoms such as pain and objective data such as heart rate (HR) were measured.

Objectives: We aimed to 1) correlate nursing recordings with mobile technology recordings; 2) get feedback from patients about usability.

Design/Method: We enrolled patients with SCD >8 years old and <36 hours from admission for uncomplicated vaso-occlusive crisis, excluding patients admitted to ICU. Patients were given an iPad and a wearable device. They were instructed to record in the application at least once per day and to keep the wearable on, removing only to charge. Prior to discharge, patients completed a feasibility questionnaire.

Results: We enrolled 20 patients, 40% females, median age 17.5 (range 13 to 54) who were admitted for a median 5 days (range 2 to 8) for uncomplicated pain crisis. Patients used the application throughout hospitalization and made one entry/day (range 0 to 2). Pain scores recorded via TRU-Pain correlated well ($r = 0.74$, $p<0.005$) with pain scores recorded in EMR. There was an average of 10,930 data points recorded per day, by the wearable, with a maximum of 54,693 data points/day. The median amount of hours of wearable data per day was 4.21 (maximum of 18.05). The HR recorded via the wearable correlated significantly with the HR recorded in EMR ($r = 0.69$, p-value < 0.005). As for usability, 70% of patients indicated never having a problem with the technology, 90% found TRU-pain 'very easy' or 'somewhat easy' to use, and 60% were 'very satisfied' with their participation in the study, indicating that it helped them track their pain.

Conclusion: Our pilot study during hospitalization shows strong potential for using TRU-pain for patients with SCD. Pain data from application and HR from wearable correlated well to the EMR data. According to the feedback received, our application was easy to use and helped patients track their pain. Despite limitations of battery life, the use of wearable technology is feasible, providing additional data such as activity. We are optimistic that we can continue to improve our TRU-pain system to help improve care in patients with SCD.

Poster # 338 | COMPARATIVE EFFECTIVENESS OF A PATIENT DECISION AID FOR THERAPEUTIC OPTIONS FOR SICKLE CELL DISEASE

Lakshmanan Krishnamurti, Diana Ross, Nitya Bakshi, Cynthia Sinha, Kirshma Khemani, George Lowenstein

Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University, Atlanta, Georgia, United States

Background: Hydroxyurea, chronic blood transfusion, and bone marrow transplantation can reduce complications, and improve survival in sickle cell disease (SCD), but are associated with a significant decisional dilemma because of the inherent risk-benefit tradeoffs, and the lack of comparative studies. These treatments are underutilized leading to avoidable morbidity and premature mortality. There is a need for tools to provide patients high-quality information about their treatment options, the associated risks, and benefits, help them clarify their values, and allow them to share in the process of informed medical decision making.

Objectives: To develop a health literacy sensitive, web-based, decision aid (PtDA) to help patients with SCD make informed choices about treatments, and to estimate in a randomized clinical trial the acceptability and effectiveness of the PtDA in improving patient knowledge, involvement in decision-making and decision-making quality.

Design/Method: We conducted qualitative interviews of SCD patients, caregivers, stakeholders, and healthcare providers for a decisional needs assessment to identify decisional conflict, knowledge, expectations, values, support, resources, decision types, timing, stages, and learning, and personal clinical characteristics, and to guide the development of a PtDA. Transcripts were coded using QSR NVivo 10. Stakeholders completed alpha and beta testing of PtDA. We conducted a randomized clinical trial of adults, and of caregivers of pediatric patients to evaluate the comparative efficacy of the PtDA, vs. standard of care.

Results: PtDA (www.sickleoptions.org) was developed per decisional needs described by 223 stakeholders and finalized following alpha testing, and beta testing by 68 and 87 stakeholders respectively. In a randomized trial of 120 subjects considering various treatment options, qualitative interviews revealed a high level of usability, acceptability, and utility in education, values clarification, and preparedness for decision making of the PtDA. A median 68% rated the acceptability of PtDA as good or excellent and provided narrative comments endorsing the acceptability, ease of use, and utility in preparation for decision making. The PtDA met international standards for content, development process, and efficacy with the exception of having a full range of positive and negative experiences in patient stories. Compared to baseline PtDA group had statistically significant improvement in preparedness for decision making ($p = 0.005$) and informed subscale of decisional conflict ($p = 0.02$) but not for decisional self-efficacy, knowledge, choice predisposition, or stages of decision-making.

Conclusion: A PtDA for patients with SCD developed following extensive engagement of key stakeholders was found to be acceptable, useful, easy to use, to improve preparedness for decision making, and decrease decisional conflict.

Poster # 339 | AURA ASSOCIATED WITH SICKLE CELL PAIN: A MOBILE PHONE APPLICATION TO STUDY THE RELATION BETWEEN THE DYSAUTONOMIA OF SICKLE CELL DISEASE AND SUBSEQUENT PAIN

Jacquelyn Baskin, Anna Ratiu, Payal Shah, Saranya Veluswamy, Juan Espinoza, Lonnie Zeltzer, Thomas Coates

Children's Hospital Los Angeles, Los Angeles, California, United States

Background: Painful vaso-occlusive crisis (VOC) accounts for the majority of emergency department (ED) visits and hospitalizations in sickle cell disease (SCD). We are interested in studying mental stress and associated autonomic nervous system (ANS) imbalance that cause vaso-constriction as possible triggers of SCD pain. To this end, we developed a mobile phone application (app) to record daily pain frequency and intensity as clinical endpoints that might be predicted by ANS parameters measured in the laboratory. In particular, we think that the aura may represent ANS instability that precedes or even triggers change in blood flow and VOC.

Objectives: To assess the feasibility of using an app to evaluate frequency and severity of VOC and its potential association with mental stress and presence of aura.

Design/Method: An app was developed for both iOS and Android systems to allow patients to track pain, stress, and aura. The idea was to create an app that was easy to use with the intent to only capture pain episodes, rather than detailed description of the pain. All SCD patients were eligible and a parent version was available for younger children. De-identified data was automatically transferred to a HIPAA compliant database via a cloud-based server interfaced to the main research project database. A feedback questionnaire was implemented after at least a month of utilization to assess usability.

Results: Of the 51 SCD patients enrolled, 39 participants utilized the app and 21 of the 23 participants that provided feedback indicated the app was easy to navigate. The mean pain scale was 6 out of 10 (standard deviation 1.97) for those that entered they had pain that day. Although the mean stress level was 3 out of 10, there was a statistically significant correlation between increasing stress levels and increasing pain scores ($p < 0.05$). Aura was reported by 26 patients, with 5 patients reporting more than 10 episodes. Moreover, on days aura was present there was greater incidence that pain was present as well ($p < 0.05$). However, there was no statistically significant association between pain intensity and presence of an aura ($p = 0.14$).

Conclusion: Consistent with prior research, reported pain intensity is significantly associated with reported stress intensity. Although there was an association between presence of aura and pain, it did not seem to correlate with pain intensity. This uniquely designed app can monitor SCD pain clinically and help understand the role of sickle dysautonomia in the genesis of SCD pain.

Poster # 340 | CLINICAL OUTCOMES OF CHILDREN WITH SICKLE CELL DISEASE HOSPITALIZED FOR FEVER

Michael Massari, Vandy Black

University of Florida College of Medicine, Gainesville, Florida, United States

Background: Evidenced-based guidelines recommend the emergent evaluation of fever in children with sickle cell disease (SCD). As the prevalence of bacteremia has decreased, outpatient management has become more common. However, fever can sometimes herald other complications of SCD, such as acute chest syndrome, vaso-occlusive pain crisis, splenic sequestration, or aplastic crisis. Institutional practices regarding fever management in SCD remain variable, and little is known about the clinical outcomes of children hospitalized for uncomplicated fever.

Objectives: The primary objective was to determine the rate of bacteremia or SCD-related complications per febrile episode in children with SCD admitted to a single institution between January 2014 and June 2017 for uncomplicated fever.

Design/Method: This was a retrospective cohort study of febrile patients up to 21 years of age with SCD, any genotype, admitted to the University of Florida during the defined study period. Eligible patients were identified by a database search using admitting diagnosis codes for SCD and fever based on the International Classification of Diseases 9th and 10th revisions. Encounters were manually reviewed to confirm eligibility. Patients were excluded if they had other indications for hospitalization apparent at the time of admission, such as an acute vaso-occlusive episode requiring parental narcotics, asthma exacerbation, or additional complications of SCD.

Results: The database search identified 211 encounters, of which 83 were excluded based on confounding indications for hospitalization. Sixty-three eligible patients accounted for 128 hospitalizations. The median age was 2 years (range 5 weeks-17 years); 60.2% were male. Mean duration of hospitalization was 2.6 days (range 1–13 days). Eight positive blood cultures were identified; six of these were classified as contaminants. Bacteremia or the development of a SCD-related complication was identified in 18 (14.06%) admissions. These included acute chest syndrome (n = 4), bacteremia (n = 2), splenic sequestration (n = 1), and red cell transfusion (n = 11). Exploratory analyses of potential predictors of bacteremia or SCD-related complications showed no association with the presenting white blood cell count or degree of fever (p = 0.36). Of the patients classified as having a SCD-related complication, 94% had hemoglobin SS disease and 78% had at least one prior documented complication. 64% of the patients transfused had at least one prior transfusion.

Conclusion: While improvements in preventative care have substantially lowered rates of bacteremia in children with SCD, fever warrants careful evaluation for other acute SCD-related complications. Providers should consider inpatient observation in select cases. Additional studies are warranted to define subsets of patients suitable for outpatient fever management.

Poster # 341 | A RANDOMIZED CONTROLLED TRIAL OF HOME-BASED COMPUTERIZED WORKING MEMORY TRAINING FOR CHILDREN WITH SICKLE CELL DISEASE

Steven Hardy, Sarah Bills, Shane Wise, Emily Meier, Jeffrey Schatz, Kristina Hardy

Children's National Health System, Washington, District of Columbia, United States

Background: Children with sickle cell disease (SCD) exhibit lower neurocognitive functioning than healthy peers, even in the absence of stroke. Among the domains commonly affected, working memory (WM) seems particularly affected by disease processes and WM deficits have significant implications for academic achievement and disease self-management. Few interventions to improve working memory in pediatric SCD have been evaluated.

Objectives: To determine the effects of Cogmed, a home-based computerized WM training intervention, in children with SCD using a randomized controlled trial design.

Design/Method: Participants (ages 7–16) with SCD completed a baseline neuropsychological assessment and those with WM deficits were randomized to either begin Cogmed immediately or enter an 8-week waitlist. Cogmed is a home-based intervention completed on an iPad that consists of 12 increasingly challenging exercises targeting visual-spatial and verbal WM, practiced over 25 sessions. At the end of training, participants completed a post-intervention neuropsychological assessment, including tests of visual-spatial and verbal WM from the Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V).

Results: Ninety-one participants (M age = 10.43, SD = 2.93; 59% female; 69% HbSS) enrolled in the study; 52% (n = 47) exhibited WM deficits and were randomized to either begin Cogmed immediately or wait 5–8 weeks before starting Cogmed. Among those that have received the intervention and reached the end of their training period (n = 42), 27 participants (59%) completed at least 5 Cogmed sessions, 19 (41%) finished at least 10 sessions, and 7 finished at least 20 sessions (15%). The mean number of completed Cogmed sessions was 9.10 (SD = 7.77). Paired Samples t-tests revealed significant improvements on the Working Memory Index (t[38] = -2.44, p = 0.020) and on the Digit Span (t[40] = -3.02, p = 0.004), and Spatial Span-Backward (t[39] = -2.83, p = 0.007) subtests. Improvements were especially pronounced for

participants completing at least 10 sessions. Partial correlations controlling for respective baseline scores indicated that the number of Cogmed sessions completed was positively correlated with post-test scores on Digit Span (r = .38, p = .017) and Spatial Span-Backward (r = 0.45, p = 0.004) subtests. Among participants who completed at least 10 Cogmed sessions, 77% scored in the Average range or higher on the Working Memory Index at the post-intervention assessment, compared to 58% at baseline.

Conclusion: Results support the efficacy of Cogmed in producing significant improvements in WM. A dose-effect was observed such that participants who completed more Cogmed sessions had greater improvements in WM. Home-based cognitive training programs may ameliorate SCD-related WM deficits but methods for motivating and supporting patients as they complete home-based interventions are needed to enhance adherence and effectiveness.

Poster # 342 | HYDROXYUREA USE IN INFANTS WITH SICKLE CELL DISEASE: THE EARLIER THE BETTER

Sarah Schuchard, Jennifer Lissick, Amanda Nickel, Dave Watson, Mike Finch, Kristin Moquist, Rae Blaylark, Stephen Nelson

Children's Hospitals and Clinics of Minnesota, Minneapolis, Minnesota, United States

Background: Sickle cell disease is associated with myriad complications that lead to significant morbidity and early mortality. Hydroxyurea has been used successfully to reduce the incidence of these complications and has led to significant improvements in quality and duration of life. At Children's Minnesota we recommend hydroxyurea in all patients with Hb SS/Sβ0 thalassemia as early as 5 months of age with a goal of starting all patients before 12 months of age.

Objectives: The purpose of this study was to evaluate the use of hydroxyurea therapy in young patients with sickle cell disease, with particular attention to those children less than one year of age.

Design/Method: A retrospective chart review was conducted on patients less than 5 years of age with sickle cell disease who began hydroxyurea therapy between January 1, 2008 and December 31, 2016. The study population was divided into three cohorts based upon age at hydroxyurea initiation: cohort 1 (0-1 year), cohort 2 (1-2 years), and cohort 3 (2-5 years). Outcomes included laboratory data, clinical events (hospitalization, dactylitis, pain crisis, transfusion, splenic sequestration, acute chest syndrome), and toxicity occurring in the first 2 years of life.

Results: A total of 65 patients were included in cohorts 1 (n = 35, mean age 7.2 months), 2 (n = 13, mean age 19.5 months), and 3 (n = 17, mean age 35.5 months). Patients in cohort 1 had higher hemoglobin (p = 0.0003) and MCV (p = 0.0199) and lower absolute reticulocyte count (p = 0.0304) when compared to cohort 3. The WBC (p = 0.0007, <0.0001) and ANC (p = 0.0364, 0.0025) were significantly lower compared to both older cohorts. However, no patient had therapy held because of neutropenia. The mean baseline hemoglobin F in cohort 1 was 31.5% compared to 19.7% and 16.5% in cohorts 2 and 3 respectively (p = 0.002, p<0.0001). The mean duration of therapy in cohort 1 was 31.3 months, compared to 57.6 months in cohort 2 (p = 0.018) and 29.1 months in cohort 3 (p = 0.401). During this time, Hb F levels remained higher in cohort 1 (mean 29.9%) compared to cohorts 2 and 3 (mean 20.4%, p = 0.007 and mean 20.6%, p = 0.003). Patients in cohort 1 experienced fewer hospitalizations (p = 0.0025), pain crises (p = 0.0618), and transfusions (p = 0.0426). There was no difference in toxicity between groups.

Conclusion: Hydroxyurea was used safely in infants 5 to 12 months of age and resulted in more robust hematologic responses and a decrease in sickle-related complications when compared with patients starting hydroxyurea later in life.

Poster # 343 | DISCRIMINATING CEREBRAL INFARCTS IN PEDIATRIC SICKLE CELL DISEASE USING BRIEF COMPUTERIZED NEUROCOGNITIVE ASSESSMENTS

Steven Hardy, Anthony Gioia, Sarah Bills, Judith Tsoi, Emily Meier, Kristina Hardy

Children's National Health System, Washington, District of Columbia, United States

Background: Children with sickle cell disease (SCD) have a significantly greater risk of silent or overt cerebral infarction than the general population. Infarcts are associated with declines in cognitive functioning and academic achievement. While infarcts are reliably identified using MRI, scans are expensive and occasionally necessitate sedation. Moreover, MRI's are not recommended for routine monitoring of cerebral infarcts. Additional tools are needed for discriminating the presence of a cerebral infarct that are brief, noninvasive, inexpensive, and repeatable.

Objectives: To evaluate differences in performance on Cogstate, a computerized neurocognitive assessment, in patients with SCD with and without history of cerebral infarct.

Design/Method: Participants included 112 children with SCD ages 7–16 (M = 10.61, SD = 2.91; 58% female; 70%

HbSS) enrolled in a cognitive intervention trial. Participants completed the Cogstate Pediatric Battery, which measures processing speed, sustained attention, verbal learning, working memory, and executive functioning. History of silent or overt infarct was determined via health record review. Participants also completed measures of intelligence (IQ) and math fluency.

Results: Participants' standard scores across most neurocognitive measures were lower than expected compared to the standardization sample (Mean IQ = 91.03, SD = 13.34). Thirty percent of participants (n = 33) had a documented history of cerebral infarct. Participants with a history of cerebral infarct scored lower on Cogstate tasks measuring sustained attention (t[108] = 2.93, p = 0.004) and executive functioning (t[98] = 2.46, p = 0.016), as well as on a measure of math fluency (t[88] = 2.16, p = 0.033). Receiver Operating Characteristic (ROC) analyses demonstrated that the Cogstate task measuring sustained attention was a fair discriminant of patients with and without a history of infarct (AUC = 0.75, CI95 = 0.65-0.84, p = 0.0001), whereas IQ score was not (AUC = 0.58, CI95 = 0.46-0.71, p = 0.19). Cogstate processing speed and sustained attention tasks fairly discriminated between patients with at least average or below average intelligence (AUC = 0.77, CI95 = 0.67-0.86, p = 0.00001 and AUC = 0.74, CI95 = 0.64-0.84, p = 0.0001, respectively). Finally, the Cogstate processing speed task was good at discriminating between at least average or below average math fluency (AUC = 0.80, CI95 = 0.70-0.90, p<0.00001).

Conclusion: Multiple tasks in the Cogstate Pediatric Battery appear to adequately identify patients with a history of cerebral infarcts. In addition, Cogstate tasks appear to be fair predictors of impairments in IQ and academic achievement outcomes. Cogstate is inexpensive and can be easily administered in a medical setting with minimal training in approximately 20 minutes. Results support the potential for Cogstate to be used as a screening tool for medical and neuropsychological abnormalities in children with SCD.

Poster # 344 | CORRELATION BETWEEN HYDROXYUREA USE AND LEFT VENTRICULAR REMODELING AND FUNCTION IN CHILDREN WITH SICKLE CELL DISEASE

Jacquelyn Klicka-Skeels, Shuping Ge, Bruce Bernstein, Deepti Raybagkar

St. Christopher's Hospital for Children, Philadelphia, Pennsylvania, United States

Background: Cardiovascular disease contributes to the morbidity and mortality of patients with sickle cell disease (SCD). Hydroxyurea therapy in SCD has known clinical efficacy including improving anemia, decreasing episodes of vaso-occlusive crisis and acute chest syndrome, and decreasing mortality. Effect of Hydroxyurea on cardiac function in children with SCD is not well studied. An earlier study suggested the protective effect of Hydroxyurea on left ventricular (LV) hypertrophy in SCD. We hypothesized that Hydroxyurea use would be associated with decreased LV remodeling and improved cardiac function.

Objectives: We aimed to evaluate the association between Hydroxyurea use and LV remodeling and cardiac dysfunction in children with SCD.

Design/Method: We completed a retrospective study of patients with SCD who were 10 to 22 years old, followed at St. Christopher's Hospital for Children and had an echocardiogram completed in the past 18 months. Data collected included gender, BMI, SCD genotype, Hydroxyurea use, chronic transfusion use, and 2D and Doppler echocardiographic parameters. Cardiac structure, geometry, systolic function, and diastolic function echocardiogram parameters were included. Analysis of variance (ANOVA) tests were performed to assess for statistical significance of differences in cardiac parameters between patients with and without Hydroxyurea use. Analysis of Covariance (ANCOVA) tests were performed to control for age.

Results: Demographic and echocardiogram data was collected on all 93 patients who met inclusion criteria. Of the 93 patients included, 31 (33%) were on Hydroxyurea therapy. Patients on Hydroxyurea had significantly lower mean relative wall thickness (p = 0.026) and significantly higher mean peak early LV filling velocities (p = 0.032) and peak early LV filling/septal annuli early peak (E/Ea) velocities (p = 0.002); however, only the E/Ea velocities remained significant when controlling for age (p = 0.001). Mean peak early LV filling velocities approached significance when controlling for age (p = 0.052).

Conclusion: Hydroxyurea therapy resulted in a significantly higher E/EA velocity, suggesting that these patients had worse diastolic function. It is possible that the patients initiated on Hydroxyurea already had worse disease manifestations than those not on Hydroxyurea, possibly accounting for the decreased diastolic function. When controlling for age, Hydroxyurea use did not result in significant differences in cardiac structure parameters, systolic function parameters or cardiac geometry. Prospective studies and larger sample size are needed to validate our findings, examine for additional statistically significant differences, and develop preventive strategies for cardiovascular disease in children with SCD.

Poster # 345 | RISK FACTORS FOR RESPIRATORY FAILURE AMONG PEDIATRIC ACUTE CHEST SYNDROME IN SICKLE CELL DISEASE

Takuto Takahashi, Yusuke Okubo, Maria Pereda, Atsuhiko Handa, Scott Miller

SUNY Downstate Medical Center, Brooklyn, New York, United States

Background: Acute chest syndrome (ACS) is now the leading cause of death in children with sickle cell disease; mortality in the U.S. is reported to be 1–2% and is mostly due to respiratory failure. Early transfusion improves clinical outcomes. Although patients with concurrent asthma are considered at increased risk for poor outcomes, risk factors for respiratory failure in pediatric ACS have not been well-defined.

Objectives: To determine whether specific epidemiological and clinical features of children hospitalized with ACS are predictive of the need for mechanical ventilation.

Design/Method: Data from the Kids' Inpatient Database were reviewed to identify patients age < 20 years with a discharge diagnosis of ACS for the years 2003, 2006, 2009, and 2012. Outcomes were defined by the International Classification of Diseases, Ninth Revision, Clinical Modification Code. Data were weighted to estimate total annual hospitalizations according to hospital characteristics in the United States. Trends in healthcare costs, length of hospital stay, transfusion, and mechanical ventilation use were analyzed using multivariable linear regression. In addition, multivariable logistic regression was used to ascertain specific clinical or epidemiologic factors associated with mechanical ventilation use after adjusting for patient and hospital characteristics.

Results: The total hospitalizations for ACS were 5,018 in 2003; 6,058 in 2006; 6,072 in 2009; and 6,360 in 2012. Reported use of mechanical ventilation ranged from 2.8% to 5.6% and was associated with non-black compared to black children (OR, 1.53; 95%CI, 1.02 to 2.31) and the fall season (OR, 1.36; 95%CI, 1.05 to 1.74), but not with age, preexisting asthma or Hb-genotype. Comorbidities of obesity (OR, 3.35; 95%CI, 1.94 to 5.78), obstructive sleep apnea (OR, 3.72; 95%CI, 2.23 to 6.20) and heart disease (OR, 2.19; 95%CI, 1.47 to 3.27) were associated with mechanical ventilation use. The use of simple and exchange transfusion during all ACS admissions ranged from 30.1% to 40.5% and 2.6% to 2.9%, respectively.

Conclusion: Among pediatric ACS patients, those with obesity, obstructive sleep apnea or heart disease were at increased risk for respiratory failure and might benefit from early intervention (e.g., transfusion). Surprisingly, asthma in children with ACS does not appear to be a distinct risk factor for respiratory failure, and further studies are needed to clarify whether differences in treatment approach (e.g., addition of corticosteroids, bronchodilators) might impact on ACS progression and/or severity even in high risk patients without asthma.

Poster # 346 | A COMPARISON STUDY OF PULMONARY FUNCTION IN AMERICAN AND KUWITI CHILDREN WITH SICKLE CELL DISEASE

Asmaa Azab, Sharef Al-Mulaab, Fernanda Kupferman, Adekunle Adekile, Mayank Shukla, Mario Peichev, Nataliie Sommerville- Brooks, Kusum Viswanathan

Brookdale Hospital and Medical Center, Brooklyn, New York, United States

Background: American and Kuwaiti children with Sickle Cell Disease (SCD) vary in disease severity due to different haplotypes. It is unknown what impact the different haplotypes have on lung function. African American (AA) mainly have the Benin haplotype with low fetal hemoglobin (HbF) level compared to Kuwaiti (K) who have the Arab-Indian haplotype with a high HbF. The higher HbF contributes to a milder clinical course. Pulmonary complications are considered a major complication of SCD. In the United States and in Kuwait, studies show an obstructive pattern for children with SCD.

Objectives: To compare pulmonary functions between AA and K Children with SCD and to assess if a high Hb F level contributes to better function.

Design/Method: A cross sectional study was done on children with SCD (Hb SS disease) followed in comprehensive sickle cell programs. AA patients were followed at Brookdale Hospital, NY and K patients were followed in Mubarak hospital, Kuwait. Children between the ages of 6 and 22 years who had Pulmonary function tests (PFT) done as a routine screening were enrolled. PFT was done using spirometer and plethysmography. Patients with congenital or anatomical lung abnormality, heart disease, pulmonary disease such as Acute chest syndrome, Acute asthma or Pneumonia within 4 weeks were excluded.

Results: There were 74 children (37 in each group) with SCD,. Restrictive pattern on PFT was seen in 18/37 (49%) of AA vs. 10/37 (27%) of K ($p>0.05$). Obstructive pattern was seen in 6/37 (16%) of AA vs. 13/37 (35%) of the K group ($p>0.05$). In both groups, 13 children (35%) had normal PFT. Three/13 (15%) in the AA group had a Hb F>20% as compared to 11/13 (85%) in the K group ($p<0.01$). Abnormal PFT was noted in 24/37 children (65%) in each group. HbF was >20% in 3/24 (13%) in the AA group vs. 15/24 (63%) in the

K group ($p<0.01$). In patients with abnormal PFT, mean HbF was 10.4±8.4 in AA group, compared to 22.4±8 in K group ($p<0.01$).

Conclusion: Abnormal PFT is highly prevalent among children with SCD in both groups. AA children are more likely to have restrictive disease and K to have an obstructive pattern. Level of HbF did not seem to protect K patients from abnormalities on PFT. This finding should emphasize the importance of performing PFT as part of the initial evaluation of all children with SCD.

Poster # 347 | MEAN PLATELET VOLUME IN SICKLE CELL DISEASE PREDICTS MORTALITY AND DISEASE SEVERITY

Aravind Thavamani, Krishna Kishore Umapathi, Geetanjali Bora, Aparna Roy, Mammen Puliyel

Metro Health Medical Center - Case Western Reserve University, Cleveland, Ohio, United States

Background: Sickle cell disease (SCD) is a life-threatening disease with varied clinical spectrum and severity leading to premature death. There is a lack of validated prognostic marker in SCD. Recent evidence suggests that inflammation and platelet adhesion plays a critical role in the pathophysiology of vaso-occlusion in SCD. Elevated Mean Platelet Volume(MPV) values are associated with a higher degree of inflammation in many disease states but it's effect on sickle cell disease or it's severity is unknown.

Objectives: To analyze the role of MPV in predicting disease severity/mortality in pediatric patients with SCD.

Design/Method: This is a single center retrospective study and included patients with sickle cell disease between 6 months and 18 years of age during a 10-year period (2006-2016). Demographic information, lab data and clinical information including acute chest syndrome (ACS), priapism, transfusions, sepsis, pain crisis, avascular necrosis were collected. All laboratory data were collected in steady state with no crisis in the recent past 3 months. The disease severity score/probability of death was calculated using a validated model to predict risk of death in sickle cell disease (Sebastiani et al. Blood 2007). Pearson test was used to analyze correlation between MPV and probability of death.

Results: Total no. of patients = 92; Male 45 (48.9%); Female 47(51.1%). Median age is 6.0 years. All patients were of African-American origin. Disease severity, Hb SS -58(63%); Hb SC – 25(27.2%) and Sickle-Beta thalassemia 9(9.8%). Patients on hydroxyurea has significantly lower MPV, $p = 0.023$ and this is independent of Hb F levels. MPV has a significant positive correlation with the probability of death, $p = 0.016$ and correlation coefficient, $r = 0.254$. On subgroup analysis, the correlation is even more significant in the age group between 6 and 18 years, $p = 0.004$, $r = 0.405$. Using linear regression model, with probability of death as a dependent variable and hydroxyurea, MPV as independent variables, MPV maintains a significant association with probability of death ($p = 0.016$).

Conclusion: MPV is an independent biomarker predicting disease severity and probability of death in pediatric patients with sickle cell disease. Hydroxyurea a known disease ameliorating agent is associated with lower MPV values. This effect is independent of the levels of fetal hemoglobin and may be due to anti-inflammatory effect of hydroxyurea or effect on the platelets.

Poster # 348 | ADVANTAGES OF USING QUALITY IMPROVEMENT (QI) PROCESSES TO IMPROVE THE CARE OF A SICKLE CELL POPULATION

Kay Saving, Nicole Alwan, Diana Simmons, Linda Drawhorn

OSF St. Francis Medical Center, Peoria, Illinois, United States

Background: Major success with initial QI projects by the Sickle Cell Care Team at Children's Hospital has precipitated ongoing inclusion of the QI approach to many other aspects of patient care.

Objectives: To optimize SCD patient care utilizing QI processes.

Design/Method: Success of the SCD QI team's initial project on Transcranial Doppler studies (TCDs) and a second more complex project on Hydroxyurea (HU) adherence, led to additional projects on completion of key immunizations, RBC phenotyping, and Vitamin D level testing. Using similar processes and principles from the HU adherence project, Plan-Do-Study-Act (PDSA) cycles were used to conduct small-scale tests of change. Patient chart prep sheets, created for bi-monthly pre-appointment chart prep meetings, were significantly modified to include these focused care QI objectives. Because of difficulty with EMR database capability, data collected from the EMR was tracked in Excel spreadsheets or other unique tracking vehicles for the various parameters. For example, due to the clinic's diffuse, geographically scattered population, many separate non-shared primary care EMRs, and lack of a mandatory state immunization registry; immunization records needed to be retrieved from PCPs, outlying hospitals, public health departments, and FQHCs, and added to the EMR and Excel database. Starting in 12/2016, all such data was collected and updated monthly.

Results: In one year's time (2016 – 2017), the average immunization completion rate for seven key immunizations (PCV 13, PCV 23, hepatitis A, hepatitis B, meningococcal A, meningococcal B, and HPV) has increased by 20%. The biggest improvements were a 57% and 44% increase in completion for meningococcal A and meningococcal B, respectively. Completion rate for RBC phenotyping rose from 34.8% to 74.4%. Patients with at least one Vitamin D lab test increased from 27.8% to 67.9%. Since starting the TCD project in 2013, the percent of patients who have completed their annual TCD has gone from a baseline of 50% to a sustained value of > 80%.

Conclusion: These QI projects have not only increased adherence to national recommendations for care of SCD patients, they have helped establish a SCD Clinic methodology to create and implement sustainable processes. Having the focused care initiatives prominently displayed on the patients' chart prep sheet serve as a reminder to medical team members to check the status of that item. This methodology is currently being used to formulate additional QI projects on annual renal function parameters and specialty visits, such as annual eye and dental exams.

Poster # 349 | STROKE AVOIDANCE FOR CHILDREN IN REPUBLICA DOMINICANA (SACRED)

Luisanna Sanchez, Rosa Nieves, Teresa Latham, Judy Luden, Gabriela Urcuyo, Melissa Berges, Carla Florencio, Carla Gonzalez, Paola del Villar, Rafael Mena, Russell Ware

Robert Reid Cabral Children's Hospital, Santo Domingo, Dominican Republic

Background: Dominican Republic has a high burden of sickle cell disease, and 5–10% of children with homozygous HbSS (sickle cell anemia, SCA) will develop primary stroke. Transcranial Doppler (TCD) ultrasonography is an effective screening tool for primary stroke risk, but is not routinely available in Dominican Republic. Hydroxyurea and blood transfusions are available, but no prospective screening and treatment program for stroke prevention has been implemented to date.

Objectives: (1) to screen a large cohort of children with SCA living in Dominican Republic, using TCD to identify elevated stroke risk; (2) to determine the effects of treatments for stroke prevention (hydroxyurea for conditional velocities and transfusions for abnormal velocities). We hypothesized that both hydroxyurea and blood transfusions will decrease elevated TCD velocities and help prevent primary stroke.

Design/Method: Stroke Avoidance for Children with REpública Dominicana (SACRED, NCT02769845) features a research partnership between Cincinnati Children's Hospital and Robert Reid Cabral Children's Hospital in Dominican Republic. The protocol, consent forms, and REDCap database were prepared collaboratively and translated into Spanish, and then IRB approval was obtained at both institutions. In the initial prospective phase, children receive TCD screening over a 12-month period; those with conditional TCD velocities (maximum time-averaged velocity 170–199 cm/sec) receive fixed-dose hydroxyurea at 20 mg/kg/day, followed by dose escalation to maximum tolerated dose, while those with abnormal TCD velocities (≥200 cm/sec) receive monthly transfusions for stroke prevention.

Results: A total of 283 children were enrolled in SACRED, with an average age of 8.7 ± 3.4 years. Initial TCD screening revealed 200 (70.7%) normal, 63 (22.3%) conditional, 11 (3.9%) abnormal, and 9 (3.1%) inadequate velocities. Among 48 children (25 males, 23 females, average age 6.8 ± 2.8 years) who initiated hydroxyurea at 20 mg/kg/day for conditional TCD velocities, 42 completed six months of treatment with expected hematological benefits including significant increases in hemoglobin concentration (7.5 to 8.5 g/dL) and fetal hemoglobin (15.8 to 28.4%). No clinical strokes have occurred in the treatment group. Repeat TCD examination after 6-months of hydroxyurea treatment revealed 69% (29/42) with previous conditional velocities had normal TCD velocities.

Conclusion: The prevalence of conditional TCD velocities in the Dominican Republic is high, indicating an elevated stroke risk among children with SCA. Hydroxyurea treatment is associated with improved hematological parameters, lower TCD velocities, and probable decreased stroke risk. SACRED is an important prospective and collaborative research trial providing epidemiological data regarding TCD screening, stroke risk, and hydroxyurea effects among children with SCA.

Poster # 350 | METHODOLOGICAL DIFFERENCES IN MEASUREMENT ALTERS AGGREGATION RESULTS IN PATIENTS WITH SICKLE CELL DISEASE VERSUS HEALTHY SUBJECTS

Christopher Denton, Silvie Suriany, Payal Shah, Obdulio Carreras, Thomas Coates, Jon Detterich

Children's Hospital Los Angeles, Los Angeles, California, United States

Background: Red blood cell aggregation is a rheologic property that explains the shear-thinning behavior of blood. At lower shear rate blood flow, red cells tend to aggregate,

whereas in higher shear rate blood flow, these aggregates are dispersed. This property is especially important in the venous system, where low shear rate blood flow predominates. There is inconsistent data in the literature concerning aggregation and aggregability in sickle cell disease (SCD).

Objectives: Because the LORRCA and Myrenne instruments have been shown to be similarly effective methodologies in red cell aggregation measurements, we aimed to determine whether the measurement of aggregation indices in SCD, by Myrenne and by LORRCA, is consistent in our lab.

Design/Method: We measured aggregation in blood samples corrected to 40% hematocrit. Aggregability was measured using 70kDa dextran in the Myrenne but not the LORRCA. Aggregation index using LORRCA was measured in 26 patients with SCD and 22 healthy subjects enrolled in a study of blood flow between 2014 and 2017. Aggregation and aggregability using the Myrenne was measured in 67 patients with SCD and 15 healthy subjects enrolled in a separate study of blood flow between 2008 and 2013.

Results: Using LORRCA, we found that aggregation index in patients with SCD was less than that of healthy subjects ($p<0.001$). In the Myrenne, aggregation at stasis was slightly higher in patients with SCD compared to healthy subjects ($p = 0.05$) but aggregation at low shear rotation was not different. Aggregability was higher in the patients with SCD compared to healthy subjects at both stasis and low shear rotation ($P<0.0001$).

Conclusion: Red cell aggregation is an important determinant of low shear blood flow. Deoxygenated venous blood is particularly important to low shear blood flow in patients with sickle cell disease. We found that two different aggregometers predict different aggregation results for SCD. It is unclear why there is a systematic difference between the two methods, but there are some possibilities. First, the syllectogram in the LORRCA is generated by the backscatter of light from the laser, while the Myrenne measures transmitted light. Second, the distance between the bob and cup in the LORRCA is 300 microns, while the gap between plates in the Myrenne is 50 microns, which might affect the disaggregation of red cells. Further work is needed to understand the differences in red cell aggregation and aggregability when using these instruments, particularly when using aggregation as a predictor of blood flow and tissue perfusion.

Poster # 351 | MANAGEMENT OF ACUTE SPLENIC SEQUESTRATION CRISIS: A CLINICAL PRACTICE SURVEY

Benjamin Larsen, Melissa Frei-Jones

University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States

Background: Children with Sickle Cell Disease (SCD) are at risk of acute splenic sequestration crisis (ASSC). ASSC is a life-threatening complication characterized by splenomegaly, pain and severe anemia. ASSC most often occurs in young children with the most severe forms of SCD and one-third of patients will have more than one episode. Treatment is based primarily on expert opinion and includes blood transfusion and surgical splenectomy.

Objectives: We plan to assess the clinical practice patterns of physicians treating children with ASSC.

Design/Method: A survey study was performed. The survey included six scenarios of severe SCD with variation in age, hydroxyurea-use, and episode number of ASSC; questions focused on the acute and chronic management of ASSC. The survey was disseminated on three occasions over a six-month period, using an online survey tool, SurveyMonkey, to pediatric hematologist-oncologists participating in the American Society of Pediatric Hematology-Oncology Hemoglobinopathy Special Interest Group.

Results: The survey had a response rate of 43% (28/65). Most respondents were recent graduates (61%; 17/28) practicing in academic urban centers with greater than 100 sickle-cell patients. Seventy-nine percent (22/28) recommended hydroxyurea initiation in 9–12 m/o with severe SCD. Prophylactic penicillin after surgical splenectomy was continued by 93% (26/28) after 5 years. For the acute management of ASSC results did not vary despite patient age, hydroxyurea use, and the number of previous ASSC episodes. Simple transfusion was preferred by 89% (25/28), with 54% (15/28) recommending slow transfusion and 36% (10/28) recommending routine simple transfusion. For the chronic management of ASSC, results varied based on patient age and the number of previous ASSC episodes. For a 12 m/o after the first episode, 36% (10/28) recommended observation and 32% (9/28) hydroxyurea initiation. For a 12 m/o with any prior episode of ASSC, 39% (11/28) recommended chronic transfusion therapy and 36% (10/28) surgical referral for splenectomy. For a 3 y/o after the first episode, 39% (11/28) recommended surgical splenectomy and 32% (9/28) increasing hydroxyurea dose. For a 3 y/o with any prior ASSC episode, 64% (18/28) recommended referral for surgical splenectomy.

Conclusion: In this survey, we found most providers continue to recommend simple transfusions for ASSC and surgical splenectomy after two episodes. The majority of providers continue to delay referral for surgical splenectomy until age two, but earlier referral in children under two and use of chronic transfusion therapy were also reported. Variability in

chronic management highlights the need for further research of splenic sequestration.

Poster # 352 | NOVEL TRIAL DESIGN TO EVALUATE ORAL VOXELOTOR FOR THE TREATMENT OF SICKLE CELL DISEASE: PROTOCOL OF THE PHASE 3 HEMOGLOBIN OXYGEN AFFINITY MODULATION TO INHIBIT SICKLE HEMOGLOBIN POLYMERIZATION (HOPE) TRIAL (GBT440-031)

Carolyn Hoppe, Kenneth Ataga, Russell Ware, Jo Howard, Margaret Tonda, Jitendra Ganju, Josh Lehrer

Global Blood Therapeutics, South San Francisco, California, United States

Background: Developing therapies for sickle cell disease (SCD) is challenging in part because the accepted endpoint, vaso-occlusive crisis (VOC), occurs infrequently, does not measure full disease burden, and is a measure of healthcare utilization. In phase 1/2 studies of patients with SCD, voxelotor (GBT440) has demonstrated increased hemoglobin (Hb) levels and reduced hemolysis and has been safe and well-tolerated. Voxelotor is being evaluated in the ongoing HOPE phase 3 trial.

Objectives: To report the innovative phase 2/3 HOPE trial design with novel primary and secondary outcomes to accelerate drug development.

Design/Method: HOPE (NCT03036813) is a phase 3, randomized, placebo-controlled, multicenter study of oral voxelotor in patients with SCD (aged 12–65 years) with baseline Hb 5.5-10.5 g/dL and 1–10 episodes of VOC in the prior year. To accelerate clinical trials to support drug development, the study combines a phase 2 exploratory, dose-selection phase (Group 1) with a pivotal phase (Groups 2/3). Patients in Group 1 will be randomized 1:1:1 to voxelotor 900 or 1500 mg/day or placebo. Analysis for dose selection will occur when the final patient has received 12 weeks of treatment. Group 2 will continue enrollment with randomization 1:1:1 until dose selection based on analysis of the Group 1 cohort. Group 2 will allow for a seamless transition into Group 3, which will randomize patients 1:1 to the selected dose or placebo. The final data analysis set will include Group 2 patients who received placebo or the selected dose and all Group 3 patients. The primary endpoint is an objective laboratory measure and surrogate of clinical benefit, increase in Hb >1 g/dL, from baseline to 24 weeks based on voxelotor mechanism of action (inhibition of Hb polymerization). This trial is the first to use a patient-reported outcome (PRO), the 9-item Sickle Cell Disease Severity Measure, as a secondary endpoint. This novel electronic PRO, developed specifically for the HOPE study following FDA guidance, will evaluate changes in SCD symptom exacerbation and Total Symptom Score from baseline to 24 weeks. Additional secondary endpoints include measures of hemolysis, rates of VOC, transfusions, and opioid use. The study was designed to enable selection of PRO-defined symptom exacerbations or traditionally defined VOC as the key secondary endpoint after the Group 1 analysis.

Results: This study is ongoing.

Conclusion: The HOPE trial, expected to complete enrollment by late 2018, will evaluate the efficacy and safety of voxelotor compared with placebo in patients with SCD. Supported by Global Blood Therapeutics.

Poster # 353 | EFFECTS OF SC411 (ALTEMIATM) ON BLOOD CELL MEMBRANE OMEGA-3 INDEX AND SELECT SICKLE CELL DISEASE BIOMARKERS IN THE SCOT TRIAL: A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTI-CENTER STUDY

Ahmed Daak, Mathew Heeney, Carlton Dampier, Beng Fuh, Julie Kanter, Ofelia Alvarez, Vandy Black, Melissa McNaull, Michael Callaghan, Alex George, Lynne Neumayr, Lee Hilliard, Fredrick Sancilio, Adrian Rabinowicz

Sancilio Pharmaceutical Company, Riviera Beach, Florida, United States

Background: Inflammation, coagulation activation, oxidative stress and blood cell adhesion are elements of sickle cell disease (SCD) pathophysiology. Patients with SCD have low levels of the omega-3 fatty docosahexaenoic acid (DHA) and eicosatetraenoic acid (EPA) in plasma and blood cell membranes. DHA is a bioactive fatty acid with anti-inflammatory, anti-blood cell adhesion and anti-oxidant properties. AltemiaTM is a novel DHA ethyl ester formulation with a proprietary delivery platform (Advanced Lipid Technology® (ALT®)) that enhances oral DHA bioavailability. The SCOT trial investigated the effects of AltemiaTM in children with SCD.

Objectives: To demonstrate the effects of AltemiaTM on blood cell membrane omega-3 index and selected biomarkers of inflammation, coagulation, adhesion and haemolysis associated with SCD.

Design/Method: Children with SCD, aged 5–17 years (n = 67), were enrolled. Subjects were randomized to receive either placebo or one of three daily oral doses of AltemiaTM (12-26, 26–48 or 51–72 mg/kg/day DHA) for two months. The effects of AltemiaTM on red blood cell (RBC), white blood cell and platelet membrane omega-3 fatty acids index (total DHA + EPA levels) were assessed after four weeks of treatment. The effects of AltemiaTM on markers of inflammation, adhesion, coagulation, and hemolysis were assessed after eight weeks of treatment. Cell membrane DHA and EPA concentration was determined by using LC-MS/MS method. The percent changes from baseline on blood cell membrane omega-3 index and select SCD biomarkers were compared between the three dose groups and placebo using a mixed-model repeated-measures (MMRM) analysis with baseline blood cell membrane omega-3 index, hydroxyurea use, and treatment as fixed effects and patient as a random effect.

Results: After four weeks of treatment, blood cell membrane DHA and EPA levels were significantly increased in all AltemiaTM doses ($p<0.01$). After eight weeks of treatment, significant reductions were observed in sE-selectin ($p = 0.0219$), and D-dimer ($p = 0.025$) in patients exposed to AltemiaTM dose level 2 vs. placebo. Hemoglobin was significantly increased at AltemiaTM dose level 1 versus placebo. Plasma high-sensitivity C-reactive protein, lactate dehydrogenase, soluble vascular cell adhesion molecule-1 and white blood cell count showed improvement after 8 weeks of treatment in all three AltemiaTM doses levels but did not reach significance.

Conclusion: Treatment with AltemiaTM enriches DHA and EPA in blood cell membranes of patients with SCD and improves select sickle cell disease biomarkers of blood cell adhesion and thrombin generation. These findings provide insight into the mechanisms of action of AltemiaTM in sickle cell disease.

Poster # 354 | PHYSICAL THERAPY IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH SICKLE CELL DISEASE: ASSESSING POTENTIAL BENEFITS AND BARRIERS

Daniel Callaway

Brown University - Hasbro Children's Hospital, Providence, Rhode Island, United States

Background: Despite clinical advances in the treatment of sickle cell disease (SCD) in pediatric and young adult patients, pain remains a significant source of disease-related morbidity. Physical therapy has been shown to be useful for the treatment of pain in children and young adults with various chronic illnesses of which pain is a significant component, however no data exists regarding potential benefits of physical therapy in pediatric and young adult patients with SCD.

Objectives: To query healthcare providers and others involved in the care of pediatric and young adult SCD patients regarding possible benefits of and barriers to physical therapy as a potential treatment modality.

Design/Method: We conducted a web-based survey of healthcare providers within the New England Pediatric Sickle Cell Consortium (NEPSCC) in an attempt to identify potential benefits of and barriers to outpatient physical therapy in this patient population.

Results: Nearly 92% of survey participants felt that physical therapy had the potential to be "somewhat beneficial" or "very beneficial" in pediatric and young adult patients with SCD. A majority of physicians reported having referred patients with SCD for physical therapy in the past. The most frequently identified perceived potential benefits included improved functional mobility, improvement of chronic pain symptoms, decreased use of opiates, improved mood symptoms, improved acute pain symptoms, and improved adherence with medications and clinic visits. Significant perceived barriers identified included lack of transportation, time constraints, patient lack of understanding, and difficulty with insurance coverage.

Conclusion: Our study indicates that healthcare providers have an overwhelmingly positive view of the use of physical therapy in the management of pediatric and young adult patients with SCD. Significant barriers exist which need to be addressed. Future research should focus on patient and parent perspectives regarding physical therapy, as well as a randomized controlled trial of a physical therapy intervention in this patient population.

Poster # 355 | PREVALENCE OF VITAMIN D DEFICIENCY AMONG CHILDREN AND YOUNG ADULTS WITH SICKLE CELL DISEASE AND ITS RELATIONSHIP WITH DISEASE SEVERITY

Daniel Ortiz, Dristhi Ragoonanan, Andrea Webster, Lilibet Fernandez, Ofelia Alvarez

University of Miami, Miami, Florida, United States

Background: Vitamin-D deficiency is fast becoming increasingly recognized in patients with Sickle Cell Disease (SCD). While it is estimated that these patients are five times more

likely to develop vitamin-D deficiency, the exact clinical significance of this is largely unknown. Given that this deficiency can be inexpensively and easily treated, our study sought to establish the prevalence of vitamin-D deficiency in our patient population and its relationship with disease severity.

Objectives: To estimate the prevalence of vitamin-D deficiency in patients with SCD in our institution and to analyze their disease severity in relation to their vitamin-D level.

Design/Method: Through retrospective chart review we analyzed subjects that represent a cohort of patients followed at the adult and pediatric hematology services at University of Miami with known diagnosis of SCD that had a Vitamin-D level drawn between January 01st, 2013 and August 31st, 2016. We conducted a cross-sectional study and recorded the first vitamin-D level during this period. Patient demographics, medical and social history information were collected along with laboratory data. The number of admissions for Vaso-Occlusive Crisis (VOC) and Acute Chest syndrome within one year preceding the collection the vitamin-D level was also recorded.

Results: A total of 476 charts were reviewed, 279 adult charts and 207 pediatric charts. After exclusion, 119 patients were enrolled. Subclinical Vitamin-D deficiency is only evident on laboratory blood testing of vitamin-D (25-hydroxy) and according to this laboratory result patients were classified as sufficient (≥32 ng/ml), insufficient (<32 to 20 ng/ml) and deficient (<20 ng/ml). Out of the 119 cases, 61.7% (74/119) were deficient, 21.7% (26/119) were insufficient and 15.8 % (19/119) were optimal. After statistical analysis two negative correlations were identified, increasing vitamin-D levels with decreasing white blood cell count (CI 95%-0.1931133 (-0.36057544, -0.01359017)and decreasing incidence VOC (CI 95%–0.3149722 (-0.4684118, -0.1430889).

Conclusion: This study confirms that there is a significant prevalence of vitamin-D deficiency in patients with SCD. Furthermore, the results of this investigation proved that vitamin-D deficiency is associated with acute pain and leukocytosis in patients with SCD. Given the multitude of confounding factors that affect vitamin-D absorption and intake, multivariate analyses are required to truly further investigate this relationship.

Poster # 356 | A CASE OF SEVERE EBV VIREMIA PRESENTING WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A PATIENT WITH UNDIAGNOSED SICKLE CELL ANEMIA

Lauren Scherer, Alex George, Daniel Zinn

Texas Children's Hospital, Houston, Texas, United States

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening condition of hyper-inflammation that is characterized by splenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia, hemophagocytosis and coagulopathy. Although timely diagnosis is imperative, it is often challenging as these individual signs and symptoms may occur in a variety of clinical conditions.

Objectives: To report a case of undiagnosed sickle cell anemia presenting with severe EBV viremia and associated hemophagocytic lymphohistiocytosis

Design/Method: Case Report

Results: A 21-month-old previously healthy male presented with respiratory distress, increased fatigue, and a focal seizure following a two-week history of cough and low-grade fevers. Physical exam was consistent with hypovolemic shock and revealed significant splenomegaly. Laboratory testing revealed severe hypoglycemia, acidosis and electrolyte disturbances including hyperkalemia, hyperphosphatemia, and hyperuricemia. Labs showed a leukocytosis (WBC 53,000), severely low hemoglobin (1.9), and platelets of 56,000. Coagulation testing revealed prolonged PT/INR and PTT, hypofibrinogenemia and a highly elevated D-dimer. Additional workup was completed to determine etiology of acute presentation, given broad differential diagnosis. Infectious studies were consistent with an acute EBV infection (plasma EBV PCR >550,000). Elevated levels of soluble IL-2 and ferritin completed 6/8 criteria for the diagnosis of HLH. Bone marrow evaluation showed trilineage hematopoiesis with no abnormal blast population or hemophagocytosis. Results from hemoglobin electrophoresis sent from the initial CBC sample were notable for HbS 72.5%, HbF 25.0%, and HbA of 0%, confirming the diagnosis of sickle cell disease. The patient was started on hydroxyurea and penicillin and splenomegaly resolved. With supportive care, he demonstrated gradual improvement in symptoms and laboratory abnormalities, including normalization of soluble IL-2, ferritin, CD163, IL-18 levels, immunoglobulins, and declining EBV titers. NK cell function has remained abnormally low, not eliminating the possibility of acquired HLH despite spontaneous improvement.

Conclusion: Splenic sequestration associated with sickle cell disease in combination with acute infectious mononucleosis could have explained many of the presenting symptoms including anemia, thrombocytopenia, and splenomegaly. However, it does not explain the unusually high EBV titer and degree of inflammation meeting diagnostic criteria for HLH, which raises concern for an underlying immunologic abnormality such as X-linked lymphoproliferative disorder (XLP). Although testing for XLP was negative, he will require

continued monitoring in the future for signs of relapse. This case illustrates the complexity of diagnosing lymphohistiocytic disorders and the significant overlap in presentation between these disorders and other medical conditions.

Poster # 357 | EVALUATION OF VASO-OCCLUSIVE CRISIS MANAGEMENT WITH PATIENT CONTROLLED ANALGESIA IN CHILDREN WITH SICKLE CELL DISEASE REQUIRING ADMISSION

Claire Arbitre, Evelyne Trottier, Pastore Yves, Nancy Robitaille, Benoit Bailey, Annie Viau, Marie Joelle Doré Bergeron, Niina Kleiber, Edith Villeneuve

Hôpital Sainte Justine, Montreal, Quebec, Canada

Background: Vaso-occlusive crisis (VOC) is one of the most distressing occurrences in patients with sickle cell disease (SCD). Patient controlled analgesia (PCA) is recommended by NIH and expert opinions favor its early use.

Objectives: We aim to review the use of PCA in patients with VOC and to evaluate if its early use is associated with faster pain control and reduced length of stay (LOS).

Design/Method: This retrospective single center study included all pediatric patients admitted and treated with PCA for a severe VOC from 2010 to 2016. "Early" use was defined as start of PCA within 48 hours of arrival in the emergency department (ED) and "late" use after 48 hours. Time to reach adequate analgesia was defined as OUCHER, verbal scale or Faces Pain Scale < 5/10 obtained twice consecutively in a 4-hours interval. Time to reach adequate analgesia and LOS were compared between early-PCA and late-PCA groups.

Results: A total of 46 patients presented 87 episodes of VOC treated with PCA during the study. Sixty-one episodes (70%) were treated with early-PCA and 26 (30%) with late-PCA. Both groups were comparable in terms of age (13.2 vs 12.8 years old), gender (55.8% female vs 57.7%), hemoglobin phenotype (80.3% HbSS vs 76.9%), but median pain score at admission was higher in early-PCA than in late-PCA (9/10 vs 7/10, median difference 1 (95% CI 0, 2). Early-PCA was associated with a median reduction in LOS of 3.15 days (95% CI 1.65, 4.82) (median early-PCA LOS 6.4 vs late-PCA 10.0 days). Time to reach analgesia could be evaluated only in a subset of patients (20 in early-PCA and 12 in late-PCA group). Although time to reach adequate analgesia tended to be shorter in the early-PCA group, it was not statistically different: median102.9 hours vs 123.5 hours, difference of 30.4 (95% CI -4.0, 72.5). Side effects were observed during 29 (33.3%) PCA treatments (19/61 (31.2%) episodes in early-PCA, 10/26 (38.5%) in late-PCA group) among which 16 (18.6%) were significant adverse events. These were observed in 15 patients who required interventions: 2 desaturations requiring oxygen without intubation, 8 neurologic abnormalities (hallucinations, visual abnormalities, no stroke), 6 urinary retentions.

Conclusion: Early use of PCA for severe VOC was associated with a reduced length of hospital stay despite that these patients had higher pain score on admission. Prospective studies are needed to support these positive outcomes.

Poster # 358 | FAT EMBOLISM SYNDROME IN SICKLE CELL SC DISEASE: A CASE PRESENTATION AND REVIEW

Ryan Desanti, Rafat Ahmed, Tara Smith

Cooper University Hospital, Camden, New Jersey, United States

Background: Acute chest syndrome is one of the leading causes of death in children with sickle cell disease1-2. While the cause of acute chest syndrome most commonly is not identified, fat embolism and infectious causes are believed to be most common. With an extremely high mortality rate, rapid identification and initiation of therapy is essential for survival. Case presentation: We describe the case of an 18-year-old female with sickle cell SC disease who was admitted for vaso-occlusive pain crisis and quickly progressed to multi-system organ failure due to fat embolism syndrome and Parvovirus B19 infection

Objectives: The case highlights the presentation and diagnosis so other providers can optimize outcomes for those with this under-recognized syndrome

Design/Method: Her parvovirus studies returned after 7 days which showed: Parvovirus B19 DNA PCR detected; Parvo IgG 1.99 (positive > 1.1); and IgM 12.98 (positive > 1.1).

Results: The patient experienced an approximately 2.5 g/dL drop in hemoglobin(8.7 to 6.0 g/dL/24 hrs) with progressive thrombocytopenia (from 269,000 to 54,000/uL) and a peripheral smear showed microcytic,normochromic red cells with nucleated RBCs and occasional nuclear budding, slight polychromasia, schistocytes, and polymorphic cells with toxic granules that suggested leukoerythroblastosis. She was emergently transferred to the regional quaternary care hospital for ongoing ECMO therapy where she experienced a change in her pupillary exam prompting a stat CT scan that showed severe, diffuse cerebral edema with transtentorial herniation. The decision was made to withdraw life-sustaining therapies and her family refused a post-mortem autopsy examination.

Conclusion: Fat embolism syndrome is a severe and uncommonly recognized complication of sickle cell disease, seen most commonly in those with a non-SS phenotype and previous mild disease course who present with severe, unrelenting vaso-occlusive pain episode and/or acute chest syndrome that progresses to respiratory distress with altered mental status and cutaneous changes. Rapid identification and initiation of exchange transfusion therapy should be initiated with clinical suspicion because of the extremely high mortality rate. Although previously considered rare, it needs to be considered in the differential diagnosis of more commonly encountered complications of sickle cell disease.

Poster # 359 | COLD EXTERNAL TEMPERATURES AND SICKLE CELL MORBIDITY IN CHILDREN: A RETROSPECTIVE ANALYSIS

Cielle Wachnian, Nicholas Tompkins, Mark Belletrutti, Catherine Corriveau-Bourque, Aisha Bruce

University of Alberta and Stollery Children's Hospital, Edmonton, Alberta, Canada

Background: Patients with Sickle Cell Disease (SCD) experience vaso-occlusive crisis (VOC), which results in extreme pain, often requiring opioids and admission. Genetic and environmental factors affect the frequency and severity of these episodes. Previous research has born conflicting evidence on whether environmental temperature is contributory. Edmonton, Alberta is the northern most city with a population over a million in North America. There is an increasing sickle cell population which is exposed to extreme winter conditions. This provides a suitable population and atmosphere to study the influence on cold external temperatures in SCD.

Objectives: This study sought to identify if pediatric patients with SCD, experience greater morbidity in cold external temperatures.

Design/Method: We performed a Heath Research Ethics Board approved retrospective case control series. Patients were identified through a clinical database, and emergency visit, phone call and admission data was collected over a five-year period. The average, minimum and change in temperature on day of presentation, 24 and 48 hours prior, was collected from the Government of Alberta, and was statistically analyzed using descriptive statistics, to determine the relation to vaso-occlusive events.

Results: One-hundred and eighteen patients were identified, and 258 VOC events reviewed. The mean patient age was 6.6 years of age with a range from 0.3-17 years old. The female to male ratio was equivalent with 133 female (51.6%) and 125 male (48.4%) VOC events. Eight records (3%) had documented cold exposures. The analysis between the temperature and the frequency of events did not yield significant correlation. Average and minimum temperature on day of admission had the largest percentage of VOC events occur at mild temperatures, from -4.99 to 20 °C and -4.99 to 5 respectively. Change in temperature on day of admission, 24 and 48 hours had the largest percentage of VOC events at a mild to moderate change in temperature of 10–15 degrees. Data at 24 & 48 hours prior to admission showed similar results. Secondary data analysis accounting for the lower proportion of extreme weather days in comparison to moderate temperate days showed no significant impact.

Conclusion: There was no correlation of average, minimum or change in temperature on day of admission, 24 or 48 hours prior. Multiple cofounding factors likely contribute to these results. As it was a retrospective study many confounding and precipitant factors may not be recorded or identified. A prospective study to better record specific cold exposure is warranted.

Poster # 401 | CONTINUOUS ANTITHROMBIN INFUSION PROTOCOL TO OVERCOME HEPARIN RESISTANCE IN PEDIATRIC EXTRACORPOREAL MEMBRANE OXYGENATION: A SINGLE-CENTER EXPERIENCE

Courtney Lawrence, Jennifer Meldau, Yaser Diab

Children's National Health System, Washington, District of Columbia, United States

Background: Achieving optimal anticoagulation with unfractionated heparin (UFH) in pediatric patients receiving extracorporeal membrane oxygenation (ECMO) is often challenging due to antithrombin (AT)-mediated heparin resistance (HR). Intermittent AT dosing during pediatric ECMO support does not maintain adequate AT levels. Continuous AT infusion (CATI) presents an alternative strategy to achieving consistent goal AT levels and optimizing heparinization. However, CATI during pediatric ECMO has not been adequately studied.

Objectives: To describe our center's experience with an ECMO CATI protocol.

Design/Method: In 2014, we modified our ECMO anticoagulation protocols to include UFH titration according to anti-Factor Xa (anti-FXa) levels and CATI in patients with AT-mediated HR. The CATI rate was calculated using baseline and goal AT levels while accounting for the circuit volume. CATI was administered with UFH into the circuit via a

Y-infusion set. AT and anti-FXa levels were monitored every 6 hours. Recombinant AT (r-AT) concentrate was used at our center until 2015 with subsequent transition to a plasma-derived AT (pd-AT) concentrate. Due to the longer half-life of pd-AT concentrate, the protocol was modified so CATI is stopped once target AT and anti-FXa levels are achieved. We conducted a retrospective study of all patients who received CATI during ECMO support at our center. Data are reported as median and interquartile range and compared using the Mann-Whitney U test. Two-tailed p-value <0.05 was considered statistically significant.

Results: Since 2014, 24 patients [13 males, age 1 month (0.03-8)] on ECMO support received 27 CATIs (12 rAT, 15 pd-AT) per our protocol (3 patients received 2 pd-AT infusions during one ECMO run). The duration of CATI was 48 hours (23-72). CATI administration led to significant increases in AT and anti-FXa levels from baseline of 43% (39-53) and 0.11 units/mL (0.08-0.22) to the first level within goal of 64% (55-83) and 0.39 units/mL (0.35-0.5), respectively ($p<0.00001$). The respective times to achieve goal AT and anti-FXa levels were 9 hours (5-21) and 13 hours (6-23). The respective peak AT and anti-FXa levels were 83% (70-99) and 0.53 units/mL (0.35-0.63). During CATI, no patient required circuit change, 1 patient developed cannula thrombosis and 5 patients experienced non-fatal major bleeding.

Conclusion: CATI in pediatric patients receiving ECMO support with close monitoring of AT and anti-FXa levels was associated with significant rapid increase in AT, optimization of heparin effect, and reduction in thrombotic complications without increase in major bleeding compared to prior reports. A prospective study of this AT dosing strategy is warranted.

Poster # 402 | FACTOR XIIIA1 GENE VARIANTS IN THREE SIBLINGS WITH VARYING BLEEDING PHENOTYPES

Noreen Islam, Geetha Puthenveetil, Diane Nugent, Shirley Williams

Children's Hospital of Orange County, Orange, California, United States

Background: Inherited Factor XIII (F13) deficiency is a rare bleeding disorder with wide heterogeneity in clinical manifestations ranging from mild bruising, and mucosal and umbilical stump bleeding to spontaneous, severe intracranial bleeding. The bleeding phenotype is influenced not just by zygosity of the FXIII mutation alone, but also by co-inheritance of variants in other clotting protein genes that also play a major role in clot formation and stability.

Objectives: We present a series of three siblings found with F13A1 gene variant and platelet dysfunction linked to bleeding phenotype.

Design/Method: Retrospective chart review of the index case, coagulation studies and whole gene sequencing.

Results: The index patient presented at two years of age with a subdural hematoma after a fall, requiring emergent craniotomy. A week after initial evacuation, she re-bled, prompting an extensive work-up for potential bleeding disorders, including F13 activity, von Willebrand profile, comprehensive fibrinolysis panel, PAI-1 antigen level, platelet mapping thromboelastogram (plt-TEG), and F13 genetic analysis. The patient's identical twin and older sibling, who had symptoms of bruising, underwent a similar evaluation. The index patient demonstrated consistently low F13 activity (31-49%), and platelet function testing revealed decreased response to ADP agonists. The twin and older sibling had normal F13 levels, and only slightly decreased response to ADP in platelet studies. Whole gene analysis of F13 and 21 other genes on our Next Generation panel, revealed several intronic deletions in the index patient that were not shared by her siblings, which likely account for her decrease in circulating F13 levels. Her symptoms have responded well to monthly treatment with factor 13 concentrate. All three children shared the F13 variant, Pro564Leu, previously described as a risk factor for intracranial hemorrhage.

Conclusion: The F13 mutation, Pro564Leu, has been associated with intracranial hemorrhage in young women, but the presence of the variant alone may not be enough to cause a severe bleeding phenotype. Family studies identified novel deletions in the index patient which may account for her decreased F13 levels, which would have been overlooked with standard sequencing. Future studies, including evaluation of 'platelet' F13 levels, should be performed when platelet dysfunction is detected. Further laboratory and clinical evaluation is required to delineate the long term implications of the interaction of even mild F13 deficiency if present with additional clotting disorders such as the platelet function defect in these siblings.

Poster # 404 | MECHANICAL HEMOLYSIS AND ACQUIRED TYPE 2A VONWILLEBRAND SYNDROME IN PATIENT WITH CONGENITAL HEART DISEASE

Amy Moskop, Lynn Malec

Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Background: Acquired hemolytic anemia can occur due to mechanical shearing of red blood cells and is classically seen in patients with prosthetic heart valves. There are reports of this same traumatic effect with other repairs, including annuloplasty. Following valvular procedures flow disturbances can exist across the valve that lead to shear stress and hemolysis. Although von Willebrand disease (VWD) is typically seen due to an inherited disorder in the pediatric population, flow disturbances in the setting of valve abnormalities can lead to acquired von Willebrand syndrome (aVWS). Von Willebrand factor multimers become unfolded and elongated in the setting of shear stress resulting in increased susceptibility to cleavage by ADAMSTS-13. Specifically, loss of high molecular weight multimers (HMWMs) can lead to a syndrome akin to type 2A VWD.

Objectives: To describe a case of mechanical hemolysis with acquired type 2A VWD

Design/Method: A 3-month-old girl with history of hypoplastic left heart syndrome and severe tricuspid valve insufficiency underwent Norwood procedure, Blalok-Taussig shunt placement and subsequently a bidirectional Glenn and tricuspid valve annuloplasty. During the following month she requires weekly red blood cell (RBC) transfusions due to intermittent anemia. She also experienced bloody stools and dark urine. Laboratory evaluation was notable for normocytic anemia, reticulocytosis, elevated lactate dehydrogenase, and low haptoglobin consistent with hemolytic process. Immune-mediated hemolysis from transfusion reaction or presence of autoimmune or alloimmune antibodies testing was negative. To investigate GI bleeding, work up for VWD revealed normal VW activity and antigen but with loss of high molecular weight multimers consistent with acquired type 2A VWD.

Results: In consultation with cardiology, it was felt her tricuspid valve insufficiency jet could be leading to mechanical hemolysis and aVWS. A repeat ECHO showed persistent moderate tricuspid insufficiency but no other significant changes. Due to the patient's continued need for weekly RBC transfusions she was subsequently trialed on pentoxifylline which is used in adult patients to decrease blood viscosity and increase erythrocyte flexibility in patients with mechanical hemolysis. Her transfusion needs remained the same and the medication was discontinued after two weeks. She required one transfusion a week later but no transfusions since that time.

Conclusion: Although not commonly seen in pediatric patients, the diagnosis of mechanical hemolysis accompanied by aVWS should be pursued in a patient with congenital heart disease with significant anemia and/or bleeding. The work up in these patients is difficult as echocardiograms can be inconclusive thus an extensive hematologic evaluation is usually necessary.

Poster # 405 | CENTRAL LINE-RELATED DEEP VEIN THROMBI IN CHILDREN: A CLEVELAND CLINIC EXPERIENCE

Aditi Dhir, Archana Ramgopal, Samantha DeMarsh, Aron Flagg, Grace Onimoe

Cleveland Clinic, Cleveland, Ohio, United States

Background: An increased incidence of deep vein thrombus (DVT) has been reported in pediatric patients over the past decade, and the presence of central venous catheters is a major contributing risk factor. Raffini et al. reported an overall incidence of line related thrombi as 34-58 cases per 10,000 admissions from 2001-2007, with incidence increasing by nearly 10% each year. The incidence of thrombi was similar in a study conducted by Kanin et al. with peripherally inserted central catheters (PICC) and tunneled catheters in 2013. On the contrary, Vidal et al. reported a higher risk of DVT with PICC lines compared to tunneled catheters in 2014.

Objectives: Our aim was to assess incidence of and potential risk factors for central line-related DVT at our institution between 2011-2016. Additionally, our goal was to analyze if that incidence differed between the three central line types and identification of line-specific risks.

Design/Method: A retrospective chart review of 377 central line placements in pediatric patients at Cleveland Clinic between 2011-2016 was conducted. Data included demographics, potential risk factors, line characteristics and any related thrombotic events.

Results: The study cohort consisted of 377 lines in 326 pediatric patients aged 1-18 years of age. There were 1.5 thrombi (95% CI 1.0-2.3) per 10,000 line days. Statistically significant risk factors for thrombus include diagnosis group (liquid tumor highest rate of 16%, solid tumor lowest at 2%), type of line (PICC 5%, Broviac 29%, and Mediport 4%), location of line, greater number of lines per patient, PEG Asparaginase (23% vs 4%), sepsis, and history of procoagulant state. Line characteristics such as lumen size and number of lumens were not identified as a significant risk. There was a significantly higher rate of thrombus in 2016 than in the previous years when pooled (12% in 2016 vs 4.3% from 2011-2015, $P = 0.020$).

Conclusion: The incidence of DVT in pediatric patients at our institution was highest with Broviac lines, and significant risk factors in our patient population included liquid tumor, femoral vein location, PEG Asparaginase, sepsis, and history of a procoagulant state. The incidence of thrombi was highest in 2016, and therefore highlights the urgent need for improvement in nationwide hospital practices to minimize risk of thrombi formation and early detection in the higher-risk

populations. There is still much to be learned regarding the characteristics specific to different central lines, which would influence thrombi formation.

Poster # 406 | MEDICAL MANAGEMENT IN A CASE OF SPLENOSIS IN A RELAPSED IMMUNE THROMBOCYTOPENIC PURPURA PATIENT

Sucharita Bhaumik

NYU Winthrop Hospital, Mineola, New York, United States

Background: Pediatric Immune Thrombocytopenic Purpura (ITP) is an autoimmune disorder with platelet counts <100000 causing increased risk for significant hemorrhage. There is increased immunologic platelet destruction due to production of specific autoantibodies along with inhibition of platelet production. Few randomized trials exist to guide management and ultimately each patient requires an individualized treatment plan. ITP may be acute (diagnosis to 3 m) or chronic (> 12 months). One of the treatments of chronic ITP is laparoscopic splenectomy (LS), which is very well tolerated. A rare complication of LS is splenosis, an autotransplantation or implantation of ectopic splenic tissue within the abdominal cavity or in any other unusual body compartment. Splenosis is sometimes associated with relapsed ITP due to preserved immune activity. The usual management of symptomatic splenosis is surgical resection.

Objectives: To describe medical management in a young patient with ITP relapsed due to extensive unresectable splenosis following LS

Design/Method: Our patient was originally diagnosed at 2 years with ITP and was treated with LS at 5 years of age for chronic severe thrombocytopenia and persistent bleeding not responding to first line therapies. She tolerated it well and had a complete response (CR) defined as a platelet count of >100000 measured on 2 occasions >7 days apart and absence of bleeding. She maintained a normal platelet count for twelve years after which she relapsed (loss of response after CR) with severe thrombocytopenia and hematuria necessitating high dose steroids. CT scans showed multiple well-circumscribed soft tissue masses in the left lower quadrant adjacent to uterus and left ovary, involving left omentum and the anterior abdominal wall partly. Findings were confirmed by damaged RBC nuclear scan to be splenosis. During laparoscopy the splenosis lesions were deemed too extensive and were not resected completely to avoid postoperative morbidity. She was started on sirolimus around the same time for treatment of her relapsed ITP and steroids were weaned off.

Results: Eight months since beginning sirolimus with therapeutic levels she remains in CR with no bleeding and has not required any steroids, immunoglobulins or anti D immunoglobulin.

Conclusion: Sirolimus is a safe and effective steroid-sparing agent in treatment of chronic ITP. This is the first instance of a patient with poorly resectable splenosis responding well to medications for ITP. More data is needed regarding the long-term efficacy of such an intervention and whether it will eliminate the need for a second surgery in relapsed ITP patients with extensive splenosis.

Poster # 407 | LACK OF CORRELATION BETWEEN BLEEDING SCORES AND PLATELET ELECTRON MICROSCOPY IN DELTA-GRANULE STORAGE POOL DISORDER

David Taylor, Charles Nathaniel Nessle, Soutik Ghosal, Arun Ranjan Panigrah

University of Louisville School of Medicine, Louisville, Kentucky, United States

Background: Storage pool disorders affecting platelets result in bleeding symptoms related to a deficiency or defect in alpha granules or delta granules. In delta-storage pool disorders (DSPD,) there is a deficiency of the delta granules and their constituents, which results in the inability of platelets to properly activate as well as lack of proper constriction of blood vessels during bleeding episodes. Amongst patients with DSPD, females most commonly present with menorrhagia, while males tend to present with epistaxis and easy bruising. The International Society on Thrombosis and Hemostasis (ISTH) developed a screening bleeding assessment tool (BAT) for mild bleeding disorders, shown to be a validated tool in children. Diagnosis of DSPD is classically made with a platelet electron microscopy (PEM) value <3.69 delta granules per platelet (dg/pl), but recently lower diagnostic thresholds of 2 dg/pl or even 1.2 dg/pl have been suggested.

Objectives: Evaluate the correlation between PEM and bleeding scores, and also examine various cut-off values used to diagnose and risk stratify patients with DSPD.

Design/Method: Retrospective chart review of 96 pediatric patients followed by hematology with a diagnosis of DSPD was performed. Clinicians obtained bleeding scores for each

patient as standard of care in the hemostasis clinic. Quartile ranges were established to appropriate three stages of severity based upon bleeding scores. Statistical analysis was performed using software R and exploratory data analysis to evaluate for a correlation.

Results: Amongst all patients, the average BAT score was 6.17 and PEM was 2.37 dg/pl. The average bleeding score for PEM between 3.69 dg/pl and 2 dg/pl was 6.17, while the average bleeding score for PEM below 2 dg/pl was 4.65. The correlation coefficient between PEM and bleeding scores is 0.30. Using a threshold of 2 dg/pl, 31% of patients would have met diagnostic criteria. Quartile ranges for the bleeding scores are as follows: 1st quartile was 2–4, 2nd quartile was 5–7, and 3rd quartile was >8.

Conclusion: Patients with a more marked granule deficiency do not exhibit a more severe bleeding phenotype, suggesting proper platelet function is not solely determined by granule quantity in these patients. Bleeding severity may be more appropriately assessed with bleeding scores rather than PEM values, and using quartile ranges may aide in risk stratification and therapeutic interventions for DSPD patients. Further work remains to determine the optimal diagnostic threshold of PEM DSPD in pediatric populations.

Poster # 408 | INTERNATIONAL NORMALIZED RATIO (INR) DOCUMENTATION OPTIMIZATION: A CLINICAL AND INFORMATICS COLLABORATIVE APPROACH

Heather Soni, Michelle McLendon, Aleida Stark, Viia Anderson, Ashley Wilrich, Felicia Hughes, Jennifer Cox

Texas Children's Hospital, Houston, Texas, United States

Background: Warfarin management has many challenging aspects including pharmacogenomics, food and drug interactions, lack of standardized dosing, patient compliance, tracking lab results from multiple lab locations, and the potential for significant bleeding or thrombotic complications. A literature review revealed limited data highlighting anticoagulation monitoring workflow and EMR documentation and specifically, no data in the pediatric population. Historically, the Texas Children's Hospital Cardiology and Hematology Centers were each documenting anticoagulation data within the EPIC™ system differently. EPIC's™ original design for anticoagulation documenting resulted in the necessity to duplicate documentation in order to see at-a-glance critical anticoagulation monitoring information.

Objectives: The objective of this project was to standardize INR documentation across departments to reduce the risk of patient safety events and improve workflow.

Design/Method: A workgroup assembled consisting of nurses from the Cardiology and Hematology departments, along with staff members from the Epic™ IS support group. The workgroup identified current documentation practices, available Epic™ tools, and brainstormed ideas to streamline and improve both documentation with the current Epic™ tools. Physician partners were identified in Cardiology, Hematology and Coagulation Laboratory to gain their input. A new Anti-Coag (AC) Encounter was developed and first made available in an Epic™ practice environment, then once approved, Epic™ written education and training session were completed by both departments' staff.

Results: Surveys were sent to 19 health care providers in the Cardiology and Hematology Centers prior to the new AC Encounter, and also to 27 health care providers six months after implementing the AC Encounter. Six responses were received for each survey. The pre-implementation survey showed the most problematic part of the documentation system for anticoagulation was no single place in the EMR to find a complete anticoagulation picture. Post AC encounter implementation survey results revealed more health care providers using the Epic™ INR reminder pool, less time needed to compile a report of three months of anticoagulation information, less time needed to document individual encounters, less locations needed to document AC information and decreased amount of types of documentation used.

Conclusion: Standardized AC encounters improves workflow with less time needed to document and compile information, less types of documentation utilized and easier access to patients AC information. Next steps include retrospective review of patients' INR time in therapeutic range to determine if there was an impact on patient compliance and continue to evaluate and modify the AC Encounter to enhance user friendliness.

Poster # 409 | EXTREMITY DEEP VENOUS THROMBOSIS IN ASSOCIATION WITH VENOUS ANATOMIC ABNORMALITIES: INCIDENCE, CHARACTERISTICS AND OUTCOMES OF MULTIDISCIPLINARY CARE AT A SINGLE PEDIATRIC CENTER

Caitlin Tydings, Jennifer Meldau, Christine Guelcher, Carole Hennessey, Eena Kapoor, Michael Guerrera, Yaser Diab

Children's National Health System, Washington, District of Columbia, United States

Background: Venous anatomic abnormalities (VAAs) are considered a risk factor for developing deep vein thromboses (DVTs) that occur as a result of significant alterations in venous blood flow. Identification of predisposing VAAs can be challenging. Hence, diagnosis can be delayed or overlooked especially in pediatric patients. DVTs in children or adolescents with predisposing VAAs have been only described in sporadic case reports and small case series.

Objectives: To describe characteristics and outcomes of DVTs in pediatric patients with underlying VAA treated at our center.

Design/Method: We conducted a retrospective chart review of all pediatric patients with objectively confirmed extremity DVT treated at our institution over a 6-year period from 2011 to 2017 and identified all patients with underlying VAAs. Patients were managed according to standardized institutional protocols based on published guidelines. Post-thrombotic syndrome (PTS) was assessed at our center using the Manco-Johnson instrument. Relevant data were collected and summarized using descriptive statistics.

Results: During the study period, 20 of 227 pediatric patients (9%) [14 females, median age 17 years (range 11–20)] diagnosed with extremity DVT at our center were found to have an underlying VAA. VAAs included May-Thurner anomaly (13 patients), venous thoracic outlet obstruction (5 patients) and inferior vena cava (IVC) atresia (2 patients). Additional provoking factors were identified in 14 patients at time of presentation. DVT locations included upper extremity veins (5 patients), lower extremity veins (9 patients) and lower extremity veins and IVC (6 patients). The majority of DVTs [17 patients, (85%)] were completely occlusive. High risk thrombophilia (defined as inherited deficiency of antithrombin, protein C, or protein S, or antiphospholipid antibody syndrome) was present in 6 patients (30%). All patients were treated with therapeutic anticoagulation with 6 patients continuing indefinite anticoagulation. Endovascular interventions were performed in 18 patients and included percutaneous pharmacomechanical thrombectomy and/or catheter-directed thrombolysis (15 patients), balloon angioplasty (11 patients) and stent angioplasty (9 patients). Surgical interventions included thoracic decompressive surgery (5 patients) and surgical thrombectomy (1 patient). Complications of DVT included pulmonary embolism [4 patients (20%], DVT progression [1 patient (5%)], DVT recurrence [3 patients (15%)] and PTS [8 patients, (44%)]. PTS was physically and functionally significant in 4 patients (22%).

Conclusion: VVAs represent an important risk factor for developing extensive extremity DVT in adolescents. This special population is at risk for short-term and long-term complications. Early identification and correction of VAAs may improve outcomes. However, multicenter, prospective studies are needed for developing optimal evidence-based treatment approaches.

Poster # 410 | MANAGEMENT OF BUDD CHIARI SYNDROME IN CHILDREN

Alexander Glaros, Roland Chu, Sureyya Savasan, Meera Chitlur, Madhvi Rajpurkar, Yaddanapudi Ravindranath

Children's Hospital of Michigan, Detroit, Michigan, United States

Background: Acute Budd-Chiari Syndrome (BCS) is a rare thrombotic emergency in children, and etiologies/treatment are less well-defined than in adults. In adults, a systematic approach including anticoagulation, relief of venous obstruction, and treatment of the underlying cause has proven successful. More recently treatment has tilted towards aggressive surgical interventions, which carry significant risk and are often not feasible.

Objectives: Review our experience with three different patients with BCS and suggest a mechanistic based approach to treatment.

Design/Method: The records of three patients with BCS were reviewed and their presentations, etiologies, treatment, and outcomes were reported.

Results: Patient A was a 17-year-old female with paroxysmal nocturnal hemoglobinuria who presented with recurrent worsening abdominal pain over several months. Narrowing of inferior vena cava (IVC) and hepatic veins was noted on imaging. Liver transplant was not considered surgically feasible. She was treated with eculizumab, steroids, and anticoagulation with restoration of hepatic venous flow in 4 weeks. Patient B was a 14-year-old male with several weeks of right upper quadrant pain, fatigue, and pre-syncopal episodes, with a history of blunt abdominal trauma from football scrimmage 4 weeks earlier. He was found to have near complete occlusion of the IVC and hepatic veins. Liver transplant was not considered feasible. He was successfully treated with anticoagulation alone. Patient C was a 3-year-old male with acute myeloid leukemia in induction cycle 2 who developed severe pancytopenia; typhlitis was diagnosed and managed medically. Days later he acutely decompensated, arrested, and was placed on extra corporeal membrane oxygenation, and imaging showed complete occlusion of the portal vein, hepatic veins, and IVC to the level of the atrium, with bilateral pulmonary emboli. Emergency liver transplant or catheter based interventions was deemed not feasible. Treatment with eculizumab was considered for presumed inflammation induced complement activation (C3 59mg/dl [normal 77-171]; CH50 was 12u/mL [normal 42-91]) as a trigger for

thrombosis, but the patient progressed quickly and died before it could be initiated.

Conclusion: Our experience with BCS shows that invasive interventional options and liver transplant may not be feasible in most patients for multiple reasons. Rapid diagnosis and aggressive etiology-based medical management are paramount to successful treatment of this rare complication. Eculizumab may be considered in treating BCS with complement activation not only due to innate disorders, but also secondary to acute inflammation when proper laboratory evidence is present.

Poster # 411 | UTILITY OF PLATELET AGGREGATION TESTING AS A DIAGNOSTIC TOOL IN PEDIATRIC PATIENTS WITH BLEEDING PROBLEMS

Hope Wilson, Valerie Cruz, Rachel Herdes, Leah Nuss, Gloria Coker, Maria Velez

Louisana State University Health Sciences Center/Children's Hospital of New Orleans, New Orleans, Louisiana, United States

Background: Platelet aggregation studies are the gold standard for the diagnosis of platelet function defects during the evaluation of a patient with bleeding problems. The platelet aggregation test measures how well platelets clot in response to different concentrations of epinephrine, adenosine diphosphate (ADP), collagen, arachidonic acid and ristocetin. Because platelet function defects are often under-recognized and under-diagnosed in the pediatric patient, the true incidence is unknown. We report our experience in the diagnosis of platelet defects at our institution over a 5-year period in order to add some clarity to the limited pediatric data available.

Objectives: Our primary objective is to document correlations/trends between less well-known platelet function abnormalities and clinically significant bleeding at our institution over a 5-year period.

Design/Method: After appropriate IRB approval obtained, we performed a retrospective chart review of all children who had platelet aggregation testing done from 2011 to 2015. Data collected included demographics (age, sex, race), personal and family history of bleeding, screening for coagulation defects and platelet aggregation test results. Symptoms examined in our data were limited to epistaxis and heavy menstrual periods. For each of these symptoms, results were further analyzed to those with abnormal responses to ADP and epinephrine. Patients with existing bleeding diagnoses and those with incomplete medical records were excluded.

Results: We identified 159 patients. Of the patients with epistaxis, 70% had abnormal platelet aggregation testing while only 36% of those with heavy menstrual periods had abnormal results. Within our population, abnormal platelet function assay (PFA-100) results or race did not appear to correlate with abnormal platelet aggregation testing. In the cases of epistaxis, sex was also noncontributory.

Conclusion: Our preliminary results suggest that platelet aggregation testing was more useful in predicting platelet defects in those with a clinical bleeding history of epistaxis as opposed to heavy menstrual periods. For other presenting symptoms, platelet aggregation testing did not offer diagnostic benefit. Abnormal response to ADP in the platelet aggregation test was the most common finding in our population; the clinical significance of which is not well understood. Going forward, we plan to document whether abnormal results correlated significantly with the subsequent final diagnoses of our patients.

Poster # 412 | ETHICAL DECISION MAKING FRAMEWORK IN PREVIOUSLY UNTREATED SEVERE HEMOPHILIA A PATIENTS

Ashley Foster Lanzel, J. Michael Soucie, Leonard Ortmann, Drue Barrett, Robert Sidonio, Jr., Shannon Meeks

Emory University, Atlanta, Georgia, United States

Background: Decision making for severe hemophilia A in previously untreated patients (PUPs) has recently become a significant ethical debate. Recombinant factor VIII (rFVIII) products previously were recommended to avoid transmission of blood borne pathogens associated with plasma-derived FVIII (pdFVIII) products. However, the increased incidence of FVIII alloantibody inhibitors with rFVIII products compared to pdFVIII products has challenged this former standard of care. Despite the support of the Medical and Scientific Advisory Council, recommendations considering pdFVIII products for a PUP remains controversial.

Objectives: Develop an ethical decision making framework for severe hemophilia A PUPs

Design/Method: We used a modified utilitarian approach involving clinical, public health, and research ethics. Shared decision making permeates the framework to maximize understanding, minimize bias, respect informed consent or dissent, and provide care that aligns with patient and family values when medically and practically feasible.

Results: The framework has three tiers. First, it evaluates whether resources are scarce or abundant for equitable resource allocation. If FVIII products are scarce, we

recommend developing a central supply for emergency use and then evaluating the needs of the severe hemophilia A patients. Prioritization of who receives the factor products would be decided by a designated team based on the availability of the factor products and clinical scenarios, with no preference given to those on research trials. However, if resources are abundant, treatment for acute bleeding and standard of care prophylaxis measures, including primary prophylaxis, could continue. The second tier accounts for whether there is a new infectious epidemic or concern where a pathogen cannot be eliminated. If there is, healthcare and public health workers may limit the use of pdFVIII products. If not, pdFVIII and rFVIII products are to be equally considered. The third tier evaluates whether the clinical scenario is emergent or not. If there is acute, emergent bleeding, the immediately available resource should be used, along with bypassing and/or adjuvant resources as needed until the bleeding has resolved or improved. To align with patient and family preferences, attempts to have both pdFVIII and rFVIII products available at similar costs in institutions would be ideal.

Conclusion: This ethical framework endeavors to balance autonomy, beneficence, nonmaleficence and justice in helping guide discussions among providers, PUPs with severe hemophilia A, and their families. Disclaimer: Findings and conclusions are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention, Emory University, or Children's Healthcare of Atlanta.

Poster # 413 | EVALUATION OF THE HYPERMOBILE PATIENT IN BLEEDING DISORDERS CLINIC: REPORTS OF COMORBID EHLERS-DANLOS SYNDROME AND VON WILLEBRAND DISEASE

Sarah Hall, Manjusha Kumar

Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana, United States

Background: Von Willebrand Disease (VWD) is a common bleeding disorder which affects up to 1% of the population without gender predilection. Bleeding associated with this condition results from a deficiency or abnormality in von Willebrand factor interfering with formation of primary hemostasis. Ehlers-Danlos Syndrome (EDS) is a group of rare inherited connective tissue disorders which may have an associated bleeding manifestation without abnormalities in coagulation testing. Bleeding symptoms reported in EDS result from capillary and tissue fragility. Joint hypermobility syndrome (JHS) is an inherited condition which is nearly indistinguishable from EDS III. Reports of coinheritance of VWD and EDS or JHS are infrequent.

Objectives: The objective of this retrospective study was to review patients with coexisting VWD and EDS or JHS at the Indiana Hemophilia and Thrombosis Center in order to describe the type and severity of bleeding symptoms, physical examination findings, and pertinent laboratory data.

Design/Method: The electronic medical record database of the Indiana Hemophilia and Thrombosis Center was queried for patients with a diagnosis of VWD and one of the following descriptors: hypermobility syndrome, hypermobility, hypermobile joints, or Ehlers-Danlos syndrome. The records of identified patients were reviewed for demographics, type and severity of bleeding symptoms, Beighton scores (BS), VWD antigen, ristocetin cofactor, factor VIII levels, VWD multimer pattern, VWD subtype, genetic testing for EDS, and family history of EDS.

Results: A total of 6 patients with dual diagnoses of VWD and EDS and 21 patients with VWD and hypermobility were identified with this query. Two patients had completed genetic testing for EDS, and one had a COL1A1 gene mutation identified. Significant bleeding symptoms in the VWD and EDS group included hematuria and postoperative hemorrhage. Two of these patients had delayed wound healing postoperatively. Seven of the 19 patients identified to have type I VWD and JHS had moderately severe and somewhat unusual bleeding episodes reported including hematuria, hematemesis, and hemoptysis; 4 of these patients had significant perioperative bleeding. Females composed 83% of the VWD and EDS group and 76% of the VWD and JHS group.

Conclusion: Coinheritance of VWD and EDS is an uncommon phenomenon. Patients with VWD and EDS or JHS may have atypical and moderately severe bleeding, especially with procedural intervention. Incorporation of BS into the assessment of patients with bleeding disorders is useful to identify potential inherited collagen disorders, as diagnosis of these conditions may impact clinical management.

Poster # 414 | PHASE II STUDY OF SIROLIMUS AND COMPLICATED VASCULAR ANOMALIES: LONG TERM OUTCOMES IN KAPOSIFORM HEMANGIOENDOTHELIOMA

Denise Adams, Cameron Trenor, Kiersten Ricci, Manish Patel, Gulraiz Chaudry, Megan Metcaff, Paula Mobberley-Schuman,

Justyna Klajn, Anita Gupta, Carol Chute, Arnold Merrow, Roshni Dasgupta, Belinda Dickie, Adrienne Hammill

Boston Children's Hospital, Boston, Massachusetts, United States

Background: Sirolimus treatment for Kaposiform Hemangioendothelioma (KHE) has shown impressive results particularly in hematologic response of KHE patients with Kasabach Merritt phenomenon (KMP). In the year-long Phase II study (RO1FD003712), 11/12 KHE patients responded. Patients were followed for 5 years after study completion, collecting data on growth and development, complications of therapy, unexpected toxicities, and need for continuing sirolimus.

Objectives: After study therapy treatment of one year, objectives include: 1. Assess long term toxicity over the 4–5 year period after study therapy completion 2. Assess unexpected toxicity 3. Assess overall condition of the patient 4. Assess need for restart or continuation of sirolimus therapy

Design/Method: Prospective follow-up of patients with a diagnosis of KHE from 2 institutions. Inclusion criteria: follow-up for 4–5 years post-study.

Results: Follow-up included data at 5 year (n = 5) and 4-4.5 year (n = 4) time points. Average age at the start of treatment was 12 months. 9 of 12 patients were available for follow up. Four patients are no longer on sirolimus: one patient completed study therapy and remains off treatment (OT) (7 years), 1 required 2 years of treatment and is now 2.5 years OT and 2 required an additional treatment course prior to successful discontinuation now 17 and 22 months OT. Of the 5 patients still on sirolimus, all restarted medication for symptoms of pain, swelling and/or edema interfering with quality of life and have made an average of 2.5 attempts to discontinue sirolimus. No patient had reoccurrence of KMP. All patients had improvement in clinical and radiologic appearance of KHE but all have residual lesions noted on imaging and/or clinical exam. No unexpected toxicity, growth delay, developmental issues or other long term toxicity of sirolimus was noted.

Conclusion: This is the first prospective data on long-term follow up of KHE patients treated with sirolimus. Although numbers are small, sirolimus is well tolerated; however, over half the patients were still on medication at 4–5 year follow up. This stresses the need for continued long term follow up in these young patients and investigation of the mechanism of sirolimus effect.

Poster # 415 | HEMATURIA PREVALENCE IN PEDIATRIC PATIENTS WITH HEMOPHILIA: A NATIONAL DATABASE REVIEW

Kyle Davis, Joseph Stanek, Amy Dunn

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: Recent studies have identified that adult persons with hemophilia (PWH) have a higher prevalence of hypertension and renal disease than the general population. While hematuria is a known complication of hemophilia A and B (HA, HB), its long-term impact on PWH is not currently known. By annually screening our patients with urinalysis, our pediatric center identified that just under half of our patients demonstrated hematuria over a four-year period. Motivated by a desire to identify early markers of hypertension and renal disease, we sought to determine if this finding is reflected in the pediatric hemophilia population as a whole.

Objectives: Establish the population-wide prevalence of hematuria in pediatric PWH.

Design/Method: We used the Pediatric Health Information System (PHIS) database, which contains clinical and resource utilization data for inpatients from 45 hospitals nationwide, to analyze the prevalence of hematuria, hypertension, renal disease and related diagnosis codes in pediatric PWH who were admitted from January 2010 to September 2015.

Results: During the five-year period, 2,197 unique pediatric PWH accounted for 4,802 admissions. While the majority of admissions were for bleeding or infectious concerns, 96 (4.4%) patients had an affiliated admission code for hematuria. For admissions as a whole, the median age was 7 years with 12% of those admitted being infants, 32% toddlers, 27% children, 28% adolescents, 2% older than 21. We identified 83% of admissions were for HA with the remaining 17% were for HB. There were 1254 (26%) admits in which a bypassing agent was administered. The median length of stay for persons with hematuria was 2 days compared to 3 days for non-hematuria/other bleeding. There were 120 (2.5%) admissions with hypertension reported; though, only 3 patients received an antihypertensive medication during that admission. Additionally, only 31 (0.6%) admissions reported a diagnosis code of renal disease.

Conclusion: Our study demonstrated that pediatric PWH are experiencing hematuria. In general, only patients with persistent hematuria require hospital admission so we suspect this data underrepresents the numbers of PWH experiencing hematuria that is managed in the outpatient setting. We also suspect that hypertension is grossly underreported and undertreated in pediatric PWH. Additionally, there are a low number of patients experiencing renal disease requiring hospital admission among this cohort. Given that there is little research into the long-term impact of hematuria in hemophilia, we feel these findings support the need for further vigilance of our pediatric PWH.

Poster # 416 | A MULTI-INSTITUTIONAL RETROSPECTIVE ANALYSIS OF SIROLIMUS AND BISPHOSPHONATES FOR THE TREATMENT OF GENERALIZED LYMPHATIC ANOMALY (GLA) AND GORHAM-STOUT DISEASE (GSD)

Yaser Diab, Cameron Trenor, Ionela Iacobas, Sherry Bayliff, Karen Fernandez, Laura Tosi, Gulraiz Chaudry, Denise Adams

Boston Children's Hospital, Boston, Massachusetts, United States

Background: GLA and GSD can aggressively destroy bone, with significant impact on morbidity and mortality. The mTOR inhibitor, sirolimus has been shown to be effective in the treatment of these diseases. Based on the addition of mTOR inhibition to bisphosphonate therapy in metastatic cancer therapy, regimens have been used for refractory or high risk GLA and GSD but there is heterogeneity of diagnosis, and variability of drug regimens and assessment of effectiveness.

Objectives: 1. Assess the variability of clinical features of GLA and GSD 2. Assess the heterogeneity of diagnosis 3. Assess drug regimens and response assessment across multiple institutions

Design/Method: We conducted a retrospective review from 5 institutions of 19 cases of GLA and GSD treated with sirolimus and a bisphosphonate for at least 2 months with assessment of clinical features, treatment protocols, response regimens and side effects.

Results: Patients included GLA (n = 8) and GSD (n = 11). The average age at diagnosis was 10 years. Clinical features included effusions: GLA (n = 4), soft tissue lymphatic malformations: GLA (n = 3), GSD (n = 1), multiple splenic lesions: GLA (n = 3), and soft tissue swelling at the site of bony lesion: GSD (n = 3). The presenting symptom in 17 patients was pain with 2 patients (GLA) presenting with shortness of breath. Fracture was noted in 5 patients: GLA (1), GSD (4). Diagnostic and/or response imaging included MRI, CT, bone scan, skeletal survey and Dexa scan. Treatment consisted of: initial sirolimus use with the addition of bisphosphonate secondary to worsening disease (n = 4), initial therapy with other agents (interferon, chemotherapeutic agents, radiation) and change to sirolimus and bisphosphonate secondary to toxicity (n = 6), sirolimus and bisphosphonates (n = 7) and sirolimus, bisphosphonates and interferon (n = 2). Seventeen patients had stable disease and 8 patients had improvement of disease. Sirolimus protocol was standard; however, bisphosphonate protocol varied in dosing and frequency. Side effects were tolerable and expected with no Grade III or IV toxicity.

Conclusion: Sirolimus and bisphosphonates are a safe and effective therapy for GSD and GLA. A consistent medication regimen, redefined response and an improved radiologic classification will be important for the development of a prospective clinical trial.

Poster # 417 | COMPARISON OF BODY MASS INDEX AND JOINT HEALTH OUTCOMES IN PEDIATRIC HEMOPHILIA A PATIENTS

Jacqueline Sun, Kerri Narasaki, Susan Knight, Guy Young

Children's Hospital Los Angeles, Los Angeles, California, United States

Background: Hemophilia A is a bleeding disorder from the deficiency of clotting factor VIII. The most significant sequelae of Hemophilia A is the tendency to develop hemarthrosis that incites joint destruction. The prevalence of overweight and obesity has been increasing in the general and hemophilia population and leads to several morbidities including arthropathy. This is a particular concern for hemophilia A as arthropathy is a consequence of joint bleeding.

Objectives: The purpose of this study was to detect the relation between body mass index (BMI) and joint health endpoints in a pediatric hemophilia population.

Design/Method: Participants in this study included 64 patients from the Hemostasis and Thrombosis Center at Children's Hospital Los Angeles. Participants were pre-screened and approached for this study during routine follow-up appointments. Patients aged 4–18 years old who have been diagnosed with Hemophilia A, including mild, moderate, and severe, qualified for the study. Informed consent was obtained from the patients or parents before enrollment. Joint health was objectively measured by physical therapists from Children's Hospital Los Angeles using the Hemophilia Joint Health Score (HJHS). An HJHS total score is calculated by assessing: swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain, and muscle strength in 6 major joints. Subjective data was also obtained by patients recording their annual bleed rate within the past year.

Results: Of the 64 patients, 28 (44%) were normal weight, 12 (19%) overweight, and 24 (38%) obese. We used chi-square analysis to compare joint scores across BMI classifications (chi square = 2.87, df = 2, p-value = 0.24). Although, this did not approach statistical significance, the average HJHS score in patients who had a HJHS >0 shows an increasing trend among BMI classifications: 6.19 in normal BMI patients, 6.75 in overweight BMI patients, and 7.00 in obese BMI patients.

The average number of annual bleeds in those with positive values show: 8 in normal BMI patients, 5 in overweight BMI patients, and 12 in obese BMI patients.

Conclusion: Although a positive effect of adiposity was found in the joints of hemophilia A pediatric patients, the effect shows there was not enough evidence to conclude a difference. Future studies are needed to address whether obesity has an effect on hemophilia and to determine whether overweight/obesity can lead to further complications in hemophilic joints.

Poster # 418 | EFFECT OF SIROLIMUS ON COAGULOPATHY OF SLOW-FLOW VASCULAR MALFORMATIONS

Bethany Verkamp, Joana Mack, Gresham Richter, Kelly Stewart, Shelley Crary

Arkansas Children's Hospital, Little Rock, Arkansas, United States

Background: Stagnant blood flow in slow-flow vascular malformations (VM), particularly in their venous components, can lead to localized intravascular coagulation (LIC) that is characterized by elevated D-Dimer levels, low fibrinogen and decreased platelet count This coagulation derangement can lead to localized thrombosis or bleeding which can result in pain, functional limitations, and possible progression to disseminated intravascular coagulopathy (DIC). The treatment of VM and their associated coagulopathy has proven difficult. Patients with complex VM are frequently managed with sirolimus, an mTOR inhibitor, and have clinical benefits, including reduction of pain and improvement in functional impairment. It is possible that some of these improvements from sirolimus could be secondary to improvement in the coexisting LIC.

Objectives: This study assessed the use of sirolimus to manage the coagulopathy seen in slow-flow VM.

Design/Method: We reviewed charts of patients with VM who are followed in the Vascular Anomalies Center at Arkansas Children's Hospital and were started on sirolimus. Efficacy was objectively assessed through improvement of D-dimer, fibrinogen and platelet count. Three sets of lab values (pre-sirolimus, 1–3 months post-sirolimus, and most recent) were obtained for each patient when available.

Results: We identified a total of 35 patients who had been prescribed sirolimus. Eighteen were excluded based on underlying condition other than slow-flow vascular malformation and 1 for inadequate medical records. A total of 16 patients (13 combined vascular, 3 venous) were included in the study. All 16 had elevated D-dimer levels (mean 4.64 mcg/mL FEU, median 2.99 mcg/mL FEU, range (0.83-14.65)) prior to treatment. Two patients had an associated low fibrinogen (below 175 mg/dL), indicating severe LIC. With treatment, 14 (87.5%) patients showed an overall decrease in D-dimer levels with an average decrease of 1.52 mcg/mL FEU between pre- and post-sirolimus labs, and an average decrease of 1.03 mcg/mL FEU between pre-sirolimus and most recent values. The two patients with low fibrinogen prior to treatment showed a decrease in D-dimer levels (mean decrease of 7.845 mcg/mL FEU) and an increase and normalization in fibrinogen (mean increase 83.95 mg/dL) after beginning sirolimus. No patient had thrombocytopenia.

Conclusion: We report that treatment with sirolimus was effective in improving coagulopathy associated with slow-flow VM as evidenced by decreased D-dimer levels and increased fibrinogen and/or platelets. Long-term use of this medication in this population may decrease the bleeding and thrombotic complications that these patients experience, especially following invasive vascular procedures.

Poster # 419 | EFFECTIVE PROPHYLAXIS WITH BAY 94–9027 IN ADOLESCENTS WITH HEMOPHILIA A: RESULTS FROM THE PROTECT VIII MAIN STUDY AND ONGOING EXTENSION

Bryce Kerlin, Jonathan Ducore, Sanjay Ahuja, Olubunmi Afonja, Kapil Saxena

Bayer, Leverkusen, Germany

Background: Safety and efficacy of BAY 94–9027, a site-specifically PEGylated B-domain–deleted recombinant factor VIII, in previously treated adolescents and adults aged 12–65 years with severe hemophilia A was demonstrated in the phase 2/3 PROTECT VIII study and ongoing extension.

Objectives: This subanalysis examines the efficacy and safety of BAY 94–9027 in adolescents in PROTECT VIII and the ongoing extension study (data cutoff, January 2015).

Design/Method: In PROTECT VIII, 134 patients (including 12 adolescents) received BAY 94–9027 on demand or as prophylaxis for 36 weeks. Prophylaxis regimens for weeks 10–36 were twice-weekly (30–40 IU/kg), every-5-days (45–60 IU/kg), or once-weekly (60 IU/kg) infusions based on bleeding during a 10-week run-in period of 25 IU/kg twice-weekly prophylaxis. Patients continued their prophylaxis regimens in the extension or changed regimens at any time.

Results: Twelve patients aged 12–17 years were included in the PROTECT VIII intent-to-treat population; 1

additional patient discontinued after 1 dose (included in safety population). For 11 patients receiving prophylaxis before study enrollment, median (range) number of total and joint bleeds in the 12 months before study entry was 8.0 (0–15) and 6.0 (0–10), respectively. Ten patients (83.3%) had target joints at baseline (median [range],1 [0–4] per patient). During weeks 10–36 of PROTECT VIII for the entire time patients remained on their designated prophylaxis dosing frequency, the median (quartile [Q]1; Q3) annualized bleeding rate (ABR) for patients receiving twice-weekly (n = 3), every-5-days (n = 6), and once-weekly prophylaxis (n = 3) was 0 (0; 2.0), 1.1 (0; 8.2), and 18.4 (0; 19.3), respectively (overall prophylaxis [n = 12], 1.0 [0.0; 10.1]). Two patients switched from once-weekly to twice-weekly (n = 1) or every-5-days prophylaxis (n = 1), and number of bleeds decreased from 2 to 1 in one patient and 6 to 4 in the other. All 12 patients from the main study continued in the extension; mean ABR in the extension was 3.2 and varied by dosing regimen (twice weekly [n = 3], 3.2; every 5 days [n = 5], 5.2; once weekly [n = 2], 0.9). Two patients changed from every-5-days to once-weekly prophylaxis during extension (mean ABR, 0.6). One patient had a nonneutralizing antibody to BAY 94–9027 at baseline; end-of-study titers were negative. No patient developed anti-PEG antibodies or factor VIII inhibitors or experienced a serious adverse event related to BAY 94–9027 during the main study or extension.

Conclusion: In previously treated adolescents with severe hemophilia A, BAY 94–9027 prophylaxis was effective in prevention of bleeds, with less bleeding overall versus prestudy, and was generally well tolerated. Funded by Bayer.

Poster # 420 | TOPICAL SIROLIMUS FOR CUTANEOUS MANIFESTATIONS OF VASCULAR MALFORMATIONS

Priscila Badia, Kiersten Ricci, Juan Gurria, Roshni Dasgupta, Manish Patel, Adrienne Hammill

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Vascular malformations (VMs) consist of a heterogeneous group of congenital disorders characterized by the abnormal development of blood and/or lymphatic vessels, which cause a broad spectrum of clinical manifestations. Although considered benign, VMs are frequently associated with cutaneous complications that can cause significant morbidity such as nodular overgrowth, skin thickening, pruritus, oozing or bleeding of lymphatic blebs and secondary infection. Oral Sirolimus has shown to be effective in the treatment of complicated vascular malformations but has known side effects and need for frequent laboratory monitoring. Currently, there are limited studies on the use of topical Sirolimus for the treatment of cutaneous manifestations of vascular malformations.

Objectives: To evaluate the efficacy and safety of topical Sirolimus in VMs with cutaneous complications and propose indications for use.

Design/Method: This is a retrospective review of medical records of patients with vascular malformations treated with topical Sirolimus from January 2012 to December 2017. Response was determined by subjective and objective improvement.

Results: Twenty-four patients, 16 (66%) females and 8 (33%) males, with vascular malformations and cutaneous manifestations were treated with topical Sirolimus. Age ranged from 4–27 years. Indications for treatment were: blebs (79%, n = 19) causing either leaking, bleeding, pain, pruritus, swelling or recurrent infection; nodular overgrowth 8% (n = 2); pyogenic granuloma 4% (n = 1); bleeding 4% (n = 1) and cosmetic 4% (n = 1). Treatment course ranged from 1–18 months. No major side effects were reported. One patient reported burning and itching sensation. Regarding clinical response: 83% (n = 20) patients had improvement in cutaneous lesions; 12% (n = 3) had a stable lesions; and 4% (n = 1) stopped treatment due to side effects. For prior/concomitant treatment: 83% (n = 20) had prior surgery, laser or sclerotherapy; 37% (n = 9) had concomitant oral Sirolimus. Of the 15 patients not receiving concomitant systemic Sirolimus, only 13% (n = 2/15) had been on oral Sirolimus. Of these patients, 80% (n = 12/15) had a very good response to topical treatment.

Conclusion: Topical Sirolimus appears to be beneficial and well-tolerated with a minimal side effect profile for the treatment of cutaneous manifestations of vascular malformations as a single agent or as adjuvant therapy with systemic Sirolimus when symptoms are not adequately controlled. Further studies are needed to prospectively analyze efficacy and safety of topical Sirolimus in this patient population.

Poster # 421 | FINAL SAFETY AND EFFICACY DATA OF LONG-TERM OPEN-LABEL DOSING OF SUBCUTANEOUS (SC) ROMIPLOSTIM IN CHILDREN WITH IMMUNE THROMBOCYTOPENIA (ITP)

Michael Tarantino, James Bussel, Victor Blanchette, Donald Beam, John Roy, Jenny Despotovic, Ashok Raj, Nancy Carpenter, Bhaki Mehta, Melissa Eisen

Amgen Inc., Thousand Oaks, California, United States

Background: Children with ITP for ≥6 months completing a romiplostim phase 1/2 or 3 study could enroll in this open label extension.

Objectives: To evaluate the safety and efficacy of long-term romiplostim in children with ITP.

Design/Method: All patients received weekly SC romiplostim from 1–10 μg/kg to target platelet counts of 50–200 × 10(9)/L.

Results: Median (min–max) treatment for the 65 patients was 135 (5–363) weeks for a total of 182 patient-years, or 2.8 years per patient. At baseline, median (min–max) age was 11 (3–18) years; 56% were female; 9.1% had prior splenectomy. Median (min–max) average weekly dose was 4.8 (0.1–10.0) μg/kg, including escalation to a stable dose; 20 patients started on 1 μg/kg. Reasons for discontinuing romiplostim (n = 28, 42%) included consent withdrawn (n = 10), required other therapy (n = 6), and AE (n = 2) (asthenia, headache, dehydration, and vomiting in one patient and anxiety in the other; none treatment related). Fifty four serious AEs occurred in 19 patients but were treatment related in one (concurrent grade 4 thrombocytopenia, grade 3 epistaxis, and grade 2 anemia). Anti-romiplostim neutralizing antibodies were detected in one patient who discontinued to receive other therapy; antibodies were absent on retesting. From week 2 on, median platelet counts remained >50 × 10(9)/L; median platelet counts were >100 × 10(9)/L from weeks 24–260. Nearly all (94%, 61/65) patients had ≥1 platelet response (platelet counts ≥50 × 10(9)/L, excluding ≤4 weeks after rescue medication). Most (72%, 47/65) patients had a platelet response ≥75% of the time and 58% (38/65) did ≥90% of the time. Sixty (92%) patients (or caregivers) self-administered romiplostim. Fifteen (23%) patients had treatment-free periods of platelet counts ≥50 × 10(9)/L for ≥24 weeks (ie, remission); these patients (9 girls, 6 boys) had had ITP for a median (min–max) of 3.5 (1.3–13) years, none had prior splenectomy, and had received romiplostim for 2.1 (0.7–6) years. All 15 had platelet counts >100 × 10(9)/L for ≥3 months and 12/15 for ≥6 months; the median (min–max) duration of being ≥100 × 10(9)/L was 42 (13–109) weeks. Of baseline characteristics such as sex, platelet counts, ITP duration, and number of past ITP treatments (1, 2, 3, >3), only age <6 years was predictive of developing treatment-free periods ≥24 weeks (p = 0.0035).

Conclusion: In this seven-year open-label extension, >90% of children with ITP achieved a platelet response and romiplostim was well tolerated. Importantly, 23% of patients were able to discontinue all ITP medications for ≥6 months. Funded by Amgen Inc.

Poster # 422 | UNDERSTANDING THE IMMUNE STATUS OF PATIENTS WITH NON-COMPLICATED VASCULAR OR LYMPHATIC ANOMALIES TREATED WITH SIROLIMUS

Karen Fernandez, Bhuvana Setty, Kristin Shimano, Sara Regina Kreimer, Michael Jeng

Valley Children's Healthcare, Madera, California, United States

Background: Sirolimus is an immunosuppressive drug that is widely used in solid organ and bone marrow transplantation, and more recently for the treatment of vascular and lymphatic anomalies. Sirolimus has been associated with decreased immunity in the transplant setting in patients that have received other immunosuppressive drugs or were immunosuppressed from previous chemotherapy. The effects of Sirolimus on the immune system in chemotherapy naïve children who have not received other immunosuppressive agents are not well understood, and there is variability in the approach to fever and PCP prophylaxis.

Objectives: To understand the effects of Sirolimus on the immune system of patients with non-complicated vascular or lymphatic anomalies by evaluating ANC, ALC prior to and after Sirolimus therapy.

Design/Method: Multi-institutional retrospective review was done to include patients with non-complicated vascular or lymphatic anomalies. Those with effusions/ascites, multi-organ involvement, or history of vascular-anomaly-related infections prior to treatment were excluded.

Results: Twenty patients with Kaposiform hemangioendothelioma (n = 6), Generalized lymphatic anomaly (n = 2), CLOVES syndrome (1), and simple vascular malformation (n = 11) were included. Age at initiation of Sirolimus treatment ranged from 0.5 – 20 years. Male to female ratio was 9:11. Sirolimus was initiated due to extensive disease, lack of response to steroids or bisphosphonates, pain, dment, lymphatic drainage, and prevention of ongoing overgrowth. Prior to the start of Sirolimus (SIR-0) the mean ANC was 3850 and ALC was 2875. The target level of Sirolimus varied by indication and patient, and ranged from 6 to 10. After the 1st steady state level, 1 month after Sirolimus (SIR-1) the mean ANC decreased to 2951 and ALC was 2793. At 3 months after Sirolimus (SIR-3) the mean ANC was 3108 and ALC was 2874. The first Sirolimus levels (SIR-1) mean was 11.3; and SIR-3 level was 7.8. Nine patients were placed on PCP prophylaxis at the start of Sirolimus. None of these patients had an infectious complication while on Sirolimus at a median f/u of 13 months. One patient had mild neutropenia (ANC >500) which normalized after discontinuation of PJP prophylaxis.

Conclusion: In this small cohort of patients we found that the ANC and ALC level in patients with non-complicated vascular or lymphatic anomalies at SIR-0 was not different from the SIR-1 or SIR-3. Prospective studies that specifically track ANC, ALC, IgG, and lymphocyte function should be conducted to better understand the effects of Sirolimus in the immune system. This data will allow for uniform recommendations regarding prophylaxis and management of febrile episodes.

Poster # 423 | ACUTE INFECTIONS AND VENOUS THROMBOEMBOLISM IN CHILDREN: A SINGLE-CENTER RETROSPECTIVE ANALYSIS

Keri Toner, Carole Hennessey, Yaser Diab

Children's National Health System, Washington, District of Columbia, United States

Background: Acute infections and the associated systemic inflammation can increase the risk of venous thromboembolism (VTE) and in certain well-defined clinical scenarios may be the primary trigger of VTE in pediatric patients. Pediatric data on VTE in the setting of acute infection are sparse.

Objectives: To describe characteristics and outcomes of VTE in pediatric patients with acute infections.

Design/Method: We conducted a retrospective chart review of all pediatric patients with objectively confirmed VTE treated at our institution since 2011 and identified all patients in whom an acute infection was identified as a VTE trigger. Patients were managed according to standardized institutional protocols based on published guidelines. Relevant demographic, clinical and laboratory data were collected and summarized using descriptive statistics.

Results: Since 2011, acute infection was identified as a trigger in 147 of 429 VTEs (34%) diagnosed at our center. The median age at time of VTE diagnosis in this group was 2.3 years (interquartile range 0.3-16). Males were more commonly affected than females, representing 56% of cases. Neonatal VTE events accounted for 14% of cases. Sepsis was the most common acute infection to be identified as a VTE trigger [59/147 cases (40%)]. Most VTE events (80%) associated with acute infections were considered hospital-associated VTEs. At time of VTE diagnosis, 61% of patients were critically ill. Extensive VTE (defined as completely occlusive thrombosis involving >1 venous segment) occurred in 16% of patients. Acute infection was deemed to be the primary trigger for VTE in 30/147 patients (20%). Infection-associated VTEs in this cohort included cerebral sinus venous thrombosis due to sinus or CNS infection (13 patients, 43%), septic thrombophlebitis (11 patients, 37%), Lemierre's or Lemierre's-like syndrome (4 patients, 13%) and osteomyelitis-associated deep vein thrombosis (2 patients, 7%). Systemic anticoagulation was prescribed in 124/147 patients (84%). Anticoagulation-related major bleeding occurred in 10/124 patients (8%). VTE complications included VTE recurrence (16 patients, 10%), VTE progression (1 patient), acute pulmonary embolism (2 patients) and arterial ischemic stroke (2 patients).

Conclusion: Our study indicates that acute infection is a common risk factor for pediatric VTE, especially in critically ill children, and can be the primary trigger in a significant proportion of VTE cases associated with acute infections. Anticoagulation appeared to be overall safe in this population and was associated with low rates of serious VTE-related acute complications. However, our study also suggests that this population may be at increased risk for VTE recurrence and anticoagulation-related major bleeding.

Poster # 424 | CHARACTERIZATION OF LONG-TERM OUTCOMES FOR PEDIATRIC PATIENTS WITH EXTRAHEPATIC EPITHELIOID HEMANGIOMA

Kevin Liu, Eileen Duggan, Alyaa Al-Ibraheemi, Raja Shaikh, Denise Adams

Boston Children's Hospital, Boston, Massachusetts, United States

Background: Epithelioid hemangiomas (EH) are rare benign vascular tumors that occur in soft tissues and bone and present between the third and sixth decades of life. A subset (29%) of EH harbor FOS rearrangement. EH has been described in children, but little is known about the long-term outcomes of pediatric EH.

Objectives: The main objective is to obtain data to be used for improved understanding of this rare disease in order to provide standardization of care and development of future research studies.

Design/Method: We conducted an Institutional Review Board-approved retrospective review of clinical, pathologic, and radiographic characteristics, and treatment outcomes in 11 patients diagnosed with EH between 1999 and 2017.

Results: Eight patients were male; mean age at diagnosis was 14.8 years (range: 6–23). Lesions involved the lower extremities (n = 5), cranium (n = 3), pelvis (n = 2), and spine (n = 1). Multifocal disease was identified in five patients. The most common presentations involved significant localized pain and neurologic symptoms: headache, cranial nerve injury, loss of consciousness. Radiographic studies identified variable features, such as multifocal lytic bony lesions with sclerotic

margins, enhancing soft tissue component, and surrounding inflammatory edema. Histologically, all specimens were composed of vascular channels lined by epithelioid endothelial cells without significant cytologic atypia; solid cellular areas (n = 2). Endothelial cells were positive for CD31 and EGR, and negative for CAMTA1. FOS rearrangement was assessed in only one specimen and detected. Mean follow-up time was 545 days (range: 23–2642). Patients were treated with surgical resection, intravascular embolization, bisphosphonates, propranolol, interferon, and sirolimus. One patient treated with interferon and one with sirolimus exhibited partial response for mean follow-up of 1566.5 days.

Conclusion: Although EH is a benign neoplasm, it is difficult to manage without standard protocols and portends considerable morbidity. Our findings suggest medical management, particularly sirolimus, may benefit these patients; however, long-term follow-up is needed in treated children. Novel FOS inhibitors are in development and may benefit patients with FOS rearrangement.

Poster # 425 | CONTINUOUS LOW-DOSE HEPARIN INFUSION FOR CATHETER RELATED THROMBOSIS PROPHYLAXIS IN CRITICALLY ILL CHILDREN

Kenneth Bujold, E. Scott Halstead, Frederico Xavier

Penn State Health Children's Hospital, Hershey, Pennsylvania, United States

Background: Central venous catheters (CVC) are often required in critical care settings in order to provide a secure point of access for life sustaining care. Clinical studies identify CVC presence as the single most important risk factor for deep vein thrombosis (DVT) in children. Venous thromboembolic event (VTE) incidence rates in critically ill children with a CVC range from 0.3-18% and 0.06-32.5 per 1000 catheter days depending on the population studied. Per institutional protocol, the Penn State Health Children's Hospital PICU (Hershey, PA) utilizes a low dose continuous infusion of unfractionated heparin (LDUFH) at 10 units/kg/hr as prophylaxis against CVC-related VTE and to maintain line patency. The efficacy of this approach has never been evaluated.

Objectives: To determine if LDUFH for prophylaxis results in lower incidence of CVC-related VTE, catheter dysfunction and central line associated blood stream infection (CLABSI) without increasing morbidities.

Design/Method: To determine if the incidence of catheter related VTE is lower than historical published data, a retrospective chart review was conducted utilizing the institutional electronic medical record for all patients in 2015, aged 0–17.99 years, who had a CVC during a PICU admission. Secondary objectives such as the incidence of catheter dysfunction, CLABSI, and any associated bleeding complications are also being analyzed.

Results: Interim data analysis revealed 478 CVCs (400 non-tunneled CVC, 18 totally implantable devices, 19 tunneled lines, 41 peripherally inserted central catheters [PICC]) in 374 total patients with a median age of 1.9 years. Overall VTE incidence was 1.88% (9/478) with 7 VTEs associated with non-tunneled CVC and 2 with PICCs. Sixty one percent of non-tunneled CVCs received LDUFH and 85% (6/7) of the patients with VTEs associated with non-tunneled CVCs did receive LDUFH prophylaxis. VTE incidence rate of non-tunneled CVCs with LDUFH was 2.5% (6/243) and 2.56 per 1000 PICU catheter days. The only other VTE events identified within our study cohort were in the PICC group where two patients experienced VTE, one of which was receiving LDUFH. CLABSI incidence was 1.2% (4 non-tunneled CVC, 1 tunnel CVC, 1 PICC). No major bleeding complications were associated with LDUFH.

Conclusion: Preliminary data demonstrates LDUFH is efficacious in preventing CVC-related VTE in comparison to published reports. Further analysis will compare another similar sized and acuity level PICU which does not practice the same method.

Poster # 426 | SIROLIMUS FOR REFRACTORY FIBROADIPOSE VASCULAR ANOMALY

Cameron Trenor, Geetha Puthenveetil, Ionela Iacobas, Taizo Nakano, Meghan O'Hare, Irina Pateva, Clifford Takemoto, Denise Adams

Boston Children's Hospital, Boston, Massachusetts, United States

Background: Fibroadipose vascular anomaly (FAVA) is a rare, challenging disorder associated with PIK3CA mutations. FAVA often causes painful replacement of muscle and soft tissues with fibrotic and adipose tissue and is associated with ectatic draining veins. Treatments for focal lesions are surgical excision, cryoablation or sclerotherapy and the role of medical therapy is unclear. Some FAVA lesions are too extensive or directly involve neurovascular structure, resulting in refractory pain.

Objectives: To retrospectively evaluate the efficacy of sirolimus in patient with residual symptoms after procedural therapies for FAVA

Design/Method: Retrospective review of individual 7 cases from 6 institutions of FAVA refractory to other therapies treated with sirolimus for at least 3 months. Cases were

identified by polling member of the ASPHO Vascular Anomalies Special Interest Group.

Results: All seven patients report improvement on sirolimus therapy. All patients had received prior procedures, including sclerotherapy (6 patients), cryoablation (2 patients) and/or resection (3 patients). Mean age at sirolimus initiation was 16y (range 6–29y). Mean length of therapy is 18.4 months (range 3–29 months). Six patients were treated with BID dosing and one adult received daily dosing. Goals of sirolimus were improvement in pain or musculoskeletal dysfunction. Pain and function improved in all patients, including discontinuation of narcotic use and resumption of participation in sports. Time to symptom improvement ranged from 1–4 weeks. In four patients for whom dose was lowered, pain recurred in all four and responded to restarting or increasing sirolimus dose. While all patients do not have pre- and post-sirolimus imaging, decrease in FAVA lesion size is seen in cases with available imaging. Sirolimus side effects are similar to prior reports, most commonly mouth sores, elevated lipids and acne.

Conclusion: We report the first known data supporting a role of sirolimus in refractory FAVA cases. Sirolimus is well-tolerated and initial improvement is rapid, within 4 weeks of initiation. Whether sirolimus has a role in upfront therapy to reduce lesion size prior to procedures deserves further study.

Poster # 427 | A SINGLE-ARM, OPEN-LABEL, LONG-TERM EFFICACY AND SAFETY STUDY OF SUBCUTANEOUS (SC) ROMIPLOSTIM IN CHILDREN WITH IMMUNE THROMBOCYTOPENIA (ITP)

John Grainger, James Bussel, Michael Tarantino, Nichola Cooper, Donald Beam, Jenny Despotovic, Alexey Maschan, Nancy Carpenter, Melissa Eisen, Joseph Park

Amgen Inc., Thousand Oaks, California, United States

Background: Romiplostim is being evaluated in children with ITP. Here, children with ITP are receiving open-label SC romiplostim for ≤3 years.

Objectives: To assess platelet responses in children with ITP receiving romiplostim.

Design/Method: Eligible children had ITP for ≥6 months, ≥1 prior therapy, and screening platelet counts ≤30 × 10(9)/L or uncontrolled bleeding. Weekly dosing was from 1–10 μg/kg to target platelet counts of 50–200 × 10(9)/L. Bone marrow biopsies were evaluated in Europe at baseline and after 1 or 2 years (cohorts 1 and 2).

Results: As of Mar 2017, 203 patients received ≥1 dose. At baseline, median (min-max) age was 10 (1-17) years, ITP duration was 1.8 (0.5-13.8) years, and platelet count was 14 (2-265) × 10(9)/L; 10 patients (5%) had had prior splenectomy. The median (Q1, Q3) % time with a platelet response (platelet count ≥50 × 10(9)/L, no rescue medications past 4 weeks) in months 0–6 was 50% (17%, 83%) (primary endpoint). Over the course of the study, 88% (179/203) of patients had a platelet response. Four patients maintained platelet counts ≥50 × 10(9)/L with no ITP medications for ≥24 weeks. Median (min-max) treatment duration was 53 (8-119) weeks for 226 patient-years in total. Median (min-max) average weekly romiplostim dose over the course of the study was 6.9 (0.2-9.5) μg/kg; the median dose was 9 μg/kg at 1 year (n = 106) and 10 μg/kg at 2 years (n = 17). Most (63%) patients initiated self-administration. Sixty-four patients (31%) discontinued treatment, most frequently for lack of efficacy (n = 38), patient request (n = 7), and adverse event (AE) (n = 7). Forty-one (20%) patients had serious AEs (SAEs) including epistaxis (5%) and decreased platelet count (3%). Five patients had treatment-related SAEs: 2 headaches, 2 abdominal pain, and 1 each of presyncope and neutralizing antibodies (Ab). There were 6 cases of neutralizing Ab to romiplostim (of 201 patients tested), but none to TPO; 5/6 had continued elevated platelet counts and in 2/6 cases Ab were not found on retesting. For cohort 1, of 30 patients with baseline bone marrow biopsies, 27 had evaluable on-study biopsies scheduled for 1 year; 1 patient had an increase from grade 0 to 2. There were no findings of collagen or abnormalities.

Conclusion: In this interim datacut of a romiplostim open-label study in children with ITP, 88% of children had a platelet response. Overall, the median dose was 6.9 μg/kg; the median romiplostim dose over time reached 10 μg/kg. No new safety signals were observed over 226 patient-years. Funded by Amgen Inc.

Poster # 428 | GUIDANCE DOCUMENT FOR HEPATIC HEMANGIOMA (INFANTILE AND CONGENITAL) EVALUATION AND MONITORING

Ionela Iacobas, Thuy Phung, Denise Adams, Cameron Trenor, Francine Blei, Douglas Fishman, Adrienne Hammill, Prakash Masand, Steven Fishman

Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, United States

Background: Hepatic hemangiomas are benign vascular tumors without a medical home, managed by multiple specialties. The diagnosis has been assigned historically to various vascular lesions affecting the liver with completely

different clinical presentations, resulting in difficult standardized management.

Objectives: The Consensus Steering Committee identified an acute need of clear definitions and evaluation guidelines using the updated International Society for the Study of Vascular Anomalies (ISSVA) classification. The goal was to formulate recommendations that will be adopted by all specialties involved in the care of children with hepatic hemangiomas.

Design/Method: We used a rigorous, transparent consensus protocol, with input from multiple pediatric experts in vascular anomalies from hematology-oncology, surgery, pathology, radiology and gastroenterology.

Results: In the first section, we precisely define the subtypes of hepatic hemangiomas seen in children (congenital and infantile) using clinical course, histology and radiologic characteristics. Inclusion and exclusion limits to the diagnosis are noted. The following two sections describe these subtypes in further detail, including complications to be considered during monitoring and respectively recommended screening evaluations.

Conclusion: While institutional variations may exist for specific clinical details, a clear understanding of the diagnosis of hepatic hemangiomas affecting the pediatric population and the possible complications that require screening during the monitoring period should be standard. As patients with hepatic hemangiomas are managed by different medical and surgical specialties, a multidisciplinary consensus based on current literature, on the data extracted from the liver hemangioma registry and on expert opinion was required and was accomplished by this manuscript.

Poster # 429 | BAY 81-8973 PROPHYLAXIS FREQUENCY AND PHARMACOKINETICS IN RELATION TO BLEEDING RATES IN PEDIATRIC PATIENTS: SUBANALYSIS OF LEOPOLD KIDS DATA

Olubunmi Afonja, Anita Shah, Martin Sanabria, Guido Senatore, Stephan Rauchensteiner, Nikki Church

Bayer, Leverkusen, Germany

Background: Individualizing FVIII prophylaxis is important to optimize treatment effectiveness in hemophilia A. BAY 81–8973 (Kovaltry®) is a recombinant factor VIII product approved for the treatment of hemophilia A in children, adolescents, and adults. Efficacy and safety of BAY 81–8973 were demonstrated in the LEOPOLD clinical development program.

Objectives: To investigate the association between routine prophylaxis with BAY 81–8973 and bleeding outcomes after adjusting for key patient and pharmacokinetic (PK) characteristics.

Design/Method: The LEOPOLD Kids study evaluated safety and efficacy of BAY 81–8973 prophylaxis in 51 previously treated boys aged ≤12 years with severe hemophilia A. Patients received BAY 81–8973 25–50 IU/kg 2x/wk (n = 21) or >2x/wk (n = 30) and were followed up for 6–8 months. Prophylaxis dose and frequency were assigned by investigators. PK parameters, including area under the curve (AUC), half-life, and clearance, were derived from a population PK model and reflect predicted PK values with a 50-IU/kg dose. Patient characteristics were compared between the 2x/wk and >2x/wk groups using Wilcoxon rank sum or chi-square tests. Negative binomial regression was used to model the association between prophylaxis frequency and annualized bleeding rate (ABR) for total bleeds, first without adjustment and then adjusting for age, PK parameters, and bleed history.

Results: Mean ± SD age for patients in this analysis was 6.4±3.0 years. Patients receiving prophylaxis 2x/wk had more bleeding episodes in the 12 months before study entry (mean ± SD, 13.0±16.6 [median, 6.0] for 2x/wk vs 4.3±5.7 [1.0] for >2x/wk; P = 0.027) and were more likely to have been treated on demand (38% vs 10%; P = 0.035). PK parameters were similar between the 2x/wk and >2x/wk groups. Without adjustments, ABR during the study was 12% higher in the 2x/wk group compared with the >2x/wk group (rate ratio [RR], 1.12; 95% CI, 0.44–2.90; P = 0.81). ABR was 36% lower in the 2x/wk group (RR, 0.64; 95% CI, 0.24–1.70; P = 0.37) after adjusting for age, AUC, and number of bleeds in the prior 12 months.

Conclusion: ABR was numerically lower but not significantly different between the 2x/wk and >2x/wk groups after adjusting for age and PK parameters. These findings suggest that even among patient groups that are homogeneous with respect to age, PK, and bleed history, further individualization of BAY 81–8973 prophylaxis based on other characteristics may help reduce bleeding episodes even at a lower treatment frequency. Larger real-world studies are needed to verify these findings. Funded by Bayer.

Poster # 430 | ANTICOAGULATION FOR TREATMENT OF PAIN IN VENOUS MALFORMATIONS

May Chien, Sara Kreimer, Joyce Teng, Anne Marqueling, Michael Jeng

Stanford, Palo Alto, California, United States

Background: Vascular malformations may be of lymphatic, arterial, venous or capillary endothelial origin. They may be simple or complex, with complex malformations being a combination soft tissue and skeletal overgrowth. Although likely present at birth, these malformations often become symptomatic with puberty or infection, and range from little or no clinical impact to life threatening symptoms. In malformations primarily of venous origin, pain may be significant and hypothesized to be caused by phlebolith development (intra-malformation thrombi), inflammation, consumptive coagulopathy, vascular engorgement, and endothelial proliferation. Anti-angiogenic and anti-platelet therapies have been reported to relieve pain. However, the use of anticoagulation for pain is not well described.

Objectives: To report clinical features and outcomes of patients with vascular malformations of venous origin treated with anticoagulation for pain.

Design/Method: We performed a retrospective review of patients with vascular malformations followed by the hematology service between January 2010 and December 2017 who were treated for pain with anticoagulation. Pain relief was determined both by Wong-Baker pain scales and patient report. Clinical data were extracted from electronic medical records.

Results: We identified five patients with venous malformations (VM) who had received anticoagulation for pain. Four patients were female and median age was 8 years old (range 4 to 29 years old) at time of initiation of anticoagulation. All five patients had VM of the extremity, two with VM of the lower extremity, and three patients had VM of the upper extremity. Two patients had concomitant coagulopathy and demonstrated decreased D-dimer after initiation of anticoagulation. Four patients received enoxaparin, and one adult patient received rivaroxaban. All patients reported improvement in pain after administration of anticoagulation. One patient exhibited mild epistaxis and bruising at the injection site. There was no significant bleeding or other complications.

Conclusion: Pain is a significant complication in patients with venous malformations. Our case series suggests that anticoagulation is a safe and effective therapy for pain relief in this population. Further investigation is indicated to compare the effect of anticoagulation to other therapeutic interventions such sclerotherapy, surgery, and sirolimus in the treatment of pain associated with venous malformation.

Poster # 431 | RISK FACTORS AND OUTCOMES OF DEEP VEIN THROMBOSIS IN PEDIATRIC OSTEOMYELITIS

Maria Ahmad-Nabi, Christine Knoll, Sanjay Shah, Lucia Mirea

Phoenix Children's Hospital, Phoenix, Arizona, United States

Background: Estimates of the incidence of DVT in patients with osteomyelitis range widely from 5%-30%, however risk factors and outcomes of DVT in this cohort have not been thoroughly established.

Objectives: This study aims to estimate the incidence of DVT in patients with osteomyelitis, and to assess risk factors and outcomes of DVT in this cohort.

Design/Method: After IRB approval, a retrospective chart review was conducted for patients aged 0–18 years seen at Phoenix Children's Hospital between 2012–2016 with ICD 9/10 codes for osteomyelitis. Exclusion criteria included chronic recurrent multifocal osteomyelitis, and chronic DVT. Demographics, clinical factors and outcomes were compared between osteomyelitis patients with and without DVT using the Fisher-exact and Wilcoxon-rank sum tests, as appropriate for the data distribution.

Results: A total of 179 study subjects with osteomyelitis had a mean (standard deviation) age of 8.4 (5.7) years. DVT was present in 14 (8% of 179) patients, and 4 (28%), 5 (36%) and 5 (36%) patients received anticoagulation for < 6, 6–12 and ≥ 12 weeks, respectively. Patients with vs without DVT were more likely to be male (86% vs 59%; p-value = 0.05), and had significantly higher rates of bacteremia (64% vs 24%; p-value = 0.003). Rates of central lines were comparable between DVT and non-DVT patients (71% vs 68%; p-value = 1.00); however patients with DVT vs without DVT had significantly longer mean length of stay (18 vs 9 days; p-value <0.0001) and higher rates of ICU admission (71% vs 16%; p-value <0.0001).

Conclusion: The incidence of DVT among osteomyelitis pediatric patients was estimated at 8%, with risk increased by male sex and bacteremia. Patients with DVT had significantly higher rates of ICU admission and longer length of hospital stay. Many of these patients had standard practice management of their DVT with 6–12 weeks of anticoagulation. Our data highlights the need for recognition of high risk patients, and the need for future efforts targeting DVT prophylaxis.

Poster # 432 | PEDIATRIC HEAD AND NECK LYMPHATIC MALFORMATIONS: PRENATAL PLANNING AND MANAGEMENT STRATEGIES IN THE MULTIMODAL ERA

Priya Mahajan, Tara Rosenberg, Sheena Pimpalwar, Judith Margolin, Ionela Iacobas

Baylor College of Medicine, Houston, Texas, United States

Background: Lymphatic malformations (LM) frequently occur in the head and neck and can often be disfiguring and even life-threatening. Management options include observation, surgery, sclerotherapy, and sirolimus. The optimal sequence of therapeutic interventions has not been determined due to the lack of comparative clinical trials or established guidelines. Thus, prenatal planning with a multidisciplinary team is beneficial.

Objectives: We present a case series of ten children with head and neck LMs evaluated in 2017 at our multidisciplinary vascular anomalies center. A chart review was performed to assess treatment modalities and recent trends.

Design/Method: Case series.

Results: Seven of 10 patients (70%) with head and neck LMs were diagnosed prenatally. Six patients required an Ex Utero Intrapartum Treatment procedure. All patients were started on sirolimus at a median age of 12.5 months (range 12 days – 18 years). Four patients most recently started on sirolimus were less than 3 months of age at the time of initiation. Six patients underwent partial excision of LM during the first year of life; none of whom received sirolimus prior to surgery. Sirolimus was discontinued in one patient given chronic Clostridium difficile infections, and non-compliance in another patient. Five patients received sclerotherapy. Tracheostomy was necessary in six patients; one patient was de-cannulated after 7 months on sirolimus. All patients have had radiographic and clinical improvement of LM with varying treatment modalities. Current clinical observations show improved response with sirolimus and demonstrate tolerability of sirolimus at a young age.

Conclusion: Treatment of pediatric head and neck LMs is challenging and a multidisciplinary approach is necessary. As the majority of patients are diagnosed prenatally, prenatal planning and discussion of potential use of sirolimus is beneficial. Availability of vascular anomalies experts in the prenatal/neonatal period offers the best management results, and early initiation of sirolimus should be considered for complex lesions. Long-term follow up is warranted to investigate the efficacy and timing of treatment options.

Poster # 433 | TRANSFUSION OF PATHOGEN-REDUCED (PR) SINGLE DONOR PLATELETS (SDP) TO THROMBOCYTOPENIC NEONATES AND PEDIATRIC PATIENTS: EVALUATION OF PLATELET USAGE AND TRANSFUSION REACTIONS (TR)

Wade Schulz, Jacob McPadden, Bryan Spencer, Edward Snyder

Yale School of Medicine, New Haven, Connecticut, United States

Background: To mitigate transfusion of pathogen-contaminated platelets, amotosalen, a synthetic psoralen compound, is added to SDP components. Exposure to UV-A light activates amotosalen and crosslinks DNA/RNA base pairs, preventing replication of a broad spectrum of viral, bacterial, and other pathogens that may contaminate platelets. PR-SDPs were FDA approved for clinical use with no age restrictions in 2014. We initiated use of PR-SDPs in November of 2016 for all patients.

Objectives: We retrospectively analyzed usage of PR-SDP vs conventional (non-PR) platelets (CP) in neonatal and pediatric patients with thrombocytopenia to compare hemostatic efficacy and the incidence of transfusion reactions (TR) for these products, after one year of a dual platelet inventory.

Design/Method: Since PR-SDP were FDA-licensed, no IRB approval was required; PR-SDP and CP were both considered standard of care. We evaluated transfusions for all pediatric patients age 0–18 years who received any platelet transfusion between November 2016 and November 2017. We determined the volume (mean mL ± 1SD) of each type of platelet component transfused, the number of platelet transfusion episodes, and reported TRs based on CDC Hemovigilance Guidelines. A subgroup analysis was performed for thrombocytopenic neonates (0-4 months).

Results: Patients 0–18 years who received only CPs (N = 46) received a total of 8,030 mL of platelets (175 ± 151 mL/patient) over 62 transfusions (1.3 ± 0.6 episodes/patient). For comparison, in 38 patients who received only PR-SDP, a total of 4,350 mL of platelets (115 ± 107 mL/patient, $p = 0.04$) were infused over 61 transfusions (1.6 ± 0.9 episodes/patient, $p = 0.12$). For neonates (0-4 months, N = 26) who received only CPs, 2,195 mL of CPs (84 ± 105 mL/ patient) were transfused over 36 episodes (1.4 ± 0.6 episodes/patient). For comparison, those who received only PR-SDP (N = 27), received 1,613 mL of PR-SDP (60 ± 41 mL/patient, $p = 0.27$), transfused over 48 episodes (1.8 ± 0.9 episodes/patient, $p = 0.08$). For all recipients 0–18 years (N = 162), including additional patients who received both CP and PR-SDP, there were three reported allergic TRs over 757 transfusion episodes, while no allergic reactions were reported with 537 PR-SDP transfusions. One febrile TR was reported to CP transfusion, while three were reported for PR-SDP.

Conclusion: In conclusion, PR-SDPs, in our pediatric population age 0–18 years, were comparable to CP products in regards to volume and episodes of platelet transfusions, and incidence/type of transfusion reactions. PR-SDP were safe and effective for use in this pediatric patient population.

Poster # 434 | A FIBRO-ADIPOSE VASCULAR ANOMALY MASQUERADING AS AN INTRAMUSCULAR HEMATOMA IN THE SETTING OF IMMUNE THROMBOCYTOPENIA

David Stammers, Manuel Carcao, Jillian Baker

The Hospital for Sick Children, Toronto, Ontario, Canada

Background: Vascular anomalies are classified as either vascular tumors or vascular malformations. Fibro-adipose vascular anomaly (FAVA) is a newly described entity which presents with distinct clinical, radiographic and histopathologic findings. We present a case in which the diagnosis of FAVA was complicated by a persistent low platelet count secondary to immune thrombocytopenia (ITP).

Objectives: To describe a challenging diagnosis of a novel vascular anomaly (FAVA) complicated by severe thrombocytopenia.

Design/Method: Case Report

Results: A 17 year old male presented to hospital with bruising and left thigh pain related to a remote sports injury. Blood work revealed a platelet count of 9 × 109/L, but with an otherwise normal complete blood count. The following were also normal: aPTT and fibrinogen; D dimer levels were slightly increased. He was treated with one dose of IVIG (0.8 mg/kg) for presumed ITP and responded well with his platelet count increasing to 118 × 109/L. He returned to hospital 3 weeks later with recurrent thrombocytopenia and worsening leg pain. An ultrasound of the left thigh revealed a 7.7cm x 4.0cm x 2.9cm lesion within the vastus medialis. The diagnosis of an intramuscular hematoma secondary to persistent thrombocytopenia was made. The patient presented with multiple episodes of thrombocytopenia over the next several months. His ITP did not respond to oral prednisone (150 mg/day for 4 days). He continued to have short-lived responses to IVIG requiring infusions every other week as his platelet count would fall below 10 × 109/L. His leg pain progressed, restricting him to a wheelchair. Further imaging by MRI brought into question the diagnosis of a hematoma and a biopsy of the thigh lesion was performed. The results were consistent with a diagnosis of FAVA; this was subsequently excised.

Conclusion: This is a unique case where a vascular anomaly was misdiagnosed as a hematoma due to a patient's persistent thrombocytopenia and history of an injury. FAVA is a newer entity which, unlike other vascular anomalies, has not been linked to thrombocytopenia or a localized consumptive coagulopathy. After excision of the FAVA, the patient's chronic pain, and mobility resolved, though his ITP persisted.

Poster # 435 | ANALYSIS OF REAL-WORLD CLAIMS DATA ASSOCIATED WITH A STANDARD AND AN EXTENDED HALF-LIFE RECOMBINANT FACTOR IX PRODUCT IN U.S. PEDIATRIC PATIENTS WITH HEMOPHILIA B

Patrick Fogarty, Dean Spurden, Amit Chhabra, Emily Rubinstein, Bartholomew Tortella, Andreas Pleil, José Alvir

Pfizer Inc, New York, New York, United States

Background: Real-world data on units dispensed and factor-related expenditures associated with use of recombinant (r) standard half-life (SHL) or extended half-life (EHL) factor IX (FIX) replacement products in U.S. pediatric patients with hemophilia B are limited.

Objectives: This preliminary, exploratory analysis of real-world administrative data was conducted to determine units dispensed and factor replacement product-related direct expenditures associated with a currently marketed SHL or EHL rFIX product.

Design/Method: De-identified claims data from the commercially available Truven Health MarketScan® Research U.S. claims database were used to identify direct expenditures and number of international units (IUs) dispensed for all patients aged 0–17 years with a diagnosis code of ICD-9 286.0/ICD-10 D66 who used nonacog alfa or eftrenonacog alfa during the study period (June 1, 2014 to July 31, 2017). Reference weight measurements from the Centers for Disease Control and Prevention National Center for Health Statistics' (CDC NCHS) anthropometric data were used to estimate product dispensation on an IU per kg basis.

Results: The nonacog alfa and eftrenonacog groups comprised 37 and 11 patients, respectively. The median [IQR] age in the two groups was 8.0 [9.0] and 13.0 [4.0] years, respectively. While 10 of the 11 patients in the eftrenonacog alfa group had >1 calendar quarter of available data, only 23 of the 37 patients in the nonacog alfa group had >1 available quarter. The median rFIX product dispensation per quarter was 29,074IUs (IQR, 13,113-52,967 IUs) in the nonacog alfa group and 62,268IUs (IQR, 18,623-94,882 IUs) in the eftrenonacog alfa group. Incorporating attributed weight values, the median rFIX product IU dispensation per kg per week was 97.39 IU/kg/wk (IQR, 31.92 IU/kg/wk-153.92 IU/kg/wk) in the nonacog alfa group, and 96.27 IU/kg/wk (IQR, 53.05-154.03 IU/kg/wk) in the eftrenonacog alfa group. Applying 2016 WAC prices (eftrenonacog alfa = $2.97/IU; nonacog alfa = $1.37/IU), the calculated estimates of $/kg/week were $133 and $286 in the nonacog alfa and eftranonacog alfa groups, respectively.

Conclusion: Preliminary real-world data derived from a large U.S. claims database revealed differences in product dispensation and factor product-related expenditures among pediatric patients with any severity of hemophilia B to whom an SHL or EHL rFIX product was prescribed. Refinements of these data, potentially to exclude instances of sporadic usage, may shed light on real-world dispensation of rFIX products among pediatric hemophilia B patients.

Poster # 436 | MULTIDISCIPLINARY APPROACH TO TREATMENT OF VASCULAR MALFORMATIONS - A SINGLE INSTITUTION EXPERIENCE

Geetha Puthenveetil, Daniel Jaffurs, Kevin Huoh, Jill Stites, Kim Hai, Mahmood Razavi

Children's Hospital of Orange County, Orange, California, United States

Background: Vascular malformations can be classified as simple (including capillary, venous, lymphatic, arteriovenous), combined, malformations of major named vessels or associated with other anomalies. Multiple modalities including laser treatments, sclerotherapy, embolization, surgery and pharmacological intervention (with mTOR inhibitors like Sirolimus) have been used for treatment of vascular malformations. These interventions have been used alone or in combination with varied outcomes.

Objectives: We present our institution's experience with a multimodal approach to simple and combined vascular malformations.

Design/Method: We performed a retrospective chart review of patients with vascular malformations who were referred to our center for an interventional radiology evaluation from June 2015 –July 2017.

Results: We included 22 patients (age at presentation:4 months – 25 years), referred initially for Interventional Radiology procedures (IRP) for vascular malformations. All patients had symptoms of pain and/or swelling/deformity. Diagnosis of was based on vascular imaging (Doppler ultrasound, MRI/A/V). Nine patients had venous malformations (VM), five had macrocystic lymphatic malformations (LM), six had lymphatic-venous malformations (LVM), and two arteriovenous malformations (AVM). 19 patients initially underwent Interventional Radiology procedures. All the VM patients responded to sclerotherapy alone. Three patients with LM responded to sclerotherapy alone, remainder required surgical intervention. One AVM patient responded well to embolization, the other needed surgical resection after embolization. Four LVM patients underwent IRP with minimal improvement in symptoms (3-8 procedures attempted), surgical resection was attempted in 3 patients with poor response and 5 patients were started on Sirolimus (0.8mg/m2/dose twice a day). All LVM patients started on Sirolimus have responded well (decreased pain and swelling); time to initial symptom response ranged from 2 weeks – 1 month from starting medication.

Conclusion: In this case series, patients with simple VM responded well to sclerotherapy alone, AVM and LM patients needed IRP and/or surgery for complete response. Complex LVM did not respond well to surgery or IRP; 83.3% had improvement in clinical symptoms with addition of Sirolimus to the treatment regimen. Response to various modalities of treatment varied based on the type of vascular malformation. A multidisciplinary approach to management of vascular malformations is essential to provide multimodal therapeutic options for rapid symptom relief and improve the quality of life of these fragile patients, especially those with complex malformations.

Poster # 437 | VON WILLEBRAND DISEASE, DDAVP, AND FLUID MANAGEMENT IN PEDIATRIC SURGICAL PATIENTS

Steven Garbin, James Cooper

University of Pittsburgh / Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, United States

Background: Von Willebrand Disease (vWD) is the most common bleeding disorder in humans, affecting ~1% of the United States' population. Desmopressin (DDAVP) is a long-acting vasopressin analog that induces vasoconstriction and release of vWF. DDAVP is used in patients with vWD and as a surgical prophylaxis, but carries anti-diuretic properties. To avoid electrolyte imbalance and hyponatremia, fluid restrictions are recommended in the 24 hours post-DDAVP administration.

Objectives: This study sought to examine perioperative practices and outcomes following DDAVP administration and a fluid restriction protocol in a population of pediatric patients with von Willebrand disease.

Design/Method: A retrospective chart review was conducted for patients with von Willebrand Disease who underwent surgical procedures at Children's Hospital of Pittsburgh of UPMC between January 1, 2015 and December 31, 2016. Patient age, sex, weight, diagnosis, surgical procedure, total fluids administered, and post-operative sodium level were recorded. The primary outcomes noted were the proportion of patients exceeding 50% of the recommended fluid consumption for the 12- and 24-hour periods post-DDAVP

administration, as defined by local guidelines. Secondary outcomes were the presence of any bleeding requiring an ER visit or readmission or hyponatremic seizures within 72 hours of DDAVP administration.

Results: Data was compiled for 42 patients (23 females, 19 males). The mean age was 11.19 years (SD 5.13 years), median age was 12 years (range 3 to 19 years). Procedures included dental (13), otolaryngology (9), orthopedics (7), gastrointestinal (5), plastics (3), neurosurgery (1), ophthalmology (1), dermatology (1), general surgery (1) and gynecology (1). 30% of patients exceeded 50% of the fluid volume recommended for the first 12-hour period post-DDAVP administration while still in the surgical setting. No patients exceeded 50% of the fluid volume recommended for the total 24-hour period post-DDAVP administration. Post-operative sodium levels were obtained in only 7 of 42 patients. No patients returned to the ER or were admitted for bleeding in the 72 hours post-DDAVP administration. No patients returned to the ER or were admitted for hyponatremia or seizures in the 72 hours post-DDAVP administration.

Conclusion: Maintenance of a fluid restriction protocol effectively deterred negative outcomes in this cohort. However, a significant fluid volume was administered in nearly a third of patients despite the restrictions. Given the risk of hyponatremia, and limited compliance with fluid restrictions, postoperative sodium levels should be recorded in following DDAVP administration to assess the possibility of a hyponatremia and to reinforce the importance of fluid restrictions and their communication.

Poster # 438 | LIFE-THREATENING EFFUSIONS IN KAPOSIFORM HEMANGIOENDOTHELIOMA RESPONDING TO ORAL RAPAMYCIN

Lucy Duan, Samuele Renzi, Danielle Weidman, Nicolas Waespe, Rose Chami, Michelle Fantauzzi, Michaela Cada, Manuel Carcao

The Hospital for Sick Children, Toronto, Ontario, Canada

Background: Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor that may be associated with a potentially life-threatening consumptive coagulopathy known as Kasabach-Merritt Syndrome (KMP). There are currently no standardized treatment protocols for KMP-associated KHE that have been validated in clinical trials. Since 2013, mTOR inhibitors (beginning with rapamycin) have changed the available therapeutic options for the treatment of vascular malformations including KHE.

Objectives: To describe a complex case of KHE with KMP and response to rapamycin therapy.

Design/Method: A case-report of a male term-infant with KHE associated with KMP. Literature review performed.

Results: A male fetus required in utero insertion of a pleuroamniotic shunt for bilateral pleural effusions diagnosed antenatally by ultrasound. Shortly after delivery at term, he developed respiratory distress and was found to have reaccumulation of the pleural effusions. Blood work on day 1 of life showed a platelet count of 157,000/μL, which then decreased precipitously. He demonstrated schistocytes on blood-smear, signs of consumptive coagulopathy with hypofibrinogenemia and high D-dimers, and compensatory reticulocytosis. He required multiple transfusions and admissions to the Intensive Care Unit for respiratory support. Investigations ruled out congenital TTP, neonatal alloimmune thrombocytopenia, and Noonan syndrome. Given high clinical suspicion for an underlying vascular lesion causing KMP, a full body MRI without contrast was undertaken. This showed a focal area of suspicious signal intensity in the upper paraspinal musculature. An ultrasound and MRI with contrast demonstrated an extensive infiltrative vascular lesion involving the paraspinal musculature, prevertebral space, posterior extrapleural space, mediastinum, and neck. The child was commenced on prednisone (2mg/kg/day) and rapamycin (0.9 mg/m2 twice/day). There was no clinical or laboratory improvement after one month. A biopsy was performed which confirmed KHE. In the second month of rapamycin therapy, the platelet count gradually normalized and the patient was discharged from hospital at 3.5-months of life. Prednisone was weaned off at 4.5 months of life. A repeat MRI at 7 months showed significant reduction in the KHE. He is now almost 2 years into therapy and doing well.

Conclusion: This is a unique case of KHE with KMP that initially presented with extensive and recurrent pleural and pericardial effusions. This case demonstrates the importance of suspecting an underlying vascular malformation in the presence of KMP. Our patient had a delayed but overall good response to rapamycin. Further studies investigating duration of rapamycin therapy is key for the optimal management of these patients.

Poster # 439 | PREVALENCE AND BLEEDING PHENOTYPE OF COMBINED DEFICIENCIES IN FACTOR VIII AND VON WILLEBRAND FACTOR

Rosa Diaz, Donald Mahoney, Lakshmi Srivaths, Donald Yee

Texas Children's Hospital, Houston, Texas, United States

Background: Since Von Willebrand disease (VWD) is the most common inherited bleeding disorder, it must co-exist with other less common bleeding disorders in some dually affected patients. However, reports of combined deficiencies in factor VIII (FVIII) and von Willebrand factor (VWF) are rare.

Objectives: To study the prevalence and bleeding phenotype of combined deficiencies of FVIII and VWF in males with hemophilia A in a Hemophilia Treatment center.

Design/Method: We retrospectively reviewed the electronic medical records of 99 males with hemophilia A followed at our institution during the past 10 years. The primary and secondary outcomes for the study were (1) the prevalence of combined FVIII and VWF deficiencies and (2) the bleeding phenotype of these patients.

Results: We identified VWF deficiencies in 9% (n = 9) of the patients with hemophilia A. Most (n = 6, 67%) patients were tested for VWF deficiency as part of the initial hemostatic evaluation, but one-third were tested due to clinical concern for inadequate response to FVIII concentrate. The median duration of follow up was 9.5 years (range 3.4 to 17.2). Patients were referred to our clinic at a median age of 12 months (range 0 to 6 years) for evaluation of easy bruising (n = 4, 45%), mucosal (n = 3, 33%) and surgical bleeding (n = 2, 22%). Primary diagnoses included 4 with severe, 3 moderate and 2 mild discrepant hemophilia A. Secondary diagnoses included 6 with low VWF activity, 2 type 1 VWD and 1 with type 2 unclassified. Patients experienced episodes of musculoskeletal (n = 7, 78%), mucocutaneous (n = 6, 67%) and CNS bleeding (n = 1, 11%). A total of 8 patients received factor prophylaxis. Half of the patients were initially treated with FVIII concentrates but subsequently changed to combined FVIII/VWF products due to the frequency of breakthrough bleeding despite good compliance. All patients are on combined FVIII/VWF products at the time of this review. A total of 7 (78%) of this cohort developed chronic joint disease manifest as decreased range of motion and/or abnormal MRI findings.

Conclusion: Combined deficiencies of FVIII and VWF were present in 9% of our center's hemophilia patients. These patients exhibited a severe bleeding phenotype as evidenced by the high frequency of hemarthrosis, need for prophylaxis and high prevalence of chronic joint disease. While the optimal treatment strategy remains to be elucidated, early recognition of a combined deficiency may have important clinical implications, particularly in patients who demonstrate a suboptimal response to FVIII concentrate alone.

Poster # 440 | FIRST CASE OF CYTOPENIAS IN THE SETTING OF CEREBRAL CAVERNOUS MALFORMATION 3

Clay Cohen, Katie Bergstrom, Ghadir Sasa

Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, United States

Background: Childhood neutropenia is heterogeneous and may be congenital or acquired. Cerebral cavernous malformation 3 (CCM3) is a neurovascular malformation disorder where lesions consist of low flow, dilated capillary endothelial channels with increased permeability, predisposing to hemorrhage and thrombosis. Programmed Cell Death Protein 10 (PDCD10) activity has been implicated in glia and neuron migration, and recently linked to the dysregulation of the actin and microtubule cytoskeleton, thereby affecting cellular morphology and migration. Variants of PDCD10 encoding PDCD10 have been associated with CCM3. CCM3 causes a greater and earlier disease burden than other CCMs, with 26% presenting younger than 10 years. Some patients have associated extra-neuronal manifestations, suggesting that PDCD10 plays a role in other tissues.

Objectives: We describe a patient with significant blood cytopenias associated with CCM3.

Design/Method: Retrospective chart review to obtain patient data.

Results: An 8-month old female presented with seizure and was found to have multiple intracranial cystic lesions and abscesses due to S. pneumonia serotype 33F. During her treatment, she developed anemia (hemoglobin 7.6-8.7 g/dL), thrombocytopenia (platelets 73,000-128,000 cells/L), and profound neutropenia (absolute neutrophil counts of zero). Initial bone marrow evaluation revealed a normocellular marrow but with marked granulocytic hypoplasia and 38% hematogones on flow cytometry. Florescent in situ hybridization excluded cytogenetic changes characteristic of myelodysplastic syndrome. Further evaluation included testing for neutrophil antibodies, chromosome breakage, and telomere length and results were normal. Whole exome sequencing excluded mutations affecting congenital neutropenia genes, but detected a de novo PDCD10 variant (c.474+5G>A), thereby diagnosing CCM3. The neutropenia has responded well to granulocyte colony stimulation factor (GCSF), which is still needed at 26 months of age. Moreover, the thrombocytopenia has progressed, requiring periodic platelet transfusions. Over time, the bone marrow hematogone population has decreased to 8% at 20 months of age, though the granulocytic hypoplasia persists.

Conclusion: Our case describes the first patient with neutropenia and thrombocytopenia associated with CCM3. We hypothesize the PDCD10 variant is the etiology of bone marrow dysfunction due to its role in actin and microtubule cytoskeleton formation, akin to the pathophysiology of X-linked neutropenia. Supportive features of an underlying genetic cause of marrow dysfunction include the persistence of cytopenias beyond infection resolution as well as presence of hematogones. Hematogones were previously reported to occur in patients with other congenital neutropenia disorders, indicating they could be a feature of congenital neutropenia and may be reactive to surrounding cell apoptosis. Further testing of PDCD10 role in hematopoiesis should be explored.

Poster # 441 | A PILOT STUDY OF SOCIAL AND ACADEMIC IMPLICATIONS OF HEAVY MENSTRUAL BLEEDING IN ADOLESCENT AND YOUNG ADULT FEMALES

Anjali Pawar, Jessica Cheng, Angela Tran, Ranjani Krishnan

University of California Davis Health, Sacramento, California, United States

Background: 10–15% of adult women will suffer from heavy menstrual bleeding (HMB) during their lifetime. 90% of women with inherited bleeding disorders suffer from HMB. There is a paucity of data about HMB among adolescents and young adults (AYA), a population in which HMB may have large social and educational effects.

Objectives: To study the social and academic implications of HMB in an AYA population.

Design/Method: This is a questionnaire based survey conducted in a medium-sized city in California. We recruited females 14–24 years of age from one high school and from local university. The questionnaire was set up in Research Electronic Data Capture (REDCap) at our institute which allowed us to obtain objective data about the respondents' menstrual cycles. A link was sent to the high school students via their online portal SchoolLoop and to the university students via social media and word of mouth. Data was collected over 12 weeks from May 2017 to August 2017.

Results: We received 145 replies, some were not complete. Using regression analysis, data was analyzed from 115 respondents in the age group of 18–24 (with a mean age of 19) years. We developed a composite score for HMB based on factors including saturation levels, number of pads, duration of bleeding, soaking of a pad within two hours, passage of clots, size and number of clots, and gushing sensation. We conducted statistical analysis of the drivers and implications of HMB based on the composite score. Results indicate that having a relative with HMB, having other bleeding problems, and having anemia are drivers of higher HMB score. The results also indicate that HMB adversely affects quality of life as measured by participation in sports, social activities, after-school activities, tiredness, absenteeism, and GPA. HMB is also associated with increased rates of anemia and use of anti-depressants. HMB-driven anemia further adversely affects GPA. Under-represented minorities are more likely to have a higher HMB score, as well as an increased adverse effect of HMB on GPA.

Conclusion: The results suggest that the social costs of HMB are pervasive in the AYA population, and especially pronounced among minorities. A relative with HMB is a significant driver of heavy menstrual bleeding. A hemostatic screen should be included when assessing the AYA population with HMB.

Poster # 442 | WHY WE SHOULD TREAT HEMANGIOMA-ASSOCIATED HYPOTHYROIDISM WITH TRIIODOTHYRONINE (T3)

Jennifer Mayer, Allen Root, Stephen Rottgers, Mark Bittles, Michael Gallant

Johns Hopkins All Children's Hospital, St. Petersburg, Florida, United States

Background: Propranolol is a non-cardioselective beta blocker medication frequently prescribed for hemangiomas and hyperthyroidism. Propranolol inhibits types I and II iodothyronine deiodinases, enzymes that convert bioinactive thyroxine (T4) into bioactive triiodothyronine (T3). Hypothyroidism is a well-recognized complication of diffuse hepatic hemangiomas that produce type III deiodinase, an enzyme that converts T4 into bioinactive reverse T3 and T3 into diiodothyronine. Thyroxine is typically selected for replacement in this population, even though doses up to 60% above physiologic may be necessary. We hypothesized that low dose, nearly physiologic T3 would be safer and equally effective because it bypasses propranolol's impact on the pituitary-thyroid axis.

Objectives: We report an infant with diffuse hepatic hemangiomatosis and acquired hypothyroidism successfully treated with propranolol, prednisone, and triiodothyronine.

Design/Method: A 7mo healthy female presented with abdominal distension, poor oral intake, and hepatomegaly. MRI confirmed diffuse hepatic hemangiomatosis, the largest lesion measuring 4.4 cm by 3.9 cm. Thyrotropin (TSH) was elevated at 47.9 (Reference Range* 0.5-6 mcgIU/mL),

total T3# 165 (RR 60–300 ng/dL), and total T4^ 18.8 (RR 6–14 mcg/dL). Treatment was started with prednisone (2 mg/kg/day) for three weeks, propranolol (3 mg/kg/day) and T3 (0.64mcg/kg/day). The T3 dose was slowly titrated to a maximum of 1.72 mcg/kg/day.

Results: Thyroid hormone levels rapidly improved on T3 replacement. After two weeks, the TSH was 14.4, TT3 92, and TT4 16.5. After eight months, the TSH was 2.9, TT3 161, and TT4 10.1. At twelve months, the TSH dropped to 0.6, TT3 294, and TT4 3.7, suggesting decreased tumor production of type III iodothyronine deiodinase. Liver MRI confirmed fewer hemangiomas, largest being 1.3 cm by 1.6 cm. The patient's T3 dose was reduced. Both propranolol and T3 were discontinued after twenty-four months of treatment. One year off all therapy, this child has normal growth and development, only two <1.3cm hepatic hemangiomas and no evidence of hypothyroidism (TSH 2.2; TT3 153; TT4 6.4).

Conclusion: T3 at near physiologic doses corrects the consumptive hypothyroidism associated with diffuse hepatic hemangiomas. T3 replacement is preferable to thyroxine due to its lower risk of rebound hyperthyroidism as the hemangiomas involute and type III deiodinase production declines. There are two prior case reports describing T3 use without T4, one employing propranolol and the other utilizing steroids for hemangioma management. This is the first case report with long term follow-up of a child treated with multimodal therapy including propranolol, prednisone, and triiodothyronine. *RR = reference range; #TT3 = total T3; ^TT4 = total T4

Poster # 444 | MULTIFOCAL LYMPHANGIOENDOTHELIOMATOSIS WITH THROMBOCYTOPENIA: DIAGNOSIS AND TREATMENT OF AN INFANT WITH UNCOMMON FINDINGS OF A RARE DISORDER

Rebecca MacDonell-Yilmaz, Thomas Renaud

Hasbro Children's Hospital, Providence, Rhode Island, United States

Background: Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) is a rare congenital disorder first described in 2004 that is characterized by multiple vascular abnormalities commonly involving the skin and gastrointestinal tract as well as consumptive coagulopathy often resulting in GI bleeding in infancy(1).

Objectives: To describe an unusual presentation and successful management of MLT in a neonate.

Design/Method: Baby H was born at full term after a pregnancy complicated by maternal sinus venous thrombosis requiring anticoagulation beginning at 28 weeks. At birth, she was diagnosed with multiple hemangiomas based on clinical exam. At two weeks of age, she developed melena and hematemesis. CBC revealed platelet count of 70 and she was referred to the ED. Abdominal ultrasound was concerning for abnormal hepatic waveform; CXR showed multiple pulmonary nodules. Workup revealed no other lesions and no further hematologic abnormalities. Biopsy of presumed hemangioma ultimately revealed a smooth muscle-lined vascular proliferation without GLUT-1 immunoreactivity, consistent with MLT. Her early course was complicated by an acute hemodynamically significant GI bleed; esophagogastroduodenoscopy identified six bleeding vascular malformations within the stomach that were injected with epinephrine and sclerosed with successful hemostasis. She received multiple PRBC and platelet transfusions. Central access was obtained and she was started on oral Sirolimus based on previous reports of successful use in management of vascular malformations given its antiangiogenic and immunosuppressive effects (2). She has tolerated it well with no evidence of toxicity and has achieved a partial response with stable of hemoglobin >8 and platelet count >90. Cutaneous lesions have diminished in intensity and she has had no further signs of GI bleeding. She receives Pentamidine for PCP prophylaxis. She continues to have appropriate growth and development.

Results: We describe here an unusual presentation of an already rare disease. While cutaneous and GI lesions are typical of MLT, pulmonary involvement is not well-described in the literature. Early identification of tissue-based diagnosis enabled timely stabilization and treatment of the patient. Five months later, she continues to tolerate Sirolimus and has shown significant response with diminished coloration of cutaneous lesions, stable blood counts, and no further bleeding.

Conclusion: MLT is a relatively newly-recognized disorder with significant phenotypic variability. Given that bleeding secondary to a Kasabach-Merritt-type consumptive thrombocytopenia is the major cause of morbidity and mortality in the first year of life in children with MLT, it is essential to recognize the diagnosis and initiate appropriate treatment as early as possible. 1North, Arch Dermatol, 2004 2Adams, Pediatrics, 2016

Poster # 446 | CHARACTERIZING ADOLESCENTS WITH HEAVY MENSTRUAL BLEEDING AND GENERALIZED JOINT HYPERMOBILITY

Nicole Kendel, Fareeda Haamid, Myra Christian-Rancy, Sarah O'Brien

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: Patients with generalized joint hypermobility (JHM) may experience easy bruising or bleeding given the association between these symptoms and abnormalities in collagen, a required component of primary hemostasis. Heavy menstrual bleeding (HMB) is a common initial presentation for females with underlying hemostatic defects and may be the sole manifestation of a bleeding disorder. However, limited reports describe JHM as a cause of HMB, leading to under recognition.

Objectives: To describe the clinical characteristics and management of young women presenting with HMB in the setting of JHM.

Design/Method: This study utilized our HMB Research Registry. We included subjects 11–18 years, seen in the Nationwide Children's Young Women's Hematology Clinic between February 2014 and November 2017 with both HMB and JHM. Medical records were retrospectively reviewed for history of presentation, Menorrhagia Impact Questionnaire (MIQ): a validated quality-of-life tool for females with HMB, medication profiles and relevant laboratory studies.

Results: Twenty-five patients met inclusion criteria (median age 15 years, range 11–18) with an average Beighton score of 6.2 (range 4 to 9). Participants presented an average of 3.2 years (range 5 months to 6 years) after menarche despite 76% of patients reporting heavy to very heavy menses since menarche. According to the MIQ responses, most participants expressed HMB-associated limitations in physical activities (84%), social activities (68%), and work or school activities (64%). Of the participants, 92% reported bleeding symptoms in addition to HMB, most commonly easy bruising (56%), epistaxis (48%) and cutaneous bleeding (44%). Forty percent of young women presented with anemia due to chronic blood loss. Results of hemostatic testing were unremarkable, with the exception of one patient who was also found to have type 1 von Willebrand disease. Additionally, 44% of females reported arthralgia, with knees and ankles the most commonly affected joints. At time of presentation, 32% of participants reported failure of initial therapies and most patients (88%) were managed long-term with oral hormone therapy.

Conclusion: In a small population of young women found to have JHM who initially presented with HMB, patients were likely to have prior bleeding symptoms as well as substantial delays from menarche to timing of presentation at our Young Women's Hematology clinic despite limitations in activities of daily life. Greater awareness of the associations between bleeding symptoms and JHM, despite typically normal hemostatic laboratory results, is necessary so that patients can more easily be identified and receive appropriate therapy.

Poster # 501 | PARENTAL EDUCATION OF THE CENTRAL LINE CARE BUNDLE IS ASSOCIATED WITH A LOWER AMBULATORY CENTRAL LINE ASSOCIATED BLOODSTREAM INFECTION RATE

Daniel Willis, Aditya H. Gaur, Jonathan Rodean, Troy Richardson, Cynthia Winkle, Megan Esporas, Frederick Huang

Children's Hospital Association Childhood Cancer and Blood Disorders Network, Lenexa, Kansas, United States

Background: Central line associated bloodstream infections (CLABSI) are a significant cause of morbidity and mortality for pediatric oncology patients. Proper central line (CL) management plays an important role in reducing the risk of CLABSI. The impact of CL care practices involving the home environment on ambulatory CLABSI rates is unknown. The Children's Hospital Association Childhood Cancer and Blood Disorders Network (CCBDN) Practice Inventory (PI) provides a means of addressing this knowledge gap. The CCBDN is a collaborative focusing on CLABSI prevention, and the PI is a database containing information about the CL care practices of the CCBDN member hospitals.

Objectives: The objective is to determine the impact of CL care practices involving the home environment on ambulatory CLABSI rates.

Design/Method: Information for the PI was collected through a comprehensive survey that was completed annually by the CCBDN member hospitals. Responses to the questions about CL care practices involving the home environment were selected from the PI for 2015. Ambulatory CLABSI rates and ambulatory total bloodstream infection (BSI) rates were obtained from another CCBDN database. The proportion of hospitals that did or did not employ a particular CL care practice was tallied. The mean ambulatory CLABSI rate and mean ambulatory total BSI rate of the hospitals that did or did not employ a particular CL care practice were compared using generalized linear model techniques assuming an underlying negative binomial distribution.

Results: Twenty-five hospitals submitted responses to the 8 questions about CL care practices involving the home environment. One hospital was excluded for lack of BSI data. Sixty-three percent of the hospitals programmatically educated parents about all aspects of the CL care bundle. The mean ambulatory CLABSI rate for the hospitals that educated parents was significantly lower than that of the hospitals that did not (0.20 infections/1000 CL days vs. 0.30 infections/1000 CL days; $p = 0.02$). The mean ambulatory total BSI rate was also significantly lower (0.35 infections/1000 CL days vs. 0.53 infections/1000 CL days; $p = 0.01$). The mean ambulatory

CLABSI rates and mean ambulatory total BSI rates were not significantly different for the other 7 CL care practices.

Conclusion: An analysis of CL care practices involving the home environment reveals that parental education of all aspects of the CL care bundle is associated with a lower ambulatory CLABSI rate and lower ambulatory total BSI rate. This finding highlights the importance of systematically teaching family members the proper method of handling CL.

Poster # 502 | CHEMOTHERAPY INDUCED NAUSEA VOMITING: NURSING ASSESSMENT AND UTILITY OF THE BAXTER RETCHING FACES (BARF) NAUSEA SCALE

Lindsey Young

Children's National Health System, Washington, District of Columbia, United States

Background: Children undergoing chemotherapy are at a high risk for developing nausea. Dr. Amy Baxter in collaboration with pediatric oncology patients and nurses, developed and validated a pictorial nausea rating scale for children aged 7–18 years, called the Baxter Retching Faces (BARF) Nausea Scale. Staff nurses at a large, academic, pediatric hospital located within Washington, D.C., have identified variability in nursing assessment and documentation of chemotherapy induced nausea and vomiting (CINV) in pediatric oncology patients. The purpose of this quality improvement project was to utilize the BARF scale to standardize assessment and documentation of nausea in pediatric oncology patients receiving chemotherapy.

Objectives: The primary aims of this project were to: assess feasibility of the BARF scale in clinical practice; increase nursing knowledge about CINV through education sessions; increase documentation of nausea assessments through the use of the scale. The secondary aim of this project was to: increase the recognition of nausea through the use of a standardized assessment tool.

Design/Method: The PDSA Model was used to guide the design and implementation plan. In the first phase of the project data was collected to identify the prevalence of nausea in patients admitted for chemotherapy in the prior three months. Education sessions discussing CINV and the utilization of the BARF scale were conducted. Pre and post assessment of nurses' knowledge of CINV and documentation were assessed. In the second phase the BARF scale was implemented into practice. Nurses were asked to utilize the BARF scale to assess and document nausea scores in patients, aged 7 to 18 years, receiving chemotherapy. At the end of the implementation period nurses were surveyed about the feasibility of the scale. Post data was collected to identify the prevalence of nausea documented in the electronic health record. This project was undertaken as a Quality Improvement Initiative at Children's National and it does not constitute as human subjects research. As such it was not under the oversight of the Institutional Review Board.

Results: All data has been collected; however complete data analysis will be conducted in the upcoming weeks.

Conclusion: Key preliminary results indicate perception of clinical feasibility of the BARF scale and an increase in nursing knowledge following education sessions. Additional results indicate the use of the BARF scale did not increase recognition of nausea; however the use of the scale did increase nursing documentation of nausea. Baxter AL, Watcha MF, Baxter WV, Leong T, Wyatt MM, Pediatrics, 2011.

Poster # 503 | RESULTS OF A NATIONAL PROVIDER SURVEY IN SICKLE CELL DISEASE MANAGEMENT

Julie Kanter Washko, Marsha Treadwell, Anne Marsh, Naomi Bardach, Michael Cabana

University of California at San Francisco, San Fransisco, California, United States

Background: Sickle Cell Disease (SCD) is the most common inherited blood disorder in the United States (US); however, there are few quality measurements to evaluate SCD practice. In 2014, the NHLBI published guidelines that include two key interventions for children with sickle cell anemia (SCA): the use of transcranial Doppler (TCD) screening for stroke prevention and Hydroxyurea (HU) to prevent SCD pain crisis.

Objectives: We conducted a national survey of SCD management sent to providers in over 20 institutions in the US to better assess knowledge of the guidelines and barriers to HU counseling and TCD screening guideline implementation. It was hypothesized that the barriers to TCD screening are different than barriers to HU counseling and prescribing.

Design/Method: A 33-question anonymous survey was sent to 49 providers by mail (follow-up by email). Survey themes included NHLBI guidelines knowledge and comfort with understanding and implementing both TCD screening and HU use.

Results: The response rate was 59% (29/49) however one survey was incomplete. Thus, 28 were analyzed in the final data set. All of the respondents are in active practice, 96%

in academics and all care for children with SCD. The majority of providers (96%) felt "very" or "extremely" confident in their knowledge of TCD screening and interpretation. Similarly, 100% of providers felt "very" or "extremely" familiar with HU dosing and management. For TCD screening, 36% of providers estimated their screening rates were >90% and 64% providers felt their annual screening rates were 75–90%. The two biggest barriers to TCD screening noted by providers (of moderate to extreme significance) included: lack of support staff (36%) and lack of time during a patient visit (26%). Regarding HU prescribing practices, 71% of providers offered HU to at least 90% of children with SCA over nine months of age. The biggest barrier to HU prescribing noted by 46% of providers was concerns about patient adherence or access to the medication. Only 7% providers felt that lack of support staff was a moderately significant barrier to HU prescribing.

Conclusion: The pediatric SCD providers surveyed all have access to the NHLBI guidelines. Despite widespread guideline knowledge, there are different barriers for TCD screening versus HU prescribing, which prevent optimal implementation. As a result, although both recommendations are from the same NHLBI guideline, they likely will require different implementation strategies (systems-based interventions for TCD screening; interventions to improve patient adherence for HU counseling) to improve outcomes.

Poster # 504 | NON-INVASIVE PATHOGEN DETECTION IN PEDIATRIC ONCOLOGY AND HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS AT RISK FOR DEEP FUNGAL INFECTIONS USING NEXT GENERATION SEQUENCING

Amy Armstrong, Jenna Rossoff, Desiree Hollemon, David Hong, William Muller, Sonali Chaudhury

Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, United States

Background: Invasive fungal disease (IFD) is a major cause of mortality and morbidity among pediatric immunocompromised patients such as those who receive chemotherapy or hematopoietic stem cell transplantation. The current diagnostic 'gold standard' of IFD remains culture of infected tissue obtained by biopsy. Noninvasive biomarker testing for galactomannan or 1,3-beta-D-glucan (BG) can have low sensitivity and does not provide species-level identification. Next-generation sequencing (NGS) of cell-free plasma is a promising noninvasive approach to providing species-level identification of IFD via a blood test and can further guide specific treatment.

Objectives: Describe the incidence of positivity for fungal specific pathogens on NGS analysis in a high-risk immunocompromised pediatric population and correlate results with other 'standard' infectious studies if performed.

Design/Method: Immunocompromised pediatric patients with suspected IFD were enrolled and plasma was collected at time of enrollment. NGS was performed on extracted DNA in cell-free plasma (Karius, Redwood City, CA). After removing human reads, remaining sequences were aligned to a curated database including 1251 pathogens. Organisms present at a significance-level above a predefined threshold were reported.

Results: Twenty-seven samples from 33 enrolled patients have been processed thus far. Of these 27 subjects, 14 were enrolled for prolonged febrile neutropenia (≥96 hours) despite broad-spectrum antibiotics, 5 for recrudescent febrile neutropenia, 5 for abnormal imaging, and 3 with other findings. After evaluation of routine studies performed, 4 patients met criteria for proven IFD, 2 for probable IFD, and 9 for possible IFD using EORTC/MSG guidelines. The NGS plasma test identified the same pathogen as cultured from infected tissue or blood in 100% (4/4) of the proven cases. In the probable cases, Pneumocystis jirovecii was identified in a patient with a positive BG (389 pg/mL) and pneumonia. Among the possible cases, Toxoplasma gondii was detected in a patient with prolonged febrile neutropenia and lung imaging suggestive of IFD. Additionally, Candida glabrata was isolated in a patient with prolonged febrile neutropenia but no other criteria for IFD. Numerous pathogens were also identified that could explain the above clinical parameters, including HSV1, CMV, VZV, HHV6, EBV, BK polyoma virus, and Ureaplasma parvum.

Conclusion: The cell-free plasma NGS test can detect invasive fungal infections from blood. The test identified fungi from proven IFD, detected pathogens in both probable and possible IFD cases, and is a useful diagnostic tool in the evaluation of IFD. Supplies and sample shipment and processing supported by Karius, Inc.

Poster # 505 | STRATEGIES FOR IMPLEMENTING AN EFFECTIVE MORBIDITY, MORTALITY, AND IMPROVEMENT (MMI) CONFERENCE

YoungNa Lee-Kim, Sarah Whittle, Timothy Porea, Ernest Frugé, Maria Gramatges

Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, United States

Background: Practicing medicine is a lifelong learning process. As noted in the Institute of Medicine's seminal report, 'To Err is Human,' adverse outcomes do not typically result from individual recklessness; rather, they result from faulty systems, processes, or conditions that provide an environment conducive to making a mistake, or failing to prevent one. Learning to systematically review errors and translate lessons learned into quality improvement (QI) initiatives is a critical component of practice-based learning and improvement for practitioners at all career levels.

Objectives: To develop a methodical, self-reflective and non-threatening approach to incident analysis and translation of lessons learned into QI initiatives.

Design/Method: We used a validated, structured case audit approach, modified from Szostek et al: 1) review all documentation relating to the case and identify all health care providers involved; 2) interview stakeholders, including those who directly provided and supported care; 3) use a QI tool to conduct a root-cause analysis; 4) identify a systems issue that contributed to the outcome; and 5) propose systems-level interventions and prioritize initiatives based on effort-yield projections.

Results: PDSA Cycle 1: Plan: Establish a committee to 1) identify potential cases, 2) triage cases for conference presentation, 3) determine timing and frequency of conferences, 4) develop a training manual, 5) record identified QI initiatives. Do: We established a quarterly section-wide meeting to which all members of the Pediatric Hematology/Oncology service are invited, including administrative and nursing leadership. We developed a training manual and structured presentation template. Prioritized cases were discussed in advance during multidisciplinary case review sessions, and presented by senior fellows who were instructed to focus discussion on potential opportunities for QI. Study: We identified 23 cases, 10 meeting criteria for MMI presentation. QI initiatives identified from this conference resulted in a number of systemic practice changes; however, we encountered challenges to sustaining these changes over time. Act: Objectives for the next PDSA cycle are to 1) establish a method for tracking the adherence to recommended changes in practice, 2) maximize sustainability by integrating QI initiatives into institutional QI leadership and practice standardization committees.

Conclusion: We have successfully implemented an MMI conference that meets 5 out of 6 Institute of Medicine Quality domains: safety, effectiveness, patient-centeredness, timeliness, and efficiency. A standardized, consistent approach to MMI presentations that includes identification of contributing factors and specific QI implications has the potential for improving both provider education and patient care/safety.

Poster # 506 | COMMUNICATION OF PEDIATRIC CANCER DIAGNOSES: THE EXPERIENCES OF CAREGIVERS, PATIENTS AND GENERAL PEDIATRIC PROVIDERS

Wynne Callon, Stacy Cooper

Johns Hopkins University, Baltimore, Maryland, United States

Background: Receiving a cancer diagnosis is a life-changing event for patients and caregivers, although little is known about the experience. While some oncologists receive dedicated training in delivering this bad news, the initial conversation is often with a primary pediatrician, and these providers often feel they do not receive adequate training in the communication of a cancer diagnosis.

Objectives: Our objectives were two-fold: First, to better define the experiences of caregivers/patients when told of a cancer diagnosis, and to query how caregivers/patients believe providers can improve the disclosure of this bad news. Secondly, to assess what, if any, training primary pediatricians received in this skill, and to assess how comfortable providers in various settings and stages of training are with communicating cancer diagnoses.

Design/Method: From November 2016–2017, semi-structured, in-depth interviews were conducted with pediatric oncology patients and caregivers of patients (N = 6) diagnosed in the past year regarding their experiences receiving the diagnosis at our institution. In addition, pediatric residents (N = 6), outpatient pediatric primary care physicians and pediatric emergency medicine physicians (N = 6) were interviewed regarding their experiences delivering cancer diagnoses. Interviews were analyzed following principles of thematic analysis.

Results: Interviewers with patients and caregivers had two common themes: 1) All emphasized their wish for direct and thorough information; 2) both patients and caregivers emphasized the gratitude they felt for physicians who gave them hope by emphasizing the good prognosis of their child's cancer. Lack of training in this area, as well as lack of comfort delivering this news was common will all providers. Additionally, providers report variable approaches to giving bad news, including 1) whether to tell caregivers separately or tell the child and parents together, and 2) whether to give favorable prognostic information. Additionally, attending physicians also differed significantly in their approaches to teaching residents. While some believed residents should give the news to gain experience, others felt that this is not appropriate if residents are inexperienced. Only one resident reported ever receiving feedback on his communication skills in this type of discussion.

Conclusion: We plan to build on these interviews to develop a national survey of patients, caregivers, and providers to better understand the issues surrounding this discussion. We will use the findings to develop a communication curriculum for pediatric residents, focusing on the discussions that occur in the outpatient setting by primary pediatricians.

Poster # 507 | KNOWLEDGE OF AND ATTITUDES TOWARDS HPV VACCINE IN PREADOLESCENTS AND TEENS

Lauren Raney, Renee Gardner, Elizabeth Owers, Pinki Prasad

Louisiana State University Health Sciences Center, New Orleans, Louisiana, United States

Background: Human Papilloma Virus (HPV), common in both females and males, is responsible for pathologies ranging from benign genital warts to cervical and penile cancer. HPV strains 16 and 18 are responsible for 21,000 malignancies each year in the United States, and one third of them arise in men. Pharmaceutical companies have now developed a vaccine that will help prevent the virus-associated malignancies. The CDC initially recommended that females ages 11–26 years receive the vaccine series, then starting in 2011 they expanded the eligibility to males ages 11–21 years. Despite being widely available and highly publicized, only 40% of eligible females receive the full vaccine series.

Objectives: This study aims to assess the knowledge of HPV, the attitudes towards the HPV vaccine, and identify barriers preventing its full utilization. Once identified, we aim to overcome the barrier(s) in order to improve vaccination rates in eligible adolescents.

Design/Method: We distributed a standardized questionnaire to the parents of eligible female and male patients in our pediatric hematology-oncology clinic. It assessed the parents' knowledge of HPV and the vaccine, their views of the vaccine, and reasons why they may oppose it.

Results: Approximately 80% of parents claim they have been educated about HPV, mostly by their primary care physician. However, 35% did not know what disorders HPV caused; 35% felt the vaccine should not be added to the typical vaccine schedule; 25% of parents do not intend to vaccinate their child. Of those that opposed the vaccine, one-third were concerned about potential side effects and nearly 35% feel they do not have enough information. Additionally, 25% of parents are not aware that the vaccine is available at their child's doctor and only 30% of parents have discussed the HPV vaccine with their child's doctor.

Conclusion: The largest barrier to the utilization of the HPV vaccine that we have identified appears to be lack of education. As a result, we have begun distributing the CDC's HPV and vaccine patient guide to our patients' families as an intervention. We are currently in the process of re-administering our survey to these families after implementing the intervention to assess its success in increasing both knowledge and utilization of the HPV vaccine.

Poster # 508 | EFFICACY OF SINGLE DOSE RASBURICASE (1.5 MG) FOR PROPHYLAXIS AND MANAGEMENT OF TUMOR LYSIS SYNDROME

Venkatraman Radhakrishnan, Ashwin Philips

Cancer Institute, Chennai, Chennai, Tamilnadu, India

Background: Rasburicase is a recombinant urate oxidase enzyme approved for use in tumor lysis syndrome (TLS) and it acts by reducing serum uric acid levels. Using rasburicase at the recommended dose of 0.2mg/kg/day for 5 days is expensive and it is not known whether this extended schedule is clinically beneficial compared to a single fixed dose of 1.5 mg.

Objectives: The aim of the present study was to evaluate the efficacy of single dose rasburicase 1.5 mg in prevention and management of TLS.

Design/Method: Rasburicase is available as single use 1.5 mg vial. At our institution a single dose of rasburicase 1.5 mg irrespective of bodyweight has been used in adults and in children a dose of 0.15 mg/kg (maximum 1.5 mg) has been used since 2012 for prevention and management of TLS and subsequent doses are given based on biochemical response and clinical condition. We retrospectively analysed the case records of patients who had received rasburicase from January 2012 to January 2017.

Results: The study included 186 patients with hematological malignancies who received rasburicase. Children accounted for 56.4% (n = 105) patients and males comprised 73% (n = 135). Rasburicase was used prophylactically in 59 (31.7%) patients, for laboratory TLS in 76 patients (40.8%) and for clinical TLS in 51 (27.4%) patients. Single fixed dose rasburicase prevented laboratory/clinical TLS in 87% of the prophylactic group and prevented clinical TLS in 72% of the laboratory TLS group. None of the patients in prophylactic and laboratory TLS group developed clinical TLS. However, majority of the patients with clinical TLS required more than one dose rasburicase.

Conclusion: Single dose of 1.5 mg (1 vial) rasburicase is efficient in preventing and managing laboratory TLS and is economically viable in resource constrained settings.

Poster # 509 | STANDARDIZING MEDICATION RECONCILIATION FOR A SAFE AND SUCCESSFUL DISCHARGE HOME IN NEWLY DIAGNOSED PEDIATRIC ONCOLOGY PATIENTS

Nicole Wood, Lauren Amos, Nicholas Clark, Chris Klockau, Karen Lewing, Alan Gamis

Children's Mercy Kansas City, Kansas City, Missouri, United States

Background: Medication reconciliation for newly diagnosed oncology patients is complicated and cumbersome. These patients are often admitted on no medications, and leave on multiple. Chemotherapy and supportive medications are crucial. Despite numerous individuals overseeing this process, prescribing errors or omissions still occur. When reviewing the literature, improvement occurs when there is an interprofessional and standardized process to medication reconciliation.

Objectives: This project's aim was to improve the accuracy of the discharge medication reconciliation process from 74% to 90% from February 2017-August 2017. The process measure was the percentage of patients discharged with an accurate checklist. Additional time for staff spent in completing the checklist and avoiding an increased error rate by changing the prescribing process were followed as balancing measures.

Design/Method: We created a discharge medication checklist which included a list of required home medications prescribed by the resident, ideally 24 hours prior to discharge. It required fellow or attending review and pharmacy to review the list and educate the family. Checklists were collected monthly and reviewed against the electronic medical record (EMR) for accuracy.

Results: Six PDSA cycles were completed. There were 2 errors during the data collection time frame. In PDSA cycle 1, a patient received acetaminophen for pain control which is avoided at home. In addition, this patient received diphenhydramine instead of ondansetron, which is preferred as an antiemetic. In PDSA cycle 4, a patient with a pending diagnosis was sent home with acetaminophen. Of note, this patient did not have a checklist completed upon discharge.

Conclusion: This project provides a novel and important method to standardize the discharge medication reconciliation process in a complex patient population. It clarifies which types of medications these patients need, provides pharmacy teaching to families which was not done previously, and prescribes discharge medications to families sooner. After the first medication reconciliation error, the checklist was revised. No further errors were made following revision, with the exception of one patient without a completed checklist at discharge. Our accuracy rate increased from 74% at baseline to 92% following implementation. We are in the process of making the checklist electronic and accessible in the EMR. In the interim between the end of data collection and implementation into the EMR, a leukemia patient was sent home without an epinephrine pen, further demonstrating the importance of this standardized discharge process. For this reason, we have re-instituted the checklist until the electronic version is available.

Poster # 510 | LOSS OF PROTECTIVE HUMORAL IMMUNITY AGAINST MEASLES IN PEDIATRIC ONCOLOGY PATIENTS: A RISK WITH THE RISE OF UNDERVACCINATION

Nupur Mittal, Stephen Dvorak, Paul Kent

Rush University Children's Hospital, Chicago, Illinois, United States

Background: Survivors of pediatric cancer are at risk of losing pre-existing protective antibodies to vaccine preventable diseases. In a prior study, 35% of children < 7 Years lost humoral immunity to measles as a result of chemotherapy induced alterations in immune system. Measles in recipients of immunosuppressive chemotherapy has mortality rates up to 50%. Because of volitional vaccine refusal, there has been a dramatic increase in measles infection from 63 cases in 2010 to 677 in 2014, including several statewide outbreaks. Small pediatric oncology practices frequently share floor/clinic space with the general pediatric patients putting them at risk for measles since virulence starts 48 hours prior to symptoms. There is no standard protocol for revaccinating post-chemotherapy patients.

Objectives: To assess measles risk based on serial humoral immune status in a cohort of pediatric oncology patients receiving intensive chemotherapy

Design/Method: Patients < 21 years age with known vaccination status receiving intensive chemotherapy between July 2015-June 2017 at our institution's pediatric oncology practice were included in this prospective study. Serial measles IgG antibodies were measured at diagnosis, 6 months and 12 months after initiation of chemotherapy using ELISA. Measles immunity was defined per lab standards. A comparison of pre-chemotherapy and serial post-chemotherapy immunization titers was made for all patients by diagnosis.

Results: The study population consisted of 31 children (17 male); 8 patients had ALL, 7 non-Hodgkin lymphoma, 11 sarcoma and 5 other solid tumors. Two patients (6.4%), both unvaccinated had non-protective measles antibody levels at

baseline. Of the remaining 29 patients, 13.7% patients (2 leukemia, 1 lymphoma and 1 Sarcoma) lost protective antibody titers at 6 months after initiation of chemotherapy and 27.5% (4 leukemia, 1 lymphoma and 3 sarcoma) at 12 months after initiation of therapy. 60% of the remaining 21 patients who retained measles antibody titers within protective range at 12 months also demonstrated a steady decline in antibody titers at 6 and 12 months from therapy initiation. The loss of protective measles humoral immunity occurred significantly more often in patients with leukemia compared to other malignancies.

Conclusion: Oncology patients in our practice undergoing intensive chemotherapy demonstrated progressive waning of protective measles IgG titers. Our data suggests that it should be standard practice to check all patients for measles humoral immunity prior to starting chemotherapy and at completion. Larger studies need to be performed to establish guidelines for revaccinating post-chemotherapy pediatric patients, an intervention that is easily applicable and of low cost.

Poster # 511 | COMPARING GFR ESTIMATING EQUATIONS, 24-HOUR URINE AND MEASURED IOHEXOL GFR IN PEDIATRIC PATIENTS WITH CANCER

Shirley Abraham, Craig Wong, Mary Vilay

University of New Mexico, Albuquerque, New Mexico, United States

Background: The accurate determination of glomerular filtration rate (GFR) is important to screen for acute kidney injury, to dose chemo- therapy, and to identify risk for chronic kidney disease.Being correlated with inulin clearance, measured GFR by iohexol plasma disappearance (iGFR) is a new gold standard for measurement of GFR in pediatric cohort studies. iGFR is based on the clearance of an exogenous marker and is unaffected by endogenous compounds or a patient's muscle mass.

Objectives: We compared iGFR with 24-hour urine creatinine clearance (24CrCl) and GFR estimating equations using serum creatinine (sCr) and serum cystatin C (cystC) in pediatric patients with cancer.

Design/Method: We recruited participants who were ages 6 to 16 yrs, continent of urine, and diagnosed with a malignancy in the past 5 years. Eligible subjects had stable kidney function for at least two weeks prior to the assessment of iGFR. Consented subjects had baseline assessments including height, weight and vital signs. Blood samples were obtained for serum chemistry, and time zero iohexol. iGFR determined by 5mL iohexol solution infused over 1–2 minutes followed by 10mL of sterile saline. Blood was drawn at 10, 30, 120 and 300 minutes.At the same time of iGFR, the 24CrCl was collected. iGFR was calculated using a two-compartment model and area under the curve. We compared iGFR to published GFR equations (Schwartz et al, Kidney Int 2012).

Results: Ten subjects (7 female/3male) agreed to participate. The distribution of diagnoses for the subjects: ALL = 6, lymphoma = 1, brain tumors = 2 and hepatocellular carcinoma = 1. Six patients were off therapy. The lower GFRs are noted in patients who had malignancies other than leukemia, likely due to the use of cisplatin based therapy. The average iGFR was 85ml/min/1.73m^2 whereas 24CrCl was 155.8 ml/min/1.73m^2; demonstrating the 24CrCl overestimates GFR compared to iGFR. Comparing iGFR to univariate equations using sCr, cystC, and the multivariate equation with both, the univariate cystC equation correlated well with iGFR; the others overestimated iGFR.

Conclusion: We found that 24CrCl overestimated iGFR. The univariate cystC equation better correlated to iGFR than equations with sCr. The poor performance of sCr based methods to assess GFR might be due to decreased muscle mass and inadequate nutritional status. Creatinine-based determinations of GFR alone, may not be accurate in this population. Further study is needed to determine if iGFR should be a standard of care to assess GFR in children with cancer particularly who are receiving nephrotoxic medications and incontinent of urine.

Poster # 512 | MANAGEMENT OF EARLY SEPSIS IN NEUTROPENIC PEDIATRIC ONCOLOGY PATIENTS IN AN ARTICLE 28 INSTITUTION IN THE OUTPATIENT SETTING TO OPTIMIZE PATIENT OUTCOME

Sucharita Bhaumik, Arsenia Asuncion, Brittany Francisco, Mark Weinblatt, Linda Skelley, Colleen Messmer

NYU Winthrop Hospital, Mineola, New York, United States

Background: Pediatric oncology patients undergoing chemotherapy through indwelling venous catheters are at increased risk for severe sepsis especially when neutropenic due to chemotherapy. Rapid triage and early recognition are essential because delayed initiation of antibiotics and fluids in these patients or delayed transfer to higher level of care after initial stabilization is associated with poor clinical outcome. Our pediatric oncology out-patient clinic is designated as an article 28 unit whereby the providers can initiate and give treatment such as intravenous fluid, antibiotics, chemotherapy and blood products.

Objectives: Global Aim- Optimize management of early sepsis and decreased morbidity, mortality and hospital length

of stay in the high risk pediatric oncology patients. Smart Aim- Improve timely management with initiation of fluids and antibiotics and transfer of septic patients to higher levels of care by 10% in 6 months in above patients

Design/Method: Multidisciplinary team with physicians and nurses was created. Retropective chart review of sepsis patients treated at the clinic from April 2016 to October 2016 was done using an audit sheet to identify the barriers in the delivery of care. Three patients were identified and data analyzed prior to intervention; two were analyzed post interventions. A key driver diagram was created by the group to drive intervention. A process map was designed to identify the different steps in the care of these patients to pinpoint areas needing improvement. Different timed data points were used starting from time of arrival to clinic, time to antibiotics and fluids and time to transfer to higher level of care. Rapid PDSA cycles were done to improve the processes and delivery of care. Run charts were created.

Results: There was an improvement close to the goal of 10 % for all data points used. PDSA cycles for improvement included conducting frequent mock codes with appropriate feedback real time coaching and process planning with nursing staff. We partnered with pharmacy for close loop communication with clinic staff and we improved communication between physicans at different levels.

Conclusion: Sepsis in neutropenic pediatric oncology patients is deadly and can be reversed with timely management at different levels. Given the promising results of the above project, we want re-inforcement of the processes to be a part of the daily practice of first line clinical staff. Eventually we will extend the principles learnt in management and triage of sepsis to other outpatient emergencies chemotherapy related anaphylaxis

Poster # 513 | IMPROVING HOSPITAL PRACTICES FOR THE PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING WITH EARLY PROPHYLACTIC USE OF OLANZAPINE IN CHILDREN WITH CANCER

Jessica Seaborn, Anderson Collier, Betty Herrington, Cynthia Karlson, Laura Newman

University of Mississippi Medical Center, Jackson, Mississippi, United States

Background: Chemotherapy-induced nausea and vomiting (CINV) is a common side effect in children receiving antineoplastic chemotherapy. Recommended prophylactic antiemetic medications are based on the classification of chemotherapy emetogenicity. However, despite appropriate use of these antiemetic agents, some patients will still experience nausea and/or vomiting. Children's Oncology Group clinical practice guidelines recommend the addition of olanzapine to prophylactic regimens for management of breakthrough CINV.

Objectives: Our pediatric hematology oncology center implemented a quality improvement (QI) project aimed to increase the use of olanzapine in pediatric cancer patients 7 years of age and older receiving moderately or highly emetogenic chemotherapy and experiencing breakthrough CINV over a 3 month period.

Design/Method: This QI project was conducted utilizing plan-do-study-act (PDSA) cycles. For the first PDSA cycle, baseline data was collected through chart review to determine the rate of olanzapine use for breakthrough CINV over a 6 month period from July 2016 to December 2016. Breakthrough CINV was defined as use of 2 or more doses of antiemetic agents other than those given for CINV prophylaxis. Guidelines for treatment of breakthrough CINV were reviewed with pediatric hematology/oncology attending physicians and fellows. Flyers were created that listed chemotherapy regimens considered moderately and highly emetogenic. If a patient experienced breakthrough CINV, a flyer was to be placed in the patient's roadmap binder to signal olanzapine should be added to the next chemotherapy block. Data was collected over a 1 month period in September 2017 following this first intervention. The second PDSA cycle consisted of didactic education and training of pediatric oncology nurses as well as pediatric residents regarding the addition of olanzapine for breakthrough CINV. Rates of olanzapine use were then collected from October 2017 through November 2017.

Results: Olanzapine use increased from 3.8% at baseline to 58.3% after the first PDSA cycle ($\chi 2 = 14.666$, $p = 0.000$). After the second PDSA cycle, olanzapine use increased another 14.1% to 72.4% ($\chi 2 = 0.777$, $p = 0.378$).

Conclusion: The administration of olanzapine was successfully increased by modifying patients' roadmaps after patients experienced breakthrough CINV as well as with education and training of pediatric oncology staff, fellows, residents, and nurses.

Poster # 514 | ASSESSING RISK OF HOSPITAL-ACQUIRED PEDIATRIC VENOUS THROMBOEMBOLISM USING A NOVEL SCORING SYSTEM

Zachary Prudowsky, Joseph Stanek, Stephanie Stafford, Bryce Kerlin, Sarah O'Brien, Riten Kumar

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: Venous thromboembolism (VTE) is increasingly affecting children. According to an administrative database study, there was a 70% increase in the incidence of VTE among children admitted to free-standing children's hospitals in the United States from 2001 to 2007. Risk factors for hospital-acquired VTE are well-known and well-studied in adults, with evidence-based preventative measures available. Similar guidelines are lacking for children.

Objectives: There is an ongoing national-initiative to develop and institute methods for screening and preventing hospital-acquired VTE in children. In 01/2014, Nationwide Children's Hospital instituted an electronic screening form required for all patients admitted ≥24 hours. Patients were scored and risk-stratified based on eight risk-categories. A summated score was used to determine the VTE risk level, and used to make prophylaxis recommendations for patients ≥18 years; as well as patients ≥14 years who were admitted to an intensive care (ICU), surgical, or trauma unit. The purpose of this IRB exempt, quality improvement initiative was to retrospectively review our experience with this risk-stratification tool.

Design/Method: Retrospective review of a prospectively maintained database.

Results: 262 hospital-acquired VTE events occurred in 232 unique subjects. Median age at VTE diagnosis was 2 years. Only 69 (26%) VTE occurred in children ≥14 years of age. 237 (91%) VTE were deep vein thrombosis (DVT), and 16 (6.1%) involved pulmonary embolism. VTE was most common in subspecialty units including the pediatric and cardiac ICUs 87 (33.2%); neonatal ICU, 43 (16.4%); and hematology-oncology, 31 (11.8%). 184 (70%) VTE were associated with central venous catheters (CVC) and 144 events (55%) were associated with altered mobility. Congenital heart disease/heart failure was the most common chronic medical condition associated with VTE (69 (26.3%) events); whereas infection and trauma/surgery were the most common acute medical conditions associated with VTE (137 (52.3%) and 89 (34%) events, respectively). During 249 (95%) events, subjects scored a summated score ≥3.

Conclusion: In summary, in this single institution, prospectively maintained database, CVC remains the most common risk factor for VTE, followed by cardiac disease, infection and trauma/surgery. Most subjects who developed VTE scored high (score ≥ 3) on our screening tool. Only a small proportion of VTE occurred in patients older than 14 years and thus eligible for thromboprophylaxis. Our results indicate that future VTE prevention endeavors should include these age groups in addition to exploring more aggressive prophylactic modalities including pharmacological prophylaxis.

Poster # 515 | APPLICATION OF A HOSPITAL-WIDE BLOOD CULTURE CLINICAL DECISION ALGORITHM TO AN INPATIENT PEDIATRIC ONCOLOGY POPULATION: A FELLOW-LED QUALITY IMPROVEMENT PROJECT

Kathryn Lemberg, David Young, Danielle Koontz, Anne King, Christopher Gamper, Allen Chen, Aaron Milstone, Stacy Cooper

Johns Hopkins School of Medicine, Baltimore, Maryland, United States

Background: Pediatric fellows are required to have active engagement in quality improvement (QI) activities, and yet a national ACGME review found most trainees had "limited knowledge of QI methods" and "limited participation in interprofessional QI teams". The twenty fellows in our pediatric hematology/oncology training program identified blood culture utilization as their QI priority. Our institution recently introduced a hospital-wide decision algorithm to guide providers regarding when to obtain blood cultures. There is often a low threshold to obtain blood cultures in immunocompromised pediatric oncology patients, but these are often low-yield or result in false-positives. Our fellows spearheaded a project to implement the algorithm in the inpatient pediatric oncology population and improve the proportion of appropriately drawn blood cultures.

Objectives: We investigated how appropriately the algorithm was being utilized on the inpatient pediatric oncology floor prior to and after several educational steps aimed at disseminating the algorithm to members of the care team. Our primary endpoint was to quantify the proportion of culture episodes drawn "inappropriately", with a goal of reducing inappropriate episodes to ≤10%.

Design/Method: The algorithm was initially introduced to the nursing staff and residents covering the twenty-bed inpatient unit in September 2016. QI project planning took place with upper level fellows in January 2017. Fellows and faculty received intensive training on the algorithm in July-August 2017. We then conducted a retrospective chart review of blood culture episodes drawn between August 2016 and November 2017. Upper level fellows scored ~500 culture episodes as to whether the decision to culture and number of cultures drawn were "appropriate" or "inappropriate", and catalogued the indications for culture episodes and if applicable, why the episode was found to be inappropriate. Additionally, fellows discussed inappropriate culture episodes with the team on-service, to provide direct feedback on where the algorithm failed.

Results: Between August – December 2016 on average 337 cultures/1000 patient-days were drawn. Forty-nine percent of culture episodes were inappropriate. From January – October 2017, following targeted education on the algorithm, the rate of blood cultures drawn decreased to 263 cultures/1000 patient-days. The average proportion of inappropriate culture episodes fell to 16.7%, representing a 66% decrease in inappropriate culture utilization.

Conclusion: Correct application of a decision algorithm for blood culture utilization can reduce total cultures drawn on an inpatient pediatric oncology unit. Fellow-led education of the multi-disciplinary team decreases the rate of inappropriate culture episodes as well as provides active engagement in QI.

Poster # 516 | A KNOWLEDGE SCREENING EDUCATION SYSTEM IN ADOLESCENTS WITH SICKLE CELL DISEASE

Allison Bechtel, Cynthia Gauger, Manisha Bansal

Nemours Children's Specialty Care, Jacksonville, Florida, United States

Background: Inadequate understanding of sickle cell disease (SCD) is common and can affect patients' compliance and therefore their morbidity and mortality, especially after transition to adult care. Optimal clinical care for SCD includes disease education, which can be difficult given the breadth of possible topics and limited time in clinic. It is unclear how best to provide personalized, efficient education for adolescents with SCD. This quality improvement (QI) study aimed to implement a questionnaire-based system to improve patients' knowledge of their SCD and documentation of education by the nurse or physician.

Objectives: The study objective was to improve provider documentation and patient knowledge about their SCD by identifying patients' gaps in comprehension. By January 2017, the study aimed to increase education documentation from 50% to 75%. By April 2017, the study aimed to increase use of a smart phrase for education documentation from 0% to 50%. By June 2018, the study aimed to increase patients' knowledge about their disease by 20%.

Design/Method: Twenty-one SCD patients enrolled on an IRB approved QI study, with twenty active patients. Our comprehensive team generated a questionnaire with knowledge-based questions for two age groups: 12–14 and 15–18 years old. At each comprehensive visit, a questionnaire was distributed, with at least 3-month intervals. The provider scored questionnaires and reviewed two educational topics, with wrong answers taking priority. Plan-do-study-act (PDSA) cycles included PDSA#1: Patients completed questionnaire. PDSA#2: A smart phrase addressing questionnaire topics was created and shared with providers. PDSA#3: Patients received education handouts during clinic education. Documentation in clinic notes was the process measure and questionnaire scores was the outcome measure.

Results: PDSA#1 is complete, PDSA#2 has four patients remaining, and PDSA#3 is ongoing. Due to variable visit frequency, there are multiple concurrent cycles. After PDSA#1, free text documentation was completed an average of 61% over the course of 3 months. After PDSA #2 documentation increased to 100% within 3 months and questionnaire scores increased from an average of 59% to 78%. Of the questions that patients got wrong on their first visit, they were significantly more likely to improve on retesting if the topic was taught to them than if it was not addressed (72% vs. 33%, $p = 0.04$). We are currently completing PDSA#3 and collection of post PDSA#3 data.

Conclusion: Questionnaire-based SCD education coupled with standardized smart phrases improves patients' SCD knowledge and documentation by providers. Further improvement in knowledge is expected with the addition of handouts.

Poster # 517 | HELPING OUR PEERS ENDURE STRESS (HOPES) – A PEER SUPPORT INITIATIVE IN PEDIATRIC HEMATOLOGY / ONCOLOGY

Brittney Whitford, Amy Nadel, Nancy Barbach, Jonathan Fish

Cohen Children's Medical Center at Northwell Health, New Hyde Park, New York, United States

Background: Exposure to suffering can have a profound impact on the wellness of caregivers, often referred to as the "cost of caring". This cost is especially high in pediatric hematology/oncology. Repeated exposure to suffering has the potential to negatively impact resilience and increases the risk of burnout, thus impacting quality of care and patient satisfaction.

Objectives: We have developed a peer support team utilizing the Critical Incident Stress Management (CISM) model. This model has been successfully used in other professions that frequently face traumatic events such as fire fighters, police and emergency medical technicians. The H.O.P.E.S. Team (Helping Our Peers Endure Stress) consists of 18 volunteer multidisciplinary staff members who have received training to provide both group and peer support following any 'critical incident' that may impact one or more staff members. We hypothesize that implementation of the H.O.P.E.S. team will improve staff resilience, decrease overall rates of burnout and improve compassion satisfaction.

Design/Method: We are using both empiric metrics and anecdotal reports to assess the impact of the H.O.P.E.S. team. Prior to the activation of the team, all Pediatric Hematology/Oncology clinical staff members were surveyed using validated tools to assess their levels of resilience, burnout, secondary trauma and compassion satisfaction (ProQOLv5 and Brief Resilience Scale). They were also asked to rate the number of times they had experienced critical incidents, as well as their perceived level of distress after dealing with traumatic events. After the H.O.P.E.S. team has been functional for 6 months, we will send the same survey to staff members to measure changes, paying special attention to resilience and rates of burnout and compassion satisfaction.

Results: Enthusiasm for development of the team has been high. 18 of 19 people approached to volunteer their time to participate in the multidisciplinary team agreed, including attending physicians, fellows, nurses, nurse practitioners, child life specialists, social workers, clergy and psychologists. All volunteers participated in a 3-day training conducted by an instructor from the International Critical Incident Stress Foundation. Engagement in the first staff survey has been high, with 91 of 150 responding to date. Data collection is ongoing.

Conclusion: Clinical staff in Pediatric Hematology/Oncology may be particularly vulnerable to burnout and decreased resilience by repeatedly witnessing suffering and trauma. Peer support interventions following critical incidents may lead to increased resilience and compassion satisfaction while decreasing rates of burnout. Enthusiasm for the development of a peer support team has been high.

Poster # 518 | QUALITY IMPROVEMENT: TEXT-BASED APPOINTMENT REMINDERS FAIL TO IMPROVE RATES OF MISSED TRANSFUSION APPOINTMENTS

Jennifer Webb, Patricia Pope, Katelin Heltz

Children's National Health System, Washington, District of Columbia United States

Background: Monthly blood transfusions are an indicated therapy for pediatric patients with sickle cell disease with certain complications. Maximizing transfusion efficiency in a busy infusion clinic requires: ensuring that appropriate blood units are available in the hospital blood bank; laboratory specimens are obtained from patients in advance; and coordination of clinic appointment and nursing availability.

Objectives: We sought to improve clinic efficiency through identifying ways to better communicate with patients/families regarding upcoming laboratory and transfusion appointments, and to assess the efficacy of implementing a web-based personalized text reminder (Pinger.com).

Design/Method: We measured the baseline frequency with which transfusion appointments were missed by families, moved to later within the week, or delayed due to late labs. A convenience sample of patients receiving monthly transfusions received a questionnaire about patient/parent preferences for appointment reminders and barriers to keeping appointments. Those patients/parents who did not opt-out of an additional text reminder received personalized texts from their care team reminding them of lab and transfusion appointments. Rates of missed/moved/delayed appointments were compared between the group receiving the additional text messages and the group only receiving standard, hospital-generated appointment reminders (telephone call).

Results: Forty-one families (45 patients) responded to the survey, capturing information on 63% of patients receiving chronic transfusion therapy. Thirteen families (32%) declined the additional text reminders. Families reported a preference for text reminders (66%), more often than email (49%) or telephone (37%), and 80% of families wanted to receive reminders for both transfusion and laboratory appointments. The majority (43%) of families reported competing work/life priorities as the reason for missed/late appointments. Other families noted transportation/travel (29%), fear/illness/pain (21%), and lack of reminders (21%) as the reason for missed appointments. At baseline (twelve weeks), 3.7% of appointments were missed on a weekly basis (range 0–3 of 20 available per week), 10.4% were moved, and 5% of appointments were delayed. During our intervention period (twelve weeks), 7% were missed, 9.2% were moved, and 8.7% were delayed (combined, both groups). There was no difference in missed (7.0% texted vs 7.1% standard), moved (8.0% texted vs 10.0% standard) or delayed (8.0% text vs 9.3% standard) appointments.

Conclusion: Though families at our center reported a preference for a text-based reminder, personalized text reminders for appointments did not improve clinic efficiency as measured by missed, moved or delayed transfusion appointments. There was no improvement in appointment adherence in the group receiving personalized texts in addition to standard hospital reminders.

Poster # 519 | CAREGIVER DECISION-MAKING REGARDING ENROLLMENT IN CHILDREN'S ONCOLOGY GROUP THERAPEUTIC TRIALS

Lauren Draper, Anne Kirchhoff, Yelena Wu, Mark Fluchel

University of Utah, Salt Lake City, Utah, United States

Background: Childhood cancer outcomes have improved significantly, in large part due to multi-institution collaborative clinical trials run by the Children's Oncology Group (COG). Approximately half of eligible children with cancer will enroll on a therapeutic trial, but little is known about the factors affecting caregiver decision-making regarding enrollment or how well the required elements of informed consent are conveyed during the consent process.

Objectives: 1. Assess coverage of ten of the required elements of informed consent for COG therapeutic trials. 2. Describe factors affecting caregiver decision-making regarding therapeutic trial enrollment.

Design/Method: We surveyed families of children who were offered enrollment onto a phase 3 COG therapeutic study for an initial cancer diagnosis in the previous 18 months. Fisher's Exact or Wilcoxon rank-sum tests were utilized to compare demographic and other motivating factors related to enrollment decision-making.

Results: Seventy participants were surveyed. Regarding 10 of the basic required elements of informed consent, 96% knew the trial involved research, 99% knew consent was required, 76% knew the enrollment length for the trial, 97% knew they could continue care independent of enrollment, 73% knew who to contact with questions, 71% knew there were options besides enrollment, 83% knew they could withdraw at any time, 93% knew the information was confidential, 34% knew there were risks associated with the trial, and 46% knew there were benefits. Of all participants, 84% (n = 59/70) enrolled onto a therapeutic study. Among enrollees, 37% (n = 22/59) of the primary caregivers had completed college compared to 18% (n = 2/11) of those not enrolled (p = 0.3). When asked about factors impacting their decision, 69% (n = 41/59) of those enrolled said they felt there were no risks or did not know if there were risks associated with the study compared to 45% (n = 5/11) of those choosing not to enroll (p = 0.17). Of those enrolled, 61% (n = 36/59) reported the physician recommendation "somewhat" or "strongly" affected their decision to enroll compared to 0% (n = 0/11) of those not enrolling (p = 0.0001). Of those who enrolled, 17% (n = 10/59) reported feeling pressured to enroll while 45% (n = 5/11) of those not enrolled reported pressure (p = 0.05). Of enrollees, 10% (n = 6/59) reported they did not have enough time to decide compared to 36% (n = 4/11) of those not enrolled (p = 0.03).

Conclusion: Failure to convey all 10 required elements of informed consent highlights possible deficiencies in the consent process for COG therapeutic trials. Caregivers' perception of being pressured and lack of time to make an informed decision may impact clinical trial enrollment.

Poster # 520 | IMPROVING THE EVALUATION AND MANAGEMENT OF ABNORMAL UTERINE BLEEDING IN ADOLESCENT FEMALES PRESENTING TO EMERGENCY CARE

Allison Close, Gina Sequeira, Lauren Alessi, Gerald Montano, Meghan McCormick, James Cooper, Rebecca Epperly, Noel Zuckerbraun

Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, United States

Background: Abnormal uterine bleeding (AUB) is a frequent adolescent gynecologic complaint. However, limited research exists to guide management, and acute care varies.

Objectives: We sought to improve emergency care for adolescents with AUB by developing a clinical effectiveness guideline (CEG) and assessing its impact on quality of care.

Design/Method: A stakeholder engagement group consisting of members from the departments of hematology/oncology, adolescent medicine, general pediatrics, and emergency medicine designed a CEG algorithm for emergency AUB management. Pediatric residents received CEG training and their knowledge and attitudes were assessed using pre and post intervention surveys. ICD-9 and 10 codes identified electronic health record data for patients presenting to the pediatric Emergency Department (ED) for AUB 6 months before and after CEG implementation. Pre-pubertal patients and those with vaginal bleeding from trauma were excluded. A weighted, 20-point scoring system consisting of prioritized aspects of history, laboratory studies and management was developed to quantify the quality of care provided. T-test, Chi Square Test, Wilcoxon Rank Sum Test, and a run chart were used for analysis.

Results: Of the 91 patients identified, 62 met inclusion criteria. There were 37% of patients currently using some form of contraception, while 12.9% had bleeding related to a current or recent pregnancy. Median AUB quality care scores were 14 pre- and 16 post-intervention (p = 0.064). Run chart data showed no shifts or trends (overall median score, 14-points). Both pre and post-implementation, points were deducted most frequently for not assessing personal/family clotting disorder history and inappropriate use/dosing of oral contraceptives.

Conclusion: We successfully designed and implemented a CEG and educational intervention for AUB management in a pediatric ED. These data suggest our CEG may be an effective tool to improve emergency AUB care for adolescents, though additional cycles are needed.

Poster # 521 | REDUCING LENGTH OF STAY OF HIGH-DOSE METHOTREXATE ADMISSIONS

Claire Stokes, Rebecca Coughlin, Nicole Benedict, Virginia Borunda, Julie Bradley, Laurel Heath, Mary Kohlman, Nicole Kaiser, Mya Merrow, Kali O'Dell, Joanne Hilden

Children's Hospital Colorado, Aurora, Colorado, United States

Background: High-dose methotrexate (HD-MTX) is a common chemotherapy administered inpatient at most centers. Its administration is particularly susceptible to error due to the need for frequent drug levels with resulting changes in supportive care. Errors can prolong patient stay and cause patient harm.

Objectives: Global aim- To reduce the length of stay (LOS) of HD-MTX admissions. SMART aims- to increase the percentage of patients whose pre-hydration fluids are started by 10am from 0% to 20% by 1/31/18, and to increase the percentage of patients who receive HD-MTX by 5pm from 43% to 100% by 6/30/18.

Design/Method: We used rapid process improvement methods to target earlier methotrexate administration. A key driver of prolonged LOS was hypothesized to be drug levels returning overnight rather than in the day time due to delayed HD-MTX start. Changes implemented have included scheduling HD-MTX patients as the first patients of the day for their exam in clinic and scheduling labs to pass for HD-MTX on the day prior to admission. There are ongoing PDSA cycles to change the location of pre-hydration start from the inpatient room to the clinic exam room in order to meet HD-MTX administration time goals. We are piloting two different education materials to improve patient experience. One explains HD-MTX levels in a red/yellow/green stoplight format and the other reminds patients how to prepare for the admission. Other interventions regarding how we test urine pH and safety checks in the ordering process for history of delayed clearance are in the planning stage.

Results: The project is ongoing, but as of 12/12/17, we start methotrexate by 5pm 50% of the time which is improved from a baseline of 43%. When the project was started, pre-hydration was never started before 10am. Now, fluids are started by 10am 40% of the time. PDSA cycles are ongoing and we have yet to sustain reductions in LOS, but some months have shown decreased LOS by as much as 19 hours from baseline measurements.

Conclusion: Rapid cycle improvement can be utilized to decrease LOS HD-MTX admissions. This has important financial implications as well as the potential to reduce secondary harm from unnecessary time in the hospital. Pediatric cancer centers should schedule HD-MTX admissions first thing in the morning so that data regarding kidney injury and drug clearance can be interpreted by the day team and children are not cleared for discharge in the middle of the night.

Poster # 522 | INCORPORATING BEREAVED PARENTS AS FACULTY FACILITATORS AND EDUCATORS IN TEACHING PRINCIPLES OF PALLIATIVE AND END-OF-LIFE CARE TO ONCOLOGY PROVIDERS

Jennifer Snaman, Erica Kaye, Holly Spraker-Perlman, Deena Levine, Melody Cunningham, Justin Baker

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: Education and training for interdisciplinary pediatric oncology providers requires training in principles of palliative and end-of-life (EOL) care. The experiences of bereaved parents can inform and enhance palliative care educational curricula in uniquely powerful and valuable ways.

Objectives: The objective of this study is to present an innovative palliative care educational program for oncology providers facilitated by trained bereaved parents who serve as volunteer educators in local and national palliative care educational forums and to describe how incorporation of bereaved parents in these educational forums affects participant comfort with communication and management of children at the EOL.

Design/Method: Survey tools were adapted to determine how bereaved parent educators affected participant experiences in 3 different educational forums: institutional seminars on pediatric palliative and EOL care, role-play based communication training sessions, and an international symposium on pediatric palliative oncology. Pre- and post-session surveys with incorporation of retrospective pre-program assessment item to control for response shift were used in the evaluation of institutional seminars and communication training sessions. Results from feedback surveys sent to all attendees were used to appraise the participants experience in the international oncology symposium.

Results: Involvement of trained parent educators across diverse, interdisciplinary educational forums improved attendee comfort in communicating with, and caring for, patients and families with serious illness. Importantly, parent educators also derive benefit from educational with interdisciplinary clinicians.

Conclusion: Integration of bereaved parents into palliative and EOL care education is an innovative and effective model

that benefits both interdisciplinary clinicians and bereaved parents.

Poster # 523 | ADHERENCE TO ANTIEMETIC GUIDELINES IN PEDIATRIC PATIENTS WITH CANCER: HOW DO WE TRANSLATE EVIDENCE INTO PRACTICE?

Florence Choo, Angela Girvin

University of Rochester, Rochester, New York, United States

Background: Poorly controlled chemotherapy-induced nausea and vomiting (CINV) significantly impairs patients' quality of life and contributes to ongoing medical costs through increased length of stay in the hospital or readmissions and outpatient visits for control of nausea, vomiting or dehydration. Lack of adherence to national evidenced-based guidelines that dictate antiemetic prescribing for variably emetogenic chemotherapy leaves patients vulnerable to increased CINV and its ensuing complications.

Objectives: To review our institution's antiemetic prescribing practices and their consistency with the Antiemesis guidelines from the National Comprehensive Cancer Network (NCCN) and Children's Oncology Group (COG)-endorsed supportive care guidelines and to further develop tools to increase adherence to these national-based guidelines to improve control of CINV.

Design/Method: We performed a retrospective chart review of inpatient chemotherapy encounters. We evaluated emetogenicty of chemotherapy (high, medium, low), initial antiemetic regimen ordered, number of as needed medications required and adherence to national evidenced based guidelines tailored to each level of emetogenicity in the prescription of antiemetics.

Results: Fifty-five total inpatient chemotherapy encounters were reviewed over 8 months. Eighteen of these encounters were considered to have been highly emetogenic chemotherapy (HEC) with the remaining 37 of these considered to be moderately emetogenic. Only 9 out of 18 HEC encounters completely included all guideline-recommended agents. There was a demonstrable lack of consistency across providers with dosing of Aprepitant and most as needed medications. There was significant variation in order of first, second and third line anti-emetics ordered – with lorazepam and promethazine being used most frequently. With an aim of improving antiemetic prescribing practices for our patients, we are currently rebuilding chemotherapy treatment plans in our electronic medical record to incorporate antiemetic drug order sets that follow evidenced-based guidelines for variably emetogenic chemotherapy. This will be used in conjunction with an education initiative about best practices in supportive care for all prescribers of antiemetics.

Conclusion: Review of our department's recent inpatient chemotherapy encounters show we are falling short in following nationally recommended standards for appropriate antiemetic coverage during chemotherapy. Identification of these deficiencies allows for implementation of quality initiatives to improve prescriber adherence to evidenced- based guidelines for better control of CINV.

Poster # 524 | OUTCOMES OF OBSERVATION WITHOUT EMPIRIC IV ANTIBIOTICS IN FEBRILE, NON-NEUTROPENIC PEDIATRIC ONCOLOGY PATIENTS

Natalie Wu, William Muller, Elaine Morgan

Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, United States

Background: There are currently no consensus guidelines for the management of pediatric oncology patients presenting with fever without neutropenia. Historically, these patients had been treated similarly to neutropenic patients with empiric antibiotics. While there has been a shift towards reducing unnecessary empiric treatment, there has been limited research into the outcomes associated with withholding empiric IV antibiotics in this patient population.

Objectives: We assessed the safety and efficacy of our institution's current protocol of observing well-appearing patients who present with fever without neutropenia and compared the outcomes of the patients who did and did not receive empiric IV antibiotics.

Design/Method: This was a prospective, single-institution cohort study. Patients were included if they were currently undergoing chemotherapy for an oncologic diagnosis and presented initially as an outpatient with fever and non-neutropenia (defined as ANC $\geq$ 500 cells/mm3). For each episode we recorded lab and blood culture results, signs and symptoms of initial presentation, and clinical outcomes, including antibiotic administration and hospital admission.

Results: A total of 242 episodes of well-appearing patients with fever without neutropenia were identified. Compliance with the institutional protocol was high; 81.8% of patients were observed without receiving empiric IV antibiotics. The majority of patients were discharged home and there were no serious complications or infectious deaths. The incidence of positive blood cultures was low (3.7% including several likely contaminants), despite the presence of central venous catheters in the majority (84.7%) of patients. There were no significant differences in age, oncologic diagnosis, central

line access, ANC value, or incidence of bacteremia between patients who did and did not receive empiric IV antibiotics. Patients who were admitted to the hospital were significantly more likely to have received IV antibiotics ($p < 0.001$) despite documentation of a reassuring exam. However, admitted patients who initially received IV antibiotics were just as likely to discharge within 48 hours compared to patients who were observed.

Conclusion: We propose that empiric IV antibiotic administration in febrile, non-neutropenic, otherwise well-appearing patients is unnecessary. Our study demonstrated no adverse consequences of observation and no significant differences in clinical outcomes between patients who did and did not receive IV antibiotics aside from rate of hospitalization. This supports the practice of observation without empiric antibiotics for such patients.

Poster # 525 | ROUTINE IMAGING FOR DETECTION OF RELAPSE AND ASSESSING TREATMENT RESPONSE IN ALPHA FETO PROTEIN (AFP) POSITIVE HEPATOBLASTOMA- IS IT REALLY NECESSARY?

Monica Davini, Caroline Hastings, James Feusner

Children's Hospital & Research Center Oakland, Oakland, California, United States

Background: Children with Hepatoblastoma (Hb) undergo repetitive computed tomography (CT) scans to determine response to treatment and assess for relapse. This imaging exposes children to radiation, anesthesia, and imposes financial and emotional burden.

Objectives: Review our institutional experience to determine if AFP measurements are sufficient to assess response to treatment and detect relapse.

Design/Method: We conducted a retrospective chart review of all patients diagnosed with Hb at our institution between 1978–2017. Data collected included serum AFP, total number and type of imaging studies during and post treatment, and how relapse or progressive disease was detected.

Results: Thirty-one patients were diagnosed with AFP positive Hb. During therapy, 173 CT scans were performed: 118 to assess for response to therapy or surgical planning (average 4 scans/patient) and 55 due to concern for progression with rising AFP. Off therapy, 213 surveillance CT scans were performed (average of 5.3 scans/patient) and 72 (33%) included the chest in patients with no lung metastasis at diagnosis. Relapsed patients averaged 12.5 surveillance scans, 6.5 of which were done before relapse was noted on imaging. There were no cases of radiographic evidence of relapse without a prior increase in AFP.

Conclusion: During treatment, response to therapy based on imaging correlated with a decline in AFP in all patients, arguing that repetitive scans are not needed in this setting unless required for surgical planning. Only 3 of 213 scans performed during off therapy surveillance displayed evidence of relapse, all of which were preceded by rise in AFP. Our study represents the largest cohort of Hb patients. Prior studies suggest similar results, but included fewer patients, lower stage of disease and less than 10 years of surveillance monitoring. At our institution, the cost of a CT C/A/P is $15,169 with reimbursement varying from 30–50%. In comparison, the cost of an AFP measurement is $101.50. Many scans also require anesthesia and result in emotional toil for families concerned about this procedure as well as the results. Thus, AFP demonstrates greater sensitivity, with significant cost savings and decreased emotional burden, and should be used for monitoring both during and off therapy, replacing routine serial imaging.

Poster # 526 | CHANGING BLOOD CULTURE STRATEGY: A QUALITY IMPROVEMENT PROJECT TO ELIMINATE THE PRACTICE OF AUTOMATIC DAILY BLOOD CULTURES IN HOSPITALIZED PEDIATRIC PATIENTS WITH FEVER AND NEUTROPENIA

Joanna Grossman Newton, Alexis Carter, Cheryl Head, Sarah Leahy, Thomas Olson, Frank Keller, Karen Wasilewski-Masker

The Aflac Cancer & Blood Disorders Center at Children's Healthcare of Atlanta, Atlanta, Georgia, United States

Background: We observed that our practice of drawing daily blood cultures in hospitalized patients with fever and neutropenia was wasteful; it resulted in excessive negative cultures that did not add to patient care.

Objectives: The SMART aim of this quality improvement project was to reduce the number of negative blood cultures drawn on hospitalized patients with fever and neutropenia by 25% in 6 months.

Design/Method: After reviewing published evidence suggesting drawing daily blood cultures in febrile neutropenic patients was unnecessary, a new blood culture guideline was implemented: cultures were drawn at presentation for fever with neutropenia and, if negative at 24 hours, repeat

cultures were not drawn except for clinical change, new fever after being afebrile >24 hours, or antimicrobials were being changed/broadened. To impact key drivers, we educated staff and changed blood culture order sets to require providers to select a reason for ordering the culture and to eliminate a nursing order to draw daily cultures with fever. We compared the number of blood cultures drawn per 1000 central line-days (/1000-CLD) and the proportion of positive versus negative cultures pre-guideline (July 2015-May 2016) and post-guideline (June 2016-December 2016). We calculated the cost savings from reducing cultures. To assess patient safety, potential septic events without a corresponding positive blood culture were reviewed. Data were analyzed by service (oncology and stem cell transplant). A chi-square test was used to compare rates.

Results: In stem cell transplant patients, pre vs. post-guideline, there were 492 vs. 258 total cultures drawn/1000-CLD; 25 vs. 21 positive (16% decrease, $p = 0.404$) and 467 vs. 237 negative cultures/1000-CLD (51% decrease, $p<0.0000001$). In oncology patients, pre vs. post-guideline, there were 266 vs. 181 total cultures drawn/1000-CLD; 17 vs. 13 positive (24% decrease, $p = 0.024$) and 249 vs. 168 negative cultures/1000-CLD (32% decrease, $p<0.0000001$). The decreased positive culture rate among oncology patients may be due to decreased culture contaminants and/or the effect of a concurrent initiative to decrease CLABSI in that group. There were 2 safety concerns; however, chart review concluded that the guideline did not lead to missed infections in these patients. For the first 6 months of the guideline, the total cost savings in blood cultures was $31,454.31.

Conclusion: The implementation of our new blood culture guideline successfully led to a substantial reduction in the collection of negative cultures and a cost savings without compromising the detection of bacteremia in hospitalized pediatric patients with fever and neutropenia.

Poster # 527 | CHEMOTHERAPY TREATMENT CONSISTENCY FOR NEWLY-DIAGNOSED PEDIATRIC ONCOLOGY PATIENTS AT A SINGLE CENTER

Amy Billett, Hope Schneider, Kelly Eng

Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts, United States

Background: There are various evidence-based guidelines for treatment of adult cancers, such as the NCCN guidelines. Previously, care was standardized for most new diagnosis pediatric cancer patients through enrollment on a clinical trial. With decreasing clinical trial availability and enrollment and few, if any, evidence-based guidelines for pediatric cancer, care standardization is challenging for pediatric cancers.

Objectives: To assess consistency of care, as determined by plan of treatment by diagnosis, for pediatric patients receiving chemotherapy for newly diagnosed cancer at a single center.

Design/Method: Patients with a new cancer diagnosis at a large, tertiary care pediatric oncology center in calendar year 2016 were identified through reports from the chemotherapy order entry (COE) system. Reports included diagnosis (recorded through standardized options) and the plan of treatment. Chart review was used to exclude patients who started treatment elsewhere and patients being treated for relapse, to clarify diagnosis if the standardized options in COE were unclear, and to clarify treatment plan if needed. Data was entered and analyzed in a RedCap database. Specific diagnoses were clustered into higher level disease groups and the distribution of treatment plans for patients within each was determined. This project was deemed exempt from IRB approval for human subject research as a qualifying quality improvement project.

Results: Of the 324 patients with a first chemotherapy order in 2016, 142 were excluded due to one or more reasons: stem cell transplant (62), transfer of care (54), relapse (25), and other (9). An additional 61 patients were excluded because <5 patients/year/diagnosis. There was no CNS tumor disease group with >5 patients. Thus, 121 patients with hematologic malignancies or non-CNS solid tumors are the focus of this analysis. For patients with intermediate risk rhabdomyosarcoma, the plan of treatment was the standard arm of a COG protocol, ARST0531 for 3 patients and ARST 1431 for 1 subsequent patient after protocol activation. For all other diseases including lymphoblastic leukemia/lymphoma (excluding infants), classical Hodgkin lymphoma, AML (excluding trisomy 21 and APML), stage III/IV Burkitt lymphoma/diffuse large B-cell lymphoma, post-transplant lymphoproliferative disease, Wilms tumor, rhabdomyosarcoma, Ewings sarcoma, osteosarcoma, neuroblastoma, and retinoblastoma, only one treatment plan per risk category was used.

Conclusion: This analysis demonstrates highly consistent chemotherapy treatment at a single center for patients with hematologic malignancies and non-CNS solid tumors. Next steps include exploring strategies to group diagnoses for CNS tumors and assessing the quality of evidence supporting the treatments given.

Poster # 528 | A PATIENT-CENTERED INTERVENTION TO IMPROVE THE TIME-TO-ANTIBIOTICS FOR PEDIATRIC FEBRILE NEUTROPENIA PATIENTS AT A LARGE ACADEMIC MEDICAL CENTER

Alisha Bouzaher, Alyssa Goodman, Etana Zack, George Waterman, Lauren Weintraub

Albany Medical Center, Albany, New York, United States

Background: Rapid initiation of empiric antibiotics in patients with fever and neutropenia has been shown to reduce morbidity and mortality. Current practice guidelines call for the initiation of antibiotics in these patients within sixty minutes and time-to-antibiotic (TTA) has been suggested as a quality-of-care measure. Many institutions, including our own, face barriers to meeting this time limit.

Objectives: Utilizing a quality improvement model, determine barriers and implement an intervention to reduce the time-to-antibiotics for pediatric febrile patients with suspected neutropenia who present to the Emergency Department (ED) at our institution.

Design/Method: We have identified and implemented an intervention utilizing the Plan-Do-Study-Act model for quality improvement. A twelve-month retrospective review was conducted to evaluate the efficacy of the current practice algorithm at our large, academic tertiary-care hospital. Subjects identified were pediatric oncology patients undergoing active chemotherapy who presented to the ED with febrile neutropenia. We identified two specific barriers, triage level assignments and delay in ordering antibiotics. To address these barriers, we have created a wallet sized "Fever Card" that patients were instructed to show upon arrive to the ED. In collaboration with the ED staff, efforts were also made to educate all pediatric staff on the use of the Fever Card. Post-intervention data collection is currently underway and pre- and post-intervention antibiotic delivery times will be compared.

Results: The pre-intervention cohort consisted of thirty-three encounters with a mean time-to-antibiotic delivery of 135 minutes, or seventy-five minutes greater than the accepted standard of care. Only one patient received antibiotics within sixty minutes of arrival. Post-intervention data collection is currently underway.

Conclusion: Since identifying two barriers to meeting the standard of care at our institution, we have implemented a quality improvement measure that empowers patient families to direct appropriate triage in the ED as well as simplifying the treatment protocol for ED providers. We expect to identify an improvement in time-to-antibiotics from the pre-intervention to the post-intervention period.

Poster # 601 | QUALITY OF CARE IN US CHILDREN WITH SICKLE CELL DISEASE

Julie Kanter Washko, Carlton Dampier, Irene Agodoa, Robin Howard, Sally Wade, Virginia Noxon, Samir Ballas

Lifespan Comprehensive Sickle Cell Center, Medical University of South Carolina, Charleston, South Carolina, United States

Background: Sickle cell disease (SCD) is a genetic disorder in which sickle hemoglobin (HbS) triggers multiple downstream effects, including red cell sickling, hemolysis, vaso-occlusion, and inflammation. SCD, a lifelong disease initiated at birth with injury that accumulates over time, causes significant end-organ damage and clinical complications that are undertreated and associated with early death. Homozygous mutation (HbSS) causes the severe form of SCD. Individuals with SCD are at increased risk of infection, stroke, and retinopathy. Clinical guidelines for pediatric patients with SCD recommend prophylactic penicillin use (ages 2–5), annual screening for stroke with transcranial doppler (TCD) imaging (ages 2–16), and annual ophthalmology exams to assess for retinopathy (ages $\geq$10). There are limited real-world data on implementation of these NHLBI-based recommendations.

Objectives: To describe utilization of penicillin, TCD screening, and ophthalmology care in children with HbSS disease.

Design/Method: The Truven MarketScan® Commercial and Medicaid administrative claims databases were used to identify US patients aged 2–16 years at first indication of HbSS recorded in each calendar year from 2009 to 2014. Patients were required to have medical and pharmacy benefits for the calendar year in which they were identified and for 12 months prior to their first recorded HbSS indication. Prior year utilization of penicillin, TCDs, and ophthalmologist visits was measured for each annual cohort.

Results: Annual cohorts included 347–438 Commercial (mean age 9.5 years, 52% female) and 1024–1557 Medicaid (mean age 8.3 years, 48% female) patients with HbSS disease. Fewer than half of all patients had received a TCD scan in the previous year, with similar rates seen across all age groups for both payers. Ophthalmologist visits increased as patients aged, and while patients aged 12–16 years had the highest proportion with an ophthalmologist visit in both payer populations, the overall implementation remained low. In contrast to the low use of TCD and ophthalmology visits, penicillin use

was highest in the 1–5 year age group: >80% use in any given year for both payers.

Conclusion: Although our data demonstrated high penicillin use in the 1–5 year age group, consistent with guidelines there is an opportunity to improve implementation of other guidelines-based recommended screening. For example, TCD screening can identify children at risk of SCD-related stroke in order to initiate preventive therapies. Further research to understand potential barriers to proper screening and to evaluate strategies to improve awareness, adherence, and implementation of recommended screenings in children with SCD is warranted. Supported by Global Blood Therapeutics.

Poster # 602 | PREVALENCE OF INTERNALIZING PROBLEMS IN PEDIATRIC CANCER PATIENTS AT ENTRY INTO A SURVIVORSHIP CLINIC

Afsoon Gaxor, Debra Friedman, Zhiguo Zhao, Michelle Reising, Emily Hardcastle, Bruce Compas, Adam Esbenshade

Vanderbilt University Medical Center, Nashville, Tennessee, United States

Background: Childhood cancer therapy has improved where there are many long-term survivors. While psychosocial difficulties in pediatric cancer survivors are recognized, the prevalence of these problems at initial survivorship presentation is unclear.

Objectives: To examine the prevalence of overall internalizing symptoms (e.g., depression/anxiety) in pediatric cancer survivors presenting to a survivorship clinic and to examine how this is mitigated by receiving psychological services and by evidence of parental depression/anxiety.

Design/Method: Pediatric cancer survivors attending their first visit at the REACH for Survivorship Clinic at Vanderbilt (ages 3–18) were included. Survivors' parents (93% female) completed the Child Behavior Checklist (CBCL), Beck Depression Inventory-II, and Beck Anxiety Inventory. Survivors >12 years completed a self-report. The Wilcoxon rank-sum and Pearson's $\chi 2$ test were used for univariate analyses. The effect size and 95% confidence intervals (CI) estimated from the multivariable linear regressions were reported.

Results: 142 childhood cancer survivors a median of 12 years old and 3.3 years off therapy were included. Thirty one survivors (22%) showed at least borderline clinical internalizing problems (T score >60) on the CBCL, but only 8 of these patients (26%) reported receiving psychological services. Nine other survivors with normal T score ≤60 also reported receiving psychological services. Parental depressive and anxiety symptoms were correlated to the parental report of survivor overall internalizing symptoms (Spearman $\rho = 0.415$, p = <0.001 and $\rho = 0.476$, p = <0.001 respectively), however they were not correlated to survivor self-reports. Furthermore, parents with mild to severe depressive symptoms or mild to severe anxiety symptoms were more likely to rate their child as having higher overall internalizing symptoms (p = 0.001; p = 0.008, respectively). Multivariable linear regression showed that when adjusted for age, gender, cancer diagnosis and time off treatment, reported utilization of psychological services ($\beta = 8.58$, 95% CI [3.54, 13.62],p = 0.001), and parent depressive symptoms ($\beta = 0.43$, [.22, .65],p<0.001) were significantly associated with child overall internalizing symptoms. In an otherwise identical alternate model substituting parental anxiety for parental depression, parental anxiety was also a significant risk factor ($\beta = 0.70$, [.38, 1.03], p<0.001). Alternatively, parent anxiety/depressive symptoms were not significantly associated with child self-report of internalizing symptoms.

Conclusion: Childhood cancer survivors have an elevated prevalence of experiencing internalizing symptoms but seldom report receiving psychological services. Childhood cancer survivors' parents with anxious/depressed symptoms are more likely to rate their children as having more internalizing problems, compared to patient self-reports. Ongoing longitudinal analyses will help clarify the best timing for potential interventions.

Poster # 603 | A STEP ON THE PATH TO BUILDING A NOVEL TRANSITION PROGRAM: ONLINE LEARNING MODULES INCREASE FAMILY MEDICINE RESIDENTS' KNOWLEDGE ABOUT HYDROXYUREA AND COMPREHENSIVE CARE OF ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE BUT NOT TRANSITION BEST PRACTICES

Kelly Mullen, Amy Dawson, Brian Henriksen, Natalie Duncan, Dennis O'Brien, Emily Meier

Fort Wayne Medical Education Program, Fort Wayne, Indiana, United States

Background: Life expectancy for adults with sickle cell disease (SCD) has remained unchanged over the past 30 years despite improvements in pediatric SCD survival. At greatest risk are the adolescents and young adults (AYAs) transitioning from pediatric to adult care. Allen County ranks 3rd in SCD incidence among the 92 counties in Indiana, and has 2 board certified Pediatric Hematologist-Oncologists. When children "age out" of the pediatric system, there are few providers knowledgeable about managing adults with SCD in the region. A novel partnership between hematologists and the Family Medicine residency program in Allen County was initiated to educate Family Medicine residents (FPs) about SCD, hydroxyurea (HU), and management of SCD-related complications with the goal to increase the number of knowledgeable providers to care for adults with SCD.

Objectives: To determine the effectiveness of online learning modules in educating FPs about HU, best practices for AYA SCD care and transition.

Design/Method: Three online learning modules about SCD (Comprehensive care of AYAs with SCD, HU, best practices in AYA transition) were developed and CME-accredited. Electronic pre- and post-tests were distributed to 32 FPs with five questions for each module covering: contraception; screening tests; HU indications, dosing and monitoring; developmental milestones and SCD knowledge assessments. The St Vincent IRB reviewed the protocol and granted a waiver of consent.

Results: Twenty-six FPs (81%) completed the pre- and post-tests. Over two-thirds correctly identified the clinical benefits of HU on both assessments. Knowledge about the rationale for HU therapy increased after the completion of the HU module (30% correct on pre-test vs. 62% on post-test, $p = 0.009$). The proportion of correct responses increased for all comprehensive AYA SCD care post-test questions, but only the leading cause of death and the priapism-related questions reached statistical significance (15% vs. 35%, $p = 0.048$; 0% vs. 23%, $p = 0.003$, respectively). The proportion of correct responses for 2 of the transition-focused questions was unchanged (89% for both), while the proportion of correct post-test responses on the self-care assessment question significantly increased (0% vs. 12%, $p = 0.04$).

Conclusion: After module completion, FPs were able to correctly identify common SCD complications and why HU is an effective treatment for individuals with SCD. The best practices of transition clinic module may need modification to improve physician understanding of the intricacies in establishing and maintaining a SCD transition clinic. Overall, online training is effective at educating FPs and could be used to increase the number of providers knowledgeable about SCD care.

Poster # 604 | OUTCOMES WITHIN FIVE YEARS FROM THERAPY COMPLETION IN PEDIATRIC HODGKIN LYMPHOMA PATIENTS FOLLOWING CONTEMPORARY THERAPY

Karen Effinger, Frank Keller, John Bergsagel, Taylor Lawrence, Rebecca Williamson Lewis, Lillian Meacham, Ann Mertens, Sharon Castellino

Emory University/Children's Healthcare of Atlanta, Atlanta, Georgia, United States

Background: Survival rates for pediatric Hodgkin lymphoma (HL) exceed 95% with contemporary therapy. Studies of pediatric HL survivors treated in the 1970s-1990s have shown increased risk for treatment-related chronic health conditions. Risk-adapted therapy, including tailored radiotherapy, has been developed to reduce long-term morbidity while maintaining excellent survival. Little is known about chronic conditions associated with contemporary therapy presenting during the first 5 years from therapy completion (early outcomes).

Objectives: To analyze survival and early outcomes of pediatric HL patients treated with contemporary therapy.

Design/Method: We conducted a retrospective review of HL patients diagnosed <21 years of age at our institution from 2010–2014. Three-year overall (OS) and event-free (EFS) survival were calculated with Kaplan Meier statistics using SAS 9.4. Results of standardized screening for targeted toxicities that developed between 2 -5 years from therapy completion were identified and graded per CTCAE criteria. Censoring occurred at date of death, 5 years from therapy completion, or December 31, 2016. Data from the last collection point were used for prevalence calculations in cases with multiple evaluations.

Results: We identified 83 patients (51% male; 43% non-Hispanic white; mean age at diagnosis 13.6 ± 3.7 years) with a median time since therapy completion of 3.3 years (range 0.1-5.0). Initial treatment included: 56 (67%) chemotherapy only and 27 (32%) multimodality treatment. All patients received anthracyclines (median dose 200mg/m2) and 96% received alkylating agents (median cyclophosphamide equivalent dose [CED] 3600mg/m2). The 3-year OS was 99% with an EFS of 90% (90% chemotherapy only, 91% multimodality treatment; $p = 0.76$). Patients with relapsed/refractory disease received salvage treatment including chemotherapy only ($n = 1$), multimodality therapy ($n = 1$), or multimodality treatment including stem cell transplant (autologous $n = 4$; autologous+allogeneic $n = 1$). No patients developed thyroid dysfunction, cardiac dysfunction, subsequent neoplasm, or male gonadal dysfunction during the study period. Pulmonary

dysfunction was limited to CTCAE Grade 1. Anti-mullerian hormone (AMH) below the normal range was found in 10/11 pubertal females who received CED ≥7000mg/m2 compared to 0/12 females who received CED <7000mg/m2. Two of the females with low AMH also had follicle stimulating hormone >30IU/ml.

Conclusion: This study is the first to evaluate early outcomes in pediatric HL survivors. The results indicate contemporary chemotherapy and a lower rate of radiotherapy utilization lead to excellent 3-year survival rates with minimal early toxicities. Females exposed to CED ≥7000mg/m2 are at increased risk for gonadal dysfunction and should be prioritized for fertility preservation approaches prior to initiation of cancer therapy.

Poster # 605 | INCIDENCE RATES AND TRENDS OF PEDIATRIC CANCER — UNITED STATES, 2001–2014

David Siegel, Jun Li, S. Jane Henley, Reda Wilson, Natasha Buchanan Lunsford, Eric Tai, Elizabeth Van Dyne

Centers for Disease Control and Prevention, Atlanta, Georgia, United States

Background: Cancer is one of the leading disease-related causes of death among individuals aged <20 years in the United States. Recent evaluations of national trends of pediatric cancer used data from before 2010, or covered ≤28% of the US population.

Objectives: This study describes pediatric cancer incidence rates and trends by using the most recent and comprehensive cancer registry data available in the US.

Design/Method: Data from US Cancer Statistics were used to evaluate cancer incidence rates and trends among individuals aged <20 years during 2001–2014. Data were from 48 states and covered 98% of the US population. We assessed trends by calculating average annual percent change (AAPC) in rates using joinpoint regression. Rates and trends were stratified by sex, age, race/ethnicity, US Census region, county-based economic status, and county-based rural/urban classification, and cancer type, as grouped by the International Classification of Childhood Cancer (ICCC).

Results: We identified 196,200 cases of pediatric cancer during 2001–2014. The overall cancer incidence rate was 173.0 per 1 million; incidence rates were highest for leukemia (45.6), brain tumors (30.8), and lymphoma (26.0). Rates were highest among males, aged 0–4 years, non-Hispanic whites, the Northeast US Census region, the top 25% of counties by economic status, and metropolitan counties. The overall pediatric cancer incidence rate increased (AAPC = 0.7, 95% CI, 0.5–0.8) during 2001–2014 and contained no joinpoints. Rates increased in each stratum of sex, age, race/ethnicity (except non-Hispanic American Indian/Alaska Native), region, economic status, and rural/urban classification. Rates were stable for most individual cancer types, but increased for non-Hodgkin lymphomas except Burkitt lymphoma (ICCC group II(b), AAPC = 1.2, 95% CI, 0.4–2.0), central nervous system neoplasms (group III, AAPC = 0.4, 95% CI, 0.1–0.8), renal tumors (group VI, AAPC = 0.6, 95% CI, 0.1–1.1), hepatic tumors (group VII, AAPC = 2.5, 95% CI, 1.0–4.0), and thyroid carcinomas (group XI(b), AAPC = 4.8, 95% CI, 4.2–5.5). Rates of malignant melanoma decreased (group XI(d), AAPC = -2.6, 95% CI, -4.7– -0.4).

Conclusion: This study documents increased rates of pediatric cancer during 2001–2014, in each of the demographic variables examined. Increased overall rates of hepatic cancer and decreased rates of melanoma are novel findings using data since 2010. Next steps in addressing changing rates could include investigation of diagnostic and reporting standards, host biologic factors, environmental exposures, or potential interventions for reducing cancer risk. Increasing pediatric cancer incidence rates may necessitate changes related to treatment and survivorship care capacity.

Poster # 606 | METABOLIC SYNDROME IN CHILDHOOD CANCER SURVIVORS IN SOUTH INDIA

Sandhya Rajan, Latha Sneha, Divyalakshmi J, Santhini Tamilselvan, Julius Scott

Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India

Background: While childhood cancer treatment modalities have improved, the delayed effects of cancer treatment continue to compromise the quality of life in survivors. Metabolic syndrome (MS) is diagnosed based on the presence of three of the following findings – obesity, dyslipidemia, hypertension and insulin resistance per the World Health Organization (WHO) criteria. The increased risk of MS among childhood cancer survivors was first reported in the 1990's and is known to increase the incidence of cardiovascular disease in these individuals.

Objectives: Assess the frequency of MS in childhood cancer survivors at our institution. .

Design/Method: We conducted a retrospective chart review on pediatric cancer survivors, 4 – 18 years of age, who had been treated at Sri Ramachandra Medical Institute and Research Foundation between August 2015 and August 2017. Patients who received at least one year of treatment with

chemotherapy and/or radiation and surgery were included. Medical history, family history of diabetes, cardiovascular diseases, and hypercholesterolemia, Tanner staging, weight for height (<5y per WHO criteria), BMI (>5y per Indian Academy of Pediatrics IAP), blood pressure (NHLBI criteria), fasting blood sugar levels and lipid profile were obtained from the charts. Statistical analysis of the data was done using IBM SPSS statistical software (version 22).

Results: 97 patients were studied, 63.9% were male. 22.68% were under 5 years of age, 38.14% between 6–10 years and 39.18% above 11 years. Leukemia survivors comprised 39.18% of the sample and non- leukemic's were 60.82%. 51.5% were treated with chemotherapy alone, 19.5% with radiotherapy and chemotherapy, and 28.8% underwent surgery with radiotherapy and chemotherapy. Hypertension was found in 19.5% of the study group, dyslipidemia in 68%, impaired fasting blood glucose in 4.12% and 36.08 % were found to be obese. 10% of the study group was diagnosed with MS based on WHO criteria.

Conclusion: 10 % of our study population was found to have MS per WHO criteria. Individual metabolic complications were detected in 68% of the population. Acute Lymphoblastic leukemia (ALL) survivors appeared to be at high risk in our population. MS has been known to increase cardiovascular complications in cancer survivors. A multidisciplinary team approach to management of these patients is important to closely monitor and manage the long-term complications related to MS such as Type 2 Diabetes and atherosclerosis. Such an approach is essential to decrease long term morbidity and mortality from MS in this vulnerable population.

Poster # 607 | PROGNOSTIC GOALS OF CARE CONVERSATIONS FOR CRITICALLY ILL PEDIATRIC HEMATOLOGY/ONCOLOGY PATIENTS

Laurel Metzler, Tsovinar Arutyunyan, Raymond Hutchinson, Fola Odetola

Division of Pediatric Critical Care Medicine, University of Michigan, Ann Arbor, Michigan, United States

Background: The 5-year survival rate for childhood cancer exceeds 80%. However, up to 38% of these children require admission to the pediatric intensive care unit (PICU) within three years of diagnosis. These children account for approximately 10% of all PICU deaths, with mortality being higher for those post-hematopoietic stem cell transplant (HSCT). National guidelines recommend that providers share information regarding prognosis and treatment options within the first 48 hours of ICU admission. These prognostic goals of care conversations (PGOCC) are critical to the care of children with malignancies, a subpopulation at risk for increased mortality.

Objectives: To determine the frequency of PGOCC as well as describe differences in patient characteristics and critical care therapies by PGOCC status.

Design/Method: A retrospective cohort study was conducted using the University of Michigan Virtual PICU System database. PICU Admissions lasting longer than 24 hours for patients ages 0 to 25 years between July 1, 2011 and June 30, 2016 with an oncologic diagnosis and/or HSCT were identified. Data on PGOCC, patient demographics, diagnoses, PICU interventions, and outcomes were recorded and compared between children with PGOCC and those without using Chi square test for categorical variables and Kruskal-Wallis test for continuous data.

Results: Of 128 PICU admissions, 53% were male; the mean age was 10.5 years. The leading diagnoses were acute lymphoblastic leukemia (46%), acute myeloid leukemia (14%), lymphoma (14%), neuroblastoma (5%), and brain tumors (5%), and 43% of patients were post-HSCT. PGOCC was documented in 35 (27%) patients. In comparison with patients who did not have a PGOCC, children with a PGOCC were more likely to be readmitted to the PICU (45% vs. 15%, $p < 0.01$) and more likely to have had relapse of disease (41% vs. 18%, $p<0.01$). Patients with a PGOCC had higher severity of illness scores ($p = 0.02$), higher use of non-invasive (22.9% vs. 8.6%, $p = 0.04$) and invasive conventional ventilation (68.6% vs. 23.7%, $p<0.01$), and high frequency ventilation (25.7% vs. 4.3%, $p < 0.01$). Also, patients with PGOCC were more likely to receive continuous renal replacement therapy (37.1% vs. 5.4%, $p<0.01$), arterial catheterization (54.3% vs. 23.7%, $p<0.01$), and cardiopulmonary resuscitation (22.9% vs.1.1%, $p<0.01$).

Conclusion: In only 1 in 3 critically ill children with hematologic-oncologic disease is PGOCC held. Children with PGOCC were sicker and received more critical care interventions. Future research is needed to evaluate the content of PGOCC.

Poster # 608 | CNS TUMORS AND NEURODEVELOPMENTAL DISORDERS: A BRIEF SURVEY OF IN COMMON GENE ALTERATIONS

Michael Barbato, Maria Carter, Ziad Khatib

Nicklaus Children's Hospital, Miami, Florida, United States

Background: Central nervous system (CNS) tumors and autism spectrum disorder (ASD) represent significant disease cohorts in the pediatric population. ASD diagnoses in children have a prevalence of 2%, 1 in every 88 children in the United States. Additionally, more than 4,000 CNS tumors are reported in children age 0 to 19 years in the United States with brain tumors being the most common solid tumor and the leading cause of death among all childhood cancers. The genetic etiology of autism and CNS tumors is complex. Specific gene alterations present in certain cancers have similarly been described and suspected to play a role in ASD subtypes. Targeted therapy panels, like Foundation One (FO), have been beneficial in guiding treatment for some cancers based on distinct gene alterations. Given the genetic overlap, the potential for therapeutic benefit and crossover from such actionable gene target panels merit further exploration in ASD and CNS tumors.

Objectives: We aim to identify and describe genetic alterations with known actionable targets in cancer therapy from FO as potential diagnostic, therapeutic and research targets for neurodevelopmental diseases. We plan to discuss the common genetic alterations between our cancers and neurodevelopmental diseases described in the literature.

Design/Method: A retrospective chart review of pediatric patients (<21 years old) with CNS tumors was performed. FO data was extracted and compared to the literature. Each reported gene alteration from FO plus the keywords "autism", "psych" were used on PubMed to search for a suspected association if any with a neurodevelopmental disorder.

Results: Twenty-one patients representing a cohort of six unique (astrocytoma-five, ependymoma-six, GBM-four, glioma-three, nerve sheath tumor-one, ETMR-two) CNS tumors were investigated. FO produced eighty total with sixty unique gene alterations. Thirty-one (52%) of these yielded at least one published, suspected association to a neurodevelopmental disorder. The most common gene alterations were TP53-four, CDKN2A/B-five and BRAF-four. The main functional categories were cellular: proliferation, structure, differentiation and degradation; chromatin modeling; histone transcriptional modification; DNA methylation and repair; stRNA; and neural signaling.

Conclusion: Sixty unique gene alterations were found in our CNS tumor set using Foundation One. Thirty-one (52%) of these discrete alterations paired with at least one description in the literature as having been similarly altered in an ASD subtype. Many of these alterations have actionable targeted therapies presented through Foundation One for our CNS tumors and may be a relevant guide in the future of targeted therapy and research in ASD subtypes.

Poster # 609 | MONOCLONAL ANTIBODY UTILIZATION IN ADOLESCENTS AND YOUNG ADULTS: A POPULATION BASED STUDY

Pinki Prasad, Maria Velez, Heng-Yuan Tung, Lauren S. Maniscalco, Lauren S., Yong Yi, Xiao-Cheng Wu

Louisiana State University Health Sciences Center / Children's Hospital of New Orleans, New Orleans, Louisiana, United States

Background: Monoclonal antibodies (Mab) such as Rituximab were introduced as targeted agent for the treatment of B cell lymphomas in 2006. However, information on use of these drugs in the adolescent and young adult (AYA) population and its impact on survival are lacking.

Objectives: The objective of our study is to examine changes in use of Mab over time, factors associated with the use, and the survival benefit for the AYA population.

Design/Method: Data were from the Surveillance, Epidemiology and End Results (SEER) Patterns of Care Study which included 15-39-year-old AYA patients diagnosed with B-cell Non-Hodgkin Lymphoma (NHL) in 2006 and in 2013. We examined the association of age, race, gender, insurance, hospital residency, hospital bed, physician specialty, protocol registration, and diagnosis year with the utilization of Mab using multivariable logistic regression. The effect of Mab on survival was examined with a Cox proportional hazards survival model. Only 2006 data was used for survival analysis since 2013 data did not have sufficient follow-up time.

Results: A total of 1,413 AYA patients were diagnosed with B-cell NHL in 2006 (n = 502) and 2013 (n = 911). The use Mab increased from 71.6% in 2006 to 75.8% in 2013. The use of Mab did not vary significantly by age or gender. Compared to white patients, black AYAs were less likely to receive Mab (adjusted Odds Ratio (OR) 0.66, p = 0.02). Privately insured patients were significantly less likely to be treated with Mab when compared to Medicaid patients (adjusted OR 0.69, p = 0.03). Several factors that had statistical significance and were associated with utilization of Mab in 2006 diminished in 2013, such as no insurance and hospital bed size. In 2006, patients who received the drugs had significant improvement in survival (hazard ratio 0.56, 95% CI (0.35, 0.89)). We estimated that if the AYA population in 2006 who had not received Mab had received the drugs their estimated 5-year survival rates would have improved from 82.2% to 89.7%.

Conclusion: Monoclonal antibody therapy usage is associated with significantly improved survival in B-cell NHL AYA patients. Although the usage has increased in the AYA population from 2006 to 2013, the magnitude of the increase is low. Factors that affect the use of Mab include race and insurance

type. Further research is warranted to identify why privately insured patients are less likely to receive these drugs.

Poster # 610 | USE OF AN INSTITUTIONAL-TREATMENT ALGORITHM TO IMPROVE THE CONTROL OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

Joshua Goldman, Dorothy Wakefield, Regan Pulaski, Andrea Orsey

Connecticut Children's Medical Center, Hartford, Connecticut, United States

Background: Prevention of chemotherapy-induced nausea and vomiting (CINV) remains a challenge despite advances in pharmacotherapy and the development of CINV clinical practice guidelines by the Pediatric Oncology Group of Ontario (POGO) that have been endorsed by the Children's Oncology Group. Achieving control of CINV in pediatrics further is complicated by the difficulty young children have vocalizing their symptoms. Use of a validated nausea-assessment tool in conjunction with improved adherence to evidence-based guidelines may result in better quantification of symptoms and reduction of both nausea severity and vomiting frequency for pediatric patients undergoing chemotherapy. The Pediatric Nausea Assessment Tool (PeNAT) has been validated for children ages 4–18, and its integration into clinical practice may help optimize CINV control.

Objectives: This single-institution study sought to improve control of CINV in patients admitted for chemotherapy by standardizing the antiemetic regimens prescribed by all providers according to an institutional CINV algorithm developed from the POGO guidelines. We hypothesized that treatment using a standardized guideline would improve CINV control in patients admitted for chemotherapy.

Design/Method: A baseline cohort of 70 admissions for chemotherapy completed PeNAT assessments and CINV diaries prior to receiving chemotherapy, four times daily during each admission, and daily for 7 days following completion of chemotherapy from May 1, 2013 to January 31, 2014. Providers then were provided an institutional CINV treatment algorithm based on the POGO guidelines and received education at departmental meetings on appropriate implementation of this algorithm. A second cohort of 78 admissions completed PeNAT assessments and CINV diaries in a similar fashion from July 1, 2014 to December 31, 2016.

Results: Complete control of vomiting markedly improved following CINV guideline implementation (72% vs 52%, $p < .0001$) with treatment failure also significantly reduced (6% vs 23%, $p < .0001$). After controlling for the degree of emetogenicity of chemotherapy received, a patient was 3.33 times more likely to vomit prior to guideline implementation (OR 3.33, CI 1.96-5.56). There was no difference in nausea control, even after adjusting for the emetogenicity of chemotherapy.

Conclusion: Control of chemotherapy-induced vomiting (CIV) improved following widespread implementation of an institutional CINV treatment algorithm at a single institution. The severity of nausea reported remained unchanged which may reflect the difficulty of assessing nausea or an inadequate sample size. Future research may focus on CINV treatment management through the use of guidelines specifically for breakthrough CINV and delayed CINV.

Poster # 611 | EVALUATING THE PROFESSIONAL DEVELOPMENT NEEDS OF PEDIATRIC HEMATOLOGISTS-ONCOLOGISTS SERVING IN THE UNITED STATES MILITARY

Vandy Black, Thomas Russell, Mona Shah, Gary Crouch, Thomas Newton, Timothy Porea, Shelton Viola, Coleman Bryan, Sarah Vaiselbuh

University of Florida College of Medicine, Gainesville, Florida, United States

Background: ASPHO's Professional Development Committee (PDC) recognized pediatric hematologists-oncologists (PHOs) serving in the United States (US) military have unique professional development needs that may not be addressed by ASPHO or a similar professional society. These individuals may also encounter challenges when transitioning to a civilian career. However, barriers to professional development have not been systematically characterized.

Objectives: The objectives were to characterize the number of PHOs with current or prior military service (MPHOs) and to identify any unmet professional development needs.

Design/Method: A working group consisting of PDC members and both senior and early career MPHOs was formed. Initial comments were solicited by email from known MPHOs regarding potential gaps in professional development and interest in working with ASPHO to improve support of MPHOs. A survey was developed and piloted with four members of the advisory group, questions were revised based on their feedback, and a final version was distributed via the ASPHO website and online community forum. Targeted emails were sent to MPHOs identified through ASPHO and

military databases. Eligibility to complete the survey included 1) completion of a fellowship in pediatric hematology-oncology, AND 2) current or prior service as an active duty military provider. Quantitative and qualitative information were collected, including demographic data and perceived barriers to professional development. Responses were summarized using descriptive statistics.

Results: Sixty-five MPHOs were identified and 34 surveys were completed for a 52% response rate. Respondents were engaged in a variety of professional activities; 64% were male, 52% were serving active duty commitments, and 32% felt there were professional development gaps. Areas of concern were categorized into nine themes with the most concerning being 1) limited civilian knowledge of MPHO practices (76% of participants), 2) inability to attend professional society meetings (60%), and 3 possibility of deployment (56%). Participants expressed a desire for educational products to meet their specific needs and for networking opportunities with civilian colleagues. Qualitative analyses identified concerns about low patient numbers and practice size.

Conclusion: A subset of MPHOs perceive significant gaps in professional development. Additional research is needed to better define areas for intervention, but many of the concerns align with those of similarly sized civilian programs and may be addressed through professional society networking opportunities, such as an ASPHO special interest group.

Poster # 612 | EXAMINING PREDICTORS AND OUTCOMES OF FERTILITY CONSULTS AMONG CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH CANCER

Amanda Saraf, Stacy Whiteside, Nick Yeager, Kate McCracken, Daniel DaJusta, Jennifer Hansen-Moore, Joseph Stanek, Leena Nahata

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: Infertility is an established cause of distress and has a negative impact on quality of life among childhood cancer survivors. The American Society of Clinical Oncology has established guidelines on fertility counseling for individuals of reproductive age diagnosed with cancer, with the goal of improving reproductive and psychosocial outcomes. Studies have shown that instituting a fertility team that can provide counseling and discuss fertility preservation (FP) options results in improved patient satisfaction in patients with cancer.

Objectives: The goal of this study was to examine predictors of referrals to the multidisciplinary fertility team, and documented FP interventions among these patients.

Design/Method: An IRB-approved retrospective medical record review was performed at a large pediatric academic center. All patients with new cancer diagnoses receiving chemotherapy were included from January 2015 (when the fertility team was established) to present. A standardized abstraction form was used to collect information about: age at diagnosis, gender, cancer type, whether a fertility consult was placed, and documented FP interventions. Data were summarized descriptively and comparisons were made using non-parametric statistical methods.

Results: 265 patients met inclusion criteria, of which 152 (57%) were male. Cancer types were as follows: 126 leukemia/lymphoma, 51 CNS tumors, 44 sarcomas, 37 embryonal tumors, and 7 Langerhan's cell histiocytosis (LCH). The mean age was 8.2 years, (range <1-31 years). Overall, 27% of all patients had a consultation with the fertility team. Patients were significantly less likely to have a fertility consult if they were younger ($p<0.001$). Further, there were differences in the consultation rate between diagnoses, with 53% of sarcoma patients completing a consult, compared to 31% of those with CNS tumors, 41% of those with embryonal tumor, 44% of those with leukemia/lymphoma and none of the patients with LCH.

Conclusion: Our findings show that many children, adolescents, and young adults newly diagnosed with cancer are still not receiving fertility counseling despite: 1) an expanding body of literature supporting the need to provide this counseling, 2) guidelines published by several organizations recommending discussions about infertility risk and FP options, and 3) presence of a multidisciplinary fertility team. Specific strategies need to be developed to improve access for younger children, and for disease groups in whom fertility consults are underutilized, such as youth with CNS tumors, embryonal tumors, and leukemia/lymphoma.

Poster # 613 | SOCIOECONOMIC IMPACT ON PARENTAL TREATMENT RATES OF PAIN AND NAUSEA

Cristiana Hentea, Stephen Downs

Indiana University, Indianapolis, Indiana, United States

Background: Socioeconomic status (SES) has on impact on overall survival in the pediatric oncology population. Unfortunately, data are insufficiently detailed to explain the mechanism behind this phenomenon. How parents handle the health management demands placed on them at the time of a child's cancer diagnosis may represent a point of differentiation in health outcomes.

Objectives: Determine the association between socioeconomic factors, cancer literacy, and parents' understanding of home emergency management and their responses to instances of pain, nausea, and fever.

Design/Method: In a prospective observational study of parents whose children were newly diagnosed with cancer, we obtained demographic information and, using a validated instrument, (Dumenci, 2014) we evaluated cancer literacy. We tested understanding of the education parents received about home emergency management with a 6-item multiple-choice vignette-based questionnaire focused on actions needed in home scenarios. We then followed parents' actual behavior through periodic phone calls assessing instances of nausea, pain, and fever and their responses to these episodes.

Results: Preliminary analysis of 24 participants showed an average score of 4 on the 6-item parental understanding questionnaire (range 0–6). Variables associated with increased score were college-level education by 1.2 points (95% CI [.3 to 2.1]), private insurance by 0.9 points [.13 to 1.7] and adequate cancer literacy by 1.2 points [.2 to 2.2]. Actual behavior reported by families indicated that married parents and those with income above $75,000 were less likely to treat instances of pain by 51% (95% CI [28 to 72]) and 43% [6.6 to 79], respectively. White parents, those with college-level education, and those with adequate cancer literacy were less likely to treat instances of nausea by 31% [6 to 57], 29% [5 to 53] and 29% [5 to 53], respectively. No associations were found between socioeconomic markers and parental responses to instances of fever.

Conclusion: Our findings suggest an association between demographic and socioeconomic markers and improved parental understanding of home emergency management. Paradoxically, the same markers show a decrease in treatment response to pain and nausea. Larger prospective studies are needed to link this behavior pattern to health outcomes, and help inform the extent of SES impact on home emergency management.

Poster # 614 | WORKING TO STANDARDIZE CARDIOLOGY CARE IN SURVIVORS OF CHILDHOOD CANCER: A PEDIATRIC CARDIO-ONCOLOGY SCORE

Karen Effinger, William Border, Kirsten Rose-Felker, Elizabeth Record, Ann Mertens, Sharon Castellino, Lillian Meacham

Emory University/Children's Heathcare of Atlanta, Atlanta, Georgia, United States

Background: Cardiovascular disease is a leading cause of morbidity and mortality in childhood cancer survivors (CCS). Previous research showed wide practice variation in referral patterns to cardiology from the survivor clinic and in recommendations from cardiologists about the need for further testing or exercise restrictions.

Objectives: To develop a cardio-oncology algorithm in order to standardize referrals to cardiology and provide guidelines for cardiologists evaluating pediatric CCS.

Design/Method: Survivorship and cardiology experts developed a weighted scoring system for pediatric CCS who received cardiotoxic therapy based on time since treatment and risk factors identified by the Children's Oncology Group (COG) and American Heart Association (AHA). The cardio-oncology algorithm assigned a score of 1–21. The score range was categorized to guide cardiology referral: screening ECHO only (1-3), consider cardiology referral (4-6), recommend cardiology referral (7-9), and regular cardiology follow-up ($\geq$10). The algorithm also provides recommendations to cardiologists for screening and exercise modifications based on the score. After establishment of the algorithm, a convenience sample of institutional survivor clinic patient charts were retrospectively reviewed from the first month of each quarter from April 2015-March 2016 to validate the algorithm, evaluate referral patterns to cardiology, and assess cardiology recommendations.

Results: The retrospective chart review evaluated 243 patients (51% male; 61% non-Hispanic white; 46% leukemia survivors; median age at diagnosis 4.0 years [range 0–19.7]; median time off-therapy 7.2 years [range 2.3-18.2]). 230 patients (95%) received anthracyclines (median dose 154mg/m2, range 30–512) and 73 (30%) received cardiac radiation. Assigned cardio-oncology scores resulted in: 35% ECHO only, 47% consider cardiology referral, 16% recommend cardiology referral, and 3% regular cardiology follow-up. When evaluating detection rates of late effects by cardio-oncology score, 12 survivors (5%) had an abnormal ECHO: 1/83 ECHO only, 4/115 consider referral, 4/38 recommend referral, and 3/6 regular cardiology follow-up. Assessing referral patterns prior to initiation of the algorithm revealed forty-two survivors (17%) referred to cardiology: 8/83 ECHO only, 16/115 consider referral, 14/38 recommend referral, and 4/6 regular cardiology follow-up. Of the 37 patients seen by a cardiologist at our institution, 4 had further diagnostic testing ordered (i.e., stress test) and 7 received exercise restrictions.

Conclusion: A cardio-oncology algorithm and guidelines will standardize cardiac care for survivors by assigning a score to guide referral and cardiology practice after referral. Prospective clinical use has begun and review will occur in one year to determine changes in detection rates of cardiac late effects, referrals, and recommendations from cardiologists.

Poster # 615 | DELIRIUM: A PROSPECTIVE STUDY WITHIN THE PEDIATRIC HEMATOLOGY, ONCOLOGY, AND BONE MARROW TRANSPLANT (PHO) POPULATION AT A SINGLE INSTITUTION

Katrina Winsnes, Paul Sochacki, Carl Eriksson, Evan Shereck, Michael Recht, Kyle Johnson, Rebecca Loret De Mola, Linda Stork

Oregon Health and Science University, Portland, Oregon, United States

Background: Delirium affects 10–30% of patients (pts) in pediatric intensive care units (PICU) and is associated with increased length of stay, decreased attention in school, and post-traumatic stress disorder. The Diagnostic and Statistical Manual of Mental Disorders (DSM V) defines delirium as a "disturbance of consciousness […] with reduced ability to focus, sustain or shift attention" due to an underlying medical condition. Despite the medical complexity of the hospitalized PHO population, there are no published prospective studies looking at delirium in these pts.

Objectives: Hypothesizing that delirium is under recognized in the PHO population, we designed a year-long prospective study using a validated screening tool to determine the frequency of delirium in hospitalized PHO pts and to identify associated clinical factors.

Design/Method: Baseline frequency of pts with symptoms suggestive of delirium was determined through retrospective chart review using a data mining program of electronic medical records (EMR). For the prospective study, PHO and PICU nurses were trained to use the Cornell Assessment for Pediatric Delirium and to record scores within the EMR on all PHO pts once every 12-hour shift. Predetermined demographic and clinical variables were entered daily into a REDCAP database on all hospitalized PHO pts.

Results: Baseline frequency of delirium, without active screening, was determined to be 4.5% of hospitalized PHO pts. In the first 6 months of the prospective study, 405 consecutive admissions occurred among 152 unique PHO pts: 347 oncology, 30 hematology, and 23 stem cell transplant pts. 25 pts had at least 1 positive delirium screen, for a prevalence per admission of 6.2%. Statistically significant variables associated with delirium, at $p < 0.0002$ by univariate logistical regression, included prolonged length of stay, pt location (PICU vs PHO unit), and fever. Adjusting for length of stay, administration of benzodiazepines and opiates were also significantly associated with delirium, $p = 0.048$ and 0.044, respectively. On average, nurses completed delirium screening in 70% of each pts' 12-hour shifts. Study accrual ends in Jan 2018 and final data analyses will be reported in the abstract presentation.

Conclusion: Delirium does occur in the PHO hospitalized population and screening by trained nursing staff is feasible. Pts at highest risk appear to be pts with prolonged hospital stays, PICU admissions, or frequent use of benzodiazepines/opioids. Routine screening should improve our recognition of delirium and allow us to promptly intervene, or prevent delirium in an effort to avoid potential acute and long term consequences.

Poster # 616 | HEALTH OUTCOMES IN CONTEMPORARY SURVIVORS OF PEDIATRIC HODGKIN LYMPHOMA

Pranav Santapuram, Tatsuki Koyama, Cindy Schwartz, Nicholas Richardson, Louis Constine, Qinglin Pei, Kara Kelly, Suzanne Wolden, Debra Friedman

Vanderbilt University Medical Center, Nashville, Tennessee, United States

Background: With high survival rates for children and adolescents with Hodgkin lymphoma (HL), treatment regimens are now designed to maximize cure while decreasing risk of long-term health outcomes associated with chemotherapy and radiation therapy. Within contemporary treatment regimens, the comparison of toxicities experienced by patients receiving chemotherapy plus radiotherapy (CRT) versus only chemotherapy (CO) has not been studied extensively.

Objectives: This study examines select self-reported adverse health outcomes in survivors of contemporarily-treated pediatric HL to better understand the balance between efficacy and toxicity associated with chemotherapy and radiation therapy.

Design/Method: This is a prospective cohort of patients treated from 2002–2009 on Children's Oncology Group (COG) AHOD0031 that evaluated a response-based treatment paradigm in pediatric HL. Patient who received initial chemotherapy were randomized based on early response to continued chemotherapy, chemotherapy plus radiotherapy or augmented chemotherapy plus radiotherapy. Patients completed self-report questionnaires on health problems at 0, 1, 3, and 5 years following therapy. We examined selected patient-reported pulmonary, gastrointestinal (GI), cardiac and endocrine outcomes. Kaplan-Meier survival curves were used to determine probability of survival without the selected adverse health outcome. Log-rank tests were used to compare the CO versus the CRT group.

Results: A total of 1,051 enrolled patients, 251 patients in the CO group and 800 patients in the CRT group, completed 2,134 questionnaires at a median of 1.3 years after

completion of therapy (Q1, Q3: 0.6, 3.3) which were analyzed. The cumulative 10-year incidence of endocrine dysfunction was significantly greater in the CRT group versus those in the CO group (17% versus 6%; p<0.001), driven by the incidence of hypothyroidism (11% versus 2%; p<0.001). There were no significant differences in cardiac (7% versus 9%; p = 0.226), pulmonary (11% versus 10% p = 0.068), and gastrointestinal dysfunction (20% versus 17%; p = 0.317) between the CO and CRT patients.

Conclusion: This study demonstrates low cumulative incidence overall of organ dysfunction early post completion of contemporary therapy for HL. The addition of radiation therapy significantly increased risk for hypothyroidism, but with no higher risk noted for cardiac, pulmonary or GI dysfunction. Limitations include self-report status, potential selection bias, and relatively short latency period following end of therapy. Longer follow-up is needed to determine more delayed risks for organ dysfunction in order to best define the balance between therapeutic efficacy and long-term adverse health outcomes related to chemotherapy and/or radiation therapy.

Poster # 617 | COST ANALYSIS OF BRONCHOALVEOLAR LAVAGE AND RESPIRATORY TRACT BIOPSIES IN THE DIAGNOSIS AND MANAGEMENT OF SUSPECTED INVASIVE FUNGAL INFECTION

Jenna Rossoff, Margaret Locke, Surabhi Batra, Ben Katz, Nobuko Hijiya

Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, United States

Background: Identification of an organism via bronchoalveolar lavage (BAL) or respiratory tract biopsy (RTB) has historically been considered the gold standard for diagnosis of invasive fungal infection (IFI); however, data previously published by our group showed that these procedures infrequently lead to a change in management in children with an oncological diagnosis or undergoing hematopoietic stem cell transplant (HSCT). There is also a paucity of data on the cost of IFI in this population.

Objectives: To compare the costs of work-up and management of pulmonary IFI diagnosed based on CT scan alone versus CT scan or chest x-ray prompting a BAL or RTB.

Design/Method: We collected cost data on patients at Ann & Robert H. Lurie Children's Hospital of Chicago undergoing chemotherapy or within 6 months of HSCT who were suspected of having an IFI between 2007 and 2012. In order to include sufficient time to account for post-procedure complications but avoid including costs unrelated to IFI, data were included for 14 days from the day of their diagnostic scan or procedure.

Results: Cost data was available for 76 of the 101 patients previously studied. Thirty-six of these patients were diagnosed with suspected IFI based on CT only and 40 patients underwent BAL or RTB. When evaluating specific costs, inpatient beds costs were higher in the BAL and RTB group (median $1,555 versus $1,255, p = 0.01), yet there was only a trend towards higher costs for antifungal agents (median $1,635 versus $1,089, p = 0.26) and respiratory support (median $257 versus $0, p = 0.14). Many of the initial CT scans were not captured in the 14-day evaluation period for the BAL or RTB group based on the study design; however, even when accounting for CT scans up to a week prior these procedures, the total cost of CT scans was higher in the CT only group (median $963 versus $635, p = 0.0002), as they had more scans. Despite this, total costs were significantly higher for patients who underwent BAL or RTB versus CT scan only (median $14,087 versus $5,900, p <0.0001).

Conclusion: Combined with our previous data that BAL and RTB infrequently leads to a change in management in children with an oncological diagnosis or undergoing HSCT suspected to have an IFI, the significantly higher costs associated with these procedures makes these invasive diagnostic techniques even less desirable. Batra, Pediatr Blood Cancer, 2015.

Poster # 618 | COMPARISON OF INPATIENT MORTALITY AND SUPPORTIVE CARE UTILIZATION IN INFANTS AND NON-INFANTS WITH ACUTE LEUKEMIA

Azada Ibrahimova, Kelly Getz, Tamara Miller, Yuan-Shung Huang, Yimei Li, Alix Seif, Rochelle Bagatell, Brian Fisher, Richard Aplenc

Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States

Background: While infants >12 months of age with acute lymphoblastic leukemia (ALL) have a poor prognosis, infants with acute myeloid leukemia (AML) fare better despite more intensive therapy. There are limited data on this difference, particularly differences in supportive care requirements during induction therapy for infants.

Objectives: To compare induction mortality and resource utilization in infants relative to non-infants aged <10 years, separately for ALL and AML.

Design/Method: We used previously established cohorts of children treated for new onset ALL or AML at children's

hospitals in the US contributing to the Pediatric Health Information System. Patients with Down syndrome were excluded. Follow-up started on the first day of induction chemotherapy and continued until the earliest of: 35 days after commencement of chemotherapy, start of the subsequent course, or death. High acuity of presentation, defined as ICU requirements involving 2 or more organ systems within the first 72 hours following initial admission were compared using log binomial regression. 35-day inpatient mortality was compared using Cox regression. Resource utilization rates (days of use per 100 inpatient days) were compared using Poisson regression.

Results: A total of 10359 ALL (405 infants, 9954 non-infants) and 871 AML (189 infants, 682 non-infants) were included in the analyses. Infants were more likely to present with high acuity compared to non-infants for both ALL (12% and 1%, RR = 12.2, 95% CI:8.6, 17.5; p<0.0001) and AML (6% vs 3%; RR = 2.0, 95% CI: 0.96, 4.3; p = 0.06). Infants with ALL had higher inpatient mortality compared to non-infants even after accounting for differences in acuity of presentation (2.7% vs 0.5%, adjusted HR = 2.7 95% CI: 1.2, 6.1; p = 0.015). In contrast, inpatient mortality was more similar for infants and non-infants with AML (3.2% vs 2.1%, adjusted HR = 1.2 95% CI: 0.3, 3.9; p = 0.73) and comparable to rates among infants with ALL. Infants with ALL and AML had higher rates of utilization of fresh frozen plasma, cryoprecipitate, diuretics, supplemental oxygen, and ventilation relative to non-infants. Infants with ALL also had higher rates of total parenteral nutrition, ECMO, and patient controlled analgesics compared to non-infants.

Conclusion: Infants with ALL experienced significantly higher induction mortality compared to noninfants, a difference not entirely explained by acuity at presentation. Differences in RU among infants may reflect higher presentation acuity and greater treatment related toxicity. Further work is needed to elucidate the contribution of treatment related toxicity to early mortality in infants with ALL.

Poster # 619 | REDUCTION IN RISK OF BACTEREMIA BASED ON RESPIRATORY PATHOGEN PANEL RESULTS

Jessica Geaney, Matthew Schefft

Children's Hospital of Richmond and the Massey Cancer Center at Virginia Commonwealth University, Richmond, Virginia, United States

Background: Fever in a child with cancer is a medical emergency due to the significant risk of a serious bacterial infection. Many attempts have been made to risk stratify these patients. The respiratory pathogen panel (RPP) is a panel of polymerase chain reaction tests that identify seventeen common respiratory viruses and three bacterial infections. Samples are taken via nasopharyngeal swab. RPPs are frequently sent, but we do not have data to determine whether a positive result can lead to stratification to a lower risk of bacterial infection.

Objectives: (1) to determine the epidemiology of respiratory virus-associated fever in pediatric oncology patients (2) to determine whether a positive RPP is associated with reduced risk of bacteremia in this population.

Design/Method: This was a single-center, retrospective cohort study. We identified and reviewed the medical records of all pediatric oncology patients seen in our emergency department (ED) with fever from the introduction of the RPP in April 2014 to September 30, 2017. We reviewed the results of blood cultures, RPP, chest radiographs, and discharge summaries to identify sources of infection. We also identified the patients' cancer diagnosis, age, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC).

Results: 107 positive RPPs were found among pediatric oncology patients who presented to the ED with fever. The most common positive RPP findings were rhinovirus/enterovirus (REV) (45%), parainfluenza (14%), influenza (11%), coronavirus (11%), and polyviral (10%). Among patients with a positive RPP, 4% had bacteremia compared to 12% bacteremia among all pediatric oncology patients with fever (OR 0.42 [0.18-0.99], p 0.048). All cases of bacteremia were associated with REV. There was no bacteremia identified in patients with RPPs positive for other viruses (OR 0.0596 [0.0037-0.9715], p 0.048). REV positivity did not confer a lower risk of bacteremia than RPP negative patients (OR 1.01 [0.42-2.46], p 0.97). ANC (p = 0.87) and ALC (p = 0.89) less than 500, and number of patients with severe neutropenia (p = 0.27) were not statistically different between the REV and non-REV positive RPP groups.

Conclusion: RPPs positive for viruses other than REV reduced the likelihood of bacteremia in febrile pediatric oncology patients in the ED setting. Patients with bacteremia may have concurrent infection with REV. A larger study is warranted to determine if positive RPP results can inform clinical management of a child with febrile neutropenia.

Poster # 620 | SURVEY OF MOBILE TECHNOLOGY USAGE AND PERCEPTIONS BY CAREGIVERS OF CHILDREN WITH CANCER

Emily Mueller, Anneli Cochrane, Seethal Jacob, Aaron Carroll

Riley Hospital for Children at Indiana University Health, Indianapolis, Indiana, United States

Background: The usage of mobile health (mHealth), which refers to the application of mobile or wireless communication technologies to health and healthcare, has grown exponentially in recent years. mHealth tools have been used by caregivers of other vulnerable populations, but little has been focused on caregivers of children with cancer.

Objectives: To conduct a survey to understand the mobile technology usage, barriers, and desired mHealth tools by caregivers of children with cancer.

Design/Method: We conducted a mailed cross-sectional paper survey of caregivers of all children who were diagnosed with cancer at Riley Hospital for Children between June, 2015 and June, 2017. The survey contained 13 questions, both fixed and open-ended, in both English and Spanish. Up to three rounds of surveys were sent to those who did not respond.

Results: Of the 121 respondents, they were primarily parents (93.2%), median age was 40.7 years (range 23–63), and most were white (78.5%) and non-Hispanic/Latino (87.1%). The top three annual household income brackets included $50,000 to $74,999 (21.2%), $25,000 to $49,999 (20.3%) and under $25,000 (17.8%). The majority had an education: 35.6% college graduates, 22% graduate degree, and 18.6% high school education or GED. Nearly all respondents owned a smart phone (99.2%) and 61.2% owned a tablet. The majority used an iOS operating system (62.8%), while 49.6% reported use of a device with an Android operating system. All caregivers reported use of at least one mobile website/app regularly for their personal use. While 35.5% of respondents reported no barriers to mobile technology use, the top barrier selected was "data limitations" (21.5%). Overall, 84.5% wanted at least one medical management-related website/app: medical knowledge (58.7%), healthcare symptom tracking/management (47.1%), and medication reminders (43%). Healthcare system-related desires were high, as 59.5% wanted access to their child's medical record and 56.2% wanted a website/app to facilitate better communication with medical providers. There were no significant associations between socioeconomic status (income or education) with barriers or types of websites/apps desired by caregivers.

Conclusion: Since the vast majority of caregivers use mobile technology with minimal barriers, future research should focus on designing an mHealth tool to address the medical management needs by caregivers of children with cancer. By supporting caregivers through this type of mHealth tool, it could positively impact patient clinical outcomes through greater adherence to medications and treatment protocols.

Poster # 621 | A PROSPECTIVE PROTOCOL TO ASSESS RATES OF BACTERIAL RESISTANCE TO CEFTRIAXONE IN PEDIATRIC HEMATOLOGY-ONCOLOGY PATIENTS WITH FEBRILE NEUTROPENIA

Rachel Gallant, Phillip Bonney, Kristen Brannan, Amy Cruickshank, Leigh Peek, Cindy McCloskey, David Crawford

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States

Background: In children with fever and neutropenia, early initiation of targeted antibiotic therapy improves outcomes, yet there are no standards for choice of empiric antibiotics. In 2013 our institution implemented an Early Empiric Ceftriaxone (EEC) protocol to reduce time to antibiotic administration in febrile hematology-oncology patients who are potentially neutropenic when the absolute neutrophil count is not yet know. Ceftriaxone is given immediately after obtaining blood for culture and lab studies. In patients found to be neutropenic, ceftriaxone is discontinued and cefepime is initiated.

Objectives: The purpose of this retrospective study was to evaluate our EEC protocol in neutropenic patients by assessing ceftriaxone sensitivity of positive blood cultures and comparing rates of adverse outcomes with a cohort of patients treated prior to implementation of the protocol. We are now conducting a prospective study to more thoroughly investigate antibiotic sensitivities of organisms isolated from blood cultures of neutropenic patients.

Design/Method: Hematology-oncology patients with at least one positive blood culture between January 2011 and December 2013 were identified. Patient demographics, neutrophil count, antibiotic treatment, isolated organisms and sensitivities, and adverse outcomes (increased respiratory support, hypotension requiring intervention, and ICU admission) were obtained by retrospective chart review. Fisher exact test was used to compare dichotomous variables between patient groups. We are now prospectively identifying febrile neutropenic patients with positive blood cultures and performing antibiotic sensitivity testing to several antibiotics commonly used as empiric therapy for febrile neutropenia.

Results: Retrospectively, we identified 58 neutropenic patients with a total of 127 bacterial isolates from blood cultures. Of organisms isolated, 47 were tested for sensitivity to ceftriaxone and 23 (49%) were not sensitive, 6/18 (33%) of Gram-positive cultures and 18/29 (62%) of Gram-negative cultures. Ten of 16 (63%) EEC patients had an adverse outcome versus 13/26 (50 %) of non-EEC patients ($p = 0.277$). Notably, 31% of EEC patients required ICU admission

versus 4% of non-EEC patients (p = 0.049). Thus far our data obtained prospectively is revealing similar rates of ceftriaxone resistance with 9/19 cultures not sensitive to ceftriaxone (47%, CI 24.9%-71.1%).

Conclusion: In our retrospective study, no statistically significant difference was seen in overall adverse outcome rate between the two cohorts, though ICU admission rates were significantly higher in EEC patients. Ceftriaxone resistance rates were high in tested isolates, which is further supported by preliminary data from our ongoing prospective study. Given these data, EEC may not be effective at improving outcomes in febrile neutropenic pediatric hematology-oncology patients.

Poster # 622 | BEREAVED PARENT PERSPECTIVES ON END OF LIFE CARE FOR PEDIATRIC ONCOLOGY PATIENTS

Laura Sedig, Jessica Spruit, Trisha Paul, Melissa Cousino, Kenneth Pituch, Raymond Hutchinson

University of Michigan, Ann Arbor, Michigan, United States

Background: Approximately 1 in 5 children diagnosed with cancer will die of their disease, despite advances in treatment. While services such as palliative care are known to improve the experiences of children at the end of life, it is not clear what components of palliative care or similar end-of-life care are most beneficial.

Objectives: To identify what is most helpful, what is least helpful and what is lacking in end of life care from the perspective of bereaved parents.

Design/Method: We convened focus groups of bereaved parents who lost their child to malignancy within the past seven years. A clinical psychologist guided discussion about their experiences at the end of their child's life.

Results: Two focus groups of six parents each met in June 2017. The parents were predominantly female (11 female, 1 male) and had lost their children an average of 2.8 years prior (range 1–5.3 years). Two parents were in the same family. Nearly all patients were offered palliative care (10/11), all were offered hospice and most died at home (9 at home, 2 in the ICU). Parent discussion uncovered six broad themes: beneficial provider qualities, optimal communication, helpful systematic supports, struggles to feel like a good parent, struggles with a loss of control and unmet needs. Parents appreciated providers who were consistent, reliable and honest. Parents desired communication that was sensitive to the needs of the patient and family with a balance of hope and realism. Parents appreciated the tangible supports provided by social work and the emotional support of child life both for the patient and their siblings. Some parents struggled to define and advocate for their child's quality of life, especially when it led to disagreeing with the medical team. Several parents expressed frustration with unfamiliar caregivers in the hospital, especially trainees. They expressed a strong desire for more anticipatory guidance about the end of life including how to discuss it with their children. They also wished for a cancer-specific support group for bereaved parents.

Conclusion: Bereaved parents of pediatric oncology patients in our focus groups appreciated consistent, reliable providers who communicated with a balance of realism and hope. They appreciated the tangible and emotional support they received and wanted more anticipatory guidance at the end of their child's life. These results can help guide clinical care, especially in communities without strong palliative care support. Further research is needed to develop interventions to improve end of life care.

Poster # 623 | EDUCATING THE NEXT GENERATION: DEVELOPMENT AND IMPLEMENTATION OF A DELIVERY OF INFORMED CONSENT CURRICULUM FOR PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWS TO ENHANCE COMMUNICATION SKILLS

Paula Aristizabal, Bianca Perdomo, Nicholas Gloude, Courtney Thornburg, Dennis Kuo, Erin Fisher, William Roberts

University of California San Diego, San Diego, California, United States

Background: Clinical trials involving human subjects depend on informed consent (IC) to ensure ethical protections for participants. Parents of children with cancer often lack full understanding of the basic elements of IC for clinical trials. Additionally, the stress of their child's cancer diagnosis may affect their decision-making capabilities. This is especially problematic as these children rely on parents to fully comprehend clinical trials and weigh their benefits and risks. Physician communication is critical for effective family-centered care. The ACGME mandates that training programs teach and assess trainees' communication skills. However, there are currently no published curricula aimed at training pediatric hematology/oncology fellows to deliver IC effectively for cancer clinical trials.

Objectives: To develop and pilot-test a simulation-based curriculum to enhance communication skills of pediatric

hematology/oncology fellows in the delivery of IC for cancer clinical trials.

Design/Method: We developed, tested, and implemented the curriculum from 2016 to 2017 in two phases. In Phase-1, we reviewed literature on simulation-based curricula and completed a needs assessment to create a clinical scenario and full curriculum using standardized patients. Using Miller's pyramid model, fellows' assessments included: immediate de-brief, surveys to assess pre/post confidence and knowledge of the basic IC elements ("knows" and "knows how"), and 360-degree summative assessments compiled from fellow self-assessments, faculty, and standardized patients ("shows how"). After initial testing and refinements done with 1 fellow, in Phase-2, we implemented the curriculum with our 8 fellows. Likert scale (1 strongly disagree-5 strongly agree) and basic p values are reported.

Results: Fellows gave high mean ratings for training relevance (4.7) and standardized patients' preparedness (5). Almost all (4.9) reported they have used the knowledge gained in their clinical practice. Increase in self-reported confidence (pre/post) was noted in all domains: General -describing possible benefits of the clinical trial 3.5/5 vs.4.1/5 ($p = 0.025$), risks and potential side effects 3.5/5 vs.4.3/5 ($p = 0.004$), and explaining alternatives 3.1/5 vs.3.6/5 ($p = 0.016$); Research -discussing purpose of the clinical trial 3.1/5 vs.3.7/5 ($p = 0.006$), and randomization 3.3/5 vs.4.0/5 ($p = 0.046$); and Family-centered -addressing emotions during IC 3.6/5 vs.4.5/5 ($p = 0.004$), and delivering bad news 3.1/5 vs.3.6/5 ($p = 0.016$). Summative evaluation mean ratings for all fellows were 4.5 (range 4.1-4.9).

Conclusion: Our novel simulated-based IC Curriculum, significantly increased fellows' self-reported confidence and skills during IC delivery. Importantly, our IC Curriculum addressed not just research-related content but also management of parental emotional needs during the IC discussion. Next phase includes Kirkpatrick model program evaluation and dissemination across other training programs in our institution.

Poster # 624 | BRING THE CLASS TO THE HOSPITAL: SUCCESS STORIES OF CHILDHOOD CANCER SURVIVORS RETURNING TO MIDDLE SCHOOL IN TAIWAN AND WHAT WE CAN LEARN FROM THEM

Chen-Chen Cheng

National Kaohsiung Normal University, Kaohsiung, Taiwan, Province of China

Background: Taiwan's Childhood Cancer Foundation reported in 2016 that the 5-year survival rate of childhood cancer was 75%. As a result, many childhood cancer survivors were back in school after treatment. However, childhood cancer survivors' educational outcomes suffered because of their long-term absence from school and late effects of cancer and cancer treatment. A few school reentry protocols have been developed by the nursing professionals in Taiwan to facilitate students' return to school but remained experimental in nature and hardly accessible. Parents, students, and teachers were left to their own devices to make individual school reentry plans.

Objectives: This study aimed to examine and uncover the commonalities among three middle school students' successful school reentry experiences from their teachers' perspectives and to analyze the factors contributing to their success.

Design/Method: This is a qualitative interview study. In-depth semi-structured interviews were conducted with three middle school teachers in December 2017 about their perceptions, observations, and experiences working with adolescent childhood cancer survivors. The students were two boys with leukemia and one girl with bone cancer. They were diagnosed in the first year of middle school when they were 12–13 years old and returned to school for the third and the final year. These students met the following criteria for successful school reentry: regular school attendance, average/above average academic performance, friendship maintenance, and high school diploma.

Results: The theme – bring the class to the hospital was found to be the key to the adolescents' successful return to school. Without a prescribed school reentry protocol and in the face of limited bedside education services, the homeroom teachers, as links between school, home, and hospital, brought the class to their hospitalized students. They doubled as bedside teachers conducting lessons at the hospital or students' homes, became friends with the parents, witnessed firsthand the students' pain and triumph during treatment, brought the students back to school for visits and celebrations, delivered the classmates' wishes and news to the students, encouraged and welcomed classmates' visits to the hospital, and, together with parents and other teachers, developed flexible school reentry schedules for the students.

Conclusion: This on-going study demonstrated the critical roles and functions of homeroom teachers in successfully bringing the students back to school during and/or after cancer treatment. Further analysis will be focused on how and why these three homeroom teachers were able to carry out this unexpected task on top of their already full workload.

Poster # 625 | HUMANISM AND PROFESSIONALISM TRAINING IN PEDIATRIC HEMATOLOGY-ONCOLOGY FELLOWSHIP: RESULTS OF A MULTI-CENTER RANDOMIZED TRIAL

Jennifer Kesselheim, Shicheng Weng, Victoria Allen, Collaborative Group Fellowship Program Directors

Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts, United States

Background: A novel, 4-module, case-based curriculum entitled "Humanism and Professionalism for Pediatric Hematology-Oncology" (HP-PHO) aims to foster PHO fellows' reflection on grief and loss, competing demands of fellowship, difficult relationships with patients and families, and physician well-being and burnout. In small group facilitated sessions, fellows work to identify coping strategies and explore how the challenges of fellowship influence both their own doctoring and the patient experience.

Objectives: To administer the HP-PHO curriculum in a prospective, cluster-randomized trial, measuring whether exposure to this educational intervention, compared to standard conditions, fosters humanism and professionalism and improves satisfaction with training.

Design/Method: PHO fellowship programs (N = 20) were cluster-randomized to deliver usual training in humanism and professionalism (control) or the novel curriculum (intervention) during the 2016–2017 academic year. The primary outcome measure was the Pediatric Hematology-Oncology Self-Assessment in Humanism (PHOSAH). Secondary measures included a 5-point satisfaction scale, the Maslach Burnout Inventory (MBI), the Patient-Provider Orientation Scale, and the Empowerment at Work Scale. Participating fellows were pre-tested in summer 2016 and post-tested in spring 2017. A change score was calculated for each study instrument. We compared each outcome between arms using mixed effect models adjusted for pre-test score as a fixed effect and site as a random effect.

Results: Randomization yielded 59 intervention and 41 control fellows. The two arms did not significantly differ in distribution of fellow age, gender, or post-graduate year. The 9 intervention sites successfully administered 33 of 36 (92%) modules. Change scores on the PHOSAH were not significantly different between the control and intervention arms (adjusted mean difference = 0.5; 95% confidence interval [CI] -1.0, 2.0; p = 0.5). Compared to the control arm, fellows' exposed to the curriculum gave significantly higher ratings on several items within the satisfaction scale including satisfaction with their training on "physician burnout" (adjusted mean difference = 0.8; 95% CI 0.4, 1.2; p<0.001), "physician depression" (adjusted mean difference = 0.9; 95% CI 0.4, 1.4; p<0.001), "balancing professional duties and personal life" (adjusted mean difference = 0.7; 95% CI 0.3, 1.1; p = 0.002), and "humanism overall" (adjusted mean difference = 0.4; 95% CI 0.03, 0.9; p = 0.03). Change scores on other secondary measures were not significantly different between study arms.

Conclusion: Exposure to the HP-PHO curriculum did not alter fellows' self-assessed humanism and professionalism. However, the curriculum proved feasible to administer and intervention fellows expressed higher levels of satisfaction in their humanism training, indicating the curriculum's positive impact both for fellows and their learning environment.

Poster # 626 | A PATIENT-CENTERED APPROACH TO DEVELOPING A MOBILE-BASED PSYCHOSOCIAL INTERVENTION FOR ADOLESCENTS AND YOUNG ADULTS WITH SARCOMA

Elizabeth Donovan, Tara Cousineau, Lonnie Zeltzer, Laura Payne, Sarah Martin, Laura Seidman, Meredith Trant, Margie Weiman, Marla Knoll, Joe Burton, Noah Federman

UCLA David Geffen School of Medicine, Los Angeles, California, United States

Background: Recent work has documented significant levels of unmet needs among adolescents and young adults with cancer, particularly psychosocial challenges during the transition to adulthood, (e.g., abrupt disruption to school and social life, and social isolation). Given that adolescents and young adults drive mobile app use, a mobile-phone may be an ideal way to deliver a psychosocial intervention to adolescents and young adults with cancer.

Objectives: To use a patient-centered approach to inform a mobile-based mindfulness and social support intervention for adolescent and young adult patients with cancer.

Design/Method: Participants were ten AYA with sarcoma (50% female; 50% adolescents); parents of the five adolescents, and six healthcare providers (N = 21). Formative research involved three steps: (1) In-depth interviews were conducted with ten AYA with sarcoma; parents of the five adolescents, and six healthcare providers (N = 21). (2) Adaptations were made to an existing mindfulness app which offers a program for youth. Modifications included creating a 4-week "Mindfulness for Resilience in Illness" program, with 28 relaxation exercises, and the addition of videos featuring two sarcoma survivors as program hosts. Content

was informed by the mindfulness curriculum for adolescents, Learning to Breathe. (3) A private Facebook usability group was organized to (i) elicit beliefs about the mindfulness app and potential future enhancements, and (ii) promote social support.

Results: Results of the in-depth interviews revealed themes around adolescents' functioning and coping, including body image concerns; recurrence-related anxiety; anger over loss; and being overwhelmed by medical information. Themes from the interviews were incorporated into a demonstration version of the mobile app.

Conclusion: A patient-centered approach is widely recommended in the development of mobile-based health behavior change interventions and may be a useful way to inform development of a mobile-based mindfulness and social support intervention for adolescents and young adults with cancer.

Poster # 627 | COMMUNICATION TRAINING EXPERIENCE AND NEEDS ASSESSMENT FOR FELLOWS IN PEDIATRIC HEMATOLOGY-ONCOLOGY

Jennifer Snaman, Erica Kaye, Holly Spraker-Perlman, Zhaohua Lu, Deena Levine, Austin Dalgo, Melody Cunningham, Justin Baker

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: Medical trainees consistently report suboptimal instruction and poor self-confidence in communication skills. Despite these deficits, few training programs provide comprehensive pediatric-specific communication education, particularly in the provision of "bad news." An in-depth survey to examine the historical experience and communication needs of pediatric fellows was conducted at a large academic pediatric center as the first step towards the development of a comprehensive communication curriculum.

Objectives: To determine the previous educational and clinical experiences of pediatric subspecialty fellows, assess their levels of comfort in the context of various communication topics, and query potential modalities and topics for future communication training.

Design/Method: The needs assessment survey was developed using previously developed and validated questions and review of the literature. The survey was reviewed by internal and external pediatric oncology and palliative experts and pre-tested with a subset of trainees to enhance content validity.

Results: Thirty-two out of a total of 38 fellows completed the survey (84% completion rate), of which 81% were pediatric hematology-oncology or subspecialty fellows. Most fellows had participated in previous teaching sessions (97%), including those involving role play or simulation (75%). However, few fellows had received feedback from senior clinicians on their communication skills (31% of fellows had received feedback $\leq$ 3times). On a scale of 1-x, with 1 indicating "not well prepared," the mean score for 12 of 23 communication items was <3. Fellows felt least prepared to lead discussions around informed consent for experimental therapies, end of life care, and autopsy. Fellows indicated that didactic educational sessions and additional coursework were less useful strategies for improving their communication skills, whereas small group role play sessions with faculty and/or bereaved parent educators were most useful. Fellows' overall communication preparedness score was not correlated with post-graduate year but was positively associated with the number of times they previously had delivered bad news to patients and families. Fellows requested additional training on many topics, with greatest interest in learning skills to optimize communication with an angry patient or family. Additional topic requests included placing limitations on resuscitation, withdrawing/withholding further therapy, and age-appropriate inclusion of patients in difficult discussions.

Conclusion: Despite self-report of prior communication skills training, pediatric subspecialty fellows felt underprepared to participate in difficult discussions with patients and families. Learners identified role-playing and coaching with real-time feedback from other physicians and bereaved parents as more useful training strategies as compared to didactic sessions.

Poster # 628 | "THEY HELP WEAVE IT ALL TOGETHER": STAFF IMPACT ON BEREAVED PARENTS' GRIEF AFTER THEIR CHILD DIES OF CANCER

Carlos Torres, Lindsay Blazin, Robert Neimeyer, Justin Baker

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: When children die of cancer, parents must adjust to their child's absence amidst the lingering turmoil of what preceded their death: Witnessing their child undergo painful treatments, making difficult decisions, and anticipating a devastating loss, all the while hoping for a recovery. Adjustment to a child's death, as depicted by current bereavement literature, necessitates making meaning of one's loss. Professional care staff can help parents make sense of their

child's illness, and in turn, of their own parental experience during treatment. However, the extent to which relationships with professional care team members influence parents' ability to make sense of, and successfully cope with, their loss has not been examined.

Objectives: To examine how bereaved parents' interactions with their deceased child's pediatric oncology professional care team have impacted their grief symptoms

Design/Method: To better understand how interactions with professional care staff relate to parents' grief outcomes, we conducted a mixed-methods study examining staff impact on parental grief. Thirty participants whose children died of cancer one to three years ago completed an in-depth interview and psychometrically validated surveys measuring meaning-making, depression, and grief symptoms.

Results: Correlational analyses of the measures found that an increase in meaning making was associated with lower depressive and grief symptoms. A content analysis of the interviews found that many participants regarded staff "like family," had on-going relationships with staff after their child died, and described various ways staff interactions during treatment and after the child's death helped them make sense of their loss. In particular, participants described how interactions with staff have helped them find benefits in their loss and learn to create a new relationship with their child despite their physical absence. Quantifying the interview data and statistically analyzing it along with the measures found that participants' increased frequency of describing staff's positive impact on their grief correlated with higher meaning-making scores and lower grief symptom scores.

Conclusion: Our study found that bereaved parents who lost their children to cancer were articulate in sharing their experiences of staff engagement and communication during treatment, offering numerous examples of how staff aided them in making meaning of their loss that were reliably associated with their subsequent grief. We hope the results of this mixed methods research encourage further study of the importance of staff interaction with families during the critical period of their children's care, and the lasting impact this can have regardless of the treatment outcome.

Poster # 629 | BUILDING RESILIENCE DURING PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWSHIP: IMPLEMENTING SYSTEMATIC DEBRIEFING SESSIONS AND RESILIENCY CURRICULUM TO SUPPORT TRAINEES

Hiroto Kiguchi, Sonia Singh, Nitya Gulati, Viola Kivovich, Prachi Kothari, Eileen Nicoletti, Sameer Sait, Damani Taylor, Margery Davis, Reggie Saldivar, Julia Kearney, Stephen Roberts

Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Although resiliency has been recognized as necessary for healthcare professionals, trainees feel unprepared for the emotional challenges inherent in caring for sick and dying patients. Compounded by long hours, challenging work environments, and lack of formal training on handling emotionally difficult situations, many institutions are recognizing the need for interventions to reduce trainee distress.

Objectives: The goals of this fellow-led quality improvement initiative were: 1) to determine whether there is a need for emotional support amongst pediatric hematology and oncology fellows, 2) to provide formal resiliency and debriefing sessions, and 3) to measure feasibility, acceptability and effectiveness of implemented curriculum.

Design/Method: An anonymous survey to determine need for resiliency and debriefing sessions following a traumatic event was distributed to 24 active pediatric hematology & oncology fellows at Memorial Sloan Kettering Cancer Center in January 2017. Once need was established, an intervention consisting of a formal curriculum was developed and initiated in June 2017, involving: 1) scheduled and ad hoc debriefing sessions in response to traumatic events (including patient death, codes, interpersonal conflicts, end-of-life care); led by a psychiatrist and social worker with fellows and a pediatric oncologist mentor in attendance, and 2) a resiliency didactic curriculum, led by a palliative medicine specialist, focused on skills such as contesting cognitive distortions and mindfulness. The effectiveness of these sessions will be measured using follow-up anonymous surveys at 6 months (currently underway) and 12 months post-initiation of intervention.

Results: The initial survey demonstrated most trainees (19/24) were present at 3 or more deaths during their training, while less than half of respondents had attended a post-event debriefing session. 85% of respondents felt there was not sufficient emotional support from the institution for physicians caring for dying patients. A separate pre-intervention survey found all respondents (14/14) expressed a need for regular debriefings, and nearly all anticipated that they would benefit from such debriefings. Concerns identified by trainees that would preclude participation in the curriculum included preference to deal with emotional situations privately and time constraints.

Conclusion: Trainees identified a need for formal debriefings and resiliency skill development. The program was easily implemented, and is both feasible and acceptable with good attendance. Feedback received at the 6-month mark will determine deficits and possible improvements to the curriculum.

The 12-month survey will measure effectiveness of the program and whether it should be continued.

Poster # 630 | APPLICATION OF KDIGO GUIDELINES IN ASSESSING AKI IN PEDIATRIC PATIENTS NEWLY DIAGNOSED WITH ALL

Trevor Memmott, Daniel Ranch, Chatchawin Assanasen

UT Health San Antonio Long School of Medicine, San Antonio, Texas, United States

Background: Acute kidney injury (AKI) is a common but under-recognized complication among patients with leukemia. It is associated with prolonged hospital stays, increased mortality, progression to chronic kidney disease, and delays or changes in cancer therapy which may affect a patient's prognosis. However, data on AKI in pediatric patients with cancer is still lacking overall.

Objectives: We investigated the incidence of AKI in patients who were newly diagnosed with ALL at our center from January 2009 to September 2017.

Design/Method: We performed a retrospective chart review of all patients who were newly diagnosed with ALL from neonate to 18 years in our facility. We determined the incidence of AKI in our population using the Kidney Disease: Improving Global Outcomes (KDIGO) diagnostic criteria. We also assessed for nephrotoxic exposures, NCI ALL risk stratification and risk of AKI, and tumor lysis syndrome (TLS).

Results: We identified 62 patients diagnosed during the study period who met inclusion criteria. Median follow-up time was 29.5 months (range 3.6-60.3). The cohort was predominantly male (54.8%) and Hispanic (93.5%). Our analysis showed 51.6% had AKI by KDIGO criteria (29% Grade 1, 14.5% Grade 2, and 8% Grade 3), 62.5% had AKI on presentation, and 75% had multiple AKI episodes during the study period. Older age and longer length of hospitalization were associated with AKI ($p = 0.019$ and $p = 0.009$, respectively). There was no association between AKI and NCI ALL risk classification, contrast exposure, hyponatremia, elevated white blood cell count, uric acid levels, antimicrobial therapy, or diuretic use in this study.

Conclusion: AKI was a common finding in our study population. The majority had Grade 1 AKI by KDIGO criteria. However, AKI was associated with older age and a longer length of stay. Further study is needed to determine the short- and long-term impact of AKI on pediatric patients with ALL.

Poster # 631 | REGIONAL IMPACT OF A PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWSHIP PROGRAM

Daniel Moreira, Federico Antillón, Nickhill Bhakta, Paola Friedrich, Alvaro Pineda, Claudia Garrido, Patricia Valverde, Carlos Rodriguez-Galindo, Mauricio Castellanos, Monika Metzger

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: In some regions, the availability of trained pediatric oncologists is a limiting barrier for the care of children with cancer. In 2003, the Unidad Nacional de Oncología Pediátrica (UNOP) and the Universidad Francisco Marroquín School of Medicine in Guatemala established a pediatric hematology/oncology fellowship program sponsored by St Jude Children's Research Hospital to provide Central America and the Caribbean with well-trained specialists. A systematic analysis of the impact of fellowship programs in pediatric oncology has never been done, especially in the context of a regional education program.

Objectives: This study sought to analyze the impact of the UNOP fellowship program based on the regional number of providers, pediatric cancer centers and patient volume. In addition, it sought to characterize the jobs and scientific output of the graduates. The impact will be evaluated in the context of a cost analysis.

Design/Method: To define the volume of providers, pediatric cancer centers and patients, the directors of pediatric cancer centers in Central America were sent an online survey to obtain these data. All the centers contacted maintain an updated hospital-based patient registry. In addition, the 22 graduates of the fellowship program were also sent an online survey, asking about their job at graduation, current role and scientific productivity. The cost analysis will include assessment of direct costs including salaries and stipends for away rotations, as well as the indirect costs of faculty time spent teaching.

Results: Since the establishment of the UNOP fellowship program, the region has more providers for pediatric cancer ($p<0.05$) and centers treat a larger volume of patients ($p<0.05$). Two new centers have opened with graduates of the program. All but one graduate practice pediatric oncology (21/22) and the majority do it in their country of origin (19/21). No graduate practices outside of this region. Almost half of the graduates (44%) hold a leadership role at their institution. The majority of their time is spent in the public sector (>95%). The majority of graduates participate in clinical research (61%) and have participated in the creation or implementation of therapeutic protocols (67%). On average,

the graduates have published 2 peer-reviewed articles since completion of training.

Conclusion: The UNOP fellowship program has had a favorable impact on pediatric cancer care in the region, contributing to the capacity to treat a larger volume of patients. Graduates practice pediatric oncology in the region in the public sector, frequently hold leadership roles and are scientifically productive.

Poster # 632 | FACTORS ASSOCIATED WITH ABANDONMENT OF PEDIATRIC CANCER TREATMENT IN PERU: A MULTICENTER COHORT STUDY

Liliana Vasquez, Rosdali Diaz, Sharon Chavez, Ivan Maza

Edgardo Rebagliati Martins Hospital, Lima, Peru

Background: Abandonment of treatment is a major cause of treatment failure and poor survival in children with cancer in low- and middle-income countries. The incidence of abandonment in Peru has not been reported.

Objectives: The aim of this study was to examine the prevalence and associated factors of treatment abandonment in pediatric patients with cancer of Peru.

Design/Method: We retrospectively reviewed the socio-demographic and clinical data of children referred between January 2012 and December 2014 to the two main tertiary centers for childhood cancer, located in Lima, Peru. Definition of treatment abandonment was used from the SIOP (International Society of Paediatric Oncology) PODC (Paediatric Oncology in Developing Countries) Abandonment of Treatment Working Group recommendation.

Results: Data of 1135 children diagnosed with malignant solid tumors and lymphomas were analyzed, of which 209 (18.4%) abandoned treatment. Univariate logistic regression analysis showed significant higher abandonment rates in children living outside the capital city, Lima ($p<0.001$); prolonged travel time to a tertiary center (> 5 hours; OR 2.75, $p = 0.002$); living in a rural setting (OR 3.44; $p<0.001$) and lack of parental formal job (OR 4.39; $p = 0.001$). According to cancer diagnosis, children with retinoblastoma were more likely to abandon compared with other solid tumors. In multivariate regression analyses, rural origin and lack of formal parental employment were independently predictive of abandonment.

Conclusion: Treatment abandonment prevalence in our country is high and closely related to socio-demographical factors. Treatment outcomes could be substantially improved by strategies that help prevent abandonment of therapy based on these results.

Poster # 633 | CREATION OF A STANDARDIZED ASSESSMENT TOOL FOR GLOBAL PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWSHIP PROGRAMS

Daniel Moreira, Monika Metzger, Paola Friedrich, Carlos Rodriguez-Galindo

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: To improve the quality of a pediatric hematology/oncology fellowship program, a systematic assessment must be performed that can evaluate its current state and identify areas of opportunity, as well as modifications over time. Unfortunately, widely agreed-upon metrics of quality for pediatric hematology/oncology fellowship programs currently do not exist. This is particularly important in this field due to the global shortage of specialists. For this reason, an assessment instrument that is applicable throughout the world must be created.

Objectives: The St. Jude Global Education Program Assessment Tool (EPAT) is a novel instrument that seeks to evaluate pediatric hematology/oncology fellowship programs around the world in systematic and objective way. EPAT will help determine key performance indexes that are relevant for quality education in pediatric hematology/oncology fellowship programs and establish the framework for improvement.

Design/Method: Firstly, key domains to be evaluated for program assessment were identified a priori based on the continuum of pediatric hematology/oncology fellowship programs in the context of geography and educational structure. Subsequently, questions were formulated to evaluate these key domains, seeking to assess elements involved in ensuring competence in clinical practice, academic productivity and regional impact. Due to the novelty of this tool and the lack of defined metrics of quality, EPAT relies on expert opinion in a two-step process: internally in the Department of Global Pediatric Medicine at St. Jude Children's Research Hospital and, subsequently, from a panel of experts in global pediatric oncology and medical education from around the world.

Results: Ten key domains were identified to evaluate all aspects relevant to training programs around the world, regardless of educational and geographic context. Questions have been created to assess these domains and, to make EPAT quantitative, these have assigned weights with a value reflective of their relative importance. This grading system allows for a score in each key domain, permitting monitoring of

changes over time. EPAT is currently at the stage of external expert review, and subsequently will be piloted in five fellowship programs around the world to provide different geographical and patient care contexts for its validation. Once EPAT is finalized, it will be distributed to pediatric hematology/oncology fellowship programs around the world to be applied.

Conclusion: EPAT proposes a novel strategy to assess training programs in a systematic way that includes all aspects relevant for a training program in a global context. This tool will help guide improvements in pediatric hematology/oncology fellowship programs and assure a well-trained workforce.

Poster # 634 | ADAPTATION OF CANCER CENTER SURVIVORSHIP CARE PLAN GUIDELINES IN THE PEDIATRIC ONCOLOGY POPULATION

Christine Smith, Barron Patterson, Debra Friedman

Vanderbilt University Medical Center/Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, United States

Background: With the improvement in pediatric oncology patient survival and outcomes in the past several decades, monitoring for recurrence and long-term effects of therapy has become even more important. The utilization of personalized treatment summaries and survivorship care plans (SCPs) is one way to communicate this information with patients and families. The American College of Surgeons Commission on Cancer (CoC) created a standard regarding provision of SCPs to 50% of eligible patients by December 31, 2017 as a metric for accreditation of all cancer centers. The standard applies to all patients with stage I, II, and III cancer diagnoses and requires creation of the SCP within one year of diagnosis or six months of completing treatment. During implementation at our pediatric cancer center, we identified barriers to use of the guidelines in the childhood cancer setting.

Objectives: Define eligibility for an SCP for pediatric oncology patients to include all patients with curative intent and to deliver SCPs within six months of finishing therapy.

Design/Method: Using chart review and a cancer center registry query, we identified childhood cancer patients potentially eligible for an SCP by collecting stage, goal of therapy, and dates of treatment. All patients with curative intent were deemed eligible for an SCP regardless of stage I-IV. Patients being followed in the oncology clinic for post-treatment surveillance and care were included even if they had received an SCP in the survivorship program or were greater than six months off therapy at time of implementation. As expected in the pediatric oncology population, acute lymphoblastic leukemia (ALL) was the most common diagnosis comprising 31.5% of patients. ALL is stratified into risk groups instead of surgical staging categories, and treatment duration is greater than one year, unlike many adult-onset malignancies. These differences required interpretation of the guidelines to apply to our pediatric population for ALL and other pediatric diagnoses with non-surgically based staging.

Results: Our pediatric oncology clinic has to date provided SCPs to 141 of 277 eligible patients by adapting the guidelines to focus on patients with curative intent to receive an SCP by six months off therapy.

Conclusion: Cancer staging guidelines and goals for curative intent as well as lengths of treatment vary between the pediatric and adult populations. The CoC guidelines require adaptation for optimal applicability to the pediatric oncology population.

Poster # 635 | INITIAL SUCCESS OF AN INTERDISCIPLINARY COMMUNICATION COURSE FOR FELLOWS

Daniel Cannone, Mark Hoffman, Mark Atlas, Alice Fornari, Maria Labarca, James Dolimpio, Jane Wickey, Thomas Bradley, Beatrice Bloom, Diana Martins-Welch, Sindee Weiss-Domis, Anna Levy

Northwell Health Monter Cancer Center/Cohen Children's Medical Center, Lake Success, New York, United States

Background: Education in communication for fellows in fields that require difficult discussions with families are few in nature. Adult learning pedagogies such as role play are under-utilized in medical education, and have been shown to be as effective as traditional teaching methods such as lecture. An 8-module course for fellows in Hematology/Oncology, Hospice and Palliative Medicine, Radiation Oncology, and Pediatric Hematology/Oncology was implemented in January/February 2017. 12 fellows participated in the program. Topics covered including fundamentals of communication, coping and spirituality, delivery of bad news, communicating with families, sexual dysfunction during treatment, palliative care/death and dying, and burnout.

Objectives: Overall goal of this course is to foster holistic physicians who views their patients as people with cancer, not cancer patients, and physicians that can communicate effectively with their patients throughout the disease continuum. By the end of the course, learners should be able to practice the fundamental principles of good communication.

Design/Method: Fellows initially participated in a pre-course OSCE to establish baseline skills. OSCE was facilitated by the Center for Learning and Innovation at Northwell, and included actors portraying a pediatric patient and family member to whom the fellow had to break bad news. Two months later, the course was carried out over the span of eight weeks and included didactic sessions followed by 45 minutes of role play scenarios. Five of the eight modules included role play, with faculty members serving as simulated patients. After the course, a second breaking bad news OSCE was held. Both OSCEs were filmed, and feedback was given by the on-site actors. Additionally, faculty members were given access to the videos in an on-line format and were given an evaluation tool to assess the fellows' performance pre- and post-intervention. Fellows were given subjective surveys pre- and post-course as well.

Results: Subjective data from participants showed a noticeable increase in comfort level in all areas on the pre- and post-course survey. Data obtained from OSCE videos showed improvement in communication skills as assessed by SPs and faculty members using a new evaluation tool developed by faculty.

Conclusion: Initial first-run data shows that this course is successful in improving communication skills as well as increasing fellows' comfort level across several domains of communication. Future directions for our course include improving and validating our assessment tool, expanding our topic base to include more AYA and pediatric scenarios, faculty development for improved role play, and investigating impact on practice after course completion.

Poster # 636 | PHYSICAL ACTIVITY INITIATIVE IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS: A PILOT STUDY

Jennifer Dean, Kathy Scarbalis, Mike Reing, Stacey Stuart, Hannah Mason, Alissa Mills

Pediatric Specialists of Virginia, Falls Church, Virginia, United States

Background: Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer with approximately 2900 children diagnosed each year. Survival rates have improved significantly over the past several years. Children with ALL are at risk for developing musculoskeletal complications during and after completion of treatment, which can contribute to impaired activity, elevated body mass index (BMI), and risk for complications. Interventions involving physical activity could improve musculoskeletal strength as well as overall health in these children.

Objectives: The aims of this study are to examine the feasibility of a directed physical activity program for children with newly diagnosed ALL during the initial intensive phase of therapy and to evaluate the overall health and quality of life of children participating in the directed physical activity program.

Design/Method: All subjects will receive education materials about the importance and safety of physical activity and a nutrition handout. All subjects will also participate in the directed physical activity program under the supervision of a trained physical therapist for at least 40 minutes every week for 12 weeks. The program will entail four stations including a cardiovascular, balance/proprioception, strength and flexibility, and coordination and cardio. Feasibility will be assessed by tracking the participation rate throughout the study period. Other assessments will be made at study entry, at the end of 12 weeks of physical activity initiative and 3 months after completion of the intervention. Assessments include overall strength and flexibility, weight, height, BMI, blood pressure and performance scores. Descriptive statistics will be used for this study.

Results: A total of 10 patients, 3 male and 7 female, enrolled in the study over a 9.5 month period. Patient ages ranged from 5–16 years. Half of the patients enrolled have completed the 12 week program and all 5 patients had stability or improvement of their physical functioning scores. Further data collection and analysis is ongoing.

Conclusion: Patients in the early intensive phase of ALL therapy are at risk for complications that can affect their physical functioning. A directed physical activity protocol may improve their overall physical functioning. Patients may not need specific physical therapy; however a directed physical activity program appears to be beneficial for these patients. The main roadblocks to successful completion of the program were difficulty with scheduling, strain on the parents and patient from treatment, unplanned admissions for fever, as well as nausea and fatigue at time of visit.

Poster # 637 | COMMUNICATION SKILLS TRAINING FOR PEDIATRIC RESIDENTS: LEARNING TO GIVE BAD NEWS

Katharine Halligan, Yevgeniya Bamme, Heather Frenz, Lauren Weintraub

Albany Medical Center, Albany, New York, United States

Background: Communication skills are a core competency highlighted by the ACGME. Increasing resident confidence in delivering difficult news has been shown to lead to more

effective communication. Currently, the majority of residency programs lack formal training in communication skills.

Objectives: Our objective was to demonstrate feasibility and efficacy of integrating a standardized-patient based training program for communication skills into the curriculum of pediatric residents

Design/Method: To date, 10 pediatric and 4 medicine/pediatric residents have participated in the program during the intern year. The program consists of three, two-hour long sessions, in which each resident is given several opportunities to act out case scenarios with a standardized patient. Scenarios included informing a parent of their child's new cancer diagnosis and disclosure of a positive HIV test to a teenager. Residents received post hoc peer to peer, and preceptor to learner feedback. Pre and post-program surveys were completed by residents.

Results: Following course completion residents reported an increase in confidence in multiple areas of communication including giving a difficult diagnosis ($p<0.05$), discussing a poor prognosis ($p<0.02$), responding to different patient/family member emotional responses i.e. crying or anger ($p<0.01$), and organizing vital information to be relayed ($p<0.01$).

Conclusion: In conclusion, communication skills training of pediatric residents is feasible and provides a platform for developing valuable skills not taught elsewhere within the curriculum.

Poster # 638 | HETEROGENEITY IN SCHOOL RE-ENTRY PROGRAMS FOR CHILDREN RETURNING TO SCHOOL FOLLOWING TREATMENT FOR CANCER

Cassandra Hastings, L. Kate Gowans

Oakland University William Beaumont School of Medicine, Rochester, Michigan, United States

Background: For children with cancer, transitioning back to school during or after treatment can be challenging. Literature supports the need for school re-entry programs to ease this transition. However, these programs vary widely among pediatric cancer institutions with little data addressing their program components. Data from this study provides information on current school re-entry programs across these institutions.

Objectives: One objective of this study was to assess for correlation between the presence of a school re-entry program and other factors, such as geographic location and institution size. A second objective was to establish a list of differences between institutions' school re-entry program components. Finally, we aimed to describe current school re-entry practices, as well as program benefits and perceived areas for improvement.

Design/Method: Pediatric institutions in the United States with membership in the Children's Oncology Group were offered enrollment in this study. A member of each institution was invited to participate in a survey established by the research team. This person was closely associated with the institution's school re-entry practices. Each interview queried institution demographics, as well as program components (e.g., participants, target audience, resources). Comment was also collected on program benefits and potential for improvements. Analysis of transcripts was performed using Pearson's correlation to assess for relationships between institution size, geographic location, and program presence. Grounded theory was used for analysis of benefits and improvements.

Results: Thirty-nine of forty-one pediatric institutions who were offered enrollment participated in this study. Twenty-nine institutions (76%) indicated the presence of a school re-entry program, and ten (24%) stated they had none. No correlation was found between institution size and the presence of a school re-entry program ($p = 0.627$, ns). There was also no correlation found between institution location and the presence of a school re-entry program ($p = 0.921$, ns). A major theme surrounding the benefits of having a program included education for the returning student's peers. For those with programs, perceived improvements included increasing staffing and the ability to offer more services.

Conclusion: The results do not support the hypothesis that the presence of a school re-entry program is influenced by the size and geographic location of the treating institution. However, data seem to suggest that available staffing may influence the presence of a program. Future studies are needed to address other potential influences, as well as to take an evidence-based approach to determine the effectiveness of the interventions present in these programs.

Poster # 639 | GENETICS/GENOMICS CURRICULUM FOR PEDIATRIC HEMATOLOGY/ONCOLOGY FELLOWS

Mark Atlas

Cohen Children's Medical Center/ Zucker School of Medicine at Hofstra-Northwell, New Hyde Park, New York, United States

Background: Genetics/Genomics is evolving at an extremely rapid pace. Current advances lead to individual algorithms

toward disease treatment for each disease with multiple branch points. Fellows learn only a fraction of the knowledge and there is no formal approach to teaching critical analysis of information and application algorithms toward disease. Additionally, as knowledge evolves extremely rapidly, any approach must teach self-acquisition and application of evolving discoveries.

Objectives: To create, implement and evaluate a novel curriculum for Genetics/Genomics targeted toward Pediatric Hematology/Oncology Fellows

Design/Method: The curriculum includes four components: 1) Genetic and Genomic Medical Knowledge, with one initial Team-based Learning session and weekly online multiple choice questions; 2) Essential Pathways, which will teach molecular pathways common in oncogenesis and relevant to targeted therapy in microteaching sessions with using auditory, visual and tactile learning; 3) Knowledge Acquisition and Clinical Judgment, to allow learners to gain experience into researching data available, then developing and prioritizing potential treatment plans using Problem-based Learning sessions in which they will Stage a patient, research treatment options, prioritize and present findings; and 4) Synthesis to demonstrate independent ability to research and recommend therapy through an independent project in which the learner, given a case, will present the case and research findings, genetics/genomics, molecular pathways and make recommendations for therapy in molecular tumor board for faculty and fellows. To evaluate, we plan to recruit 12 to 16 institutions, match for size of programs and implement in half and evaluate 2nd and 3rd year fellows in both groups by MCQ exam and satisfaction surveys.

Results: IRB submission and pilot in progress.

Conclusion: The creation of a multi-module, adult-learning based curriculum for Genetics and Genomics in Pediatric Oncology is feasible. Implementation and evaluation are necessary to demonstrate efficacy.

Poster # 640 | RETROSPECTIVE STUDY OF NEUROLOGIC, BEHAVIORAL, AND OPHTHALMOLOGIC SIDE EFFECTS OF DINUTUXIMAB THERAPY AT A SINGLE INSTITUTION

Hannah Lust, Laura Sedig, Sindhu Ramchandren, Beth Stuchell, Rhonda McDougall, Rajen Mody, Rama Jasty Rao

University of Michigan, Ann Arbor, Michigan, United States

Background: Neuroblastoma is the most common extracranial solid tumor in children. Chimeric anti-GD2 antibody ch14.18 (dinutuximab) therapy has improved the survival of children with newly diagnosed high-risk, neuroblastoma patients as well at the time of first relapse/progression. Acute neuropathic pain is a well-documented side effect of dinutuximab administration. However, additional adverse effects including sensorimotor neuropathy, ocular symptoms, and behavioral changes have been described. The incidence and severity of these effects are currently not well-documented in pediatric patients. With improved long term survival of patients receiving this modality, it is important to look for the potential late effects of dinutuximab.

Objectives: To determine the incidence and severity of neurologic, ophthalmologic, or behavioral changes after dinutuximab administration at our institution.

Design/Method: We performed a retrospective chart review using our electronic medical record. We included all patients with high-risk neuroblastoma between the ages of 1 and 21 years at our institution diagnosed between 1997 and 2017 who received dinutuximab. Patients with history of opsoclonus-myoclonus syndrome or gross sensorimotor neuropathy prior to receiving dinutuximab were excluded. We examined clinical documentation for subjective reports and objective exam findings of neurologic, ophthalmologic, or behavioral changes. We also looked for referrals made to neurology, ophthalmology, physical medicine & rehabilitation (PM&R), and psychology.

Results: Twenty-two patients met inclusion criteria. At the time of chart review, 15 patients were alive and 7 were deceased. Eighteen patients received dinutuximab per ANBL0032; 5 patients received dinutuximab per ANBL1221. Of these 22 patients, 11 patients reported symptoms of interest and 5 reported multiple symptoms. Six patients reported symptoms that began at least 12 months after completing dinutuximab. Nine patients had objective findings on exam, including decreased deep tendon reflexes, abnormal pupils, and nearsightedness. For 10 patients, 15 referrals were made to ophthalmology, PM&R for neuropsychologic testing, or neurology. Two patients who reported symptoms of interest were not referred to a specialist.

Conclusion: Neurologic, ophthalmologic, and behavioral symptoms were commonly reported and demonstrated on exam among pediatric patients with high-risk neuroblastoma who received dinutuximab. It is important to identify these effects so that appropriate specialist referrals can be placed for adequate management of these changes. We recognize that these symptoms may not be solely due to dinutuximab as these patients receive other agents including opioids, so a prospective trial is needed to further evaluate the long-term effects of dinutuximab and to determine how best to screen for these effects.

Poster # 641 | NUTRTIONAL STATUS AND NUTRIONAL SUPPORT THERAPY AFTER ONCOLOGIC DIAGNOSIS: A RETROSPECTIVE, DESCRIPTIVE STUDY

Courtney Culbertson, Ann-Marie Brown, Sieglinde O'Neil, Vicki Vitale, Ann Stratton

Akron Children's Hospital, Akron, Ohio, United States

Background: Pediatric cancer is the leading cause of disease-related death in children in the United States (U.S.). In 2014, over fifteen thousand children were diagnosed with cancer in the U.S. This population is at high risk for malnutrition due to the multimodal therapies they receive: surgery, chemotherapy, radiation therapy, antibody therapy, and/or bone marrow transplant. Adverse effects of these therapies include taste changes, loss of appetite, diarrhea, vomiting, and/or mucositis, making it difficult for the children to be able to consume adequate amounts of nutrition during therapy. There is no "gold standard" measurement tool for identifying patients at risk for malnutrition. Nutritional status is not frequently evaluated as a component of clinical trials. Assessment of anthropometric measurements (weight, height, Z-scores) at diagnosis, as well as over the duration of treatment, can assist in the early identification of malnutrition. The incidence and prevalence of malnutrition in this population is unknown at Akron Children's Hospital. The purpose of this study is to describe the nutritional status and provision of nutritional support therapies in pediatric patients during their first year post new oncologic diagnosis.

Objectives: Identify the incidence and prevalence of malnutrition across oncologic diagnostic categories over the first twelve months post diagnosis.

Design/Method: We performed a retrospective records review of all patients newly diagnosed with cancer in 2015 at Akron Children's Hospital. Demographic and anthropometric data was collected at time of diagnosis and nutritional status categorized by Z score. Anthropometric and nutrition support data was then collected every two months for the first year after diagnosis along with incidence of unplanned inpatient admissions.

Results: A total of 65 patients were included in the analysis, with 6.2% malnourished at time of diagnosis; 12.3% developed malnutrition the first year. Patients with solid tumors represented 50% of patients with pre-existing or acquired malnutrition. Overall, 47% of patients received at least one nutritional support modality. Patients with pre-existing or acquired malnutrition had a non-significant increase in unplanned admissions ($p = 0.1196$).

Conclusion: Our study demonstrated that patients with solid tumors were found to be at increased risk of pre-existing and acquired malnutrition, followed by leukemias, and experienced higher incidence of unplanned admissions in the time period observed. Prospective, multi-center replication of this study, including detailed collection of nutrition therapies is recommended to guide development of diagnosis specific nutrition support guidelines.

Poster # 642 | A STANDARDIZED APPROACH USING PHLEBOTOMY TO TREAT TRANSFUSIONAL IRON OVERLOAD IN PEDIATRIC AND YOUNG ADULT ONCOLOGY PATIENTS

Rachel Phelan, Nathan Schloemer, Melissa Acquazzino, Debra Schmidt, Sandra Steffes, Lynnette Anderson, Richard Tower II, J. Paul Scott

Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Background: Pediatric and young adult oncology patients treated with intense chemotherapy have a high incidence of transfusional iron overload. Iron deposition can lead to heart failure/arrhythmias, liver abnormalities, endocrine dysfunction, ineffective erythropoiesis, and increased cancer and mortality risk. However, there is a paucity of data regarding recommendations for management of transfusional iron overload in these cancer survivors. Consequently, long-term complications of transfusional iron overload specific to these patients have not been assessed.

Objectives: To assess screening and phlebotomy-based treatment algorithms for this population.

Design/Method: A retrospective chart review of pediatric and young adults who completed oncology management, had iron overload, and initiated phlebotomy treatment was conducted. Tiered screening occurred in patients that received at least 5 packed red blood cell (pRBC) transfusions. Patients were recommended for evaluation and possible phlebotomy if: (1) liver iron concentration (LIC) >5 mg of iron/gram dry weight liver tissue by ferriscan and/or (2) cardiac MRI T2* < 20 ms. During phlebotomy, iron status was assessed quarterly and phlebotomy discontinued with LIC <5 or normalization of ferritin/imaging LIC verification. Descriptive statistics were employed to report the characteristics of the study population. Spearman correlations were utilized to describe associations between transfusions, LIC, ferritin, iron saturation and number of phlebotomy sessions.

Results: Twenty five survivors underwent phlebotomy. The mean age was 11.6 years (SD 6.1) and 10 (40%) were female. Oncologic diagnoses: ALL (36%), AML (8%), NHL (12%), Ewing sarcoma (16%), Osteosarcoma (4%), Neuroblastoma (12%) and CNS (12%). Patients received a median of 25.0 (IQR 17 – 34) transfusions. Median number of phlebotomy sessions was 6 (IQR 4–8) over 0.36 years (IQR 0.28 – 0.59). Prior to phlebotomy, median LIC was 7.5 mg/g (IQR 5.6-9.0) and ferritin was 1110.0 ng/mL (IQR 700 – 2030). No patients demonstrated abnormal cardiac T2* MRI (n = 18). 23 (92%) patients completed phlebotomy. One discontinued due to poor vascular access. No patients developed iron deficiency. LIC was reduced by a median of 2.4 mg/g (IQR 1.1 – 3.6) and ferritin by 586 ng/mL (IQR 366–875). Correlation between number of transfusions and phlebotomy sessions was poor (R2 = 0.017).

Conclusion: Management guidelines are lacking for transfusional iron overload in pediatric and young adult survivors of cancer. We demonstrate a phlebotomy algorithm that is effective and tolerated. Correlation between number of transfusions received and phlebotomy treatments was poor, necessitating serial assessments. Using this management algorithm, prospective studies can evaluate the effect of iron removal on iron overload complications in this patient population.

Poster # 643 | RETENTION OF VACCINE-MEDIATED HUMORAL IMMUNITY IN THE POST-THERAPY PEDIATRIC ONCOLOGY POPULATION

Jamie Cashell, Smita Dandekar, Melanie Comito, Amy Brown, Doug Leslie, Myron Levin, Scott Schmid

Penn State Children's Hospital, Hershey, Pennsylvania, United States

Background: Cancer therapy leads to an impaired immune system that takes time to recover. It is important to ensure that these survivors have adequate immunity to prevent common yet potentially severe childhood illnesses. No validated guidelines currently exist for surveillance testing or re-immunization in this population. Retrospective analysis involving a small cohort of pediatric cancer patients treated at Penn State Children's Hospital showed 46% of patients screened for varicella immunity after therapy completion did not have adequate disease titers.

Objectives: To determine the proportion of pediatric cancer survivors who have lost humoral immunity to previously received vaccines; to determine the rate of response to single dose boosters or full vaccine series in seronegative subjects after one booster.

Design/Method: Pediatric cancer survivors treated at the Children's Hospital who are at least 12 months from completion of cancer therapy are prospectively tested for antibody levels to hepatitis B, tetanus, varicella, measles, and 6 strains of pneumococcus (4, 6B, 9V, 18C, 19F, and 23F). Samples are analyzed by the CDC for measles and varicella avidity. Seronegative subjects by commercial studies, are eligible to receive booster vaccines. Titers are rechecked at least 6 weeks after boosters to re-evaluate immunity; if still seronegative, subjects will receive the entire vaccine series. Titers are finally tested at least 6 weeks after the final dose of the vaccine series. Immunity analyzed after therapy, after boosters, and after vaccine series.

Results: Of 37 pediatric cancers survivors who completed therapy, 78% were non-immune to hepatitis B, 92% non-immune to >50% of pneumococcal strains tested, 24% non-immune to measles, 54% non-immune to varicella, and 2% non-immune to tetanus. 1 of 13 subjects who received MMR vaccine after therapy and prior to study enrollment did not have protective antibodies to measles. Of the 15 subjects who received varicella vaccine after end of therapy and prior to study enrollment, 6 did not maintain protective antibody levels. CDC results for measles and varicella are pending, as well as repeat studies after vaccine boosters and series.

Conclusion: A significant percentage of pediatric cancer survivors do not retain immunity to hepatitis B, pneumococcus, measles, and varicella. After one booster, a high percentage of subjects did not develop protective immunity to varicella. Only 1 subject did not have immunity to tetanus, which is consistent with the high immunogenicity of tetanus toxoid. Formal guidelines are needed to protect this population from vaccine-preventable illness post-therapy.

Poster # 644 | CANCER SURVIVORS WHO EXERCISE REGULARLY SEE IMPROVEMENTS IN PHYSICAL FITNESS EVEN WITHOUT WEIGHT LOSS

Madhu Gowda, Anne Mauck, Lisa Collins

Children's Hospital of Richmond at Virginia Commonwealth University Health System, Richmond, Virginia, United States

Background: Childhood cancer survivors are at risk for being overweight. Diet and physical exercise are important in maintaining a healthy lifestyle and weight; however, it has been reported that cancer survivors are less active than their peers. One reason for this may be that there are no clearly established risk-based exercise recommendations for cancer survivors. Another reason may be that providers tend to focus

recommendations for exercise more towards patients who are overweight.

Objectives: To describe changes in physical fitness of childhood cancer survivors who exercise.

Design/Method: 'Moving Forward' is a wellness and physical fitness program that The Center for Care Beyond the Cure at CHOR offers in partnership with the ASK Childhood Cancer Foundation and the YMCA. The program is available for any childhood cancer survivor between 8y and 18y age, being seen at our center. Survivors define their fitness or wellness goals and then work with a trainer once a week (at least) for 30 min sessions throughout the year to achieve these goals. Baseline and ongoing measurements for core strength, endurance, overall strength and balance were collected. The average of each of the parameters of all participants were compared from the beginning to the end of the program.

Results: During the time period of 2016–2017, we had 13 survivors, ages 8–18, representing 7 childhood cancer diagnoses (Wilm's tumor, Leukemia, Non-Hodgkin's Lymphoma, Osteosarcoma, Ewing's Sarcoma, Langerhans Cell Histiocytoma and Medulloblastoma) who completed the program. Over the year, there was a 30% increase in endurance as measured by the average of the miles walked in 6 minutes, 40% increase in core strength as measured by the average number of sit-ups in 30 secs, an 80% and 44% increase in overall strength as measured by the average weight lifted by leg press and the average weight lifted by chest press, and a 10% increase in balance as measured by the average number of seconds balancing on a single leg. In addition, each child had actually gained weight in the process with an approximately 10% increase in the average of the weights of all children.

Conclusion: There are benefits to regular exercise beyond weight control, and improvements in physical fitness can be seen even without weight loss. Regular physical exercise results in improved physical fitness and should be universally advocated to all patients. Determining insulin resistance, measuring changes in fatigue and wellness perception following exercise are future directions that we intend to explore.

Poster # 645 | IDENTIFYING OPPORTUNITIES FOR IMPROVED COMMUNICATION BETWEEN ADOLESCENT AND YOUNG ADULT ONCOLOGY PATIENTS AND THEIR ONCOLOGY CLINICIANS

Natasha Frederick, Anna Revette, Kevin Campbell, Kerry Moss, Ashley Speckhart, Lisa Kenney, Jennifer Mack

Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Improvements in adolescent and young adult cancer patient (AYA) survival rates and quality of life outcomes have lagged behind those of children and older adults, highlighting a need for research targeting this unique population. Current literature supports the value of strong AYA-clinician communication, notably in facilitating therapeutic alliance, however little is known about AYA communication priorities during cancer care and barriers to optimal AYA-clinician communication.

Objectives: To explore AYA and oncology clinician communication priorities and to identify barriers and facilitators to AYA-oncology clinician communication.

Design/Method: Semi-structured interviews were held with 21 AYA cancer patients and survivors (ages 15–25 years) from a single large academic institution and 22 oncology clinicians (physicians and nurse practitioners) from 7 academic institutions in the northeastern United States. Interviews were conducted in English by phone or in person. All interviews were audio-recorded and transcribed verbatim. Analyses were aided by Nvivo11 software.

Results: AYAs identified a wide range of topics as important to discuss with clinicians. The most frequently identified topics were 1) side effects of treatment (with an emphasis on physical appearance and function, n = 16), 2) social issues (including friendship, family, and school, n = 13), 3) looking ahead to the future (n = 12), and 4) sexual & reproductive health (including future fertility, contraception, and romantic relationships, n = 8). Clinicians prioritized 1) cancer treatment and side effects (n = 17), 2) emotional and psychological health (n = 11), and 3) sexual and reproductive health with a focus on fertility risk and fertility preservation (n = 8). AYA reported facilitators to good communication including an open and long-established relationship with the clinician (n = 16) and clinician engagement in age-appropriate and patient-directed conversations (n = 7). Barriers included parental presence during visits (n = 7). Clinicians reported barriers including 1) clinician discomfort (not feeling well-equipped to discuss psychosocial topics such as sexual health, spirituality, and relationships with peers, n = 13), 2) presence of parents/family (n = 12), and 3) perceived patient discomfort discussing specific topics (such as sexual health, n = 10). Clinicians acknowledged the need for collaborative efforts with additional team members (i.e. nurses, psychosocial providers) to assist in meeting AYA communication needs.

Conclusion: AYA and clinician-reported communication priorities are largely aligned. However, AYAs emphasize some topics, such as social function, appearance, and sexual health that are not highly prioritized by clinicians, which may result in gaps in care for AYAs in treatment and in survivorship. These data identify opportunities for intervention, including clinician education, patient and family education, clinic-based

intervention, and systems-based changes that can be developed and tested.

Poster # 646 | TELEPHONE COMMUNICATION BETWEEN NURSES AND PRIMARY CARE PHYSICIANS (PCPS) USING THE SITUATION, BACKGROUND, ASSESSMENT, AND RECOMMENDATION (SBAR) TOOL TO COORDINATE SURVIVORSHIP CARE: A FEASIBILITY STUDY

Wilhelmenia Ross, Jaime Rotatori, Nina Kadan-Lottick

Yale University School of Medicine, New Haven, Connecticut, United States

Background: Primary care physicians (PCPs) cite lack of knowledge and inadequate communication with the oncology team as major barriers to providing recommended surveillance for late effects of treatment to childhood cancer survivors. A standardized telephone handoff to PCPs post-therapy is a potential strategy to increase survivorship care by PCPs through interactive communication.

Objectives: To determine the feasibility of a structured telephone communication using the Situation, Background, Assessment, and Recommendation (SBAR) communication tool delivered by a trained oncology nurse to increase PCP knowledge and willingness to provide survivorship care.

Design/Method: From 12/12/16 to 1/23/17, a registered nurse expert in childhood cancer survivorship attempted to contact by telephone the PCPs of the 30 most recent patients attending Yale's Childhood Cancer Survivorship Clinic that were <18 years old, English-speaking, and ≥2 years post-treatment. All PCPs had been previously sent an individualized survivorship care plan (SCP) that listed the patient's previous treatment history and recommended surveillance tests. Upon successful contact and after confirming receipt of the SCP, the nurse explained the definition of late effects, description of patient's diagnosis and treatment history, and associated potential late complications and schedule of recommended surveillance tests. The PCP was also asked about his/her ability and willingness to provide needed surveillance for late effects in the future.

Results: Overall, 26 of 30 PCPs were successfully contacted with a median of 1 phone call (range: 1–3) that lasted a median of 6 minutes (range: 3–10) after a median of 1 business day (range: 0–18). No PCPs ended the call mid-conversation. All 26 PCPs were receptive and expressed appreciation for the call. Twenty-five of 26 (96%) PCPs expressed an understanding of the material discussed and endorsed belief in their ability and willingness to provide late effects surveillance for their patients. No PCPs questioned discussing their patient's care with a nurse versus a physician.

Conclusion: Interactive, structured communications between nurses and PCPs by telephone are feasible and are associated with high-levels of PCP confidence in providing survivorship care.

Poster # 647 | PEDIATRIC CANCER HOSPITALIZATIONS PAID FOR BY MEDICAID ARE LONGER THAN THOSE PAID FOR BY COMMERCIAL INSURANCE

Sarah Whittle, Heidi Russell

Baylor College of Medicine, Houston, Texas, United States

Background: Childhood cancer (CC) admissions account for 5% of non-newborn pediatric hospitalizations. These hospitalizations are longer and more expensive than other hospitalizations. Admission payer (Medicaid or commercial) reflects both health policy and sociodemographic status.

Objectives: The objective of this study was to determine if length of stay (LOS) or cost of CC admissions differed by payer.

Design/Method: We used the 2012 Kids Inpatient Database, a sampling of all pediatric hospital discharges in the United States. Analysis for this study was limited to admissions containing a cancer diagnosis in any discharge ICD-9 codes. Admissions were further subcategorized by discharge codes according to diagnosis (leukemia, lymphoma, solid tumor and brain tumor) and reason for admission (chemotherapy, procedure, infection, non-infectious toxicity or "other"). Charges were converted to costs using cost-to-charge ratios. Multivariable linear regression models were performed to control for age, gender, race, reason for admission, and diagnosis.

Results: There were 105,752 weighted admissions for children with a cancer diagnosis in 2012. Of these admissions, 40.5% had Medicaid, 50.6% had commercial insurance, and less than 1% had other payers. The mean LOS for Medicaid admissions was 7.37 days (95% CI 7.2-7.5), compared with 6.33 days (95% CI 6.2-6.4) for commercial insurance. Surgical admissions accounted for the largest difference in length of stay with Medicaid admissions being 2.77 days longer than those covered by commercial insurance (11.19 days vs 8.42 days), however, the difference was significantly different for all reasons for admission. In multivariable analysis admissions associated with commercial insurance were 6% shorter

($p<0.001$), accounting for approximately one hospital day, than admissions associated with Medicaid after controlling for other variables including race. The mean overall cost for Medicaid admissions was $23,464 (95% CI 22840–24088), compared with $21,849 (95% CI 21343–22356) for commercial insurance. In the multivariable model, cost was collinear with race.

Conclusion: LOS and cost of admissions associated with Medicaid differed from those associate with commercial payers. Medicaid admissions were 6% longer on average than commercial insurance, accounting for a difference in length of stay of approximately one day although the difference varied with the reason for hospitalization (chemotherapy, surgical procedure, infection, other toxicity, other). Costs of admissions were not independent of race. Further investigation into potential explanations for this difference including differential access to home care needs, outpatient reimbursement differences, social indications for prolonged hospitalization, and provider biases, is warranted.

Poster # 648 | THE STATE OF PEDIATRIC ONCOLOGY IN ARMENIA: CHALLENGES AND ACHIEVEMENTS

Ruzanna Papyan

Yerevan State Medical University, Yerevan, Armenia

Background: Pediatric cancer is a major cause of morbidity and mortality among children surpassed only by accidents. Despite improved outcomes in high income countries (HIC) survival rates remain poor in the developing word. There are various diagnostic and therapeutic limitations contributing significantly for the survival gap.

Objectives: The main objective of the study is to to evaluate the outcomes of pediatric cancer in Armenia and identify diagnostic and therapeutic limitations in the country.

Design/Method: We conducted a retrospective study among 97 (≤18 years old) children with cancer (solid tumors and hematological malignancies), who were diagnosed and treated at the Clinic of Chemotherapy of Muratsan Hospital Complex of Yerevan State Medical University between 2008 and 2016. Those patients, who didn't receive chemotherapy for any reason were not included in the study cohort. Epidemiological, social, medical information was collected through the patient charts review. This included patient age at diagnosis, sex, place of residence (city vs village), the educational level and employment status of parents, type of cancer, stage, presentation of symptoms, first medical specialty consulted and the time consulted, initial work-up, the type of treatment received, information on the diagnosis/treatment received abroad.

Results: At our clinic during the mentioned period of time the majority of patients presented with hematologic malignancies-71%. 77 (74.6%) patients had information on diagnosis delay. Average delay in diagnosis was about 42 days. In 33% of cases the first contact with "healthcare system" was through pediatrician, and in 20% with surgeon. Out of 19 relapsed patients 10 received salvage treatment in Armenia and 4 abroad. From those who stayed for treatment in Armenia 4 patients survived. Majority of relapsed patients had acute lymphoblastic leukemia. From 35 leukemia patients immunophenotyping and cytogenetics were available for 26 (74.3%) patients; the majority of missing cases were between 2008 and 2012, when these diagnostic modalities were not available or affordable in the country. 43 (45%) patients received part of diagnosis and/or treatment abroad. The most frequent reason for going abroad was bone marrow transplantation, otherwise none available in Armenia. Out of 97 patients 22 were lost to follow-up, 15 patients had a fatal outcome. 60 patients were in remission at a median follow up of 3.57 years.

Conclusion: Unavailability of cancer registry and several essential diagnostic/treatment modalities, luck of multidisciplinary care and palliative support, high rate of out-of-pocket expenses were among the main challenges of pediatric cancer care in Armenia.

Poster # 649 | DEVELOPMENT AND IMPLEMENTATION OF PHARMACOGENETIC RISK PREDICTION MODELS IN PEDIATRIC ONCOLOGY

Tessa Bendyshe-Walton, Shahrad Rassekh, Gabriella Groeneweg, Colin Ross, Bruce Carleton

University of British Columbia, Vancouver, Canada

Background: Adverse drug reactions (ADRs) are increasingly recognized as important and sometimes irreversible complications of cancer treatment. Anthracyclines and cisplatin are effective chemotherapeutic agents, but their use can be limited by cardiotoxicity (anthracyclines) and ototoxicity (cisplatin) in up to 60% of patients. Genetic variants that can be used to predict who is most at risk of developing these ADRs have been discovered and replicated.

Objectives: To create pharmacogenetic risk prediction models for anthracycline and cisplatin toxicities and discuss results with oncologists to facilitate incorporation into treatment decision-making when appropriate.

Design/Method: Risk prediction models were developed from the linear regression of strongly-predictive genomic variants (odds ratios ≥ 3) discovered and replicated in at least three patient populations. These models were used to assess an individual patient's genomic risk of developing cardiotoxicity from anthracyclines or hearing loss from cisplatin. Risk results were returned to oncologists showing where the specific patient's genetic risk of toxicity lies on a continuum between the lowest and highest risk groups across all studied patients using a multi-gene model. Interviews were conducted with patients, families, and oncologists to determine how results were valued and utilized.

Results: 227 patients have been genotyped and had their genetic risk results returned to their oncologists. The first 140 patients have been characterized to determine the impact these test results have had on their clinical care. Results were described as being useful in decision-making by patients and/or oncologists in 100% of cases. Additionally, for patients in the most extreme risk groups (highest and lowest risk), a change in treatment plan was ordered 30% of the time for cisplatin patients and 35% of the time for anthracycline patients. This included increased cardiac and audiological monitoring, the addition of a protective agent, or choosing an alternative treatment protocol if the risk outweighed the benefits of remaining on the current treatment plan. In interviews, patients indicated that they felt more involved in decision making, and felt reassured by understanding their genetic risk of toxicities.

Conclusion: Genetic risk prediction models for anthracycline cardiotoxicity and cisplatin ototoxicity were highly utilized by patients and oncologists in decision-making. Results were found to be an important tool for informing patients of the risk of ADRs during cancer treatment, and resulted in patients and their families feeling more involved in decision-making.

Poster # 650 | THE ASSOCIATION OF BLOCK GROUP POVERTY STATUS AND EXECUTIVE FUNCTIONING AMONG CHILDHOOD CANCER SURVIVORS

Hamza Gorsi, Christine Trask

Hasbro Children's Hospital/ Rhode Island Hospital, Providence, Rhode Island, United States

Background: Childhood cancer survivors are at increased risk of developing executive dysfunction, and low socioeconomic status (SES) has been identified as one of the mediators of executive functioning. Previous studies have used traditional measures of SES, such as parents' education level, family annual income and occupation. But more recently, area based socioeconomic measures like block group poverty status are deemed to be more useful in monitoring of social inequalities in health in the United States. Block Groups are statistical divisions of census tracts and generally contain between 600 and 3,000 people.

Objectives: The current study aims to understand the association of block group poverty status (percentage of households in family's block group of residence living below the federal poverty level) with executive functioning among cancer survivor children.

Design/Method: We used a retrospective cohort of 67 childhood cancer survivors. Relevant information was collected from the medical record, administrative data sets and parent-filled surveys. Address information was geocoded using ArcGIS 10.2 to obtain data on the block group poverty status. A priori cut-points were set to represent block groups with families living below poverty level at 0%, 0.1% to 9.9%, and ≥10.0%. Executive functioning were assessed through a parent-rated instrument, the Behavior Rating Inventory of Executive Functions (BRIEF). Multiple linear regressions were used to determine the relationship between block group poverty status and the BRIEF scores.

Results: Data was examined from 67 families of childhood cancer survivors, ranging in age from 6 to 18 years. In this sample, 32.8% families reported an annual income <$60,000, 32.8% reported income between $60,000 and $100,000 while 34.3% reported annual income ≥$100,000. Primary care giver of 85.1% of cancer survivors had more than more high school education, and 31.3%, 41.8% and 26.9%, of families were living in a block groups with 0%, 0.1-9.9% and ≥10% poor households respectively. Block group poverty level was not significantly associated with annual income levels (Spearman's rho = 0.14, p = 0.25), or parental education level (Spearman's rho = -0.02, p = 0.84). In a step-wise multiple linear regression, there was no statistically significant association seen between block group poverty status and executive functioning after adjusting for co-variables in the final model.

Conclusion: Future prospective study with a bigger sample size, longer follow up period and more robust measures of the executive functioning like a clinician administered test are needed to understand the effect of block group poverty status on executive functioning.

Poster # 651 | THE DAY 100 TALK: FEASIBILITY AND ACCEPTABILITY OF A STRUCTURED INTERDISCIPLINARY COMMUNICATION INTERVENTION TARGETED TO THE EARLY TREATMENT PERIOD FOR CHILDHOOD CANCERS

Angela Feraco, Sarah Brand, P. Jeet Das, Hasan Al-Sayegh, Clement Ma, James Tulsky, Joanne Wolfe

Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Current communication practices in pediatric oncology may not facilitate optimal information exchange and family support. Parents may withhold hopes, worries, and cancer-related beliefs, and during the initial months of childhood cancer treatment, they perceive insufficient anticipatory guidance. Additionally, oncologists tend to surmise rather than to probe these concerns, particularly when psychosocial or "non-medical" in nature.

Objectives: The Day 100 Talk (D100) is an interdisciplinary communication intervention that uses a 3-part conversation tool (Family Worksheet, Conversation Guide, and Summary Sheet) to guide a 30-minute interdisciplinary discussion. D100 seeks to facilitate family adaptation and engagement with cancer care by: 1) enhancing parental illness understanding, 2) promoting therapeutic alliance between parents and pediatric oncologists, and 3) decreasing parental distress. We sought to pilot test D100 feasibility and acceptability.

Design/Method: Parents of children with non-relapsed cancer are eligible to enroll within 14 weeks of treatment initiation. Enrolled oncology and psychosocial providers undergo training that introduces D100 conversation tools, communication strategies, and pitfalls. Enrolled parents complete pre- and post-D100 surveys. This ongoing single-arm pilot study set the following feasibility thresholds: 70% enrollment and training of eligible fellow and NP providers and 60% D100 completion (n = 20) among enrolled parents (target n = 33). Acceptability of D100 is defined as: 70% of parents and providers who participate in D100 will "agree/strongly agree" that D100 was helpful, and <10% of parents will feel more worried due to the intervention.

Results: To date, 14/22 (64%) frontline oncology providers enrolled and trained, and 27/31 parents enrolled (87%). Of these 27, 10 (37%) completed D100, 4 (15%) are scheduled for D100, 7 (22%) are still in the eligibility window but not yet scheduled, 1 (4%) parent and oncology team disagreed about whether D100 took place, and 5 (19%) did not complete D100. Of 10 completed D100s, median time from enrollment to D100 completion was 45.5 days (range 21–63). All parents strongly agreed/agreed that D100 was helpful and would recommend D100 participation to another family. Ten parents (100%) reported time spent on D100 was "just right." No parent felt more worried due to the intervention, though 1 parent found D100 participation stressful.

Conclusion: This interim analysis suggests that parents have a favorable D100 experience and recommend the intervention. To date, <20% of enrolled parents fail to participate. D100 shows promise as an acceptable interdisciplinary communication intervention targeted to the early treatment period for childhood cancer.

Poster # 652 | YIELD OF SCREENING ECHOCARDIOGRAMS DURING TREATMENT AND IN THE EARLY POST-THERAPY PERIOD IN CHILDHOOD CANCER

Manasi Vivek Madiwale, Jennifer Kim, James Feusner, Robert Raphael

Children's Hospital and Research Center Oakland, Oakland, California, United States

Background: Screening echocardiograms are recommended by Children's Oncology Group (COG) guidelines to assess for anthracycline-induced left ventricular (LV) systolic dysfunction. The yield of screening echocardiograms during chemotherapy and in the immediate post-therapy period is uncertain.

Objectives: To assess the incidence of LV dysfunction detected by screening echocardiograms during chemotherapy and in the immediate post-therapy period, defined as 0–24 months off-therapy.

Design/Method: Children diagnosed with cancer between January 2013-March 2016 who received anthracycline chemotherapy were identified. Echocardiograms were performed as per protocol, institutional and COG guidelines, and were reviewed retrospectively. LV dysfunction was defined as fractional shortening (Fs) <28% or ejection fraction (EF) <55% (1)

Results: In this cohort (n = 195, median age 6 years), the most common diagnosis was ALL (54.8%), followed by AML (9.7%). Of 357 echocardiograms, 224 (62.7%) were performed during treatment and 133 in the immediate post-treatment period. Thirty-eight (19.3%) patients had a >10% decrease in Fs compared to their pre-treatment echocardiograms. None of these patients required any treatment modification or cardiac medications. Only 1 patient (0.5%) had echocardiogram-proven LV dysfunction discovered on a

screening echocardiogram during her treatment course. She eventually died due to multi-organ failure following septic shock. This patient was receiving treatment for AML and had received 300 mg/m2 of doxorubicin-equivalent anthracyclines at the time of the abnormal echocardiogram. One patient with metastatic Ewing sarcoma had borderline LV dysfunction with a Fs of 30% detected a month before completion of therapy. She had received 375mg/m2 of doxorubicin equivalent anthracyclines at the time of the abnormal echocardiogram. She did not require any therapy modification or additional cardiac medications. Serial echocardiograms done on this patient have shown stable ventricular function. No off-therapy screening echocardiograms identified LV dysfunction.

Conclusion: In our experience, the yield of echocardiograms to detect anthracycline-related cardiac dysfunction during treatment and in the immediate post-therapy period is very low. One patient developed LV dysfunction during treatment and one had borderline Fs, while no LV dysfunction was identified within 24 months of completing chemotherapy. Though Fs decreased in 19% of patients, none required intervention. Further study is needed to optimize the use of echocardiography screening in children treated with anthracyclines. References: 1. Landier W et al. JCO 2012.

Poster # 653 | ASSOCIATION OF HEARING LOSS WITH COGNITIVE AND EMOTIONAL FUNCTIONING IN NON-CNS TUMOR CHILDHOOD CANCER SURVIVORS TREATED WITH PLATINUM-BASED CHEMOTHERAPY

Victoria Li, Wilhelmenia Ross, Lyn Balsamo, Jaime Rotatori, Heather Haversat, Nina Kadan-Lottick

Yale University School of Medicine, New Haven, Connecticut, United States

Background: Platinum-based chemotherapy increases the risk of sensorineural hearing loss in children with cancer. Little is known about the impact of hearing loss on cognitive and emotional functioning in survivors.

Objectives: To determine the association of severe/profound hearing loss after platinum-based chemotherapy with 1) cognitive impairment and 2) emotional distress (i.e. anxiety and/or depression).

Design/Method: Cross-sectional study of all patients attending Yale's Childhood Cancer Survivorship Clinic ≥2 years off therapy for cancer diagnosed at <21 years and treated with cisplatin and/or carboplatin, but with no history of CNS tumor, cranial radiation, congenital hearing loss, or developmental delay. Hearing loss severity and hearing aid data were abstracted from audiograms and detailed clinical history. Cognitive impairment was defined as Behavior Rating Inventory of Executive Function T score ≥65, assessment by neuropsychologist, and/or history of special education. Emotional distress was determined by Brief Symptom Inventory T score ≥63 (global or two subscales) or Behavioral and Emotional Screening System T score ≥61, psychologist interview, and/or history of psychotropic medication/psychotherapy. The most recent available patient data were used. Logistic regression with SAS software, Version 9.4 was performed.

Results: Overall, 37 patients (57% female, 78% white) met eligibility criteria with a median age of 9.0 years (IQR = 12.1) at diagnosis and 22.3 years at evaluation (IQR = 10.4) after a diagnosis of sarcoma (36%), neuroblastoma (32%), or other (32%) for which 84% received cisplatin and 30% received carboplatin. Fifteen patients (41%) had severe/profound hearing loss in at least one ear. Patients with severe/profound hearing loss had a significantly increased risk of cognitive impairment (OR = 5.14; 95% CI = 1.17-22.69), but not emotional distress, compared to patients without severe/profound hearing loss. There was no significant association between age at diagnosis, current age, time since diagnosis, sex, race, ethnicity, or diagnosis with either cognitive impairment or emotional distress. Similarly, there was no significant interaction between 1) age at diagnosis and hearing loss or 2) sex and hearing loss with either cognitive impairment or emotional distress. Ten of the 15 (67%) patients with severe/profound hearing loss in at least one ear were recommended hearing aids, of which 3 (30%) reported compliance most of the time.

Conclusion: We conclude that severe/profound hearing loss is significantly associated with cognitive impairment, but not emotional distress, in childhood cancer survivors. Our data supports the need for interventions to improve hearing in these patients, including compliance with hearing aids.

Poster # 654 | PREGNANCY IN A YOUNG ADULT TREATED FOR ANAPLASTIC ASTROCYTOMA WITH RADIATION THERAPY AND BEVACIZUMAB

Beth Speckhart, Karen Fernandez, Nalinee Upalakalin, Stephen Thompson, Reuben Antony

Children's Hospital of Illinois /University of Illinois College of Medicine - Peoria, Peoria, Illinois, United States

Background: WHO Grade 3 Anaplastic Astrocytoma is a high grade glioma dependent on vascular endothelial

growth factor (VEGF) mediated angiogenesis for its growth and infiltration. Bevacizumab is a recombinant humanized monoclonal antibody which binds VEGF-A and inhibits angiogenesis. Common adverse effects of Bevacizumab are hypertension, proteinuria, thrombosis and bleeding. While animal model based studies have shown that Bevacizumab may impair ovarian function the effects of Bevacizumab therapy on human fertility are not clear. Since the physiology of pregnancy involves neovascularization/angiogenesis it is recommended that conception be avoided for at least 6 months following exposure to Bevacizumab.

Objectives: To describe the course of a young adult who became pregnant after receiving Bevacizumab and radiation therapy for treatment of an anaplastic astrocytoma.

Design/Method: Case Report

Results: A 20 year old woman diagnosed with a localized hemispheric WHO 3 anaplastic astrocytoma was treated with chemotherapy and radiation (Temozolomide/59.4 Gy) followed by 12 cycles of bi-weekly Bevacizumab/Temozolomide. Patient opted not to pursue fertility preservation prior to initiation treatment. She experienced Bevacizumab-associated proteinuria and hypertension during treatment but received all protocol mandated doses (Cumulative doses: Bevacizumab = 240 mg/kg; Temozolomide = 15.78 gm/m2). She had a spontaneous unassisted pregnancy 18 months after completing treatment. Her pregnancy was uneventful and she was normotensive throughout. Fetal ultrasonography at 16, 20, 27, 33 weeks revealed no abnormality of the brain, heart, great vessels, kidney, extremities, placenta and umbilical cord. At 39 weeks she delivered a female infant via cesarean section (Birth weight: 3890 grams, Apgars: 95 and 1010) Excessive post-partum hemorrhage was not reported. Placenta was bi-lobed and weighed 604 g. Histological analysis revealed normal placental villous development and maturation and two small infarcts.

Conclusion: Exposure to Bevacizumab in our patient had no detrimental effect on fertility and on placental/fetal vascular development. We hope this report will add to the existing data on the effects of Bevacizumab therapy on fertility.

Poster # 655 | IMPACT OF TUMOR TYPE AND TREATMENT INTENSITY ON WEIGHT-FOR-AGE THROUGH CANCER THERAPY IN CHILDREN LESS THAN 3 YEARS OLD

Daniel Runco, Karen Wasilewski-Masker, Courtney McCracken, Claire Mazewski, Briana Patterson, Ann Mertens

Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, Georgia, United States

Background: Reports of malnutrition incidence and prevalence in young cancer patients are variable and not well established. Previous research suggests children, especially less than 3 years old, treated with intensive cancer-directed therapy are at higher risk for malnutrition. However, no standardized assessment has been used to evaluate risk in this population.

Objectives: We aim to assess the trends of weight-for-age for patients following cancer diagnosis. This study will be the first to use a standardized measure of treatment intensity (Intensity Treatment Rating Scale, ITR-2) and will assist in targeting interventions for identification and treatment of malnutrition.

Design/Method: This observational, retrospective study obtained data through the center's pediatric cancer registry and electronic medical record. Patients were classified by tumor type (brain or non-brain tumor) and treatment intensity (ITR-2). ITR-2 incorporates diagnosis, chemotherapy, radiation, and surgery, beginning with lowest intensity (1) to highest intensity (4). Inclusion criteria included new cancer diagnosis 2007–2015 at less than 3 years old, with weight obtained and available within 2 days of therapy start date. Incomplete data, alternate growth charts, or treatment intensity of 1, were excluded. Weight was obtained at start of therapy and through 2 years after treatment initiation (approximately 750 days) and converted to z-scores adjusted for age and sex. Weight trajectories were modeled using generalized linear mixed models with subject-specific random intercepts and spline functions. Separate functions were constructed for subgroups of interest (tumor type and ITR).

Results: There were 402 patients included: 53 patients with brain tumors (13.2%) and 349 with non-brain tumors (86.8%). Of included patients, 165 had treatment intensity of 2 (41.0%), 192 of 3 (47.8%) and 45 of 4 (11.2%). Over the observation period, 34,593 valid weights were recorded. At initiation of treatment, no difference existed between z-score by tumor type ($p = 0.880$) or by intensity (2 vs. 3, $p = 0.879$; 2 vs. 4, $p = 0.665$; 3 vs. 4, $p = 0.558$). Tumor type did not affect z-score through the follow up period. Z-scores were higher for intensity rating 2 vs. 3 and 2 vs. 4 ($p = <0.001$ and $p = 0.015$ respectively) at 240 days after the start of treatment and persisted through 720 days ($p = 0.003$ and $p<0.001$ respectively).

Conclusion: Higher treatment intensity is associated with decline in z-score and failure to return to baseline. Future directions include further analysis on specific risk factors and timing of weight loss, longer-term follow-up of weight trends, and targeted interventions for identification, prevention, and treatment of malnutrition.

Poster # 656 | PROPHYLACTIC PLATELET TRANSFUSIONS WITH A ≤ 10 × 109/L THRESHOLD DOES NOT RESULT IN A HIGHER INCIDENCE OF BLEEDING EPISODES IN PEDIATRIC PATIENTS UNDERGOING CHEMOTHERAPY: A COHORT STUDY

Jose Martinez, Diana Rendon Ceballos, Pablo Sepúlveda, Carla Lorca, Pamela Zúñiga C, María Angélica Wietstruck, Nicolas Rojas del Rio, Francisco Barriga C, Andrea Salgado

Pontificia Universidad Católica de Chile, Santiago, Región Metropolitana, Chile

Background: Prophylactic platelet transfusions (PTs) in pediatric cancer patients (PCP) treated with chemotherapy and/or hematopoietic stem cell transplantation (HSCT) are used as prevention of bleeding episodes. Despite current JCO guidelines, few studies have compared different plt count thresholds for prophylactic PT in children.

Objectives: Asses the PT requirements for bleeding episodes in a prospective cohort of PCP using a <10 × 10e9 threshold compared to a <20 × 10e9/L threshold in a historical cohort.

Design/Method: We collected PT data in all PCPs treated at our center between January/2013 through December/2017. Diagnosis, prescription for PT (prophylaxis vs bleeding disorder), plt count and transfused units were assessed for each PT. PCPs treated from January/2013 through June 2015 received Prophylactic PT with a <20 × 10e9 threshold (Cohort A), and pts treated from July/2015 through December/2017 received prophylactic PT with a <10 × 10e9 threshold. PTs done for procedures and pts with concomitant hemorrhagic pathology were excluded. We compared the number of PTs prescribed as prophylaxis vs bleeding episode between cohorts. Data analyzed: GraphPad Prims 6.0®. Statistical analysis: Percentages with Confidence Interval (CI); T-student test (parametric variables) and Mann-Whitney test (nonparametric variables). Statistical significance: p<0.05.

Results: We reviewed 2093 PTs (871 in cohort A, 1222 cohort B) in 209 patients. 62% had acute leukemia, 33% received and auto or allo HSCT. Diagnoses and the proportion of patients undergoing HSCT was comparable in both cohorts. The average number of PTs per patient was 8,54 in cohort A and 8,24 in cohort B (p = NS), but a significant difference was found when HSCT patients were excluded from this comparison (7,34 PT per patient in cohort A vs 6,07 in cohort B, p = 0,005), which resulted in an estimated 16,4% reduction in PTs prescription. Furthermore 61 (7,1%) PTs were prescribed for bleeding episodes in cohort A versus 99 (8,2%) in Cohort B (p = NS). Patients receiving HSCT in the entire group versus those not receiving HSCT had similar PT requirements for bleeding episodes (10% vs 8,5% p = NS)

Conclusion: A <10 × 10e9 plt count threshold for prophylactic PTs is safe in PCP in chemotherapy and HSCT. It can result in a significant reduction in PT usage. KEY WORDS: Platelets, Transfusions, prophylaxis, cancer, childhood.

Poster # 657 | TRANSITION OF CARE FOR YOUNG ADULT SURVIVORS OF CHILDHOOD CANCER

Robert Raphael, Dina Hankin, Erin Gelgoot, Nicole Salman

UCSF Benioff Children's Hospital Oakland, Oakland, California, United States

Background: Transition of care for adolescent and young adult (AYA) survivors of childhood cancer from pediatric to adult-oriented long-term follow-up (LTFU) is complex. Loss to follow-up is common, and little is known about the success rates among different models. The Survivors of Childhood Cancer Program (SCCP) at UCSF Benioff Children's Hospital Oakland employs a community-based model for transitional care. Our multidisciplinary team provides AYA survivors a comprehensive treatment summary and recommendations, then facilitates transition to primary care or adult oncology LTFU programs.

Objectives: Evaluate the success rate for transition of care among AYA survivors of childhood cancer in our LTFU program, and identify barriers to successful transition.

Design/Method: AYA patients seen from November 2010 to August 2017 in the SCCP with intent to transition were asked by email or telephone if they had followed up with their designated provider. The primary outcome was successful transition, defined as establishing care within 18 months of their visit. Patients were also asked about barriers to transition and to rate the new provider's familiarity with their cancer history and LTFU needs.

Results: Transition was intended for 88 patients. Eighty-seven were contacted and 43 responded. Of these, 29 (67%) successfully transitioned, while 14 (33%) were lost to follow-up. Ages ranged from 19 to 48 years, at 2 to 32 years since completion of therapy. Ten (34%) transitioned to a primary care provider, 20 (69%) to an adult oncology LTFU program, and 1 (3%) to a pediatrician. Patients rated their new provider's knowledge above average (3.76) on a 5-point scale from Poor (1) to Excellent (5). Survivors lost to follow up indicated the following barriers to transition: loss/change of insurance (3), inability to find a provider (1), too busy/forgot (4), problems with transportation (1), concerns about cost/copay (2), and

other (4). Twelve patients requested further assistance with transition.

Conclusion: Two-thirds of responding patients successfully transitioned. More work is needed to overcome various barriers to transition for one third of AYA survivors.

Poster # 658 | MEASURING LEVELS OF STRESS IN PARENTS OF CHILDREN WHO HAVE RECENTLY COMPLETED CANCER TREATMENT

Alyssa Goodman, Alexaner Gozman, Samantha Quinn

Albany Medical Center, Albany, New York, United States

Background: The transition from active treatment, to off-therapy follow-up, is a stressful event for parents of children with cancer. The psychosocial needs of parents after therapy have received limited attention in the United States with only 3 published quantitative studies, the largest with 35 parents. We have secured funding for and recruited a transition care coordinator (TCC) to investigate this further.

Objectives: Our objective is to assess and screen parents at the end of their child's treatment, and to develop interventions to support parents during this time and thereafter.

Design/Method: After informed consent, a standardized questionnaire, the Psychosocial Assessment Tool (PAT 2.0), was administered to parents at end of therapy (T1), 6 months later (T2) and 1 year later (T3). The TCC provided "universal" intervention to all families with an end of therapy binder containing a treatment summary, follow-up roadmaps, information on late effects, and survivor scholarships. Based on their PAT2.0 scores, some parents were provided intervention specific to symptoms (targeted intervention for scores 1-1.99) or referred to a behavioral health specialist through the clinic social worker for counseling (for scores >2).

Results: Analysis of PAT1 data showed that 45% of parents (n = 45) scored in the targeted or clinical ranges; 19% of parents scored in those ranges at PAT2. Significant gender differences were revealed with the mean score for men of 0.7 and for women of 1.13. This was confirmed by showing statistical significance (p = 0.017) when analysis was conducted for only a subgroup of data composed of couples (n = 24). Analysis of PAT2 data by couples (n = 10) showed the mean score for men was 0.64 and for women was 0.93 (p = 0.12). Gender differences were most apparent in caregiver stress reaction questions that focused on PTSD symptoms. When the subgroup of couples' scores (n = 24) for caregiver stress reaction at PAT1 was analyzed, there was a significant difference (p = 0.005) in caregiver stress reaction with a mean of 0.08 for men versus 0.3 for women. [Note: Subcategory scores range from 0 to 1].

Conclusion: This study was initiated in October 2013 using a TCC and the PAT2.0 screening tool. The results suggest greater stress on mothers after therapy, with a substantial proportion of parents having symptoms of PTSD after therapy.

Poster # 659 | CHARACTERIZING PULMONARY DYSFUNCTION IN SURVIVORS OF CHILDHOOD HODGKIN LYMPHOMA

Jennifer Agrusa, Austin Brown, Viral Kothari, Wanda LeJeune, Gary Lewis, Bin Teh, Arnold Paulino, Manuel Silva Carmona, Ernestina Melicoff, Carl Allen, Monica Gramatges

Baylor College of Medicine, Houston, Texas, United States

Background: Hodgkin lymphoma (HL) is a common childhood cancer characterized by an inflammatory microenvironment. Chemotherapy and radiation may exacerbate this inflammation and contribute to the development of late effects (pneumonitis or pulmonary fibrosis). In a heterogeneous cohort of childhood cancer survivors exposed to pulmonary-toxic therapy, no association between pro-inflammatory cytokines and late pulmonary dysfunction was observed. Our objective was to test this association in a relatively uniform cohort of survivors of HL, given the well-recognized pro-inflammatory background of this disease.

Objectives: To characterize off-therapy pulmonary function in survivors of HL treated with contemporary therapy, and to investigate its association with persistent systemic inflammation.

Design/Method: Blood samples, clinical data, and pulmonary function tests were obtained from survivors of HL ≥6 months off therapy. Lung function score (LFS), a validated method for assessing degree of pulmonary dysfunction on a scale of I to IV, was determined from diffusion capacity and forced expiratory volume in one second (FEV1). For a control group, blood samples from patients with benign, non-inflammatory hematologic conditions were used. Plasma concentrations of 50 inflammatory cytokines were measured on a Luminex platform (EMD Millipore). Associations between clinical features or cytokine levels and LFS I (normal) vs. II-IV were evaluated using logistic regression or Wilcoxon rank sum tests, respectively.

Results: Of 77 survivors (mean age at diagnosis: 14 years, range: 3–18; mean time off therapy: 3.3 years, range: 0.5-24), 70% were categorized as LFS II (mild dysfunction), 8% as LFS III (moderate dysfunction), and no survivors as LFS IV (severe dysfunction). Higher LFS was associated with female

sex (p = 0.01) but not other demographic, disease, or treatment factors. Forty-eight survivors had blood samples collected at a mean age of 18.5 years (range: 10–32) with a mean time since treatment completion of 3.8 years (range: 0.6-6.1). Of 31 controls, the mean age at time of blood collection was 12 years (range: 4–17). Survivors did not have significantly elevated cytokine levels compared to controls.

Conclusion: Female survivors of HL ≥6 months off therapy are at increased risk of pulmonary dysfunction. Neither evidence for pulmonary dysfunction, as measured by LFS, nor duration of time off therapy were related to systemic inflammation in this study. Pulmonary function deterioration and clinical pulmonary symptoms are rarely observed immediately following therapy but increase over time. Future studies may consider exploring the contribution of systemic inflammation to pulmonary late effects in survivors farther off therapy, when risk for this late effect is greater.

Poster # 660 | SECOND TUMOR IN THYROID CANCER PEDIATRIC SURVIVORS

Wafaa Rashed, Marwan Adly, Mohamed Sobhy, Mohamed Rezk, Medhat Ishak, Mahmoud Afifi, Ayman El Shafie, Mahmoud Ali, Wael Zekri, Ahmad Alfaar

Children's Cancer Hospital 57357, Cairo, Egypt

Background: Thyroid carcinoma is a very rare tumor in pediatrics, accounting for 1.5–3% of childhood carcinomas in the United States and Europe.

Objectives: We aim to detect the risk of second malignancies among pediatric thyroid cancer survivors.

Design/Method: The cohort analysis consisted of pediatric cancer patients aged less than 20 years diagnosed with a primary thyroid cancer and identified by site code ICD-0-3: C739, reported to a SEER 9 database between 1973 and 2013. They were followed up by death or the end of the study period (December 31, 2013).

Results: Out of 1769 patients diagnosed primarily with thyroid carcinoma, there were 42 patients who had 45 incidences of subsequent malignancies. The mean age of patients at initial diagnosis of thyroid cancer was 16 years. Females (90.5%) had significantly higher incidence of second malignancies (SM) than males (9.5%). The overall Standardized Incidence Ratio (SIR) of SM in thyroid pediatric patients was higher than expected (SIR = 1.48). Some specific sites showed significantly higher incidences: Salivary gland (SIR = 33.95), gum and other mouth (SIR = 24.53) and Kidney (SIR = 5.72). The overall risk of SM in patients received radioactive iodine was higher than expected (SIR = 4.41). The cumulative incidence of SMs from the initial diagnosis of thyroid cancer was calculated with the survival methodology of competing risk, death treated as a competing event. Cumulative incidence of SM was 2.7% [95 % CI (1.62, 3.83 %)] at 25 years and substantially expanded after 15 years, reaching 11.92% [95 % CI (4.9, 18.8%)] at 40 years. The cumulative incidence of each tumor type at 40 years was 0.452% [95 % CI (0.139, 0.765 %)] for breast cancer, 0.28% [95 % CI (0.034, 0.53 %)] for salivary gland, 0.22% [95 % CI (0.00034, 0.448 %)] for each one of kidney and cervix uteri and 0.169% [95 % CI (0, 0.361 %)] for each one of ovary and melanoma of the skin. Cumulative incidence of SM was stratified based on race, gender and radiotherapy exposure, but there was no statistical difference in each of them.

Conclusion: Race, gender, histological subtypes, and radioactive iodine may play an important role as prognostic factors for developing SM among pediatric thyroid cancer survivors. Identification of underlying mechanisms that raise the risk of SM is important for both treatment and follow-up strategy.

Poster # 661 | FACTORS AFFECTING COMPREHENSION AND VOLUNTARINESS DURING INFORMED CONSENT IN PEDIATRIC ONCOLOGY

Paula Aristizabal, Arissa Ma, Bianca Perdomo, Courtney Thornburg, M. Elena Martinez

University of California San Diego, San Diego, California, United States

Background: The ethical practice of informed consent requires it be both voluntary and understood by the research participant. In pediatric oncology, parents must undergo informed consent to enroll their child with cancer into clinical trials, but often it can be difficult to understand especially for parents with low English proficiency. Previous research has shown that parents of children with cancer have difficulty understanding voluntariness, and that parental satisfaction with informed consent does not always correlate with adequate comprehension.

Objectives: To examine socio-demographic and contextual correlates of comprehension of informed consent, voluntariness, and satisfaction in parents who consented to participation of their child in a cancer clinical trial. We focused on characterizing differences between non-Hispanics and Hispanics, the fastest growing ethnic group in the U.S.

Design/Method: Parents/guardians (n = 121) of children aged 0–17 years with newly diagnosed cancer, who had consented to participation of their child in a clinical trial for cancer treatment at Rady Children's Hospital-San Diego were

prospectively recruited. Parents completed questionnaires assessing comprehension, voluntariness, satisfaction, health literacy, socio-demographics, and acculturation level, if Hispanic. Comprehension was surveyed at baseline and longitudinally at 3 months. Comprehension, voluntariness and satisfaction outcomes were analyzed by socio-demographics, health literacy, and acculturation level using logistic regression.

Results: Of the 121 participants surveyed, 61 (50.4%) were Hispanic and 60 (49.6%) were non-Hispanic. We found that higher health literacy was associated with greater objective comprehension ($p<0.001$), voluntariness ($p<0.001$), socioeconomic status ($p<0.001$), and acculturation ($p<0.001$). Hispanics reported lower objective comprehension ($p = 0.025$), voluntariness ($p = 0.029$), health literacy ($p<0.001$) and SES ($p = 0.015$) compared to non-Hispanics. Spanish-speakers reported lower voluntariness ($p = 0.016$), health literacy ($p<0.001$), and acculturation ($p<0.001$) compared to English-speakers. At the 3-month follow-up, comprehension in Hispanics significantly improved ($p = 0.012$) compared to their baseline comprehension. Satisfaction was moderately high across all subgroups and was not significantly impacted by socio-demographics, health literacy, or acculturation.

Conclusion: In this study, with equivalent numbers of Hispanic and non-Hispanic participants, we found that Hispanic and Spanish-speaking parents of children with newly diagnosed cancer had inadequate informed consent comprehension, voluntariness and health literacy despite high satisfaction. Our study suggests that Hispanics and individuals with limited English proficiency are not making truly informed decisions for their child with cancer. To ensure the ethical practice of research in pediatric oncology, the informed consent and decision-making process must be improved with culturally and linguistically interventions for these underserved populations.

Poster # 662 | REPPAIR TRIAL: REDUCING PROCEDURAL PAIN AND IMPROVING RECOVERY OF QUALITY OF LIFE IN PEDIATRIC NEUROBLASTOMA PATIENTS UNDERGOING BONE MARROW PROCEDURES, A PROSPECTIVE, RANDOMIZED, CROSS-OVER CLINICAL TRIAL

Sara Zarnegar, Katharine Lange, Melissa Mathias, Miho Nakajima-Hatano, Katharine Offer, Ugochi Ogu, Michael Ortiz, Kay See Tan, Michael Kellick, Ellen Basu, R. Scott Dingeman

Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Pediatric oncology patients undergo repeated bone marrow aspirations and biopsies (BMA/Bx). These potentially painful procedures can exacerbate anxiety and distress. Standard practice at Memorial Sloan Kettering (MSK) Department of Pediatrics is to use propofol, which has amnestic but no analgesic properties. We sought to evaluate whether the addition of local anesthetic would improve patient experience with BMA/Bx.

Objectives: The purpose of RePPAIR: Reducing Procedural Pain And Improving Recovery of Quality of Life (QOL) (NCT02924324) is to evaluate the efficacy of local anesthesia with ropivacaine in reducing procedural pain and improving post-procedure QOL in pediatric neuroblastoma patients undergoing BMA/Bx with general anesthesia.

Design/Method: RePPAIR is a prospective, randomized, crossover clinical trial that opened for enrollment October 2016. Eligible patients were 3 – 18 years old with neuroblastoma. Participants were observed on trial for two sequential BM procedures; one procedure with intervention A: propofol alone (PA), and the other with intervention B: propofol plus ropivacaine (P+R). Participants were randomized to intervention sequence AB or BA and were blinded to the order of interventions. Participants and recovery room (RR) nurses, who were also blinded, followed a standardized post-procedure pain management algorithm. The primary endpoint was percentage of participants requiring opioid analgesia in the 24 hours post-procedure. Secondary endpoints included total opioid in 24 hours, non-opioid analgesia use, pain scores, time to first opioid, and short-term QOL. QOL was assessed by a parent-proxy metric that evaluated pain interference with sleep, physical, emotional, and social recovery.

Results: As of January 2018, 105 patients were assessed for eligibility and 56 patients were randomized (47 have completed both procedures). For the primary endpoint, a slightly higher proportion of participants required opioid for PA than P+R (24% versus 21%, $p = 0.6$). Pain scores in the RR were significantly higher for PA than P+R (median [25th, 75th percentile]: 2 [0,4] versus 0 [0,2], $p = 0.004$). There were no statistically significant differences in total opioid or non-opioid analgesia, 6- and 24-hour pain scores, median time to first opioid, or pain interference scores. There were no adverse events.

Conclusion: Preliminary findings of the RePPAIR trial suggest that local anesthesia does not reduce the need for opioid analgesia or improve short-term QOL in pediatric patients undergoing BMA/Bx with general anesthesia. Local anesthesia did improve pain scores in the immediate recovery period. Final results of this study will help establish evidence-based guidelines and optimize the experience of pediatric patients with bone marrow procedures at our center.

Poster # 663 | PROSPECTIVE SYMPTOM ASSESSMENT IN CHILDREN WITH ADVANCED CANCER

Kathleen Montgomery, Jennifer Raybin, Chelsea Balian, Elizabeth Gilger, Jessica Ward

University of Wisconsin Health, American Family Children's Hospital, Madison, Wisconsin, United States

Background: Children with advanced cancer experience a range of symptoms throughout treatment or at end of life, some of which are poorly controlled. Minimizing suffering, including effective symptom management, in children with advanced cancer is a central value for pediatric oncology clinicians. Patient-reported outcomes have been used in symptom-related research in pediatric oncology patients; however the majority of literature specific to symptoms during palliative care and end of life for children and adolescents with advanced cancer is based primarily upon medical record reviews and to a lesser extent, patient self-report.

Objectives: The purpose of this study was to prospectively describe symptom frequency, severity, and level of distress in children/adolescents with advanced cancer using patient self-report and parent proxy.

Design/Method: A prospective cohort design was used for this study. Five pediatric oncology institutions from across the United States participated. Children and adolescents were eligible to participate if they were 7–18 years of age, English-speaking, and had a diagnosis of advanced cancer, defined as a 2-week history of progressive, recurrent, or non-responsive disease or a decision not to pursue curative-focused therapy. A modified version of the Memorial Symptom Assessment Scale (MSAS) was used to measure symptom frequency, severity, and level of distress and was administered to child/parent dyads electronically via smartphones every two weeks. Information regarding disease status and cancer treatment was collected concurrently. Data was analyzed using descriptive statistics and univariate logistic regression analysis.

Results: A total of 47 children and adolescents and 47 parents participated in the study. The median age of child participants was 13 years, with half being male. The median age of parents was 46 years. The child participants had a variety of primary diagnosis, including: leukemia/lymphoma (n = 11, 23%), solid tumor (n = 21, 45%), and brain tumor (n = 15, 32%). The most frequently reported symptoms by children with advanced cancer and parents were pain (n = 195/562, 34.70%), lack of energy (n = 186/561, 33.16%), and nausea (n = 156/560, 27.86%). Presence of disease (P = <0.0001), recent disease progression (P = 0.0002), and receiving cancer therapy (P = 0.0004) were significant factors on the presence of pain. High intensity cancer therapy was a significant factor on pain frequency (P = 0.0445) and level of distress (P = 0.0224).

Conclusion: It is feasible to collect data prospectively in children with advanced cancer regarding symptom frequency, severity, and level distress. Clinicians' increased understanding of the symptom experience may promote communication with children and adolescents and timely intervention. More research is needed to understand symptom clusters in children with advanced cancer.

Poster # 664 | INDICATIONS FOR EXPANSION OF EMPIRIC ANTIBIOTIC COVERAGE IN FEBRILE NEUTROPENIA IN PEDIATRIC HEMATOLOGY-ONCOLOGY PATIENTS

Stephanie Hadley, Kathleen Montgomery, Kelly Garcia, Zhiguo Zhao, Ritu Banerjee, Daniel Dulek, Debra Friedman, Adam Esbenshade

Vanderbilt Children's Hospital, Nashville, Tennessee, United States

Background: Febrile neutropenia (FN) is a frequent occurrence in children undergoing chemotherapy. Though guidelines recommend adding a second antibiotic to broad-spectrum antipseudomonal coverage in specific scenarios, augmenting empiric therapy with a second antibiotic is common practice. Additional empiric antibiotic (AEA) use increases the risk of antibiotic toxicity and future antimicrobial resistance. Data clarifying the indications for AEA are limited in pediatric patients.

Objectives: To identify risk factors for gram-positive (GP) and gram-negative (GN) bacteremia in patients presenting with FN to determine situations in which AEA use is warranted.

Design/Method: A retrospective chart review was conducted of pediatric severe FN with absolute neutrophil count <500/μl occurring at a single institution between 2006 and 2013. Potential a priori risk factors based on clinical reasons for antibiotic expansion were chills, hypotension, mucositis, skin or soft tissue infections (SSTIs), recent administration of high-dose cytarabine (HDAC), and a diagnosis of acute myeloid leukemia (AML). Potential factors for GN bacteremia were chills, hypotension, mucositis, and abdominal pain. The association between each potential risk factor and GP or GN

bacteremia was identified. Logistic regression was used for multi-variable analysis.

Results: The review yielded 701 episodes. GP bacteremia was isolated in 75 cases (10.7%) and GN bacteremia in 37 episodes (5.3%). In multivariable analysis, hypotension (OR 3.5 (95% CI 1.7, 7.2), p = 0.001) and SSTIs (OR 3.1 (1.1, 8.7), p = 0.036) were independently associated with increased risk of GP bacteremia, while mucositis (p = 0.376), recent administration of HDAC (p = 0.34) and chills (p = 0.161) were not. Ten patients with AML didn't receive HDAC, thus the association between AML and GP bacteremia could not be reliably estimated. Hypotension (OR 4.9 (2.2, 11.0), p<0.001) and chills (OR 5.0 (2.5, 10.1), p<0.001) were independently associated with a higher risk of GN bacteremia, while mucositis (p = 0.196) and abdominal pain (p = 0.509) were not. Of the 37 GN infections, 6 (16%) were resistant to cefepime, the empiric agent of choice at our institution.

Conclusion: Patients with FN with SSTIs, hypotension, or recent HDAC had increased risk of GP bacteremia indicating potential benefit of empiric vancomycin in these settings, while mucositis and chills were not associated with GP bacteremia. Hypotension and chills were associated with GN bacteremia, potentially warranting empiric antibiotic expansion, while mucositis and abdominal pain were not. Identifying specific indications for AEA use in pediatric severe FN use may improve antimicrobial utilization, decrease unnecessary antibiotic use, and improve patient outcomes.

Poster # 665 | DECISION-MAKING IN THE FACE OF INCURABLE HIGH GRADE GLIOMAS: A QUALITATIVE ETHICAL ANALYSIS

Ashley Foster Lanzel, Katharine Brock, Abby Rosenberg, Justin Baker, Amy Caruso Brown, Ann Mertens, Rebecca Pentz, Karen Wasilewski-Masker

Emory University, Atlanta, Georgia, United States

Background: For children/young adults with incurable high grade gliomas (HGGs), like diffuse intrinsic pontine glioma (DIPG) or glioblastoma multiforme (GBM), oncologists endeavor to align therapy with patient/family goals of care, but may be influenced by providers' preferences or limited resources. Ethical challenges can arise around the perceived purpose, risks and benefits of therapy options, provider conflicts of interest, access to care, deciding decisional priority between patients and families, and conflicts around end-of-life care.

Objectives: Evaluate factors that play into longitudinal decision making for children and young adults with HGGs, their families and oncologists using a qualitative approach with ethnographic elements.

Design/Method: Eligible patients were aged 0–21 with DIPG, GBM, or secondary HGG. Patient exclusions included: non-English speaking, in state custody, death prior to diagnosis, seen by oncology once, or an oncologist declined participation. Key decision making visits (e.g. MRI reviews) were serially audio-recorded, along with subsequent 1:1 semi-structured interviews with patients and/or parents about the decision making process. Field notes from clinician meetings, chart notes, and oncologist questionnaires were obtained. Discussions and interviews were transcribed and independently coded by three investigators. Inter-rater reliability was assessed during code book development. Discrepancies were discussed until consensus met. Constant comparison analysis with MAXQDA software continued until thematic saturation.

Results: Twenty-two of 34 eligible patients were approached; 15 agreed to participate. One withdrew upon transferring care. Mean age was 9.9 years (SD 5.9); 71% male, 50% Caucasian, 29% African American, 14% Hispanic, and 7% Asian. Four encounters, (2.5 hours), were recorded on average per patient. Parent/patient interview themes included: 1) hope (for a cure, prolonged life, and quality of life), 2) importance of physician recommendations, 3) importance of support systems (family, community, social media), 4) food (as cancer etiology, intervention) 5) finances (personal, research funding), 6) communication (with medical providers, family, community), 7) death, and 8) God (beliefs, prayer, existential questions). Oncologists desired prolonged quality of life, while patients/families transitioned to that hope from hope for a cure.

Conclusion: Decisions made in the setting of HGGs are multi-factorial, ultimately reflecting the competing values of decision makers. Optimism about treatment efficacy is held in tension with poor prognosis, allowing for functional hope. Acknowledging patients' and families' shifting hopes allows for changes in goals of care and shared decision making. Future work is needed to 1) develop preference tools for pediatric patients and families to inform medical providers and 2) provide training in communication and shared decision making with oncologists.

Poster # 666 | PATIENTS WITH SICKLE CELL DISEASE AND THEIR CAREGIVERS WANT TO LEARN ABOUT BONE MARROW TRANSPLANT AS A TREATMENT OPTION

Nitya Bakshi, Cynthia Sinha, Diana Ross, Lakshmanan Krishnamurti

Emory University, Atlanta, Georgia, United States

Background: Bone marrow transplantation (BMT) is a potentially curative but underutilized treatment for SCD. Our previous work has shown that there is variation in physician philosophy and practice in considering BMT as a treatment option for patients with SCD, and physicians may not discuss this with patients and families as a potential treatment option. In a randomized clinical trial to test the effectiveness of a decision aid for disease modifying therapies for sickle cell disease, adult patients with SCD as well as caregivers of adult/pediatric patients were interviewed about how they seek or have sought information related to SCD, made decisions about treatments for SCD, and identified a treatment option they were interested in learning more about using the decision aid tool. We performed a secondary analysis of these baseline data to understand patient information needs and attitudes regarding BMT as a treatment option for SCD.

Objectives: The goals of this analyses was to understand patient and caregivers' attitudes and perceived information needs regarding BMT as a treatment option for SCD.

Design/Method: We performed an analysis of baseline interviews from caregivers of patients with SCD or adult patients from a randomized control trial for a decision aid tool for SCD. 13 of the 38 interviews belonged to caregivers of patients with SCD. In addition to reviewing interviews for discussion of BMT, we interrogated for mention of terms such as 'bone marrow transplant' or 'cure' or 'stem cell transplant'. Interviews were coded using NVivo10 and analyzed for emerging themes.

Results: Of the 98 baseline interviews, 38 interviews met selection criteria. Thirteen of the 38 interviews were with caregivers of pediatric patients, and the remainder were with adult patients, including young adult patients with SCD. The majority of participants want to learn about BMT or curative options. In many participants, this was expressed despite knowledge that they were not a likely candidate for transplant. Desired information about BMT included eligibility, benefits, risks, long-term effects, quality of life and financial aspects related to BMT. Of the patients who discussed how they learnt about BMT, approximately half mentioned that their healthcare provider had not previously mentioned this to them. We then examined knowledge of BMT and attitudes with demographic and clinical variables.

Conclusion: Patients and caregivers of pediatric patients with SCD want to learn about BMT as a treatment option. Healthcare providers should consider discussing BMT with their patients with SCD.

Poster # 667 | LET'S TALK ABOUT SEX: ADOLESCENT AND YOUNG ADULT CANCER PATIENT SEXUAL AND REPRODUCTIVE HEALTH COMMUNICATION NEEDS

Natasha Frederick, Anna Revette, Alexis Michaud, Jennifer Mack, Sharon Bober

Dana-Farber Cancer Institute, Boston, Massachusetts, United States

Background: Adolescents and young adults (AYAs) consistently identify the need for improved patient-clinician communication on sexual and reproductive health (SRH) issues. However, oncology clinicians do not routinely integrate SRH conversations with AYAs through disease treatment and survivorship. Little is known about why these conversations do not take place.

Objectives: explore AYA perceptions of and receptiveness to SRH communication with oncology clinicians and to identify barriers and facilitators to these conversations.

Design/Method: Semi-structured interviews were held with 21 AYA cancer patients and survivors (ages 15–25 years, 6 men, 15 women). Twelve participants were on active treatment and 9 were within 2 years of treatment completion. Interviews were conducted in English by phone or in person. The interview transcript underwent pre-testing with AYAs. All interviews were audio-recorded and transcribed verbatim. Transcripts were analyzed and summarized by two trained qualitative researchers according to standard comprehensive thematic qualitative analysis methods. Analyses were aided by Nvivo11 software.

Results: AYAs perceived existing SRH communication between AYAs and oncology providers as inadequate. All AYAs reported a need for improved SRH communication with oncology providers, and three key areas of need emerged: 1) general education; 2) addressing specific SRH issues experienced during treatment and survivorship; and 3) understanding the long-term impact of cancer and treatment on SRH. AYAs felt that current SRH discussions are limited and too narrow in scope and scale. AYAs reported that most SRH conversations focus exclusively on fertility (n = 17), usually taking place at the start of treatment. Other additional yet limited communication reported was about sexual activity (n = 7), contraception (n = 7), sexual function (n = 1). No AYAs reported conversations about potential treatment complications related to sexuality other than infertility. Key barriers to SRH conversations include patient discomfort initiating conversation (n = 14) and presence of family members (n = 10), with additional reported barriers including perceived provider discomfort (n = 4), lack of rapport with provider (n = 4), and age/gender differences (n = 4). AYAs felt that

communication tools such as handouts, brochures, and websites would be helpful facilitators to direct communication from the oncology clinician, and wanted conversations to start before treatment initiation and to continue through treatment and survivorship

Conclusion: AYAs identify a key role for pediatric oncology providers in SRH care from diagnosis through survivorship, however multiple barriers interfere with discussions about SRH on a regular basis. Identified barriers suggest that future efforts should focus on provider education and training in SRH and SRH-related communication in order to optimize care provided to this unique patient population.

Poster # 668 | CAN PICC LINE ASSOCIATED VENOUSTHROMBOEMBOLISM BE PREVENTED BY EARLY REMOVAL?

Ravi Talati, Bryan Combs, MaryAnn O'Riordan, Moira McErlean, Sanjay Ahuja

Rainbow Babies and Children's Hospital, Cleveland, Ohio, United States

Background: Peripherally inserted central venous catheters (PICC) provide secure vascular access in pediatric patients for the delivery of necessary therapies. The ease of placement in the inpatient and outpatient settings has expanded their utilization. However, recent data analyses show a significant increase in venous thromboembolism (VTE) risk with the use of PICC lines. With its rising use, modifiable risk factors need to be understood for preventative measures.

Objectives: In this study we aim to understand patient and catheter specific characteristics in relation to the development of VTE.

Design/Method: With IRB approval, a retrospective interrogation of the electronic medical record and a PICC database, at Rainbow Babies and Children's Hospital, was completed. The study cohort contained patients < 18 years of age who had a PICC line placed between January of 2004 and December of 2016. Data collected included indication for line placement, line dwell time, location of insertion including blood vessel and extremity, number of attempts at line placement, lumen size and indwelling line length. In addition, we collected number of days to VTE formation, associated symptoms and location of VTE. Chi-squared analyses and Fischer's exact test were used where appropriate for statistical analysis.

Results: We analyzed 3729(1098 neonatal) newly placed PICC lines. Fifty line-associated VTE events were found, for an incidence of 1.3%. All VTE occurred with the placement of the first PICC line. Intravenous therapies were the most common reason for line placement. No statistical significance was found between various indications for placement. The most common symptom of VTE manifestation was extremity swelling, follow by extremity pain. Right extremity PICC was found to have a higher incidence of VTE. Larger catheter lumen sizes (> 4 French) had a higher incidence of VTE. We found a mean time of 20.07 days to VTE detection.

Conclusion: We were unable to find any clinical, patient or line specific factors leading to increased VTE formation after statistical analysis. Special consideration should be given to the duration of PICC line use as this may reduce the incidence and comorbities associated with VTE. There is still much to be understood about catheter associated VTE formation as our analyses indicates the need for prospective data collection on a larger scale in hopes to create guidelines related to catheter use in pediatrics.

Poster # 701 | HEMOGLOBIN AND PLATELET THRESHOLDS FOR RED BLOOD CEEL AND PLATELET TRANSFUSIONS IN CHILDREN UNDERGOING TREATMENT FOR ONCOLOGIC DISEASES

Margaret Shatara, Ozgonenel Bulent

Children Hospital of Michigan, Detroit, Michigan, United States

Background: The decision to transfuse a patient is a complex one and is never based solely on a number; however, certain hemoglobin or platelet count thresholds have been proposed in aiding physicians make transfusion decisions. In our hospital, the thresholds for packed red blood cell (pRBC) and platelet transfusion in pediatric oncology patients are hemoglobin levels below 8.0 g/dL and platelet counts below 20,000/mm3 (< 35,000 for brain tumors), respectively. Recently, these thresholds have been questioned and we were asked whether we could safely lower the thresholds to < 7.0 g/dL of hemoglobin and < 10,000 /mm3 platelet count

Objectives: To investigate platelet and hemoglobin transfusion thresholds for oncology patients at Children Hospital of Michigan

Design/Method: Retrospective chart review over a 6-month period, examining platelet and hemoglobin pretransfusion levels for each pRBC and platelet transfusion given to oncology patients

Results: Over the course of 6 months, 60 eligible oncology patients (median age 6 years) received 584 transfusions (233 pRBC transfusions and 351 platelet transfusions). The mean pretransfusion hemoglobin level was 7.6 ± 1.0 g/dL (range 2.3-11.9) (n = 233) for total pRBC transfusions and this was

not different among disease categories (p = 0.146). Patients who had anemia symptoms and signs (n = 190) had a slightly lower hemoglobin level compared to those who did not (n = 43): 7.5 ± 1.0 vs 7.8 ± 0.9 g/dL (p = 0.058). The mean pretransfusion platelet count was 24,570 ± 15,151 /mm3 (range 2,000 – 104,000) for total platelet transfusions (n = 351); 32,800 ± 14,586 /mm3 in patients with brain tumors (n = 84); 20,610 ± 15,270 in patients with leukemia (n = 119); and 23,090 ± 13,628 in patients with solid tumors (n = 148). The mean pretransfusion platelet count was significantly higher in transfusions for brain tumors compared to that in the other disease groups (p<0.001 for both). The mean pretransfusion platelet count was not different among those patients who had bleeding/bruising symptoms (25,150 ± 17,898, n = 115) versus those who did not (24,290 ± 13,648, n = 236) (p = 0.620). The bleeding/bruising rate was slightly but insignificantly higher in those who had platelet counts <10,000 vs those who had ≥ 10,000 (38.2% vs 32.2%, p = 0.564).

Conclusion: Since most patients develop symptoms of anemia at hemoglobin above 7 g/dL and about 1/3 of patients develop bleeding/bruising symptoms at platelet counts above 20,000 /mm3, our current policy so far reflects a safe threshold for transfusion, and further lowering of the thresholds should be investigated in prospective studies.

Poster # 702 | SERUM CREATININE SIGNIFICANTLY UNDERESTIMATED THERAPY RELATED CHRONIC KIDNEY DISEASES AMONG CHILDHOOD CANCER PATIENTS

Ashraf Mohamed, Mohamed Kabbani, Grace Davis, sanaz Ibrahimi, Victoria Burris, Henock Rodriguez, Luma Aldabbagh, Garrett Klutts

St Jude Affiliate Clinic at St Francis Hospital, Tulsa, Oklahoma, United States

Background: Renal impairment is an important complication of childhood cancer and its treatment. Serum creatinine level is frequently used as a screening test to monitor renal function; however, patients can have significantly decreased glomerular filtration rate (GFR) with normal serum creatinine.

Objectives: To determine the prevalence of Chronic Kidney Disease (CKD) among children with cancer diagnosis, based on calculated GFR. To compare the difference between using serum creatinine value alone versus GFR in detecting CKD.

Design/Method: Retrospective review of medical records of 150 patients, age 1–18 years, diagnosed between 1/2011-12/2016 with solid tumors were analyzed. Serum creatinine and calculated GFR using Schwartz formula were recorded. CKD as classified by the Foundation of Kidney Disease and Outcome Quality Initiative was used: CKD stage 2: GFR (60 to 89 mL/min per 1.73 m2) CKD stage 3: GFR (30 to 59 mL/min per 1.73 m2) Statistical analysis using SPSS software v.23. Chi-squared test for proportions within group, and Pearson chi-squared and Fisher Exact tests for statistical differences between groups. p-value <0.05 was considered to indicate significance

Results: Out of the 150 records reviewed, 81 (54%) were males and 69 (46%) females, with mean age of 9.2±5.6 years. 37 (24.6%) patients received one or more of nephrotoxic chemotherapy drugs; Cisplatinum, Carboplatinum, or Ifosphamide mainly in the non-Wilms solid tumors group (94.5%) compared to (5.5%) in the Wilms tumor (WT) group. Based on calculated GFR (by Schwartz formula) CKD stage 2/or 3 was diagnosed in 66 (44%) patients with overwhelming majority (98%) were in the mild stage 2 CKD, only 3 (4.5%) of those patients had abnormally high serum creatinine levels (p = 0.006). 56.7% of patients who received nephrotoxic chemotherapy developed CKD, compared to 39.4% in those who did not receive it, (P = 0.01). Despite that only 2/18 (11%) of WT group patients received nephrotoxic chemotherapy, yet this group had higher percentage of CKD (83.3 %) compared to non-WT group (34.8%) P = 0.02. Significantly lower mean GFR 73.8±10 was noticed in the WT group compared to 99.8±29 in non-WT group (P = 0.001)

Conclusion: High prevalence of mild CKD was found among solid tumor patients. Using serum creatinine alone as measure of renal function significantly under estimates renal impairment in those patients. Early identification of CKD is easily achieved by using calculated GFR, which can helps providers and care givers to avoid potential nephrotoxic antibiotics, contrast media, NSAIDs and dehydration that may further deteriorate renal function

Poster # 703 | TISAGENLECLEUCEL (CTL019) THERAPY APPEARS SAFE AND EFFECTIVE IN PEDIATRIC PATIENTS WITH DOWN SYNDROME WITH RELAPSED/REFRACTORY (R/R) ACUTE LYMPHOBLASTIC LEUKEMIA

Theodore Laetsch, Shannon L. Maude, Stephan A. Grupp, Michael Boyer, Andrew Harris, Muna Qayed, Christine Phillips, Michael Pulsipher, Henrique Bittencourt, Patricia Wood, Karen Thudium Mueller, Yanqiu Weng, Carl June, Bruce Levine, Hidefumi Hiramatsu

The University of Texas Southwestern Medical Center, Dallas, Texas, United States

Background: Children with Down syndrome (DS) have increased risk of developing leukemia. Pediatric patients with DS-associated acute lymphoblastic leukemia (DS-ALL) are known to have significant toxicities with reinduction chemotherapy and historically poor outcomes with stem cell transplant (SCT). Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, tisagenlecleucel, demonstrated high rates of durable complete remission (CR) and a manageable safety profile in children with r/r B-cell acute lymphoblastic leukemia (B-ALL).

Objectives: Characterize the efficacy and safety of tisagenlecleucel in pediatric/young adults with DS-ALL.

Design/Method: Pooled data from 2 single-arm, multicenter, phase 2 trials of tisagenlecleucel in pediatric/young-adult patients with r/r B-ALL (ELIANA, NCT02435849; ENSIGN, NCT02228096) were analyzed.

Results: Eight patients with DS-ALL were enrolled (data cutoff: ELIANA, 23 November 2016; ENSIGN, 1 February 2016). Seven were infused with tisagenlecleucel; 1 patient died from ALL progression and intracranial hemorrhage before infusion. No manufacturing issues occurred during production. 5/7 infused patients were male, 2/7 had prior SCT (age range, 6–16 years). 6/7 patients achieved CR or CR with incomplete blood count recovery (CRi) by day (d) 28 (CR+CRi, 86%); 1 died before d28 and was not evaluable. Analysis of minimal residual disease was negative in bone marrow in responding patients. Two patients had CD19-negative relapses at 5 and 8 months. Ongoing remissions in 4 patients without relapse ranged from 2 to 11 months. The safety profile (n = 7) appears similar to that in patients without DS in the same trials (n = 90). Grade (G) 3/4 cytokine release syndrome occurred in 43% (3/7) of patients with DS and in 44% without DS. Rates of other G3/4 adverse events of special interest did not appear to favor a consistent trend between patients with/without DS (febrile neutropenia: 43% vs 36%; neurological events: 14% vs 11%; tumor lysis syndrome: 14% vs 2%). G3/4 infections were not observed in patients with DS (0% vs 23%). One patient died after infusion due to intracranial parenchymal hemorrhage on d15 associated with ongoing coagulopathy. Time and extent of tisagenlecleucel expansion and long-term persistence were similar between groups.

Conclusion: This is the first analysis of CAR T-cell therapy in pediatric patients with r/r B-ALL and DS. These data suggest that toxicities appear similar to those in patients with B-ALL without DS, remission rates in DS-ALL are high, and long-term outcomes with sustained persistence appear promising. Further exploration of tisagenlecleucel as an alternative to SCT in children with r/r DS-ALL is warranted. Sponsored by Novartis.

Poster # 704 | UNDERSTANDING PEDIATRIC LEUKEMIA HEALTH DISPARITY: REGULATION OF CRLF2 BY IKAROS AND CASEIN KINASE II

Chandrika Gowda, Chunhua Song, Zheng Ge, Kimberly Payne, Sinisa Dovat

Pennsylvania State University, Hershey, Pennsylvania, United States

Background: Hispanic adolescence and young adults are twice as likely to develop Acute Lymphoblastic leukemia (ALL) with high risk features as non-Hispanic whites. They also have poor prognosis and 39% higher death rate. B-ALL with CRLF2 overexpression caused by genetic alteration of the cytokine receptor, CRLF2 is five times more common in this subgroup. Approximately 80% of CRLF2 B-ALL cases also have IKZF1 genetic alterations. Ikaros is involved in transcriptional regulation of several important genes involved in leukemogenesis. Overexpressed Casein Kinase II (CK2) impairs functions of Ikaros.

Objectives: Understand the molecular mechanisms that regulate CRLF2 expression in CRLF2 B-ALL. Here we present evidence that Ikaros-mediated repression of CRLF2 transcription in B-ALL in Hispanic children is regulated by CK2.

Design/Method: Primary B-ALL patient samples from Hispanic children were used. Ikaros retroviral transduction, Ikaros ShRNA transfection, real time-PCR, luciferace assay, quantitative chromatin immunoprecipitation (qChIP) coupled with the next-generation sequencing (ChIP-seq), cytotoxicity assay and western blot.

Results: Ikaros binding to promoter of CRLF2 was confirmed using quantitative ChIP. Functional experiments such as overexpression of Ikaros in B-ALL primary cells results in transcriptional repression of CRLF2 whereas Ikaros silencing using shRNA resulted in increased transcription. These results suggest that Ikaros negatively regulates CRLF2 expression. Molecular inhibition of CK2 with shRNA targeting the CK2 catalytic subunit, as well as pharmacological targeting of CK2 with CX4945 resulted in transcriptional repression of CRLF2. CK2 inhibition was associated with increased Ikaros DNA-binding to the promoter of CRLF2. However, the ability of CX4945 to repress CRLF2 is lost or severely reduced, in cells with shRNA silencing of Ikaros, as compared to cells with intact Ikaros. Moreover, similar results were noted following treatment with CX4945 in leukemia cells obtained from high risk B-ALL patients with deletion of one IKZF1 allele. Ikaros binds poorly to promoters of CRLF2 gene in these cells. Treatment with CX4945 restores Ikaros DNA-binding to the promoters of CRLF2, which is associated with

its strong repression. Serial qChIP analysis of the epigenetic signature at the CRLF2 promoter showed that increased Ikaros binding to the CRLF2 promoter, following CK2 inhibition, is associated with enrichment for the H3K9me3 histone modification, which is a marker of repressive chromatin.

Conclusion: Results demonstrate that CRLF2 expression is epigenetically regulated by the CK2-Ikaros axis .CX4945 show antileukemic effect via restoration of Ikaros tumor suppressor function, resulting in CRLF2 repression suggesting advantage of using CK2 inhibitors as potential therapeutic approach in CRLF2 altered B-ALL.

Poster # 705 | POOR OUTCOME FOR CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH HYPODIPLOID ALL IS NOT IMPROVED BY HEMATOPOIETIC STEM CELL TRANSPLANT: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Jennifer McNeer, Meenakshi Devidas, Yunfeng Dai, Eric Larsen, Kelly Maloney, Leonard Mattano, Kirk Schultz, Andrew Carroll, Nyla Heerema, Julie Gastier-Foster, Samir Kahwash, Michael Borowitz, Brent Wood, Naomi Winick, William Carroll, Stephen Hunger, Elizabeth Raetz, Mignon Loh

University of Chicago, Chicago, Illinois, United States

Background: Hypodiploid ALL is associated with poor survival and often considered an indication for hematopoietic stem cell transplant (HSCT) in first remission (CR1).

Objectives: To describe event-free (EFS) and overall survival (OS) rates of children, adolescents and young adults with hypodiploid ALL and the impact of CR1 HSCT.

Design/Method: We assessed EFS/OS of hypodiploid ALL patients enrolled on COG AALL03B1 (2003-2011). Cytogenetic analyses and DNA index (DI) were performed at COG-approved laboratories. Minimal residual disease (MRD) was determined using flow cytometry at 2 COG reference laboratories. EFS and OS were estimated using the Kaplan-Meier method with standard errors calculated per Peto and curves compared using the log-rank test.

Results: Hypodiploid ALL (modal chromosome number <44 and/or DI <0.81) was identified in 131 patients (1.6% of all patients; 0.9% of NCI standard risk (SR) and 2.9% of NCI high risk (HR)), who were removed from frontline protocol therapy post-induction. Overall 5-year EFS and OS were 52.1%±4.9% and 58.9%±4.8%. Transplant status was retrospectively available for 113/131 (86%), 61 of whom underwent HSCT in CR1. Five-year EFS with HSCT was 57.4%±7.0% vs. 47.8%±7.5% without (p = 0.48). 5-year OS with and without HSCT was 66.2%±6.6% vs. 53.8%±7.6% (p = 0.34). When corrected for the median time to HSCT (137 days), there were no significant differences in 5-year EFS or OS rates with and without HSCT: 53.1%±7.3% and 64.2%±6.9% vs. 48.8%±7.8% and 53.8%±7.8%. No NCI risk group or MRD subset benefitted significantly from CR1 HSCT. SR patients (n = 42) had 5-year EFS and OS of 68.8±10.3% and 77.3%±9.2% with HSCT (n = 27) vs. 57.1%±13.2% and 64.3%±12.8% without. HR patients (n = 71) had 5-year EFS and OS of 48.3%±9.0% and 57.6%±8.8% with HSCT (n = 34) vs. 44.4%±9.2% and 49.9%±9.4% without. For those with end-induction MRD <0.01% (n = 74), 5-year EFS and OS were 66.3%±7.9% and 79.5%±6.7% with HSCT (n = 39) vs. 60.3%±9.2% and 66.7%±8.8% without. End-induction MRD-positive patients (n = 30) fared poorly with both 5-year EFS and OS of 29.4%±14.3% with HSCT (n = 18) vs. 16.7%±10.8% and 22.2%±13.9% without. Multivariate regression analysis including NCI risk group, MRD, and CR1 HSCT, showed only MRD negativity was significantly associated with EFS (HR 0.256, p<0.0001) and OS (HR 0.216, p<0.0001).

Conclusion: Patients with hypodiploid ALL fare poorly, particularly those with end-induction MRD ≥0.01%. While CR1 HSCT is a standard treatment approach, it does not confer significant benefit. We were unable to assess bridging therapy prior to HSCT, and comparator groups are small. Taken together, however, new strategies are urgently needed for these patients.

Poster # 706 | COMBINATION OF KRAS MUTATION AND TET2 LOSS LEADS TO MYELOID SKEWING AND SYNERGISTIC ACTIVATION OF RAS SIGNALING IN A NOVEL MURINE MODEL

Matthew Miller, Rachel Rau, Jason Rogers, Padmini Narayanan

Baylor College of Medicine, Texas Children's Hospital Caner and Hematology Center, Houston, Texas, United States

Background: Ras-pathway mutations are known to play a pivotal role in a significant proportion of myeloid malignancies, including upwards of 20% of pediatric AML cases.

Ras-pathway mutations in myeloid malignancy commonly co-occur with mutations of epigenetic regulators, suggesting cooperative leukemogenesis. Among the epigenetic modifiers most frequently mutated in myeloid malignancy are regulators of DNA methylation. This indicates that the alteration of DNA methylation contributes to leukemogenesis. The Ten-eleven Translocation 2 (TET2) is an epigenetic regulator that plays an important role in regulation of DNA methylation through its action of hydroxylation of 5-methylcytosine, which ultimately leads to passive de-methylation of DNA cytosines. In myeloid malignancy, loss of function TET2 mutation is one of the most frequently co-occurring lesions in RAS mutated malignancy. How specifically the altered methylation patterns in Ras-pathway driven diseases promotes leukemogenesis is unclear.

Objectives: We hypothesize in mice with a Ras-pathway mutation, that when an epigenetic modifier co-occurs, such as loss of function of Tet2, this primes stem cells and/or early differentiating progenitors for transformation by preventing the repression of stem cell self-renewal genes, inhibiting differentiation, enhancing Ras signaling and leading to leukemogenesis.

Design/Method: We have generated a novel murine model with constitutive deletion of Tet2 (Tet2-/-) combined with an inducible activating KrasG12D mutation (KrasG12D/WT). Mice have been tracked for evidence of hematologic malignancies and compared to mice with corresponding single genetic lesions. Cooperative leukemogenesis will be demonstrated by decreased latency to disease onset, impact on malignancy lineage, in addition to investigating mechanistically through which pathways leukemogenesis may be promoted.

Results: KrasG12D/WT/ Tet2-/- mice demonstrate statistically significant differences in peripheral white blood cell count, hemoglobin, and platelet levels as early as 4-weeks post Ras-pathway activation. Peripheral cell lineage analysis demonstrates early skewing toward myeloid differentiation and marked splenomegaly in mice harboring both genetic lesions compared to wild type or mice with single genetic lesions. Phospho-flow cytometric analysis reveals increased pErk and pS6 activation in KrasG12D/WT/ Tet2-/- Sca-1 enriched bone marrow cells compared to either genetic lesion alone.

Conclusion: Our study utilizing a murine model to examine how in Ras-pathway mutations the addition of a co-occurring epigenetic lesion demonstrates that these lesions appear to cooperate to promote early myeloid differentiation with attendant changes in signaling pathways. This exploration to elucidate the mechanics of RAS-pathway mediated disease lay the foundation for identification of patients who may benefit from existing therapies, such as DMTIs, or identify new signaling targets for therapeutic exploration.

Poster # 707 | IMPACT OF HUMORAL IMMUNOGENICITY (ANTI-MCAR19 ANTIBODIES) ON TISAGENLECLEUCEL (CTL019) CELLULAR KINETICS, EFFICACY, AND SAFETY

Karen Thudium Mueller, Edward Waldron, Denise Sickert, Stephan A. Grupp, Shannon L. Maude, John Levine, Theodore Laetsch, Michael Pulsipher, Michael Boyer, Keith August, Rakesh Awasthi, Bruce Levine, Carl June, Tetiana Taran, Patricia Wood, G. Douglas Myers

Novartis Institutes for BioMedical Research, East Hanover, New Jersey, United States

Background: The humoral immunogenicity of CAR19, a chimeric antigen receptor (CAR) with a murine scFV domain developed for treatment with tisagenlecleucel in relapsed/refractory (r/r) pediatric/young-adult acute lymphoblastic leukemia (ALL), was evaluated in 2 studies. Little is known about the presence/impact of preexisting/treatment-induced anti-murine CAR19 (mCAR19) antibodies in patients treated with CAR therapy.

Objectives: Patients from ELIANA (NCT02435849; n = 68) and ENSIGN (NCT02228096; n = 29) were evaluated before and after tisagenlecleucel infusion to determine the impact of anti-mCAR19 antibodies on cellular kinetics, efficacy, and safety.

Design/Method: Anti-mCAR19 antibodies were determined by flow cytometry and reported as median fluorescence intensity. Assay validation included evaluation of the interferences of intravenous immunoglobulin (IVIG) treatment with the anti-mCAR19 antibody assay. Impact of preexisting and treatment-induced immunogenicity on cellular kinetics, efficacy, and safety was determined. Treatment-induced immunogenicity was defined by a positive increase in anti-mCAR19 antibody levels over baseline and was assessed by calculating the fold-change between preexisting (ie, baseline) and postinfusion levels.

Results: 90% of patients displayed preexisting anti-mCAR19 antibodies; a similar incidence was detected in healthy volunteer samples during method validation. 35% of patients developed treatment-induced anti-mCAR19 antibodies. No relationship was identified between tisagenlecleucel expansion (AUC0-28d) and preexisting/treatment-induced anti-mCAR19 antibodies ($r2<0.001$ and $r2 = 0.006$, respectively); similar results were seen for Cmax. Presence of treatment-induced anti-mCAR19 antibodies did not appear to impact transgene persistence or response. Kaplan-Meier estimates showed that preexisting/treatment-induced anti-mCAR19 antibodies did not appear to impact duration of response or event-free survival. Strip plots showed

consistent levels of preexisting/treatment-induced anti-mCAR19 antibodies across patients with safety events, including cytokine release syndrome, neutropenia, thrombocytopenia, and neurological events. There was no apparent relationship between treatment-induced anti-mCAR19 antibodies and B-cell recovery categories (≤3months, >3 and ≤6months, >6months, and ongoing sustained aplasia). No association existed between time of B-cell recovery and presence of treatment-induced anti-mCAR19 antibodies. B-cell aplasia requiring IVIG occurred following tisagenlecleucel in the majority of patients. The tisagenlecleucel concentration-time profiles in patients with treatment-induced anti-mCAR19 antibodies were categorized by time following IVIG administration. Time of IVIG administration had no impact on in vivo transgene expansion and persistence.

Conclusion: We report the first comprehensive assessment of the impact of anti-mCAR19 antibodies on clinical endpoints with CAR therapy. Pediatric/young-adult patients with r/r ALL had a high frequency of baseline anti-mCAR19 antibodies, and preexisting/treatment-induced anti-mCAR19 antibodies did not impact the cellular kinetics, safety, and efficacy of tisagenlecleucel. Cell-mediated immunity studies are ongoing. Sponsored by Novartis.

Poster # 708 | INDUCIBLE COSTIMULATION TO ENHANCE THE ANTI-AML ACTIVITY OF CD123-ENG T-CELLS

Erin Doherty, Abishek Vaidya, Challice Bonifant, Melinda Mata, Ann Leen, Stephen Gottschalk, Paulina Velasquez

Texas Children's Hospital/Baylor College of Medicine, Houston, Texas, United States

Background: Adoptive immunotherapy, using CD123 Engager (CD123-ENG) T-cells, has shown success in preclinical studies, recognizing and killing acute myeloid leukemia (AML) blasts in vitro and in vivo. CD123-ENG T-cells secrete bispecific molecules that recognize CD3 (T-cells) and CD123 (AML blasts), and are able to direct transduced T-cells and recruit bystander T-cells to kill CD123-positive blasts. However, CD123-ENGs do not provide costimulation and have not shown the capability for sequential killing of targets in vitro.

Objectives: We are seeking to improve the expansion, persistence and sequential killing capabilities of CD123-ENGs by genetically modifying these cells with an inducible costimulatory molecule, which can be activated by a chemical inducer of dimerization (CID).

Design/Method: We generated a retroviral vector encoding CD123-ENG and the inducible costimulatory molecule MyD88.CD40 linked by a 2A sequence (CD123-ENG.2A.iMC). CD123-ENG and CD123-ENG.iMC T-cells were generated by retroviral transduction, and their effector function was compared with and without CID. We used flow cytometric analysis to assess transduction efficiency, chromium release assays to evaluate cytolytic activity, and ELISA to determine cytokine production.

Results: We successfully generated CD123-ENG.iMC T-cells and achieved a mean initial transduction efficiency of 63% that was maintained above 50% throughout our study period. CD123-ENG.iMC T-cells +/-CID and CD123-ENG T-cells readily killed CD123-positive AML blasts (MOLM13 and KG1a) in cytotoxicity assays when compared to the CD123-negative control (K562). In co-culture assays, CD123-ENG.iMC T-cells secreted increased IL-2 and IFN-gamma in the presence of CID and CD123-positive targets (KG1a and MOLM13) when compared to co-culture with CD123-positive targets in the absence of CID. In addition, CD123-ENG.iMC T-cells displayed enhanced sequential killing capabilities and IFN-gamma secretion when stimulated weekly with CID and tumor cells at a 1:1 ratio when compared to CD123-ENG T-cells.

Conclusion: CD123-ENG.iMC T-cells are able to recognize and kill CD123-positive AML blasts in an antigen dependent manner. CD123-ENG.iMC T-cells have improved effector function in the presence of CID as judged by cytokine production and their ability to sequentially kill CD123-positive target cells. Thus, inducible MyD88 and CD40 costimulation is a promising strategy to improve the effector function of CD123-ENG T-cells, and warrants further active exploration in preclinical studies.

Poster # 709 | PHARMACOKINETICS AND PHARMACODYNAMICS OF TOCILIZUMAB FOR THE MANAGEMENT OF CYTOKINE RELEASE SYNDROME (CRS) IN PEDIATRIC AND YOUNG-ADULT PATIENTS WITH RELAPSED/REFRACTORY (R/R) B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL) TREATED WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY TISAGENLECLEUCEL (CTL019)

Rakesh Awasthi, Clarice Lee, Henrique Bittencourt, Susana Rives, Michael Boyer, Michael Pulsipher, Michael R. Verneris, Gregory Yanik, Birgit Jaitner, Lan Yi, Kathryn Lund, Mimi Leung, Patricia Wood, Shannon L. Maude, Stephan A. Grupp, Karen Thudium Mueller

Novartis Institutes for BioMedical Research, East Hanover, New Jersey, United States

Background: ELIANA (NCT02435849; N = 75) is a pivotal multicenter study testing the efficacy of tisagenlecleucel, anti-CD19 CAR-T, in children/young adults with r/r B-ALL. Tocilizumab (toci) has been used for management of moderate/severe (grade 3/4) CRS in ≈38% of patients treated with tisagenlecleucel at equivalent doses used in approved nononcological pediatric indications (<30kg received 12mg/kg; ≥30kg received 8mg/kg [800mg max dose]).(1) CRS onset, as graded by the Penn Grading Scale, generally occurred at a median of 3 days (range, 1–22) after infusion, requiring administration of 1–3 toci doses in some patients via a protocol-specific treatment algorithm. Toci is a humanized monoclonal antibody that inhibits IL-6 receptor (IL-6R) signaling. The pharmacokinetics (PK) and pharmacodynamics (PD) of toci in pediatric patients with B-ALL with CAR-associated CRS have not previously been described.

Objectives: Characterize toci PK/PD for CRS management following tisagenlecleucel infusion and describe its impact on cellular kinetics.

Design/Method: Toci PK and levels of soluble IL-6R (sIL-6R) were determined from serum and quantified using validated assays. Maximum toci concentration (Cmax) was derived using noncompartmental methods. sIL-6R, proinflammatory cytokines, and CRS resolution time were characterized to describe toci PD. Summary statistics and graphical analyses of tisagenlecleucel exposure by number of doses were performed to describe the impact of toci on tisagenlecleucel kinetics in patients responding to tisagenlecleucel infusion.

Results: 28/58 patients with CRS received the first toci dose at a median of 5 days (range, 1–18) after CRS onset. Seventeen patients received 1 dose (range, 6.9-12 mg/kg); 8 received 2 doses (8-12 mg/kg); 3 received 3 doses (8-12 mg/kg), per the CRS treatment algorithm. First-dose mean Cmax (SD) was ≈111(30.6)μg/mL; second dose, ≈265(376)μg/mL. Individual patient PD concentration-time profiles showed increased sIL-6R levels after the first toci dose which remained elevated following the second dose. Following toci administration, median time to CRS resolution (including fever resolution) was 5 days (range, 2–29). CRS onset coincided with tisagenlecleucel expansion, followed by a peak in serum cytokines, including IL-6. The geometric mean AUC0-28day and Cmax of tisagenlecleucel transgene (by PCR) were 358% and 216% higher in tisagenlecleucel-responding toci-treated patients.

Conclusion: CRS symptoms resolved within a median of 5 days after toci administration. Toci levels achieved in patients with B-ALL were similar to reported pediatric nononcological indications (tocilizumab label) and resulted in concentration/time-dependent sIL-6R increases. Transgene continued to expand and persist following toci administration. These data support treatment with toci for CRS management. (1) Buechner, EHA, 2017. Sponsored by Novartis.

Poster # 710 | A NOVEL METHOD OF ISOLATING PRIMARY BONE MARROW MESENCHYMAL STEM AND STROMAL CELLS IN LEUKEMIA

Shelton Viola, Chantel Aftab

Naval Medical Center San Diego, San Diego, California, United States

Background: In Acute Myeloid Leukemia (AML), Mesenchymal Stem and Stromal cells (MSCs) in the bone marrow microenvironment contribute to extrinsically mediated chemo-resistance and are therefore important potential therapeutic targets. The study of patient-derived MSCs is at a competitive disadvantage, however, because traditional means of isolating MSCs from a bone marrow aspirate interferes with isolating the more highly prioritized leukemic cells. Many opportunities to study MSCs are therefore missed.

Objectives: To develop a novel method of isolating MSCs using the otherwise discarded portion of a bone marrow aspirate, thereby de-coupling the isolation of primary MSCs from the isolation of leukemia cells.

Design/Method: AML patient bone marrow aspirates were obtained prospectively from the Children's Oncology Group. Healthy patient marrow was purchased. Experimental MSCs were isolated from the bottom-most layer (RBC-layer) produced by density-gradient separation of a bone marrow aspirate, which is typically discarded. Control MSCs were isolated from the buffy coat (MNC Layer). Non-adherent cells were removed after 72 hours, and adherent cells were cultured at 5% CO2 with MEM-alpha containing 20% FBS. Growth curves were obtained by seeding 6-well plates with 10,000 cells per well. Cells were stained using Oil Red O to observe adipocyte differentiation.

Results: RBC-layer MSCs grow successfully following overnight shipment of the aspirate. Identical to MNC-layer MSCs, RBC-layer MSCs exhibit a fibroblastic morphology and are adherent to plastic. RBC-layer MSCs persist in culture up to 14 passages before senescence. They exhibit a slower growth curve relative to MNC-layer MSCs, but their overall

doubling time is similar at approximately 120 hours. Surprisingly, MSCs from the RBC-layer exhibit adipocyte differentiation on stimulation, revealing their stem-cell like qualities.

Conclusion: We present a method of isolating MSCs from the discarded portion of a bone marrow aspirate that does not interfere with the isolation of leukemia cells from the same patient. This portion of the aspirate can be shipped, or can sit for at least 24 hours, without sacrificing its MSCs. RBC-layer MSCs are nearly identical to MSCs obtained conventionally. Perhaps most importantly, RBC-layer MSCs retain a stem-cell like capacity, showing them to be a highly valuable cell population in AML research. Future plans include investigating potential selective enrichment of stem-cell MSCs in the RBC-layer, which could explain the unexpected difference in growth kinetics. AML researchers now have the opportunity to study this exciting component of the bone marrow microenvironment without sacrificing valuable leukemic cells in the process.

Poster # 711 | IMPACT OF GENETIC POLYMORPHISMS DETERMINING LEUKOCYTE/NEUTROPHIL COUNT ON INDUCTION TOXICITY IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: A COMPLEMENTARY STUDY

Sophie Gatineau-Sailliant, Sanja Glisovic, Caroline Laverdière, Jean-Marie Leclerc, Daniel Sinnett, Maja Krajinovic, Yves Pastore

Sainte-Justine University Health Center, Montreal, Quebec, Canada

Background: Neutropenia is one of the most frequent side effect of chemotherapy associated with an increase in the risk of infection, especially in the cases when the depth and duration of neutropenia are extended. Some genes, as variations of DARC, GSDMA and CXCL2 are known to influence white blood cell and neutrophil counts. Our previous study conducted in children with acute lymphoblastic leukemia (ALL), showed that polymorphisms in these genes might play a role in the onset of chemotherapy complications during consolidation and maintenance treatment.

Objectives: In order to support our previous finding, we have expanded the study to the induction period in a cohort of 233 ALL children treated at the Sainte-Justine University Health Center between July 1995 and July 2005.

Design/Method: Previous associated single nucleotide polymorphisms (SNPs) in DARC, GSDMA and CXCL2 genes were analyzed for an association with the complications occurring during induction including the duration of low neutrophil count (PNN) and low absolute phagocyte count (APC), proven infections and delay between induction and consolidation phases.

Results: Significant effect was found for all studied polymorphims. Minor alleles of DARC rs3027012, CXCL2 rs1680408 and GSDMA rs3859192 were all associated with higher risk of complications during induction treatment, whereas that of DARC rs12075 (particularly GG genotype) had a protective effect. The GG genotype of rs12075 was associated with a lower risk of post-induction delay ($p = 0.02$ OR = 0.1, 95%CI 0.02-1.0), less frequent febrile episodes ($p = 0.02$) and lower number of days with APC/PNN count reduction ($p = 0.008$ for APC<0.5 and $p = 0.02$ for PNN<0.5). In contrast, the minor T allele of another DARC polymorphism (rs 3027012), was associated with longer APC/PNN count reduction ($p = 0.01$ for APC<0.5 and $p = 0.02$ for PNN <0.5), as it was the TT genotype of GSDMA rs3859192 ($p = 0.02$ for APC<0.5 and $p = 0.04$ for PNN<0.5). The patients with the GSDMA rs3859192 had also a higher risk of documented febrile episodes ($p = 0.04$ OR = 2.4 95%CI 1–5.5). The AA genotype of rs1680408 CXCL2 was associated with a higher risk of post-induction delay due to infection ($p = 0.04$, OR = 3.4, 95% CI 1.1-11.5).

Conclusion: This complementary study confirmed our previous results, showing overall that variations in DARC, GSDMA and CXCL2 genes influence the onset of chemotherapy complications in pediatric ALL, regardless of treatment phases. These polymorphisms might be useful pharmacogenetics markers possibly guiding an adjustment of chemotherapy intensity.

Poster # 712 | GENERATION AND CHARACTERIZATION OF FLT3 LIGAND-CONTAINING CHIMERIC ANTIGEN RECEPTOR (CAR) T-LYMPHOCYTES

Suraj Pratap, Wanke Zhao, Tina Ho, Joe Zhao

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States

Background: Pediatric acute myeloid leukemia (AML) has a poor survival rate of about 70% and there is an urgent need for newer targeted therapies. CAR T-cell based therapies are effective against ALL but similar therapies against AML are still under development. Recent clinical trials have highlighted the concerns about toxicity and therapy related deaths from CAR T-cells. Antigen selection is the key factor determining the specificity, efficacy and toxicity of CAR

T-cells. While contemporary adoptive T-cell therapies use monoclonal antibodies against tumor associated antigens we employed the naturally occurring FLT3 ligand (FL) to target AML cells expressing FLT3 receptors. FLT3 receptor is expressed on multipotent and myelomonocytic progenitors as well as myeloid leukemia cells.

Objectives: To generate FL containing chimeric T-lymphocytes designated FLCAR T-cells and to evaluate their efficacy against AML cells.

Design/Method: FLCAR was constructed by fusing the coding sequences of the human FL, CD28 costimulatory domain, and CD3-zeta chain (intracellular region) in series. It was then cloned into the pHIV-EGFP lentiviral vector for expression in cell lines and primary T cells obtained from healthy donors. The empty pHIV-EGFP vector was used as a negative control. FLCAR was expressed on both CD4+ and CD8+ T-lymphocytes, confirmed by western blot. Cell cytoxicity was evaluated by co-culturing FLCAR T-cells and AML cells followed by flow cytometric analyses. Cytokine production was assessed by analyzing expression of interleukin-2 using quantitative RT-PCR.

Results: FLCAR T-cells were generated from CD4+ Jurkat and CD8+ TK-1 cell lines with up to 70% lentiviral transduction efficiency. The efficiency for primary T cells was lower (5-10%). FLCAR was expressed as a ~42 kDa protein in cells and was partially phosphorylated on tyrosine. The expression of FLCAR on lymphocytes lead to increased basal IL-2 expression in the cells. This was further augmented (by > 5 folds) upon co-incubating FLCAR T-cells with FLT3-expressing target cells. Jurkat cells, TK-1 cells and primary human T cells expressing FLCAR suppressed the growth of FLT3-expressing AML cell lines and primary AML cells in vitro. Notably, FLCAR T-cells generated from healthy donors caused strong inhibition of AML cells even at a lower transduction efficiency. In vivo experiments using NSG-SGM mice xenografted with human AML cells are underway.

Conclusion: Our data demonstrate that FLCAR can be effectively expressed on T-lymphocytes and mediate potent cytotoxicity against FLT3-expressing AML cells in vitro. Being a completely human derived chimeric protein, it represents a promising candidate for further therapeutic development.

Poster # 713 | IDENTIFICATION OF NOVEL THERAPEUTIC TARGETS IN DOWN SYNDROME ACUTE LYMPHOBLASTIC LEUKEMIA

Holly Pacenta, Kelly Sullivan, Ahwan Pandey, Kelly Maloney, Joaquin Espinosa

Children's Hospital Colorado, Denver, Colorado, United States

Background: Individuals with Down syndrome (DS) have a 20-fold higher risk of developing Acute Lymphoblastic Leukemia (ALL) than the typical population. There are several important differences between ALL in individuals with DS (DS-ALL) and ALL in individuals without DS (NDS-ALL): First, patients with DS-ALL have a lower percentage of favorable cytogenetic features compared to NDS-ALL. Second, patients with DS-ALL are more likely to have activating mutations in JAK2, CRLF2 overexpression, and IKZF1 deletions. Despite these clear genotypic differences, this knowledge has not yet been exploited for therapeutic purposes in DS-ALL. When outcomes for DS-ALL are compared to NDS-ALL with similar cytogenetic features, the survival rates are similar. However, individuals with DS-ALL have an increased risk of treatment-related mortality (TRM). Current therapy for DS-ALL is similar to that for NDS-ALL, with the exception of small changes to decrease toxicities that are more prevalent in DS-ALL. It was recently identified that interferon signaling is constitutively activated in healthy individuals with T21. We hypothesize that aberrant interferon signaling could play a role in the unique leukemias observed in DS patients.

Objectives: To identify differences in gene expression and intracellular signaling cascades that are unique to individuals with DS-ALL, relative to both NDS-ALL and healthy individuals with DS that can be exploited for therapeutic use.

Design/Method: Bone marrow samples were obtained from DS-ALL patients and matched NDS-ALL patients based on clinical characteristics and genetic features. RNA sequencing of these samples was performed and a total of 19 samples were used for the transcriptome analysis (6 DS-ALL vs. 13 NDS-ALL). The differential expression data was generated by DESeq2 and analyzed using Ingenuity Pathway Analysis.

Results: The analysis revealed that the chromosome 21 genes that have been implicated in leukemogenesis are not differentially expressed in the DS-ALL samples, relative to NDS-ALL. An inflammatory signature was identified, which included interferon gamma as an upstream regulator with predicted activation in DS-ALL. This finding is consistent with prior observations from healthy individuals with DS. Other examples of results with potentially actionable targets include the upregulation of several genes in the RAS pathway and genes involved in histone methylation.

Conclusion: The increased interferon signaling seen in healthy individuals with DS was also identified in DS-ALL. This may contribute to the development of mutations in inflammatory pathways such as JAK2 and CRLF2 in DS-ALL. Targeting these common pathways with small molecule inhibitors may have a therapeutic benefit in DS-ALL.

Poster # 714 | A PEDIATRIC LEUKEMIA PATIENT-DERIVED XENOGRAFT SYSTEM FOR PRE-CLINICAL TESTING OF THERAPEUTIC TARGETS IDENTIFIED BY NEXT-GENERATION SEQUENCING

Anthony Sabulski, Robert Berwanger, Christina Sexton, Nicole Manning, John Perentesis, Mark Wunderlich, Benjamin Mizukawa

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Next-generation sequencing (NGS) guides precision medicine approaches in oncology using therapies targeting molecular alterations found within an individual cancer. Increased availability of NGS coupled with a proliferation of targeted drugs in development heightens the need for reliable pre-clinical animal models. Here we report a patient-derived xenograft (PDX) system with integrated molecular profiling for pre-clinical testing of conventional cytotoxic and novel targeted agents.

Objectives: To utilize NGS from patients with pediatric leukemia to guide rational pre-clinical trials in PDX leukemia avatars, and to determine PDX mice tolerance of and response to cytotoxic and targeted therapies.

Design/Method: Pediatric acute lymphoblastic leukemia (ALL) samples were obtained in adherence to an IRB-approved protocol and xenografted into NOD/RAG/interleukin-2 (IL-2)RG (NRG) mice. NGS was performed clinically using the FoundationOne® Heme panel. A de novo ALL sample bearing mutations involving JAK2, CRLF2, NTRK3, CDKN2A/B, PTPN11 and WT1 was used for pre-clinical testing. Thirty-seven NRG mice were transplanted with 2 million patient cells/mouse via IV injection. Standard 4-drug induction chemotherapy was administered consisting of vincristine, dexamethasone, PEGaspargase, and daunorubicin [VXPD, n = 6 mice], in comparison to vehicle control [n = 8]. Parallel PDX cohorts were treated with single agent targeted therapies based on NGS findings, including ruxolitinib [n = 7], crizotinib [n = 8] and LOXO-101 [n = 8]. The four-week treatment period began on day +30 from transplant after confirmation of engraftment. Following completion of therapy, residual disease burden was analyzed by flow cytometry (hCD19+, mCD45- cells) in the bone marrow [BM].

Results: To date, PDX models have been established using over thirty NGS-profiled pediatric ALL samples, including six samples bearing Philadelphia (Ph) chromosome or Ph-like mutations. Pre-clinical testing was performed in a representative Ph-like ALL PDX cohort. LOXO-101 significantly reduced leukemia burden [BM 77.3%] compared to control [BM 83.4%; $p<0.05$]. The PDX mice showed no significant response to ruxolitinib [BM 85.1%; $p = 0.52$] or crizotinib [BM 82.8%; $p = 0.85$]. PDX mice treated with the 4-drug induction regimen VXPD had low level residual leukemia [BM 0.04%; $p<0.0001$]. Clinically, the patient achieved MRD negative status at end of induction.

Conclusion: NGS reveals concomitant mutations in Ph-like ALL that may represent additional targets for therapy, or predict tyrosine kinase inhibitor (TKI) resistance. We show that ALL xenograft NRG mice can tolerate a 4-week multi-agent cytotoxic chemotherapy induction regimen, as well as rational targeted agents, and serve as a robust pre-clinical model for precision medicine trials.

Poster # 715 | OSTEONECROSIS IS ASSOCIATED WITH IMPROVED EVENT FREE (EFS) AND OVERALL SURVIVAL (OS) IN HIGH-RISK ACUTE LYMPHOBLASTIC LEUKEMIA (HR-ALL): RESULTS OF CHILDREN'S ONCOLOGY GROUP (COG) STUDY AALL0232

Leonard Mattano, Meenakshi Devidas, Si Chen, Elizabeth Raetz, Mignon Loh, Naomi Winick, Stephen Hunger, William Carroll, Eric Larsen

HARP Pharma Consulting, Mystic, Connecticut, United States

Background: Osteonecrosis is a well-characterized ALL therapeutic toxicity attributed to glucocorticoids, asparaginase, and methotrexate that disproportionately affects adolescents. In CCG-1961, alternate-week dexamethasone during double delayed intensification (DI) reduced osteonecrosis vs continuous dexamethasone with single DI in rapid early responders (RER) ≥10y.

Objectives: To compare EFS and OS between HR-ALL patients with vs without osteonecrosis.

Design/Method: HR-ALL patients 1–30y on AALL0232 (2004-11) received COG augmented therapy with a 2 × 2 randomization to: (1) induction dexamethasone (10 mg/M2 d1-14) vs prednisone (60 mg/M2 d1-28), and (2) interim maintenance (IM) high-dose methotrexate (HDM) vs escalating-dose methotrexate/pegaspargase (EMA). RER received single, and slow early responders (SER) double, IM/DI. Initially, all received monthly dexamethasone maintenance pulses, patients ≥13y received DI alternate-week dexamethasone, and patients ≤12y received DI continuous

dexamethasone. There were 2 osteonecrosis-related amendments: after 10/2006 all patients ≥10y received DI alternate-week dexamethasone; after 6/2008 all patients ≥10y were assigned to induction prednisone, and all patients received DI alternate-week dexamethasone and maintenance prednisone pulses.

Results: Osteonecrosis was confirmed in 315/2817 patients. The 5y cumulative incidence (CI) was 12.7% overall and increased with age: 1–9y 2.6%, 10–12y 15.3% (alternate-week dexamethasone 10.2% vs continuous dexamethasone 23.5%; P<0.0001), ≥13y 19.7% (P<0.0001). Among randomized RER patients ≥10y, CI differed by glucocorticoid (dexamethasone 25.0% vs prednisone 15.0%; P = 0.0003) but not methotrexate assignment (HDM 18.8% vs EMA 21.5%; P = 0.7). Among randomized SER patients ≥10y, CI was 18.9% with no difference by regimen. Results were similar for patients ≥13y. In the entire study population, patients with osteonecrosis had superior 5y EFS (89.0% vs 76.1%; P<0.0001) and OS (95.8% vs 85.9%; P<0.0001) than those without osteonecrosis. 5y EFS was significantly higher among randomized patients ≥10y with vs without osteonecrosis (88.5% vs 72.9%; P<0.0001); this finding was present in different age ranges (≥10y, ≥13y, ≥16y) and RER/SER subsets within each, especially in the ≥10y RER (92.6% vs 81.8%; P = 0.0004) and SER (74.0% vs 43.7%; P<0.0001) cohorts. Across groups, asparaginase allergy was significantly associated with reduced osteonecrosis risk (≥10y: HR 0.43; P = 0.0013).

Conclusion: Patients who develop osteonecrosis have significantly increased EFS and OS, suggesting host differences that increase sensitivity to develop osteonecrosis and render ALL cells more chemo-responsive.

Poster # 716 | ROLE OF RHO-GTPASE CDC42 IN LEUKEMIA AND ITS REGULATION BY IKAROS AND CASEIN KINASE II

Chandrika Gowda, Chunhua Song, Zheng Ge, Yali Ding, Charyguly Annageldiyev, Mary McGrath, Sinisa Dovat

Pennsylvania State University, Hershey, Pennsylvania, United States

Background: CDC42 (Cell Division Cycle protein 42) belongs to Rho family of small GTPases in Ras-oncogene superfamily. Pro-oncogenic role of overexpressed CDC42 in Ras driven solid tumors are well known. However, role of CDC42 in leukemia is yet to be established. IKZF1 encodes Ikaros protein which has important role in regulation of lymphoid development and tumor suppression in leukemia. Casein Kinase II (CK2) oncogene is overexpressed in leukemia. CK2 impairs Ikaros function which can be restored by using CK2 inhibitors.

Objectives: To investigate role of CDC42 in leukemia and regulation of CDC42 by Ikaros and CK2 in B-cell Acute Lymphoblastic Leukemia (B-ALL).

Design/Method: Ikaros retroviral transduction, Ikaros ShRNA transfection, real time-PCR, luciferace assay, quantitative chromatin immunoprecipitation (qChIP) coupled with the next-generation sequencing (ChIP-seq), cytotoxicity assay and western blot.

Results: CDC42 is identified as one of the Ikaros target genes by analysis of genome-wide DNA binding of Ikaros using ChIP-seq and qChIP in B-ALL primary cells. Expression of CDC42 was also noted to be higher in ALL patient samples compared to normal bone marrow. Functional experiments showed that Ikaros overexpression via retroviral transduction results in transcriptional repression of CDC42. Ikaros silencing using shRNA resulted in increased expression of CDC42. These data suggest that Ikaros negatively regulates transcription and expression of CDC42. CK2 directly phosphorylates Ikaros and impairs its function as transcription factor. We noted that molecular inhibition of CK2 via SiRNA as well as treatment with specific CK2 inhibitor, CX4945 also decreases expression of CDC42. Treatment with CX4945 of primary B-ALL with Ikaros haploinsufficiency restores Ikaros binding to CDC42 promoter and represses CDC42 expression. However, this effect is evident only in presence of Ikaros. Treatment with CX4945 in Ikaros silenced (Ikaros ShRNA) cells showed no change in expression of CDC42. These results emphasizes the importance of Ikaros in regulating CDC42 expression. Furthermore, we analyzed the changes in epigenetic signature at the CDC42 promoter following treatment with CX4945. Results show that loss of histone marker of open chromatin (H3K9ac) and increased histone marker for repressive chromatin (H3K27me3), at the CDC42 promoter. These data suggest that Ikaros transcriptionally represses CDC42 via chromatin remodeling. A specific CDC42 inhibitor, ML141 showed cytotoxic effects on primary B-ALL cells.

Conclusion: CDC42 may have important role in hematologic malignancies. Expression of CDC42 in B cell ALL is regulated by Ikaros and CK2. These results suggest that targeting CDC42 could be a potential therapeutic strategy in leukemia.

Poster # 717 | STEROID INDUCED BRADYCARDIA IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Caitlyn Duffy, Laura Hall, Justin Godown, Koyama Tatsuki, Scott Borinstein

Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee, United States

Background: Systemic corticosteroids are widely used as treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma. There are anecdotal reports of bradycardia in pediatric patients receiving corticosteroids, but a more extensive analysis of this effect is needed.

Objectives: The aim of this study was to describe the incidence, severity, and timing of steroid-induced bradycardia and document any adverse events associated with bradycardia.

Design/Method: We performed a retrospective review of all newly diagnosed patients at our center (2010-2016) with ALL/lymphoblastic lymphoma who received corticosteroids (dexamethasone 3–5mg/m^2/dose or prednisone 30mg/m^2/dose) during induction chemotherapy. Patients were excluded if they had a pre-existing cardiac abnormality or if they received prior corticosteroids. The average 24 hour heart rate (HR) was assessed for the period prior to initiating steroid therapy and for the 24 hour period surrounding the nadir following steroid administration. The degree and time of steroid induced bradycardia was assessed. Adverse patient events and concomitant medication use was documented to identify other contributing factors to bradycardia.

Results: A total of 153 children (80 females, 73 males, 16 months-27 years) were included in the analysis with 159 demonstrating a decrease in mean HR following steroid administration. Median HR decrease was 22.9 beats per minute (quartiles 12.5-32) from prior to initiating steroids to surrounding nadir. Sixty one percent developed bradycardia less than or equal to the 1st percentile for their age range. Nadir occurred 7 doses (range 5–10) into treatment, which corresponded to 79 hours (55-109) after initiation of therapy. Of 94 patients who experienced bradycardia, 78% were associated with dexamethasone rather than prednisone. HR nadir was not associated with other vital sign abnormalities. After completion of induction chemotherapy, 87% of patients had documented resolution of bradycardia with HR greater than the 5th percentile for age. It was observed that the children who continued to have relatively low HR were often younger (20 months-5 years old). Examination of nadir HR during subsequent hospitalizations in which steroids were not being administered (excluding HR during procedural sedation) did not demonstrate a significant incidence of bradycardia. Concomitant opioid, beta-blocker, or other medication exposure did not contribute to the incidence of bradycardia.

Conclusion: Corticosteroid-induced bradycardia is extremely common in children, teenagers, and young adults with ALL receiving induction chemotherapy. Bradycardia was not associated with clinical adverse events and resolved after completion of corticosteroid treatment. Therefore, further cardiac assessment may not be warranted in the presence of bradycardia suspected to be secondary to steroid administration.

Poster # 718 | THE UNFOLDED PROTEIN RESPONSE AS A PREDICTOR OF CHEMOSENSITIVITY IN PEDIATRIC ACUTE MYELOID LEUKEMIA

Saman Hashmi, Mia Hofstad, Nenggang Zhang, Gaye Jenkins, Terzah Horton

Baylor College of Medicine, Houston, Texas, United States

Background: Survival in newly diagnosed pediatric acute myeloid leukemia (AML) is approximately 65%; however survival falls dramatically if a patient relapses. Currently, approximately one–third of patients with pediatric AML relapse on standard chemotherapy regimens. AML cells are exposed to proteotoxic stress at baseline due to their rapid and inefficient metabolism; proteotoxic stress increases after chemotherapy due to accumulation of reactive oxygen species resulting in misfolded proteins. This leads to activation of cell stress pathways, such as the unfolded protein response (UPR) in the endoplasmic reticulum. Because an activated UPR can make cells more sensitive to proteotoxic stress, we hypothesize that UPR activation correlates with response to chemotherapy.

Objectives: Determine the status of UPR in pediatric AML and its correlation with chemosensitivity;

Design/Method: Peripheral blood samples from pediatric patients with AML were collected at the start of induction chemotherapy, 6–10 hours (h) and 24 h post initiation of systemic chemotherapy. Tumor cells were sorted from peripheral blood mononuclear cells. Expression of UPR proteins was determined by chemiluminescence using an automated capillary electrophoresis system. Clinical correlations were performed using an annotated database.

Results: We measured five UPR proteins: Grp78 (glucose regulated protein 78kDa), phospho-eIF2α, inositol-requiring enzyme 1 (IRE1) and activating transcription factor (ATF6). Patients with AML had 2–5 times higher expression of UPR proteins (except ATF6) at baseline than normal controls. Grp78- the key UPR driver- had the highest level of protein expression in myeloid blasts. There was a wide variability in the level of baseline UPR expression. Eight out of 38 samples expressed >5 fold increase in Grp78 above those with the lowest Grp78 levels. Similarly, 7 and 9 patients respectively, had a >5 fold increase in peIF2α and IRE1, compared

to patients with low basal expression of these UPR proteins. In our limited sample set, there was a trend towards lower overall survival (OS) and event-free survival in patients with low baseline Grp78 and IRE1.

Conclusion: UPR has a variable expression at baseline in pediatric AML, with a trend towards lower OS in patients with a low basal Grp78 and low IRE1 expression, suggesting less chemosensitivity in this subgroup. Conversely, it is possible that blasts with an upregulated UPR prior to chemotherapy manage proteotoxic stress less effectively, having faster apoptosis and hence a better response to chemotherapy in patients with a high basal UPR. We are currently expanding our findings in a larger cohort of patients enrolled in the Children's Oncology Group AAML1031 protocol.

Poster # 719 | EVALUATION OF CHEST X-RAYS AND THE ASSOCIATED CLINICAL COURSE FOR CHILDREN WITH NEWLY DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA

Wesley Smith, Kenneth Shiao, Elena Varotto, Yinmei Zhou, Cheng Cheng, Ching-Hon Pui, Sima Jeha, Sue Kaste, Hiroto Inaba

St Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: Children with newly diagnosed acute lymphoblastic leukemia (ALL) undergo chest X-ray (CXR) evaluation during initial diagnostic workup to ensure safe airway management. However, to our knowledge, no systematic assessment of CXR findings has been reported.

Objectives: To evaluate CXR findings at diagnosis of ALL and their associations with clinical characteristics.

Design/Method: We reviewed the CXR findings at diagnosis of ALL in patients treated on the TOTAL XV and XVI protocols at St. Jude Children's Research Hospital. Findings were evaluated for associations with clinical characteristics at presentation, and the clinical management of mediastinal masses was reviewed.

Results: Mediastinal masses were seen in 107 (10.8%) of 990 patients evaluated and were more common in older patients (mean age, 8.51 years) than in younger patients (mean age, 7.14 years) ($P = 0.005$), in males than in females ($P = 0.017$), and in patients with T-ALL than in those with B-ALL ($P<0.001$). Also associated with mediastinal masses were a higher white blood cell count (WBC) at diagnosis (mean, 107.02 × 109/L) (vs. a lower WBC; mean, 36.65 × 109/L) ($P<0.001$), CNS involvement (vs. no involvement) ($P = 0.028$), and standard/high-risk disease (vs. low-risk disease) ($P<0.001$). Other CXR findings included pulmonary opacity (160 patients [16.2%]), bronchial/perihilar thickening (187 patients [18.9%]), cardiomegaly (68 patients [6.9%]), and osteopenia/fracture/periosteal lesions (132 patients [13.3%]). Pulmonary opacity was more common in younger patients (mean age, 6.51 years) than in older patients (mean age, 7.44 years) ($P = 0.023$) and in those with T-ALL (vs. B-ALL) ($P = 0.010$). Bronchial/perihilar thickening, cardiomegaly, and osteopenia/fracture/periosteal lesions were also more common in younger patients than in older ones ($P<0.001$, $P = 0.002$, and $P<0.001$, respectively) and in those with low-risk disease (versus standard/high-risk disease) ($P<0.001$, $P = 0.001$, and $P = 0.005$, respectively). Of the 107 patients with a mediastinal mass on CXR, 56 underwent a confirmatory chest CT scan, and 48 (85.7%) were confirmed to have a mediastinal mass. Notably, 23 patients (41.1%) had airway compression, and compression of venous structures was identified in 18 of 48 patients (37.5%) who received IV contrast. The clinical course was evaluated for 107 patients with mediastinal masses detected by CXR. Fifty patients (46.7%) required ICU admission (mean stay, 3.0 days). General anesthesia was used for only 52 patients (48.6%), and 68 patients (63.6%) had a less invasive peripherally inserted central catheter. No deaths occurred in the acute phase.

Conclusion: CXR at the time of ALL diagnosis can detect various intrathoracic lesions and is helpful in planning initial diagnostic workup and management.

Poster # 720 | BONE MARROW STROMAL CELL MEDIATED RESISTANCE TO MERTK INHIBITION IN AML

Katherine Minson, Madeline Huey, Eleana Vasileiadi, Irene Perez, Xiaodong Wang, Stephen Frye, H. Shelton Earp, Deborah DeRyckere, Douglas Graham

Emory University and Children's Healthcare of Atlanta, Atlanta, Georgia, United States

Background: MERTK is a receptor tyrosine kinase that is aberrantly expressed in 80% of pediatric primary AML samples. MERTK inhibition with the small molecule tyrosine kinase inhibitor (TKI) MRX-2843 decreases tumor burden and prolongs survival in AML xenografts. While treatment with MRX-2843 reduces leukemia in the peripheral blood, it is less effective in the bone marrow, suggesting a role for the marrow microenvironment in therapeutic resistance. The JAK/STAT pathway has been implicated as a mediator of bone marrow derived resistance to TKIs and inhibitors of this pathway are in clinical development for the treatment of AML.

Objectives: To determine the role of the bone marrow stromal niche in mediating resistance to MERTK inhibition and to evaluate the efficacy of combined MERTK and JAK/STAT inhibition.

Design/Method: AML cell lines were cultured with or without the HS27 stromal cell line or HS27 conditioned medium, then treated with MRX-2843 +/- the JAK/STAT inhibitor ruxolitinib, or control. Induction of apoptosis and cell cycle arrest in AML cells was measured by flow cytometry. Expression of γH2AX and total and phosphorylated STAT5 were determined by immunoblot.

Results: Co-culture with stromal cells significantly reduced AML cell death and G2/M phase arrest in response to treatment with 200nM MRX-2843 compared to no co-culture (cell death: 31.9% versus 61.2%, $p<0.05$; G2/M arrest: 8.9% versus 14.8%, $p<0.01$). G2/M arrest was accompanied by an increase in γH2AX expression which was similarly abrogated in co-culture. Conditioned medium did not provide protection from MRX-2843 induced apoptosis, G2/M arrest, or γH2AX induction. MRX-2843 inhibited STAT5 phosphorylation but direct co-culture and conditioned medium potently increased basal STAT5 phosphorylation which was not inhibited by MRX-2843. To determine whether the observed induction of STAT5 phosphorylation was functionally relevant, co-cultures were treated with both MRX-2843 and ruxolitinib. While ruxolitinib potently inhibited the phosphorylation of STAT5 in the presence of co-culture, combination treatment did not overcome stromal mediated protection from MRX-2843 induced apoptosis. Similarly, the addition of exogenous GM-CSF induced STAT5 phosphorylation but did not yield protection from MRX-2843 functional effects in the absence of co-culture.

Conclusion: Together these data support a model whereby direct cell-cell contact with stromal cells in the bone marrow niche protects leukemia cells from MRX-2843 induced apoptosis, cell cycle alterations, and DNA damage. While co-culture potently induces phosphorylation of STAT5 in leukemia cells, this is neither necessary nor sufficient for stromal-cell mediated protection from MERTK inhibition and combined treatment with JAK/STAT inhibitors is unlikely to be therapeutically efficacious.

Poster # 721 | USE OF ALLOPURINOL TO REDIRECT 6-MERCAPTOPURINE METABOLISM IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Austin Stuckert, Eric Schafer, M. Brooke Bernhardt, Patricia Baxter, Julienne Brackett

Baylor College of Medicine, Houston, Texas, United States

Background: Mercaptopurine (6-MP) is an immunosuppressive thiopurine drug that is a key component of acute lymphoblastic leukemia (ALL) treatment. 6-MP is metabolized into 6-thioguanine (6-TGN), which is responsible for anti-leukemic effects, as well as 6-methylmercaptopurine nucleotides (6-MMPN/6-MMP), which are associated with hepatotoxicity. Some patients preferentially metabolize 6-MP to 6-MMPN/6-MMP, increasing their risk for hepatotoxicity and potentially reducing anti-leukemic effects. Hepatotoxicity can cause interruptions or delays in therapy that may jeopardize cure rates. Allopurinol has been increasingly used in patients with inflammatory bowel disease (IBD) to shunt 6-MP metabolism toward 6-TGN and away from 6-MMPN to minimize hepatotoxicity and preserve therapeutic effects.

Objectives: This retrospective chart review expands upon our previously published case series of three patients with ALL in whom allopurinol was successfully used to redirect 6-MP metabolism. Twelve additional patients have subsequently received allopurinol and 6-MP combination therapy at Texas Children's Hospital. Data from this larger patient sample, with longer follow up, is being analyzed to increase knowledge of the effectiveness and longitudinal effects of adding allopurinol to 6-MP to reduce risk of hepatotoxicity.

Design/Method: Data were abstracted from the electronic medical records of 15 patients with ALL treated at Texas Children's Hospital from 2012 to present, who had been found to have evidence of altered 6-MP metabolism and in whom allopurinol was added to 6-MP therapy due to concern for risk or recurrence of hepatotoxicity. Metabolite levels, 6-MP dose, and alanine transaminase (ALT) prior to initiation of allopurinol and approximately 8 weeks later were compared. Wilcoxon signed-rank test was applied for statistical analysis.

Results: After the addition of allopurinol, patients experienced a significant decrease in mean levels of 6-MMPN ($p = 0.0007$), correlating with a significant decrease in mean ALT ($p = 0.004$). With the initiation of allopurinol, the mean 6-MP dose was decreased from 84 to 32 mg/m2/day over an 8-week period. Mean 6-TGN levels increased ($p = 0.14$). In follow up beyond 8 weeks, no patients had further holds in 6-MP due to hepatotoxicity.

Conclusion: Addition of allopurinol appears to shift metabolism from 6-MMPN toward 6-TGN, with increases in mean 6-TGN levels despite a decrease in mean 6-MP dose. This may limit negative side effects, thus resulting in fewer gaps in therapy and possible improved outcomes. Further analysis of 6-MP dose titration and effects on ANC over time as well as effects on overall survival is ongoing. Prospective

study of the use of allopurinol in conjunction with 6-MP is also underway as a multi-site collaborative project.

Poster # 722 | EFFECTS OF DISRUPTION OF PIRNA PATHWAY IN AML CELL LINES TREATED WITH DNA METHYLTRANSFERASE INHIBITORS

Dragon Do, Stephen Dalby, Meghan McFadden, Supraja Prakash, David Lee, Elisabeth Heuston, Jason Farrar

University of Arkansas for Medical Sciences, College of Medicine, Little Rock, Arkansas, United States

Background: Alterations in epigenetic patterning are a fundamental feature in acute myeloid leukemia (AML). Treatment with DNA methyltransferase inhibitors (DNMTi) yields responses in AML, but the molecular mechanisms underlying this effect are poorly understood. In prior work, we demonstrated induction of genes involved in the piRNA RNA (PIWI) silencing pathway as a common gene feature of 4 AML cell lines treated with decitabine. The PIWI pathway is an RNA silencing system, distinct from classical small RNA transcriptional silencing, responsible for transposon-silencing in gametogenesis; emerging data suggest a role for this system in somatic cells. Based on these data, we postulate that PIWI induction plays a crucial role in AML recovery following demethylation and that disruption of this pathway would modulate response and/or recovery from decitabine treatment.

Objectives: To assess the effect contribution of the piRNA pathway response following DNMTi treatment in AML.

Design/Method: To choose target genes in the piRNA pathway for disruption, Molm13 cells were first treated with escalating doses of decitabine. Using quantitative RT-PCR, the dose-dependent expression of several piRNA-associated genes were analyzed. Two genes, MAEL and PIWIL2, were selected for disruption experiments based on preliminary data suggesting decitabine dose-dependent responses. Molm13 cells were transduced with shRNA targeting these genes using a lentivirus delivery system with selection in puromycin. Knockdown efficiency was assessed by RT-qPCR. To determine how gene disruption affected cell growth, knockdown cells were treated with decitabine 20nM. Proliferation was assessed by CellTiter Glo assay following decitabine treatment. Clonogenic potential was assessed by colony forming assays of transduced cells after treatment with decitabine at 5nM and 10nM.

Results: Following decitabine exposure in Molm13, there was a markedly increased expression of MAEL and PIWIL2 compared to untreated cells (2363:1 and 41:1, respectively). Thus, these were the candidate genes chosen for disruption. Of 4 MAEL shRNA constructs, two resulted in a 25% relative expression of MAEL compared to controls. Of the 3 PIWIL2 shRNA constructs, the best knockdown showed 75% relative expression. There were no significant differences in proliferation or clonogenicity of stably selected MAEL or PIWIL2 knock-down Molm13 cells following decitabine treatment.

Conclusion: Using gene knockdown procedures, MAEL and PIWL2 do not appear to have a marked effect on growth and response to decitabine treatment in Molm13. However, these results may be limited by inefficient knockdown using shRNA targeting methods. Further work using a Cas9/CRISPR based inactivation of these genes is ongoing.

Poster # 723 | IMPACT OF MINIMAL RESIDUAL DISEASE ON OUTCOME OF CHILDREN WITH HYPODIPLOID ACUTE LYMPHOBLASTIC LEUKEMIA

Iman Sidhom, Sherine Salem, Nesreen Ali, Seham Gohar, Khaled Shaaban, Sonia Soliman, Hadeel Magdi, Dina Hammad, Alaa El-Haddad

Children Cancer Hospital Egypt-CCHE,57357-Hospital, Cairo, Egypt

Background: Hypodiploidy <44 chromosomes is very uncommon and have particularly poor outcomes in childhood acute lymphoblastic leukemia (ALL). It is subdivided into: near-haploid (24-31chromosomes), low-hypodiploid (32-39chromosomes) and high-hypodiploid (40-43chromosomes).

Objectives: To determine if minimal residual disease (MRD) can identify a group of patients with better prognosis in the hypodploid population who can be treated with intensive chemotherapy alone.

Design/Method: A retrospective study that included all patients under age of 18 diagnosed as hypodiploid B-Precursor ALL during the period between January 2008-December 2015 and treated at Children's Cancer Hospital Egypt on SJCRH total study-XV for IR/HR ALL.

Results: Sixteen patients had <44 chromosomes (9 near-haploid and 7 low-hypodiploid), constituting 1% of all pediatric patients with B-Precursor ALL during the study period. Patients with near-haploid ALL had a median age of 6 years (range 2–17), initial leukocyte count (WBC) median of 7.5 × 109/L (range 1.3-86.6), 4 (44.4%) were males and 5/9 (55.6%) had HR-NCI criteria. Four patients (44.4%) are alive in complete remission(CR) (range 25–48 months, median 30), one died in induction and 4 (44.4%) had hematological relapse (range 6.8-33 months, median 15).

Patients with low-hypodiploid ALL had significantly older age (median 15 years, range 13–17), median WBC 4.3 × 109/L (range 3.5-13.5), 5/7 (71.4%) were males. One patient (14.3%) is alive in CR, one died in induction, one failed to achieve CR post-induction and 4 patients(57%) had hematological relapse (range 3.9-5.6 months, median 4.8). MRD<0.01% by flow-cytometry on day-15 and end of induction was achieved in 5/9 (55.6%) and 6/8 patients(75%) with near-haploid, compared with 1/6 (16.7%) and 3/6 patients(50%) with low-hypodiploid; respectively ($p = 0.287$, $p = 0.58$;respectively). Allogeneic transplantation was performed during initial remission only in 2 MRD negative patients (one relapsed and one is in CR) and in the patient with induction failure (relapsed post-transplant). Five of the total six patients who had negative MRD on day-15 and end of induction are alive in CR (4/5 with chemotherapy alone). All 3 patients with negative MRD at end of induction but with MRD levels≥0.01% on day-15 (range 0.02-0.33%) relapsed as well as all 4 patients with detectable MRD at the end of induction. The difference in relapse was statistically significant in relation to negative-MRD on day-15 ($p = 0.005$), but not at end of induction($p = 0.105$).

Conclusion: Children with hypodiploid ALL and negative MRD on day-15 of induction are highly curable with intensive chemotherapy alone, while patients with negative MRD at the end of induction and detectable MRD on day-15 had dismal outcome.

Poster # 724 | INCIDENCE AND PREDICTORS OF RESPIRATORY ADVERSE EVENTS DURING INDUCTION THERAPY IN CHILDREN WITH ACUTE MYELOID LEUKEMIA

Lane Miller, Sharon Castellino, Ann Mertens, Frank Keller, William Woods

Emory University School of Medicine, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, Georgia, United States

Background: Overall survival in pediatric acute myeloid leukemia (AML) has plateaued between 60–70%, with death during induction chemotherapy seen in 4–11% of patients. Respiratory complications contribute to morbidity and mortality in pediatric AML induction, however the incidence, patterns, and predictors of respiratory adverse events (AEs) during this period are unknown.

Objectives: To estimate the incidence of respiratory AEs during induction therapy for de novo pediatric AML, to characterize and grade these respiratory AEs, and to identify predictors of respiratory AE development.

Design/Method: We conducted a retrospective longitudinal study from presentation to day 42 in institutional de novo pediatric AML patients (≤ 21 years) between March 2009 and December 2016. Outcomes included any NCI CTCAE grade 2–5 respiratory AE or death from another cause. Demographic, disease, and treatment-related data were abstracted. The most specific, best-fitting CTCAE category and grade for each AE was determined. Descriptive statistics, survival analysis, multivariable logistic regression analysis, and time-to-event distributions were performed (SAS v9.4, Cary, NC).

Results: Among 113 eligible patients, 54.0% (n = 61) experienced 69 discrete respiratory AEs. Incidence of grade 3–5 AEs was 46.0% (n = 52). A bimodal time-to-event distribution demonstrated peaks at treatment days 0 and 14. Induction death occurred in 4.4% (n = 5) including 3 deaths from respiratory failure associated with disseminated fungal disease. In univariate analysis, those experiencing AEs differed significantly in regards to older age at diagnosis ($p<0.0001$), higher initial WBC ($p = 0.012$), higher initial peripheral blast percentage ($p = 0.002$), coagulopathy at diagnosis (PT ($p = 0.004$), D-dimer ($p = 0.002$)), fluid overload status ($p<0.0001$), occurrence of infection ($p = 0.01$), and occurrence of tumor lysis syndrome (TLS) ($p = 0.016$). Patients with hyperleukocytosis ($p = 0.005$), fluid overload ($p<0.0001$), and FAB M3 morphology ($p = 0.0016$) each had a significantly decreased probability of completing the follow up period without experiencing a respiratory AE. On multivariable analysis, fluid overload (aOR 45.2 [95% CI: 5.4-376.0) and older age (aOR 1.10 [95% CI: 1.01-1.20) were significantly associated with AE occurrence when gender, hyperleukocytosis, TLS, and infection status were held constant.

Conclusion: We describe a high incidence of respiratory AEs during pediatric AML induction. Fluid overload and older age at diagnosis are independently associated with AE development when controlling for other proposed risk factors. Interventions focused on conservative fluid management and offset of fluid overload should be explored in newly diagnosed pediatric AML in an effort to reduce respiratory complications during induction.

Poster # 725 | CONTINUED IMPROVEMENTS IN OVERALL SURVIVAL (OS) IN CHILDREN WITH NEWLY DIAGNOSED ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): A CHILDREN'S ONCOLOGY GROUP (COG) REPORT

Elizabeth Raetz, Xiaomin Lu, Meenakshi Devidas, Mignon Loh, Naomi Winick, William Carroll, Stephen Hunger

University of Utah, Salt Lake City, Utah, United States

Background: While overall ALL outcomes have continued to improve with contemporary risk-adapted therapy, there remains heterogeneity in survival rates among ALL subgroups.

Objectives: To compare 5-year OS rates in children, adolescents and young adults treated on frontline COG ALL trials from 2000–05 and 2006–10 to determine if improvements in outcome have continued across different ALL subgroups.

Design/Method: 5-year OS was estimated using the Kaplan-Meier method with standard errors (SE) calculated per Peto and curves compared using the log-rank test among patients enrolled on frontline ALL therapeutic trials from 2000–10. Outcomes were analyzed among gender, age, lineage, NCI risk group and racial/ethnic ALL subgroups over two sequential time eras: 2000–05 and 2006–10.

Results: 5-year OS improved significantly from 90.3% (SE 0.4%) in 2000–05 (n = 7842) to 91.5% (SE 0.4%) in 2006–10 (n = 8090), p = 0.0286 among all patients. The most dramatic improvement was observed in T-cell ALL (T-ALL) where 5-year OS rose from 80.8% (SE 1.9%) in 2000–05 (n = 515) to 90.6% (SE 1.7%) in 2006–10 (n = 676), p<0.0001. Significant improvements in outcome were also observed in NCI standard risk patients and in children 1–9 years of age regardless of NCI risk-group, where 5-year OS now exceeds 95%. Non-significant improvements in survival were observed among boys and their 5-year OS now matches that observed in girls. While the survival gap between blacks and whites decreased by 50% from 2000–05 to 2006–10, outcomes for Hispanics remained inferior and static with 5-year OS of 87.9% (SE 0.9%) in 2000–05 vs. 87.7% (SE 1.1%) in 2006–10, p = 0.5898. Importantly, no survival improvements were observed at either end of the age spectrum. The 5-year OS for infants < 1 year of age was 53.5% (SE 4.1%) in 2000–05 (n = 159) vs. 47.2% (SE 7.9%) in 2006–10 (n = 82), p = 0.4858. While many more (4.7% vs. 7.6%, p<0.0001) adolescents and young adults (AYAs) 16 years or older were enrolled in the recent era, 5-year OS was unchanged: 78.0% (SE 2.5%; n = 369) in 2000–05 and 77.3% (SE 2.4%; n = 618) in 2006–10.

Conclusion: Overall, ALL survival rates are outstanding and have continued to improve with risk-adapted therapy. The most striking improvement occurred in T-ALL where 5-year OS rates now exceed 90% and parallel B-ALL. Survival improvements, however, have not been observed uniformly across ALL subgroups. While the gap in outcome differences narrowed among blacks, outcomes for Hispanics have remained static. Further, no improvements in survival were observed in infants or AYAs and new treatment approaches have been implemented for these populations.

Poster # 726 | CHEST X-RAY FINDINGS IN NEWLY DIAGNOSED PEDIATRIC ACUTE MYELOID LEUKEMIA

Shanna White, Kenneth Shiao, Lei Wang, Stanley Pounds, Ching-Hon Pui, Raul Ribeiro, Jeffrey Rubnitz, Sue Kaste, Hiroto Inaba

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: Acute myeloid leukemia (AML) accounts for approximately 18% of new childhood leukemia cases. Chest x-ray (CXR) is performed in all newly diagnosed AML cases to evaluate the safety of airway management for anesthesia during diagnostic procedures; however, CXR results in pediatric patients with AML have not been described.

Objectives: The primary objective was to evaluate CXR findings at diagnosis in patients with AML. The secondary objectives included assessing associations between CXR findings and clinical characteristics, with the overall goal of aiding in the evaluation of the use of CXRs as an initial diagnostic study in pediatric patients with AML.

Design/Method: CXR findings and clinical characteristics were evaluated in patients with newly diagnosed AML who were enrolled in one of three protocols at St. Jude Children's Research Hospital (AML97, AML02, and AML08). The findings were categorized based on radiologic reports. Further, the associations of these findings and clinical characteristics were evaluated.

Results: We evaluated CXR findings in a total of 302 patients: 85 from AML97; 101 from AML02; and 116 from AML08. Common CXR findings were pulmonary opacity (n = 51, 16.9%), bronchial/perihilar thickening (n = 38, 12.6%), splenomegaly (n = 38, 12.6%), mediastinal mass and lymph nodes (n = 27, 8.9%), pleural effusion/thickening (n = 17, 5.6%), demineralization/fracture/periosteal lesions (n = 10, 3.3%), scoliosis (n = 10, 3.3%), and granulomatous disease (n = 7, 2.3%). Three CXR findings were associated with younger age at diagnosis: pulmonary opacity (median age, 4.5 years in patients with positive findings vs. 10.1 years in those with negative findings, P<0.01), bronchial/perihilar thickening (median age, 2.7 years vs. 10.3 years, P<0.01), and demineralization/fracture/periosteal lesions (median age; 2.7 years vs. 9.3 years, P = 0.04). Two CXR findings were associated with older age at diagnosis: scoliosis (median age, 16.5 years vs. 9.0 years, P<0.01) and granulomatous disease (median age, 15.1 years vs. 9.1 years, P = 0.02). Higher white blood cell counts (WBCs) at diagnosis were associated with CXRs showing pulmonary opacity (median WBC; 33.7 × 10^9/L vs. 14.8 × 10^9/L, P = 0.01) or splenomegaly (median WBC; 36.4 × 10^9/L vs. 15.2 × 10^9/L, P = 0.02). French-American-British (FAB) M4/M5 subtypes were more frequently associated with pulmonary opacity compared

with others (P<0.01). We did not find significant differences between female and male patients.

Conclusion: CXR in patients with newly diagnosed AML showed a variety of thoracic, abdominal, and bony lesions that are important for the initial evaluation and management. Pulmonary opacity was the most common finding and was frequently seen in patients who were younger or had higher WBCs at diagnosis or FAB M4/M5.

Poster # 727 | COMPLICATIONS ASSOCIATED WITH PLACING A PORT VERSUS AN EXTERNAL CATHETER DURING INDUCTION THERAPY IN CHILDREN DIAGNOSED WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Claire Atkinson, Hanumantha Pokala, Daniel Zhao, Allshine Chen

University of Oklahoma H, Oklahoma City, Oklahoma, United States

Background: Children diagnosed with Acute Lymphoblastic Leukemia (ALL) require a central venous catheter (CVC) to administer chemotherapy safely. Both external and internal CVCs carry risks of complications including thrombosis, infection, and possible replacement. Internal catheters, such as a port, are generally used for the majority of patients for the duration of treatment since therapy lasts for several years. Many institutions place a port at the time of diagnosis. Other institutions prefer to start Induction therapy via placement of a peripherally inserted central catheter (PICC) and defer port placement until the completion of Induction therapy due to concerns of increased risk of infectious complications with port placement.

Objectives: To compare rates of common CVC associated complications by type of CVC placed at start of Induction therapy in children treated for newly diagnosed ALL at the Jimmy Everest Center (JEC) at the University of Oklahoma Health Sciences Center.

Design/Method: A retrospective chart review analyzed data from newly diagnosed ALL patients treated at the JEC between 2010–2017. Data was collected on complications including thrombosis, bacteremia, insertion site infection, CVC malfunction and need for removal. Data collection began at the start of Induction and was completed at the end of Induction therapy. Statistical analysis used a univariate and multivariate logistic regression model to compare complication rates between those who had a port versus those who had a PICC placed at start of Induction.

Results: Data was collected on 128 patients. Fifty-six patients had a port placed at start of therapy while 72 had a PICC placed. Fourteen percent of patients had a CVC associated complication. Univariate analysis showed no statistically significant difference in rates of CVC associated complications between the groups (Port 16%, PICC 12.5% P = 0.564). The rates of hospitalization for CVC associated complications were similar between both groups (Port 14%, PICC 11% P = 0.590). Rates of CVC removal were also similar between both groups (Port 4%, PICC 4% P = 0.863). Multivariate model that included baseline patient characteristics including type of ALL, patient body surface area, gender, ethnicity and age continued to demonstrate no significant difference in CVC associated complications between both groups.

Conclusion: This single institution study showed that there was no significant difference in CVC associated complications between port and PICC line placement at the start of childhood ALL Induction therapy. Port placement can be considered as a safe option at the start of Induction therapy.

Poster # 728 | RESULTS OF A PHASE 2, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY OF LENALIDOMIDE IN PEDIATRIC PATIENTS WITH RELAPSED OR REFRACTORY (R/R) ACUTE MYELOID LEUKEMIA (AML)

Maureen O'Brien, Todd Alonzo, Todd Cooper, John Levine, Patrick Brown, Tamra Slone, Bouchra Benettaib, Noha Biserna, Jennifer Poon, Jackie Quan, Mathew Simcock, Daniel Weiss, Linda Zimmerman, Edward Kolb

Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Treatment options for pediatric patients with R/R AML remain unsatisfactory.

Objectives: To determine activity and safety of lenalidomide in the treatment of pediatric patients with R/R AML.

Design/Method: Eligible patients (aged ≤18 years with R/R AML [≥2 relapses or refractory to ≥2 prior induction attempts]) in this phase 2 multicenter study performed across 16 sites in the USA received lenalidomide (starting dose 2 mg/kg/day; maximum 70 mg/day) for days 1–21 of each 28-day cycle (maximum 12 cycles). The primary outcome was rate of morphologic complete response (proportion achieving

complete remission [CR] or CR with incomplete blood count recovery [CRi]) within treatment cycles 1–4. Interim data are reported (NCT02538965).

Results: Seventeen patients were enrolled and received ≥1 dose of lenalidomide; median age was 12 years (range 5–18); 7 patients were female. Patients received median 5 prior regimens (range 2–13). Nine patients had previously undergone bone marrow transplantation (BMT). Four patients had relapsed AML and 13 were refractory to immediate prior treatment. Median duration of study treatment was 4 weeks (range 1–12); patients completed a median of 1 treatment cycle (range 0–3). All patients were evaluable for primary outcome; 1 achieved morphologic CRi after 2 cycles (no patients achieved CR). The responder was a 13-year-old male with history of R/R AML after first- and second-line treatment, BMT, and salvage chemotherapy. At baseline, he had a complex cytogenetic karyotype (monoallelic −21q22.12, −3q, −4q13.3, −8p12) with no identifiable molecular mutation; he was also positive for del(5q) (−5q11, −5q23). His post-treatment karyotype showed no abnormalities. Sixteen patients experienced treatment failure; 12 due to resistant disease, 3 of indeterminate cause, and 1 had treatment failure before a post-baseline assessment was performed. All patients experienced ≥1 grade 3–4 treatment-emergent adverse event (TEAE). The most commonly reported were thrombocytopenia (n = 10), anemia (n = 7), febrile neutropenia (n = 7), and hypokalemia (n = 7). Fifteen patients experienced ≥1 TEAE related to lenalidomide. All patients discontinued treatment; 3 remain in follow-up. The study is now closed to enrollment. Ten patients died on study: 3 during treatment, 7 during follow-up. All deaths were attributed to AML or complications due to AML.

Conclusion: Third-line lenalidomide monotherapy was associated with clinical response in 1 of 17 pediatric patients with R/R AML; however, treatment exposure was limited. Safety data are consistent with the known profile of lenalidomide. Lenalidomide was not an efficacious treatment for R/R pediatric AML. Funding: Celgene Corporation, Summit, NJ, USA.

Poster # 729 | PREVALENCE AND RISK FACTORS FOR MALNUTRITION DURING PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA INDUCTION THERAPY

Rachel Hill, Tyler Hamby, Charles Boren, Mir Ali, Danielle Johnson, W. Paul Bowman, Anish Ray

Cook Children's Medical Center, Fort Worth, Texas, United States

Background: It is well documented that pediatric patients with acute lymphoblastic leukemia (ALL) often experience significant weight gain during induction therapy and later struggle with obesity. However, some patients experience unintended weight loss during induction therapy; since this issue is not well reported, it often goes undertreated. Although malnutrition is reported to be associated with decreased survival, increased risk of infection, and loss of lean body mass, there remains a scarcity of in-depth analysis of prevalence and risk factors that contribute to this problem. Our study attempts to address this critical yet unmet need.

Objectives: Our aim was to identify the clinical risk factors and outcomes associated with weight loss during induction therapy for pediatric ALL.

Design/Method: This was a retrospective chart review of patients between 2 and 20 years of age diagnosed with ALL at Cook Children's Medical Center from 4/1/14 to 3/31/17. For each patient, we collected height, weight, age, body mass index (BMI) z-scores at diagnosis and end of induction therapy, risk stratification, and whether consolidation was delayed. Patients with a BMI >85th percentile at diagnosis were categorized as being overweight or obese. Using logistic regression analyses, we examined which variables predicted whether the patient had an increase or decrease in BMI z-score throughout induction. A critical alpha level of 0.05 indicated statistical significance.

Results: Ninety-six patients met our inclusion criteria. Of these, 40% experienced a decrease in BMI during induction therapy. Compared to patients whose BMI increased during induction, patients with a decrease in BMI were more likely to be overweight or obese at diagnosis (55% vs. 22%; $p<0.001$), to be ≥10 years of age (53% vs. 16%; $p<0.0001$), to have a high- or very-high-risk stratification (87% vs. 31%; $p<0.0001$), and to experience a delay in the start of consolidation therapy (47% vs. 21%; $p<0.01$).

Conclusion: This research highlights a risk not previously identified in the literature that may impact outcomes. Patients treated on high- or very-high-risk protocols, who are overweight or obese at diagnosis, and who are ≥10 years of age at diagnosis should be monitored closely for weight loss during induction therapy. Patients who experience weight loss should receive prompt intervention. It is our hope that this information can be used for future prospective studies and to help develop evidence-based guidelines.

Poster # 730 | FREQUENCY OF 17P ABNORMALITIES IN IRANIAN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML)

Saman Raftari, Azadeh Mirzaei, Marjan Yaghmaei, Ardeshir Ghavamzadeh

Hematology Oncology and Tem Cell Transplantation Research Center, University of Tehran, Tehran Iran, Islamic Republic of Iran

Background: 17p abnormalities have been observed in some patients with hematologic malignancies. Loss of p53 function as a tumor suppressor gene in the chromosome 17 plays an important role for development of leukemia. These patients usually have poor outcome due to the chemotherapy and are associated with poor prognosis.

Objectives: This study aimed to identify Frequency of 17p abnormalities between Iranian children and adult patients with AML (Acute Myeloid Leukemia) malignancy.

Design/Method: The 17p abnormalities were analyzed via bone marrow karyotyping and FISH method in 669 acute myeloid leukemia patients.

Results: In this study, 17p abnormalities were observed in 52 (8%) patients out of 669 diagnosed cases. A significant strong correlation between 17p abnormalities and other high risk factors (poor risk cytogenetic) were observed. From 52 patients with AML malignancy (17p abnormalities), 45 (86%) patients have complex karyotype, 35 (67%) patients monosomal karyotype and 34 (65%) patients have monosomal karyotype accompanied with a complex karyotype.

Conclusion: Overall, 17p abnormalities are independent risk factor in acute myeloid leukemia and evaluation of these abnormalities by FISH or other complementary techniques prior to treatment, might help for better risk stratification of high risk AML patients.

Poster # 731 | HEPATOTOXICITY REQUIRING LIVER BIOPSY IN CHILDREN WILL ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE SERIES

Nathan Yarnall, Karen Effinger, Frank Keller

Emory University School of Medicine, Department of Pediatric Hematology-Oncology, Atlanta, Georgia, United States

Background: Hepatotoxicity in treatment of acute lymphoblastic leukemia (ALL) is well studied and transiently affects most patients receiving antimetabolite therapy. Rarely, patients develop liver injury severe or prolonged enough to undergo a liver biopsy. Little is known about how these patients differ from patients that develop transient hepatotoxicity.

Objectives: We sought to describe disease and treatment characteristics for ALL patients that developed hepatotoxicity severe enough to undergo liver biopsy. We also looked for predictive factors for liver biopsy, including signs of early hepatic injury from the initial treatment protocol.

Design/Method: Pathology reports of ALL patients from the liver biopsy database at Children's Healthcare of Atlanta were collected. Controls were matched 2:1 for age, ALL subtype, and treatment protocol. Demographics, treatment protocols, and overall outcomes were collected through the electronic health record. Hepatic lab results for transaminases, coagulation, and albumin were collected for induction, consolidation, interim maintenance, delayed intensification, and maintenance.

Results: Sixteen patients diagnosed between 2003–2013 (median age at diagnosis 10 years, range 1–16; 50% male; 75% pre-B ALL) were included in the case series. The median time from diagnosis to liver biopsy was 1.5 years (range 1–11). Eight patients (50%) were in maintenance at the time of biopsy; none had active disease. Eight (50%) were post-bone marrow transplant. Biopsy results included: steatosis (3), acute inflammatory/infectious (3), liver infiltration (1), fibrosis (6) and graft-vs-host disease (GVHD) (2). Six patients were deceased; 5-year all-cause mortality from diagnosis was 31%. Thiopurine methyltransferase (TPMT) status was known in 44% cases and 80% controls. All cases had intermediate or wildtype status, which did not differ from controls ($p > 0.05$). Patients requiring liver biopsy did not have evidence of acute hepatotoxicity (AST/ALT > 10× normal values) during their initial treatment protocol.

Conclusion: Hepatotoxicity requiring liver biopsy is a rare outcome of ALL treatment. These patients had elevated rates of relapse, BMT, and 5-year all-cause mortality, suggestive of a more severe disease process. However, it is difficult to sort out the temporality of relapse, BMT, and hepatoxicity requiring biopsy in this limited sample. Additionally, patients with BMT preceding liver biopsy have other confounding factors that makes them difficult to include in the analysis. Finally, our limited descriptive data show no notable correlation between early hepatotoxicity and later indication for liver biopsy. Future cohort or case-control studies with larger sample sizes are required to further explore early predictive factors for severe hepatotoxicity requiring liver biopsy.

Poster # 732 | BVGP: A NOVEL PROTOCOL FOR HODGKIN'S LYMPHOMA WITH EXCELLENT RESPONSE, MINIMAL ACUTE TOXICITIES AND REDUCED RISK OF LATE EFFECTS

Nathan Gossai, Joanna Perkins, Michael Richards, Yoav Messinger, Bruce Bostrom

Children's Minnesota, Minneapolis, Minnesota, United States

Background: Pediatric and young adult Hodgkin lymphoma (HL) has five-year survival rates >90%. Chemotherapy required to achieve this rate is associated with a lifetime risk of cardiac deaths, second malignancies, pulmonary disease and infertility. As effective salvage therapy exists, outcomes may be improved by de-intensifying initial therapy to lessen toxicity.

Objectives: We piloted a regimen in low and intermediate risk HL patients using agents without known association to significant late effects. This retrospective chart review was approved by Children's Minnesota IRB.

Design/Method: The BVG(P) regimen incorporated bortezomib (1.3 mg/m2 day 1,4,8,11); vinorelbine (25 mg/m2 day 1,8); gemcitabine (1000 mg/m2 day 1,8) every 21 days and prednisone (20 mg/m2/dose BID x 11 days). We treated 5 newly diagnosed patients, ages 10–18 years, with non-bulk stage IIA (n = 4) or IIB (n = 1) HL. Two patients received BVG and 3 received BVGP with the addition of prednisone.

Results: Newly diagnosed patients were all PET negative after the first or second cycle and remained PET negative at end of therapy, 4 cycles. Nausea was well controlled with 5-HT3 antagonists and scopolamine. Pegfilgrastim was not necessary due to the high absolute neutrophil count nadir [median 1.16 and minimum 0.56 × 109/L]. There were no episodes of febrile neutropenia, infection or transfusion need. No patients experienced alopecia. One patient developed sensory neuropathy after the eighth dose of bortezomib that was controlled with gabapentin and a switch to subcutaneous bortezomib administration. Of the five newly diagnosed patients, four remain in remission at 227, 270, 557, 1191 days; 1 relapsed at previous disease sites at 861 days and subsequently achieved remission with BVGP with the addition of brentuximab.

Conclusion: This series provides early evidence to stimulate expansion of this pilot experience and subsequent multi-institutional study leading to a randomized trial of BVGP and current chemotherapy for low and intermediate HL.

Poster # 733 | YOUNG AGE IS HIGHLY ASSOCIATED WITH MORNING HYPOGLYCEMIA AMONG CHILDREN RECEIVING ALL THERAPY

Ashraf Mohamed, Mohamed Kabbani, Lori Berry, Mohamed Sleim

St Jude Affiliate Clinic at St Francis Hospital, Tulsa, Oklahoma, United States

Background: Symptoms suggestive of morning hypoglycemia has been noticed in children receiving ALL chemotherapy. Only few small studies looked at this therapy related complication. Factors increase risk of hypoglycemia in ALL patients include accelerated starvation, steroid induced adrenal suppression, mercaptopurine therapy and prolonged fasting for procedures.

Objectives: to study the prevalence and risk factors for hypoglycemia during ALL therapy

Design/Method: Medical records of of children (up to 18 years old) treated for ALL between 2011–2016 (86 patients) were studied for evidence of morning hypoglycemia defined as blood sugar (BS) < 60 mg/dL. Statistical mean differences between the subgroups were analyzed with SPSS using a non-parametric Mann-Whitney U test.

Results: Fifty two percent (52%) of patients developed hypoglycemia during ALL treatment, with an average of 2.2 episodes/patient. 59% were males and 41% females. Almost 2/3 (65%) of patients with hypoglycemia were in maintenance phase of therapy. 34% of hypoglycemic episodes occurred in 10% of patients. Majority of hypoglycemic episodes (78.2%) occurred on the day of procedure when patients were fasting overnight. 48.9% of hypoglycemic episodes occurred in children ≤3 years, with 75.8% in ≤6 years. Patients who developed hypoglycemia were significantly younger (mean age at time of diagnosis of ALL was 4.93 ± 3.69 at the hypoglycemia group versus the non-hypoglycemia (7.27 ± 4.98) $p<0.05$. No statistically significant difference was found regarding sex, or TPMT genotype. 6% of hypoglycemic children—all <3years of age—presented with life threatening hypoglycemia symptoms including seizure and loss of consciousness.

Conclusion: This study showed high prevalence of hypoglycemia during childhood ALL therapy. Younger age, especially ≤ 3 years, is associated with higher risk of hypoglycemia as well as life-threatening episodes. To decrease fasting hypoglycemia during therapy for childhood ALL, we recommend that children under the age of 6 years receive bed time snack high in proteins and complex carbohydrates, and to get them up early the day of procedure to take clear sugary drink.

Poster # 734 | PREGNANCY TESTING AND CONTRACEPTIVE COUNSELING IN FEMALES WITH NEWLY DIAGNOSED HODGKIN LYMPHOMA: EXPERIENCE AT A PEDIATRIC CENTER

Laura Wheaton, Sarah Alexander

Hospital for Sick Children, Toronto, Ontario, Canada

Background: The majority of chemotherapeutic agents used to treat Hodgkin lymphoma are teratogenic. Pregnancy screening prior to the start of chemotherapy is supported by clinical guidelines and baseline testing is a standard component in therapeutic trials. There is limited data available on the incidence of pregnancy screening prior to the start of Hodgkin therapy but previous studies suggest that pregnancy screening, especially at pediatric institutions, is not consistently completed.

Objectives: The objective of this study is to evaluate the incidence of pregnancy screening and contraceptive counseling prior to the start of therapy in females diagnosed with Hodgkin lymphoma.

Design/Method: A retrospective chart review was performed for all female patients newly diagnosed with Hodgkin lymphoma from 2000 to 2015 at the Hospital for Sick Children in Toronto, Ontario. All patients who were intended to receive multi-agent chemotherapy were included, regardless of age. Data collected included demographic and disease information, chemotherapy regimen and enrollment on clinical trial. All pregnancy testing within two weeks prior to the start of therapy was captured, as well as type of pregnancy test performed, documentation of menstrual status, contraceptive counseling and contraceptive provision. Univariate and multivariate analyses were used to describe factors influencing the incidence of pregnancy testing.

Results: A total of 122 female patients with newly diagnosed Hodgkin lymphoma between the ages of 5 and 17 years were identified. Sixty patients (49%) had pregnancy testing done prior to the start of therapy. Testing modalities included serum and urine screens as well as quantitative beta-HCG measures. Older age ($P = 0.0016$), documentation of menstrual status at diagnosis ($P = 0.019$) and diagnosis between 2008 and 2015 ($P = 0.004$) were associated with higher incidence of screening. Enrollment on a therapeutic trial was not associated with a higher incidence of screening ($P = 0.374$). Contraceptive counseling was documented for 19 patients (16%) and 11 patients (9%) were prescribed contraceptive medications during therapy.

Conclusion: Pre-chemotherapy pregnancy testing was completed on 49% of females with newly diagnosed Hodgkin lymphoma. Improvement is required and interventions, including clarification of institutional standards, modification of chemotherapy order sets and staff education, are planned. (Rao et al., Cancer, 2016).

Poster # 735 | GRANULOCYTIC SARCOMAS IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE SERIES

Justin Farge, Alexandra Cheerva

University of Louisville, Louisville, Kentucky, United States

Background: Granulocytic sarcomas (also known as chloromas or leukemia cutis) were first described by A. Burns in 1811. They are solid tumors comprised of immature granulocytic cells and represent extramedullary manifestations of underlying leukemia. Chloromas are most commonly associated with acute myeloid leukemia. They may arise in other myeloproliferative disorders but are rarely seen in B or T cell acute lymphoblastic leukemia (ALL).

Objectives: Although patients with ALL rarely have chloromas, it should remain on the differential for patients with unusual swelling or masses.

Design/Method: We present a case series of two patients from our institution diagnosed with B cell ALL who had a chloroma as the presenting symptom.

Results: The first patient is a 4yo who presented to his primary provider with nasal congestion and a one-week history of bilateral eye swelling and was referred to an allergist when the symptoms did not resolve with anti-histamines. His review of systems was otherwise negative. He was referred urgently to ENT two months later for a 3×3cm mass palpated along the medial border of the left eye. An MRI showed a left facial mass surrounding the zygoma and extending into the anterior inferior left orbit. Biopsy revealed B cell acute lymphoblastic lymphoma, and bone marrow aspirate and biopsy confirmed the diagnosis as B cell ALL. The second patient is a 10yo who presented to his primary doctor for rapid growth of a scalp nodule that had been present for about 2 months. He was referred to Dermatology and treated for a supposed kerion from tinea capitis. The lesion continued to grow and became more irritated with this treatment. Punch biopsy revealed a complicated phenotype of lymphoblastic lymphoma. However, after a lymph node biopsy and bone marrow aspirate and biopsy, the diagnosis was confirmed as B ALL. His only other positive point on review of systems was a questionably pathologic 20-pound weight loss and an area of matted cervical lymph nodes.

Conclusion: For both of our patients, the chloromas completely disappeared during Induction therapy. It is worth noting that both of these patients presented with the chloroma as the only symptom of the underlying leukemia. This led to initial misdiagnosis and delay in identifying their leukemia. Therefore, while it is very rare for a patient with B ALL to present with a chloroma, our experience shows that ALL should be on the differential for patients presenting with unusual swelling or masses.

Poster # 736 | RARE PRESENTATIONS OF HODGKIN LYMPHOMA IN CHILDREN AND ADOLESCENTS: A MULTICENTER EXPERIENCE IN LATIN AMERICA AND THE UNITED STATES

David Veron, Patricia Streitenberger, Patricia Obando, Alejandra Zapata, Darrell Espnoza, Patricia Calderon, Jong Hee Chung, Reuben Antony, Mauricio Castellanos, Karen Fernandez

Valley Children's Healthcare, Madera, California, United States

Background: Hodgkin lymphoma (HL) is a lymphoproliferative neoplasm that commonly presents with history of adenopathy and a predictable pattern of disease involvement with or without systemic symptoms of fever and/or weight loss. In the hands of an experienced oncologist the diagnosis of HL is usually not a challenge. Occasionally a diagnostic challenge is presented by a patient who has an atypical presentation which is suggestive of an alternative diagnosis.

Objectives: We describe a case series of patients diagnosed with HL whose initial clinical presentations lead to a diagnosis different form HL.

Design/Method: Multi institutional retrospective review at various oncology centers located in Argentina, Guatemala Honduras, Nicaragua and the United States.

Results: Six pediatric oncology centers from the American continent conducted a retrospective review of patients diagnosed with HL since 2010. Patients that had an initial presentation not suggestive of HL or who were initially diagnosed with a disease other that HL were included for a total of 25 patients. Argentina n = 8, Guatemala n = 7, Honduras n = 1, Nicaragua n = 2, United States n = 7. Five patients were female and 20 male. Patient's ages ranged from 2 to 18 years. Most patients (n = 19) were older than 11 years. Three patients (15%) presented with non-immune cytopenias without overt lymphadenopathy, of those one had active hemophagocytic syndrome. Five patients (20%) were suspected to have localized solid tumors: Ewing Sarcoma n = 2, Rhabdomyosarcoma n = 1, hepatocellular carcinoma n = 1, and soft tissue tumor of the cheek n = 1. Two (8%) metastatic solid malignancy as they presented with disseminated pulmonary nodules. Five (20%) with autoimmune disorders: Hashimoto thyroiditis n = 1, autoimmune hemolytic anemia n = 1, nephrotic syndrome n = 3. Ten (40%) with chronic infectious processes: Brucella n = 1, tonsillar abscess n = 1, splenic abscess n = 1, and tuberculosis (TB) n = 7. Patients with suspected tuberculosis were diagnosed outside of the United States. Six of 7 patients were ultimately diagnosed as having both TB and HL. Seventeen patients had Ann-Arbor stage III or IV, seven patient had stage II with either B symptoms or bulky disease. Patients were treated with various chemotherapy regimens according to the treating center: ABVD, ABVE-PC OEPA-COPDAC, AVPC, BEACOPP. Two patients had recurrent disease, one died of disease progression and one died from causes not related to HL

Conclusion: A small proportion of HL patients have atypical or unusual presentations. HL should be included in the differential diagnosis of solid tumors, autoimmune disorders, infections or cytopenias. The most common atypical presentation is an infectious process.

Poster # 737 | SURVIVAL OF FILIPINO CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA DIAGNOSED IN A TERTIARY REFERRAL CENTER FOR CHILDHOOD CANCER: A RETROSPECTIVE COHORT STUDY

Trixy Chu, Arden Mae Shiu, Ma. Cecilia Cruz, Ma. Beatriz Gepte

Philippine Children's Medical Center, Quezon City, Philippines

Background: Acute lymphoblastic leukemia (ALL) represents the largest group of pediatric malignancies. The high cure rate of childhood ALL represents one of the most remarkable success stories in the war on cancer. In a lower middle income country (LMIC) like the Philippines, we reviewed the five year survival in a tertiary referral center.

Objectives: This retrospective cohort study aims to determine the survival of children 1–18 years old with ALL treated at a tertiary referral center for childhood cancer in the Philippines from January 2012 to December 2016.

Design/Method: This is a retrospective cohort study that reviewed medical charts of newly diagnosed ALL ages 1 to 18 years old from January 2012 to December 2016.

Results: A total of 435 subjects were included in the study. The 5 year overall survival (OS) and event free survival (EFS) were 65.3% and 62.8%, respectively. The 5 year OS for standard risk ALL was 68.8% and for high risk patients was 50%. The 5 year OS for the patients on remission was 83.7% and for those who relapsed was 21.1%. Univariate and multivariate by Cox proportional hazards regression revealed WBC count at diagnosis, risk classification, immunophenotyping, and development of relapse showed significant prognostic impact for mortality. Age and gender were reported with no prognostic significance.

Conclusion: The 5-year OS and EFS were lower compared to developed countries but are comparable with other LMICs. The prognostic factors for relapse and mortality were compatible with the literature. Overall, the adopted treatment protocols for childhood ALL in this institution showed acceptable results. Relapse has a significant prognostic impact for mortality. Development of accessibility to care, increase awareness, early detection and resources at hand should be achieved. Improvement in the follow up protocol to prevent delays in the treatment, patient education to prevent non-compliance and psychosocial support, to developed better supportive care, and expand facilities should be given emphasis to further improve survival and prevent relapse.

Poster # 738 | BURKITT-LIKE LYMPHOMA WITH 11Q ABERRATION: A DISTINCT PATHOLOGIC AND CLINICAL ENTITY

Aroop Kar, Melissa Stalling, Madina Sukhanova, Girish Venkataraman, Katrin Carlson Leuer, Lawrence Jennings, Kristian Schafernak, Shunyou Gong, Nobuko Hijiya

Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States

Background: Burkitt-like lymphoma with 11q aberration is a new provisional entity included in the 2016 revision of the World Health Organization classification, with pathologic features resembling those of Burkitt lymphoma but lacking MYC rearrangements. Instead, this entity shows recurrent chromosome 11q alterations, particularly proximal gains and telomeric losses, although there have only been limited cases reported.

Objectives: Here, we seek to further characterize this entity by describing the pathologic and clinical features of 4 pediatric cases of Burkitt-like lymphoma with 11q aberration.

Design/Method: We collected pathologic and clinical data from the medical record on all pediatric high grade B-cell lymphoma (HGBCL) cases diagnosed at our institution over a 5-year period (2012-2017). For those cases classified as neither Burkitt lymphoma nor diffuse large B-cell lymphoma (DLBCL), FISH for MYC, BCL-2 and BCL-6, as well as array comparative genomic hybridization (aCGH), were performed.

Results: We identified 38 cases of HGBCL, including 5 cases of Burkitt lymphoma presenting as purely leukemic phase. Of the HGBCL cases, 20 had Burkitt lymphoma as defined by MYC rearrangements, and 13 had DLBCL. Collectively, the majority of these 33 patients had primary disease outside of the head/neck, and most patients presented with advanced stage (III-IV) disease. Of the 5 remaining cases, 11q aberration was identified in 4 cases using aCGH. All 4 cases histologically and immunophenotypically resembled Burkitt lymphoma but lacked MYC rearrangement, instead showing proximal gains in 11q13-q23 and telomeric losses in 11q24.1-qter. All 4 cases involved primary disease in the cervical lymph node and/or tonsil. Three of these cases were localized (stage II), and the fourth case involved a few metabolically active but non-enlarged lymph nodes in the chest and abdomen (stage III). All 4 patients achieved complete remission with standard therapy for mature B-cell lymphoma, and were alive with no clinical evidence of disease at a median follow-up of 23 months.

Conclusion: Although the number is small, our results suggest that the majority of non-Burkitt, non-DLBCL cases of pediatric HGBCL carry 11q aberrations. In addition, patients with 11q aberrations appear to be more likely to present with lower stage disease, thus requiring less intensive therapy, and also tend to have primary disease in the head/neck. These findings further support the classification of Burkitt-like lymphoma with 11q aberration as a distinct pathologic and clinical entity, and we propose that all pediatric non-Burkitt, non-DLBCL cases of HGBCL regularly undergo further workup for possible 11q aberrations.

Poster # 740 | EPIDEMIOLOGICAL PROFILE OF LYMPHOMAS MANAGED AT A PEDIATRIC HOSPITAL IN PORT-AU-PRINCE, HAITI, FROM JANUARY 2006 TO DECEMBER 2016

Marie Claire Milady Auguste, Joseph Bernard

St Damien Hospital, Port-au-Prince, Port-au-Prince, Haiti

Background: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) account for 7% of cancers in the United States pediatric population (1, 2). In Central America and the Caribbean, they are in second position among all types of pediatric cancers (3). A previous study on pediatric cancers in Haiti showed that the lymphomas were in fifth place after the leukemias, Wilms tumor, retinoblastoma and the sarcomas (4).

Objectives: The main objective of this study is to present the epidemiological profile of lymphomas managed at a Haitian pediatric hospital.

Design/Method: This is a retrospective study conducted on the cases of lymphoma diagnosed and managed at St Damien Hospital from January 2006 to December 2016. Key variables

such as age, gender, stage at diagnosis, histopathological types and outcome were collected to present the characteristics of this retrospective cohort.

Results: Of the 407 cases of cancer diagnosed during the study period, 23 (5.7%) had the diagnosis of lymphoma. The sex ratio was 2.8 (17 males for 6 females) and the average age was 8.9 years [0-19 years]. There were 11 cases of HL (47.8%) and 12 cases of NHL (52.2%). 69.6% of the patients were diagnosed at stages III and IV. Among the HL cases, 6 (54.5%) were nodular sclerosis lymphoma, 3 (27.3%) with mixed cellularity and 2 (18.2%) with lymphocytic predominance. For the NHL cases, 4 (36.4%) were Burkitt's lymphoma and 3 (27.3%) lymphoblastic T-cell lymphoma. Among the 12 patients for who immunohistochemistry was found, the 4 cases of HL were CD30-positive and 6 out of 8 cases of NHL were CD20-negative. Only 1 patient was HIV-positive, and 4 patients had a confirmed exposure to Epstein-Barr virus. 8 patients (34.8%) were lost to follow-up, 7 (30.4%) were in remission, 3 (13 %) relapsed, 2 (8.7%) were still in treatment and 3 (13%) were deceased.

Conclusion: Although most likely underdiagnosed, lymphomas are among the main pediatric cancers diagnosed and managed in St Damien Hospital. There is a late presentation and a high number of lost to follow-up. The predominance of CD20-negative NHL needs further investigation. References: 1) Ward E, DeSantis C, Robbins A, et al. CA Cancer J Clin, 2014. 2) Kaatsch P. Cancer Treat Rev, 2010. 3) Valsecchi1 MG, Tognoni G, Bonilla M. et al. Annals of Oncology, 2004. 4) Lucien JG, Bernard J. Pediatric Blood Cancer, 2016.

Poster # 741 | A STUDY OF THE ASSOCIATION BETWEEN CYTOGENETICS, RACE AND ETHNICITY AMONG PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AT THE UNIVERSITY OF CHICAGO

Gabriela Villanueva, Christine Timmer, Brian Chiu, Madina Sukhanova, Sandeep Gurbuxani, Susan Cohn, Jennifer McNeer

University of Chicago, Chicago, Illinois, United States

Background: Due to the adoption of risk-adapted therapy, pediatric and adolescent acute lymphoblastic leukemia (ALL) is associated with high cure rates. Despite excellent outcomes in most children, patients with certain blast cytogenetic features do not fare as well. Furthermore, African American, Native American, and Hispanic patients have worse outcomes than Caucasian patients. While the outcome discrepancies are certainly multifactorial, and blast cytogenetics are related to age, it remains unclear whether ethnicity and blast cytogenetics correlate. The diverse patient population at The University of Chicago provides an opportunity to evaluate for such a correlation.

Objectives: To describe cytogenetic findings in a racially and ethnically diverse population of patients of all age groups diagnosed with ALL at University of Chicago from 2006 to 2016 and determine if there is a correlation between race/ethnicity and blast cytogenetics.

Design/Method: This is a retrospective, single institution chart review

Results: A total of 191 newly diagnosed patients with ALL between the ages of 1–100 from 2006–2016 were included in this study. Of those, 167 patients (87.4%) had B-ALL, 22 had T- ALL (11.5%), one had early T-cell precursor ALL and one had mixed phenotype ALL (B/T). Caucasians accounted for 46% of patients, African Americans (AA) 22%, Hispanics 24.6%, Asians 5.24%, and 2% were of other races. Age distribution had a bimodal pattern, with a peak in incidence at 5 and another at 58 years of age, consistent with published data. Cytogenetic categories included: t(12;21)(p13;q22), 11q23 rearrangements (KMT2A), iAmp21, t(1;19)(q23;p13.1), t(9;22) (q34;q11), hypodiploidy, hyperdiploidy and double trisomy of chromosomes 4 and 10. AA and Hispanic patients with B-ALL presented more frequently between the ages of 10–18 years compared to Caucasians ($p = 0.002$ and 0.02, respectively). In AA patients, t(1;19) (q23;p13.3) was overrepresented ($p = 0.04$ when compared to Caucasians), and was mainly observed in patients between 10–18 years. Caucasian patients were more likely than non-Caucasians to have hyperdiploidy ($p = 0.04$), especially in patients aged 1–9 years.

Conclusion: The rate of t(1;19)(q23;p13.2) was significantly higher in AA patients in our cohort, in particular in patients between the ages of 10–18 years. Hyperdiploidy was more likely in Caucasians aged 1–9 years. These findings may suggest that varying blast cytogenetics could contribute to outcome differences between races.

Poster # 742 | DOES CONSOLIDATION RADIOTHERAPY IMPROVES THE OUTCOME OF CHILDREN WITH STAGE IV HODGKIN LYMPHOMA IN COMBINATION TO CHEMOTHERAPY?

Ahmed Elgammal, Yasser Elborai, Mohamed Fawzy, Asmaa Salama, Eman D El-Desouky, Lobna Shalaby

National Cancer Institute, Cairo, Cairo, Egypt

Background: Hodgkin lymphoma (HL) in children is one of the malignancies that have a high chance of cure. Stage IV HL remains a challenge for getting good clinical outcome as in other stages. Many treatment protocols used to give combination chemotherapy while combined modality treatment is the mainstay in other treatment protocols.

Objectives: We aimed in to assess the outcome using consolidation radiotherapy to chemotherapy (combined modality treatment) versus combination chemotherapy alone in treatment of stage IV HL.

Design/Method: We included patients with stage IV HL and whose data were retrieved from the medical records of the Pediatric Oncology department, National Cancer Institute, Cairo University, Egypt from 2005 till June 2013 and were followed till August 2015. Treatment was either to give 8 cycles of ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) only or to give 6 cycles of ABVD followed by consolidation radiotherapy.

Results: The study included 22 cases; 17 were males and 5 were females. Mean age was 10.66 years ranging from 4 to 17 years. The histopathology subtype was nodular sclerosis in the majority of cases (15 cases) followed by mixed cellularity (6 cases) then only one case of lymphocyte rich. Nine cases were initially bulky while 13 cases were not. Constitutional manifestations were present in 10 cases while it was absent in 12 cases. Bone marrow was involved in only 4 cases. Radiotherapy was given after completion of chemotherapy to 10 cases while 12 cases received chemotherapy only. The 5-year overall survival for patients who received radiotherapy was superior to those who received chemotherapy alone; 100% versus 45.8% respectively with statistical significance ($P = 0.02$). The 5-year progression free survival was also higher with radiotherapy than others; 90% versus 44.4% ($P = 0.095$).

Conclusion: Patients with stage IV HL who received consolidation radiotherapy apparently had a better outcome than those who received chemotherapy only. This suggests that radiotherapy contributes significantly with chemotherapy to the cure rate for those patients.

Poster # 743 | EXOSOMAL MICRO RNA-181a INHIBITION CURBS LEUKEMIC PROLIFERATION IN PEDIATRIC ALL

Sarah R. Vaiselbuh, Shabirul Haque

The Feinstein Institute for Medical Research, Manhasset, New York, United States

Background: MicroRNA (miRNAs) are short non-coding RNAs that play a decisive role in cancer biology, including leukemia. Exosomes are microvesicles (30-100 nm) produced by most cells in biological fluids. Exosomes represent the fingerprint of the parental tumor and are loaded with bioactive markers such as miRNAs, which may regulate tumor growth. Exosomal cargo can be transferred into target cells changing their biological properties. Our study investigates a functional role for exosomal miR-181a in pediatric acute lymphoid leukemia (P-ALL).

Objectives: 1/ To demonstrate that P-ALL exosomes induce cell proliferation2/ To confirm that exosome-induced cell proliferation is disease-stage specific 3/ To analyze exosomal miR-181a expression profiles in P-ALL4/ To authenticate that inhibition of exosomal miR-181a reduces leukemia proliferation

Design/Method: Exosomes were isolated by ultracentrifugation from healthy donors (HD) & P-ALL serum and conditioned medium (CM) of SUP-B15, JM1, and CL-01 (control) human cell lines. Cell lines were exposed to different sources of leukemia-derived exosomes in a paracrine or autocrine fashion for 24hrs in triplicates. Proliferation was assessed by microscopic cell counting and confirmed by gene expression for proliferation, pro-survival and pro-apoptotic genes. miRNA profiling was performed with the Human Cancer Pathway Finder microarray (Qiagen). Silencing of exosomal miR181a was carried out by a miR-181a inhibitor (Qiagen), utilizing Exo-FectTM exosome transfection reagent (SBI, System Biosciences). Further, exosomal miR-181a silencing was confirmed by q-PCR. Cellular uptake of TexRed-siRNA (SBI, System Biosciences) was confirmed by flow cytometry. Transfer of exosomal miR181a to the target cells was evaluated by q-PCR.

Results: We elucidated that CM-derived exosomes from SUP-B15 and JM1 cell lines induce cell proliferation in SUP-B15, JM1 (autocrine and paracrine) and CL-01 cells (paracrine) ($p<0.01$). Serum P-ALL exosomes promote paracrine cell proliferation in ALL cell lines compared to HD-derived exosomes ($p<0.0001$). Heatmap analysis of miRNA profiles of leukemia exosomes (ALL cell lines and P-ALL) identified miR-181a significantly upregulated in leukemia exosomes compared to controls. miR-181a was also upregulated in ALL cell lines after exposure to leukemia exosomes that induced proliferation. Moreover, exosomal miR-181a inhibition reduces leukemic proliferation in pediatric ALL.

Conclusion: Our data suggest that ALL exosomes induce cell proliferation of leukemic cell lines in both paracrine and autocrine fashion. Exosomes regulate these phenomena in a highly orchestrated way, by transfer of functional exosomal miRNAs such as miR-181a. The results of this study suggest

that exosomal miR-181a inhibition can act as a novel way for growth-suppression of pediatric leukemia.

Poster # 744 | ROLE OF FDG-PET/CT IN THE MANAGEMENT OF PEDIATRIC BURKITT LYMPHOMA

Ahmed Elhussein, Hany Rahman, Mohamed Fawzy, Walid Omar, Hany Hussein

Children Cancer Hospital Egypt, Cairo, Egypt

Background: Burkitt lymphoma (BL) is highly FDG-avid even though its usefulness in the management of pediatric patients with BL is still controversial.

Objectives: We analyzed the role of positron emission tomography/computerized tomography (PET/CT) in staging and evaluation of tumor response in newly diagnosed children with BL receiving LMB 96 protocol.

Design/Method: A total of 180 PET/CTs were performed in 94 patients (94 at diagnosis and 91 at time of evaluation). Involved areas were prospectively compared with those observed in contrast enhanced CT. Residual lesions in both PET/CT and contrast-enhanced CT were correlated with patient outcome at one year after end of treatment.

Results: A total of 199 disease sites were detected at PET/CT, while 172 sites were detected at contrast-enhanced CT and bone marrow biopsy (BMB). PET/CT showed improved detection of nodal lesions ($P < 0.0001$) (Kappa value = 0.633), extranodal lesions ($P < 0.0001$) (Kappa value = 0.632) and bone marrow ($P < 0.0001$) (Kappa value = 0.728) compared to contrast enhanced CT and BMB. PET/CT had upstaged 15 cases (16%) and down-staged 4 cases (4.3%) ($P < 0.001$) (Kappa value = 0.649). Among the upstaged 15 cases, 10 patients (10.9%) were upstaged from stage II to III, based on residual in PET/CT not seen in contrast enhanced CT after abdominal mass excision. Four patients (4.3%) were upstaged from stage III to IV based on bone marrow uptake in FDG-PET without positivity in BMA or BMB.Regarding response assessment, sensitivity was 60% for PET and 80% for contrast-enhanced CT ($p = 0.56$). Specificity was 100% for PET and 65% for CT ($p < 0.0001$). Positive predictive value for PET was 100%, while was 12% for CT scan ($p < 0.0001$). Negative predictive value for both PET and CT was 98% ($p = 0.82$). Five patients had 2nd biopsy to confirm viability of the residual lesions, 4 lesions were negative in pathological examination (all of them were metabolic negative in PET/CT; Deauville score below 4). One lesion was positive in pathological examination (was positive in PET/CT; Deauville score of 4).

Conclusion: PET/CT detected additional sites compared with contrast-enhanced CT and resulted in changing stage of disease. PET scan is significantly more specific than CT in the management of children with Burkitt lymphoma.

Poster # 745 | ULTRA-DEEP SEQUENCING DEMONSTRATES VARYING CLONAL COMPOSITION BETWEEN DISEASE SITES IN B CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B ALL)

Carol Fries Simpson, Diana Adlowitz, Janice Spence, John Spence, Philip Rock, W. Richard Burack

University of Rochester, Rochester, New York, United States

Background: Deep sequencing of the immunoglobulin heavy chain (IGH) locus indicates that each B ALL is composed of innumerable subclones. In many cases, subclones exhibit differing phenotypic qualities. However, it remains unclear whether subclones demonstrate distinct tissue distribution within a patient.

Objectives: 1. To quantify the extent of clonal heterogeneity in diagnostic B ALL specimens; 2. To identify variability in clonal composition between bone marrow (BM) and peripheral blood (PB) disease sites.

Design/Method: IGH sequencing was performed on purified DNA from 10 pairs of matched BM and PB patient specimens. Multiplex PCR was used to globally amplify the IGH locus; next generation sequencing (NGS) was performed using Illumina® MiSeq. Index clones (defined as $\geq 5\%$ of all sequence reads in a specimen) and their subclone progeny (defined by 6 shared nucleotide bases immediately upstream of a common Jh, or 6N_Jx) were identified using IgBlast-determined Vh and Jh alignments (http://www.ncbi.nlm.nih.gov/igblast/) and an established in-house computational pipeline.

Results: Up to 3 index clones per specimen were discovered in 16 of the 20 samples. In the remaining 4 (2 BM/PB pairs), 1 pair did not reveal a clonal IGH and was eliminated from analysis; in the other, clone frequency did not reach the 5% index threshold, but predominant clonal precursors were inferred by the prevalence of their subclone progeny. Subclone counts ranged from 2 to 2,619 per index clone. A combined 2,900 subclones derived from 11 PB index clones were observed; in contrast, 12 BM index clones gave rise to only 400 subclones. Subclone heterogeneity was observed between all paired specimens. In 6 BM/PB pairs, index clones existed in equivalent proportions between disease sites. In contrast, 1 BM/PB pair demonstrated 2 high-frequency index clones in the BM (32.6% & 12.5%) with limited representation of these

clones in the PB (0.6% & 1.4%, respectively); in this case, the most prevalent clone in the PB (10.8%) matched the least frequent index clone in the BM (5.0%). Similarly, another pair showed a predominant index clone in the PB (5.8%) which was below index threshold (3.6%) in the BM.

Conclusion: In 2 paired patient specimens, index clone predominance was discovered to be overtly distinct between BM and PB. Among all pairs, the extent of subclone progeny derived from each index clone showed marked variability, with far higher subclone frequency in the PB than in the BM. Our data indicate that B ALL clonal composition differs between disease sites.

Poster # 746 | HODGKIN LYMPHOMA AND TUBERCULOSIS IN CHILDREN AND ADOLESCENTS IN GUATEMALA AND ARGENTINA

David Veron, Patricia Obando, Castellanos Castellanos, Karen Fernandez

Valley Children's Healthcare, Madera, California, United States

Background: Tuberculosis (TB) presenting with Hodgkin Lymphoma (HL) is rare. Their coexistence could lead to delay in diagnosis of both TB and Hodgkin lymphoma due to the similarities in signs and symptoms of presentation. Most cases have been reported in the adult literature.

Objectives: We describe a case series of 11 children that were suspected to have TB and were found to have coexisting TB and HL.

Design/Method: Retrospective review

Results: A retrospective review of HL patients in Guatemala and Argentina over 6 six years, uncovered 11 patients with simultaneous diagnosis of TB and HL. Eight patients were from Guatemala (incidence of 4.5%) and 3 from Argentina (incidence of 2.5%). There were 4 females and 7 males. Age ranged from 4 – 17 years (mean 10.5 years, media 9 years). Nine patients were suspected to have TB at presentation by the referring physician. Two patients were found to have TB at the time of relapse through routine tissue culture. Initial systemic symptoms included fever (n = 5), weight loss (n = 2), and night sweats (n = 2). Six patients had a second systemic symptom in addition to fever. Time for referral to oncology center ranged from 2 weeks to 5 months. Nine patients were diagnosed with TB and HL through a tissue cultures and 1 with serum Quantiferon. One patient was found to have HL without TB. Two patients had no systemic symptoms and the diagnosis of TB came to light through routine tissue culture. Five patients had stage IIIB and IVB, two stage IIA and one IIB at diagnosis. HL treatment was given according to the institutional standards depending on stage and risk with ABVD, OEPA/COPDac +/- Radiation therapy, and ICE for relapse. Five patients started anti TB treatment (Isoniazid, Rifampin, Pyrazinamide +/- Ethambutol for 2 months followed by Isoniazid and rifampin for 30–52 weeks) simultaneously with chemotherapy, and three others after completing 2 cycles. The two relapsed patients started TB treatment after 2 cycles of chemotherapy. Seven patients are alive and have been followed for 5 months - 6 years. One patient died during therapy, another died for causes not related to TB or HL and one is currently receiving treatment.

Conclusion: Tuberculosis can coexist with HL. In areas were the prevalence of TB is high, microbiology investigations of biopsy specimen should be strongly considered. Therapy for TB can be given simultaneously with chemotherapy. Coexistence of TB and HL does not appear to affect outcomes.

Poster # 747 | FUNCTION AND MECHANISM OF PI3K/AKT SIGNALING PATHWAY IN PEDIATRIC T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Shi Lixiao, Jianhua Wang, Xiaodong Shi

The Children's Hospital Affiliated to the Capital Institute of Pediatrics, United States

Background: The PI3K/Akt signaling pathway plays a central role in cell growth, proliferation and survival in physiological conditions. This signal pathway is considered to be an innovative targeted therapy of cancer, and its abnormal activation has been proved to be related to T-cell acute lymphoblastic leukemia (T-ALL). Despite improved treatment strategies, such as multi-drug combination, high-dose chemotherapy and all kinds of application and popularization of hematopoietic stem cell transplantation, children with drug resistance or relapse T-ALL are still rather worse and its overall outcome and prognosis are much poorer than the more common B-lineage ALL.

Objectives: To explore the relationship between the PI3K/Akt pathway and the pediatric T-ALL, so as to probe the exact molecular mechanisms of T-ALL and provide more directions for its treatment.

Design/Method: 7 cases of new or recurrent acute T lymphocyte leukemia children with clinical information were collected in the children's hospital affiliated to the capital institute of pediatrics from Dec.2015 to Oct.2017, with 7 age and gender matched healty children as control (All was informed consent). The expressions of key genes in PI3K pathway were

analyzed by western blot RT-PCR analysis, the PI3K enzyme activities were detected by ELISA,and the CCRF - CEM's proliferation and its apoptosis were tested by MTT and flow cytometry technology on T-ALL cell lines CCRF-CEM in different treatment group.

Results: The results of T-ALL children in clinical showed that PI3K protein and gene expression level were higher apparent than the control group (P<0.05), and PI3K enzyme activity increased as well (P<0.05); PI3K inhibitor LY294002 made a significant inhibition of cell proliferation and promoted cell apoptosis. LY294002 also enhanced the effectiveness of clinical commonly used chemotherapeutic drug DNR. In combination LY294002 and DNR treatment group cell viability dramatically declined, apoptosis and the apoptosis relation protein Casepase3 expression in T-ALL patients was obviously higher than the control and the single drug group; PI3K/Akt signaling pathway related proteins and gene expression level, PI3K, Akt, GSK3β transcription in CCRF-CEM were significantly higher than the control (P< 0.05), while PTEN transcription was significantly lower than the control (P<0.05).

Conclusion: The abnormal activation of PI3K/Akt signaling pathway might play an important role in pediatric T-ALL patients, especially in the cell proliferation or apoptosis. The results might provide new train of thought and direction in targeted suppress this signal pathway or in combination with other chemotherapy drugs therapy in looking for the more effective and less cytotoxic treatment of pediatric T-ALL.

Poster # 748 | INCREASED TUMOR GROWTH AND ANGIOGENESIS IN ABSENCE OF KININOGEN IN T-CELL LYMPHOMA MURINE MODEL

Huseyin Erdemir, Meenal Shukla, Keith McCrae

Cleveland Clinic Children's Hospital, Cleveland, Ohio, United States

Background: Non-Hodgkin Lymphomas (NHLs) are a heterogeneous group of lymphoproliferative diseases which comprise 7% of all childhood malignancies. NHLs can be divided in to B cell lymphomas and T cell/Natural Killer (NK) cell lymphomas depending on immunophenotype, molecular biology, and clinical response to treatment. Although NK/T cell lymphomas occurring in childhood and adolescence comprise a small portion of all lymphomas, they present many diagnostic and therapeutic challenges. The role of angiogenesis in lymphoma pathogenesis is becoming more evident. High molecular weight kininogen (HK) is a central component of the kallikrein-kinin system. It has been previously reported that cleaved HK (HKa) induces apoptosis of proliferating endothelial cells and inhibits angiogenesis in matrigel plug and corneal angiogenesis models. However, the role of endogenous kininogen in regulation of angiogenesis is in tumor microenvironment is unknown.

Objectives: To elaborate the role of HK in lymphoma angiogenesis, we used a murine T-cell lymphoma model and compared angiogenesis and tumor growth between wild-type and kininogen deficient (mKng1-/-) mice. We also evaluated the effect of HKa on lymphoma cell proliferation.

Design/Method: EL-4 murine T-cell lymphoma cells (5 × 10^5) were implanted into wild-type and mKng1-/- mice. Tumor size was measured using calipers and tumor volume was calculated using the formula Volume = length × width^2 × 0.52. Seventeen days after cell implantation, tumors were harvested and processed by immunoblotting and immunofluorescent staining. Cell proliferation assays (MTS) were performed to investigate any possible inhibitory effect of HKa on EL-4 cell growth, with human umbilical vein endothelial cells (HUVEC) were used as a positive control.

Results: EL-4 lymphomas grew more rapidly and to larger sizes in mKng1-/- mice compared to wild-type mice, with significant differences apparent by day 11 after tumor implantation (p<0.01). By Day 17, the volume of tumors in mKng1-/- mice was approximately 1.4-fold larger than in wild-type mice (mean volume ± standard deviation; 2120 ± 536 vs. 1485 ± 272 mm3, respectively, p<0.01). MTS assays showed that HKa does not directly inhibit the proliferation of EL-4 cells in vitro, though it does significantly impair the viability of ECs studied simultaneously.

Conclusion: These findings suggest that HK is an important endogenous regulator of angiogenesis and tumor growth in this T- cell Lymphoma model, and suggests that HKa specifically modulates endothelial proliferation in tumor microenvironment. Further work is needed to understand the mechanisms underlying these findings and provide future anti-angiogenic approaches to increase the therapeutic options for patients with NHL.

Poster # 749 | CAN PROPHYLACTIC PAMIDRONATE INFUSIONS REDUCE THE INCIDENCE OF SYMPTOMATIC OSTEONECROSIS IN PATIENTS AT HIGH RISK?

Bruce Bostrom, Jack Knudson, Nathan Gossai, Joanna Perkins, Michael Richards, Jawhar Rawwas, Susan Sencer, Julie Chu, Nancy McAllister, Yoav Messinger

Children's Minnesota, Minneapolis, Minnesota, United States

Background: Osteonecrosis causes significant pain and morbidity in older patients treated for acute lymphoblastic leukemia. Besides altering the schedule of dexamethasone in delayed intensification there is no other intervention known to reduce the incidence of symptomatic osteonecrosis. Pamidronate has been shown to reduce bone pain from osteonecrosis but not to prevent joint collapse when advanced.

Objectives: To compare the incidence of symptomatic osteonecrosis in patients who received prophylactic pamidronate compared with concurrent controls. To describe any increase in side effects from the use of pamidronate.

Design/Method: Patients age 10 to 28 years at time of ALL diagnosis were given intravenous pamidronate monthly for one year at the discretion of the primary oncologist starting in the first year of therapy. Concurrent controls were patients age 10 to 28 who did not receive pamidronate. All patients were treated according to the concurrent COG protocols and received intermittent dexamethasone during delayed intensification. Patients with BCR-ABL ALL were excluded as the use of imatinib may increase the risk of osteonecrosis. Imaging was only done if osteonecrosis was suspect based on clinical symptoms. Patients were censored at the time of relapse. Data were analyzed as of 1/1/2018. This retrospective study was approved by the Children's Minnesota IRB.

Results: Of the 62 patients evaluated 58% were male and 42% female, 74% had B-cell and 26% T-cell. The median follow-up is 2.4 years with a range of 0.3 to 7 years. Pamidronate was given to 23 patients with 2 developing symptomatic osteonecrosis. There were 39 concurrent controls with 14 developing osteonecrosis. There was no significant difference in the leukemia lineage, gender distribution or body mass index (BMI) at diagnosis between groups. For all patients the median BMI was 22 with a range of 15 to 47. The age at diagnosis was significantly higher in the pamidronate group with a median of 18.6 years vs. 15.7 in the controls ($p = 0.014$). By Kaplan-Meier analyses the incidence of symptomatic osteonecrosis was significantly lower in the pamidronate group at 14% vs. 43% in controls. The log-rank p-value was 0.049 and the Breslow p-value, which is more sensitive to early events, was 0.039. There were no untoward side-effects from pamidronate.

Conclusion: Pamidronate infusions significantly reduced the incidence of symptomatic osteonecrosis in patients over the age of 10 compared to concurrent controls who did not receive pamidronate.

Poster # 750 | POLATUZUMAB VEDOTIN (PV) ALONE OR IN-COMBINATION WITH OBINUTUZUMAB SIGNIFICANTLY ENHANCES IN-VITRO/IN-VIVO CYTOTOXICITY AGAINST BURKITT LYMPHOMA (BL)/PRIMARY MEDIASTINAL LARGE B CELL LYMPHOMA (PMBL)

Arahana Awasthi, Dina Edani, Janet Ayello, Christian Klein, Mitchell Cairo

New York Medical College, Valhalla, New York, United States

Background: Mature B-NHL, including BL and PMBL express CD20+/CD79b+ and have an excellent prognosis, however, subset of patients relapse secondary to chemoimmunotherapy resistant disease and have a dismal prognosis ($\leq$ 20% 5 yr. EFS, Cairo et al. Blood. 2007; Gerrard/Cairo et al., Blood, 2013, Goldman/Cairo et al. Leukemia, 2013). PV has been demonstrated to possess significant preclinical activity against indolent CD79b+NHL (Polson et al. Can. Res.2009). We previously observed that obinutuzumab (Anti-CD20 mAb) significantly enhanced cell death and increased overall survival against BL (Awasthi/Cairo et al., BJH 2015) in xenografted NSG mice. However, additive/synergistic effects of PV with obinutuzumab against mature PMBL/BL are unknown.

Objectives: To determine the efficacy of the PV or obinutuzumab/RTX alone or in combination against PMBL and rituximab (RTX) sensitive/resistant BL cell lines.

Design/Method: Raji4RH (provided by M. Barth, MD, Roswell Park Cancer Institute) and Raji/ Karpas1106P (ATCC, USA) were cultured in RPMI. Tumor cells were incubated with PV, and/or anti-CD79b, MMAE (generously supplied by Genentech Inc.) with obinutuzumab /rituximab (100ug/ml) for 4 hr with NK cells at 10:1 E: T ratio and cytotoxicity was determined by DELFIA cytotoxicity assay. Six to 8 week old female NSG (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ), were divided into 5 groups: PBS, isotype control, PV, antiCD79B mAb and MMAE (5mg/kg). Mice were xenografted with intravenous injections of Luc+ BL and PMBL cells and tumor burden was monitored by IVIS spectrum system.

Results: OS of mice receiving PV alone was significantly increased compared to antiCD79b Ab or isotype control in Raji (35.5 vs.17 vs.19.5 days, $p = 0.0001$, 0.0003), Raji4RH (50 vs.18 vs.18.5 days, $p = 0.0001$, 0.0001) and Karpas1106P (150 vs 89 vs 64 days, $p = 0.03$, 0.003), respectively. Obinutuzumab+NK, rituximab+NK compared

to PV+NK cells significantly enhanced cell lysis in Raji, 65.9±2.4% vs. 38.9±5.4% vs. 44.24±8.1% (p = 0.001 & p = 0.001), Raji4RH, 52.8±9.4% vs. 16.04±7.2% vs.47.0±8.2% (p = 0.03 & p = NS) and Karpas1106P, 66.10±5.3% vs.48.2±3.9% vs. 61.6±10.06% (p = 0.004 & NS), respectively. PV+ obinutuzumab+NK, significantly improved cytotoxicity compared to PV+ rituximab+NK in Raji, 93.6±6.1% vs 79.9±5.3% (p = 0.007), Raji4RH, 78.07±2.05% vs 63.5±0.16% (p = 0.004) and Karpas1106P, 88.3±6.3 %vs.73.03±3.03% (p = 0.003), respectively.

Conclusion: Our preliminary data indicates that PV significantly increased survival in BL and PMBL NSG xenografts compared to anti-CD79b Ab alone. Furthermore, PV in combination with obinutuzumab significantly enhances in-vitro cytotoxicity in BL and PMBL compared to obinutuzumab or PV alone.

Poster # 751 | MANAGEMENT OF COAGULOPATHY ASSOCIATED WITH TISAGENLECLEUCEL CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

Jochen Buechner, Stephan A. Grupp, Shannon L. Maude, Hidefumi Hiramatsu, David Teachey, Patricia Wood, Rakesh Awasthi, Lan Yi, Barbara De Moerloose

Oslo University Hospital, Oslo, Norway

Background: Tisagenlecleucel (CTL019), an anti-CD19 CAR T-cell therapy, has demonstrated durable response rates and a manageable safety profile in pediatric/young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL). Cytokine release syndrome (CRS), a systemic inflammatory response caused by elevated serum cytokine levels, occurred in 81% of patients treated in 2 multicenter trials. Coagulopathy was associated with CRS and macrophage activation syndrome (MAS) in previous reports of tisagenlecleucel. Similar coagulopathy was reported in cases of MAS/hemophagocytic lymphohistiocytosis associated with other events, including infections or chemotherapy.

Objectives: Outline treatment guidelines and the US/global multicenter experience with coagulopathy in 97 pediatric/young adult patients with relapsed/refractory B-ALL.

Design/Method: Pooled data from 2 single-arm, multicenter, phase 2 trials (ELIANA [NCT02435849]; ENSIGN [NCT02228096]) were used to characterize coagulopathy during tisagenlecleucel-associated CRS.

Results: Maximal grades (G)1/2, 3, and 4 CRS occurred in 36, 19, and 24 patients, respectively. Median lowest fibrinogen levels were 3.5, 3.3, and 1.2g/L in patients with maximal G1-2, 3, and 4 CRS, respectively. 3%, 11%, and 25% of patients with maximal G1-2, 3, and 4 CRS had lowest reported fibrinogen levels of ≥1 to <1.5g/L. Eight patients (all with G4 CRS) had very low fibrinogen levels (<1g/L), which occurred before (n = 1) or during (n = 6) maximal CRS grade or at time of improvement (n = 1). No patients with maximal G1-3 CRS had <1g/L fibrinogen levels. At the onset of <1g/L fibrinogen levels, 1 patient had concurrent G3, and 7 had G0-2 increased international normalized ratio and activated partial thromboplastin. Cryoprecipitate was the primary treatment in the US, and fibrinogen concentrate (FC) guidelines for tisagenlecleucel-associated coagulopathy were developed for other countries because administration of fresh frozen plasma can be problematic. FC was available at 7/25 sites for 20 infused patients: 3/7 (G4 CRS) and 0/8 (G1-3 CRS). Cryoprecipitate was available at 18/25 sites for 77 infused patients: 12/17 (G4 CRS), 2/15 (G3 CRS), and 0/32 (G1-2 CRS). Risk of bleeding increases in pediatric patients with comorbid thrombocytopenia and anticoagulant treatments. 5/8 patients had G3/4 decreased platelets within 1 day of <1g/L fibrinogen levels. 1 fatal case of intraparenchymal cranial hemorrhage occurred during resolving CRS with G3 hypofibrinogenemia, ongoing thrombocytopenia, and continuous veno-venous hemofiltration with citrate.

Conclusion: Hypofibrinogenemia was observed more frequently in patients with higher CRS grades during/when CRS was improving or resolving. FC and cryoprecipitate treatment guidelines were developed. Frequent monitoring and fibrinogen replacement are needed in patients with G3/4 CRS. Sponsored by Novartis.

Poster # 752 | REDUCED BURDEN OF ONCOLOGIC THERAPY IN ADVANCED B-CELL LYMPHOMA IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH CD20+ MATURE B-CELL LYMPHOMA

Jessica Hochberg, Matthew Barth, Stanton Goldman, Liana Klejmont, Lauren Harrison, Quihi Shi, Sherrie Perkins, Rodney Miles, Bruce Shiramizu, Mitchell Cairo

New York Medical College, Valhalla, New York, United States

Background: The addition of rituximab to chemotherapy for B-cell non-Hodgkin lymphoma by our group and others has led to significant improvements in outcomes.1 Standard therapy involves anthracyclines associated with cardiotoxicity and frequent intrathecal chemotherapy.2 It is unknown whether rituximab can be used to reduce the burden of anthracycline in patients with good risk B-NHL. Liposomal cytarabine, with

its prolonged CNS half-life, may allow a reduction in the number of intrathecal injections.

Objectives: To safely reduce the burden of therapy by reducing the number of IT injections and reducing the total dose of doxorubicin with the addition of liposomal cytarabine and rituximab.

Design/Method: Patients (3-31 years) with CD20+ B-NHL with FAB Group B good risk (=Stage I/II and Stage III with LDH < 2xULN), FAB Group B intermediate risk (=Stage III LDH ≥2xULN and Stage IV {BM blasts < 25%}) and FAB Group C high risk were eligible. Patients received FAB backbone therapy with the addition of six rituximab (375mg/m2) doses; two doses prior to each of two induction courses and one dose prior to each of two consolidation courses. Cumulative doxorubicin was reduced from 120 to 50 mg/m2 in GR patients. After systemic methotrexate clearance, patients received age based dosing of IT liposomal cytarabine. IT injections were reduced from nine to five. The primary outcome is safety and toxic deaths among 40 evaluable patients with an estimated 3-year survival above 90%, monitored by an independent DSMB.

Results: To date, 32 evaluable patients, 25 FAB Group B and 7 group C (6 CNS positive), median age 12 years (range 3–23), 20 males, 16 Burkitt/16 DLBCL with 18 GR, 7 IR and 7 HR have enrolled. There has been one Grade 3 anaphylactic reaction to rituximab and one Grade 3 facial nerve palsy. No other serious adverse events were attributable to protocol therapy. There has been 1 death from progressive disease and 1 relapse at a median follow up of 30 months. EFS and OS are 94% and 97%, respectively.

Conclusion: Our initial results show excellent EFS and OS, consistent with published standard of care outcomes, with the addition of rituximab and intrathecal liposomal cytarabine despite the reductions in therapy. Further enrollment is ongoing and continued long term outcomes are needed to confirm early results. Future randomized studies are needed to examine both short term (mucositis, infections, hospitalization days) and long term (late cardiac toxicity) endpoints. 1. Goldman etal, Leukemia, 2013 2. Cairo etal, JCO 2012.

Poster # 753 | "I'M GOING TO CHURCH ANYWAY": THE IMPACT OF SPIRITUALITY ON GRIEVING FOR PARENTS WHO HAVE LOST CHILDREN TO CANCER

Lindsay Blazin, Carlos Torres, Justin Baker

St. Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: Bereaved parents identify significant spiritual needs around time of death and throughout their bereavement journeys. Spirituality has been identified as a primary means by which bereaved parents can find meaning in their losses, and this ability to find meaning is associated with lower maladaptive grief symptoms. The use of spiritual coping strategies has been associated with improved coping and mental health outcomes among bereaved parents.

Objectives: To better understand how bereaved parents' experiences with spirituality throughout bereavement effects objective measures of grief, depression, and meaning-making.

Design/Method: Thirty participants whose children died of progressive cancer or related complications one to three years prior to participation completed an in-depth semi-structured telephone interview about their experiences with grief. Participants were prompted to describe the impact of their spirituality on their bereavement processes. Additionally, participants completed surveys related to grief (Prolonged Grief Disorder Questionnaire, PG-13), depression (Beck Depression Inventory, BDI), and meaning-making (Integration of Stressful Life Experiences Scale, ISLES). Results were analyzed using a mixed methods approach including semantic content analysis of qualitative content and Kruskal-Wallis H test and post-hoc analyses of quantitative data.

Results: Correlation analyses demonstrated significant differences between participants with positive and negative spiritual experiences of bereavement. Participants with negative experiences of bereavement had a statistically significant increase in scores on the PG-13 compared to those with positive spiritual experiences signifying greater symptoms of prolonged grief. Participants with negative spiritual experiences with grief had significantly lower scores on the ISLES, suggesting a lesser degree of adaptive integration of their losses. There were no significant differences in depression scores between groups.

Conclusion: Bereaved parents that have a negative spiritual experience of bereavement are at increased risk for prolonged grief symptoms and are less likely to find meaning in their children's deaths than bereaved parents that describe a positive spiritual experience of bereavement. Providers should consider exploration of spiritual beliefs and provision of spiritual care for parents of children facing life-limiting illnesses during treatment and bereavement.

Poster # 754 | CLINICAL OUTCOMES WITH MAPK INHIBITION IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS

Olive Eckstein, Daniel Zinn, Johannes Visser, Carolyn Fein Levy, Nicole Karras, Michael Henry, Patrick Campbell, Michael Jordan, Ashish Kumar, Carlos Rodriguez-Galindo, Kenneth McClain, Carl Allen

Texas Children's Hospital/Baylor College of Medicine, Houston, Texas, United States

Background: Langerhans Cell Histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by frequent relapse, with treatment failure associated with higher risk of death and neurodegenerative disease (LCH-ND). Activating somatic mutations in MAPK pathway genes have been identified in almost all cases, with BRAF-V600E in approximately 60% of lesions. Targeted therapies have been successful in treating other refractory cancers with BRAF V600E mutations (such as melanoma). Given the central role of MAPK pathway activation in LCH, MAPK pathway inhibition may be an effective therapeutic strategy for children with LCH.

Objectives: The purpose of this study was to report the efficacy and toxicity profile of a retrospective cohort of patients with LCH treated with MAPK pathway inhibitors.

Design/Method: Medical records from 12 pediatric patients with LCH (systemic and/or LCH-associated neurodegeneration) who were treated with a MAPK pathway inhibitor were retrospectively reviewed from five institutions. All patients had failed at least one prior systemic therapy and had a proven MAPK pathway mutation.

Results: All patients in this series were less than 21 years old (median = 10.1 years; range: 2–20 years) with a median of three prior treatments (range: 1–9). At the time of initial MAPK inhibitor use, nine of the 12 patients had LCH-ND diagnosed clinically and/or by radiographic imaging; the remaining three patients had systemic disease. Patients were treated for a median of 9 months (range: 1–20 months) with various reasons for discontinuation. Three patients received combination MAPK inhibitor therapies and three patients received other concurrent LCH-directed therapies. Four of the twelve patients had a Grade 3 or 4 toxicity reported and three of these patients required dose reduction in order to be able to successfully resume therapy. Overall survival was 92% with median 20 month follow-up (range: 1–42 months) with only one patient achieving transient complete response. The remaining ten patients had partial response or stable disease and four of these patients developed progressive disease while on therapy.

Conclusion: MAPK pathway inhibitors may be a relatively safe salvage therapy for refractory systemic LCH and LCH-ND but the efficacy and durability of this strategy remains to be defined. Combination with cytotoxic chemotherapies may be required in order to eradicate the disease-causing cell. Future prospective trials of MAPK pathway inhibitors for patients with refractory LCH are needed in order to directly compare their efficacy and toxicity relative to other current salvage strategies.

Poster # 755 | IMPORTANCE OF UTILIZING MULTIPLE OBJECTIVE MEASURES OF ADHERENCE IN PEDIATRIC CANCER: COMPARISON BETWEEN PHARMACOLOGICAL ASSAYS AND BEHAVIORAL ADHERENCE

Jessica Geaney, Jennifer Rohan, Tsuyoshi Fukuda, Alexander Vinks

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Medication adherence during maintenance therapy has been shown to have a direct relationship with disease relapse in pediatric leukemia. Previous research determined that patients who are ≤ 95% adherent to 6-mercaptopurine (6MP) have a greater risk for relapse.

Objectives: The primary aim of the present study is to examine the relationship between metabolite profiles of 6MP with behavioral adherence rates obtained via electronic monitoring at 5, 10, and 30 days. It is hypothesized that patients demonstrating low levels of thioguanine (TGN) and methylated mercaptopurine (MMP) will have lower behavioral adherence rates prior to the blood draw.

Design/Method: In a multisite, prospective study of 139 patients ages 7-19 years diagnosed with acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL), 6MP adherence was measured across 15 months of maintenance therapy using behavioral adherence (electronic monitoring) and pharmacological (metabolites) measures of 6MP. 6MP is metabolized into MMP and TGN. Cluster analysis was used to generate three mutually-exclusive profiles of 6MP adherence. Behavioral adherence rates were calculated for 5, 10, and 30 days prior to the blood draw.

Results: This study identified three metabolite profiles of 6MP across 15 months. Previous research indicated that low levels of both metabolites suggest nonadherence to medication. Low levels of one metabolite with high levels of another metabolite indicate adherence to 6MP. In this study, 51.2% of the low TGN-low MMP group had 5-day behavioral adherence rates ≥ 95% (mean = 100%); 48.8% had adherence rates < 84% (mean = 48.5%). In the high TGN-low MMP group, 77.6% had a mean 5-day adherence of 100%; 22.4% had adherence rates < 84% (mean = 32.9%). The low TGN-high MMP group had 74% of patients with a mean 5-day adherence level

of 100%; 26% had adherence rates < 84% (M = 54.6%). At 10 and 30-days, 62 to 66% of patients in the low TGN-low MMP group had adherence rates < 95%.

Conclusion: These findings suggest that electronic monitoring and metabolite concentrations can be used to monitor 6MP medication adherence during maintenance therapy. It is notable that there is a sub-sample of pediatric patients who are identified as being nonadherent to 6MP based on electronic monitoring, however, metabolite levels indicate adherence to 6MP. Similarly, a sub-sample of patients were identified as being adherent based on electronic monitoring, but metabolite profiles indicated sub-therapeutic levels of 6MP. Our findings underscore the clinical significance of using both objective measures of medication adherence to inform clinical decision making.

Poster # 756 | DISEASE-CAUSING COPY NUMBER VARIANTS IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DISEASE GENES

Elizabeth Ulm, Leandra Tolusso, Rebecca Marsh, Lisa Dyer

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by non-remitting fevers, rash, hepatosplenomegaly, cytopenias, liver dysfunction and coagulopathy, and can include central nervous system involvement. Several genetic diseases cause HLH by impairing normal lymphocyte or macrophage function. The HLH panel at the Cincinnati Children's genetics laboratories includes 14 genes associated with HLH and other lymphoproliferative diseases, including the genes that cause primary HLH (PRF1, UNC13D, STXBP2, STX11, RAB27A), X-linked lymphoproliferative diseases (SH2D1A, XIAP), ITK deficiency (ITK), Hermansky-Pudlak syndrome types 2 and 9 (AP3B1 and BLOC1S6), Chediak-Higashi syndrome (LYST), CD27 deficiency (CD27), XMEN syndrome (MAGT1) and lysinuric protein intolerance (SLC7A7). Deletion/duplication analysis is available as a reflex test for all 14 genes, as copy number variations (CNVs) are not directly assessed by sequencing.

Objectives: The prevalence of CNVs among large groups of patients with HLH in North America is unknown.

Design/Method: We assessed the frequency of CNVs in the genes on the HLH panel through a retrospective review of 522 orders for deletion/duplication analysis performed after next-generation or Sanger sequencing: 397 orders for all 14 genes on the panel, and 125 orders of 1–5 genes from the panel. Deletion/duplication analysis was performed on a custom 4 × 180K microarray annotated against NCBI build 37 (UCSC hg19, March 2006).

Results: Deletion/duplication analysis resulted in a confirmatory diagnosis in 11 of 522 cases (2.1%). Pathogenic or likely pathogenic CNVs were most common in the three X-linked genes: SH2D1A (3 deletions), XIAP (3 deletions, 1 duplication), and MAGT1 (3 deletions). Hemizygous deletions in X-linked genes in male patients were typically suspected after amplification failure during previous sequencing. Of the autosomal recessive genes, pathogenic CNVs were observed once in each of three genes: RAB27A (heterozygous), LYST (heterozygous), and STXBP2 (homozygous). In the two heterozygous cases, a second change was not identified by sequencing, so deletion/duplication analysis did not offer a confirmatory diagnosis. In 25 patients, deletion/duplication analysis was performed after a pathogenic or likely pathogenic variant was identified in an autosomal recessive gene during sequencing; however, in no case was a second mutation uncovered by CNV analysis.

Conclusion: We recommend that deletion/duplication analysis be routinely performed in all male patients with HLH who lack a genetic diagnosis after sequencing of HLH-associated genes, especially if any regions failed to amplify. Deletion/duplication analysis may be performed in female patients after sequencing if a genetic form of HLH is highly suspected, but the yield is expected to be low.

Poster # 757 | LONG-TERM OUTCOMES IN PEDIATRIC HEART TRANSPLANTATION RECIPIENTS WITH SECONDARY MALIGNANCY: A SINGLE INSTITUTION STUDY

Seth Rotz, Colleen Nasman, Aron Flagg, Rabi Hanna, Gerard Boyle

Cleveland Clinic Children's Hospital, Cleveland, Ohio, United States

Background: The development of post-transplant neoplasia, typically from lymphoproliferative disease (PTLD), is a severe complication in transplant recipients and affects approximately 12% of pediatric solid organ recipients. Rates of lymphoma in adult heart transplantation patients are comparatively low, at less two percent at ten years. There are few published reports of the long-term outcomes of neoplasia after pediatric heart transplantation.

Objectives: We aimed to identify the subsequent malignancies that occurred in pediatric heart transplantation patients

in a large single institution, and describe their treatment and subsequent clinical course.

Design/Method: We performed a retrospective chart review of all pediatric heart transplant recipients followed at the Cleveland Clinic Children's Hospital from January 1985 to October 2012. We excluded patients who died within 30 days of heart transplantation. We reviewed in depth the history and clinical course of subjects who developed neoplasms.

Results: Between 1985 and 2012, 101 patients underwent heart transplantation and survived at least 30 days post transplantation. Nine patients (8.9%) developed a subsequent malignancy. In this case series, the median age at heart transplant was 3 years old and the median time to develop neoplasia was 88.6 months. Primary neoplasia included monomorphic PTLD (3), polymorphic PTLD (1), Burkitt lymphoma (2), Hodgkin's lymphoma (1), plasmacytoma-like lymphoma (1) and Epstein-Barr Virus–Associated Smooth Muscle Tumor (EBV-SMT) (1). One patient with Hodgkin Lymphoma subsequently developed monomorphic PTLD, one patient with polymorphic PTLD subsequently developed EBV-SMT and later, an undifferentiated gastric cancer. One patient with monomorphic PTLD developed an EBV-SMT. Evidence of Epstein-Barr virus was present in six of nine patients at diagnosis of first malignancy. Four of nine patients received reduction in immunosuppression as a primary intervention for the initial malignancy, with two complete responses (CR), one partial response, and one with progressive disease. Five patients were treated with chemotherapy, with four CR and one with progressive disease. Three patients died of malignancy (recurrent EBV-SMT, undifferentiated gastric cancer, and monomorphic PTLD post-Hodgkin disease) and two patients died of other transplant related complications.

Conclusion: Secondary malignancies represent a significant disease burden to survivors of cardiac transplantation. As expected, much of the malignancy burden is driven by EBV. Despite aggressive histology, many malignancies can be successfully cured in this setting with a multidisciplinary approach.

Poster # 758 | LANGERHANS CELL HISTIOCYTOSIS: GASTROINTESTINAL INVOLVEMENT IN CHILDREN

Hoi Soo Yoon, Jeninifer Michlitsch, Michael Jeng

Stanford University School of Medicine, Palo Alto, California, United States

Background: Current treatment of Langerhans cell histiocytosis (LCH) is based on extent of organ system involvement and if high risk systems are affected. Gastrointestinal (GI) involvement is diagnosed in about 2% of LCH patients, and classically presents in children under 2 years of age with malabsorption, failure to thrive, bloody diarrhea and anemia. Although the GI system is considered standard risk, a mortality rate over 50% occurring within 2 years of diagnosis has been reported. This study was performed due to this discrepancy and the limited number of published cases.

Objectives: To review the clinical course and outcomes of patients diagnosed with GI LCH.

Design/Method: A retrospective chart review of patients with histologically confirmed GI LCH diagnosed in the last 15 years identified from the Bass Center Histiocytosis clinical database was performed. Two other pediatric hematology/oncology centers (UCSF Benioff Children's Hospital Oakland and San Francisco) were queried for additional cases.

Results: Four patients with biopsy proven GI LCH [3 subjects (2.9%) from 105 database records and 1 from center queries] were identified. Failure to thrive, hypoalbuminemia, bloody diarrhea and rash were the most common presenting symptoms. LCH of the skin was found in all patients. Risk organ systems were involved in 2 patients. Of note, 2 subjects were of African racial background. The median age at diagnosis was 3.5 months (1.5 months to 16 years), mean albumin 2.2 g/dL (1.2 – 2.9 g/dL), mean ESR of 56 mm/hr (37 – 78 mm/hr). All patients initially received combination therapy per LCHIII Protocol (vinblastine, prednisone, and 6 mercaptopurine). Two patients had recurrent disease and received second line therapy (cytarabine, 2CDA, and local radiation therapy). All patients are alive without active disease at last follow-up (8 to 107 months after completion of therapy).

Conclusion: A systematic approach to evaluate GI involvement should be performed in children diagnosed with LCH. From our experience, combination chemotherapy for patients with LCH involving the GI tract is an effective intervention for active disease.

Poster # 759 | ELECTRONIC MONITORING OF MEDICATION ADHERENCE DURING MAINTENANCE PHASE THERAPY FOR PEDIATRIC CANCER: BEHAVIORAL ADHERENCE PATTERNS

Jennifer Rohan, Jessica Geaney

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Bhatia indicated that rates of 6MP adherence ≥ 95% have better clinical outcomes. Those with adherence rates ≤ 95% have an increased risk for disease relapse. The present study investigated patterns of 6MP medication adherence using group-based trajectory modeling in a large sample of pediatric patients.

Objectives: To describe patterns of behavioral adherence during the maintenance phase of therapy for a cohort of pediatric patients ages 7–19 years who were diagnosed with acute lymphoblastic leukemia or lymphoblastic lymphoma (n = 139). Previous research has documented the relationship between optimal levels of medication adherence with positive health outcomes. It was hypothesized that three groups would be identified: optimal adherence, deteriorating adherence, and chronic nonadherence. It was hypothesized that patients in the optimal adherence group would have adherence rates ≥ 95%. Those with poor adherence would have adherence rates ≤ 95%.

Design/Method: The present study was a longitudinal, multisite study investigating adherence to 6-mercaptopurine in a pediatric cohort of patients using electronic monitoring devices. Daily adherence rates (electronic monitoring of 6MP) were examined across 15-months. Health outcomes were measured at quarterly intervals through medical chart reviews.

Results: Unconditional growth curve modeling indicated that the mean percentage of behavioral adherence was 84.4% at baseline and declined to 75.2% at 15-months. Three trajectories of 6MP behavioral adherence were identified: 1) optimal adherence (67% of patients): averaging 95% behavioral adherence across 15 months; 2) moderate adherence (20%): relatively stable nonadherence with rates of 67% across 15 months; and, 3) chronically nonadherent (13%): adherence decreased from 63% to 30%. With respect to patterns of medication adherence and relationship to clinically-relevant health outcomes, there were no significant differences in health outcomes between patients in the adherent versus nonadherent trajectories, including mean absolute neutrophil counts (ANC), risk for infection as measured by ANC, healthcare utilization, or risk for disease relapse.

Conclusion: Although longitudinal patterns of 6MP behavioral adherence were not related to health outcomes, it is notable that only 67% of the current sample had adherence rates ≥ 95%. In fact, 33% of the current sample demonstrated adherence rates ≤ 95%. Our findings are important for development of future adherence promotion studies in pediatric cancer. Our findings underscore the relative significance of tailoring adherence promotion interventions to subgroups of patients, including those with problematic patterns of adherence. Patients who demonstrate adequate levels of adherence could still benefit from less intensive, preventative interventions to sustain and improve adherence.

Poster # 760 | LANGERHANS CELL HISTIOCYTOSIS WITH VERTEBRAL INVOLVEMENT DIAGNOSED IN A SINGLE CANADIAN PEDIATRIC ACADEMIC INSTITUTION

Sophie Gatineau-Sailliant, Pascale Grimard, Marie-Claude Miron, Guy Grimard, Anne-Sophie Carret, Jean-Marie Leclerc

CHU Sainte-Justine, Montreal, Quebec, Canada

Background: Vertebral involvement in Langerhans Cell Histiocytosis (LCH) is still a subject of interest, due to its low frequency and the absence of management's guidelines.

Objectives: To provide additional information on presentation, treatment and morbidity of pediatric LCH vertebral lesions, we report cases of 11 children with vertebral lesion of biopsy-proven LCH, between January 1st 2000 and December 31st 2015, at Sainte-Justine University Health Center (Montreal, Quebec, Canada).

Design/Method: We conducted a retrospective study by reviewing charts and imaging of vertebral LCH in a population of 11 children (median age of 8.25 years at LCH diagnosis), followed for a median duration of 34 months. Symptoms at presentation, treatment modalities and morbidities were collected.

Results: Vertebral lesions were present at LCH diagnosis in 9 of 11 cases. They were usually diagnosed secondary to back pain in 10 of 11 cases and were asymptomatic in only one case. Despite an epidural extension in 6 of 11 cases, no child developed neurological symptoms. Lesions frequently involved vertebral body (10 of 11 cases) and were rarely unstable (2 of 11 cases). Out of 29 vertebral lesions, most of them had a dorsal localization (15 of 29 lesions) and 8 of 11 patients had LCH in multiple vertebrae. At diagnosis, median vertebral height loss was 37.5% compared to 25% at last imaging control. Most used imaging modalities were PET-scan and plain X-Rays. Treatments were diverse and consisted in chemotherapy in all children but three and bisphosphonates in only 3 cases. Radiation therapy was not used in any patient. Six out 11 patients did benefit of an orthosis. A LCH recurrence was observed in 6 patients and involved vertebrae in 4 cases. One patient with treatment-resistant LCH disease had 5 relapses, and required multiple lines of treatment. All children were alive and disease-free at their last follow-up, 10 patients having radiological vertebral sequelae and only 3 had clinical sequelae.

Conclusion: Our study is consistent with the epidemiological data described in larger cohorts of children with vertebral lesions of LCH and the favorable prognosis associated with such lesions. Nevertheless, aggressive treatment and long term follow-up seemed to be essential as recurrences are

not rare and spontaneous bone regeneration often incomplete. Plain X-rays appears to be a good follow-up tool for vertebral lesions as it allows reliable measures, less exposure to radiation at lower cost.

Poster # 761 | PROTECTIVE EFFECT OF DICLOFENAC AND ENOXAPARIN IN L-ASPARAGINASE INDUCED ACUTE PANCREATITIS IN RATS

Amr Elnashar

National Cancer Institue, Giza, Giza, Egypt

Background: Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer and also the most complicated in the treatment, so it requires many interventions for both treatment and to alleviate suffer form side effects. Pancreatitis is one of the toxicities, which is more common in ALL as it appears in about 16% of the patients. It occurs in many drug combinations which induce pre-pancreatitis and even direct destruction of pancreatic tissues. pancreatitis can be induced by many drugs used in the treatment such as chemotherapeutic agents or supportive treatment. L-asparaginase is the backbone drug of the treatment of ALL in which 6 to 9 doses are required to achieve complete remission status in the induction phase of treatment and 12 to 19 doses in the maintenance phase.It is an enzyme that destructs the L-asparagine amino acid into aspartic acid and ammonia thus deplete the asparagine from the extracellular matrix . Many drugs are investigated for their effect on treatment of induced pancreatitis such as Interleukin-10, NSAID as Anti-inflammatory, Glycerin tri nitrates as Improvement of microcirculation, TNF-alpha antibody, PAF inhibitor as Specific anti-inflammatory and Low Molecular Weight Heparin .None of the drugs was investigated for their ability to prevent the occurrence of pancreatitis.

Objectives: This study was designed to evaluate the protective effect of enoxaparin and diclofenac against L- asparaginase induced pancreatitis

Design/Method: Acute pancreatitis was induced in rats by intra-muscular injection of L-asparaginase (1000 I.U/Kg) given daily for five days. Enoxaparin was given subcutaneous (100 I.U/Kg) and diclofenac was given intra-peritoneal (2 mg/Kg) daily for five days. Then, markers of pancreatic injury, lipids, immune cell infiltration and oxidative stress were analyzed with histo-pathological examination of the pancreatic tissue

Results: During acute pancreatitis, oxidative stress markers were significantly changed as indicated by reduced tissue glutathione and increased malondialdehyde levels. This was accompanied with significant increase in immune cells infiltration as indicated by high levels of myeloperoxidase and pro-inflammatory cytokine TNF-alpha. Triglyceride only showed increase level. Treatment with enoxaparin and/or diclofenac restored levels of biochemical markers including serum alpha-amylase, reduced glutathione, malondialdehyde, pro-inflammatory cytokine TNF-alpha, myeloperoxidase and triglyceride. Histological injuries of pancreatic tissues as vacuolation and necrosis of epithelial lining pancreatic acini, inflammatory cells infiltration and focal pancreatic hemorrhage were also reduced by treatment with enoxaparin and/or diclofenac.

Conclusion: The present study emphasizes the potential protective effect of enoxaparin and diclofenac against L-asparaginase induced pancreatitis

Poster # 762 | LANGERHANS CELL HISTIOCYTOSIS THERAPY FOR THE TREATMENT OF LIFE-THREATENING ROSAI DORFMAN DISEASE

Nadia Chaudhry-Waterman, Paul Kent

Rush University Medical Center, Chicago, Illinois, United States

Background: Rosai Dorfman Disease (RDD), or Sinus histiocytosis with massive lymphadenopathy (SHML), is a rare condition of immune dysregulation of unknown etiology arising from the massive accumulation of non-Langerhans type histiocytic cells inside lymph nodes. The disease classically presents as bulky, painless lymphadenopathy often associated with infection showing distension of lymph node sinuses by abundant histiocytic cells (CD1a(-), S-100(+)/CD68(+)). In some cases, the disease can be self-limiting, but in cases with a prolonged chronic course of exacerbations and remissions, those with extranodal involvement, or disease that threatens vitals structures, treatment may be necessary. There is no treatment consensus.

Objectives: To describe a case of life-threatening, unresectable, recurrent RDD successfully treated with Langerhans Cell Histiocytosis (LCH) 2009-inspired therapy.

Design/Method: We compared this case to the current literature on chemotherapeutic treatments for RDD. We searched PubMed, Ovid, and Google Scholar for similar cases. We believe this to be the first reported case of using LCH therapy to successfully treat RDD. An 8-year-old male presented to an outside hospital with two years of massive neck swelling causing torticollis. Biopsy confirmed RDD. He was intermittently treated with courses of antibiotics with partial response.

Surgical removal of the affected lymph nodes was unsuccessful due to proximity to the spinal cord. Two years later, the patient presented to our institution. He was initially treated with prednisone with a fast tapering dose, but after a second relapse the decision was made to try chemotherapy following the LCH-2009 protocol of weekly vinblastine (6 mg/m2), 6-MP (75 mg/m2), and high dose steroid bursts. He experienced two additional relapses off therapy at ages 12 and 14 years old, including CMV(+) associated septic shock and cytokine storm requiring rapid response, PICU admission, and ionotropic support. This last episode was treated with a more prolonged induction and maintenance therapy. An extended and slowly tapered maintenance therapy regimen of 2.5 years of daily 6-MP, monthly vinblastine and steroids with a slowly tapered dose during his fourth remission has resulted in 38-months of continuous complete remission-the longest stretch of his life.

Results: No similar cases were found. Literature search demonstrated no consensus regarding the most effective treatment of RDD, with no previous cases being successfully treated following LCH chemotherapy protocols.

Conclusion: We hypothesize that the multi-agent relatively mild LCH-2009 therapy mitigates the immune dysregulation of RDD. This case suggests that LCH-2009 therapy can be used to treat cases of RDD that is not amendable to surgery or observation.

Poster # 763 | OUTCOMES AND CHOICES OF PLACEMENT OF CENTRAL VENOUS ACCESS IN PATIENTS WITH A NEW DIAGNOSIS OF LEUKEMIA

Gabriel Salinas Cisneros, Maria Eugenia Carter Febres, Adriana Trabal, Weize Wang, Thomas Taylor, Fuad Alkhoury, Ziad Khatib

Nicklaus Children's Hospital, Miami, Florida, United States

Background: Central venous catheters (CVC) are necessary in the management of patients with malignancies, especially children. Patients with acute leukemia (AL) have higher rates of central line associated complications such as bloodstream infections compared with other malignancies.

Objectives: To examine the choice of placement of CVC and the differences in outcome between Peripherally Inserted Central Catheters (PICC) and Ports in patients with leukemia during induction.

Design/Method: Retrospective chart review of patients with newly diagnosed leukemia at Nicklaus Children's Hospital between 2010 and 2016.

Results: Ninety four patients with a new diagnosis of leukemia undergoing induction chemotherapy were identified. The average age was 6.9 years. Overall, 51 (54.3%) patients had a Port placed and 43 (45.7%) had a PICC placed. The decision for PICC or Port was subjective and physician based. The main outcome measures were local inflammation/infection, bacteremia, thrombophlebitis, blocked catheter and premature removal. The most common complication was bacteremia (12. 8%). In a multiple logistic regression analysis for predicting whether patients had at least one complication, results showed that having at least one complication is 3.4 times the odds in patients with AML compared to patients with ALL ($p = 0.032$). When comparing PICC vs. Ports, patients with PICC had more frequent episodes of blocked catheters (23.3%) and premature removal (20.9%) compared to the patients with Ports (2.0% and 0.0%) ($p = 0.002$ and $p = 0.001$ respectively) during induction. Local inflammation, bacteremia and thrombophlebitis were not statistically different ($p = 1.0$, $p = 0.54$ and $p = 2.4$ respectively). The most common place for Port placement was the right subclavian vein (55%). There was no significant association between Port location and having at least one complication ($p = 0.112$). Acute lymphocytic leukemia subgroup analysis: Fourteen patients (61%) in the PICC group had at least one complication and 9 (39%) in the Port group but that was not statistically significant ($p = 0.128$).

Conclusion: Our series showed a higher incidence of blocked catheters and premature removals with PICC compared to Ports in patients with leukemia during induction. The choice of placement of PICC vs Port was subjective and physician based. Patients with ALL, despite receiving steroids and asparaginase during induction, did not show a statistically significant increase risk in thrombosis or infection but larger numbers may be needed in future studies.

Poster # 764 | FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN AN ADOLESCENT PRESENTING WITH NEUROPSYCHIATRIC CHANGES IN THE ABSENCE OF CLASSIC SYSTEMIC SIGNS

Julie Boiko, Michelle Hermiston

University of California, San Francisco, San Francisco, California, United States

Background: Hemophagocytic lymphohistiocytosis (HLH) is classically a disorder of young children meeting systemic hyperinflammation criteria. Presentation in late adolescence is uncommon. Furthermore, though CNS signs occur in 30–70% of cases, initial isolated neurologic presentation is rare, frequently resembling encephalitis or demyelinating disorders. These CNS signs can be isolated or precede systemic disease, delaying HLH diagnosis. HLH declaring in adolescence with predominant psychiatric features has not been well documented.

Objectives: To describe a case of CNS HLH presenting with neuropsychiatric features in absence of classic HLH criteria.

Design/Method: Retrospective review of clinical, radiologic, histologic, immunophenotypic, and molecular features of a patient with CNS HLH.

Results: A 19-year-old female presented with acute-onset headaches following nine months of progressive anxiety, short-term memory loss, emotional lability, perceptual disturbances, and hypomania. Brain MRI demonstrated numerous enhancing T2 hyperintense supratentorial and infratentorial white matter lesions in the left thalamus and caudate head. Brain biopsy showed histiocyte-rich inflammation and associated demyelination. Extensive evaluation including universal microbial PCR failed to reveal underlying infection or malignancy. Past medical history was notable for presumptive pulmonary sarcoidosis diagnosed 14 months prior with progressive respiratory failure with associated granulomatous pulmonary nodules which responded to systemic immunosuppression. At presentation of her neuropsychiatric symptoms, she had normal sIL-2R, ferritin, fibrinogen, and triglycerides. There was no pancytopenia, coagulopathy, bone marrow hemophagocytosis, fevers, or splenomegaly. Given the possibility of partial immune suppression of systemic symptoms and the prominent neurologic symptoms, HLH screening labs were sent and notable for decreased natural killer and cytotoxic T lymphocyte function, normal granzyme expression and CD107a mobilization, and absent perforin expression. Genetic testing confirmed compound heterozygous mutations in PRF1 (c.227G>A, c.626A>C) and familial HLH type 1. She was treated with low-dose dexamethasone and intrathecal chemotherapy per HLH-94. Due to lack of evidence of systemic inflammation, VP-16 and high-dose steroids were held. Within one week of initiating therapy, she had decreased anxiety and improved cognition, with sustained, incremental neuropsychiatric improvement with additional intrathecal treatments. She tolerated dexamethasone tapering without symptom flare. MRI also demonstrated parenchymal lesion improvement. For definitive treatment, she underwent unrelated allogeneic hematopoietic cell transplantation and remains at neurologic baseline as of eight months post-transplant with ongoing imaging improvement.

Conclusion: This case of familial HLH with compound heterozygous perforin mutations in an adolescent with isolated neuropsychiatric symptoms illustrates that CNS HLH may be an underrecognized phenomenon in absence of systemic signs. Standard HLH therapy may effectively reverse these symptoms with associated radiologic responses.

Poster # 765 | SINGLE INSTITUTION EXPERIENCE OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME ((PRES) ASSOCIATED WITH INDUCTION THERAPY FOR HIGH RISK PEDIATRIC ALL: IS THERE A ROLE OF PHARMACOETHNICITY

Nupur Mittal, Murali Nagarajan, Peter Heydemann

Rush University Children's Hospital, Chicago, Illinois, United States

Background: Posterior Reversible Encephalopathy Syndrome (PRES), a recognized complication of pediatric leukemia treatment has been reported in up to 5% patients in various series. Hypertension, chemotherapy and cortical spreading depression have been implicated in the pathophysiology. Due to the combinations used, it is difficult to identify the offending drug, several have been implicated. Since delay of chemotherapeutic treatment in children with high risk leukemia is unfavorable, it is important to recognize the characteristic radiologic findings, manage appropriately and reintroduce the treatment as soon as possible. Pharmacoethnicity is now recognized as an important factor for variation in neurotoxicity in children with ALL. Ethnic Differences in reported PRES events in pediatric patients with ALL has not been well described in literature.

Objectives: To describe the factors associated with PRES in a cohort of high risk pediatric ALL patients at a single institution.

Design/Method: A total of 12 children with an average age of 9 years (1-20 years) diagnosed with ALL between 2013–2017 were retrospectively reviewed for the occurrence of PRES. Various demographic factors, therapy received, clinical features, radiology related findings and management were reviewed. A search for all published articles on PRES in leukemia was conducted using PubMed databases.

Results: Five (42%) children (average age 8.5 years) developed PRES during days 10–29 of induction. 80% of the patients that developed and 45% of those that did not develop PRES were Hispanic. All the patients that developed PRES and 43% of those that did not were diagnosed with high

risk ALL. All patients received vincristine, 80% received Daunomycin and intrathecal methotrexate and 20% received Asparaginase in the 1 week prior to the event. MRI findings confirmed PRES in all 5 patients with no evidence of methotrexate related leukoencephalopathy or leukemia. At the time of PRES all patients were in remission based on MRD and spinal fluid cytology. Two-thirds of the patients had seizures and hypertension at the time of the event with no prior history of either. All patients had complete recovery of normal mental status after resolution of PRES.

Conclusion: A higher incidence of PRES than previously reported was noted in our series. Hispanic ethnicity, high-risk ALL and exposure to vincristine, daunomycin and intrathecal methotrexate in induction were associated with PRES in our cohort. A new association that emerged was that of Hispanic ethnicity with PRES .Larger studies to understand the importance of pharmacoethnicity in PRES may help in individualization of chemotherapy based on ethnic differences.

Poster # 766 | HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A PATIENT WITH HYPER IGE SYNDROME, PRESENTING TO THE PEDIATRIC INTENSIVE CARE UNIT WITH SEPSIS

Michael Mowrer, Shanna White, Eyup Keles, Jonathan Roberts

Children's Hospital of Illinois, Peoria, Illinois, United States

Background: Hyper IgE syndrome is a primary immunodeficiency characterized by susceptibility to skin and lung infections as well as increased propensity for malignancy. Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by overwhelming activation of T lymphocytes and macrophages occurring as either primary HLH caused by genetic abnormalities or secondary HLH associated with infectious, malignant, metabolic, or immunodeficiency causes. We describe the first case to our knowledge of HLH in a patient with hyper IgE syndrome.

Objectives: To describe a case of HLH in a pediatric patient with hyper IgE syndrome.

Design/Method: Case Report

Results: A 7-year old Caucasian male with known autosomal dominant hyper IgE syndrome (STAT3 mutation) was transferred to the pediatric intensive care unit secondary to concern for septic shock. The patient had persistent slow bleeding from oral lesions and central catheter sites despite the addition of aminocaproic acid and recombinant factor VIIa. He also required numerous blood product transfusions secondary to anemia and thrombocytopenia. Clinical suspicion was high for HLH and the patient met criteria for diagnosis of HLH with the following: ferritin > 40,000 ng/mL, triglycerides 264 mg/dL, decreased NK cell function with the sample only containing 1% NK cells, elevated soluble IL-2 receptor at 4215 U/mL, splenomegaly, and fever. Infectious workup was remarkable for a positive EBV qPCR with 80,700 copies/mL suggestive of EBV driven secondary HLH. Familial HLH testing was unable to be completed. Therapy was initiated based upon the HLH-94 study. The addition of ruxolitinib and anakinra were considered but the patient declined rapidly prior to treatment. CT of the head was concerning for a stroke with signs of edema and increased intracranial pressure likely leading to the development of symptoms consistent with brain stem herniation. The decision was then made to withdraw care.

Conclusion: To our knowledge, this is the first report of HLH in a patient with hyper IgE syndrome. Diagnosing HLH requires a high index of suspicion in critically ill patients, and prompt initiation of therapy is essential. This challenging case of HLH in a patient with hyper IgE syndrome highlights the diagnostic challenge, variable presentation, and need for effective therapy in this vulnerable patient population.

Poster # 767 | PSYCHOSOCIAL AND PHYSICAL DISTRESS SCREENING: WHAT DO ADOLESCENTS AND YOUNG ADULTS ON CANCER THERAPY REPORT?

Ashraf Mohamed, Meg Cardoni, Ashraf Mohamed

St. Jude Affiliate Clinic at St Francis Hospital, Tulsa, Oklahoma, United States

Background: Adolescents and young adults (AYAs) with cancer are at risk for psycho-social as well as physical symptom burden during cancer therapy.

Objectives: The purpose of this study is to explore psychological and physical symptoms endorsed by AYA while receiving therapy for cancer

Design/Method: Surveys were given in both inpatient and outpatient settings during cancer therapy. Symptom Screening in Pediatrics Tool (SSPedi) and Memorial Symptom Assessment Scale (MSAS). Symptoms severity was rated by teens on a 5 point Likert scale. SPSS 22, used for statistical analysis.

Results: : A total of 39 AYA on cancer therapy (age range 13–19.9 years) 35% female, 65% male, 43.6% acute leukemia, 48.7% solid tumors, and 7.7% diagnosis was not reported. 78% of AYA on cancer therapy reported at least 1 or more symptoms, 45% reported >3 symptoms cluster. Of the

physical symptoms that were reported as most distressing to the teens, mouth sores and headaches were the top causes. Of the physical symptoms that were most frequently endorsed; fatigue was on the top (58%), followed by change in appetite 45 %, vomiting 43%, and pain 40%., the least was bowel habit changes. AYA rated sadness as the most frequent psychological symptom 38%, followed by feeling angry 32%, and scared 30%. Statistically significant difference was noticed based on gender difference with more females reported symptoms (P = 0.01), while type of cancer (Acute leukemia versus solid tumors) was not statistically different.

Conclusion: AYA with cancer reported multiple physical and psychological symptoms with significant distress. Females seem to report more symptoms compared to males. Screening AYA for cancer therapy related symptoms is feasible during routine visits and adds important information about the AYA well-being.

Poster # 768 | SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY: CASE SERIES AND LITERATURE REVIEW TO HIGHLIGHT TREATMENT OPTIONS

Nora Rahmani, Tracey Louie, Michael Roth, Jonathan Gill, Lisa Gennarini, Deepa Manwani

Albert Einstein College of Medicine, Bronx, New York, United States

Background: Sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease, is a rare histiocytic proliferative disorder of unknown etiology. Many treatment modalities have been employed; however, no uniform guidelines exist.

Objectives: Literature review of treatment options for SHML.

Design/Method: Chart review was performed on pediatric patients diagnosed with SHML at the Children's Hospital at Montefiore between 2010 and 2012 after IRB approval. Inclusion criteria included children between the ages of 0 and 21 years with SHML. Exclusion criteria included children with cutaneous SHML. Four cases of SHML seen at Montefiore are described. A comprehensive review of the literature identified 102 additional cases published between 1978 and 2018. Manuscripts that did not include the treatment modality or outcome were excluded.

Results: Many of the 106 patients with SHML responded to observation alone. Of 106 patients, 46 patients were observed, with 35 (76%) having resolution of disease, five having stable disease, and five being lost to follow-up. One patient received subsequent systemic therapy. Surgical management was conducted upfront in 29 patients. Of those, 18 (62%) had resolution of disease, one had stable disease, and one had recurrence with no further therapy noted. Of the remaining nine patients, 77% were successfully treated with systemic therapy, consisting of either steroids (5) or steroids and chemotherapy (4). Systemic therapy was used as first-line therapy in 31 patients. Steroids alone or in conjunction with chemotherapy resulted in resolution of disease in 12/15 and 7/11 patients (19/26, 73%), respectively, with four patients having stable and three with progressive disease. Chemotherapy without steroids resulted in resolution of or stable disease in 3/5 patients. Radiation was ineffective.

Conclusion: SHML is a rare disease with no published guidelines for treatment. From the results of the cases and a detailed review of the literature, it can be suggested that observation may be considered as first line management in patients providing there are no significant symptoms. For patients who are symptomatic or have significant progression, surgery may be considered. In patients with recurrence or refractory disease, steroids and/or chemotherapy may be used. The presence of nodal or extra-nodal disease did not seem to have a significant impact on the course of treatment. Given the rarity of the disease, it is difficult to conduct a randomized control trial. Further work, involving collaboration between centers and cooperation with the International Rare Histiocytic Disorders Registry would be helpful.

Poster # 769 | DIVIDE AND CONQUER: EVALUATION OF A REDESIGN FOR INPATIENT PEDIATRIC ONCOLOGY SERVICE

Caroline Gross, Ariel Winn, Lewis Silverman, Jennifer Kesselheim

Boston Children's Hospital, Boston, Massechusettes, United States

Background: Increasing census and intensified work compression on the inpatient oncology service at our institution was identified as leading to resident dissatisfaction, impaired resident learning and decreased perceived quality of patient care.

Objectives: To evaluate the impact of a redesign of a pediatric inpatient hematologic malignancy (IHM) service on resident perceptions of the educational value of the rotation and safety of patient care.

Design/Method: During the 2016–2017 academic year, we initiated a bundled intervention on the IHM service. Modifications included 1) Decreased patient volume: The IHM service was divided into two teams, utilizing an extra attending - a teaching service consisting of residents and fellows and a team comprised of nurse practitioners. 2) Intentional patient team

assignment: Patients were deliberately assigned to a care team based on educational opportunities and provider skill sets. 3) Intentional attending faculty selection: Attending faculty with deeper clinical and teaching experience were selected to supervise on the teaching team. 4) Increased weekend staffing. After completing the service, junior residents completed an electronic survey to evaluate their perceptions of the educational value of the rotation, as well as their ability to deliver safe care while on the rotation. Fisher's exact tests were used to compare responses from residents in 2017 who experienced the redesign to residents in 2016, whose experience

Results: Survey completion rates were 70% (28/40) in 2016 and 57% (29/51) in 2017. Intervention residents were significantly more likely than comparison group residents to choose the answers "very good" or "excellent" to describe both the overall quality of the rotation (76% intervention vs. 25% comparison, P<0.001) and the educational experience on rounds (52% intervention vs. 7% comparison, P<0.001). Intervention residents also reported caring for fewer average primary patients daily on weekdays as compared to comparison residents (4.8 vs 8.7 patients, P<0.0002, 95% CI -5.14 to -2.64). Furthermore, intervention residents were more likely than comparison residents to "agree" or "strongly agree" that they could provide safe patient care on weekend days (79% intervention vs. 14% comparison, P<0.001) and on nights (69% intervention vs. 25% comparison, P<0.01) while on the oncology service.

Conclusion: A redesign initiative of an oncology service with the development of a new teaching service led to improved resident perceptions of the educational value of the rotation and ability to provide safe care to patients. This approach could be useful to other services and institutions to promote similar outcomes in resident education and patient care.

Poster # 770 | MONOTHERAPY TREATMENT WITH CYTARABINE FOR ALK-POSITIVE HISTIOCYTOSIS IN AN INFANT

Karen Chao, Kerri Becktell, Mariko Suchi, Rachel Phelan

Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Background: ALK-positive histiocytosis is a rare histiocytic proliferative disorder that has been reported in three infants presenting primarily with hepatosplenomegaly, anemia, and thrombocytopenia. Given the rarity of this disease, there are no standard treatment algorithms for this diagnosis and the disease course and outcomes remain largely unknown. The published series describes treatment ranging from monitoring alone to multi-drug chemotherapy regimens. There was ultimately resolution of presenting symptoms in all three cases despite varying treatment strategies.

Objectives: To report a newly diagnosed case of ALK-positive histiocytosis that was treated with a novel approach using cytarabine monotherapy.

Design/Method: Case Report

Results: A full term male infant presented at birth with difficulty feeding and hyperbilirubinemia. Over the first few weeks of his life, he subsequently developed thrombocytopenia, transaminitis, and profound hypoalbuminemia. By six weeks of life, he was experiencing significant abdominal ascites requiring repeat paracenteses, massive hepatosplenomegaly, respiratory distress secondary to abdominal distension, anemia, and coagulopathy. He underwent numerous diagnostic tests, including a liver biopsy followed by a bone marrow biopsy that showed ALK-positive histiocytic infiltrates in both sites. Treatment was initiated with cytarabine 170 mg/kg/day x 5 days, repeating every 4 weeks. Throughout his course of five cycles of treatment, he experienced intermittent fevers and mild nausea with no other adverse events. By the end of five cycles, his hepatosplenomegaly resolved, his blood counts normalized, he demonstrated weight gain on oral feeds, and his liver enzymes normalized. He is currently 12 months post completion of therapy and remains well with a normal physical exam and laboratory values.

Conclusion: Treatment of ALK-positive histiocytosis with lose dose cytarabine resulted in complete resolution of our patient's symptoms with minimal treatment related adverse effects, and few long-term treatment related risks. Given the rarity of the diagnosis, the reporting of effective novel treatment options is important for future patient care.

Poster # 801 | LANDSCAPE OF TARGETABLE BRAF ALTERATIONS AND RAF1 FUSIONS IN PEDIATRIC MALIGNANCY

Andrew Rankin, Adrienne Johnson, Mark Rosenzweig, Jeffrey Knipstein, Geoffrey Kannan, Nicholas Britt, Dean Pavlick, Jo-Anne Vergilio, Eric Severson, Rachel Erlich, Rachel Squillace, Phil Stephens, Vince Miller, Jeffrey Ross, Shakti Ramkissoon, Siraj Ali

Foundation Medicine Inc, Cambridge, Massachusetts, United States

Background: Adult patients with melanoma or lung cancer harboring BRAF V600E have benefitted from the development and subsequent approval of specific BRAF inhibitors. As such, delineating the subset of similarly targetable pediatric oncology patients may spur development and rational use of these inhibitors in children. Importantly, other point mutations and fusions of BRAF may also be targetable in

children analogous to recent emerging data in adult cancer patients.

Objectives: To define the genomic landscape of known and novel BRAF alterations and RAF1 fusions in pediatric malignancies and report index cases with clinical response to BRAF or MEK inhibitors.

Design/Method: DNA was extracted from 40 microns of FFPE sections of 3,633 tumors from pediatric (<21 years of age) oncology patients, and CGP was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 579X for up to 315 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. Genomic alterations (GA) included base substitutions, indels, copy number alterations and fusions/rearrangements.

Results: A total of 221 (6.1%) BRAF-altered pediatric malignancies were identified. 172 (77.8%) harbored a single kinase-activating BRAF short variant, indel, or fusion. An alteration resulting in reduced BRAF kinase activity was identified in 8 (3.6%) tumors while 7 (3.2%) tumors harbored multiple BRAF alterations, 3 of which contained at least a single activating short variant. The remaining 34 tumors (15.4%) contained functionally uncharacterized variants. Kinase-activating BRAF alterations were identified in diverse tumor spectra comprised of brain tumors (75.3%; 18 subtypes), carcinomas (10.6%; 6 subtypes, with melanoma constituting 50% of cases), hematological malignancies (8.8%; 5 subtypes), sarcomas (2.9%; 3 subtypes), and extracranial embryonal tumors (2.4%; 2 subtypes). Seventy-two (32.6% of BRAF-altered cases) BRAF fusions were identified, 64 (88.9%) of which were KIAA1549-BRAF; 2 involved the novel fusion partners: STARD3NL and KHDRBS2. Seven (0.2%) RAF1 fusion-positive cases, predominantly brain tumors (5), were identified; 2 involved the novel fusion partners: TMF1 and SOX6. Index cases of response to therapy of intracranial tumors will be presented.

Conclusion: We describe a population of pediatric patients with targetable BRAF alterations predominantly enriched in primary intracranial tumors, but spanning diverse solid tumor types and hematologic malignancies. We additionally report a cohort of RAF1 fusion-positive patients. An index case and multiple previous reports suggest RAF or MEK inhibitors may benefit pediatric patients with either intracranial or extracranial disease, and development of such drugs in pediatric indications is strongly warranted.

Poster # 802 | HDAC INHIBITION IN THALAMIC AND SPINAL CORD H3K27M+ DIFFUSE MIDLINE GLIOMA

Sara Kreimer, Pamelyn Woo, Michelle Monje-Deisseroth

Stanford University, Palo Alto, California, United States

Background: Diffuse midline gliomas (DMG) with H3K27M mutation, including diffuse intrinsic pontine glioma (DIPG), are the leading cause of brain tumor-related deaths in children. There are no effective therapeutic strategies and the median survival remains dismal. Genomic studies have identified a recurrent mutation in the majority of DMGs involving a lysine to methionine substitution (K27M) in histones 3.1 and 3.3, resulting in changes in the epigenetic landscape that dysregulate gene expression and promote gliomagenesis. Panobinostat, a multiple histone deacetylase (HDAC) inhibitor, was found to be one of the most effective agents against DIPG patient-derived cell cultures and xenograft models in previous studies and is presently in clinical trial for DIPG. HDAC inhibition with panobinostat may also exhibit activity against H3K27M+ diffuse midline gliomas of the thalamus and spinal cord.

Objectives: To evaluate the effect of panobinostat as a single agent against patient-derived thalamic and spinal cord H3K27M+ diffuse midline glioma cell cultures and in an orthotopic xenograft murine model of H3K27M+ spinal cord glioma.

Design/Method: Patient-derived thalamic and spinal cord H3K27M+ diffuse midline glioma cell cultures were treated with single agent panobinostat at a range of concentrations. Cell viability was evaluated using the CellTiter-Glo assay. Panobinostat was systemically administered to orthotopic xenograft murine models of luciferase-expressing spinal cord H3K27M+ diffuse midline glioma. Response to panobinostat was evaluated with IVIS in vivo imaging.

Results: HDAC inhibition with panobinostat significantly decreases cell proliferation with an IC50 of 30 nM and 41 nM in the spinal cord and thalamic glioma patient-derived cell cultures respectively. Panobinostat slowed tumor growth in murine models of spinal cord glioma by 1.5-fold in the brain ($p = 0.0219$, $n = 5$) and 2-fold in the spinal cord ($p = 0.0176$, $n = 5$) when compared to vehicle controls after 1 week of administration.

Conclusion: Panobinostat is in clinical trials for DIPG. This study suggests that HDAC inhibition with panobinostat may also be beneficial for patients with thalamic and spinal cord diffuse midline glioma H3K27M mutants.

Poster # 804 | TARGETING BRAIN TUMOR STEM-LIKE CELLS WITH ATYPICAL ANTIPSYCHOTIC DRUGS

Maria Carter Febres, Jessica Wein, Justin Assioun, Nicolas De Cordoba, Guillermo De Angulo, Steven Vanni, Regina Graham

University of Miami Miller School of Medicine, Miami, Florida, United States

Background: Brain tumors are the most common solid tumor of childhood and the leading cause of childhood cancer deaths. While medulloblastoma is the most common malignant brain tumor of childhood with a 5-year survival 70–80%, children with high-grade gliomas (HGGs) such as glioblastoma multiforme (GBM) fare much worse with a 5-year survival of 15–35%. Implicated in this poor outcome is the presence of treatment resistant brain tumor stem-like cells. GBM stem-like cells (GSCs) have been implicated in tumor growth, treatment resistance and patient relapse, making them a key therapeutic priority. Antipsychotic drugs (APDs) have been used for decades in various psychiatric clinical settings and are associated with a lower incidence of cancer, including malignant brain tumors. Currently, atypical APDs are being evaluated for their potential to alleviate cancer and treatment induced side effects. Furthermore these drugs may have direct anti-tumor effects, potentially via inhibition of dopamine D2 receptors (DRD2).

Objectives: Determine the anti-cancer effects of atypical APDs on GBM stem-like cells

Design/Method: The anti-cancer effects of APDs (quetiapine and risperidone) were evaluated on GBM stem-like cell lines developed in our laboratory (Glio 3 and 38) and the Group 3 medulloblastoma cell line HDMBO3. Cell proliferation/viability was determined using trypan blue exclusion and MTS assays. The effect of APDs on cancer stem cell self-renewal was determined by neurosphere assay. Receptor expression and APDs effect on cell cycle proteins were examined by western blot analysis.

Results: Western blot analysis of GSCs and HDMBO3 demonstrated robust DRD2 expression indicating a viable therapeutic target. Both APDs induced dose dependent cell death of all cell lines tested. Treatment with only 2uM of either APD for 10 days significantly reduced cell proliferation by 60% (HDMBO3) and 50–90% (GSCs). Consistent with these findings, we observed an increase in cell cycle inhibitors p21 and p27. Furthermore at day 10 both APDs induced a robust increase in GSC death, approximately 60% compared to only 10% in non-treated controls. Lastly, 1uM APDs significantly reduced GSC neurosphere formation compared to untreated controls by up to 35% suggesting inhibition of GBM stem cell self-renewal.

Conclusion: Our data indicates that clinically relevant concentrations (low micromolar) of these APDs induce anti-cancer effects in both GSCs, which are enriched with tumor initiation/propagation properties, and in the Group 3 (MYC amplified) medulloblastoma cell line. These APDs represent strong candidates as potential adjuvant therapies for the treatment of these brain tumors.

Poster # 805 | A BEAT CHILDHOOD CANCER PILOT STUDY FOR HIGH RISK NEUROBLASTOMA AT DIAGNOSIS WITH MOLECULAR GUIDED THERAPY AND EXTENDED MAINTENANCE WITH DFMO

Jacqueline Kraveka, Valerie Brown, William Ferguson, Genevieve Bergendahl, William Roberts, Jessica Foley, Don Eslin, Javier Oesterheld, Deanna Mitchell, Michael Isakoff, Kathleen Neville, Randy Wada, Virginia Harrod, Jawhar Rawwas, Gina Hanna, Jeffrey Bond, Abhinav Nagulapally, Jeffrey Trent, William Hendricks, Sara Byron, Giselle Sholler

Helen DeVos Children's Hospital, Grand Rapids, Michigan, United States

Background: While the poor prognosis for high risk neuroblastoma (HRNB) underscores the need for new treatment strategies, the elucidation of specific biologic subsets of neuroblastoma suggests a way to improve disease management. The identification of agents that target specific molecular pathways associated with the development or progression of diseases holds promise. DFMO, an inhibitor of ODC, has been shown to decrease LIN28 and MYCN and target cancer stem cells in preclinical studies. Currently 14% of patients undergoing immunotherapy relapse. DFMO is in studies to prevent relapse after immunotherapy and may be helpful during immunotherapy as well.

Objectives: The hypotheses for this study were that: 1) the incorporation of a targeted therapy, selected based upon upfront tumor genomic interrogation, into standard induction chemotherapy for HRNB is safe, feasible and may increase the PR/CR/VGPR response rate at the end of Induction therapy; and 2) the addition of DFMO as maintenance during immunotherapy is safe and feasible and may decrease the relapse rate for HRNB.

Design/Method: A multicenter feasibility pilot trial in subjects with newly diagnosed HRNB within the Beat Childhood Cancer Consortium. At diagnosis, patients' tumors underwent DNA exome and RNA sequencing which were analyzed within a molecular tumor board to identify the single best drug of 6 targeted agents to be added to cycles 3–6 of induction chemotherapy. After consolidation with ASCT and radiation, the patients received DFMO along with standard dinutuximab and retinoic acid and DFMO for 2 years after immunotherapy. Patients were evaluated for additional toxicities with the addition of targeted agents and DFMO in addition to induction response.

Results: The pilot study of 20 eligible patients has shown this process to be feasible. All 20 patients have completed induction portions of the study. The combination of targeted agent with chemotherapy was shown to be safe without any unexpected toxicities. Delays between induction cycles were < 2 weeks and related to surgery, infection, or thrombocytopenia. The induction response demonstrated 88% CR/VGPR/PR rate, which suggests improvement over historical 80%. In addition, 15 patients were eligible for the combination of DFMO with dinutuximab and retinoic acid was well tolerated and safe without additional toxicities due to DFMO.

Conclusion: The pilot study of 20 patients has shown the process of genomic sequencing and addition of a targeted agent to upfront chemotherapy and addition of DFMO to dinutuximab and retinoic acid maintenance therapy in newly diagnosed HRNB patients and is feasible and safe without any unexpected toxicities.

Poster # 806 | THE ROLE OF G-CSF RECEPTOR SURFACE EXPRESSION IN MEDULLOBLASTOMA PATHOGENESIS

Megan Paul, Jacqueline Lesperance, Peter Zage

University of California San Diego, La Jolla, California, United States

Background: Identifying sub-populations of medulloblastoma tumors with stem cell-like properties holds promise for reducing disease recurrence, but there is no known unifying marker of medulloblastoma cancer stem cells. The granulocyte stimulating factor receptor (GCSF-R or CD114) is well understood in the context of hematopoiesis, but its role in solid tumor pathogenesis is less clear. Neuroblastoma and melanoma subpopulations expressing GCSF-R have cancer stem cell properties of chemoresistance and increased tumorigenicity, and are enriched in tumors after chemotherapy. GCSF-R activation leads to signaling through the JAK-STAT pathway, suggesting a potential therapeutic target. We hypothesized that a subpopulation of medulloblastoma cells would express the GCSF-R and that this subpopulation would demonstrate chemoresistance and response to inhibitors of the JAK/STAT pathway.

Objectives: Our objective was to identify a subpopulation of medulloblastoma cells expressing the GCSF-R and determine their relative growth rates, tumorigenicity, and responses to chemotherapy and JAK/STAT inhibition.

Design/Method: Medulloblastoma cell lines were sorted via flow cytometry for GCSF-R surface expression. Subpopulations of GCSF-R-positive and -negative medulloblastoma cells were then monitored for growth by continuous live cell imaging. Responses to chemotherapy were measured in subpopulations of GCSF-R-positive and -negative medulloblastoma cells using continuous live cell imaging to measure percent cell confluence and cell viability assays. IC50 values were calculated for each cell line and each agent. Parental medulloblastoma cell lines and isolated GCSF-R-positive and -negative subpopulations were also treated with the JAK1/2 inhibitor ruxolitinib and growth rates, viability, and IC50 values were calculated.

Results: GCSF-R surface expression was identified on 0.2-1.3% of medulloblastoma cell lines. Isolated GCSF-R positive cells demonstrate a slower growth rate compared to GCSF-R-negative or parental unsorted medulloblastoma cells. GCSF-R positive cells are more resistant in vitro to vincristine, etoposide, and carboplatin, when compared to the GCSF-R negative population and an unsorted population of the same cell line. Ruxolitinib is cytotoxic to medulloblastoma cells in vitro, with higher IC50 values noted in GCSF-R positive cells compared to unsorted and GCSF-R negative cells.

Conclusion: We show that a subpopulation of GCSF-R positive cells are present in multiple medulloblastoma cell lines via flow cytometry, and that isolated GCSF-R-positive cells have a slower growth rate than GCSF-R-negative or unsorted populations. We also show that Ruxolitinib has in vitro activity against medulloblastoma cell lines. We propose that JAK inhibition may represent an adjunct therapy targeting overall tumor burden and specifically targeting the GCSF-R-positive subpopulation of medulloblastoma cells that may drive tumor recurrence.

Poster # 807 | THE EFFICACY OF INTENSIFIED ADJUVANT CHEMOTHERAPY IN OSTEOSARCOMA PATIENTS WITH METASTATIC DISEASE OR POOR RESPONSE TO NEOADJUVANT CHEMOTHERAPY

Hyery Kim, Kyung-Nam Koh, Jae Won Yoo, Sung Han Kang, Jong-Seok Lee, Se-Hoon Choi, Dong Kwan Kim, Ho Joon Im, Jong Jin Seo

Asan Medical Center, Seoul, Korea, Republic of Korea

Background: Despite advancement in outcome of patients with osteosarcoma, patients who have metastases or respond poorly to neoadjuvant chemotherapy (CT) still show poor outcome.

Objectives: We investigated the efficacy of intensified adjuvant chemotherapy in osteosarcoma patients.

Design/Method: We retrospectively analyzed the medical records of 48 children with osteosarcoma treated at Asan Medical Center between 2006 and 2015. All patients received a 3-drug induction consisting of 2 cycles of cisplatin and doxorubicin along with 4 cycles of methotrexate (MAP), and proceeded to surgical resection. Adjuvant CT was MAP or MAP with the additional ifosfamide and etoposide (MAPIE), and MAPIE was mainly considered for poor responders (tumor necrosis below 90%) or patients with metastases.

Results: Among 48 patients, 6 patients had metastases at diagnosis. Surgery was conducted in 43 patients who responded to induction CT, and 17 showed over 90% tumor necrosis. Among 43 patients who proceeded to adjuvant CT, 19 and 24 patients received to MAP and MAPIE protocols. With a median follow-up of 73 months, the 5-year overall survival (OS) and event-free survival (EFS) rates of all patients were 80% and 46.7%. Of those 43 patients, 16 patients recurred, and 5 of them died of disease progression. Relapsed patients received salvage CT and/or surgery, and 2 were rescued after autologous stem cell transplantation (SCT). Three patients developed treatment-related acute myeloid leukemia, and they are alive after allogeneic SCT. According to the response to neoadjuvant CT, the OS rates of good responders (N = 18) and poor responders (N = 30) were 100% and 68.1% (P = 0.011), and EFS rates were 63.8% and 41.7% (P = 0.084). Of the 30 poor responders, 9 patients received MAP as adjuvant CT, and the other 21 received MAPIE. The OS rates of MAP and MAPIE group were 68.6% and 70.3% (P = 0.568), and EFS rates were 30.0% and 48.3% (P = 0.247), respectively. When patients were classified into three groups: 1. Localized disease & necrosis ≥ 90% (N = 17), 2. Localized disease & necrosis < 90% (N = 24), 3. Metastatic disease (N = 6), survival rates were in the order of group 1>2>3 (OS = 100%:81.8%:16.7%, EFS = 67.6%:43.6%:0%). In each group, intensified adjuvant CT by MAPIE did not improve survival outcomes.

Conclusion: Initial metastatic disease and poor histological response to neoadjuvant CT were major risk factors for poor survival in osteosarcoma patients. We found that adding ifosfamide and etoposide to MAP did not improve survival outcomes of patients with adverse risk factors. More effective adjuvant therapy for these patients is needed.

Poster # 808 | IMMUNOTHERAPEUTIC NANOTECHNOLOGY TARGETING IDO1 FOR PEDIATRIC DIFFUSE INTRINSIC PONTINE GLIOMA

Alicia Lenzen, Lisa Cole, Lijie Zhai, Kristen Lauing, Erik Ladomersky, Rishi Lulla, Alexander Stegh, Rintaro Hashizume, Derek Wainwright

Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, United States

Background: Childhood brain tumors are the most common solid malignancy and the leading cause of cancer-related mortality in children. The most aggressive type of pediatric central nervous system (CNS) tumors is diffuse intrinsic pontine glioma (DIPG). Despite decades of clinical trials, there has been no substantial improvement with respect to therapeutic outcomes with most children eventually succumbing to the disease. Research on adult high-grade gliomas has shown a targetable pathway through the inflammation-induced expression of indoleamine 2,3 dioxygenase 1 (IDO1) and its recognized ability to suppress the anti-tumor immune response. A limited understanding into the role of IDO1 in pediatric central nervous system tumors serves as the foundation of this research project. Furthermore, the integration of nanotechnology is a fundamental step for the investigation and targeting of IDO1. Spherical nucleic acids (SNAs) composed of nanoparticles have been shown to transverse cellular membranes, exhibit stability in physiological environments, escape from degradation, and create precise targeting in brain tumors.

Objectives: The purpose of our project is to delineate the role of IDO1 in pediatric DIPG, and develop small inhibitory (si)RNA oligonucleotides and SNAs aimed at therapeutically inhibiting the gene expression of immunosuppressive IDO1. Our specific aims are to: (1) confirm the gene expression IDO1 in different human DIPG cell lines; (2) generate and characterize siRNA oligonucleotides targeting human IDO1 in vitro; and (3) generate and characterize gold nanoparticles for targeted inhibition of IDO1.

Design/Method: Unique patient-derived DIPG cell lines were grown in culture, stimulated with increasing concentrations of the proinflammatory cytokine, IFNγ, and analyzed for mRNA levels. siRNA specific to IDO1 was transfected into cells. SNA generation is in progress.

Results: IDO1 is expressed in multiple human pediatric DIPG cell lines. siRNA targeting IDO1 among exons 9 and 10 results in a significant decrease in overall IDO1 expression by DIPG cells. SNA generation for targeting IDO1 with improved penetration & stability is ongoing, with preliminary results demonstrating a robust ability to inhibit IDO1 expression.

Conclusion: The grim prognosis of children with DIPG, the lack of effective therapies, and the expression of IDO1 by human DIPG cells emphasize the importance of developing the treatment capability to inhibit IDO1 gene expression, as a

means to enhance future immunotherapeutic efficacy against this devastating disease.

Poster # 809 | NONINVASIVE MOLECULAR PROFILING BY CIRCULATING CELL-FREE DNA IN PEDIATRIC SOLID TUMORS

Prachi Kothari, Emily Slotkin, Julie Yang, Caitlin Stewart, Erika Gedvilaite, Michael Berger, Marc Ladanyi, Neerav Shukla, Shakeel Modak, Dana Tsui

Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Circulating cell-free DNA (cfDNA) that shed from tumors into circulation have been used for noninvasive molecular profiling in adult cancers but little is known about its utility in pediatric cancers. Pediatric patients with metastatic and refractory solid tumors are known to have poor survival rates, and a key challenge in their management is obtaining biopsy samples especially at times when disease is widely spread or the patient is physically unfit for sampling. The development of a noninvasive profiling strategy is critical for optimizing molecularly guided therapy and assessing response to treatment.

Objectives: In this study, we want to determine the utility of cfDNA to noninvasively analyze the molecular profiles of pediatric solid tumors such as neuroblastoma (NB), osteosarcoma (OS), and wilms tumor (WT).

Design/Method: Tumor, plasma, and matched controls were collected from patients with NB, WT, and OS, at diagnosis or time of disease progression. cfDNA was extracted from the plasma and analyzed through multiple methodologies including a targeted next generation sequencing panels and shallow whole genome sequencing (sWGS).

Results: Fifteen NB patients, 10 OS patients, and 2 WT patients had tumor molecular profiles known from different targeted next-generation sequencing platforms. In the cfDNA of 7/15 NB patients, somatic mutations and copy number alterations previously reported in the tumors were detected, including recurrent NB drivers such as MYCN amplification, ALK, and ATRX mutations. Mutations not detected in the original tumor were also found in 6/15 NB patients including NRAS, MLL2, ARID1B, some of which are potentially actionable. In OS, mutations known from the tumor were found in the cfDNA of 5 of 10 patients, including ATRX and NOTCH3 mutations, as well as copy number alterations such as CDK4 amplification, which has targetable therapeutics available. Of the two WT patients analyzed, cfDNA revealed the same mutations as tumor in one patient, however in a cohort of patients where tumor was not available, cfDNA revealed recurrent driver mutations such as AMER1, DICER1.

Conclusion: It is feasible to noninvasively identify somatic mutations and copy number alterations in cfDNA of patients with pediatric solid tumors. Establishing a platform using cfDNA to identify molecular profiles of these tumors can serve as a powerful tool for guiding treatment and monitoring response to treatment.

Poster # 810 | PERSONALIZED RNA-NANOPARTICLE VACCINES TARGETING OSTEOSARCOMA

Brian Stover, Hector Mendez-Gomez, Adam Grippin, Rowan Milner, Duane Mitchell, Elias Sayour

University of Florida, Gainesville, Florida, United States

Background: Despite multi-modality therapy, the prognosis for patients with metastatic osteosarcoma remains poor necessitating development of novel targeted therapies. Immunotherapy can be exploited to target osteosarcoma with exquisite specificity but remains limited by insufficient tumor specific targets.

Objectives: To overcome the dearth in tumor specific antigens, we have explored the use of tumor derived mRNA (representing a tumor specific transcriptome) for development of personalized nanoparticle vaccines.

Design/Method: RNA-nanoparticles (RNA-NPs) can be amplified from limited amounts of biopsied tissue for induction of tumor specific T cells against osteosarcoma. Since local vaccination strategies are mired by poor overall immunogenicity, we assessed the feasibility, immunogenicity and antitumor activity of intravenously administered RNA-NPs (tumor mRNA complexed to DOTAP nanoliposomes) in pre-clinical murine and canine tumor models.

Results: We identified a clinically translatable NP formulation for the delivery of RNA to antigen presenting cells (APCs) that induces in vivo gene expression and preserves RNA stability over time. Tumor derived RNA-NPs induced antigen specific T cell immunity and mediated anti-tumor efficacy in several pre-clinical solid tumor models (i.e. B16F10, KR158B). When administered intravenously, RNA-NPs increased expression of co-stimulatory molecules (i.e. CD80, CD86, CD40, CCR7) and PD-L1 on CD11c+ cells throughout reticuloendothelial organs (i.e. spleen, liver, bone marrow) and within the tumor microenvironment; this phenotype was strictly dependent on type I interferon. Targeted inhibition of type I interferon signaling (via INFAR1 mAbs) abrogated anti-tumor efficacy mediated by RNA-NPs. We enhanced the immunogenicity of this platform by simply combining mRNAs encoding for immunomodulatory

molecules (i.e. HCV-PAMPs, GM-CSF) or by combining RNA-NPs with immune checkpoint inhibitors. Addition of checkpoint inhibitors (PD-L1 mAbs) to RNA-NPs increased tumor infiltrating lymphocytes, and intratumoral MHC class I/II expression, and mediated synergistic anti-tumor activity in settings where PD-1 or PD-L1 inhibition alone did not confer therapeutic benefit. We then explored the feasibility of RNA-NPs in a large animal osteosarcoma model. In ongoing studies for canines with osteosarcomas, we have shown that sufficient amounts of RNA can be extracted, amplified, and manufactured into personalized RNA-NP vaccines.

Conclusion: RNA-NPs reprogram systemic immunity and mediate anti-tumor activity providing near immediate immune induction without the complexity of cellular immunotherapy. The immune correlate of preclinical response to RNA-NPs is hallmarked by interferon dependent PD-L1 expression on activated APCs (CD11c+ MHCII+ CD86+ cells). Based on these findings, we are exploring the preclinical safety, efficacy and immunologic effects of RNA-NPs targeting canine osteosarcoma before first in-human evaluation.

Poster # 811 | TARGETING EWS-FLI1 DRIVING GENE: PRELIMINARY DATA OF PHASE 1 PBI-ShRNA EWS/FLI1 LIPOPLEX

Maurizio Ghisoli, Luisa Maning, John Nemunaitis, Donald Rao, Gladice Wallraven, Chris Jay

Medical City Children's Hospital, Dallas, Texas, United States

Background: Ewing sarcoma is an aggressive bone tumor affecting mainly adolescent and young adults. Treatments are based on compressed schedule chemotherapy combined with local control (surgery and/or radiation). Prognosis is poorer for patients with metastatic disease, older age and central primaries. Survival when disease recurs within two years of diagnosis is <10%. The EWS-FLI1 fusion gene t(11; 22) (q24; q12) has been well characterized as a dominant EWS driver-gene. The most common variation is EWS exon 7 with FLI1 exon 6 (60% of fusion positive patients). We designed a novel pbi-shRNA^{TM} EWS/FLI1 Type 1 LPX which has demonstrated, safety and efficacy in animal model (Rao et all). The pbi-shRNA strategy silences target gene expression by concurrently inducing translational repression and p-body sequestration as well as post-transcriptional mRNA cleavage.

Objectives: To determine the safety and maximum tolerated dose of intravenous administration of pbi-shRNA^{TM} EWS/FLI1 Type 1 Lipoplex in patients advanced EWS.

Design/Method: Phase I Study 3 × 3 escalation cohort. Testing pbi-shRNA^{TM} EWS/FLI1 Type 1 LPX (starting IV dose of 0.04 mg/kg) on patients (≥ age 8) with advanced Ewing's sarcoma, all with a Type 1 translocation. Intravenous infusion was given twice a week for 4 weeks with the following escalation schema: 50% → 33% → 25% → 25% → 25%. Required KPS >80% and adequate organ function. Cytokines induction pre and post-infusion was analyzed (IL-12, IL-6, TNF-alpha, IL1Ra).

Results: First cohort of patients has been enrolled (ages between 17–35 years). Three relapsed patients had >3 lines of therapy and 1 patient had refractory disease, 3 patients received a complete cycle of pbi-shRNA^{TM} EWS/FLI1 Type 1 LPX with twice a week infusions. A total of 69 doses were given. The most prominent related toxicity has been hematological, 1 patient developed transient G3 neutropenia, another patient developed G3 anemia that required PRBC transfusion, and of note this patient had significant bone and bone marrow involvement. One patient only received two LPX infusions; she developed a fatal RSV pneumonia. Other reported grade 2 toxicity includes fatigue and headache. Evaluable patients (n3) had stable disease between 4 and 12 months before progression. One patient had sustained response for 12 month before progression, two patients are still alive.

Conclusion: Our preliminary experience supports the safety and potential efficacy of pbi-shRNA^{TM} EWS/FLI1 Type 1 LPX as novel treatment for advanced EWS with limited toxicity. IL-6 increase correlates with higher bi-shRNAi EWS/FLI1 LPX infusion rate and clinical symptoms. Further clinical testing is indicated.

Poster # 812 | COMPARING THE NEUROCOGNITIVE FUNCTION AMONG PATIENTS WITH PEDIATRIC BRAIN TUMORS TREATED WITH PROTON VERSUS PHOTON RADIATION THERAPY

Sara McElroy, Subha Mazzone, Rene McNall-Knapp, Sunnye Mayes, Jim Scott, Michael Anderson

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States

Background: As more children with CNS malignancies (BT) are surviving, the late effects of the therapies they receive are better described. Studies show that radiation therapy is particularly harmful to neurocognitive functioning, specifically processing speed, working memory, and attention span. These deficits have negative effects on quality of life, especially in academic and professional settings. A large proportion of

adult survivors of BT are unable to reach adult milestones such as living on their own, holding a steady job, and getting married. Proton beam radiation therapy (PBRT), is touted for the potential to have fewer and less severe side effects than traditional photon radiation therapy (XRT). Because of the properties of protons, the amount of damaging energy released in non-target healthy tissue is reduced when compared to XRT. Although a study comparing IQ testing between PBRT and XRT found no difference between the two therapies, no studies have compared the specific neurocognitive domains. It would be valuable to evaluate full neurocognitive testing scores (NCT) since the specific domains, particularly processing speed (PSI), appear to be most vulnerable to radiation therapy.

Objectives: Our primary aim was to assess differences in PSI for patients with BT who underwent PBRT versus XRT. A secondary aim was to assess differences in IQ (FSIQ) and working memory (WMI).

Design/Method: We retrospectively evaluated all patients treated for BT at the Jimmy Everest Cancer Center within the past 20 years who received RT and had NCT post radiation. We examined the full NCT results for both subsets of participants to evaluate differences in the specific domains of processing speed, working memory, and IQ by measuring percentiles scored in these domains.

Results: 35 patients received both radiation and had NCT completed (XRT n = 17, PBRT n = 18). Comparing both groups there is a trend towards improved PSI scores in patients who received PBRT-mean percentile XRT vs PBRT. PSI 17.38% vs. 35.27%. There was no significant difference in FSIQ or working memory-.FSIQ 37.53% vs. 28.72% and WMI 32.75% vs. 25.92%.

Conclusion: The effects of PBRT versus XRT on cognition were evaluated looking at PSI and WMI as well as FSIQ. PBRT shows that it might have a protective effect for PSI however no improvement was seen in WMI or FSIQ. The role of PBRT in cognitive protection compared to XRT may be minimal, however a larger multi-institutional chart review may be of benefit to further evaluate.

Poster # 813 | THE ROLE OF ROUTINE IMAGING IN CHILDHOOD MELANOMA (MM)

Hadeel Halalsheh, Sue Kaste, Armita Bahrami, Fariba Navid, Barry Shulkin, Bhaskar Rao, Alberto Pappo, Michelle Kunkel

St Jude Children's Research Hospital, Memphis, Tennessee, United States

Background: Optimal imaging for children with MM has not been established.

Objectives: We report our experience on imaging children with MM treated uniformly on an institutional melanoma trial.

Design/Method: We retrospectively reviewed the clinical and imaging findings of patients with AJCC stage IIC-IV cutaneous MM treated on our institutional MEL06 protocol. Brain MRI/CT, PET/CT, CT chest, abdomen, and pelvis (CTCAP) were performed at diagnosis in all patients. On treatment, stratum A patients (PEG-interferon; AJCC IIC, IIIA, IIIB) (n = 16) had the same imaging repeated every 6 months; stratum B1 (PEG-interferon and temozolomide; unresectable measurable disease metastatic, or recurrent) (n = 2) had PET scans every 2 months and brain imaging every 4 months; those in stratum B2 (PEG-interferon and temozolomide; unresectable non-measurable, metastatic, or recurrent) (n = 3) had the same imaging performed every 4 months. Off therapy all patients continued same imaging every 6 months for 3 years.

Results: There were 21 patients (11 female; median age 14 years). Eleven had spitzoid and 10 conventional melanoma. Primary sites included head/neck (n = 6), trunk (n = 7), and extremities (n = 8). Patients with spitzoid melanoma had 236 imaging studies (86 PET, 81 CTCAP, 11 CT chest, 10 CT brain, and 48 MRI brain) with a median of 8, 7, 0, 4 and 0 studies/patient respectively. Median cost per patient was $32,718. Thirteen studies (5.8%) showed suspicious lesions with 28 additional scans and 2 diagnostic biopsies of which one only was positive stratum A with TERT promoter mutation and died from disease). For conventional MM, 162 studies (61 PET, 57 CTCAP, 8 CT chest, 7 CT brain, and 29 MRI brain) were performed with a median of 7, 6.5, 0, 1, 3 studies/patient respectively. Median cost per patient was $23,420. Twenty (14%) showed suspicious lesions with 19 additional scans and 6 diagnostic biopsies; four were positive (two at diagnosis); both died of disease; the other two recurred locoregionally and were detected clinically; both are alive and disease free; one patient had diffuse metastases and died shortly after enrollment. After a median follow up of 6.3 years (range 0.4-9.2) 17 patients are alive and disease free.

Conclusion: Children with spitzoid melanoma should have minimal imaging at diagnosis and follow-up given the low risk of recurrence and low yield and high cost of aggressive imaging protocols. Patients with conventional MM should be imaged according to the adult guidelines.

Poster # 814 | IMPACT OF INFECTIONS ON SURVIVAL IN PEDIATRIC PATIENTS WITH BONE TUMORS

Hannah Elkus, Joseph Stanek, Bhuvana Setty

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: The role of infections in the long term outcome of patients with bone tumors is controversial. Two retrospective studies have shown increased survival in osteosarcoma patients who had a post-operative wound infection, while another showed no changes in overall survival.

Objectives: To determine the relationship between wound infections and/or bloodstream infection (BSI) on survival in pediatric and young adult patients with osteosarcoma and Ewing sarcoma treated at a tertiary children's hospital.

Design/Method: A retrospective chart review was performed for patients with diagnosis of osteosarcoma or Ewing sarcoma from 2006–2016. Patients received standard chemotherapy regimens for their disease type and stage. Local control included surgical resection and/or radiation therapy. Presence of infection was determined by BSI or wound cultures while receiving treatment for primary tumor.

Results: The median age of 85 patients was 14 (range 2–46 years) at diagnosis. 53% had a diagnosis of osteosarcoma and 47% had Ewing sarcoma. Of these, 46% of patients developed an infection during treatment; 25% had BSI, 26% had wound infections, and 5% had both. Patients with BSI had a 5 year OS of 63.3%, compared to 81% in those without BSI ($p = 0.0015$). Those with both BSI and wound infections had the poorest overall survival of 50%, compared to 80.8% for patients without any infection. Patients with wound infections alone had a 5 year OS of 80.2%, compared to 75% of patients without a wound infection.

Conclusion: Our analysis revealed decreased OS in patients with BSI; however, this could be due to other confounding factors in the presence of BSI. Those with BSI or BSI and wound infections had the poorest survival. Wound infections without BSI were associated with a slight increase in survival; however, this study was limited by the number of patients that had local wound infections. With the use of newer surgical techniques, availability of antimicrobials and routine use of prophylactic antibiotics, the incidence of infections while undergoing treatment is low. However, the importance of this clinical observation indicates a likely enhanced immune system associated with infection, supporting the role of immunotherapy for treatment of these aggressive tumors.

Poster # 815 | HYPOALBUMINEMIA IS NOT ASSOCIATED WITH INFERIOR SURVIVAL IN CHILDREN WITH CANCER

Thomas McLean, Ryan Stewart, Thomas Curley, Mark Dewsnup, Thomas Russell, Janet Tooze

Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, United States

Background: Hypoalbuminemia is a well-recognized effect of cancer and other chronic illnesses and is often regarded as a marker of malnutrition. In adults, hypoalbuminemia has been associated with adverse outcomes in patients with cancers of the lung, pelvis, head and neck, gastrointestinal tract, and bone marrow, as well as in some pediatric patients with Ewing sarcoma and Hodgkin lymphoma. Hypoalbuminemia has not been well studied in children with cancer.

Objectives: To determine the incidence of hypoalbuminemia (using age-specific references) in children with cancer receiving chemotherapy at baseline (prior to starting chemotherapy) and to determine whether hypoalbuminemia is associated with inferior 5-year overall survival.

Design/Method: We performed a single institution, IRB-approved, retrospective review of pediatric oncology patients diagnosed between 1998 and 2012. Five-year survival was estimated using the Kaplan-Meier method; groups were compared using Cox regression.

Results: We identified 863 pediatric patients with a first diagnosis of cancer, brain tumor, or other condition possibly requiring chemotherapy. Of these 863 patients, 204 were excluded for reasons including not receiving chemotherapy and missing data, leaving 659 patients who had a serum albumin level within 60 days prior to starting chemotherapy. The mean age was 8.1 years (SD 5.8 years); 62% were male; 92% were non-Hispanic. The most common diagnosis was acute lymphoblastic leukemia (201 of 659; 31%). One hundred thirty nine of 659 (21%) had hypoalbuminemia prior to starting chemotherapy. There was no statistically significant difference in 5-year overall survival between those with and without hypoalbuminemia (78% vs. 82%, respectively; hazard ratio 1.27, 95% C.I. 0.85 – 1.90).

Conclusion: Hypoalbuminemia at baseline in pediatric oncology patients requiring chemotherapy is common (one in five), and was not associated with inferior 5-year overall survival in this cohort.

Poster # 816 | EXTRANEURAL METASTASES OF A WHO GRADE II EPENDYMOMA: A CASE REPORT AND REVIEW OF THE LITERATURE

Priya Chan, Hong Zhou, Carol Bruggers

University of Utah School of Medicine, Salt Lake City, Utah, United States

Background: Ependymomas account for 10% of all pediatric intracranial tumors. Approximately 15% show

leptomeningeal metastases at diagnosis. Standard treatment for completely resected, non-anaplastic supratentorial ependymomas is close observation. Treatment for anaplastic or incompletely resected non-anaplastic ependymomas is maximal safe surgical resection followed by focal radiation. However, up to 50% of localized ependymomas recur. The role of chemotherapy in treating ependymomas is under investigation. Extraneural metastases of anaplastic ependymomas have rarely been reported and the outcome is dismal.

Objectives: To report extraneural cervical node metastases of a non-anaplastic ependymoma and successful treatment with surgical resection, radiation, and systemic chemotherapy.

Design/Method: Retrospective review of patient medical records, including radiographic imaging and tumor tissue pathology, and comprehensive literature review.

Results: A previously healthy 3-year-old girl underwent gross total resection (GTR) of an isolated right parietal lobe ependymoma (WHO grade II). At age 4 years, magnetic resonance imaging (MRI) revealed an isolated localized recurrence. She underwent GTR followed by observation. At age 6 years, she again experienced isolated localized recurrence and underwent GTR followed by 59.4 Gy focal conformal photon radiation. At each recurrence, pathology revealed a non-anaplastic ependymoma, and cerebral spinal fluid (CSF) cytopathology and spine MRI were negative. At age 10 years, she developed an enlarged right posterior cervical chain lymph node. Subsequent MRI revealed a large rim-enhancing, T2 hyperintense lymph node and multiple abnormally enhancing regional nodes consistent with metastases. Biopsy revealed a non-anaplastic ependymoma. MRI of the brain and spine, computed tomography of the chest, abdomen, and pelvis, and CSF and marrow evaluations were unremarkable. Chemotherapy according to ACNS0831 was initiated. MRI after course 3 demonstrated significant node size reduction. She underwent right neck node dissection. Only one right level II lymph node showed metastases. She was treated with 59.4 Gy irradiation to the neck and 3 additional courses of chemotherapy. She remains in remission 24 months and 17 months after diagnosis of metastatic disease and end of therapy, respectively. Literature review reveals rare reports of extraneural metastatic disease of anaplastic ependymomas to bone, lung, or liver, and only 2 involving lymph nodes, all associated with a poor outcome despite multimodal therapy.

Conclusion: To our knowledge, this is the first report of extraneural metastases of a non-anaplastic ependymoma. Extraneural metastases should be considered in children previously treated for non-anaplastic ependymomas who experience systemic symptoms, even in absence of CNS relapse. Multimodal treatment offers potential long-term disease control with acceptable toxicity.

Poster # 817 | CLINICAL UTILITY OF PET/CT IN PATIENTS WITH PIGMENTED VILLONODULAR SYNOVITIS TREATED WITH IMATINIB

Arun Gurunathan, Joel Sorger, Andrew Trout, Joseph Pressey, Rajaram Nagarajan, Brian Turpin

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Pigmented villonodular synovitis (PVNS) is a benign neoplasm of the synovium. Standard treatment is surgery, but post-operative recurrence rate is as high as 60%. Radiation therapy can be used for local control, but is associated with late effects. While PVNS is rarely fatal, aggressive disease and/or extensive surgery can result in substantial functional impairment. Colony stimulating factor-1 (CSF1) overexpression, often due to chromosomal translocation involving CSF1, drives PVNS through recruitment of synovial-like mononuclear cells expressing the CSF1-receptor. Tyrosine kinase inhibitors such as imatinib are active against the CSF1-receptor, and have shown benefit in the post-surgical relapse setting. However, questions remain regarding the broader application of imatinib and regarding optimal response assessment.

Objectives: To present three patients with PVNS, each with different clinical scenarios, who demonstrate clinical response to imatinib monitored by changes in metabolic activity (maximum SUV) on PET/CT.

Design/Method: Case series of three patients.

Results: Three patients with PVNS demonstrate PET/CT response to imatinib, guiding management of their challenging clinical scenarios. Patient 1 is a 20 year-old female with left hip PVNS and high grade articular cartilage loss, with decrease in metabolic activity (SUVmax 8.3 to 4.7 in 3 months) on neoadjuvant imatinib, enabling total hip replacement surgery planning. Patient 2 is a 16 year-old female with left knee PVNS with recurrences after synovectomies, spared subsequent surgical control attempts after clinical improvement correlating with PET/CT response to imatinib (SUVmax 10.2 to 4.3 in 2 months). Patient 3 is a 27 year-old male with right knee PVNS that recurred after total knee replacement, now with clinical improvement correlating with PET/CT response to imatinib (SUVmax 11.2 to 5.2 in 3 months). All patients would have been characterized as stable disease by Response Evaluation Criteria in Solid Tumors (RECIST). In each of these patients, imatinib has been tolerated well, with no therapy interruptions and absent or easily managed side effects (one patient takes dronabinol for decreased appetite, one patient takes prn immodium for diarrhea). All patients

are currently still taking imatinib, with therapy length ranging from five to eleven months.

Conclusion: In our series of three patients with PVNS, imatinib shows promise for disease management in neoadjuvant and adjuvant settings with a tolerable side effect profile. Imatinib should be considered in the treatment of PVNS to spare surgical and radiotherapy related morbidity, and treatment effect can be monitored by PET/CT.

Poster # 818 | TARGETING PHOSPHORYLATION OF EZRIN IN METASTATIC RHABDOMYOSARCOMA

Nabanita Bhunia, Debasis Pore, Daniel Lindner, Neetu Gupta

Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, United States

Background: Metastatic rhabdomyosarcoma (RMS) carries a poor prognosis with three-year event free survival rates ranging between 20%-69% (depending on Oberlin risk factors) due to the lack of significantly effective breakthroughs in the recent past. There is an urgent and unmet need for new treatment strategies against this disease. Metastatic RMS cell lines exhibit increased expression of the ERM family membrane-cytoskeleton linker protein Ezrin. Knockdown of ezrin expression using siRNAs decreases the metastatic potential of these cells, whereas forced expression of ezrin results in increased degree of metastasis. The activity of ezrin is controlled by its phosphorylation at the Threonine 567 (Thr567) residue at the C-terminus of the protein, suggesting that alteration of ezrin phosphorylation may control RMS growth and metastasis.

Objectives: Our goal was to determine if pharmacological inhibition of Thr567 phosphorylation in ezrin affects the growth, survival and metastasis in RMS in vitro as well as in vivo.

Design/Method: RMS cell lines representative of the alveolar and embryonal histological subtypes were used. RMS cells were treated with a small molecule inhibitor of ezrin, NSC668394, which specifically dephosphorylates ezrin at the Thr567 residue. Baseline expression of ezrin and pERM levels as well as the effect of NSC668394 on pERM levels in the RMS cell lines was determined by western blotting of cell lysates. Viability of cells was assessed by trypan blue exclusion, and morphology visualized by bright field microscopy. The extent of apoptosis was detected by imaging caspase 3/7 activation using fluorescent microscopy. Motility of RMS cells was examined by performing a wound-healing assay. Subcutaneous and orthotopic xenografts were established in NSG mice using RD cells (embryonal RMS). Mice harboring xenografts were treated with intraperitoneal injections of NSC668394 or DMSO.

Results: Ezrin is constitutively phosphorylated at the Thr567 residue in a majority of the RMS cell lines examined. NSC668394 dephosphorylates ezrin at the Thr567 residue in these cell lines. Treatment with NSC668394 inhibits growth, induces apoptosis and inhibits the migration of RMS cell lines in vitro. Further, treatment of NSG mice bearing subcutaneous or orthotopic embryonal rhabdomyosarcoma xenografts with NSC668394 significantly impedes tumor progression without any obvious adverse effects.

Conclusion: Our findings suggest that dephosphorylation of ezrin at the Threonine 567 residue may have the potential to be a novel therapeutic strategy for RMS patients.

Poster # 819 | LAPAROSCOPIC MANAGEMENT OF INTRA - ABDOMINAL TUMORS - FEASIBLE OR NOT?

Prabudh Goel, Kanika Sharma, Puneet Khanna, Minu Bajpai

All India Institute of Medical Sciences, New Delhi, New Delhi, Delhi, India

Background: The role of laparoscopy in the management of pediatric intra-abdominal solid tumors is yet to be established.

Objectives: The safety of laparoscopic management of pediatric intra-abdominal tumors is still questionable. We study the results of the initial case series of pediatric intra-abdominal tumors managed laparoscopically at our institute from July 2013 onwards.

Design/Method: Total 11 children (8-males, 3 females) who presented to us with pediatric intra-abdominal tumors were included. The tumors included Wilms tumor (n = 7), neuroblastoma(n = 2), adrenal cortical tumor(n = 1), ovarian teratoma(n = 1).Children were between 10months - 7years and 4 received neo-adjuvant chemotherapy. A 4-port laparoscopic nephrectomy and lymph node sampling for Wilms tumor and adrenalectomy for adrenal tumors was performed.

Results: The tumors were removed in-toto with no rupture (except in one). Specimens were retrieved through a lumbar incision (n = 8) or an inguinal incision(n = 1). All the children are under regular follow up. Two children with Wilms tumor had recurrence. The neuroblastoma child underwent open surgery for recurrence later.

Conclusion: Laparoscopy/laparoscopic assisted removal of pediatric intra abdominal tumor is a feasible and safe option. It has the advantage of less postoperative pain, shorter hospital stay and a better cosmetic result. Proper patient selection, port placement and laparoscopic experience are contributory.

Poster # 820 | PATTERNS OF EXPRESSION OF DISIALOGANGLIOSIDE GD2 IN PEDIATRIC SARCOMAS

Lindsey Murphy, Catherine Albert, Julie Park, Doug Hawkins, Erin Rudzinski, Navin Pinto

Seattle Children's Hospital, Seattle, Washington, United States

Background: Targeting of proteins and cell surface antigens specific to cancer cells with monoclonal antibodies has proven to be an effective form of treatment in many forms of cancer. GD2 is a cell surface disialoganglioside that is expressed on the cell surface of some normal tissues including nerve cells, melanocytes, and mesenchymal stromal cells and is overexpressed in some pediatric cancers like neuroblastoma and osteosarcoma. Dinutuximab is a chimeric monoclonal antibody that is FDA approved for the treatment of patients with high risk neuroblastoma and under investigation for the treatment of relapsed osteosarcoma. Little is known about the patterns of GD2 expression in other pediatric malignancies.

Objectives: We sought to describe the patterns of GD2 expression in the following pediatric sarcomas: synovial sarcoma, rhabdomyosarcoma and Ewing sarcoma.

Design/Method: Synovial sarcoma (n = 44), rhabdomyosarcoma (n = 35) and Ewing's sarcomas (n = 12) formalin fixed, paraffin embedded cores were obtained from the Seattle Children's Research Institute tissue microarray (TMA) biorepository. TMA blocks consisting of melanoma cores stained with and without GD2 antibody were used as positive and negative controls, respectively. Slides were incubated with Anti-Ganglioside GD2 antibody clone 2Q594 (Ab68456 from Abcam) diluted 1:50 in 10% Normal Goat Serum and 5% BSA in TBS overnight at 4˚C. The negative control of Human Melanoma section was incubated in 10% Normal Goat Serum and 5% BSA in TBS without primary antibody. The expression of GD2 was indicated by characteristic brown Diaminobenzidine staining. The intensity and location of tissue staining were assessed and compared to positive and negative controls. Staining was considered positive (+++) if the intensity of the staining was consistent with that of the positive control with 67–100% of cells staining positive. Classification of intermediate GD2 expression (++) was assigned to slides in which 34–66% of cells stained positive. Slides were classified as sporadic staining (+) if 1–33% of cells stained positive. Tissue was considered (-) if there was complete absence of staining, similar to the negative control.

Results: Table 1. Immunohistochemistry analysis of GD2 protein expression in Ewing sarcoma, Rhabdomyosarcoma, Synovial Sarcoma Disease n - + ++ +++ Could not be scored Ewing 12 17% 23% 30% 20% 10% Rhabdo 35 20% 26% 20% 26% 8% Synovial 44 15% 13% 27% 30% 15%

Conclusion: GD2 is variably expressed in synovial sarcoma, rhabdomyosarcoma and Ewing sarcoma. Investigations of GD2 immunotherapy may be warranted in these populations.

Poster # 821 | TREATMENT OUTCOMES OF MALIGNANT GERM CELL TUMOR: A SINGLE CENTRE EXPERIENCE OF 22 YEARS

Vishesh Jain, Anjan Dhua, Sameer Bakshi, M Srinivas, Sanjay Thulkar, Manisha Jana, Akshay Bishoi, Veereshwar Bhatnagar, Sandeep Agarwala

All India Institute of Medical Sciences, New Delhi, India

Background: Germ cell tumors (GCT) account for only 3% of malignancies in children and can arise from both gonadal and extragonadal site. Data relating to treatment of malignant GCT is scant from developing countries.

Objectives: To evaluate the clinical presentation, management and treatment outcomes of children with malignant germ cell tumor at our institute

Design/Method: A prospective study was conducted from June 1994 to Dec 2016 in the department of Pediatric Surgery in a tertiary care institute in a developing country. All Patients were evaluated for local disease and metastatic disease by imaging and tumor markers. Risk Stratified chemotherapy was used with low risk tumor receiving no chemotherapy, Intermediate risk: 4 courses of PEB chemotherapy and high risk: 4 courses of PEB + 2 courses of PE. Upfront resection of the primary or the residual disease after neoadjuvant chemotherapy if feasible was performed. Follow up was done with monthly tumor markers for 6 months and imaging studies every 3–6 months for initial 3 years. Five year overall survival and disease free survival was calculated.

Results: During the study we treated 152 children who formed the study group. Of these 83 (55%) were gonadal (45;30% testicular and 30;25% ovarian) and the remaining 69 (45%) were extragonadal with sacrococcygeal (SCT) being the most common site 48 (31%). One hundred and thirteen children (75%) presented to us primarily while the remaining 39 had received treatment elsewhere. Stage 3 or stage 4 disease at presentation was present in 104 (68%) children. Recurrence was noted in 50 (33%) patients. The 5 year OS and EFS of all MGCT was 90.1% (95 CI 83–94) and 61.3% (95 CI 52–69) respectively. The 5 year OS and EFS of testicular MGCT was 89.4%and 34.3% respectively. The 5 year OS and EFS of ovarian MGCT was 94%and 90.2% respectively. The 5 year OS and EFS of Malignant SCT was 82.6%and 49.5%

respectively. Patients with Testicular MGCT and children with age 2–5 years and males had significantly poor RFS rates.

Conclusion: Patients with MGCT should be staged correctly and adjuvant chemotherapy is advisable to all patients except Stage I Endermal sinus tumor of testis. Awareness regarding the same is still lacking in our country. Meticulous follow up is needed as more than 30% of will recur. Cure rates are dismal in children with recurrent MGCT especially those who are not chemotherapy naïve.

Poster # 822 | ENTERAL TUBE NUTRITION NEEDS AND PERCEPTIONS IN HIGH-RISK HEAD AND NECK PEDIATRIC PATIENTS RECEIVING PROTON THERAPY

Allison Bechtel, Eric Sandler, Daniel Indelicato

Nemours Children's Specialty Care, Jacksonville, Florida, United States

Background: Radiotherapy for pediatric head and neck tumors often results in mucositis, limiting oral intake and compromising patients' nutritional status. This may be reduced through the improved conformality offered by proton therapy. Despite widespread use of enteral tube feeding through a percutaneous gastrostomy (PEG) or nasogastric tube (NGT), there is little data available regarding overall incidence of NGT/PEG placement and perspectives of pediatric patients and caregivers.

Objectives: To (a) estimate the need for NGT/PEG support and (b) characterize patient and caregiver perceptions surrounding enteral feeding in children with head and neck tumors undergoing proton therapy.

Design/Method: Dependent on development stage, patient (n = 16) or parents (n = 6) filled out a series of customized surveys according to a prospective IRB approved study. Seventy-three percent of patients also received concurrent chemotherapy. Questions addressed their current feeding route and perception, for example, "What aspect(s) of tube feedings are beneficial to you?" and "What aspect(s) of tube feeding worry or scare you?" Fifty-five surveys were distributed before and after radiation, and with any change in feeding route.

Results: At the start of proton therapy, 1 patient had a NGT and 8 patients had PEG. Of these, 8 patients (36%) had a NGT/PEG in place exclusively for the administration of medication; only 1 patient (4%) needed a NGT/PEG for nutrition. In those patients without NGT/PEG, 46% would "consider" enteral feeds. In patients without NGT/PEG, the most commonly cited benefit was "maximizing my nutrition" (67%) and the most common negative aspect was "fear" of tube placement (100% of patients). All sub-populations (32% of patients) cited change in appearance as a negative aspect. In patients without NGT/PEG at the start of proton therapy, 46% of patients/caregivers felt enteral feeding to be "unnecessary," and 83% of these patients would not "consider" NGT/PEG even if their "physician advised it." Over the course of proton therapy, the patients/caregivers who deemed enteral feeding "unnecessary" decreased from 46% to 18%. At completion of treatment, 7 patients (32%) were using a NGT/PEG tube for nutritional support but only one (4%) patient relied exclusively on their enteral feeds. Two patients (without NGT/PEG) (9%) required parenteral support.

Conclusion: Our data does not support prophylactic placement of NGT/PEG in of children with head and neck tumors undergoing proton therapy. Ongoing research is needed to identify which patients will need NGT or PEG to supplement their diet. In this cohort, anticipatory counseling should focus on pain, cosmesis, and utility.

Poster # 823 | AN UNUSUAL CASE PRESENTATION OF A SEX CORD STROMAL TUMOR IN A 3 MONTH OLD INFANT

Scott Raskin, Christopher Rossi, AeRang Kim

Children's National Medical Center, Washington, District of Columbia, United States

Background: Ovarian Sex cord-stromal tumors (OSCT) are rare neoplasms that typically present with signs/symptoms of an adnexal mass and signs of hormonal production1 Approximately 20% of ovarian sex cord-stromal tumors in children are Sertoli-Leydig cell tumors (SLCT) with median age of presentation 25 years overall.1 To our knowledge the youngest reported case in the literature describes a 9-month old female in China with a SLCT that was treated with oophorectomy alone.2 Some studies have found an association in families between pleuopulmonary blastoma and OSCT with a germline mutation leading to DICER1 syndrome, which has been associated with a younger age at diagnosis.3,4

Objectives: To describe an unusual case presentation of SLCT in an infant

Design/Method: Case presentation

Results: 3-month old, twin female, ex-32 week premature infant presented to the Emergency Department on multiple occasions for abdominal distention and feeding intolerance initially thought to be related to previous omphalocele repair and umbilical hernia. An ultrasound demonstrated an 8×6 cm mass arising from the right ovary with large volume ascites. She required admission to the intensive care unit due to

respiratory distress from her significant ascites. Serum tumor marker including HCG, AFP and LDH were negative. Patient underwent right oophorectomy with tumor capsule noted to be open at time of surgery. Further imaging post operatively demonstrated no other sites of disease. The patient was classified as FIGO Stage IC due to the presence of her significant abdominal ascites that was presumed to be malignant pre-operative tumor rupture.5 The pathological diagnosis was challenging and eventually resulted as a mixed germ cell sex cord stromal tumor with pattern of Sertoli cell tumor with neuroendocrine differentiation. Based on the staging of FIGO IC with pre-operative rupture, the decision was made to treat with a standard platinum based regimen as there is a higher incidence of relapse in stage IC patients when compared to IA treated with observation alone.6 Our patient tolerated four cycles of chemotherapy well and end of therapy scans showed no evidence of disease. Interestingly, her DICER mutation genetics performed by Ion Torrent^{TM} Next Generation Sequencing was negative in germline and tumor studies.

Conclusion: To our knowledge, our patient is the youngest described with SLCT. She will continue to be followed with serial imaging alone as she had no evidence of elevated tumor markers at diagnosis.6,7 Due to young age and unusual diagnosis, she was referred to cancer genetics team.

Poster # 824 | EWING SARCOMA VS. PNET: COMPARING EPIDEMIOLOGY, CLINICAL FEATURES AND OUTCOMES OVER 40 YEARS USING SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS DATA

Kevin Campbell

Dana Farber Cancer Institute, Boston, Massachussetts, United States

Background: Peripheral primitive neuroectodermal tumors (PNETs) are classified under the umbrella of Ewing sarcoma family of tumors (ESFT) given their shared biology, though histologic features differ between PNET and Ewing sarcoma (ES). Potential clinical differences between PNET and ES have not been fully elucidated.

Objectives: –

Design/Method: Through the National Cancer Institute's Surveillance, Epidemiology, and Results (SEER) database, we identified 3,645 patients with histologic diagnosis of ES or PNET from 1973 – 2014. We used Fisher's exact tests to compare patient and tumor characteristics between groups. Kaplan-Meier methods were used to estimate overall survival.

Results: Patients with ES were more likely to be male, ≤ 18 years old at diagnosis, white, and Hispanic compared to patients with patients with PNET ($p = 0.016$ for sex; $p<0.001$ for all other variables). Patients with PNET were more likely to have soft tissue primary tumors ($p<0.001$) and, among those with bone tumors, a lower rate of axial or pelvic tumors ($p<0.001$). Patients with PNET had significantly worse 5-year survival compared to ES patients, though the absolute difference was small (51.3% vs. 55.5%; $p<0.001$). Survival for patients with PNET diagnosed in the 1990's and later more closely approximated those of patients with ES, while patients with PNET diagnosed in the 1980's and earlier had inferior outcomes.

Conclusion: Despite shared underlying biology, patients with PNET and ES show differences in clinical presentation and overall survival, with the latter differences largely mitigated in more recent decades.

Poster # 825 | KINOMIC ALTERATIONS OF PRIMARY AND METASTATIC WILMS TUMOR BY FOCAL ADHESION KINASE INHIBITION

Jamie Aye, Joshua Anderson, Jerry Stewart, Laura Stafman, Adele Williams, Karina Yoon, Kimberly Whelan, Christopher Willey, Elizabeth Beierle

University of Alabama at Birmingham, Birmingham, Alabama, United States

Background: Approximately 12% of patients with Wilms tumor (WT) have metastatic disease at diagnosis and often have a grave prognosis. Limited cell lines are available for the study of metastatic WT and long-term passaged cell lines do not always recapitulate the human condition. Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that controls cellular pathways involved in the tumorigenesis of pediatric renal tumors. Using a novel patient-derived xenograft (PDX) model from a patient's primary WT (COA 25) and matched isogenic metastatic WT (COA 42), we previously demonstrated that FAK is expressed and its inhibition led to decreased tumorigenicity of both the primary and metastatic PDXs. Kinomic profiling is an innovative, high-throughput method used to investigate kinase signaling to identify potential therapeutic targets. To date, the kinomic profile of primary and metastatic WT has not been examined.

Objectives: Investigate baseline kinomic differences between primary and metastatic WT and evaluate kinases upstream and downstream of FAK as potential targetable therapies.

Design/Method: Cells from COA 25 and COA 42 were treated with PF-573,228 (PF), a small molecule FAK inhibitor. Protein from cell lysates of treated and untreated COA 25 and COA 42 were combined with kinase buffer, ATP, and fluorescently labeled antibodies and loaded into a phosphotyrosine kinase or serine-threonine kinase PamChip® per the UAB Kinome Core protocol. Phosphopeptide substrate analysis with the PamStation®12 kinomics workstation (PamGene® International), PamChip® protocol using Evolve2 Software, and BioNavigator v. 6.0 were used to analyze kinases upstream and downstream of FAK.

Results: The primary WT had increased EPHA8, ROR1 SGK307 and decreased PDGFRB relative to the paired metastatic WT at baseline. Treatment with PF increased RON, PDGFRB, P70S6KB, MAK, CAMK2G, VACAMKL, CAMK2D, CK1A1 and PSKH1 in the primary WT. Treatment with PF decreased TNK1, LMR1, CCK4, EPHA5, PDK1, SGK196, LKB1 and increased PSKH1 in the paired metastatic WT.

Conclusion: Primary WT displayed a different kinomic profile compared to metastatic WT in a matched isogenic PDX model. These data reveal that alternative therapies to specifically target metastases are needed. Furthermore, FAK inhibition resulted in diverse kinomic alterations between primary and metastatic WT. Inhibitors targeting many of these pathways, such as PDGFRB inhibitors, are currently available and potentially could be combined with FAK inhibitors in the treatment of WT. The results of the current study indicate that kinases upstream and downstream of FAK in primary and metastatic WT warrant further investigation.

Poster # 826 | DEFINITION OF RISK PROFILE AND TOXICITIES OF HIGH-DOSE METHOTREXATE USE IN PEDIATRIC OSTEOSARCOMA

Elizabeth Cowell, Susan Cheng, Lisa Wang, Nino Rainusso, Jennifer Foster

Baylor College of Medicine, Houston, Texas, United States

Background: Use of high-dose methotrexate (HD-MTX, 12 g/m^2) is a mainstay of standard therapy for pediatric osteosarcoma (OS) in North America. In pediatric OS, there is a narrow therapeutic window for HD-MTX, with decreased tumor response rate with MTX concentrations <1000 μM and decreased survival due to severe toxicity with concentrations >1500 μM. Risk factors for HD-MTX toxicity have been defined in adults, including body mass index (BMI) and male gender, but such studies have not been conducted in children.

Objectives: We sought to examine the relationship between MTX levels and toxicities during HD-MTX infusion for pediatric OS, thereby identifying risk factors for increased toxicity and providing a framework for therapeutic drug monitoring.

Design/Method: This retrospective chart review included patients treated at Texas Children's Hospital with HD-MTX as first-line therapy for OS from 2009–2015. Data abstracted from electronic records included patient characteristics, BMI and body surface area (BSA), baseline and post-treatment laboratory values, MTX levels 4 and 24 hours after dose given (4h, 24h), hour MTX cleared (MTX <0.1 uM), grade 3/4 mucositis, myleosuppression, persistent LFT elevation (CTACE v4.0), and % tumor necrosis. Correlation between 4h MTX level and other covariates was summarized using descriptive statistics.

Results: We reviewed 128 HD-MTX infusions corresponding to 12 patients. BMI was found to significantly impact 4h MTX level ($P<0.05$). Female gender was also significantly associated with higher 4h MTX level ($P<0.001$). Percent necrosis (available in 9 patients) was associated with 4h MTX levels at near-statistical significance ($P = 0.07$). 4h MTX level was not found to contribute to toxicities or associate significantly with MTX clearance. Analysis in a larger cohort is ongoing.

Conclusion: We have identified at least one patient factor (BMI) that significantly impacts 4h MTX levels and is of potential use for future modeling, as current models incorporate BSA only. Our findings concord with studies in adult OS in that BMI significantly impacts 4h MTX level but diverge in that female gender is associated with higher 4h levels. Importantly, these data support targeting 4h MTX levels to ensure that minimum concentration for adequate tumor necrosis is reached. These results do not suggest that monitoring 4h levels would prevent toxicities, thus necessitating further characterization of any intrinsic patient factors that associate with toxicity. Overall, our definition of the clinical factors that associate with 4h MTX levels contributes to a framework for therapeutic drug monitoring in pediatric OS.

Poster # 827 | OUTPATIENT INTERLEUKIN 2 MAY BE A SAFE AND FEASIBLE OPTION IN CHILDREN WITH HIGH RISK NEUROBLASTOMA

Joy Bartholomew, Jill Anderson

Children's Mercy Hospital Kansas City, Kansas City, Missouri, United States

Background: Post Consolidation immunotherapy with dinutuximab, aldesleukin (IL-2), granulocyte macrophage colony stimulating factor (GMCSF) and isotretinoin is standard of care for children with high risk neuroblastoma. Dinutuximab is combined in 5 alternating cycles with

GMCSF or IL2, followed by a 6th cycle with isotretinoin alone. IL-2 is administered as a 96hour continuous infusion on days 0–4 at 3MIU/m2/day followed by a higher infusion dose, 4.5MIU/m2/day, in combination with dinutuximab on days 7–10 of cycles 2 and 4. The 3MIU/m2/day dose may be administered inpatient or in the ambulatory setting.

Objectives: To retrospectively compare the incidence of inpatient and outpatient side effects and complications associated with low dose (3MIU) IL2 to provide the tolerability data necessary to evaluate these venues for future administration options.

Design/Method: This study was a descriptive, single-centered definitive study utilizing a retrospective convenience sample population of children with high risk neuroblastoma who received low dose IL2 either as an inpatient or an outpatient without exclusion from May 2012 to June 2017. Subjects were identified by a tumor registry query post IRB approval. Electronic and paper medical records were reviewed for the dates and location of the infusions, the home health company used if applicable and all documentation regarding clinical status, side effects and toxicity. Demographics was limited to age and gender.

Results: Infusion venue was chosen by provider preference. Twenty-six infusions, 9 inpatient and 17 outpatient via 3 separate home health companies were all administered in entirety and without interruption. There were 10 males and 4 females ranging from 2–7 years of age. Two children received a single outpatient infusion due to intolerance of IL2 when combined with dinutuximab and 2 received therapy in both settings. Fever, 3 inpatient and 1 outpatient was the only common side effect. No source of infection was ever identified. There was one incidence of diarrhea and one patient with pruritus in both the outpatient and inpatient settings respectively. No planned outpatient infusions required subsequent admission however the outpatient fever did necessitate an ER evaluation.

Conclusion: Low dose IL 2 can successfully be administered outpatient. The medication has minimal side effects with fever occurring in 15%, none of which were associated with infection. No outpatient infusion required a subsequent admission. No patients who received cycle 2 infusions outpatient opted to receive the next cycle inpatient.

Poster # 828 | TARGETING INTEGRIN-MEDIATED SIGNALING IN METASTATIC EWING SARCOMA

Jade Wulff, Gargi Ghosal, Ryan Shuck, Lyazat Kurenbekova, Jason Yustein

Baylor College of Medicine, Houston, Texas, United States

Background: Metastatic Ewing sarcoma (ES) has an extremely poor overall survival, necessitating investigations into molecular mechanisms to identify novel targets and develop new therapies. We previously performed an in vivo study, using our mouse model, designed to provide insights into transcriptomic and proteomic signatures for metastatic ES to identify potential therapeutic targets. Comparing profiles of primary tumors to corresponding metastatic lesions, we identified aberrant expression of integrin ß3 (ITGB3) and downstream activation of integrin-linked kinase (ILK) in metastatic lesions compared to primary tumors, implicating this pathway as a key regulator in the ability of ES to establish and enhance metastasis. Our hypothesis is that upregulation of ITGB3 and its downstream signaling events play a key role in ES metastasis and are viable therapeutic targets.

Objectives: To investigate the role of ITGB3 and its downstream signaling pathways in driving the establishment and enhancement of metastasis in ES and to investigate this pathway as a potential therapeutic target.

Design/Method: To investigate the role of ITGB3 and ILK in ES metastasis, we used siRNA to knock down ITGB3 and ILK expression in established ES cell lines and then performed functional assays in vitro, including cell proliferation and invasion/migration assays. We also tested inhibition of this ITGB3 signaling pathway using available small molecule inhibitors targeting ITGB3, ILK and the downstream target AP-1, using Cilengitide, Compound 22 and SR11302, respectively. We are currently using these small molecule inhibitors as treatment in vivo and assessing rates of metastatic tumor formation. We generated stable ITGB3 and ILK overexpression and knockdown cell lines, which we are using for similar in vitro and in vivo investigations.

Results: Knockdown of ITGB3 and ILK in our siRNA cell lines resulted in decreased cell proliferation and decreased invasion and migration compared to controls. We also found significantly decreased cell proliferation using each of the small molecule inhibitors in vitro. Our preliminary studies using Compound 22 in vivo established a safety profile and dose escalation is underway to assess the effectiveness of inhibiting ES metastasis.

Conclusion: These results support our hypothesis that ITGB3 and its downstream signaling events play a key role in the ability of ES to establish metastatic foci and may serve as a potential therapeutic target. We continue to investigate this pathway in vitro. We are also using our small molecule inhibitors and ITGB3 and ILK overexpression and knockdown approaches to study these effects on metastatic tumor development in vivo using our mouse model.

Poster # 829 | THE EPIGENETIC MARKER 5-HYDROXYMETHYLCYTOSINE REVEALS DIFFERENTIAL PROFILES IN LOW-, INTERMEDIATE-, AND HIGH-RISK NEUROBLASTOMA AND IDENTIFIES COPY NUMBER VARIANTS

Erin Barr, Mark Applebaum, Madina Sukhanova, Ji Nie, Helen Salwen, Wei Zhang, Amy Armstrong, Yasmin Gosiengfiao, Chuan He, Susan Cohn

University of Chicago, Chicago, Illinois, United States

Background: Neuroblastoma (NBL) is characterized by phenotypic heterogeneity. Outcome is excellent for patients with low- (LR) and intermediate-risk (IR) disease, whereas only 50% of high-risk (HR) patients will survive. 5-Hydroxymethylcytosine (5hmC) is an epigenetic marker of active gene transcription, and 5hmC profiles are prognostic in many types of adult cancers. We hypothesized that 5hmC profiles will serve as robust biomarkers in children with NBL tumors, refining current risk stratification.

Objectives: Analyze genome-wide 5hmC in NBL tumors and correlate 5hmC deposition with chromosomal copy number and gene expression.

Design/Method: 5hmC was quantified by nano-hmC-Seal-Seq from the DNA extracted from 15 HR, 11 IR and 27 LR NBL tumors. Read counts and clinical data were analyzed with DESeq to identify genes with differential 5hmC patterns between risk groups. Chromosomal copy number was assessed by chromosomal microarray analysis (CMA) in a subset of samples (3LR and 9HR). Expression of genes located on chromosome 1p was evaluated using publically available microarrays (E-MTAB-1781) of 171 HR NBL tumors with known 1p LOH status.

Results: Globally, LR tumors had more 5hmC peaks (140,062) than IR (102,398, $p = 0.36$) tumors, or HR tumors (79,727, $p = 0.01$). 1,049 genes had different patterns of 5hmC deposition in HR versus LR tumors. 315 (30%) of these genes mapped to chromosome 1p and had decreased 5hmC in HR versus LR tumors (padj <0.05). In the CMA analysis 1p deletion was detected in 5 of the 9 tumors tested. In the tumors with 1p loss, 322 genes that map to 1p showed decreased 5hmC deposition compared to the 4 HR tumors without 1p loss ($p<0.05$). Further, compared to the tumors without 1p loss, the expression of 188 of the 322 1p genes was decreased ($p<1 \times 10–5$), including CHD5, CAMTA1, and ARID1A, known and proposed tumor suppressor genes in NBL.

Conclusion: Different patterns of 5hmC accumulation are associated with neuroblastoma risk classification. Nano-hmC-Seal-Seq is sensitive to copy number variations and has the potential to identify these changes in patient tumors. Our results suggest that 5hmC deposition contributes to the silencing of tumor suppressor genes in 1p and may also regulate the transcription of other genes that drive tumor phenotype.

Poster # 830 | COMBINATION THERAPY OF POLYMERIC CHLOROQUINE AND DOXORUBICIN TO TREAT PULMONARY METASTATIC OSTEOSARCOMA

Jordan Fritch, Jing Li, Parker Korbitz, David Oupicky, Daryl Murry, Yasphal Chhonker, James Ford

Colleges of Medicine and Pharmacy, University of Nebraska Medical Center, Fred and Pamela Buffett Cancer Center, Omaha, Nebraska, United States

Background: Metastatic osteosarcoma has a 5-year survival rate of 15–40%. Pulmonary metastases remain a major treatment challenge in osteosarcoma. Current treatment with conventional chemotherapy shows inadequate activity towards metastases and has toxic systemic side effects. Chloroquine is a widely used anti-malarial drug and has been shown to have promising anti-cancer and anti-metastatic activity. Polymeric drugs have been shown to have multiple advantages over their small molecular parent drugs, including enhancing the therapeutic efficacy, an improved pharmacokinetics profile and decreased systemic toxicity. We hypothesized that by developing chloroquine into a polymeric drug and combining it with conventional chemotherapy it will improve the treatment of metastatic osteosarcoma.

Objectives: To identify the optimal combination of polymeric chloroquine (pCQ) with conventional chemotherapy active in osteosarcoma as a new means of treating metastatic disease in a murine osteosarcoma model.

Design/Method: We synthesized and developed pCQ and evaluated its anti-invasive activity using an osteosarcoma cell migration and invasion assay. We evaluated the efficacy of cell killing using combination drug therapies with pCQ and a panel of conventional chemotherapy agents (doxorubicin, docetaxel, cisplatin and paclitaxel) using CellTiter Blue cell viability assay. To develop the murine osteosarcoma model, we intravenously injected luciferase-expressing human osteosarcoma cells 143B into NSG mice. We administered the drug combination that showed the strongest in vitro synergy to the mice and evaluated their anti-cancer and anti-metastatic effects in vivo. Tumor growth and suppression were evaluated using whole body bioluminescence imaging.

Results: We successfully synthesized pCQ that contains 16.7% chloroquine with a molecular weight of 18.9 kD. pCQ was also found to decrease the toxicity of the parent chloroquine. pCQ showed strong inhibition of osteosarcoma cell migration with 51% inhibition compared to 13% by chloroquine. We screened the combination drug therapies and found the combination of pCQ and doxorubicin to show the strongest synergism. The pCQ/doxorubicin combination is currently being evaluated in the murine model.

Conclusion: Combination drug therapy using pCQ and doxorubicin showed synergistic cell killing and inhibition of cell migration in vitro. The combination represents a promising treatment strategy for pulmonary metastatic osteosarcoma.

Poster # 831 | TARGETING THE YES-ASSOCIATED PROTEIN IN NEUROBLASTOMA

Jenny Shim, Kaitlyn Janssen, Amanda Arnold, Yoo Joo Lee, Alexa Fritz, Kelly Goldsmith

Emory University/Children's Healthcare of Atlanta, Atlanta, Georgia, United States

Background: Survival for relapsed high-risk neuroblastoma (rNB) is < 5%, underscoring the critical need for novel therapies. rNBs have increased RAS/RAF/MAPK mutations and increased Yes-associated protein (YAP) transcriptional activity. YAP is a transcriptional co-activator that binds with TEA-Domain (TEAD) transcription factors to regulate cellular proliferation, self-renewal, and survival. We found that shRNA inhibition of YAP decreases NB cell proliferation and sensitizes RAS-mutated NBs to MEK inhibitors, supporting YAP as a tractable therapeutic target. Verteporfin (VP), a photodynamic drug used for macular degeneration, is the only drug found to inhibit YAP expression or YAP:TEAD binding to kill tumor-derived cells. Peptide 17 is a 17mer YAP peptidomimetic that also disrupts YAP:TEAD interactions.

Objectives: We sought to determine whether these compounds are potent in NB via YAP direct effects.

Design/Method: YAP expressing (NLF, SK-N-AS) or YAP null (NGP, LAN5, SK-N-AS-shYAP) human-derived NBs were incubated with VP, with and without direct light exposure, or with Peptide 17. CellTiter-Glo and Immunoblots were used to assess for cell death and YAP-downstream protein expression, respectively.

Results: Without direct light exposure, VP inhibits YAP expression at nM dosing, yet no NB cell death was observed at equal or higher concentrations. EGFR and ERK1/2 were inhibited along with YAP, confirming YAP/RAS pathway co-regulation. When VP was exposed to direct incandescent light for 30 minutes, > 80% NB cell death occurred in all NBs tested, even those lacking YAP. Peptide 17 caused no cell death or YAP inhibition up to 75 uM.

Conclusion: Neuroblastomas are resistant to VP at doses sufficient to inhibit YAP expression. In macular degeneration, light-activated VP produces reactive oxygen species, which we hypothesize is the off target mechanism killing NBs independent of YAP. Given the off target effects and the need for light activation, VP is not an ideal preclinical or clinical YAP inhibitor. Accordingly, Peptide 17 has poor cell permeability and low TEAD affinity, leading to its lack of efficacy. Given the relevance of YAP in rNB and other cancers, we are chemically optimizing a YAP peptidomimetic with enhanced permeability, nuclear localization, and TEAD affinity to create a bonafide YAP inhibitor for preclinical and clinical application.

Poster # 832 | CHARACTERIZATION OF LOCALIZED OSTEOSARCOMA OF THE EXTREMITY IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS FROM SOUTH TEXAS: INCREASING INSIGHT INTO HISPANIC POPULATIONS

Kayeleigh Higgerson, Aaron Sugalski, Rajiv Rajani, Josefine Heim-Hall, Jaclyn Hung, Anne-Marie Langevin

UT Health San Antonio, San Antonio, Texas, United States

Background: Osteosarcoma is the most common bone malignancy in children, adolescents, and young adults. Most study cohorts have 10 to 15% Hispanic patients that encompass many different Hispanic backgrounds. The University of Texas Health Science Center at San Antonio (UTHSCSA) Sarcoma Team serves a Latino population that is predominantly Mexican American, thus providing a unique opportunity for evaluation this population. This study expands on previous data collected from January 2000 to December 2010 from the same institution, providing increased insight into outcomes of Mexican American children, adolescents, and young adults with osteosarcoma.

Objectives: To further understanding of osteosarcoma in Latino children, adolescents and young adults.

Design/Method: A retrospective analysis of demographics, tumor characteristics, response to treatment, and survival outcome of all localized osteosarcoma of the extremity patients below 30 years of age diagnosed and treated by the UTHSCSA Sarcoma Team between January 2000 and June 2017 was performed.

Results: In our original cohort from January 2000 to December 2010, we observed a significantly decreased 5-year event-free survival (EFS) in patients diagnosed before age 12 (preadolescent) relative to patients diagnosed between ages 12 and 29 (11% vs. 57%, P<0.001). Patients had a 5-year overall survival (OS) and event-free survival of 65% and 48% respectively. In our expanded cohort from January 2000 to June 2017 we evaluated sixty-six patients with a median age of 14 (range, 2 to 28 y) with localized high-grade osteosarcoma of the extremity. The expanded cohort was 68% Mexican American, with a median follow-up of 59 months (range, 5 to 192). The analysis of our expanded cohort is ongoing and we postulate that the findings will hold true, as we increase the cohort size and length of follow-up.

Conclusion: Analysis of our previous cohort, predominantly of Mexican American ethnicity, showed that preadolescent patients had an increased rate of relapse when compared with previous large studies. We also showed a trend towards decreased EFS for the entire cohort. We hypothesize that we will further validate these findings with this expanded cohort and this will support further investigation into potential causes of poor outcome in this vulnerable Latino population.

Poster # 833 | WATCH AND SEE STRATEGY IN SELECTED NEUROBLASTOMA CASE SCENARIOS; SUCCESS AND LIMITATIONS

Mohamed Fawzy, Hossam Hossam El Zomor, Salma El-Menawi, Naglaa El-kinaai, gehad taha, Amal Refaat, Mai Amr, Mohamed Zaghloul

National Cancer Institute and Children's Cancer Hospital-Egypt (CCHE), Fomelkhalig Square, Cairo, Egypt

Background: Neuroblastoma in infants has the potential to regress or mature spontaneously. Growing literature showed that some cases subjected to initial observation didn't show inferior outcome compared to actively treated similar categories.

Objectives: We investigated whether early active treatment can be safely avoided/deferred in selected favorable cases at the Children's Cancer Hospital-Egypt (CCHE).

Design/Method: Patients enrolled on the Watch and See strategy (W&S) at CCHE had small primary tumor; INSS stage 1–2, uncomplicated stage 4s or stage 3 infants (< 365 days). Tissue biopsy was not mandatory for infants below 6 months of age with localized adrenal mass (stage 1–2). On progression, immediate intervention took place according to stage and risk of disease after biological characterization.

Results: Thirty four NBL patients were enrolled on W&S strategy; M/F:2.4/1. Eighteen patients had stage 4s disease, 12 patients had stage 1–2 and 4 were stage 3. Primary adrenal site was reported in 29 patients (85.3%), 21 patients (61.77%) had small mass measuring ≤5 cm in its largest diameter. The 5-year OS & EFS were 88.2±8.8% and 72.5±9%, respectively, with 43 months median follow-up (range: 1–106 months). Spontaneous total/near total resolution of mass occurred in 16/34 patients (47%). Median time to eliciting regression was 1.7 months (range: 0.4-14.7 months), and 20.7 months (range: 7–63 months) till complete resolution. Only 8/34 patients (23.5%) witnessed progression (2 local, 2 distant and 4 combined local and distant progression); median time to progression was 8 months (range: 1–32 months) with 2/8 deaths after starting chemotherapy.

Conclusion: Watch and See strategy is a safe approach in localized and uncomplicated stage 4s neuroblastoma. Progressive cases could be rescued.

Poster # 834 | UTILITY OF GALLIUM 68 DOTATATE PET/CT SCAN IN PEDIATRIC NEUROENDOCRINE TUMORS: A REPORT FROM TEXAS CHILDREN'S RARE TUMOR REGISTRY

Priya Mahajan, Andrew Sher, Victor Seghers, Rajkumar Venkatramani

Baylor College of Medicine, Houston, Texas, United States

Background: Ga-68 dotatate binds to somatostatin receptor 2 expressed in neuroendocrine tumors (NETs). It was approved by FDA in 2016 for use with PET/CT scan for localization of somatostatin receptor positive NETs in adult and pediatric patients. Pediatric approval was based mainly on extrapolation of data from adults.

Objectives: To describe the use of Ga-68 dotatate PET/CT scan in children with neuroendocrine tumors and compare with other imaging modalities.

Design/Method: Patients with NETs enrolled in Texas Children's Rare Tumor Registry between February and October 2017 were reviewed and those patients who underwent Ga-68 scan were included.

Results: Four patients with NETs underwent Ga-68 scans without any adverse reactions. First patient was a 15-year-old female with small bowel NET with multiple liver metastases. MRI abdomen and FDG PET at diagnosis showed

multiple liver metastases but could not identify the primary lesion. Ga-68 scan was able to accurately identify the enlarged lymph nodes in the small bowel and was better than FDG PET in delineating the liver metastases. Second patient was a 13-year-old female with recurrent small bowel NET with liver, lung and paraspinal metastases. The lesions were initially detected by CT scan. Octreotide scan failed to show any uptake in the identified lesions while Ga-68 was taken up by the liver lesions, lung lesions >1 cm in size and the paraspinal lesion. Third patient is an 8-year-old male with pancreatic NET with peripancreatic lymphadenopathy, multiple liver metastases and cardiophrenic lymph node involvement. The primary lesion in the pancreas could not be identified by CT scan, CT angiogram, MIBG scan, or octreotide scan. In addition, there was uncertainty about involvement of the enlarged cardiophrenic lymph node. In addition to clearly identifying the primary lesion, Ga-68 scan was able to detect multiple peripancreatic lymph nodes not detected by other scans and revealed uptake in the cardiophrenic lymph node confirming its involvement by the tumor. Fourth patient is a 15-year-old female with malignant abdominal paraganglioma with solitary lung metastasis. Both MIBG scan and Ga-68 scan were able to identify the primary lesion. Ga-68 scan was performed after the lung metastasis was removed and thus its ability to detect it could not be confirmed.

Conclusion: Ga-68 dotatate PET/CT scan seem to be more sensitive in identifying lesions in children with NETs. Patients with refractory disease whose lesions take up Ga-68 may be candidates for lutetium [177Lu] oxodotreotide therapy.

Poster # 835 | FACTORS IMPACTING TIME TO ENGRAFTMENT IN PATIENTS WITH HIGH-RISK NEUROBLASTOMA FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANT

Kirsty Hillier, Jennifer Foster, W. Cheng

Texas Children's Hospital/Baylor College of Medicine, Houston, Texas, United States

Background: Neuroblastoma is the most common extracranial solid tumor of childhood, with overall survival for high-risk patients (HRNBL) near 50%. The outcomes of HRNBL have improved with high dose chemotherapy followed by autologous stem cell rescue (ABMT). Data about factors influencing the rate of hematopoietic recovery following ABMT in HRNBL is lacking in the literature.

Objectives: Our objective was to identify factors influencing the rate of hematopoietic recovery following ABMT in HRNBL.

Design/Method: This was a retrospective chart review of 55 patients with HRNBL treated at Texas Children's Hospital from 2006 to 2016. Neutrophil engraftment was considered the first of three consecutive days with post-transplant neutrophil count greater than 500 cells/uL. Red blood cell and platelet engraftment were considered at a hemoglobin greater than 8g/dL and platelets greater than 20,000/uL three days after the last transfusion. Race and conditioning regimen were analyzed using one-way ANOVA; amount of infused cells was analyzed using Pearson correlation coefficients; chemotherapy delay and bone marrow (BM) involvement after cycle 2 of induction chemotherapy were analyzed using independent sample t-tests.

Results: The study included 32 males and 23 females with a median age at diagnosis of 2.5 years. Thirty-eight patients were Caucasian, 6 African-American, 5 Hispanic, 2 Asian, and 4 did not have race documented. The mean dose of infused CD34+ cells was 3.36 × 10^8 cells/kg. Forty-five patients received conditioning therapy with carboplatin/etoposide/melphalan (CEM), 8 received busulfan/melphalan (Bu/Mel), and 2 received thiotepa/cyclophosphamide (thiotepa/CPM). The conditioning regimen administered was significant ($p = 0.037$) for time to engraftment of neutrophils, with Bu/Mel at 16.6 days, CEM at 12.1 days, and thiotepa/CPM at 10 days. A delay of chemotherapy during induction ($n = 25$) was significant ($p = 0.001$) for time to platelet engraftment of greater than 75,000/uL and trended towards significance ($p = 0.088$) for time to neutrophil engraftment. BM involvement at diagnosis and after cycle 2 of induction was not significant for time to engraftment. Dose of stem cells infused was the only variable significant for hemoglobin engraftment.

Conclusion: We found multiple factors that significantly impact time to engraftment for patients with HRNBL undergoing ABMT. Knowing the barriers for timely engraftment may help develop interventions and expectations for future patients.

Poster # 836 | TARGETING VCAM-1/$\alpha 4\beta 1$ SIGNALING TO AMELIORATE PULMONARY METASTATIC OSTEOSARCOMA

Kristen VanHeyst, Li-Xin Wang, Jay T. Myers, Laura Menocal, Hannah Miller, Francesca Scrimieri, Alex Huang

Division of Pediatric Hematology-Oncology, Department of Pediatrics, Case Western Reserve University School of Medicine, Angie Fowler AYA

Cancer Institute, University Hospitals Rainbow Babies & Children's Hospital, Cleveland, Ohio, United States

Background: Osteosarcoma (OS) is the most prevalent aggressive primary malignancy of the bone affecting children and young adults. Approximately 10% to 20% of patients have metastatic disease at initial presentation, and 61% of those patients have isolated pulmonary metastases. Although overall survival in patients with OS has improved with advances in therapy, there have been no significant improvements in survival outcome in patients with metastatic disease. Recent studies suggest that tumor-associated Vascular Cell Adhesion Molecule 1 (tVCAM-1 or CD106) plays a critical role in the metastatic progression of various tumors. Indirect evidence from these studies suggest that VCAM-1/$\alpha 4\beta 1$ integrin signaling promotes tumor survival and metastatic progression by changing the tumor niche and associated immune response.

Objectives: To determine if interfering VCAM-1/$\alpha 4\beta 1$ signaling between pulmonary metastatic osteosarcoma (pOS) and macrophages (MACs) by down-regulating VCAM-1, depleting MACs or blocking VCAM-1/$\alpha 4\beta 1$ signaling will reduce pOS and improve overall disease-free survival.

Design/Method: We used a pair of spontaneous, high-grade murine OS cell lines from Balb/c mouse (H-2d), K7 and K7M2 (derived from in vivo K7 metastasis). We used lentiviral shRNAs to knockdown VCAM-1 mRNA and protein expression in K7M2 (VCAM-1kd). We introduced luciferase into K7, K7M2 and various K7M2 shRNA cell lines to follow lung metastasis by bioluminescence (BLI). We depleted MACs by intranasal administration of liposomal clodronate formulation. We tested the ability of K7 and K7M2 supernatants to polarize M0 MACs into M1 or M2 phenotype in vitro. We also administered anti-$\alpha 4$ monoclonal antibody (anti-$\alpha 4$ mAb) intranasally to assess the outcome of functional blockade of VCAM-1/$\alpha 4\beta 1$ signaling.

Results: K7M2 over-expressed VCAM-1 compared to K7. MAC depletion in K7M2-bearing animals exhibited reduced pOS. Weekly administration of anti-$\alpha 4$ mAb resulted in 80% tumor-free rescue among mice with established K7M2 pOS. Interestingly, supernatant from K7M2 but not K7 preferentially induced M2-like MACs, suggesting a novel integrin-mediated mechanism of M2 differentiation. Validation data with additional OS cell lines will be presented.

Conclusion: Despite aggressive multimodal therapy, overall outcome for patients with pOS remains dismal at 25–30%. For this reason, novel and directed therapy approaches are desperately needed. Molecular targeted approaches for therapy are challenging, due to the complex genetic heterogeneity of OS. Immune-modifying therapy is a promising new alternative approach for pOS.

Poster # 837 | PROGNOSTIC SIGNIFICANCE OF METASTATIC MIBG-POSITIVE DISEASE SITES AT DIAGNOSIS IN HIGH-RISK NEUROBLASTOMA PATIENTS

Elizabeth Sokol, Jenna Rossoff, Yasmin Gosiengfiao, Susan Cohn

University of Chicago, Chicago, Illinois, United States

Background: Only half of all patients diagnosed with high-risk neuroblastoma achieve long-term survival. 123I-metaiodobenzylguanidine (MIBG) scans are routinely used to evaluate disease at diagnosis and following treatment, and the extent of disease is quantified using the Curie scoring system. A previous study by Yanik et al., has shown that for high-risk patients with MYCN non-ampliified tumors, scores less than versus greater than 2 following 6 cycles chemotherapy are associated of superior survival, whereas scores less than versus greater than 0 were prognostic in patients with MYCN-amplified tumors. However, the prognostic significance of specific sites of metastatic disease at diagnosis is not known.

Objectives: To determine if site of metastatic disease determined by 123I-metaiodobenzylguanidine (MIBG) imaging in high-risk patients at the time of diagnosis was associated with outcome

Design/Method: We performed a retrospective chart review of high-risk neuroblastoma patients treated at Comer Children's Hospital and Lurie Children's Hospital in Chicago between 2006 and 2017 with positive MIBG scans at the time of diagnosis. We collected imaging data as well as other clinical data including bone marrow status. Sites of disease were defined as Curie regions with any positive value. Kaplan-Meier analysis was performed to evaluate the association with disease sites and survival. Pearson correlation coefficients were calculated to compare bone marrow disease to sites of positivity on MIBG scan.

Results: The cohort consisted of 49 high-risk patients. 31 had skull disease, and 30 had pelvic disease. The presence of MIBG positive disease in the skull and in the pelvis trended toward worse EFS. EFS at 3 years for patients with disease in the skull at diagnosis was $52 \pm 10\%$ and for patients without skull disease was 78 ± 10 % ($p = 0.16$). EFS at 3 years for patients with and without pelvic disease was $49 \pm 10\%$ and $80 \pm 9\%$ ($p = 0.10$). Consistent with prior data, we found that the presence of bone marrow disease was associated with worse survival with 3 year EFS of $47 \pm 10\%$ and $88 \pm 8\%$ with and without marrow disease at diagnosis ($p = 0.02$). There is the highest correlation between pelvic disease on MIBG scan and bone marrow disease with Pearson coefficient 0.79. Pelvic

disease noted on MIBG scan likely reflects underlying bone marrow disease.

Conclusion: In patients with high-risk neuroblastoma, skull disease and pelvic disease on MIBG scan at diagnosis may predict worse event free survival.

Poster # 838 | INCREASED ANTITUMOR EFFICACY OF PD-1 BLOCKADE COMBINED WITH ONCOLYTIC HERPES VIROTHERAPY IN MURINE OSTEOSARCOMA IS DUE TO INCREASED CD8+/TREG RATIO

Mary Frances Wedekind, Chun-Yu Chen, Pin Yi Wang, Joe Conner, Timothy Cripe

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: Osteosarcoma is one of the deadliest cancers in the pediatric population with little progress in morbidity and recurrence rates since the 1980's. Oncolytic Herpes Simplex-1 virus (oHSV) is an attenuated virus that has shown encouraging results against certain solid tumors. Programmed cell death protein (PD)-1-mediated T cell suppression via engagement of its ligand, PD-L1, is also of particular interest due to recent successes in selected cancers, especially those with high genetic mutational loads. Most pediatric cancers do not have a wide variety of mutations; however, osteosarcoma has a chaotic genome, prone to genetic mutations. It has been shown through numerous other studies that PD-1 inhibition alone is not sufficient to result in statistically significant tumor growth delays in osteosarcoma models and patients. We hypothesize the addition of oHSV therapy as an immunologic stimulus to PD-1 inhibition is efficacious for osteosarcoma.

Objectives: (1) To determine whether oHSV therapy enhances response to PD-1 inhibition in immunocompetent murine models of osteosarcoma and (2) to quantify and characterize the anti-tumor T-cells infiltration after treatment with oHSV and PD-1 inhibition individually and in combination.

Design/Method: We utilized an immunocompetent transplantable murine model using a cell line derived from a spontaneous metastatic osteosarcoma (K7M2, Balb/C background). We transplanted established tumor wedges subcutaneously and monitored tumor volume by caliper measurement. Once tumors reached 200–400mm3, we administered intratumoral injections of HSV1716 (1×108 plaque-forming units) every other day for a total of 3 injections. We then gave intraperitoneal injections of 250ug anti-PD-1 or control antibody twice weekly, up to 4 weeks, starting from the last dose of virus treatment. We monitored tumor growth via calipers twice weekly until tumors reached 2500mm3 or 2cm diameter. We quantified and characterized innate and adaptive immune cell infiltrates in tumors using flow analysis.

Results: We found significantly prolonged survival with our combination therapy group compared to all other groups. We found that anti-PD-1 by itself had little impact on T cell recruitment while the combination group had higher influx of CD8+ cells with a reduced amount of T-regulatory cells (CD4+Foxp3+CD25+). We also found an increase in CD44+ effector memory cells.

Conclusion: Osteosarcoma is a deadly cancer with therapeutics remaining unchanged for the last 30 years. Here, we describe prolonged murine survival after treatment with combination of PD-1 inhibition and oHSV injection. The combination treatment changed the microenvironment to be more inflammatory. Our data support further preclinical and clinical studies.

Poster # 839 | B7-H3 CAR T CELLS MEDIATE IN VITRO AND IN VIVO ACTIVITY AGAINST NEUROBLASTOMA XENOGRAFTS

Meena Kadapakkam, Robbie Majzner, Peng Xu, Crystal Mackall

Stanford University School of Medicine, Palo Alto, California, United States

Background: Neuroblastoma is the second most common cause of cancer related death in children. Treatment for high-risk neuroblastoma has improved significantly over the past twenty years, however cure rates remain below 50%. Immunotherapy has emerged as an effective therapy for neuroblastoma, however new modalities and targets are needed to improve outcomes.

Objectives: Our lab has developed a chimeric antigen receptor (CAR) that targets B7-H3 (CD276), an immune checkpoint molecule overexpressed on many cancers, including neuroblastoma. We hypothesized that B7-H3 would be a good target for CAR based immunotherapy for neuroblastoma.

Design/Method: Neuroblastoma tissue microarrays of primary patient samples were screened for B7-H3 expression by immunohistochemistry and cell lines were screened using flow cytometry. B7-H3 CAR T cells were tested in vitro by measuring tumor cell killing and cytokine production after coculture with tumor cell lines and in vivo in an orthotopic model of neuroblastoma.

Results: B7-H3 expression was detected by IHC on 82% of the 186 screened neuroblastoma patient samples. B7-H3 was expressed at high levels (2+ or 3+) in more than half of these samples (56%). Almost all cell lines screened were homogeneously positive for B7-H3 by flow cytometry. Retrovirally transduced B7-H3.4-1BB.ζ CAR T cells were co-cultured with three B7-H3 positive neuroblastoma cell lines (SK-N-BE2, KCNR, and CHLA255) and robust tumor cell killing was demonstrated using an IncuCyte assay. Supernatant from the co-cultures was harvested after 24 hours and both interferon gamma and IL-2 production were detected by ELISA.In an orthotopic subrenal capsule xenograft model of neuroblastoma, mice treated with B7-H3 CAR T cells show significant reductions in tumor growth and prolonged survival compared to those treated with untransduced control T cells. However, the treatment is not always curative.B7-H3 CAR T cells express high levels of exhaustion markers (PD1, TIM3, and LAG3) when compared to CD19 CAR controls. In order to overcome inhibition from exhaustion, B7-H3 CAR T cells were co-cultured with neuroblastoma cell lines and PD-1 blocking antibody. Nivolumab significantly increased the production of IL-2 and interferon-gamma by B7-H3 CAR T cells. Further studies are underway to determine if B7-H3 CAR T cell activity is enhanced in vivo by treating animals with PD-1 blockade along with CAR T cells.

Conclusion: B7-H3 is expressed on a majority of neuroblastoma samples and appears to be a promising candidate for CAR T cell therapy. B7-H3 CAR T cells demonstrate activity against neuroblastoma xenografts that may be enhanced by the addition of PD1 inhibitors.

Poster # 840 | POLYAMINE BIOSYNTHETIC PATHWAY AS A DRUG TARGET FOR OSTEOSARCOMA THERAPY

Rebecca Weicht, Chad Schultz, Andre Bachmann

Helen DeVos Children's Hospital, Michigan State University, Grand Rapids, Michigan, United States

Background: Osteosarcoma is the most common bone tumor in children. It is often metastatic at diagnosis and in this scenario less than 30% of children survive. Polyamines, small molecules found in all cells, are involved in many cell processes including cell cycle regulation, immune modulation, cell signaling and apoptosis. They are also involved in tumor development, invasion and metastasis. In neuroblastoma, inhibition of the polyamine biosynthesis pathway with ODC inhibitor alpha-difluoromethylornithine (DFMO) results in decreased cell proliferation and differentiation. These finding have led to multiple phase I and phase 2 II multicenter clinical trials in pediatric neuroblastoma patients. DFMO is an attractive drug as it is oral, well-tolerated, can be given for prolonged periods and is already used in pediatric patients. The polyamine pathway has not been evaluated in osteosarcoma.

Objectives: Evaluate effect of inhibition of polyamine biosynthesis with DFMO on osteosarcoma proliferation and cell differentiation.

Design/Method: Up to three osteosarcoma cell lines were used: MG-63, U-2 OS and Saos-2. Cells were exposed to 5 mM DFMO for 6 days with replacement of media and DFMO on day 3. Intracellular polyamine levels were measured by High Performance Liquid Chromatography (HPLC). Cell numbers were obtained with a hemocytometer using trypan blue. Flow cytometry cell cycle distribution (FACS) and propidium iodide were used to evaluate for cell cycle arrest. The protein expression of several osteosarcoma differentiation markers was measured by SDS-PAGE and Western blot using differentiation specific antibodies. A bioluminescent cell viability assay was used to measure cell recovery over several days after DFMO was removed and replaced with standard media.

Results: DFMO exposure resulted in significantly decreased cell proliferation in all cell lines. After treatment, intracellular spermidine levels were nearly eliminated in all cells. Cell cycle arrest at G2 was observed in U-2 OS. Cell differentiation was most pronounced in MG-63 and U-2 OS cells as determined by increased osteopontin levels. Remarkably, cell proliferation continued to be suppressed for several days after removal of DFMO.

Conclusion: Based on our findings DFMO is a promising new adjunct to the current osteosarcoma therapy for high risk patients. It is a well-tolerated oral drug that is currently in phase II clinical trials in pediatric neuroblastoma patients as a maintenance therapy. The same type of regimen may also improve outcomes in metastatic or recurrent osteosarcoma patients for whom there have been essentially no medical advances in the last 30 years.

Poster # 842 | THE EWS-FLI1 ONCOPROTEIN LEVEL MODULATES CXCR4/CXCR7-NF-KB SIGNALING IN EWING SARCOMA

Kelly Bailey, Claire Coogan, Elizabeth Lawlor, Peter Lucas, Linda McAllister-Lucas

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States

Background: Recent studies demonstrate that lower levels of the EWS-FLI1 fusion oncoprotein are associated with enhanced metastatic capability in Ewing sarcoma. The NF-kB transcription factor is a critical mediator of CXCR4 and CXCR7 –driven metastasis in multiple cancers, and increased CXCR4 and CXCR7 expression have each been associated with increased metastasis and poor prognosis in Ewing sarcoma. We thus sought to investigate the impact of EWS-FLI1 on CXCR4/CXCR7-dependent NF-kB signaling in Ewing Sarcoma.

Objectives: The goals of this study are 1) to determine the impact of CXCR4/CXCR7 signaling on metastasis-associated NF-kB target gene expression in Ewing sarcoma and then 2) to investigate how the EWS-FLI1 fusion oncoprotein modulates this response .

Design/Method: We utilized multiple Ewing Sarcoma cells lines including A673, CHLA9, CHLA10, TC32 and TC71. CXCR4/CXCR7 cell surface expression was determined by flow cytometry. EWS-FLI1 level was modulated using siRNA and expression levels were confirmed by western blot and RT-PCR. p65 DNA binding was measured via ELISA. NF-kB target gene expression was assessed via RT-PCR.

Results: Consistent with IHC analysis of primary and metastatic patient tumor samples, the paired primary and metastatic Ewing sarcoma cell lines CHLA9 and CHLA10 showed dramatic differences in CXCR4 and CXCR7 expression, with the metastatic CHLA10 line demonstrating much higher expression of both receptors. Other cell lines (non-paired) showed variable CXCR4/CXCR7 expression. Genetic knock-out of CXCR4 lead to significant decrease in expression of both CXCL12/SDF-1 and IL-6, two NF-kB transcriptional targets known to play a key role in tumor metastasis. Knock-out of CXCR4 did not alter endogenous EWS-FLI1 mRNA levels. Conversely, lowering the level of EWS-FLI1 using siRNA lead to enhanced NF-kB signaling, indicated by an increase in p65 DNA binding. Consistent with this observation, treating Ewing cell lines with EWS-FLI1 siRNA also resulted in significantly increased NF-kB target gene expression compared to control cells and target gene expression was then further enhanced upon CXCR4/CXCR7 receptor stimulation with the receptor ligand CXCL12/SDF-1.

Conclusion: Our findings indicate that the EWS-FLI1 oncoprotein negatively modulates CXCR4/CXCR7-dependent NF-kB signaling. This suggests that EWS-FLI1 low, CXCR4/CXCR7 high cells, which are associated with enhanced metastasis and poor prognosis, would be anticipated to exhibit enhanced expression of key NF-kB target genes. Importantly, the NF-kB pathway is a druggable target that could potentially serve as an "Achilles heel" in this subset of high risk tumors. Current work is evaluating NF-kB inhibition as an approach to treating metastatic and refractory Ewing Sarcoma.

Poster # 901/Early Career Travel Stipend Award Recipient | PANETH CELL COUNTS INDEPENDENTLY PREDICT ACUTE GASTROINTESTINAL GVHD STAGE AND RESPONSE TO THERAPY

Zach Leblanc, Bahig Shehata, Scott Gillespie, Alton Farris, Benjamin Watkins, John Horan, Muna Qayed

Emory University, Atlanta, Georgia, United States

Background: Acute graft versus host disease (aGVHD) is a major cause of morbidity and mortality following allogeneic bone marrow transplant (BMT) in pediatric patients. Gastrointestinal (GI) aGVHD is the most serious manifestation. Recently, decreased Paneth cell (PC) in a predominantly adult cohort was shown to correlate with aGVHD clinical grading and response to treatment.

Objectives: We aim to demonstrate the relationship between PC counts and GI aGVHD stage and response to therapy.

Design/Method: Charts of patients who underwent endoscopy following BMT between 2004–2014 were reviewed. For repeated biopsies during the course of aGVHD, only the first was included for analysis. One pathologist retrospectively reviewed the biopsies and counted PCs in 3 high powered fields; the average PC count was analyzed. Twenty-six percent of biopsies were reviewed by a second blinded pathologist. Statistical associations between PC counts and day 28 (d28) response, aGVHD stage, and other study covariates of interest were gauged using general linear regression. Agreement in pathologist PC counts was quantified by intraclass correlation (ICC). The research was approved by the Children's Healthcare of Atlanta IRB.

Results: Seventy-eight biopsies were included in the analysis. Mean age at transplant was 10.5 years ± 5.8 (range: 2 months - 20 years). Most patients underwent transplant for hematologic malignancies (63, 74%). The majority of transplants used a matched unrelated donor graft – including cords (59, 69%) and myeloablative conditioning regimens (71, 82%) – 52% received total body irradiation. Of these, 64% were diagnosed clinically with GI aGVHD (Stage 1, 42%; Stage 2, 14%; Stage 3, 22%; Stage 4, 22%). ICC showed good agreement (0.833) between the pathologists. Mean PC was 16.8 for patients with no gut aGVHD, 21.3 for stage 1, 22.9 for stage 2, 9.4 for stage 3 and 5.9 for stage 4 ($p = 0.001$). On multivariate analysis PC was strongly associated with GI aGVHD stage ($p<0.001$) after controlling for age, preparative regimen intensity, and diagnosis (malignant vs. non-malignant). Mean PC counts were significantly lower in patients with no response to steroid therapy at d28 (complete response (mean 17.8) vs. persistent disease (4.2) vs. partial response (4.5) ($p = 0.001$)).

Patients diagnosed with GI aGVHD with PC counts less than 10 had a higher risk of mortality (HR 3.1, 95% CI: 1.17, 8.09; p = 0.023).

Conclusion: Lower PC count correlated with stage 4 GI aGVHD, refractory disease at d28, and mortality. Incorporating PC count in pathology review during GI aGVHD work-up may help in aGVHD risk stratification.

Poster # 902 | DIFFERING INCIDENCE AND PATTENRS OF CLOSTRIDIUM DIFFICILE INFECTION AMONG PEDIATRIC HEMATOLOGY, ONCOLOGY, AND HEMATOPOIETIC STEM CELL TRANSPLANTATION INPATIENT POPULATIONS

Tristan Knight, Jessica Spruit, Colleen Sweeney, Hossein Salimnia, Lynn Semproch, Basim Asmar, Sureyya Savasan

Children's Hospital of Michigan, Detroit, Michigan, United States

Background: There have been increasing discussions pressuring health care teams and institutions for potentially bearing the cost of Clostridium difficile infections (CDI) as a health care-associated infection in the recent years. The pediatric oncology patient population, though small, accounts for significant portion of all CDI with 10-15-fold increased risk. Hematopoietic stem cell transplant (HSCT) recipients constitute a unique subset with distinct risk factors, such as severe immune deficiency state and graft versus host disease (GvHD). Although there is ample data on CDI in adult HSCT recipients, reports on pediatric experience are limited.

Objectives: To evaluate the incidence and patterns of CDI among pediatric hematology, oncology and HSCT inpatients at our institution.

Design/Method: A retrospective review of all Clostridium difficile (CD) stool tests performed using toxin enzyme immunoassay and later, polymerase chain reaction targeting toxin genes between 2007 and 2017 in a large, urban academic children's hospital was performed. The data were analyzed for hematology, oncology, HSCT inpatient population and all the other cases separately and statistical comparisons were performed.

Results: A total of 5271 samples were submitted to the microbiology laboratory for CD testing during the study period. While hematology patients constituted 1.7%, oncology 5.9%, HSCT 2.0% and others 90.4% of the cases on whom CD testing was done; per patient average test number was 2.0, 2.8, 6.2, and 1.5, respectively. Of all the CD tests performed, 15.6% were positive. Test positivity was higher in HSCT (47.6%) and oncology (42.4%) cases tested compared with hematology (21.2%) and other cases (17.1%) with statistical significance (P<0.001). Overall recurrence rate was 4.3%; HSCT patients had the highest recurrence with a rate of 27% followed by oncology (13.6%), hematology (7.7%) and other (3.2%) cases, again reaching statistical significance (P<0.001). Again, HSCT patients had the highest average number of recurrences at 3.1 (2-6) followed by oncology 2.8 (2-10), general 2.52 (2-6) and hematology 2.25 (2-3) groups. There was no seasonal variability in the incidence of CDI among populations analyzed.

Conclusion: Prolonged hospital stay/antibiotic use and persistent diarrhea due to GvHD are the likely reasons for higher rate of CD testing in HSCT as a result of increased monitoring and thus might have even caused underrepresentation of positive CD test frequency. Higher incidence and frequencies of recurrence underscores the inevitable nature of CDI in HSCT population as a consequence of the current therapies and may lead to future radical treatment approaches like fecal implantation.

Poster # 903 | BUILDING A THIRD-PARTY VST BANK FROM SCRATCH- THE CINCINNATI EXPERIENCE

Adam Nelson, Daria Heyenbruch, Angela Damen, Nan Gong, Katie Maurer, Xiang Zhu, Jamie Wilhelm, Danielle Fohl, Christine Sper, Angela Bonavita, Stella Davies, Carolyn Lutzko, Catherine Bollard, Patrick Hanley, Thomas Leemhuis, Michael Grimley

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Viral infections remain a challenge to treat post HCT in children, and significantly contribute to morbidity and mortality. Virus specific T cells (VSTs) have shown tremendous clinical efficacy in treating viral infections post-HCT, with minimal toxicity and long term efficacy. We have used donor-derived VSTs in individual patients, however not all donors are agreeable to the process, and numerous patients may benefit from VSTs who do not have an identified donor/have other disease indications

Objectives: We sought to actively build a third-party VST bank, for "off the shelf" use in eligible patients.

Design/Method: VSTs targeting CMV, adenovirus and EBV were manufactured using one of 2 techniques. Initially EBV transformed B cells were genetically modified with an Ad5f35pp65 vector and used as antigen presenting cells (APC) to stimulate and expand EBV, Ad and CMVpp65 specific T cells. More recently, VSTs were expanded using

APC pulsed with commercially available peptide pools (PepMixes) to expand EBV/CMV/Ad specific T cells. Products were entered into the "bank" via two mechanisms: a) left over products from our "donor-derived" protocol when patients no longer required VSTs or were not at risk of developing viral infections, or b) by targeting regular blood donors based on their HLA typing to ensure an appropriate mix of high frequency HLA types for optimal patient matching and antigen presentation based on current knowledge of antigen presentation.

Results: A total of 30 products are currently in the third-party VST bank ready for use. Twenty seven of these are from our donor derived protocol, and three from targeted donors. All VST products met safety and in vitro efficacy testing. Thirteen VST infusions have been given to 7 patients. Eleven infusions have been given for CMV and two for adenovirus. Five out of seven patients responded to third-party VST infusions, with a median of 2 VST infusions per patient (range 1–4). The median HLA matching was 2 out of 10 per patient (range 1 to 4) No patients experienced adverse reactions, GVHD or other toxicity related to the VST infusion.

Conclusion: A third-party VST bank is feasible and produces clinically appropriate VSTs for use in patients with viral infections. HLA typing and matching of VST products is essential to reduce toxicity and promote appropriate antigen presentation and expansion of VSTs in vivo. Further work is underway to further characterize the VSTs using epitope mapping to better define the HLA restriction and immunogenicity of each VST product.

Poster # 904 | SUCCESSFUL USE OF BASILIXIMAB IN THE TREATMENT OF STEROID REFRACTORY GRAFT VERSUS HOST DISEASE IN A TWO YEAR OLD FOLLOWING ALLOGENEIC BONE MARROW TRANSPLANT

Erin Wright, Courtney Culbertson, Vanisha Patel, Prasad Bodas

Akron Children's Hospital, Akron, Ohio, United States

Background: Acute Graft-Versus-Host Disease (aGVHD) is a well-known complication of hematopoietic stem cell transplant (HSCT) and a major cause of post-transplant related morbidity and mortality. First line therapy of aGVHD involves corticosteroids and calcineurin inhibition. In patients with severe refractory GVHD, mortality can reach up to 90%. Currently, there is no standard of care for the treatment of steroid refractory aGVHD. Many centers have looked at the use of antibody mediated control of aGVHD to competitively inhibit the inflammatory cascade. Basiliximab, a chimeric monoclonal antibody against the T-cell IL-2 receptor, has been used in adults with steroid refractory aGVHD. Patients receiving this medication have demonstrated complete and partial responses to therapy with minimal toxicities.

Objectives: Report the successful use of Basiliximab in the treatment of aGVHD in a 2- year-old following matched unrelated (MUD) HSCT.

Design/Method: A 2-year-old male underwent MUD transplant for high risk AML with monosomy 7. Conditioning regimen included Busulfan, Fludarabine and equine ATG. His clinical course was complicated by fever, mucositis and aGVHD (stage 3 skin; stage 1 GI-biopsy proven). GVHD prophylaxis included tacrolimus and methotrexate, however with progressive skin rash, diarrhea, and early satiety, GVHD treatment with corticosteroids was initiated. As the patient continued to have worsening symptoms, Basiliximab therapy was started. The patient received 2 doses (10mg) IV Basiliximab on two consecutive days and then received weekly therapy for a total of 4 doses leading to initial improvement. The patient further developed acute on chronic GVHD on Day +100, and subsequently received a second course of Basiliximab.

Results: After initial administration of Basiliximab, the patient had near complete resolution of symptoms. However, with a small wean in his tacrolimus dose, the patient experienced another skin GVHD flare prompting the second Basiliximab course. The patient was subsequently weaned off all immunosuppression by Day +376. The only acute complication the patient experienced while receiving Basiliximab was right toe paronychia and asymptomatic low EBV titer. The patient is currently off all immunosuppression at the time of report without evidence of cGVHD.

Conclusion: This single case report, in a young pediatric patient, demonstrates the use of Basiliximab may be a safe and efficacious treatment for pediatric patients with aGVHD.

Poster # 905 | RESTORATION OF CD4+FOXP3+ REGULATORY T CELLS AND PROTECTION FROM CHRONIC GRAFT VERSUS HOST DISEASE IN PEDIATRIC TRANSPLANT PATIENTS DEPENDS ON EFFECTIVE POST-TRANSPLANT THYMOPOIESIS

Erin Trovillion, Nicholas Gloude, Eric Anderson, Gerald Morris

University of California, San Diego, La Jolla, California, United States

Background: Clinical outcomes after allogeneic hematopoietic stem cell transplantation (HSCT) depend on restoration of T lymphocyte populations. Association between recovery of CD4+FoxP3+ regulatory T cells (Tregs) and protection from chronic graft versus host disease (cGVHD) has been described in adult HSCT. In adults, T cell recovery is driven by expansion of donor T cells and Treg reconstitution is hypothesized to result from peripheral conversion. Restoration of T cells in pediatric patients has a larger contribution from thymopoiesis, however, the relationship between thymopoiesis and Treg recovery is undefined.

Objectives: We hypothesized that effective thymopoiesis is important for restoration of Treg populations and protection from cGVHD in pediatric HSCT patients.

Design/Method: We performed longitudinal flow cytometry of peripheral blood T cells from 17 pediatric HSCT patients and 9 age-matched healthy donors. Laboratory data were correlated with clinical outcomes to evaluate impact.

Results: Recovery of Tregs occurred in 11/17 (64.7%) patients by post-transplant day 90. Day 90 Treg frequency in patients that developed cGVHD (1.7 ± 1.1% of CD4+ T cells) was reduced compared to cGVHD-free patients (3.2 ± 0.7%). Failure to restore Tregs to >2.0% of CD4+ cells by day 90 was associated with increased risk of cGVHD in the first year post-HSCT (RR = 7.3, P = 0.05). A majority (60.8 ± 11.9%) of Tregs from patients recovering the peripheral Treg compartment expressed Helios, a marker of thymic-derived Tregs; only 21.5 ± 11.4% of Tregs expressed Helios in patients failing to restore adequate Tregs. This prompted examining the relationship between defects in thymopoiesis and inability to restore Tregs. We evaluated thymic function by flow cytometry quantification of CD45RA+CD31+PTK7+ recent thymic emigrant (RTE) CD4+ cells (confirmed by qPCR for TREC content). Most (13/17, 76.5%) HSCT patients had detectable RTEs by day 30 post-HSCT. Thymic production of RTEs was persistently absent in patients that developed cGVHD (<10/10^4 CD4+ cells in 5/5 patients), compared to cGVHD-free patients (7/12 patients >10 RTE/10^4 CD4+ cells by day 30, average 22.3 ± 7.1/10^4 CD4+ cells). Post-HSCT thymic activity as measured by RTE enumeration correlated with Treg restoration; 6/8 (75%) RTE+ patients restored Tregs, compared to 3/9 (33%) of RTE- patients.

Conclusion: Failure to restore Tregs after allogeneic HSCT results in increased risk for cGVHD. In pediatric patients thymic generation of new T cells is an important contributor to restoration of the Treg compartment. This data supports further investigation into mechanisms impairing post-HSCT thymopoiesis and suggests peripheral blood Tregs may be a prognostic biomarker for cGVHD.

Poster # 906 | HAPLOIDENTICAL STEM CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE IN BENIGN HEMATOLOGICAL DISORDERS – COST EFFECTIVE CURE FOR CHILDREN IN INDIA

Ramya Uppuluri, Dhaarani Jayaraman, Meena Sivasankaran, Venkateswaran Vellaichamyswaminathan, Shivani Patel, Lakshman Vaidhyanathan, Sathishkumar Kadath, Revathi Raj

Apollo Cancer Institutes, Chennai, Tamil Nadu, India

Background: Haploidentical stem cell transplantation (haplo SCT) is riddled with unique challenges.

Objectives: We present our experience in the use of haplo SCT with post-transplant cyclophosphamide (PTCy) and the adaptations required for each disorder for optimal outcome.

Design/Method: We performed a retrospective study at the pediatric blood and marrow transplant unit, Apollo Cancer Institutes, Chennai, India. Children up to 18 years of age, diagnosed to have benign disorders and underwent haplo SCT with PTCy from 2002 to July 2017 were included.

Results: PTCy was used in 36 i.e. 73% haplo transplants for children with benign disorders. The underlying conditions included Fanconi anemia 10, severe aplastic anemia 6, MDS 1, JMML 1, hemoglobinopathy 3, PRCA 1, XLD 1 and primary immunedeficiency disorders (PID) 13. Source of stem cells was peripheral blood in 58%, bone marrow in 41%. Conditioning included fludarabine with treosulphan or cyclophosphamide for PIDs and aplastic anemia respectively. Neutrophil engraftment by Day+16-21 with a durable graft was noted in 75% transplants with graft versus host disease in 20%, CMV reactivation in 35%. Mortality rate was 45% with 2 infants less than 6 months of age developing severe fatal cytokine release syndrome. The median follow up is 1 year with 3 years being the longest. No significant late effects have been noted with chronic skin GvHD in 3 children. Survival rate was superior among children with PIDs with survival of 70% in this group.

Conclusion: Haplo SCT with PTCy is a feasible and cost-effective option for cure in children with life-threatening benign disorders with no compatible family or matched unrelated donor. Careful patient selection, reducing cyclophosphamide related free radical toxicity with the use of N acetylcysteine, limiting T cell numbers by capping CD34 at 5 × 106/kg, post-transplant viral monitoring protocols are required to reduce morbidity and mortality. We have been working on universal access to care for children from

all socioeconomic background and incorporating innovations to reduce the cost of HSCT without compromising outcomes. Haploidentical HSCT using TCR α/β depletion costs 18000 USD as compared to PTCy priced at 25 USD. Children with severe aplastic anemia and PIDs can be transplanted using reduced intensity conditioning and PTCy. In hemoglobinopathies, pretransplant immunosuppression is required to prevent graft rejection. Graft versus host disease remains the main cause of mortality in children with Fanconi anemia. Mortality in infants less than 6 months after PTCy has been high, TCR α/β depletion would be superior in this cohort.

Poster # 907 | INCREASED CD34 CELL DOSE IS ASSOCIATED WITH RAPID IMMUNE RECONSTITUTION AFTER HSCT IN PATIENTS WITH FANCONI ANEMIA

Annette Urbanski, Christine Sper, Angela Bonavita, Danielle Fohl, Thomas Leemhuis, Parinda Mehta, Kasiani Myers, Stella Davies, Adam Nelson

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Fanconi Anemia (FA) is a congenital bone marrow failure syndrome with HSCT the only curative option for associated bone marrow failure. Patients with FA undergoing HSCT may experience increased toxicity related to either their underlying disease, or the effects of medications, resulting in the inability to tolerate prophylactic medications or side-effects from anti-microbial therapy.

Objectives: We postulated that increased CD34 cell dose would be associated with a rapid immune reconstitution and therefore early withdrawal of anti-infective prophylactic medications.

Design/Method: Patients with FA transplanted at CCHMC from an unrelated donor had peripheral blood stem cell grafts collected and CD34 selection performed. Where possible, patients had serial measurements of their immune system performed at varying intervals post HSCT. We defined immune reconstitution as normalization of lymphocyte subsets- CD3, CD4, CD8 and CD19 cells, as well as a normal response to mitogen stimulation including phytohemagglutinin, concanavalin A and pokeweed. The first measurement of either normal cell number or mitogen response was recorded for each patient.

Results: A total of 35 patients underwent HSCT for FA at CCHMC between 2012 and 2017. Patient demographics included a median age of 8 years at HSCT, the vast majority of patients having a fully matched or one antigen mismatched donor, and the majority of patients transplanted for bone marrow failure. There was a statistically significantly decreased time post-transplant to immune cell recovery in patients receiving >20 × 106/kg CD34 cells (median 25.7) compared to those receiving <20 × 106/kg CD34 cells (median 11.9). The median time to normalization of CD3 count was 224 days (CD34 count >20/kg) versus 371 days (CD34 count <20/kg), CD4 count 211 days (CD34 count >20/kg) versus 489 days (CD34 count <20/kg), CD8 count 193 days (CD34 count >20/kg) versus 344 days (CD34 count <20/kg) and CD19 count 93 days (CD34 count >20/kg) versus 109 days (CD34 count <20/kg). Time to normalization of mitogen response was decreased post-transplant in those patients receiving increased CD34 cell dose at time of transplant, though this was not significant, reflecting low number of patients with evaluable responses. No patients in either group experienced GVHD or graft failure.

Conclusion: Patients with FA who are transplanted with higher CD34 cell doses have quicker immune reconstitution than those who receive lower cell doses. Along with benefit to patients including less risk of infection and early termination of immune-prophylaxis medications, this supports the use of high dose CD34 selected grafts in this vulnerable population.

Poster # 908 | PARVOVIRUS B19 INFECTION MANIFESTING AS CYTOPENIA IN CONSTELLATION WITH BONE PAIN POST HEMATOPOIETIC STEM CELL TRANSPLANTATION

Trisha Kissoon, Biljana Horn, Peng Li

University of Florida, Gainesville, Florida, United States

Background: Parvovirus B19 (PVB19) infection after transplantation was first reported in 1986. Since then, numerous cases of PVB19 infections after hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT) have been reported. Most report anemia as the predominant clinical manifestation. However, PVB19 has been associated with pancytopenia, hepatitis, myocarditis, and allograft rejection. We present a patient with acute lymphoblastic leukemia who developed bone pain and pancytopenia following HSCT in the setting of PVB19 infection.

Objectives: To describe an unusual presentation of PVB19 in a patient with acute lymphoblastic leukemia following HSCT.

Design/Method: A search of the English-language medical literature was performed using PubMed and Medline databases. A review of the patient's medical history was performed.

Results: A 7 year old male with relapsed B-cell ALL and history of "fifth disease" in infancy presented four months after HSCT with focal left arm pain and difficulties fully extending the arm. Bone MRI showed enhancement of the medullary space centered within incomplete transverse cortical fracture interpreted as pathologic fracture due to neoplastic involvement of the ulna with no history of inciting injury. Subsequently, peripheral blood counts decreased from low normal values to WBC 1.9 K/microL, ANC 310/microL, PLT 57K/microL, and hemoglobin 8.6 g/dL. The patient's chimerism remained 100% donor. A bone marrow biopsy and aspirate were performed to assess for recurrent leukemia given persistence of bone pain and developing pancytopenia. Marrow findings included morphologic cytopathic effects with erythroid precursors and strong Parvovirus staining with no signs of red cell aplasia or recurrent B-cell disease by morphology or flow cytometry. PVB19 was detected in blood by PCR and immunoglobulins with resolution of cytopenia and bone pain.

Conclusion: This case highlights an unusual constellation of symptoms following HSCT in a child with ALL. Unexplained bone pain and medullary infiltrates with pancytopenia suggestive of recurrent leukemia were likely triggered by PVB19 infection. The question remains if he had reactivation of PVB19, a primary infection by a new strain, or the virus was aquired through stem cells. Bone biopsy could not be justified in light of clinical improvement. So far, bone lesions have only been described with congenital PVB19 infection. PVB19 appears to be uncommon after HSCT, with a review of literature yielding 15 pediatric cases. However, it may be underestimated due to lack of routine screening. Our patient's presentation supports that evaluating for PVB19 may be warranted in HSCT patients presenting with symptoms suggestive of relapsed leukemia.

Poster # 909 | SCREENING ECHOCARDIOGRAPH MAY NOT BE NECESSARY IN A SUBSET OF LONG-TERM SURVIVORS OF PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Seth Rotz, Adam Powell, Kasiani Myers, Michael Taylor, John Jefferies, Adam Lane, Stella Davies, Christopher Dandoy, Thomas Ryan

Cincinnati Children's Hospital, Cincinnati, Ohio, United States

Background: Cardiac injury may occur during hematopoietic stem cell transplant (HSCT) in pediatric patients and can be asymptomatic for many years. Recommendations for screening are available for patients who received anthracyclines or chest irradiation, but no guidelines exist for unexposed long-term survivors.

Objectives: We sought to define the prevalence of echocardiographic abnormalities in long-term survivors of pediatric HSCT and determine the need for screening in asymptomatic patients.

Design/Method: We analyzed echocardiograms performed on long-term survivors (≥ five years) who underwent HSCT at Cincinnati Children's Hospital between 1982 and 2006. We analyzed echocardiograms for left ventricular ejection fraction (EF), end-diastolic dimension (LVEDD), septal thickness, posterior wall thickness, and global longitudinal strain (GLS). We normalized linear measurements for age and patient body surface area. We included for further analysis patients who had echocardiogram obtained for routine surveillance.

Results: A total of 389 patients underwent HSCT and were alive more than 5 years after transplant in 2017, with 114 having an echocardiogram obtained ≥ five years post-infusion. Those with an echocardiogram were transplanted more recently (median 2003 vs. 1998). However, no difference between screened and unscreened individuals was noted for age at transplant, sex, transplant indication, anthracycline exposure, chest irradiation, or cyclophosphamide based preparative regimen. Indications for echocardiograms included: cardiac symptoms 5 (4.4%), congenital cardiac anomalies 8 (7.0%), hypertension 2 (1.8%), known cardiac or pulmonary disease 2 (1.8%), routine post-HSCT surveillance 95 (83.3%), and unknown 2 (1.8%). The mean time post-HSCT was 11.7 years. Among routine surveillance echocardiograms, the mean EF z-score was -0.97. Mean LVEDD z-score was -0.94, mean septal thickness z-score -1.00, mean posterior wall thickness z-score -0.98, and mean GLS -21.96%. For patients that had echocardiogram performed for routine surveillance, 77/95 patients (82.1%) had EF measured, and 10/77 (13.0%) had EF z-scores ≤ -2.0 (abnormally low). Patients exposed to anthracyclines had a mean z-score EF of -1.19 vs. unexposed patients -0.50 ($p = 0.003$). Among individuals who received neither anthracyclines nor TBI only 1/31 (3.2%) was found to have an abnormal EF, 51.4% (z-score -2.73) or GLS (-14.28%). Only one patient who had a normal ejection fraction (z-score -0.39, EF 61.7%) had an abnormal GLS, -15.9% (normal ≤ -16.0).

Conclusion: Long-term survivors of pediatric HSCT who are asymptomatic and did not receive radiation or anthracyclines likely do not require surveillance echocardiograms, unless indicated by clinical symptoms. Patients exposed to anthracyclines or TBI require close echocardiographic

screening and clinical monitoring for the development of cardiac complications.

Poster # 910 | FEASIBILITY AND ACCEPTABILITY OF USING A MOBILE APP AND WEARABLE FOR PATIENTS UNDERGOING PEDIATRIC BLOOD AND MARROW TRANSPLANT

Jacqueline Vaughn, Erika Summers-Goeckerman, Paul Martin, Nirmish Shah

Duke Children's Hospital, Durham, North Carolina, United States

Background: Children undergoing pediatric blood and marrow transplants (PBMT) experience significant symptom distress. Mobile health (mHealth) technologies can be leveraged to collect and monitor patient generated health data, and subsequently enhance our understanding of PBMT symptom clusters, patterns, and trajectories. Better understanding of symptom complexity can foster development of precision health strategies to improve patient outcomes. However, limited research exists in integrating mHealth technology into PBMT management.

Objectives: We aimed to explore the feasibility, acceptability, and usability of using a PBMT specific mobile application to collect and monitor symptoms and wearable technology (Apple Watch) to measure objective data such as heart rate (HR) and activity.

Design/Method: An exploratory mixed method design began in October 2017 to monitor PBMT symptoms for 20 patients using real-time data from: 1) A self-developed mHealth application (app) to collect subjective symptom data; and 2) Apple Watch to collect physiologic measures such as heart rate and number of daily steps. Data is collected pre-transplant through 90 days. Acceptability will be assessed through satisfaction surveys at study completion.

Results: We have enrolled 4 patients to date who are all currently using the app and watch. Patients' average frequency of daily charting in the app 80%. The wearable average daily recorded measurements are 144 for HR and 29 for step count. Most common symptoms recorded within the app include fatigue and pain. We have noted trends in data including a decrease in activity following transplant and GVHD and an increase following engraftment. Patients have stated "the app is helpful to keep track of how my pain is doing day to day" and "I try to take more steps each day than the day before". Patients often remove the watch for charging, then forget to put it back on, but consistently put it on upon reminder. Finally, parents often were required to make app entries with patients too sick to record.

Conclusion: We continue to enroll patients with enthusiasm from both patients and parents to use mHealth during PBMT. Preliminary findings suggest feasibility of using the mHealth devices is strongly correlated to the patient's post-transplant stage and is facilitated by caregiver participation with device management (charging devices, reminders to wear watch and record in app). Patients reported satisfaction and ease of use with devices, but found it difficult to keep up with charging and charting. These findings indicate using mobile devices may be useful methods to collect patient generated health data.

Poster # 911 | HIGH INCIDENCE OF THROMBOTIC MICROANGIOPATHY IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS WITH MULTIPLE BLOODSTREAM INFECTIONS

Liron Grossmann, Priscila Badia, Adam Nelson, Javier El-Bietar, Kasiani Myers, Christopher Dandoy

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Bacterial bloodstream infections (BSI) are a common complication following hematopoietic stem cell transplantation (HSCT) in both pediatric and adult populations, and are associated with poor outcomes. There is limited data describing the outcomes and characteristics of patients who develop three or more BSI after HSCT.

Objectives: To describe the characteristics and outcomes of pediatric patients who develop three or more blood stream infections in the first-year post HSCT.

Design/Method: We performed a retrospective chart review of 373 consecutive patients who underwent HSCT at our institution from 2011 through 2016 to compile this case series. Data were collected through the first year post-HSCT including: patient demographics, underlying disease and therapy characteristics; and transplant complications such as thrombotic microangiopathy (TMA), graft versus host disease (GVHD) and overall survival. BSIs were classified according to current Center of Disease Control Guidelines.

Results: Of 373 patients, 18 (5%) developed 3 or more BSI in the first-year post transplant (total BSI cases = 77 including all patients). Of the 18 cases, the majority underwent allogeneic HSCT (n = 17/18; 94%). Most cases were from unrelated donor (n = 15/18, 83%). More than half of patients had grade 2–4 GVHD (n = 11/18, 61%). Sixteen (89%) had TMA. Of these 16 cases, TMA preceded the first BSI in n = 10/16 (62%). The majority of BSIs were classified as central line-associated bloodstream infections (CLABSIs,

n = 37/77, 48%), followed by mucosal barrier injury laboratory-confirmed bloodstream infections (n = 29/77, 38%) and secondary BSI (n = 11/77, 14%). The majority of isolated organisms (45%) were associated with mucosal barrier injury pathogens. One-year overall survival in the cohort was 44% (n = 8/18).

Conclusion: Pediatric patients undergoing HSCT who develop 3 or more BSIs in the first-year post transplant demonstrated an increased rate of TMA compared to the overall institutional incidence of roughly 30%. TMA diagnosis preceded the first BSI in over half of patients, suggesting that TMA may predispose to recurrent BSI. Improved strategies for early detection and treatment of TMA as well as prevention of CLABSIs may help reduce the number of BSIs ultimately leading to decreased morbidity and mortality in this patient population.

Poster # 912 | GRANULOCYTE TRANSFUSIONS IN PEDIATRIC PATIENTS WITH NEUTROPENIA: ASSESSING EFFICACY AND OUTCOMES FOLLOWING THE USE OF A LOCAL GRANULOCYTE DONOR PROGRAM

Tyler Severance, Thomas Fox, Susan Perkins, Jodi Skiles, Scott Goebel, Kent Robertson, David Delgado

Riley Hospital for Children at Indiana University Health, Indianapolis, Indiana, United States

Background: In neutropenic pediatric patients, infection remains a significant cause of morbidity and mortality. While granulocyte transfusions have been utilized for decades to treat infections, including in the pediatric population, the efficacy of this intervention remains poorly described. Previous guidelines have primarily utilized information from adult populations. Furthermore, recruitment of donors typically involves friends or relatives of the patient with periodic involvement of community donors. The use of a readily available local donor population to improve availability has yet to be well described. As the immunocompromised population is particularly susceptible to worsening infection and clinical deterioration, the ability to rapidly harvest and deliver granulocytes warrants further investigation.

Objectives: To investigate the efficacy, safety, and outcomes of severely immunocompromised patients receiving granulocyte transfusions from a local altruistic granulocyte program in a pediatric tertiary care center.

Design/Method: A retrospective review was performed to evaluate the context for receiving a transfusion as well as primary outcomes including infection clearance, survival to discharge, and overall mortality. The Indiana Blood Bank assisted with timing the interval from initial order placement to onset of first granulocyte infusion.

Results: Among the patient population reviewed, 22 patients received 23 separate granulocyte regimens. Ages ranged from 0–18 years with a mean neutrophil count of 77 at time of first transfusion. Indications for transfusions included bacteremia (n = 11), fungal pneumonia (n = 6), and fungemia (n = 5). Primary outcomes included clearing infection (70%) and surviving to discharge (57%). The median time from initial order placement to infusion was 46 hours, although there was no significant difference between responders who cleared the infection and non-responders who did not. However, additional investigation found that ward patients had a 75% chance of surviving to discharge while patients in the ICU at time of initial transfusion had a 36% chance of survival to discharge.

Conclusion: The readily available granulocyte transfusion program allows patients to quickly receive therapy in neutropenic settings. This is beneficial for patients as transfusion prior to clinical decompensation correlates with increased likelihood of infection clearance, and subsequently improved mortality. Further investigation is needed, likely as a prospective study, to better explore circumstances that are beneficial for granulocyte transfusions.

Poster # 913 | INVESTIGATING THE ROLE OF CELLULAR CONTENT AND GVHD IN DONOR LYMPHOCYTE INFUSIONS TO TREAT PEDIATRIC HEMATOLOGIC MALIGNANCIES: A SINGLE-CENTER LONG-TERM STUDY

Nicole Liberio, Haley Robinson, Melodee Nugent, Pippa Simpson, Carolyn Keever-Taylor, Monica Thakar

Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Background: Donor lymphocyte infusions (DLI) are composed of immune cells to treat relapse after hematopoietic cell transplantation (HCT). To date, data regarding its efficacy is limited in pediatric populations. Furthermore, while outcomes related to CD3 content have been characterized, to our knowledge, the relationship between outcomes and other cellular content in DLI has never been reported.

Objectives: Determine whether the primary hematological malignancy, presence/absence of graft-versus-host disease

(GVHD), and unique phenotypic content of each DLI impact overall survival (OS) in pediatric patients with hematological malignancies.

Design/Method: IRB-approved, retrospective study investigating all consecutive DLIs given to patients at the Children's Hospital of Wisconsin. Analyses were conducted using Mann-Whitney, Fisher's exact, and chi-square.

Results: From 1980–2016, 30 patients ≤20 years old with hematologic malignancies [myeloid (AML/MDS/CML/JMML),n = 23; lymphoid (ALL),n = 7] underwent 55 DLIs (72%% ≥2 DLIs). The median time between HCT and DLI was 0.6 (range, 0.1-5.8) years. There were significant differences between the lymphoid and myeloid groups, respectively, in regard to median age at HCT (14.7 vs 7.5 yrs, p = 0.022) and at first DLI (20 vs 8 years, p = 0.006). Ultimately, there were no statistically significant differences in GVHD or OS in products with either higher or lower CD3, CD4, CD8, CD56, or CD19 cellular content. However, the median CD3/kg content was more than double in the patients who developed GVHD as compared to patients who exhibited no GVHD after DLI (29.99 × 106 vs 10.03 × 106, p = 0.346). Patients receiving one DLI had a 6-year OS of 21 ± 9% vs those receiving 2+ DLI of 52 ± 16% (p = 0.012). With a median follow-up of 0.74 (range, 0.04-16.61) years, the 6 year estimated OS of patients in the lymphoid group was higher at 71 ± 17% vs 22 ±9% in the myeloid group, although not significant (p = 0.11).

Conclusion: Our results indicate a survival benefit when using DLI in a subset of patients who relapse after HCT. Unlike adult studies demonstrating little effect of DLI in lymphoid diseases, many children with ALL achieved durable remission. While our analysis did not demonstrate that DLI cellular content had a statistically significant effect on GVHD or OS, it is possible that differences could be found if a larger population and more targeted cell doses were studied. More data will be needed to further define these relationships and identify patients who stand to benefit most.

Poster # 915 | ISLAM, THE QUR'AN, AND MEDICAL DECISION-MAKING – THE EXPERIENCE OF MIDDLE EASTERN MUSLIM FAMILIES WITH CHILDREN UNDERGOING STEM CELL TRANSPLANTATION IN THE UNITED STATES

Ruby Khoury, Judith Ragsdale, Mohammad Othman, Karen Geiger-Behm, Mark Mueller, Eyad Musallam, Christopher Dandoy, Stella Davies

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Many Arabic speaking Muslim parents of children requiring bone marrow transplantation (BMT) receive medical care in the United States. Providers may not understand the impact of Islamic parents' religious beliefs and practices on their health care experience.

Objectives: To explore how Islamic parents used religion in decision making and to understand the impact of their religious beliefs and practices on their overall health care experience.

Design/Method: We used grounded theory, an inductive method gathering data from interviews and analyzing text, to identify core themes. Ten caregivers of BMT children from Middle Eastern countries were interviewed by an Arabic-speaking provider; interviews were coded by an interdisciplinary team.

Results: We identified 5 key themes: 1. Patience is a core belief in Islam. Patience results from the acceptance of Allah's will. Behaviors showing patience include praying rather than questioning and crying. 2. Al Qur'an provides comfort, healing, and protection. Families listen to recitations of Al Qur'an in the patient's room because they feel that this practice not only comforts them but promotes healing as well. For some, certain portions of the Qur'an were especially meaningful such as Surat Al-Baqara, which explains that while we may think something is bad for us, Allah will know it is good for us. 3. Religious care in the medical center helped families feel respected. Religious care in the medical center included interactions with chaplains, who were understood to be "religion experts," and provision of space for prayer and religious resources. 4. Seeking religious consultation. Religious consultation from Imams or religious scholars (Muftis or Sheikhs) provides interpretations of the Qur'an applied to the family's specific situation helps families make difficult decisions and follow Allah's plan. 5. Muslim beliefs guided decision making; Muslim practices brought comfort, strength, and peace. Drawn from the parents' understanding of Islam. Parents who addressed this topic said they would only do what Islam allowed. They did indicate that most aspects of healthcare were understood to be allowed within Islam. Additionally, Muslim practices of prayer, reading/listening to Qur'an, and giving alms all provided comfort, strength and peace.

Conclusion: We identified several recurring themes through our interviews that allowed us to understand how families use their Muslim faith to deal with their children's illnesses and how it influences their decision making. We believe this better understanding will allow for more informed conversations about patients' health care and decision making, and shows respect for religious beliefs and practices.

Poster # 916 | UNUSUAL NEUROLOGIC SEQUELAE AFTER POST-TRANSPLANT ACUTE LIMBIC ENCEPHALITIS DUE TO HHV-6 INFECTION

Ellen Fraint, Emi Caywood

Nemours/duPont Hospital for Children, Wilmington, Delaware, United States

Background: Virtually all children will be infected with Human Herpesvirus 6 (HHV-6) by the age of two. HHV-6 reactivation after stem cell transplantation causes multi-organ toxicities, including encephalitis, with inflammation and destruction of the temporal lobes and hippocampi, memory loss, and seizures. Catatonia is characterized by posturing, immobility, mutism, and autonomic instability, and it's associated with various psychiatric and medical conditions. We describe a patient with HHV-6 encephalitis and unusual neurologic sequelae, including cognitive and neurobehavioral dysfunction and catatonia, which may impact our understanding of the pathophysiology of HHV-6 reactivation encephalitis.

Objectives: Describe a case of HHV6 encephalitis with practice implications for stem cell transplantation.

Design/Method: Case report.

Results: Our patient was diagnosed with Acute Myeloid Leukemia at age 14. Within 2 years, he relapsed and received two stem cell transplants. On the 29th day after his second transplant, he developed hyponatremia and refractory seizures. Brain MRI showed edema in the medial right temporal lobe with linear ischemic change. EEG showed diffuse encephalopathy. Cerebrospinal fluid (CSF) demonstrated 5 white blood cells, 2 red blood cells, and HHV-6 by PCR. His prophylactic antiviral was switched to foscarnet and ganciclovir. Repeat MRI showed abnormal signals in bilateral medial temporal lobes and the right insula. Three months later he developed episodes of diaphoresis, hypothermia, agitation, mutism, and unusual posturing, recurring almost daily, recognized as catatonia. MRI showed improvement of the abnormalities in the bilateral medial temporal lobes and hippocampi. EEGs showed diffuse slowing. After 4 months of antiviral therapy, CSF was negative for HHV-6. Over the ensuing 3 years, he had numerous episodes of diaphoresis, hypertension, hypothermia, pruritis, confusion, agitation, cogwheel rigidity, and bizarre posturing. Dopamine blocking agents did not help. Clonazepam helped reduce their frequency, and hot showers helped break acute episodes. Further MRIs showed generalized cortical volume loss. He suffered from depression and severely impaired sleep and cognitive function.

Conclusion: We describe a novel, debilitating outcome of HHV6 encephalitis which may provide diagnostic considerations as we continue to improve our understanding of the breadth of possible neurologic sequelae in transplant patients. HHV-6 is understood to infect and destroy the temporal lobes and hippocampi, but our patient's autonomic dysfunction indicate involvement of the hypothalamus and basal ganglia. Antidopaminergic agents may worsen catatonia, and they were not effective for our patient. Treatment of catatonia includes benzodiazepines; electroconvulsive therapy was not attempted in this case but may also be useful.

Poster # 917 | THE ROLE OF TONSILLECTOMY IN PATIENTS WITH LOCALIZED EPSTEIN-BARR VIRUS-RELATED POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

Alexandra Satty, Stacie Kahn, Rachel Lehrman, Farid Boulad, Nancy Kernan, Esperanza Papadopoulos, Susan Prockop

Memorial Sloan Kettering Cancer Center, New York, New York, United States

Background: Epstein-Barr Virus (EBV)-related post-transplant lymphoproliferative disorder (PTLD) is a life-threatening complication in patients following hematopoietic stem cell transplantation, with a frequency estimated at 3.2% and a cumulative incidence of mortality estimated as high as 31%. Studies of EBV have hypothesized that the tonsils are critical for propagating this infection, as tonsillar epithelial cells have been shown to be the site of primary viral infection and continued viral shedding; however, to date no studies have been performed assessing the role of tonsillectomy in patients with EBV PTLD.

Objectives: Identify patients with localized EBV PTLD treated with tonsillectomy to identify prognostic factors that may be able to help guide future treatment decisions.

Design/Method: Patients treated at Memorial Sloan Kettering Cancer Center who had received hematopoietic stem cell transplantation and had billing codes for both EBV and tonsillectomy were eligible for inclusion in this study. A retrospective chart review was performed, assessing patient demographics, transplant characteristics, laboratory values, tonsillar pathology, and clinical course. Any patient who did not have unilateral or bilateral tonsillectomy performed or who had non-localized disease (defined as disease involvement outside of the oropharynx and neck) was subsequently

excluded from this study. The remaining patients were analyzed using descriptive statistics.

Results: A total of 17 patients meeting inclusion criteria were identified. Of these, 4 patients (23.5%) received tonsillectomy alone, 1 (5.9%) underwent tonsillectomy and decreased immunosuppression, 6 (35.3%) received tonsillectomy and rituximab, and another 6 (35.3%) received tonsillectomy with additional therapy (including EBV-specific cytotoxic T-lymphocytes, donor leukocyte infusion, and chemotherapy). Of the 5 patients who received tonsillectomy with or without a decrease in immunosuppression, all were diagnosed with high-grade lymphoma and achieved clinical remission following tonsillectomy with no evidence of relapse to date. On further analysis looking at PTLD risk factors, all patients were under 50 years of age, all received T-cell depleted grafts, and none had significant graft-versus-host disease (GvHD) at the time of PTLD diagnosis.

Conclusion: We have identified a population of patients with localized EBV PTLD that achieved clinical remission with no evidence of recurrence following tonsillectomy, suggesting that tonsillectomy alone may be an adequate treatment for localized EBV PTLD in a specific subgroup of patients. Further analysis is needed to identify characteristics of this subgroup to determine which patients would be most likely to respond to this treatment.

Poster # 918 | HIGH DOSE CHEMOTHERAPY WITH CARBOPLATIN AND THIOTEPA WITH AUTOLOGOUS STEM CELL RESCUE IS A FEASIBLE AND WELL-TOLERATED THERAPY FOR MALIGNANT CNS TUMORS IN CHILDREN: A SINGLE INSTITUTION EXPERIENCE

Carol Fries Simpson, Angela Girvin, David Korones, Lauren Weintraub, Lorna Fitzpatrick, Jeffrey Andolina

University of Rochester, Rochester, New York, United States

Background: Malignant central nervous system (CNS) tumors in young children have a poor prognosis and pose a significant therapeutic challenge. Consolidation therapy with carboplatin and thiotepa was piloted in CCG-99703, COG ACNS0333, and COG ACNS0334 with the goals of intensifying therapy and omitting or delaying radiation.

Objectives: To document outcomes for patients undergoing carboplatin/thiotepa consolidation with autologous stem cell rescue (ASCR) and to demonstrate the feasibility and toxicity of this regimen.

Design/Method: Patients up to 3 years old (median age: 12 months) with malignant CNS tumors treated at the University of Rochester from 2012–2017 with at least one cycle of carboplatin (17 mg/kg/day x 2 days) and thiotepa (10 mg/kg x 2 days) followed by peripheral blood ASCR were included in retrospective analysis. Data were recorded on time to engraftment (defined by absolute neutrophil count (ANC) recovery to $> 0.5 \times 10^9/l$), length of hospitalization, toxicity with each consolidation cycle, progression free survival (PFS) and overall survival (OS). Stem cell harvest data were also collected.

Results: Eleven patients with malignant CNS tumors (6 atypical teratoid/rhabdoid tumor, 3 primitive neuroectodermal tumor, 1 glioblastoma multiforme, and 1 pineoblastoma) received a total of 30 cycles of carboplatin/thiotepa. Of these, 9 underwent stem cell harvest at our institution, with complications limited to procedure-related hypotension for 1 patient with known autonomic instability, and catheter-associated deep vein thrombosis (DVT) for 1 patient. Four patients were in complete remission (CR) 1/status-post gross total resection, 1 was in CR2, and 6 had residual tumor at the time of consolidation. Nine patients received 3 planned consolidation cycles, 1 patient 2 (of 2) planned cycles, and 1 patient 1 of an anticipated 3 cycles thus far. Average time to engraftment for these 30 cycles was 10.2 (+/- 1.4) days, with a mean hospital length of stay of 16 (+/- 3.2) days. Fever occurred in 17 of 30 cycles (57%); infectious toxicity included documented bacterial infection in 2 cases (Enterococcus faecalis bacteremia in 1, Klebsiella pneumoniae in 1). There were no regimen-related deaths. With a mean follow-up of 23 months, 2 survivors have not yet completed all therapies, and 5 patients have relapsed (4 have died of disease). Of the 7 survivors, 4 have been disease-free for >12 months.

Conclusion: Carboplatin/thiotepa consolidation with autologous stem cell rescue is a safe and well-tolerated intervention for young children with malignant CNS tumors.

Poster # 919 | EARLY INFECTIOUS COMPLICATIONS FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANT FOR HIGH-RISK NEUROBLASTOMA: HIGH IMPACT ON MORTALITY AND MORBIDITY

Dolly Noun, Khaled Ghanem, Raghida Dhayni, Nariman Hariss, Samar Muakkit, Raya Saab, Dima Hamideh, Hassan El-Solh, Miguel Abboud, Nidale Tarek

American University of Beirut Medical Center, Beirut, Lebanon

Background: Autologous hematopoietic stem cell transplantation (auto-HSCT) has resulted in improved survival for patients with high-risk neuroblastoma. Treatment intensification is however associated with greater complications. Data on early infectious complications in low-and-middle income countries are limited.

Objectives: To review the early infectious complications following auto-HSCT in patients with high-risk neuroblastoma.

Design/Method: A retrospective chart review of pediatric patients with high-risk neuroblastoma who underwent auto-HSCT at the American University of Beirut Medical Center between 2003 and 2017 was conducted. Infectious complications during the first 100 days post-transplant were reviewed.

Results: Forty-three patients (27 males and 16 females) with a median age at diagnosis of 4.35 years [range: 0.5-13.9] years underwent auto-HSCT during the above-mentioned period. Conditioning regimen consisted of Melphalan, Etoposide and Carboplatin. All patients received antiviral and antifungal prophylaxis. Median time for neutrophil engraftment was 10 days [range: 8-19]. Bacteremia and Clostridium difficile infections occurred in 16 (37%) and 12 (28 %) patients respectively. Seven (16%) patients developed enterocolitis diagnosed by imaging, 4 were adenovirus induced. CMV viremia was diagnosed in 7 (16%) patients, 5 of whom required treatment. Varicella zoster reactivation, parvovirus viremia, toxoplasmosis encephalitis, BK virus cystitis (2 patients) and central nervous system EBV related post-transplant lymphoproliferative disorder were diagnosed in 6 different patients. There was no invasive fungal infection. Sixteen (37%) patients have died, 6 of whom died in the early post-transplant period, 1 due to disease progression and 5 (11.6%) due to infectious complications. Among the 5 patients who died due to infection, 1 developed toxoplasmosis encephalitis, 4 developed severe enterocolitis, 2 of which were adenovirus related. The mean IgG level within one week post-transplant was lower in patients with clinically significant viral infection compared to others (4 vs 5.6 mg/dl, p: 0.08). The mean IgG level at the time of clinically significant bacterial infection was lower in infected patients compared to others (4.4 vs 6.3 mg/dl, p: 0.03). Neither absolute lymphocyte count nor absolute neutrophil count at day 20 post-transplant affected the incidence of clinically significant infections.

Conclusion: Our results show that the rate of infections during the early post auto-HSCT period is higher than what has been described in developed countries and has a significant impact on mortality. Prevention, early detection and improvement in the treatment is required to improve outcome.

Poster # 920 | STEROID DEPENDENT GRAFT-VERSUS-HOST-DISEASE MANAGED WITH WEEKLY BORTEZOMIB

Warren Alperstein, Martin Andreansky, Edward Ziga
University of Miami, Miami, Florida, United States

Background: Allogeneic Hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment for many malignant and non-malignant (bone marrow failure, immunodeficiency, or metabolic diseases) in pediatrics. Despite advances in medicine, graft-versus-host-disease (GVHD) remains a significant cause of non-relapsed morbidity and mortality, specifically in those with malignant diseases.

Objectives: To highlight the complexity to acute GVHD management and seldom-described treatment approach.

Design/Method: Case Report

Results: A 7 year male with a history of high risk acute myeloid leukemia (AML) due to failed induction therapy. He received a matched (10/10) unrelated donor HSCT – marrow product- conditioned with busulfan, fludarabine, and anti-thymoglobulin (ATG). His post-transplant course was complicated by HHV-6 viremia, PRES (prompting a change from prograf to cyclosporine), mucositis, and grade III acute GVHD (skin S3, Gut S2, Liver S0) around post transplant day 101, which later morphed to ocular involvement by D+120. He was started on 2 mg/kg steroids with good response but flared up with each attempt to taper steroid dose. A course of rituximab and later ATG were tried without success in weaning off steroids. Switching cyclosporine to sirolimus did not provide any additional benefit either. Extracorporeal Photopheresis (ECP) was started 3 times a week. He initially responded well, yet was not able to wean off steroids. In addition, he developed a flare when ECP session was reduced to 2 days per week. ECP was therefore increased to 5 days per week, which appeared to stabilize skin lesions. A trial of weekly methotrexate was attempted to wean off steroids and photopheresis, which provided no response. Finally, a trial of bortezomib on days 1, 4, 8, and 11 of a 21 day cycle as published in a case series of multiple myeloma patients who developed post HSCT GVHD. Skin lesions improved remarkably however dose had to be reduced due to related pancytopenia. Given the response to therapy, he was continued on a weekly dose of bortezomib, receiving a total 8 doses, which has permitted the slow taper of prednisone that has since been discontinued without a major flare. He however is currently maintained on ECP 3 times per week, which is now been slowly withdrawn.

Conclusion: Management of acute GVHD in pediatric patients after HSCT can be challenging with no definite options for those who fail steroids or become steroid dependent after initial response. In these situations, bortezomib could be a valid therapeutic option.

Pediatric Blood and Marrow Transplant Consortium Abstracts

Poster # 1001 | EFFECTS OF TOLL LIKE RECEPTOR STIMULATION ON IL-21 EXPANDED NK CELLS FOR THE TREATMENT OF NEUROBLASTOMA

Margaret G Lamb, Jennifer A. Foltz, Jena J. Edwards, Nitin Chakravarti, Prashant Trikha, Jeffrey Auletta, Dean Lee

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: Neuroblastoma (NBL) is the second most common solid tumor in children and despite recent treatment advances, overall survival for high risk NBL remains <50%. The addition of immunotherapy has improved survival and includes anti-GD2 antibody therapy. The success of antibody therapy in neuroblastoma is primarily due to natural killer (NK) cell mediated antibody dependent cellular cytotoxicity. We previously demonstrated that NK cells from patients with high risk NBL can be successfully isolated and expanded to large numbers and exhibit potent anti-tumor effects against NBL (1). Thus, infusions of autologous expanded NK cells in high risk NBL in combination with anti-GD2 antibody are being studied in clinical trials. Toll-like receptors (TLR) present on the surface of leukocytes are responsible for pathogen recognition, and activation of these receptors stimulate the production of cytokines that critically link innate and adaptive immune responses. The TLR3 agonist, Poly(IC) is a synthetic analog of dsRNA that has previously been shown to directly stimulate cytokine production and improve cytotoxicity in primary NK cells through activation of genes regulated by interferon-response elements (IRE) (2).

Objectives: We hypothesized that ex vivo activation of TLR pathways in NK cells during our normal 14-day expansion using K562 feeder cells expressing membrane bound IL-21 would enhance their function.

Design/Method: NK cells were isolated from peripheral blood mononuclear cells and expanded with our previously described expansion protocol in media containing IL-2 and 50 ug/mL poly(IC) (3). At the end of the 14-day expansion, NK cells expanded with poly(IC) were compared to controls using a calcein cytotoxicity assay to measure cytotoxicity against high risk neuroblastoma and cytometric bead array to measure cytokine production.

Results: Surprisingly, the addition of poly(IC) during NK cell expansion did not improve proliferation, cytokine production or cytotoxicity compared to our standard expansion method. RNAseq demonstrated that our standard expansion method results in a modest decrease in TLR3 expression at the transcriptional level, but significant upregulation of several IRE-regulated genes.

Conclusion: We conclude that either our standard approach interferes with TLR signaling or saturates the innate immune response pathway such that co-stimulation with poly IC does not produce an additive effect. We are performing expression analysis on NK cells receiving poly(IC) during expansion to further explore this hypothesis.

Liu, *Clin Cancer Res,* 2013.

Qui, *Innate Immunity,* 2010.

Somanchi, *J Vis Exp*, 2011.

Poster # 1002 | ANTI-MULLERIAN HORMONE AS A MARKER OF OVARIAN RESERVE IN FEMALE PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANT

Priscila Badia, Helen Oquendo-del Toro, Jonathan C. Howell, Janie Benoit, Adam Lane, Christa Krupski, Stella Davies, Michael Grimley, Sonata Jodele, Christine Phillips, Karen Burns, Pooja Khandelwal, Javier El-Bietar, Rebecca Marsh, Adam Nelson, Gregory Wallace, Christopher Dandoy, Pauline Daniels, Olivia Frias, Lesley Breech, Susan R. Rose, Holly Hoefgen, Kasiani C. Myers

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Gonadal dysfunction leading to infertility is a complication after hematopoietic stem cell transplant (HSCT). Anti-MÃ¼llerian Hormone (AMH) is a marker of ovarian reserve; it is not controlled by gonadotropins and has minimal inter-cycle variations, therefore, it can be used as a marker of ovarian reserve and aid in fertility counseling.

Objectives: Assess ovarian reserve in HSCT patients utilizing AMH levels.

Design/Method: Retrospective chart review of AMH levels of female HSCT patients from 2013–2017.

Results: One hundred female patients median age of 7, had AMH levels pre-transplant, and 33% (n = 33/100) had post-transplant levels. Thirty two percent (n = 32/100) had a diagnosis of malignancy; 19% (n = 19/100)

immunodeficiency; 17% (n = 17/100) Fanconi anemia (FA); 17% (n = 17/100) hemoglobinopathy; 12% (n = 12/100) non-FA marrow failure and 3% (n = 3/100) a metabolic disorder.

Seventy one percent (n = 71/100) had normal AMH for age pre-transplant, 29% (n = 29/100) had low AMH for age pre-transplant; of these, 37% (n = 11/29) had an oncologic diagnosis; 37% (n = 11/29) had FA; 10% (n = 3/29) had previously treated HLH; 6% (n = 2/29) had non-FA marrow failure; one had a metabolic disorder and one a hemoglobinopathy.

Of the 33 patients with post-transplant AMH measurement 72% (n = 24/33) had low levels. Of the 25 patients with previously normal pre-transplant AMH 52% (n = 13/25) underwent myeloablative conditioning (MAC) regimen with a 100% (n = 13/13) having low AMH levels post-transplant compared to 48 %(n = 12/25) who underwent reduced intensity conditioning (RIC) regimen with 25% (n = 3/12) having low AMH levels post-transplant (p 0.0002). Fifteen percent (n = 5/33) had low levels pre-transplant and underwent MAC regimen with 100% (n = 5/5) remaining low; 80% of these patients (n = 4/5) had FA. Nine percent (n = 3/33) had low levels and underwent a RIC regimen with 100% (n = 3/3) of AMH levels remaining low; 66% (n = 2/3) of these patients had HLH treated prior to transplant.

Conclusion: AMH levels can be used for detection of premature ovarian failure and fertility counseling. There is a higher risk of premature ovarian failure with MAC regimens and prior chemotherapy vs RIC regimens. Follow up of this cohort will provide more information to understand the effects of HSCT in ovarian function and the usefulness of AMH as a predictor of fertility potential.

Poster # 1003 | RANDOMIZED CONTROL TRIAL EVALUATING THE IMPACT OF XYLITOL ON ORAL HEALTH AND MICROBIOME IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Priscila Badia, Heidi Andersen, David B. Haslam, Adam Nelson, Javier El-Bietar, Sarah Golkari, Ashley Teusink-Cross, Laura Flesch, Ashley Bedel, Victoria Hickey, Kathi, Kramer, Megan Sampson, Stella M Davies, Sarat Thikkurissy, Christopher E. Dandoy

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: There are no proven strategies to prevent blood stream infections (BSI) secondary to oral mucosal barrier injury after hematopoietic stem cell transplant (HSCT). Additionally, we recently reported progressive gingivitis and dental plaque accumulation in HSCT recipients despite our current oral standard of care (three times daily oral rinse). Xylitol is a non-fermentable sugar alcohol that reduces dental caries, plaque accumulation, and oral disease progression by inhibiting bacterial growth. We hypothesized that the addition of Xylitol to standard oral care will decrease dental plaque accumulation, gingivitis and bacteremia from oral flora.

Objectives: Identify a clinically effective strategy to improve oral health and prevent BSI secondary to bacterial translocation through the oral mucosa in patients undergoing HSCT.

Design/Method: We are conducting a prospective randomized control study to test our hypothesis. Those in the intervention arm receive our current standard of care (three times daily oral rinse) in addition to daily Xylitol wipes; controls receive oral standard of care alone. Oral exams are performed at baseline and weekly for the first 28 days post HSCT. Metagenomic shotgun sequencing (MSS) of gingival samples is performed at all time points to evaluate microbiome diversity and pathogenic bacterial load. Finally, we performed whole genome sequencing of pathogenic bacterial isolates causing bacteremia to assess for genetic relatedness to corresponding strains present within the patient's oral microbiome preceding the infection.

Results: Preliminary interim analysis of 21 patients demonstrates improved oral health in patients receiving Xylitol (n = 10) over those receiving standard of care (n = 11), measured by the Oral Hygiene Index (p = 0.03) and Gingivitis Index (p = 0.02). In the nine patients having complete oral MSS analysis, Xylitol appeared to be associated with decreased Streptococcus mitis/oralis domination in the oral microbiome. Finally, patients receiving Xylitol had no incidence of Streptococcus mitis/oralis bacteremia through the first 21 days compared to three patients (27%) in standard of care arm. Interestingly, Streptococcus mitis/oralis comprised 70% of the oral microbiome in one child who subsequently developed a Streptococcus mitis/oralis BSI. We expect to complete this study in the next 4 months (n = 50).

Conclusion: The addition of Xylitol to oral standard care appears to decrease dental plaque and gingivitis in patients undergoing HSCT. Xylitol may also impede Streptococcus mitis/oralis dominance in the oral microbiome with potential reduction in blood stream infections.

Poster # 1004 | CHRONIC TGF BETA STIMULATION OF NK CELLS DURING ACTIVATION BY TUMOR TARGETS LEADS TO EPIGENETIC AND TRANSCRIPTIONAL REPROGRAMMING TOWARD CYTOKINE HYPERSECRETION

Jennifer A. Foltz, Jena J. Edwards, Meisam Naeimi Kararoudi, Nitin Chakravarti, Dean A. Lee

Nationwide Children's Hospital, Columbus, Ohio, United States

Background: TGF BETA is an immune suppressive cytokine frequently elevated in the tumor microenvironment causing tumor immune evasion. Acute TGF BETA treatment potently inhibits NK cell cytotoxicity, cytokine secretion, and proliferation. However, tumor infiltrating NK cells receive chronic inhibitory TGF BETA signals in conjunction with activating signals from tumor cells.

Objectives: To this end, we hypothesized that long-term TGF BETA-cultured NK cells would induce functional and phenotypical changes on NK cells that differ from short-term TGF BETA treatment.

Design/Method: To explore this, primary human NK cells were cultured with the leukemia cell line, K562, alone or with exogenous TGF BETA for 2 weeks.

Results: Surprisingly, NK cells cultured in TGF BETA proliferated faster, and upon challenge with a variety of cell line targets they secreted much greater quantities of IFNÎ^3 (5- to 282-fold increase against 8/8 cell lines) and TNF (3- to 33-fold increase against 7/8 cell lines). Further, the high cytokine secretion induced in these NK cells was no longer inhibited by adding additional TGF BETA. Degranulation was also increased (2/3 cell lines), however cytotoxicity was not enhanced in a 4-hour cytotoxicity assay. After resting in IL-2, the cytokine hypersecretion of TGF BETA-cultured NK cells was maintained for several weeks suggesting this functional change might involve cellular reprogramming. We investigated the mechanism behind these functional changes and profiled 92 genes involved in TGF BETA signaling. We found significant reduction of SMAD3 transcription which corresponded to a striking decrease in SMAD3 chromatin accessibility. We also found significantly increased SMAD6 and decreased TGFBR3 expression. Phenotypic analysis revealed that TGF BETA also induced remodeling of the NK receptor repertoire with decreased NKp30, CD16, and KLRG1 and upregulation of TRAIL. The functional consequences of these TGF BETA-induced changes on in vitro and in vivo NK cell function are currently under investigation.

Conclusion: In conclusion, chronic TGF BETA signaling in combination with tumor stimulation results in epigenetic changes with functional consequences that are opposite that reported for acute TGF BETA treatment. Chronic TGF BETA treatment of NK cells may have implications in cellular therapy.

Poster # 1005 | INFUSION OF DONOR MEMORY T-CELLS AS A SAFE STRATEGY TO IMPROVE IMMUNE RECONSTITUTION AFTER HAPLOIDENTICAL STEM CELL TRANSPLANT

Andreina Figueira, Alba Perez, Blanca Rosich, Yasmina Mozo, David Bueno, Sonsoles San Roman, Berta Gonzalez, Pedro Rubio, Diego Plaza, Ana Sastre, Antonio Perez Martinez

Hospital Universitario La Paz, Pediatric Hemato-Oncology and Stem Cell Transplantation Unit, Madrid, Spain

Background: The use of T-cell depleted grafts in haploidentical stem cell transplantation (HSCT) has been associated with a delay in early T-cell recovery which increases the risk of viral infections, relapse or graft rejection. Conventional donor lymphocyte infusion (DLI) after HSCT transplantation is effective but conditioned because of a high prevalence of GvHD. The infusion of selected lymphocyte subpopulations with low aloreactivity is emerging as an effective strategy to rectify this issue.

Objectives: The depletion of CD45RA+ naive lymphocytes, preserving CD45RO+ memory T-cells, could provide a safe source of functional lymphocytes with anti-infection, anti-leukemic and anti-rejection properties, and lower rates of adverse effects. Our objective is to present data of patients that have received CD45RO+ memory T-cells DLI (mDLI) and assess its safety and outcome.

Design/Method: We present data of mDLI performed after HSCT in cases of mixed chimerism, persistent lymphopenia, viral/opportunistic infections or as a strategy to accelerate immune reconstitution.

Results: Fifteen patients with diagnosis of ALL (n = 6), AML (n = 3), MDS (n = 1), SAA (n = 3), Sideroblastic Anemia (n = 1) and CGD (n = 1), received mDLI after HSCT. A total of forty-three mDLI were infused. The median dose of CD45RO+ memory T-cells infused was 5.00 × 107/kg (range:4.8 × 104-4.25 × 108/Kg), with a median dose of CD45RA+ naive T-cells of 3.90 × 102/kg (range:0-1.3 × 104/Kg). The mDLI were infused at a median of seventy-seven days after HSCT (range:14-407 days), with a median interval between mDLI of thirty-four days

(range:4-159 days). Twenty-one mDLI (49%) were administered because of lymphopenia, fourteen of them (33%) in patients with concomitant viral/opportunistic infections. Mixed chimerism/graft failure was the motive of 37% of the mDLI (n = 16) and six (14%) were administered to accelerate immune reconstitution. All infusions were well tolerated without appearance or worsening of GvHD. An increase in T-cell counts was observed following six mDLI (28.57%), although it was a transitory response (3-8 weeks) in five cases. Viral/opportunistic infections were controlled in five cases (35.71%), requiring a median of 2 mDLI to achieve this response. None of the mDLI administered in cases of mixed chimerism/graft failure were effective in reverting this situation.

Conclusion: Our preliminary data suggests that mDLI, is a safe adoptive immunotherapy strategy even with high dose of T-cells without infusion side effects or GvHD complications. Some efficacy has been observed in patients with lymphopenia and opportunistic infections, with no positive results in patients with mixed chimerism/graft failure, up to date. However, to determine the real efficacy of this strategy, prospective studies are required.

Poster # 1006 | MALE FERTILITY FOLLOWING REDUCED INTENSITY CONDITIONING REGIMEN HSCT

Jun Zhao, Kristen Beebe, Lucia Mirea, Alexandra Walsh, Shane Lipskind, Alexander, Ngwube

Phoenix Children's Hospital, Phoenix, Arizona, United States

Background: Male adolescents undergoing myeloablative hematopoietic stem cell transplantation (HSCT) develop infertility with impaired spermatogenesis with reported rates ranging from 17% to 80%. In nonmalignant diseases, myeloablative regimens have been replaced with reduced intensity conditioning (RIC) with the hopes of better survival rate, less organ toxicity and improved quality of life. Despite the increased use of RIC regimens for HSCT, the effects of RIC on fertility remain unknown.

Objectives: To assess fertility following RIC HSCT in young adult males.

Design/Method: We assessed gonadal function and semen characteristics in adolescent males (>14 years) who received a single RIC HSCT at Phoenix Children's Hospital for nonmalignant diseases during 2006–2016. Male patients who were a minimum of 1 year from RIC HSCT and had postpubertal development at Tanner Stage III or above were eligible for this study. Gonadal status was assessed by measuring FSH, LH, testosterone, and inhibin B levels, and semen analyses assessed fertility indicators (semen volume, sperm concentration, motility, viability, forward progression, morphology, and total count).

Results: Hormone levels and semen analysis have been obtained for 3 patients thus far. The median time between transplant and semen analysis was 4 years. Post HSCT, 2 (67%) patients showed abnormally elevated LH levels, but FSH, testosterone (total and free), and inhibin B levels were within normal range for all patients. Sperm morphology and viability testing were not able to be performed due to low concentrations and volumes. As a result, the total motile sperm count, the most useful estimate for fertile potential, is essentially 0 for all 3 patients.

Conclusion: Recruitment is ongoing, but so far our limited results suggest that RIC HSCT may have detrimental long-term effects on male fertility. A multi-institutional trial may be appropriate due to small patient numbers at each institution. We are currently exploring options to expand to other centers. Further consideration is warranted regarding decisions made by providers, ways to improve anticipatory counseling provided to patients and their families prior to transplant, and how to augment the preventive care of these patients in long-term follow-up. Currently all male patients being considered for RIC transplant should be counseled to sperm bank prior to transplant.

Poster # 1007 | POOLED ANALYSIS OF DEFIBROTIDE STUDIES IN TREATMENT OF PEDIATRIC PATIENTS WITH VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) OR CHEMOTHERAPY WITHOUT HSCT

Selim Corbacioglu, Saurabh Aggarwal, Ozlem Topaloglu, Kathleen F. Villa

University of Regensburg; Regensburg, Germany

Background: A previous systematic literature review identified all published studies of defibrotide treatment for patients of all ages with VOD/SOS.

Objectives: To assess Day+100 survival for defibrotide-treated pediatric patients (≤18 or ≤16 years, per study)

with VOD/SOS with and without multi-organ dysfunction (MOD).

Design/Method: PubMed and Embase databases were searched for "defibrotide" in English-language papers and conference abstracts published to July 10, 2017. Recent 2017 congress abstracts were searched using conference websites. Duplicates were removed.

Study types included were: randomized-controlled, single-arm, cohort, case series (≥10 cases), and retrospective chart reviews; excluded publication types were: case reports (<10 cases); meta-analyses; reviews; animal, modeling, pharmacokinetic, chromatography, and adult-only studies; guidelines; articles; and letters. Resulting reports were screened for exclusion criteria. Full-text articles were then reviewed for eligibility. Study characteristics of selected publications were summarized, and publications were categorized by patients' MOD status. When necessary, additional data tables were requested. A random effects model was used for pooling data for efficacy. Interstudy heterogeneity was assessed with Cochran's Q-test. Percentage of total variation across studies due to heterogeneity (I2) was evaluated. Reported adverse events (AEs) were reviewed.

Results: Eight published studies reported survival outcomes for pediatric VOD/SOS patients (n = 1036), across all defibrotide doses. Estimated Day+100 survival (95% confidence interval) was 60% (53%–67%). For VOD/SOS with MOD, 4 studies were identified (n = 402) with pooled estimated Day+100 survival of 57% (52%–61%). Only one open-label expanded-access study, the treatment-IND, reported outcomes separately for pediatric VOD/SOS patients without MOD (n = 289 patients aged ≤16 years). The Day+100 Kaplan-Meier estimated survival for those patients was 78% (72%–82%). Safety results were not pooled due to differences in reporting methodology; however, study results were consistent with the safety profile of the phase 3 historically-controlled trial in VOD/SOS patients with MOD (43% pediatric), in which 101/102 defibrotide-treated patients and all 32 controls experienced ≥1 AE. Hypotension was the most frequent AE (39%, defibrotide; 50%, controls); common hemorrhagic AEs (ie, pulmonary alveolar and gastrointestinal hemorrhage) occurred in 64% of defibrotide-treated patients and 75% of controls.

Conclusion: In this pooled analysis of studies with defibrotide-treated pediatric patients with VOD/SOS, estimated Day +100 survival was 60% (without MOD, 78%; with MOD, 57%). Safety results in individual studies were generally consistent with the known safety profile of defibrotide. Taken together, these results show a largely consistent defibrotide treatment effect in pediatric patients treated with defibrotide for VOD/SOS, with or without MOD.

Supported by Jazz Pharmaceuticals

Poster # 1008 | OUTCOMES IN EARLY INITIATION OF EXTRACORPOREAL PHOTOPHERESIS IN PEDIATRIC GRAFT-VERSUS-HOST DISEASE PATIENTS

Joanna Gendreau, Jennifer Stahlecker, Kyrie Magee, Kristen Beebe, Dana Salzberg, Holly Miller, Alex Ngwube, Leon Su, Frank Nizzi, Roberta H. Adams

Phoenix Children's Hospital, Phoenix, Arizona, United States

Background: Acute graft versus host disease (aGVHD) is a significant cause of morbidity and mortality in patients undergoing stem cell transplant. First line therapy in aGVHD is corticosteroids. However, only 50% of patients respond, and for patients who fail steroids, no clear second line therapeutic option exists. To improve initial response rates, patients at Phoenix Children's Hospital with aGVHD are started on early-initiated extracorporeal photopheresis (EI-ECP) either concurrent with high dose systemic steroids or rapidly after poor response to steroids. To date, there is no literature describing outcomes of pediatric aGVHD patients who are treated with EI-ECP.

Objectives: To describe clinical outcomes in pediatric aGVHD patients treated with EI-ECP.

Design/Method: A retrospective review was conducted of patients with aGVHD, treated with EI-ECP from 2014–2017. Inclusion criteria: Pediatric patients less than 18 years of age at the time of transplant, diagnosis of a Grade 2–4 aGVHD, and EI-ECP started within 2 weeks of the diagnosis of aGVHD.

Results: Six patients met inclusion/exclusion criteria. All patients were started on ECP while concurrently receiving 1.5 to 2 mg/kg steroid therapy for aGVHD plus a calcineurin inhibitor. Patients had initiation of ECP within a maximum of 2 weeks from initial diagnosis of aGVHD (range 3–12 days). Patients had Grade 2–4 aGVHD (3/6 patients with grade 4) with skin, liver, and GI GVHD represented.

Patients received EI-ECP 2–3 times per week for the first 6 weeks and then had EI-ECP frequency tapered based on initial response.

After 6 weeks of therapy 1 patient had a decrease in overall GVHD grade by 1 grade. All patients were able to have steroids tapered, with doses decreased by an average of 62% (33% - 100% decrease).

At 12 weeks of therapy, one patient with Grade 4 aGVHD died of MOF associated with infections. Three patients had complete resolution of aGVHD and 2 patients decreased by 1 grade. Steroid doses were decreased by an average of 91% (69% - 100% decrease).

All patients exhibited infectious complications with at least 1 viral infection. Four patients also had bacterial infections. Of note, no patient developed evidence of fungal infections.

Conclusion: Early institution of ECP in patients with high risk acute GVHD (Grade 3–4) was very effective at treating aGVHD, allowed for an aggressive steroid taper and contributed to excellent overall survival rates (83%). Infectious complications were primarily viral and bacterial, with no fungal infections in this very high risk population.

Poster # 1009 | DEFIBROTIDE TREATMENT OF NEUROBLASTOMA PATIENTS DEVELOPING HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT): FINAL DATA FROM AN EXPANDED-ACCESS PROGRAM (T-IND)

Stephan A. Grupp, Araz Marachelian, Sonata Jodele, Robert Ryan, Robin Hume, William Tappe, Paul G. Richardson

The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States

Background: VOD/SOS is a life-threatening complication of HSCT conditioning. VOD/SOS with multi-organ dysfunction (MOD) may be associated with >80% mortality. Defibrotide is approved to treat hepatic VOD/SOS with renal/pulmonary dysfunction post-HSCT in the US and severe hepatic VOD/SOS post-HSCT patients aged >1 month in the EU. There are few published data on survival of neuroblastoma patients with VOD/SOS post-HSCT.

Objectives: To report *Day+100* survival and safety *post hoc* for patients with neuroblastoma and VOD/SOS post-HSCT in the defibrotide T-IND trial.

Design/Method: VOD/SOS was diagnosed by Baltimore or modified Seattle criteria or biopsy, with/without MOD, after HSCT or chemotherapy. Defibrotide treatment (25 mg/kg/day) was recommended for ≥21 days. This *post hoc* analysis is based on 1154 adult and pediatric patients receiving ≥1 dose of defibrotide, including 571 with MOD.

Results: Among 111 patients with neuroblastoma, 106 developed VOD/SOS after HSCT. For these post-HSCT patients, 60.4% were male and 39.6% were female, median age was 3 years (range 1–17 years): 7.6% aged 0–23 months, 90.6% 2–11 years, 0.9% 12–16 years, and 1 patient >16 years. Day+100 survival data were available for 105/106 of these neuroblastoma patients (43 with MOD and 62 without MOD); 103 had autologous and 2 had allogeneic transplants. Kaplan-Meier estimated Day+100 survival for the neuroblastoma group was 87.2% (95% confidence interval [CI], 79.0%–92.4%). For the MOD and no MOD subgroups, Kaplan-Meier estimated Day+100 survival was 78.4% (95% CI, 62.6%–88.2%) and 93.5% (95% CI, 83.6%–97.5%), respectively. In the overall T-IND HSCT population aged ≤16 years (n = 570) and pediatric autologous HSCT subgroup (n = 127), Kaplan-Meier estimated Day+100 survival was 67.9% and 87.1%, respectively.

Treatment emergent adverse events (TEAEs) occurred in 45.3% (n = 48/106), with serious TEAEs in 23.6% (25/106; most common: multi-organ failure, 4.7% [5/106]). TEAEs lead to treatment discontinuation in 17.0% (n = 18; most common: pulmonary hemorrhage, n = 3); death occurred in 10.4% (n = 11; >2%: multi-organ failure, 4.7%; VOD/SOS, 2.8%). Treatment-related adverse events, as assessed by investigators, occurred in 17.0% (n = 18; most common: pulmonary hemorrhage, 2.8%).

Conclusion: This *post hoc* analysis found Kaplan-Meier estimated Day+100 survival of 87.2% in patients with neuroblastoma and VOD/SOS post-HSCT, which was consistent with outcomes in pediatric patients after autologous HSCT. The safety profile of defibrotide in neuroblastoma patients was consistent with the overall HSCT population in this study and other defibrotide studies in pediatric patients.

Supported by Jazz Pharmaceuticals

Poster # 1010 | CONTINUOUS TEMPERATURE MONITORING IN THE INPATIENT SETTING USING TEMPTRAQ

Megan Sampson, Victoria Hickey, John Huber, Priscila Davila, Jon Eager, Stella Davies, Christopher Dandoy

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Blood stream infections occur in nearly 30% of patients undergoing hematopoietic stem cell transplant (HSCT) and fever is often the first symptom. Timely administration of antibiotics is associated with improved outcomes, thus, early recognition of fever is paramount. Current standard of care (SOC) includes episodic monitoring of temperature in hospitalized patients, which may delay fever detection. Therefore, continuous real-time body temperature measurement may detect fever prior to the current SOC. TempTraq is a Food and Drug Administration cleared class II medical device and consists of a soft, comfortable, disposable patch that

continuously measures axillary temperature and wirelessly transmits real time-time data.

Objectives: The primary aim of the study was to evaluate the feasibility, safety and tolerability of continuous temperature monitoring in HSCT patients using TempTraq.

Design/Method: We are performing a prospective observational study of pediatric patients (1-12 years of age) undergoing HSCT at Cincinnati Children's Hospital in Cincinnati, Ohio. Enrolled patients wore a TempTraq patch for 5 days. A 1–10 rating scale survey was completed by the parent/guardian at the end of the study to determine tolerability, ease of use, satisfaction and desire for future use in the inpatient and outpatient setting. Temperature data from the TempTraq patch was compared to the standard episodic temperature monitoring to determine detection of febrile episodes.

Results: Seven of ten patients have completed screening. We anticipate completion of the study in early February. The TempTraq patch was well tolerated by study subjects (mean tolerability rating of 8.7/10). One patient developed skin breakdown at the site of the TempTraq patch attributed to recent Thiotepa. The patch was easy to apply with an easy of application rating of 9.7/10. Parents were overall satisfied (rating 8.4/10) and would like to use the TempTraq patches in future hospitalizations (rating 8.4/10) and at home (rating 8.9/10). TempTraq patch identified fever ($\geq$ 100.4°F) in 4 patients. The fever was never detected by episodic monitoring (SOC) in 2 patients and significantly delayed in the other 2 patients (>12 hours).

Conclusion: Continuous temperature monitoring via TempTraq was well tolerated in pediatric HSCT patients. Timely fever detection was improved in TempTraq over the current SOC.

Poster # 1011 | CHARACTERIZATION OF SEROTHERAPY-ASSOCIATED FEVER IN PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANT

Jorge Galvez Silva, Angela Smith, Weston Miller, John Wagner

University of Minnesota, Masonic Children's Hospital, Minneapolis, Minnesota, United States

Background: Serotherapy is commonly used in patients undergoing hematopoietic stem cell transplant (HSCT) to reduce the incidences of engraftment failure and graft versus host disease. However, one well-known side effect is fever. As children undergoing HSCT have compromised immune defenses, fever may also be an early indicator of bloodstream infection, which would warrant prompt use of broad-spectrum antibiotics. In a subset of patients with serotherapy-associated fever, antibiotics, which may induce antibiotic resistance and increase costs, may be unnecessary.

Objectives: We aimed to determine the incidence and characteristics of serotherapy-related fever, as well as the likelihood of concomitant bacteremia, in our institutional experience.

Design/Method: A 5-year retrospective chart review was conducted of pediatric patients who received serotherapy as part of HSCT conditioning at the University of Minnesota.

Results: One-hundred sixty eight consecutive HSCT patients who received serotherapy - either ATG (N = 99) or alentuzumab (N = 69) – were identified. The median age at HSCT was 6-years (range, 0.4-18 years). A total of 133 patients (79 %) developed fever while on serotherapy (ATG = 79, alentuzumab = 54). One-hundred sixteen patients presented fever following the first infusion, and the median onset of fever was 7 hours after commencing infusion (range, 0.1-22 hours). Fever resolved at a median 8 hours (range, 1–48 hours). One hundred and fourteen patients (98%) underwent blood cultures. Only seven patient were not started on (6%) empiric antibiotics, while 14% (N = 17) were on antibiotic treatment prior to serotherapy for previously known or suspected infections. Nine patients (7% of febrile patients, 4% of all patients) had positive blood cultures (ATG = 6; Alentuzumab = 3). No infection-associated deaths were observed.

Conclusion: While fever is common during serotherapy conditioning in children undergoing SCT, episodes of concomitant bloodstream infection are rare. Ongoing analysis identified potential risk factors for bacteremia as recent history of infection, first episode of fever following second or subsequent infusions, and previous central line placement. Further analysis is being conducted to identify subgroups of patients for whom close monitoring alone may be safe.

Poster #1012 | UNRELATED OR PARTIALLY MATCHED RELATED DONOR HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) WITH TCRA/B/CD19 DEPLETION FOR CHILDREN AND YOUNG ADULTS (CAYA) WITH ACUTE LEUKEMIAS

Sarah Lo, Yongping Wang, Dimitri Monos, David Barrett, Farah Contractor, Stephan Grupp, Nancy Bunin

Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States

Background: HSCT is potentially curative for CAYA with high-risk leukemias; however, most lack an HLA-matched

related donor. The risk of GVHD is increased with unrelated (URD) or partially matched related (PMRD) donors. Selective T-cell depletion based on the elimination of T cells carrying α and β chains of the T-cell receptor may greatly reduce the GVHD risks, while allowing the maintenance of mature donor-derived alloreactive NK cells and $\gamma/\delta(+)$ T cells, which may augment the anti-leukemia effect.

Objectives: This is a prospective study of CAYA with acute leukemia who underwent HSCT with MMRD or URDs and TCRα/β/CD19 depletion. Outcomes included engraftment, toxicities, viral reactivation, and relapse.

Design/Method: This study included 36 CAYA with acute leukemia transplanted between October 2014 and May 2017. All received a myeloablative preparative regimen with targeted busulfan (n = 15) or TBI (1200 cGy/6 fractions) (n = 21), with thiotepa (10 mg/kg) and cyclophosphamide (120 mg/kg). ATG (3 mg/kg x 3) was given to those receiving haploidentical grafts and to the first 17 who received URD grafts. Immune suppression was not given post-HSCT. The stem cell source was mobilized peripheral blood stem cells (PSCs), which then underwent TCRα/β/CD19 depletion utilizing the CliniMACS device under GMP conditions in the CHOP Cellular Immunotherapy Lab.

Results: Median age was 11 (range 1.3-21.7). Diagnoses included ALL (9-B-cell, 3-T-cell) and AML (24; 3-secondary AML). URD were used for 28; 13 were 10/10 allele matched and 15 were 9/10 matched. Haploidentical donors were used for 8. Median CD34(+) dose -

10.1 × 106, $\alpha/\beta(+)$ CD3(+) cells - 5.63 × 106, and B cells - 8.95 × 104. All patients achieved an ANC at a median of d+13 (8-30), and 94% had platelet engraftment at

median d+17 (12-40). Nine patients (25%) developed acute GVHD (all skin, grades I-IV). Five developed chronic GVHD (skin, gut, lung): limited in 4, extensive in 1. Viral reactivations included: adenovirus (5, 14%), BK virus (8, 22%), CMV (10, 28%), and

HHV6 (2, 6%). Nine (25%) patients relapsed at a median of 147 days (range 57–625)

post-HSCT, including 7 AML patients (29.2%) and 2 ALL patients (16.7%). Transplant- related mortality was 14%; causes included sepsis (6) and ARDS (2). OS was 72%; EFS was 58% (GVHD-free EFS 39%, LFS 61%).

Conclusion: HSCT with TCRα/β/CD19 depletion demonstrates excellent engraftment kinetics with limited GVHD without immune suppression. Elimination of post-HSCT immunosuppression may offer an excellent platform to augment anti-leukemic immune therapy or to enhance immune reconstitution.

Poster # 1013 | LONGTERM BONE HEALTH FOLLOWING CURATIVE HEMATOPOIETIC CELL TRANSPLANTATION FOR SICKLE CELL DISEASE

Kirshma Khemani, Lilian Meacham, Lakshmanan Krishnamurti, Elizabeth O. Stenger

Aflac Cancer and Blood Disorder's Center, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, Georgia, United States

Background: Hematopoietic cell transplantation (HCT) is the only curative treatment available for patients with sickle cell disease (SCD). Low bone mineral density (BMD) has been described in SCD, but little is known about the impact of curative HCT on this outcome.

Objectives: To determine the prevalence of low BMD and variables associated with low BMD in SCD patients after HCT.

Design/Method: We conducted a retrospective chart review of SCD patients who underwent HCT at Children's Healthcare of Atlanta (CHOA) between 12/1993 and 12/2016 and survived ≥1 year post-HCT. Transplant characteristics, post-HCT dual-energy x-ray absorptiometry (DEXA) scan results, vitamin D levels, graft-versus-host-disease (GVHD) status, and FSH levels were reviewed. For patients 2–20 years of age, height corrected Z-scores were calculated using a NIH-validated calculator, with T-scores used for older patients. BMD was categorized as low if between -1 and -2 SD below the mean and clinically significantly low if >-2 SD, in accordance with the Children's Oncology Group Long-Term Follow-Up Guidelines. Vitamin D levels <20 ng/mol were considered deficient, and FSH levels >40mIU/ml suggestive of premature ovarian failure. Fisher's exact test was used to compare variables in those with normal versus abnormal DEXA scan results, with $p<0.05$ considered significant.

Results: HCT was performed on 71 patients with SCD, with 67 surviving ≥1 year post-HCT. DEXA scans were obtained in 40 patients (55% female), with mean time from HCT to DEXA scan being 4 years (1.3-11.2 years) and mean age at time of DEXA 13.1 years (6.1-22.3 years). Patients with and without DEXA scans did not differ by sex, donor source, age at transplant, or vitamin D status. Low BMD was noted in 10 patients (25.0%), with these patients more likely to be >13 years (pubertal; 90.0 versus 40.0%, $p = 0.009$). Acute GVHD was more common in patients with low BMD (50.0 versus 16.7%), but not statistically significant ($p = 0.085$). Clinically significant low BMD was noted in 3 patients (7.5% of those with DEXA scans). These patients were older (16.2 years at testing), were more likely to be male (66.6%), and all had

acute and chronic GVHD, while none had evidence of gonadal failure.

Conclusion: Clinically significant low BMD is uncommon after HSCT for SCD. Patients at risk for low BMD include older patients and likely those with GVHD. This preliminary data suggests routine DEXAs may not be indicated for all patients who undergo HCT for SCD, but further data is needed.

Poster # 1014 | HIGH RATES OF ACUTE RENAL DYSFUNCTION AND ASSOCIATED MORTALITY AFTER HEMATOPOIETIC CELL TRANSPLANT IN CHILDREN

Mackey A, Davila Saldana B, Radha Rohatgi, Williams KM, Mistry K

Children's National Medical System, Washington, District of Columbia, United States

Background: Causes of renal dysfunction after hematopoietic cell transplantation (HCT) include damage from radiation, nephrotoxic medications, graft vs. host disease (GVHD), hepatorenal syndrome, viral infections, or transplant associated microangiopathy. We sought to investigate the incidence of, and risk factors for, acute kidney injury in pediatric HCT patients and associated risk with mortality.

Design/Method: Data from patients who underwent HCT between 2013 and 2016 at a single institution were sequentially retrospectively captured on IRB approved protocol. Acute kidney injury (AKI) was defined at multiple time points post-HCT using the standardized criteria: Kidney Disease: Improving Global Outcomes (KDIGO). Interval differences between values were analyzed using Wilcoxon rank sum testing and categorical variables were analyzed using chi-square analysis.

Results: Ninety-eight patients were included in the study: allogeneic (n = 96) and autologous (n = 2), mean age 8.7 years, of whom 50% were African American, 3% Asian, 21% Caucasian, 13% Latino, and 13% mixed race. Forty-seven percent of patients developed AKI within the first 2 years of HCT. Increased risk for AKI was associated with a lower pre-transplant creatinine level (p = 0.001), abnormal pre-transplant BUN (p = 0.019) and an unrelated donor (p = 0.022) while preparative regimen intensity, race, or primary disease were not. Twenty-six percent of patients developed AKI within 30 days of HCT. Of those with AKI, 41% were exposed to either cidofovir, aminoglycosides, and/or ambisome for at least 5 days versus 18% without AKI and 74% were exposed to vancomycin compared to 49% without AKI. Evaluating outcomes at 1 year after HCT, of those with stage 1 AKI: 10% had reduced GFR and 37% died, while 14% had reduced GFR and 43% had died for patients with AKI stage 2 or 3. The absence of AKI by day 30 was associated with 24% reduced GFR and 8% death at 1-year after HCT. Overall, those with AKI at any time in the first year post-HCT had a 3.7 fold increased risk of death compared to those without. For patients who required renal replacement therapy (RRT, n = 8), the risk of death was 19.5 fold greater compared to those who did not. In the 25% of patients who survived RRT, both recovered renal function within 2 years.

Conclusion: Acute kidney injury is common after pediatric HCT, and may be associated with low creatinine, abnormal BUN, unrelated donor pre-HCT, and renal toxic medications. Early-onset AKI post HCT is associated with an increased risk of mortality. These data should be validated in a larger prospective study but may offer opportunities to intervene and enhance outcomes.

Poster # 1015 | PATIENT CONTROLLED ANALGESIA (PCA) USE AMONG PEDIATRIC MYELOABLATIVE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS: THE FIRST THIRTY DAYS

Sara Silbert, Sonali Chaudhury

Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, United States

Background: Myeloablative hematopoietic stem cell transplant (HCT) for pediatric malignant disease is associated with significant morbidity with 90% patients experiencing mucositis. Patient controlled analgesia (PCA) utilizing opioids is an effective strategy for pain management.

Objectives: We sought to describe and analyze PCA use in D+30 days post myeloablative HCT for malignancies at Lurie Children's Hospital of Chicago from 2010–17.

Design/Method: Utilizing retrospective chart review, PCA details were collected: indication, initiation day, PCA duration, team managing PCA (anesthesia or palliative), medication and dose in morphine equivalents, and PCA toxicities. Efficacy of PCA was evaluated on PCA day + 3, +7, +14, +21 using demands %, maximum pain score (rFLACC, FACES, VAS) and subjective patient, parent and/or pain team perception of pain control. We devised a scale based on the above to designate pain control as good, moderate or poor. Variables being analyzed include recipient age, sex, donor type, source, diagnosis, TBI use, GVHD/TRM.

Results: Of 100 patients, 98 were started on a PCA in the 30 days post HCT. 65% were male with median age of 11y. 46% had ALL, and 37% AML. Matched related donors were used in 21% and 79% received TBI. PCA was initiated median D+2. Oral mucositis alone was the most common indication (80%). A majority of patients were started on hydromorphone (79%); 20% started on morphine and 1% started on fentanyl. 49% started on continuous infusion. PCA was used for a median of 20 days (range 4–144 days). Median pain score was highest D+3 of PCA use, however, there was inconsistency in charting of numerical pain scores. On D+3, 12 patients had insufficient data to determine efficacy of pain control; of the remaining 86 patients, 24% had good pain control while 60% had moderate and 15% had poor pain control using our devised scale. The most common toxicity observed was respiratory depression (~30%), however, etiology was often multifactorial and not due to opiates alone. Analysis is ongoing to assess variables predicting PCA use as well as efficacy of pain control and correlation between current reporting scales and patient perception.

Conclusion: PCA use is common in pediatric HCT yet pain control remains inadequate. There's a need for better evaluation of PCA management, especially uniform assessment of pain, thereby improving quality of life post HCT.

Poster # 1016 | NEXT GENERATION SEQUENCING USED TO IDENTIFY INDOLENT PROGRESSIVE RARE INFECTION

Emily Abbey, **Ben Hanisch**, **Kirsten Williams**

Children's National Health System, Washington, District of Columbia, United States

Background: Actinomycosis is a rare invasive anaerobic gram-positive bacterial disease caused by *Actinomyces* spp. that may colonize the oropathynx, gastrointestinal tract and urogenitial tract and can lead to abscesses. Respiratory tract actinomycosis is characterized by pulmonary cavities, nodules, consolidations and pleural effusions. Although actinomyces are nearly always sensitive to penicillin they are frequently resistant to cephalosporins and variable sensitives to fluoroquinolones. Although rare in children, immunosuppressed patients are at increased risk for actinomycosis.

Objectives: To describe a case of next-generation sequencing identification of actinomycosis.

A 13-year-old male with a history of very high risk B-Cell acute lymphoblastic leukemia who was 5 months status post a 7/8 matched unrelated donor bone marrow transplant complicated by prolonged fevers, persistent weight loss, and splenic lesions, treated with posaconazole and levofloxacin developed fever and cough in the setting of neutropenia. Blood cultures demonstrated Staphylococcus epidermidis. CT showed micronodules and effusion not consistent with S. Epi, prompting bronchoscopy. All bacterial cultures were negative. Patient was prescribed a three-week course of vancomycin with rapid improvement.

Design/Method: 16S Next generation sequencing (NGS) from bronchoalveolar levage sample was performed at the University of Washington Laboratory

Results: NGS assay from bronchoalveolar lavage showed major abundance of actinomyces most closely related to meyeri or oodontolyticus. Demonstrated actinomyces. The patient was started on a six month course of amoxicillin with continued clinical improvement. In retrospect, the splenic nodules that were presumed fungal disease were likely actinomycosis, partially treated with levofloxacin.

Conclusion: This case highlights the potential utility of NGS in the diagnosis of rare diseases in immunocompromised patients. Actinomycosis was only demonstrated through NGS and led to a change in treatment regimen and durable clinical improvement. Because actinomyces often mimics malignancy, tuberculosis or nocardiosis, the use of this novel test both targeted appropriate therapy and reduced the exposure to unnecessary medications to treat the differential diagnosis. Finally, we highlight that Actinomyces should be considered in patients who present with unexplained fevers, weight loss, and night sweats.

Wong, BMJ, 2011

Poster # 1017 | CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY CAN RENDER PATIENTS WITH ALL INTO PCR-NEGATIVE REMISSION AND CAN BE AN EFFECTIVE BRIDGE TO TRANSPLANT (HCT)

Haneen Shalabi, Cynthia Delbrook, Maryalice Stetler-Stevenson, Constance Yuan, Bonnie Yates, Terry J. Fry, Nirali N. Shah

Center for Cancer Research, National Cancer Institute, National Institute of Health, Bethesda, Maryland, United States

Background: CAR-T therapy, while effective, may not be durable for all, and antigen negative escape is a growing problem. HCT, in relapsed/refractory ALL, can be curative, particularly for those in an MRD negative remission. We demonstrated that CD19 directed CAR-T therapy effectively rendered patients into MRD negative remissions (by flow cytometry) and the leukemia free survival post-HCT was high[1]. In

this analysis, we analyze the depth of remission, CAR-T persistence, and post-transplant GVHD on our phase I anti-CD22 CAR-T protocol (NCT02315612) to better understand the role of CAR-T in the peri-HCT setting.

Design/Method: Children and young adults with relapsed/refractory CD22+ ALL treated on our phase I anti-CD22 CAR-T protocol were analyzed. MRD was assessed by flow cytometry (FC) in all, with PCR-based MRD analysis using IgH or TCR testing assessed in select patients. HCTs were performed at each patient's local institution based on standard of care and included varying conditioning regimens, donor types, stem cell source, and GVHD prophylaxis.

Results: On our CD22 CAR trial, 36 patients were treated, the majority of patients (n = 29) having relapsed following a prior HCT. 23/36 patients (64%) attained a CR, 18 of whom were MRD negative by FC. Concurrent PCR based MRD analysis available in 8 patients demonstrated that all patients achieved PCR based negativity. In 6, this was simultaneous with the 1 month MRD negative FC, and in 2, PCR negativity was achieved over time (FC remained negative). 4 patients proceeded to HCT at a median time of 70 days (range: 54–117 days) post-CAR-T, which was a first HCT in 2. These two patients remain in an MRD negative CR, 1 year post-CAR-T. No patients developed acute or chronic GVHD. CAR persistence was seen in 3 patients who had detectable CAR-T cells on the pre-HCT marrow suggesting the possibility of ongoing anti-leukemia surveillance prior to initiation of the conditioning regimen.

Conclusion: By inducing PCR negativity, CAR-T therapy may have a synergistic role with HCT to improve leukemia free survival, prior to emergence of antigen negative leukemia, without an increased risk of GVHD. While the sample size is small, CAR-T therapy may offer an effective bridge to HCT, particularly for those who are PCR negative, and those who have not had a previous transplant. Given the underlying risk of HCT related TRM, pre-HCT CAR may potentially allow for HCT conditioning de-intensification as it may not be needed to eradicate residual disease.

1 Lee DW, ASH abstract 218, 2016

Poster # 1018 | DEVELOPMENT OF AN LMP-SPECIFIC T CELL BANK FOR THIRD PARTY USE AS A CURATIVE STRATEGY FOR POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE (PTLD) AFTER SOLID ORGAN TRANSPLANT

Lauren McLaughlin, **Lauren Roesch**, **Devin Saunders**, **E. Kathy Mintz**, **Fahmida Hoq**, **Birte Wistinghausen**, **Mitchell S. Cairo**, **Patrick J. Hanley**, **Catherine M. Bollard**

Children's National Medical Center, Washington, District of Columbia, United States

Background: Post-transplant lymphoproliferative disease (PTLD) is a complication after solid organ transplantation (SOT) that is frequently due to Epstein - Barr virus (EBV) as a decrease in EBV-specific T cell immunity due to immune suppression allows for uncontrolled proliferation of EBV-infected B cells. Outcomes for PTLD are suboptimal with relapse rates approaching 50%. However, EBV-infected B cells in PTLD express the EBV antigens LMP1 and LMP2 that can be targeted with immune therapy.

Objectives: We hypothesize that third party "off the shelf" LMP-specific T cell products may improve outcomes and decrease associated co-morbidities for patients with PTLD by not only target the lymphoproliferating EBV-infected B cells but also restoring EBV-specific immunity.

Design/Method: LMP-specific T cells (LMP-TCs) are manufactured from eligible donors with a broad range of HLA types in our GMP facility to be used in a Children's Oncology Group (COG) trial (ANHL1522) for patients with PTLD after SOT. LMP-TC products are manufactured from healthy donors using autologous monocytes and lymphoblastoid cell lines (LCL) transduced with an adenoviral vector expressing ΔLMP1 and LMP2 as antigen presenting cells. LMP-TC products undergo comprehensive characterization by IFN-γ ELISPOT assay to determine LMP-specific epitopes, Class I and/or II response, and HLA restriction to guide selection of LMP-TC product for each patient.

Results: Thus far, 27 LMP-TC products have been manufactured. LMP-TCs were active against LMP2 (mean: 158 SFU/1 × 10^5 cells; range: 1–800), LMP1 (31; 0–355), and LCL (105; 0–424) as determined by IFN-γ ELISPOT assay. At the time of cryopreservation, the LMP-TC products comprised a mean of 36% CD8+ T-cells, 45% CD4+ T-cells, and 8% NK cells. No B cells or monocytes were detected in the final products. Thus far, we have identified 3 novel LMP epitopes (LMP1 specific: n = 1; LMP2 specific: n = 2). Approximately 80% of the LMP-TC products have LMP-specific activity through multiple HLA alleles, and 67% have a mixed Class I and Class II response. **Conclusion:** Thus, LMP-specific T cell products can be expanded from healthy donors to creat a third party bank, and identifying epitopes and HLA alleles with LMP activity will facilitate selecting the most appropriate product for patients. While LMP-specific T cells have previously demonstrated safety and efficacy in phase I studies, ANHL1522 is the first trial using cellular therapy within a cooperative group setting.

Poster # 1019 | TRANSPLANT CENTER PRACTICES FOR PSYCHOSOCIAL ASSESSMENT AND MANAGEMENT OF PEDIATRIC HSC DONORS

Galen E. Switzer, Nirali Shah, Bronwen E. Shaw, Gabrielle Pastorek, Jesssica Bruce, Michael A. Pulsipher, Chloe Anthias, Peter Bader, Andre Willasch, Jennifer Sees, Jennifer Hoag, Wendy Pelletier, Brent Logan, Pintip Chitphakdithai, Lori Wiener

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: More than 4,500 pediatric HSCTs are performed in North American and Europe each year. The ethics of exposing a healthy child to donation procedures which have some risks and no direct medical benefits continue to be a topic of debate. Pediatric donors may experience psychological distress and poorer quality-of-life during and after donation compared to healthy controls. Although there are FACT/JACIE requirements related to the management of pediatric donors, it is unclear what standardized practices exist for psychosocial assessment/management of this group.

Objectives: To describe transplant center practices for psychosocial evaluation/ management of pediatric donors (<18 years) and to examine differences in practices by location (CIBMTR/EBMT) and number of harvests (volume).

Design/Method: Data were collected via a single cross-sectional survey distributed electronically to CIBMTR and EBMT centers between 9/18/17 and 11/20/17.

Results: 55/98 (56%) of CIBMTR and 85/147 (58%) of EBMT centers completed the survey. Most centers had written eligibility guidelines for pediatric donors (91%). Most also had a process for ensuring that donors were freely assenting to donate (78%), managed by a transplant physician (61%). A single physician often jointly managed donor/recipient care (44%). Half of centers had a pediatric donor advocate (51%), who was most often a physician (38%) or social worker (16%). Cost was the largest barrier to having a donor advocate (82%). Most centers performed psychosocial screening of donors (69%) but rarely declined donors based on psychosocial concerns (13%). Less than half of centers provided post-donation psychosocial follow-up (41%). Comparisons by center location indicated that EBMT centers were more likely to have a physician doing joint donor/recipient care (60% vs. 23%; p = .001), less likely to have a psychosocial assessment policy (53% vs. 79%; p = .011), less likely to have a donor advocate (37% vs. 69%; p = .002), but marginally more likely to do post-donation psychosocial follow-up (49% vs. 31%; p = .063). Large volume centers were more likely to have a psychosocial assessment policy than their medium/smaller counterparts (69% vs. 23%, 27%; p = .003) â€“there were no other differences on key psychosocial management variables by volume.

Conclusion: Although most centers have written guidelines for pediatric donor eligibility and mechanisms for ensuring assent, substantial numbers of donors do not undergo psychosocial assessment, are jointly managed with the recipient by a single physician without an assigned donor advocate, and do not receive psychosocial follow-up. The field would benefit from guideline development for the psychosocial management of pediatric donors.

Poster # 1020 | OUTCOMES OF HEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS WITH GERMLINE SAMD9/SAMD9L MUTATIONS

Ibrahim A. Ahmed, Jason R. Schwartz, Erika D. Friehling, Mark T. Vander Lugt, Jeffery M. Klco, Brandon Triplett, Rakesh K. Goyal

Children's Mercy Kansas City, Kansas City, Missouri, United States

Background: Germline mutations in *SAMD9* and *SAMD9*L genes cause MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes and enteropathy) and Ataxia-Pancytopenia syndromes, respectively, and are associated with chromosome 7 deletions, MDS and bone marrow failure (BMF). There are limited data on outcomes of HCT in these patients.

Objectives: To describe outcomes of allogeneic HCT in patients with hematologic disorders associated with *SAMD9/SAMD9L* mutations.

Design/Method: Retrospective case series.

Results: Seven patients underwent allogeneic HCT for primary MDS (n = 5), congenital amegakaryocytic thrombocytopenia (CAMT)(n = 1), and dyskeratosis congenita (n = 1). Retrospective exome sequencing revealed gain-of-function mutations in *SAMD9* (n = 4) or *SAMD9L* (n = 3) genes. Constitutional mosaic monosomy 7 was present in 6 cases. Two *SAMD9* patients had features of MIRAGE syndrome. Unusual findings of panhypopituitarism, laryngeal cleft, and glomerulosclerosis were noted in one case. In another case with a *SAMD9* mutation hypospadias & bifid scrotum were the only findings. The remaining patients had no phenotypic abnormalities.

Median age at HCT was 5y (range: 1.4 -12.8). Patients received transplants from bone marrow (matched unrelated (n = 3) & HLA identical sibling (n = 2)), or unrelated cord blood (UCB) (n = 2). Five MDS patients received myeloablative

conditioning (busulfan-based (n = 3) or TBI–based (n = 2)); 2 patients (MDS (n = 1); CAMT (n = 1)) received reduced-intensity conditioning (RIC) (fludarabine, cyclophosphamide, with rATG or alemtuzumab). Syndrome-related comorbidities (diarrhea, infections, malnutrition, electrolyte imbalance, lung disease and hypoxia) were present in both patients with MIRAGE syndrome.

One patient with a familial *SAMD9L* mutation, MDS and morbid obesity failed to engraft following RIC double UCBT. She died one year later from refractory AML. All other patients achieved neutrophil and platelet engraftment, at a median (range) of 15 (12-19) and 16 (12-31) days, respectively. Post-transplant complications included severe hypertension (n = 1), pericardial effusions (n = 2), veno-occlusive disease of liver (n = 1), and recurrent aspiration pneumonias (n = 1). One patient developed grade III aGVHD which resolved with treatment. One patient developed mild skin cGVHD and suffers from chronic lung disease. All surviving patients had resolution of hematological disorder and sustained peripheral blood donor chimerism (98-100%). Overall survival was 86% with a median follow-up of 3 years (range: 1.1 – 14.7 y).

Conclusion: Patients with hematological disorders associated with germline *SAMD9 /SAMD9L* mutations tolerated transplant conditioning without unusual, or unexpectedly severe toxicities. Allogeneic HCT led to successful resolution of MDS or BMF, with excellent overall survival. More data is needed to refine transplant approaches in *SAMD9/SAMD9L* patients with significant comorbidities, and develop guidelines for their long-term follow-up.

Poster # 1021 | IMMUNE EFFECTOR CELL TRANSITION TO STANDARD OF CARE: THE CHILDREN'S CANCER HOSPITAL AT MD ANDERSON CANCER CENTER EXPERIENCE

David McCall, **Sarah Featherston**, **Joan O'Hanlon Curry**, **Sajad Khazal**, **Kris Michael Mahadeo**

Children's Cancer Hospital at the University of Texas MD Anderson Cancer Center, Houston, Texas, United States

Background: In 2017, the United States Food and Drug Administration (FDA) approved the first chimeric antigen receptor T cell (CAR-T) therapy; tisagenlecleucel. This CD19-directed genetically modified autologous T cell immunotherapy has shown response rates of almost 90% among children and young adults with B-cell precursor acute lymphoblastic leukemia (ALL) that are refractory or in second or later relapse. Cytokine release syndrome (CRS) and CAR-T cell related encephalopathy syndrome (CRES) are well described toxicities associated with CAR-T therapy. CRS is a systemic inflammatory response and is typically characterized by fever, hypoxia, tachycardia, hypotension and multi-organ toxicity. CRES may occur concurrently or following CRS, or without any associated CRS symptoms and is characterized by encephalopathy, delirium, seizures and rarely cerebral edema. Almost half of patients who receive tisagenlecleucel may require pediatric intensive care unit (PICU) support. CRS and CRES are generally reversible but may be associated with fatal outcomes. Pediatric specific management guidelines, comprehensive training of multidisciplinary staff, effective communication and phased infrastructure ensure that adequate resources are available to facilitate early diagnosis and appropriate management of pediatric patients with CRS and CRES and allow for optimal patient outcomes and accreditation by the Foundation for Accreditation of Cellular Therapy (FACT).

Objectives: Develop a comprehensive program to ensure safe administration of Immune Effector Cell (IEC) therapy to pediatric patients.

Design/Method: An inter-disciplinary pediatric CARTOX (CAR T cell therapy associated TOXicity) committee consisting of cell therapy and PICU physicians, neurologists, fellows, nursing leadership, advanced practice practitioners, pharmacists, registered nurses and social workers was created to monitor patient toxicity and establish specific clinical guidelines and diagnostic and treatments algorithms for pediatric patients receiving IEC therapy. Educational modules were developed as (i) live in-services and (ii) an online module with a competency based assessment. Electronic Medical Record (EMR) order sets and documentation and warning systems were also developed by the committee.

Results: The pediatric CARTOX committee developed a diagnostic and treatment algorithm for patients receiving IEC therapy. EMR orders and flowsheets were developed to support adherence to the algorithm. Inter-disciplinary staff training and competency assessments were closely tracked. Almost 97% of identified staff have completed training and achieved competency including, Pediatric Cell Therapy Staff, Emergency Center, PICU, Outpatient Clinic/Triage, Neurology and sub-specialty staff and nocturnalists.

Conclusion: An inter-disciplinary approach can assist in institutional readiness for an IEC Program, promote quality assurance and perhaps FACT IEC accreditation. Future directions include a program for ongoing staff competency assessments.

Poster # 1022 | THE EFFICACY OF BASILIXIMAB AND INFLIXIMAB IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS WITH STEROID-REFRACTORY ACUTE GVHD

Shyamli Singla, **Tiffany Simms-Waldrip**, **Andrew Y. Koh**, **Victor M. Aquino**

University of Texas Southwestern Children's Medical Center, Dallas, Texas

Background: Steroid-refractory acute graft versus host disease (aGvHD) is a potentially fatal complication of allogeneic hematopoietic stem cell transplantation (HSCT). Basiliximab (anti- IL2-R monoclonal antibody) as a single agent or in combination infliximab (anti-TNF-α monoclonal antibody) has demonstrated efficacy in adult cohorts with steroid-refractory aGvHD, but has not been well studied in the pediatric population. We adopted the use of basiliximab and infliximab as our institutional standard of care for steroid-refractory aGvHD in pediatric HSCT patients.

Objectives: To determine the response and survival of HSCT children who received basiliximab and infliximab for the treatment of steroid-refractory aGvHD.

Design/Method: We retrospectively reviewed children who received basiliximab and infliximab for steroid-refractory aGvHD refractory between September 2011 and December 2017.

Complete response (CR) was defined as resolution of all clinical signs of aGvHD. Partial response (PR) was defined as at least one grade reduction in one target organ (e.g. skin, gut or liver) without increased grade in another target organ. No response was defined as either no improvement or progressive worsening of aGvHD in at least one organ. Baseline demographics, transplant details, laboratory findings, and treatment outcomes were also evaluated.

Results: Of the 214 evaluable HSCT patients, 15 children (median age 11 yrs, range 9 mo-19 yrs) with steroid-refractory aGvHD received combination monoclonal antibody (MAB) therapy. The median time from the start of steroid therapy to initiation of MAB was 13 days. The overall Glucksberg grade of aGvHD at the time of initiating MAB therapy was grade I (n = 1, 6.7%) II (n = 3; 20%), III (n = 8; 53%) or IV (n = 3; 20%). The overall response rate was 53%, with 3 (20%) patients achieving CR, 5 (33.3%) patients achieving PR, and 7 (46.7 %) patients with no response at 30 days following the start of MAB therapy. The median overall survival was 613, 292, and 84 days for patients who exhibited CR, PR, and no response, respectively. The overall survival at 1 year following start of MAB therapy was 40%.

Conclusion: Basiliximab and infliximab combination therapy is effective for steroid-refractory aGvHD in pediatric HSCT patients.

Poster # 1023 | HIGH DOSE CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS STEM CELL RESCUE FOR HIGH RISK SOFT TISSUE SARCOMA: RETROSPECTIVE REVIEW

Avis Harden, **Preethi Fernandez**, **Danielle Defeo**, **Basirat Shoberu**, **Jonathan Gill**, **Richard Gorlick**, **Kris Mahadeo**, **Sajad Khazal**

MD Anderson Cancer Center, Houston, Texas, United States

Background: The role of high dose chemotherapy (HDC) and autologous stem cell rescue (ASCR) in patients with high risk (advanced metastatic or relapsed) soft tissue sarcomas is controversial. Despite multimodal chemotherapy, radiotherapy, and local control measure advancements, prognosis of patients with advanced metastatic or unresectable and relapsed sarcomas remains poor, with less than 10% 5 years disease free survival.

Objectives: to determine if consolidation with myeloablative HDC and ASCR improves relapse free (RFS) and overall survival (OS) outcomes in a high risk patient subgroup.

Design/Method: We performed retrospective review of all high risk soft tissue sarcoma patients who underwent HDC and ASCR at the Children's Hospital at Montefiore, Bronx, NY between October 2014 and January 2018. The protocol was approved by Albert Einstein College of Medicine Institutional Review Board.

Results: 7 patients (4 primary metastatic high risk disease, 3 relapsed or recurrent disease) received HDC with ASCR. Primary diagnoses were rhabdomyosarcoma (RMS) (n = 2, alveolar histology), primary site nasopharynx (n = 1) and lower extremity (n = 1). Ewing's sarcoma (EWS) (n = 5), axial site (pelvic) in 3 patients (60%). Median age 12 years (range 6–35 years), 5 (71%) were male. All patients were in complete metabolic remission before transplant. Median pre transplant comorbidity index was 3 (range 0–4). 5 patients (2 RMS and 3 EWS) received conditioning with carboplatin, etoposide and melphalan. Remaining 2 patients with EWS received conditioning with busulfan, melphalan and topotecan. All patients received peripheral blood mobilized hematopoietic stem cell transplantation. Stem cell mobilization achieved with high dose filgrastim in all patients except one who required addition of plerixafor. Median CD34+/Kg

recipient body weight cell dose infused was 6.34 × 10^6 (range 2.72-12.03 × 10^6). Median times to neutrophil and platelet (>20,000/ÂμL) engraftment were 9 (range 8–13) and 49 (20-76) days respectively. 2 patients (28%) developed BK viuria (one with grade III hemorrhagic cystitis); 3 (43%) developed CMV viremia; and one patient (14%) had asymptomatic EBV viremia. There was no graft failure, sinusoidal obstruction syndrome or transplant related mortality. Median follow up post-transplant was 452 days (range 155–1141 days). 3 year probability of OS and RFS were 80% and 50% respectively.

Conclusion: HDC with ASCR is a promising therapeutic strategy to consolidate remission and improve survival in select high risk soft tissue sarcoma patient subgroups. Prospective clinical trials will inform the impact of disease status prior to HDC and ASCR on outcome, optimal conditioning and long term relapse free and overall survival.

Poster # 1024 | DETERMINATION OF OCCULT TESTICULAR LEUKEMIA PRIOR TO ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Kendall Presti, **Mitchell Cairo**, and **Claudio Sandoval**
New York Medical College, Valhalla, New York, United States

Background: Absence of minimal residual disease is paramount for cure of pediatric acute lymphoblastic leukemia (ALL). The testis may harbor occult leukemia and this disease may result in treatment failure.

Objectives: The purpose of this study was to assess the long-term outcomes of boys with or without testicular leukemia pre-hematopoietic stem cell transplantation (HSCT).

Design/Method: Retrospective analysis of 16 boys with high-risk de novo (2 with hypodiploidy ALL) or recurrent/refractory ALL was conducted. Flow cytometry of bone marrow mononuclear cells was used to determine remission status. Testicular evaluations were performed by physical examination and wedge biopsy pre-HSCT.

Results: The median age at time of transplant was 12.3 years. All patients were in remission by flow cytometry of bone marrow mononuclear cells at the time of transplant and none had evidence of clinically apparent testicular disease. Testicular leukemia was detected in 1 patient and he underwent bilateral orchiectomy. He developed acute graft versus host disease (GvHD) of the duodenum and sigmoid colon which resolved, and the leukemia remains in second complete remission and he is free of HSCT-related morbidity 33.6 months post-HSCT. Of the 15 patients without testicular leukemia 4 died a median of 8.2 months (range, 2.5 to 12.5) post-HSCT (2 with adenovirus infection and 1 each with thrombotic microangiopathy and Aspergillus pneumonia); 6 experienced infection (Staphylococcus species, Corynebacterium, Enterococcus, Klebsiella, Citrobacter, E. coli, Epstein Barr virus, Adenovirus, BK virus, Human herpesvirus-6, Candida albicans, Fusarium, Aspergillus, Yeast, and other fungus); 11 experienced GvHD (8 of the GI tract, 6 of the skin, 5 of the liver, 3 of the eyes, 2 of the mouth, and 1 of the lungs); and 1 developed a second neoplasia (right lower leg leiomyosarcoma). One patient developed bone marrow minimal residual disease (2.7% phenotypically abnormal cells detected 9 months after 6/6 matched sibling HSCT). Reinduction therapy comprised 5 weekly doses of rituxan, 2 courses of blinatumomab and 2 donor lymphocyte infusions with IL-2. Two subsequent bone marrow evaluations were minimal residual disease negative. Thirteen months post-HSCT residual disease recurred (0.012%) and he will receive inotumumab. Overall median survival post-transplant of the 16 boys is 32.1 months (range, 2.5 to 75.3) and of the 12 surviving boys is 37.3 months (range, 11 to 75.3).

Conclusion: Testicular biopsy can detect occult leukemia pre-HSCT. Testicular leukemia pre-HSCT does not appear to increase the risk of subsequent relapse or other HSCT-related adverse events compared to those without it.

Poster # 1025 | THERAPEUTIC EFFECTS OF A NOVEL FUSION OF ALT-803, AN IL-15 SUPERAGONIST, WITH 4 SINGLE-CHAINS of ANTI-CD20 ANTIBODY (2B8T2M) IN COMBINATION WITH EXPANDED NATURAL KILLER CELLS AGAINST RITUXIMAB SENSITIVE AND RESISTANT BURKITT LYMPHOMA (BL)

Yaya Chu, Nang Kham Su, **Sarah Alter**, **Emily K. Jeng, Peter R. Rhode**, **Mathew Barth**, **Dean A. Lee**, **Hing C. Wong**, **Mitchell S. Cairo**
New York Medical College, Valhalla, New York, United States

Background: Rituximab has been widely used in front-line treatment of B-NHL including Burkitt lymphoma (BL), however, some patients retreated with rituximab relapse, which limit patient treatment options. Novel therapies are desperately needed for relapsed/refractory B-NHL patients.

Several strategies for overcoming rituximab-resistance are currently being evaluated, including engineering immune cells with chimeric antigen receptors (CAR), as well as second-generation anti-CD20 antibodies. Nature Killer (NK) cells play important roles in the rejection of tumors. However, NK therapy is limited by small numbers of active NK cells in unmodified peripheral blood, lack of tumor targeting specificity, and multiple mechanisms of tumor escape of NK cell immunosurveillance. Our group has successfully expanded functional and active peripheral blood NK cells (exPBNK). 2B8T2M was generated by fusing ALT-803, an IL-15 superagonist, to four single-chains of rituximab. 2B8T2M displayed tri-specific binding activity through its recognition of the CD20 molecule on tumor cells, activated NK cells to enhance ADCC, and induced apoptosis of B-lymphoma cells.

Objectives: To examine if 2B8T2M significantly enhances the cytotoxicity of exPBNK against rituximab-sensitive and -resistant BL cells.

Design/Method: exPBNKs were expanded with lethally irradiated K562-mbIL21-41BBL and isolated using Miltenyi NK cell isolation kit. ALT-803 and 2B8T2M were generously provided by Altor BioScience. NK receptors expression and cytotoxicity were examined as we previous described. IFNg and granzyme B levels were examined by ELISA assays. Equal doses of Rituximab, ALT-803, Rituximab+ALT-803, obinutuzumab (obinu) were used for comparison. IgG was used as controls. Anti-CD20 CAR exPBNK cells were generated as we previously described by mRNA electroporation. Rituximab-sensitive Raji and -resistant BL cells Raji-2R and Raji-4RH, were used as target cells.

Results: 2B8T2M significantly enhanced exPBNK cytotoxicity against rituximab-sensitive Raji cells, rituximab-resistant Raji-2R cells and resistant Raji-4RH cells compared to the controls IgG, Rituximab, ALT-803, Rituximab+ALT-803, obinu ($p<0.001$, E:T = 1:1). Furthermore, we confirmed the enhanced cytotoxicity by measuring IFN-g and granzyme B production. 2B8T2M significantly enhanced IFN-g and granzyme B production from exPBNK against Raji, Raji-2R and Raji-4RH compared to IgG ($p<0.001$), Rituximab ($p<0.001$), ALT-803 ($p<0.001$), Rituximab+ALT-803 ($p<0.001$), and obinutuzumab ($p<0.001$). When compared to anti-CD20 CAR exPBNK cells, 2B8T2M + exPBNK had the similar cytotoxicity against Raji, Raji-2R and Raji-4RH as anti-CD20 CAR exPBNK cells did ($p>0.05$).

Conclusion: 2B8T2M significantly enhanced exPBNK activating receptor expression and *in vitro* cytotoxicity against rituximab-sensitive and –resistant BL cells. The *in vivo* functions of 2B8T2M with exPBNK against rituximab–sensitive and -resistant BL cells using humanized NSG models are under investigation.

Poster # 1026 | ABNORMAL CARDIOPULMONARY EXERCISE TESTING IN PEDIATRIC STEM CELL TRANSPLANT RECIPIENTS DESPITE NORMAL CARDIAC FUNCTION BY STANDARD ECHOCARDIOGRAPHIC PARAMETERS

Adam W. Powell, **Clifford Chin**, **Elaine Urbina**, **John L. Jefferies**, **Peace Madueme**, **Michael Taylor**, **Wayne A. Mays**, **Christopher Dandoy**, **Seth Rotz**, **Stella M. Davies**, **Adam Lane**, **Suzanne Berger**, **Sonata Jodele**, **Thomas D. Ryan**

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

Background: Cardiac dysfunction, including left ventricular systolic dysfunction (LVSD), is a known complication in stem cell transplant (SCT) survivors. While detection of LVSD by echocardiography is important in this population, there has been minimal research to determine if subclinical cardiac dysfunction exists in SCT patients. Cardiopulmonary exercise testing (CPET) is a valuable tool to assess cardiac function, and to determine how the heart responds to the stress of exercise. No studies have been performed to determine if SCT patients with normal LVSD on standard echocardiography may have abnormal CPET.

Objectives: To determine the feasibility of CPET, as well as additional echocardiographic parameters, to detect dysfunction in SCT patients with a normal ejection fraction on echocardiogram.

Design/Method: We performed a cross-sectional analysis of SCT survivors who were at least 3 years post SCT, 8 years of age or older and with an ejection fraction > 50% (low end of normal range) on echocardiogram. We assessed the exercise capacity of all patients with CPET, and sub-clinical cardiac dysfunction through tissue Doppler and strain analysis from the echocardiogram.

Results: Seven patients (6 male) have qualified and completed this study so far with an average age of 12.2±3.4 years. The median time from transplant is 4.4±0.8 years. All seven patients had a normal ejection fraction, however four patients had abnormalities on their CPET. These abnormalities included abnormal predicted peak oxygen consumption (VO2) (61%±9.8, normal > 70%) (the best predictor of functional capacity), predicted oxygen pulse (62%±10.1, normal > 70%) (measure of cardiac stroke volume) and ventilatory efficiency (VE/VCO2 slope) (39±7.6, normal < 30). Submaximal exercise data, used when patients are unable to complete a maximal effort test, demonstrated low-normal predicted VO2 at anaerobic threshold (45.8%±7.2%, normal >45% of

predicted peak VO2) and abnormal oxygen uptake efficiency slope at the anaerobic threshold (1359.3±297.8.9, normal 1790±310). Additionally, on echocardiogram three patients had evidence of diastolic dysfunction as evidenced by an elevated E/A ratio (1.9±0.4) on tissue Doppler. Three patients demonstrated depressed longitudinal peak systolic strain (-17.7±2.8), indicating dysfunction not captured by ejection fraction.

Conclusion: In this feasibility study, SCT patients without evidence of LVSD on standard measures by resting echocardiogram can demonstrate abnormal exercise capacity. Additionally, they can demonstrate systolic and diastolic dysfunction by measures not always included in standard echocardiography. These data suggest the need for a more thorough screening of survivors, and will be further validated as additional patients are recruited for this study.

Poster # 1027 | CD45 RA DEPLETION AS AN ALLOGENIC HEMATOPOIETIC TRANSPLANTATION PLATFORM IN CHILDREN FROM HLA-IDENTICAL DONORS

Miguel Angel Diaz, **Marta Gonzalez-Vicent**, **Blanca Molina**, **Elena Sebastian**, **Josune Zubicaray**, **Julian Sevilla**

Hospital Nino Jesus Hematopoietic Stem Cell Transplant Unit, Madrid, Spain

Background: In hematopoietic transplantation, the T lymphocytes of the inoculum play a determining role in promoting hematopoiesis, transferring immunity to pathogens and acting as mediators of the graft-versus-leukemia effect (GVL). However, they are also responsible for graft-versus-host disease (GVHD), the main cause of post-transplant morbidity and mortality. The depletion of CD45 RA lymphocytes, by eliminating naive T lymphocytes from the inoculum, aims to conserve the GVL without producing GVHD.

Design/Method: Since April 2016, 14 patients (8 boys and 6 girls), with a median age of 8 years, have undergone an allogeneic hematopoietic transplant from an HLA donor identical with CD45 RA/CD19 depletion. The indication for transplant was: acute lymphoblastic leukemia (4), acute myeloblastic leukemia (4), myelodysplasia (5) and medullary aplasia (1). The donor was familiar in 4 cases and unrelated in 10. The conditioning regimen was with fludarabine, busulfan and thiotepa. The median of CD34 + cells infused was 6.82 × 10 6 / Kg. On the day 0, +15 and +30 a programmed infusion of 1 × 106 / Kg lymphocytes CD45RA- was performed.

Results: All the patients grafted with a median leukocyte (> 0.5 × 109 / L) and platelet (> 20 × 109 / L) engraftment time of 15 and 10 days, respectively. Only one patient has developed acute GVHD grade I and no patient has developed chronic GVHD. Immune reconstitution was early and rapid in all T cell subsets No patient has relapsed so far and only 1 patient with myelodysplasia has developed an AML. She has received a 2nd transplant and has died of relapse. There was no case of toxic mortality. The event-free survival (SLE) was 90 Â± 10% with a median follow-up of 10 months. At present, 13 patients are alive, out of immunosuppressive treatment and doing well.

Conclusion: Allogeneic transplantation with CD45 lymphocytes RA depletion resulted on very encouraging results, with a very low incidence of acute and chronic GVHD, but preserving the GVL effect by infusing CD45 RA- donor lymphocytes.

Poster # 1028 | INFUSION OF HEMATOPOIETIC STEM CELL PRODUCTS VIA PUMP MECHANISM

Trisha Kissoon, Kamar Godder, John Fort

Miami Children's Health System, Miami, Florida, United States

Background: Hematopoietic stem cell transplantation (HSCT) using autologous or allogeneic progenitor cells is a potentially curative treatment for patients with high-risk malignancies and nonmalignant conditions. The American Society for Blood and Marrow Transplantation developed a task force to establish consensus guidelines for defining patient care in HSCT and advocated for further studies to delineate safe procedural steps as an increasing amount of HSCT are being offered to patients. There is limited evidence to support engraftment in recipients who receive their infusions via IV or syringe pump. We present novel data from patients who achieved neutrophil engraftment following HSCT by a pump mechanism.

Objectives: To provide evidence supporting the use of pump (intravenous or syringe) infusion method in hematopoietic stem cell transplantations.

Design/Method: A retrospective review was completed for 114 patients who underwent HSCT between 2003 and 2012. Inclusion criteria included patients who had received hematopoietic stem cell transplants between 2003 and 2012 and who were ages 6 months to 21 years old. The main outcome measure was days to neutrophil engraftment (defined as the first of three consecutive days with an ANC $> 5 \times 10^9$/L).

Results: Among 114 patients who received infusion of hematopoietic stem cell products via pump mechanism, 63 patients (55.3%) received autologous products and 51 (44.7%) received stem cells from allogeneic donors. Neutrophil engraftment (ANC $> 5 \times 10^9$/L) occurred in a median of 14.5 days after stem cell infusion. The mean number of days to engraftment for patients who received allogeneic infusions

was 19.4 days while patients who received autologous infusions had a mean number of days to engraftment of 13.3.

Conclusion: Engraftment after HSCT needs to be prompt to minimize duration of neutropenia and maximize survival rates[6]. Our data demonstrates that the infusion of hematopoietic stem cell products with a syringe or IV pump is an effective method of delivery for stem cell products and does not delay the time to engraftment. The median days to neutrophil engraftment was 14.5 days. This is comparable to data from the NMDP, which reports engraftment occurs within 14–20 days. The main limitation to this study was its small sample size due to the number of transplants done at our center. However, it does provide evidence to support that infusion of stem cell products via pump mechanism is a safe alternative to the infusion by gravity method in the process of the hematopoietic stem cell administration.

Poster # 1029 | LOW-DOSE AZACITIDINE FOR RELAPSE PREVENTION AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN CHILDREN WITH MYELOID MALIGNANCIES

Benjamin Oshrine, **David Shyr**, **Gregory Hale**, **Aleksandra Petrovic**

Johns Hopkins All Children's Hospital, St. Petersburg, Florida, United States

Background: Leukemic relapse remains the most common cause of treatment failure after allogeneic hematopoietic cell transplant (alloHCT) for myeloid malignancies. Most children who relapse post-alloHCT will die of their disease, making interventions to minimize this risk a high priority.

Objectives: To evaluate the safety and efficacy of post-transplant azacitidine for relapse prevention in children undergoing alloHCT for myeloid malignancy.

Design/Method: We retrospectively reviewed the charts of children undergoing alloHCT for myeloid malignancies between February 2015 and November 2016 at Johns Hopkins All Children's Hospital.

Results: During the study period, 18 children (ages 2 to 20 years, median 12) underwent alloHCT for myeloid malignancies: *de novo* acute myeloid leukemia (AML), 11; mixed phenotype acute leukemia, 2; treatment-related AML, 2; juvenile myelomonocytic leukemia with AML transformation, 2; and myelodysplasia/AML, 1. Thirteen were in first complete remission, 5 were in CR2 or greater. Most patients (13/18) received fludarabine/melphalan/thiotepa conditioning; 11 received HLA-identical related or unrelated donors, and 7 received haploidentical bone marrow grafts with post-transplant cyclophosphamide. Three patients never received planned azacitidine (2 early relapse; 1 early TRM), leaving 15 evaluable patients. Azacitidine (32mg/m^2/dose for 5 days, in 28-day cycles for up to 9 cycles) was started at a median of 66 days post-transplant (range 42–118). Two-thirds (10/15) of patients received eight or more cycles. Of five patients who stopped therapy early, only one was due to toxicity; other reasons included severe GVHD (1), parental preference (1), and relapse (2). Cycle delays occurred in 9 patients, with a median 2 cycles delayed per patient, mostly for mild myelosuppression with early cycles. No patient required blood product transfusion during therapy, but G-CSF was used in three patients to maintain ANC>500/μL. Dose-modifications were made in 3 patients (renal tubular acidosis, acute kidney injury, and myelosuppression). There were 3 relapses (20%), two of which occurred in patients in CR2, for a relapse incidence of 9% in patients in CR1, with a median follow-up of 20 months (range 12.5 to 28). No patients who received azacitidine died of transplant-related mortality.

Conclusion: Administration of azacitidine in children undergoing alloHCT for myeloid malignancies is safe and feasible, with most patients successfully receiving all planned cycles. Toxicity was acceptable and there was no TRM or secondary graft failure. Despite the limitations of a small cohort, relapse incidence—particularly in patients transplanted in CR1—suggests a potential benefit in disease control that warrants investigation in follow-up studies.

Poster # 1030 | EXCELLENT OVERALL SURVIVAL AFTER GRAFT FAILURE IN PEDIATRIC PATIENTS WITH SEVERE APLASTIC ANEMIA: A SINGLE-CENTER EXPERIENCE

Madhuri Dave, **Tatiana Saldarriaga**, **Pippa Simpson**, **David A. Margolis**, **Monica S. Thakar**

Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Background: Despite significant improvements in the success rate of hematopoietic cell transplantation (HCT), graft failure remains an important complication in patients transplanted for severe aplastic anemia (SAA). Second allogeneic HCT can salvage patients, but 5-year overall survival (OS) rates have been reported as low as 60%[1].

Objectives: Identify patients who developed dropping donor chimerism, graft rejection, and/or graft failure after first HCT for SAA, necessitating additional HCTs or cellular boosts (defined as stem cell products infused without preceding chemotherapy), and evaluate treatment-related complications and OS.

Design/Method: A retrospective chart review was performed at the Children's Hospital of Wisconsin. Statistical analyses included Kaplan-Meier estimate for OS, Mann-Whitney Test for comparing outcomes between subjects, and descriptive analyses.

Results: From 2005–2016, 14 patients with a median age of 7.5 (4.3-23.0) years at 1st HCT were identified. Patients were conditioned with CY/ATG (n = 3), CY/FLU/ATG (n = 6), or CY/FLU/ATG/TBI (n = 5) and received marrow (n = 13) or cord blood (n = 1) with median CD34/kg dose of 6.82 (1.88-10.90) $\times 10^6$. Two patients developed grade I acute graft-versus-host disease (GVHD); none developed chronic GVHD. Due to dropping chimerism, graft rejection, or graft failure, 2nd HCT (n = 9) or boost (n = 5) was offered. The median CD3 chimerism prior to HCT/boost was 53 (0-100)%. Median time between 1st HCT and 2nd HCT or boost was 134 days (42 days- 5.1 years). In 9 patients receiving 2nd HCT, 5 used the same donor, of which 3 used the same stem cell source (marrow) and 2 switched to peripheral blood stem cells (PBSC). In 4 patients who switched donors, 3 used PBSC and 1 used cord blood. Most patients receiving 2nd HCT underwent a uniform conditioning regimen of CY200/FLU150/equine ATG/8 Gy TLI (n = 5) or CY120/FLU120/rabbit ATG/2 Gy TBI (n = 3); one received CY/ATG. Acute and chronic GVHD (limited seen in 83%) developed in 50% and 43% of patients, respectively. Four patients required 18 additional boosts and 1 additional HCT. After final intervention, CD3 and whole- blood chimerism at last follow-up was between 95–100% (n = 9) and 90–100% (n = 5), respectively. With a median follow-up of 8.6 (3.8-12.8) years, 13 of 14 patients are alive with an estimated 10-year OS of 92.3 ± 0.07%, having performance status ≥90% (n = 12) or 80% (n = 1). One patient developed chronic extensive GVHD and died of fungal infection 2.1 years after 2nd HCT.

Conclusion: Our single-center experience demonstrates excellent ability to salvage patients who develop graft failure after initial HCT. Transplant-related complications such as GVHD and infections remain significant concerns.

1. Cesaro, BJH, 2015