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Children's Oncology Group's 2013 Blueprint for Research: Rare Tumors

Carlos Rodriguez-Galindo, MD[1,*], **Mark Krailo, PhD**[2], **Lindsay Frazier, MD**[1], **Murali Chintagumpala, MD**[3], **James Amatruda, MD**[4], **Howard Katzenstein, MD**[5], **Marcio Malogolowkin, MD**[6], **Logan Spector, PhD**[7], **Farzana Pashankar, MD**[8], **Rebecka Meyers, MD**[9], and **Gail Tomlinson, MD, PhD**[10] **on behalf of the COG Rare Tumors Disease Committee**

[1]Dana-Farber/Children's Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts

[2]Department of Statistics, Children's Oncology Group, University of Southern California, Arcadia, California

[3]Texas Children's Cancer Center, Baylor College of Medicine, Houston, Texas

[4]University of Texas Southwestern Medical Center, Dallas, Texas

[5]Children's Healthcare of Atlanta, Atlanta, Georgia

[6]Midwest Children's Cancer Center, University of Wisconsin, Milwaukee, Wisconsin

[7]University of Minnesota Medical Center, Minneapolis, Mississippi

[8]Yale University, New Haven, Connecticut

[9]Primary Children's Medical Center, Salt Lake City, Utah

[10]University of Texas Health Science Center, San Antonio, Texas

Abstract

In the US, approximately 2,000 children are diagnosed with rare cancers each year, with 5-year survival ranging from <20% for children with advanced carcinomas to >95% for children with intraocular retinoblastoma or localized germ cell tumors. During the last years, 12 clinical studies have been successfully completed in children with retinoblastoma, liver tumors, germ cell tumors, and infrequent malignancies, including therapeutic, epidemiologic, and biologic studies. Current efforts are centered in the development of large international collaborations to consolidate evidence-based definitions and risk stratifications that will support international Phase 3 clinical trials in germ cell tumors, hepatoblastoma, and other rare cancers.

Keywords

germ cell tumors; hepatoblastoma; rare cancers; retinoblastoma

[*]Correspondence to: Dr. Carlos Rodriguez-Galindo, MD, Department of Pediatric Oncology, Dana-Farber/Children's Hospital Cancer Center; Department of Pediatrics, Harvard Medical School, 450 Brookline Avenue SW350, Boston, MA 02115. carlos_rodriguez-galindo@dfci.harvard.edu.

INTRODUCTION

Low numbers and heterogeneous diagnoses limit clinical and translational research in pediatric rare cancers; comprehensive multidisciplinary efforts, epidemiologic and basic science research, and the design of clinical trials that maximize efficacy and minimize toxicity are needed. Three major overarching initiatives provide a unifying framework for ongoing research in Rare Tumors at the Children's Oncology Group (COG). First, in recognition that small sample sizes and a broad array of diagnoses are a major limitation for the development of clinical trials, new evidence-based disease definition and risk stratification, and methodological innovations that will facilitate the design of large-scale international trials have been prioritized. Second, a strong initiative to investigate the epidemiology and biology of rare cancers has been created; the goal is to gain insight into causation and to identify therapeutic targets and develop rational risk stratification for use in future clinical trials. An emphasis is placed on the role and interaction of specific environmental, gene, and pathway abnormalities, and a comprehensive genome and proteome analysis. Third, as clinical trials in Rare Tumors are developed, they need to be integrated with initiatives in cancer control, adolescent and young adults, and survivorship that will guide towards optimization of therapy and enhanced quality of life (QoL) across all disease groups. These three approaches have the potential to define new ground for clinical and translational research on which further research can be developed.

STATE OF THE DISEASE—CLINICAL

Overview and Incidence

Four disease-specific subcommittees (retinoblastoma, liver tumors, germ cell tumors, and infrequent cancers), compose the Rare Tumors Committee. Collectively, these four disease categories account for approximately 15–20% of all childhood malignancies.

Retinoblastoma—The annual incidence of retinoblastoma is 3.7 cases/million children <15 years; approximately 300 children are diagnosed with retinoblastoma yearly in the US [1]. Retinoblastoma is a cancer of the very young; two-thirds of the cases occur in children under 2 years, and 95% of cases are diagnosed before 5 years. Two clinical forms of retinoblastoma are recognized: approximately 75% of children present with unilateral, sporadic disease, and the remaining 25% have bilateral, hereditary disease. Treatment of retinoblastoma aims at saving life and preserving vision; in the US, where patients present with intraocular disease, cure rates are in excess of 95%, and research priorities are focused on ocular salvage and vision preservation [2].

Liver tumors—The annual incidence of liver tumors is 1.5 cases/million children <15 years, accounting for approximately 150 cases/year in the US [1]. The most common pediatric liver tumor, hepatoblastoma (HB), affects infants and young children; median age at diagnosis is 19 months and 80% of the cases are younger than 15 years [3]. The incidence of HB is increased in children with low-birth weight and prematurity, which may in part explain recently observed increases in incidence rates [4]. Childhood hepatocellular carcinoma (HCC) occurs in two distinct forms: adult-type HCC in the setting of chronic

cirrhosis or inflammation, and *de novo* HCC that develops in otherwise healthy livers [3]. Most intriguing are the "transitional cell tumors," with characteristics of HB and HCC, which often occur in children between the ages of 5 and 15, a transitional age group between the HB and HCC ages [3,5]. Treatment of children with HB includes platinum-based chemotherapy and complete surgical resection of all sites of disease [6]. Approximately 15% of cases require liver transplantation [7].

Germ cell tumors (GCT)—The annual incidence of pediatric GCT is 3.9/million children <15 years, representing 3.5% of all cancers in this age group [1]. This group of malignancies present with a bimodal age distribution, and account for 16% of cancer diagnoses among adolescents. Approximately 60% of cases present in extragonadal sites, most commonly in the sacrococcygeal area (young children) and mediastinum (adolescents). Site correlates with age; extragonadal sites are more common in young children, while gonadal sites predominate in adolescents. Treatment of pediatric GCT follows standard platinum-based therapy and surgery [8,9].

Infrequent tumors—Infrequent tumors include neoplasms that are classified as other malignant epithelial neoplasms and melanomas in the International Classification of Childhood Cancer subgroup XI. These histologies include adrenocortical, thyroid, and nasopharyngeal carcinoma, melanoma and skin cancers, and other unspecified carcinomas. This subset of cancers accounts for 9% of all cancers seen in patients <20 years; three-fourths of these cancers affect patients 15–19 years [10].

Staging and Stratification

Retinoblastoma—Staging of retinoblastoma includes ocular grouping for prognostication of ocular and vision salvage, and disease staging. The International Classification of Intraocular Retinoblastoma distinguishes five groups (A–E) based on tumor size, location, subretinal fluid and seeding, and vitreous seeding [11]. A consensus system for disease staging (International Retinoblastoma Staging System) has been recently adopted; this system is based on surgical and pathological staging and addresses the presence of disease as intraocular, extraocular, or metastatic [12].

Hepatoblastoma—Historically the staging of liver tumors in North American studies has been surgical, based on upfront resectability (stages I–III) and the presence of extrahepatic disease (IV) [3]. More recently this traditional system has been substituted by a risk stratification system that incorporates other prognostic factors such as histological subtype (standard epithelial, pure fetal, small cell undifferentiated), tumor markers, and PRETEXT group to assign four risk categories (very low, low, intermediate, and high-risk) [13]. However, as risk stratification systems for pediatric liver tumors have evolved, the definitions of each risk category have differed across international cooperative groups, making comparison of treatment results very difficult. The Children's Hepatic tumor International Collaboration (CHIC) was established in 2010 to address this challenge (see below).

Germ cell tumors—Staging of GCT is clinical and surgical; four stages are recognized in pediatrics, based on resectability, nodal regional involvement, and presence of metastases [8,9]. An ongoing initiative is to create a consensus staging system between pediatric oncologists, adult gynecologic oncologists who use FIGO staging, and adult testicular cancer groups who use TNM staging.

Infrequent tumors—Staging and risk stratification for the neoplasms included in this category follow the standard disease-specific staging and risk categorization used in their adult counterparts.

Current Outcomes

Retinoblastoma—Treatment of retinoblastoma aims to save life and preserve useful vision, and thus needs to be individualized. Factors that need to be considered include laterality, vision potential, and intraocular and extraocular staging [2]. In the US, most patients present with intraocular disease, and survival rates are in excess of 95%. For patients with unilateral intraocular disease, standard of care includes a risk-adapted approach with enucleation and use of adjuvant chemotherapy for patients with high-risk pathology. Ocular salvage approaches, mostly including systemic [14] or intraarterial [15] chemotherapy are being investigated. Patients with extraocular disease require intensified therapy, with consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue for patients with metastases [16]. More conservative ocular and vision sparing approaches are applied to patients with bilateral disease, usually including systemic or intraarterial chemotherapy and aggressive focal therapy in order to avoid or delay enucleation and irradiation [2,15]. Using these multimodal approaches, ocular salvage rates are >70%. A major effort is to decrease the use of radiation therapy, particularly in young children with the bilateral form. This group of patients has a high cumulative incidence of second malignancies (30–40% at 50 years) and need to be followed for life [17].

Pediatric liver tumors—For low and intermediate risk HB, cisplatin-based regimens have increased overall survival to 95% and 85%, respectively [6]. Because HB occurs primarily in very young children, risk of ototoxicity is markedly increased; ongoing research is targeted at strategies to decrease this life-changing late effect. Survival for high-risk HB remains 45% and is even worse for pediatric HCC at 15% [3,6]. Strategies in high-risk HB are targeted at intensification of chemotherapy strategies (SIOPEL 4), at identification of new agents with novel up-front window study design (AHEP0731), and at biologic characterization of pediatric HCC.

Germ cell tumors—Better risk-adapted approaches have led to improved outcomes for patients with GCT. Low-risk is defined as stage I immature teratoma and testicular disease, and survival is >95% with minimal therapy; most patients can be cured with surgery only [18]. The intermediate-risk category includes patients with stages II–IV gonadal and stages I–II extragonadal tumors; survival rates are >90% with surgery and platinum-based therapy [9,19]. Patients with stages III–IV extragonadal tumors constitute the high-risk group, and their survival rates are not better than 70–75% [8,19]. Treatments of germ cell tumors in the US are based on the intensive use of cisplatin; acute and long-term platinum toxicities in this

young population are common and their amelioration is a focus of future research initiatives [20,21].

Infrequent tumors—Outcome for patients with infrequent tumors is difficult to define due to the lack of consistent data; most of the information available is extrapolated from adult studies. Prospective studies that integrate therapeutic and biological questions for nasopharyngeal carcinoma (NPC) and adrenocortical carcinoma (ACC), two rare malignancies with unique features in the pediatric population, have been designed to overcome this limitation. Childhood NPC is typically EBV+ and follows similar characteristics to the endemic form of NPC. With neoadjuvant chemotherapy and chemoradiation, 5-year overall survival rates are consistently >75–80% [22,23]. Focus of research is on maintaining outcomes while reducing acute and long-term toxicities [22]. Childhood ACC has unique biological, epidemiological, and clinical characteristics; the disease is not very chemosensitive, and stage and resectability determine prognosis [24].

STATE OF THE DISEASE—BIOLOGICAL

Retinoblastoma

Experiments with primary human retinoblastoma samples have revealed novel therapeutic targets, *MDM2* and *MDMX*, which regulate the p53 pathway; inactivation of MDM2/MDMX via Nutlin, a small molecule inhibitor, can result in p53-mediated apoptosis [25]. Other pathways are likely involved in growth and survival of retinoblastoma tumors. Whole genome sequencing has failed to identify additional mutations in oncogenic pathways; however, upregulation of *SYK* has been found. Importantly, SYK inhibitors have been shown to induce apoptosis of retinoblastoma cells in the preclinical models [26].

Hepatoblastoma

As part of the P9346 study, a large series of HB karyotypes was assembled [5,27]. These standard cytogenetic studies were expanded to include oligonucleotide array comparative genomic hybridization (oaCGH) in a series of 220 tumors; this approach has defined an area of amplification on 2q24 that may be associated with a poor prognosis [5,28]. A small genomic deletion on chromosome 22q11 including the *SMARCB1* gene has been identified, loss of which is associated with a very poor outcome in children with HB [29]. Using a combination of FISH and oaCGH, *NOTCH2* was recently discovered to be transposed from proximal 1p to proximal 1q in conjunction with the recurring translocation involving chromosome 1q. *NOTCH2* is an excellent candidate gene for liver tumorigenesis in infants and young children, as it is known to affect development of the embryonal liver and is overexpressed in HB. In addition, a detailed molecular profiling of HB tumors with clinical and histologic correlation is ongoing; this project focuses on molecular pathways involved in embryonic development including the wnt/B-catenin, the IGF, and the NOTCH pathways, and on the development of a murine model of HB.

Germ Cell Tumors

Recently, investigators uncovered a novel role of the LIN28 pathway in germ cell development [30]. LIN28 prevents the processing and function of the *let-7* microRNA, a key

regulator of cellular targets including BLIMP1/Prdm1. BLIMP1 is essential for germ cell development, and by blocking the negative effects of *let-7*, LIN28 facilitates the development of embryonic germ cells. LIN28 is overexpressed in germ cell tumors, thus linking germ cell development to germ cell tumorigenesis [30,31]. LIN28 acts through TUTase, and small-molecule TUTase inhibitors are currently in development, making this pathway an exciting target for novel therapy of germ cell tumors. A second line of research is related to bone morphogenetic protein (BMP) signaling; GCT resembling germinomas arise in the zebrafish model due to a mutation in a BMP receptor [31]. These findings have been confirmed in human germinomas; current work focuses on defining the molecular basis for aberrant signaling in the human tumors. Small-molecule modulators of the pathway are under development, which may offer an alternative therapeutic approach in GCT.

MAJOR RECENT FINDINGS

Retinoblastoma

A Study of Unilateral Retinoblastoma With and Without Histopathologic High-Risk Features and the Role of Adjuvant Chemotherapy (ARET 0332)—This trial is the first formal attempt to carefully document the prevalence of high-risk features using real-time central pathology review and to apply risk-adapted therapy. The central review committee reclassified about a quarter of patients enrolled as standard risk to the high-risk group while 13% of patients enrolled as high-risk were reclassified to standard risk.

Trial of Systemic Neoadjuvant Chemotherapy for Group B Intraocular Retinoblastoma (ARET 0331)—In this study exploring reduced therapy, treatment of patients with group B disease with two drugs (carboplatin and vincristine) resulted in EFS of 81% and ocular globe salvage rate of 88%.

A Single Arm Trial of Systemic and Subtenon Chemotherapy for Groups C and D Intraocular Retinoblastoma (ARET 0231)—This study evaluated the use of six cycles of higher doses of carboplatin with vincristine and etoposide along with periocular carboplatin in patients with advanced bilateral retinoblastoma. Preliminary analysis suggests that this approach is effective in reducing the incidence of radiation and enucleation.

A Trial of Intensive Multi-Modality Therapy for Extra-Ocular Retinoblastoma (ARET 0321)—This international study evaluates intensive chemotherapy and stem cell rescue for patients with extraocular disease. The study is ongoing and open in collaboration with the South American GALOP consortium and the Children's Cancer Hospital 57357 in Egypt.

Liver Tumors

Phase III Protocol for the Treatment of Children with Hepatoblastoma (P9645)—This study showed that treatment with cisplatin/carboplatin resulted in higher risk for disease progression when compared with standard C5V therapy for patients with advanced disease. There was no evidence that the use of amifostine provided protection from chemotherapy-induced toxicities [13,32]. Importantly, this study identified a subgroup of

patients with completely resected tumors of pure fetal histology (PFH) that can be cured with surgery only [33].

Low Birth Rate and Other Risk Factors for Hepatoblastoma (AEPI04C1)—A total of 408 cases were enrolled in this case–control study; data analysis is ongoing. We hypothesize that treatment for prematurity is the major risk factor and that endogenous determinants of the ability to activate and detoxify toxins are major risk factors. Potential correlations between risk factors and outcomes have been analyzed [34].

Pediatric Liver Unresectable Tumor Observatory (PLUTO)—This registry is an international collaborative effort with SIOPEL and SPLIT to examine outcomes in children with unresectable tumors that require a liver transplant. Preliminary reports are giving us an increased ability to predict outcome and to design optimal chemotherapy and immunosuppression strategies [35].

CHIC (Children's Hepatic tumor International Collaboration)—In this collaboration, the databases of HB clinical trials conducted by COG, SIOPEL, GPOH, and JPLT have been merged; data of over 1,500 children with HB and over 30 different prognostic variables are currently being interrogated. The ultimate goal is to establish a new framework for international collaborations that would result in the next generation of clinical trials. This initiative also includes an international pathology working-group that has developed a consensus classification of liver tumors.

Germ Cell Tumors

A Phase III Study of Reduced Therapy in the Treatment of Children with Low and Intermediate Risk Extracranial Germ Cell Tumors (AGCT0132)—This recently closed trial had two strata: a stratum for low-risk stage I gonadal germ cell tumors that tested the efficacy of observation after surgery, and an intermediate risk stratum that tested the efficacy of compressed PEB (using three cycles instead of four and delivering the drugs over 3 days instead of five). Both strata closed early to accrual because the boundary for EFS had been crossed (stopping rule on the low and intermediate risk strata were 70% and 92%, respectively). On the low-risk stratum, the higher than expected failure rate was due to ovarian stage I patients. Notably, salvage was 100% in the testicular patients and 92% in the ovarian patients after treatment with PEB. The intermediate risk stratum included stages I–II extragondal, stages II–III ovarian, and stages II–IV testicular tumors. Closure of this arm was due to poorer than expected EFS among the stage III ovarian (EFS 80%) and stage IV testicular (EFS 52%) tumors. All other subgroups had an EFS >92%.

Treatment of Recurrent or Resistant Pediatric Malignant Germ Cell Tumors with Paclitaxel, Ifosfamide, and Carboplatin (TIC) (AGCT0521)—In this Phase II study, 8 of 20 patients experienced a PR, and all 10 patients with SD had a > 1 log decline in tumor markers. These results may be inferior to those using standard TIP regimens; however, the dose of paclitaxel in the TIC combination was lower (175 mg/m^2 vs. 250 mg/m^2).

MaGIC (Malignant Germ Cell Tumor International Collaboration)—In this collaboration with the UK CCLG, we merged clinical trial data from the last 25 years including 1,110 patients. The probability of cure was estimated using the CURE model [36], based on age, gender, site, tumor marker level, and stage [37]. The event-free survival (EFS) is lower among children >11 years [38]; children with advanced stage sacrococcygeal tumors (SCT) should no longer be considered high-risk. The other significant risk factors for poor outcome were metastatic, ovarian, and extragonadal disease, but not alpha-fetoprotein. A prediction model of likelihood of cure for age, site, and stage was then used to propose three new risk groups with either >90%, 80–90%, or <70% probability of EFS, and to explore the effect of treatment (cisplatin-based PEB vs. carboplatin-based JEB) [19]. There were no significant differences in EFS or OS by risk group, including stage IV patients, and treatment regimen was not a predictor of outcome ($P = 0.29$). MaGIC has been expanded with the addition of 2,000 patients under age 30 years with ovarian and testicular germ cell tumors from the GOG (Gynecologic Oncology Group) and MRC (Medical Research Council) clinical trials; this will allow for a better nuanced appreciation of the inter-relationship of age, site, stage, histology, and tumor marker levels.

Infrequent Tumors

Treatment of Childhood Nasopharyngeal Carcinoma (NPC) with Neoadjuvant Chemotherapy and Concomitant Chemoradiotherapy (ARAR0331)—This recently completed study investigated the use of neoadjuvant chemotherapy followed by chemoradiotherapy for the treatment of pediatric NPC, the prognostic significance of circulating EBV DNA levels, and the role of EBV in the pathogenesis of NPC.

Treatment of Adrenocortical Tumors with Surgery plus Lymph Node Dissection and Multiagent Chemotherapy (ARAR0332)—This ongoing study is performed in collaboration with two institutions in Southern Brazil, and investigates risk-adapted therapies for children with ACC and the molecular epidemiology and biology of this rare cancer [24,39].

STRATEGIC APPROACH: TARGETED THERAPY

Newly Diagnosed Disease

Retinoblastoma—The next generation of studies is currently being developed; this happens at a time when the use of direct ocular delivery of antineoplastic agents (through intraarterial or intraocular administration) is becoming the new standard of care. While this is a valid therapeutic approach, its feasibility in a multi-institutional setting with monitoring for technique and toxicities needs to be tested. As we advance in the development of more sophisticated ocular-preserving approaches, a critical factor likely to influence treatment choice is the impact of each treatment modality on the QoL of children and their families. By describing the magnitude of the problem and trajectory over time of both QoL and parental stress among various therapies for retinoblastoma, QoL studies will contribute to both facilitation of future clinical treatment option prioritization and practice, and to identify the optimal time in which to consider incorporation of supportive care interventions. In parallel to the intraarterial chemotherapy initiatives, the next generation of studies will

investigate the use of MDM2/MDMX and SYK inhibitors [25,26]. Adaptation of ocular pharmacokinetics and pharmacodynamics models will be key in the incorporation of those novel agents into direct ocular delivery approaches.

Liver tumors—While the AHEP0731 study is completed, strategic planning through the CHIC initiative has been initiated to develop the next generation of HB trials. For high-risk patients the investigation of new agents is critical. The current high-risk stratum (with AFP < 100, SCU histology, or metastatic disease) includes an up-front Phase 2 window with vincristine/irinotecan (first window) and vincristine/irinotecan/temsirolimus (second window). The choice of the mTOR inhibitor temsirolimus for the second window has the added potential benefit of obtaining safety data in this patient population due to frequent use of rapamycin analogues as immunosuppressants in liver transplant patients. Ongoing genomic studies are expected to provide key information for the development of future targeted therapies.

Germ cell tumors—For patients with low-risk disease, a key question is the identification of molecular markers that predict clinical outcome. Currently, patients with stage I disease are treated with observation alone; a proportion of patients (approximately 25%) have tumor progression and require chemotherapy. A better risk stratification based on focused pathway interrogation could identify patients likely to relapse after surgery, which in the future might permit less intensive therapy.

The goal of the biology aims in the upcoming protocol is to identify actionable mutations in patients with high-risk disease. While genome-wide studies are ongoing, a more pragmatic approach will be taken with the use of the SequenomOncoCarta Panel, a mass spectrometry-based assay, to detect single nucleotide variants (SNVs) and insertions/deletions in key cancer genes. The goal is to identify mutations that are currently targeted by clinically available agents, correlating mutation spectrum with clinical outcome. These data should support longer-term efforts to provide rationally based therapies for patients with resistant.

Infrequent tumors—Phases I and II clinical trials have shown the efficacy of autologous EBV-specific cytotoxic T cell (CTL) therapy in recurrent EBV+ NPC [40]. The next trial will supplement the current treatment backbone using chemotherapy and radiotherapy with an infusion of autologous EBV-CTL in patients with EBV+ NPC. This study is designed to evaluate the feasibility of adding an autologous cellular immunotherapy product to the previous treatment schema from ARAR0331.

Biology/registry protocol—The molecular characterization of most rare cancers has not been fully explored, which is an impediment to the development of new treatment approaches. This protocol aims to collect clinically annotated biospecimens to support the development of biologically based risk stratification and treatment strategies.

Relapsed Population

Retinoblastoma—As discussed, recent studies point towards spleen tyrosine kinase (*SYK*) and *MDM4* playing a role in the development of retinoblastoma. Efforts are underway to

develop MDM4 and SYK inhibitors in refractory or progressive retinoblastoma by local delivery.

Liver tumors—Highest risk relapse HB patients are targeted for participation in Phase II trials with aurora A kinase inhibitor (ADVL0921; of particular interest for small cell undifferentiated HB) and pazopanib (ADVL1122). HCC patients with refractory disease are eligible for the Phase II study of sorafenib ADVL1129. Another important initiative is the Children's Hepatic tumor International Collaboration Ideas for Therapeutic Advancement (CHIC-ita), a multicenter collaborative effort to advance therapeutic options for rare liver and pancreatic tumors.

Germ cell tumors—Studies show that BMP and Wnt converge on the mTOR-signaling pathway in childhood yolk sac tumors. mTOR represents the first molecular target identified for yolk sac tumors of which a clinically approved agent is available. Based on these results, a clinical trial to test the efficacy of temsirolimus in refractory yolk sac tumors is being developed.

Trial Design Strategies

Modeling for cure, not relapse—For diseases that have a low-risk of disease recurrence, parametric cure models to characterize patient outcome must be explored. Cure, rather than relapse, is a feature of many diseases studied in the Rare Tumors disease group. Relative risk regression models, which are often used in the analysis of clinical trials data, do not readily reflect this. Cure models [36], however, provide a mechanism to identify factors that are associated with likelihood of cure.

Modeling 1-sided versus 2-sided probability—International collaboration will provide a substantial patient base for the execution of randomized clinical trials. Despite this resource, such studies may not be feasible in a reasonable time frame in small groups of patients with low-risk disease; single-arm studies may still be required. In COG we have designed such trials employing the Woolson one-sided log-rank test to evaluate the primary hypotheses [41]. Many clinical trials designs in pediatric oncology use EFS. For groups of patients with excellent outcome and where reduction in the intensity of current treatment is primary study question, time to second EFS-event as the primary means to evaluate patient outcome will be explored. Use of this measure acknowledges that an increased risk of initial disease progression in the context of substantially reduced treatment toxicity is acceptable provided patient outcome is not compromised by the later introduction of standard treatment.

KEY TRIALS TO BE PURSUED

Pivotal Phase 3 Trials

Advances in the treatment of rare pediatric cancers are hampered by the low number of patients, which limits the use of classic randomized Phase 3 designs, and by the use of different systems for staging and definition of risk factors, which restricts options for collaborative trials. The ongoing international collaborative efforts CHIC and MaGIC are

expected to generate large databases that will allow for the identification of treatment-independent prognostic risk factors and the development of common risk stratification systems that can be used for the joint development of key Phase III trials.

Liver tumors—While the CHIC database is being interrogated lines of collaboration with SIOPEL that could lead to the development of Phase III studies are being explored: (1) to determine the optimal surgical approach for standard risk patients; (2) to investigate best treatment approach for patients with intermediate and high-risk disease by comparing the SIOPEL approach, which is based on intensive use of cisplatin, with the incorporation of novel chemotherapeutic agents as informed by the current AHEP0731 window strategies.

Outcome in pediatric HCC remains very poor. The rarity of this malignancy will require of a large-scale collaboration, possibly through a randomized approach, with other international cooperative groups already integrated within the CHIC initiative.

Germ cell tumors—Based on the findings from ACT0132, AGCT0521, and the MaGIC analyses, a new strategy for treating GCT has been proposed as joint collaboration with CCLG (UK), GOG, and MRC. Patients will be stratified into three risk groups: low-risk includes all patients with stage I, regardless of site; high-risk includes all patients >11-year-old with either stage IV ovarian, stage III/IV extragonadal or stage IV IGCCC poor risk testicular cancer; the remainder of the patients will be considered to have intermediate risk disease. The goals of the protocol will be: (1) to evaluate whether a watch and wait strategy can maintain an overall survival rate of >95% for patients with stage I; (2) to evaluate whether the substitution of carboplatin for cisplatin will maintain a high EFS for children in the intermediate risk category; and (3) to increase EFS to >70% for patients with high-risk GCT by exploring the impact of therapy intensification.

Prioritization Strategy

The development of initiatives to help establish a foundation upon which to conduct effective and efficient research in pediatric rare cancers is a priority. New research frameworks based on evidence-based international collaborations for disease definition and risk stratification, methodological innovations in the design of clinical trials, and development of new cooperative agreements with other international groups are critical. In addition, epidemiological and biological studies of rare pediatric cancers to provide etiological and mechanistic information that may suggest therapeutic targets and rational risk stratification should be developed. Finally, initiatives in cancer control and survivorship to optimize therapy and enhance QoL should be enhanced.

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