Neuro-Oncology Practice

Neuro-Oncology Practice 1(4), 145–157, 2014
doi:10.1093/nop/npu022
Advance Access date 12 September 2014

Management of high-grade gliomas in the pediatric patient: Past, present, and future

Magimairajan Issai Vanan and David D. Eisenstat

Section of Pediatric Hematology/Oncology/BMT, CancerCare Manitoba, Departments of Pediatrics & Child Health and Biochemistry & Medical Genetics, University of Manitoba, Winnipeg, Manitoba, Canada (M.I.V.); Division of Hematology/Oncology and Palliative Care, Stollery Children's Hospital, Departments of Pediatrics, Medical Genetics and Oncology, University of Alberta, Edmonton, Alberta, Canada (D.D.E.)

Corresponding Author: David D. Eisenstat, MD, MA, FRCPC, Division of Hematology/Oncology and Palliative Care, Department of Pediatrics, 8-43B Medical Sciences Building, University of Alberta, Edmonton, AB, Canada T6G 2H7 (eisensta@ualberta.ca).

High-grade gliomas (HGGs) constitute ∼15% of all primary brain tumors in children and adolescents. Routine histopathological diagnosis is based on tissue obtained from biopsy or, preferably, from the resected tumor itself. The majority of pediatric HGGs are clinically and biologically distinct from histologically similar adult malignant gliomas; these differences may explain the disparate responses to therapy and clinical outcomes when comparing children and adults with HGG. The recently proposed integrated genomic classification identifies 6 distinct biological subgroups of glioblastoma (GBM) throughout the age spectrum. Driver mutations in genes affecting histone H3.3 (K27M and G34R/V) coupled with mutations involving specific proteins (TP53, ATRX, DAXX, SETD2, ACVR1, FGFR1, NTRK) induce defects in chromatin remodeling and may play a central role in the genesis of many pediatric HGGs. Current clinical practice in pediatric HGGs includes surgical resection followed by radiation therapy (in children aged > 3 years) with concurrent and adjuvant chemotherapy with temozolomide. However, these multimodality treatment strategies have had a minimal impact on improving survival. Ongoing clinical trials are investigating new molecular targets, chemoradiation sensitization strategies, and immunotherapy. Future clinical trials of pediatric HGG will incorporate the distinction between GBM molecular subgroups and stratify patients using group-specific biomarkers.

Keywords: brain tumor, glioblastoma, high-grade glioma, pediatric.

Gliomas are primary brain tumors derived from cells of the glial (astrocytic and/or oligodendroglial) lineage. Gliomas are the most common childhood tumor of the central nervous system, accounting for 53% of tumors in children aged 0–14 years and 37% in adolescents aged 15 to 19 years.[1,2] As per the World Health Organization (WHO) classification system, these tumors are separated into low- or high-grade tumors leading to 2 broad clinical categories: low-grade gliomas (LGGs, WHO grades I-II) and high-grade gliomas (HGGs, grades III-IV).[1] HGGs are less common in the pediatric age group when compared with adults[1] and account for 3%–7% of all childhood brain tumors.[2,3] HGGs are a histologically heterogeneous group of tumors and are further classified according to the cell of origin as astrocytic tumors (anaplastic astrocytoma [AA], glioblastoma [GBM], giant cell GBM, and gliosarcoma), oligodendroglial tumors (anaplastic oligodendroglioma), or oligoastrocytic (mixed) tumors (anaplastic oligoastrocytoma).[1] Special categories of HGG include diffuse intrinsic pontine gliomas (DIPGs, grades II-IV) and gliomatosis cerebri (grade III). All of these HGG tumors are characterized by their highly invasive nature and are poorly responsive to even the most aggressive therapies. HGGs comprise ∼17% of childhood and ∼8% of adolescent brain tumors when including DIPGs.[2] HGGs are at least 20 times more common in adults than in children, particularly GBM, which is the most common primary malignant brain tumor in adults. GBMs account for ∼3% of all brain and CNS tumors reported in persons aged 0–19 years with an equal incidence between boys and girls.[2]

Currently, pediatric HGGs (pHGGs) are the leading cause of childhood cancer mortality, and there are no effective therapies available. Global collaborative efforts using next-generation sequencing and other genomic platforms have led to a greater understanding of pHGGs. Most HGGs in children are biologically distinct from adult tumors, with the majority of pediatric GBMs arising de novo and having their own characteristic genetic and epigenetic features. This review will focus on the current treatment of pHGGs (excluding DIPGs) with a special emphasis on integrating recent genomic discoveries into future clinical trials, hopefully leading to specific targeted therapies and better clinical outcomes.

Received 13 March 2014, Advance Access publication 12 September 2014

Therapy

Treatment of HGGs in children requires a multidisciplinary approach and involves supportive care, surgery, radiation therapy (RT), and chemotherapy.

Supportive Care

Increased intracranial pressure (ICP) at presentation often requires emergency surgery to relieve obstructive hydrocephalus by placement of an external ventricular drain, a ventriculoperitoneal shunt, or a third ventriculostomy. Peritumoral brain edema (PBE), which is caused by the release of vasoactive cytokines from the tumor cells with disruption of the blood-brain barrier and the endothelial tight junctions, can cause both focal and global neurological symptoms and contribute to increased ICP. Corticosteroids, particularly dexamethasone, are currently the standard of care for the treatment of PBE both preoperatively and postoperatively. Tumor resection may be safer when performed 1–2 days following reduction in PBE and ICP by treatment with steroids and relief of obstruction, respectively. Maintaining children on corticosteroids postoperatively for long and variable periods of time, often concurrently with chemotherapy and RT, is not recommended. Corticosteroid use can inhibit apoptotic cell death of glioma cells and contribute to resistance to RT and chemotherapy, stabilization of the blood-brain barrier, and interference with drug delivery. Moreover, one must consider the severe systemic side effects of long-term steroid use.[4] Corticorelin acetate (CrA), a synthetic derivative of the endogenous human corticotrophin releasing factor is being developed as an alternative to dexamethasone in the treatment of PBE.[5] A phase III randomized control trial (RCT) showed that use of CrA had a steroid-sparing effect but also decreased long-term steroid adverse effects, such as myopathy, secondary Cushing's disease, and adrenal suppression.[5] Further clinical trials in children are warranted to determine whether CrA has a place as a steroid-sparing agent.

Seizures occurring at the time of brain-tumor diagnosis may have multiple etiologies including the tumor per se and electrolyte abnormalities specifically involving sodium (hyponatremia due to syndrome of inappropriate anti-diuretic hormone, cerebral salt wasting; hypernatremia due to diabetes insipidus, etc.[6]) It is recommended that patients with unprovoked preoperative seizures be treated with nonenzyme-inducing antiepileptic drugs (AEDs), such as levetiracetam, gabapentin and lacosamide,[6] or valproate. The general consensus is to discontinue AEDs 3 months after starting definitive treatment if the patient has had a gross total resection (GTR) and an uncomplicated postoperative course without any recurrence of seizures.[6] In other situations, AEDs are usually tapered and discontinued after 2–3 years without seizures. The routinely prescribed AEDs (carbamazepine, phenytoin, and phenobarbital) induce cytochrome p450 liver enzymes and may interfere with metabolism of the chemotherapeutic agents used to treat brain tumors.[7] Prophylactic use of AEDs is not recommended for patients who do not present with seizures.[6,7]

Surgery

The main goals of surgery include obtaining tissue for pathological diagnosis and, whenever possible, achieving a GTR. The extent of resection (EOR) in pHGG has some important limitations. First, these highly infiltrative tumors invade the surrounding brain tissue beyond the tumor margins visible on neuroimaging. Therefore, even with a GTR, microscopic disease is present beyond the surgical margins, and surgery alone is not considered curative. Second, multifocal or diffusely infiltrative tumors, deep-seated tumors, and tumors adjacent to or within eloquent areas of the brain may limit the possible EOR or even preclude any attempt of surgery beyond a biopsy. Preoperative functional (f) imaging techniques (fMRI; diffusion tensor imaging [DTI]) and intraoperative MRI scans help to achieve the maximum resection possible with minimal postoperative neurologic deficits. The diagnostic yield of stereotactic biopsy in deep-seated lesions is greatly improved by other types of functional imaging (magnetic resonance spectroscopy [MRS], diffusion weighted imaging [DWI]) for localizing the tumor tissue.[8] EOR, age at diagnosis, and tumor grade are considered to be the most important prognostic factors in pHGGs. If a GTR is not feasible, a maximum possible safe surgical resection with preservation of neurologic function should be attempted. Aggressive debulking will relieve the signs and symptoms due to mass effect and reduce the residual tumor volume to be treated by adjuvant therapies (RT, chemotherapy) and may also improve tolerance to RT. With respect to EOR, in the Children's Cancer Group (CCG) 945 study, children with HGG and a GTR (>90% resection) had a 35% 5-year progression-free survival (PFS) compared with 17% in the group with subtotal resection (STR) ($P = .006$). Children with GBM (grade IV) and GTR had a 5-year PFS of 26% compared with 4% for those with a STR ($P = .046$). In the same study, children with AA (grade III) and a GTR had a 44% 5-year PFS compared with 22% in the STR group ($P = .055$).[9] Similar findings were reported from Germany using the hirntumor studiennegruppe, glioblastoma multiforme studien (HIT-GBM) database. Eighty-five pediatric patients with malignant nonpontine gliomas were analyzed for prognostic factors based upon EOR and chemotherapy. The study revealed that EOR was the most prominent prognostic factor for overall survival (OS) and event-free survival (EFS). Four-year OS and EFS after GTR (100% macroscopic removal) was 48% ± 12% (OS) and 14.1% ± 8.9% (EFS) when compared with children without a GTR (13.2% ± 6.1%) ($P = .063$) and 2.9% ± 2.8%, respectively.[10] In summary, GTR improves survival in pediatric patients with malignant gliomas and should always be attempted when safe and technically feasible.

Radiation Therapy

Most patients (especially children aged > 3 years) with HGG are given external RT to achieve local control of microscopic or macroscopic residual disease. Adjuvant RT is an effective treatment with rapid symptomatic improvement and increased PFS and OS when offered at doses ≥5400 cGy delivered in ~30 fractions over 6 weeks (1.8 Gy/fraction). Three-dimensional conformal treatment-planning techniques, including intensity-modulated radiation therapy (IMRT), are well tolerated and may decreased short- and long-term sequelae by decreasing the exposure of adjacent brain. Adoption of these techniques has resulted in reduced margins used by radiation oncologists, including the gross target volume (GTV), the clinical target volume (CTV) for

treating microscopic disease extending beyond the GTV, and the planned target volume (PTV). The CTV is anatomically confined and is usually limited to 2 cm. The PTV compensates for movement and uncertainties regarding daily positioning of the patient and setting up the equipment and software; the PTV usually ranges from 0.3 to 0.5 cm. The use of palliative re-irradiation in relapsed cases can help by improving symptom control, but its impact regarding extending survival has yet to be established.

Radiotherapy is also part of the current standard of care for GBM after surgical resection in adults. However, most recurrences occur within a few centimeters of the tumor mass.[11] Wild-Bode et al. reported that sublethal doses of irradiation promote migration and invasiveness of glioma cells.[12] They proposed that tumor cells stimulated to invade by sublethal doses of irradiation may escape the target volume of postoperative RT, thereby evading delivery of a cumulative lethal dose and forming the basis for locoregional relapse a few months after RT. One implication of this hypothesis is that RT should be combined with an anti-invasive therapy.

Proton-beam RT (protons) for the treatment of HGG in children has not been studied. Since HGG is highly invasive, with microscopic disease extending beyond the gross tumor margin, the use of protons may be less effective than photons using current treatment delivery guidelines. However, data available from adult studies suggest that protons combined with conventional fractionated IMRT may improve local tumor control and patient survival. In a prospective phase II trial involving dose escalation with conformal protons and photons using an accelerated fractionation scheme, a dose of 90 cobalt gray equivalents (CBE) prevented central recurrence in almost all cases and also extended median survival time.[13] However, attempts to extend local control by enlarging the central volume were limited due to radiation necrosis.[13] Similar studies using hyperfractionated concomitant boost proton RT in combination with chemotherapy (nimustine, ACNU) have shown extended median survival time but no cure in these patients.[14] In a phase I-II clinical trial involving adult HGG treated with combined photons, chemotherapy (ACNU) and carbon ion radiotherapy (CRT), there was improved survival in participants who received higher carbon ion doses (14 months and 26 months in PFS and median survival time, respectively) compared with those receiving low carbon ion doses (4 and 7 months in PFS and median survival time, respectively).[15] Based on data from these studies there is an ongoing phase II clinical trial (CLEOPATRA, NCT01165671) involving adult patients, in which a carbon ion boost will be compared to a proton boost applied to the macroscopic tumor after surgery at primary diagnosis in patients with GBM given after standard radiochemotherapy with temozolomide (TMZ) up to 50 Gy.[16] Overall, existing data on RT for adult GBM indicate that dose escalation with particle RT (protons, CRT) has the potential to improve survival; there should be more trials involving pediatric patients in the future. Brachytherapy, stereotactic radiosurgery, and fractionated stereotactic radiotherapy (FSRT), as alternatives to conventional RT, are presently under study and may prove useful for selected relapsed patients.

Chemotherapy

The Past

Historically, pHGG has been treated using cytotoxic drugs either as single agents or in various combinations, schedules, and doses as an adjuvant to postoperative RT; however, the most effective combination has yet to be determined because none of the chemotherapeutic regimes has demonstrated superiority over any of the others. CCG-943 is the only randomized study to date in children that demonstrated a clear survival advantage associated with adjuvant chemotherapy. Following surgical resection, participants were randomized to RT alone (standard arm) or RT plus chemotherapy (pCV- prednisone, CCNU/lomustine, vincristine). Children who were treated with chemotherapy fared significantly better than children treated with RT alone; 5-year EFS was 46% ± 10% for RT plus chemotherapy compared with 18% ± 7% for RT alone ($P = .026$). Also, children with GBM treated with combination therapy had significantly better outcomes than those treated with RT alone (5 y EFS of 42% vs 6%; $P = .01$).[17] One explanation for the failure to replicate the results of the CCG943 study in subsequent trials was the unintentional inclusion of LGG as HGG, which resulted in better outcomes.

The subsequent CCG-945 study randomized participants to receive pCV or a more intensive chemotherapy combination known as "8-in-1" (8 drugs in 1 day); children aged >2 years received RT. There was no statistical significance in either PFS or OS between the 2 arms (5 y PFS for pCV was 26% vs 33% on the 8-in-1 regime; $P > .52$).[9] This study established the EOR to be an important prognostic factor and also highlighted the importance of central pathological review in prospective HGG studies.

The purpose of the CCG-9933 study was to determine the efficacy of intensive chemotherapy prior to RT in children with residual tumor (>1.5 cm^2). Participants were randomized to receive 1 of the 3 chemotherapy regimens before RT was administered: ifosfamide/etoposide (arm A), carboplatin/etoposide (arm B), or cyclophosphamide/etoposide (arm C). There was no difference in response rates among the 3 arms, and 42% of the participants developed progressive disease (PD) before the end of induction chemotherapy. This study concluded that neoadjuvant chemotherapy did not offer any survival benefit when compared with RT and adjuvant standard dose chemotherapy in the treatment of pHGG.[18]

Similar outcomes have been reported by European trials treating pHGG. The German HIT-GBM protocols assessed a variety of chemotherapeutic strategies. Chemotherapy was administered to patients both pre- and post-RT ("sandwich style"). Briefly, HIT-GBM-A assessed the efficacy of oral trofosfamide and etoposide.[19] HIT-GBM-B–treated participants with RT and concurrent chemotherapy (cisplatin/etoposide in the first cycle and cisplatin/etoposide/ifosfamide in the second cycle) followed by interferon-γ and/or low-dose cyclophosphamide maintenance therapy[20]; HIT-GBM-C involved administration of intensive chemotherapy (vincristine, cisplatin, ifosfamide, and etoposide) both during and after RT followed by oral valproic acid as maintenance therapy (a histone deacetylase/HDAC inhibitor)[1]; and HIT-GBM-D, a pilot phase II study, evaluated the efficacy of single-agent methotrexate (MTX) prior to RT and chemotherapy.[22] In this pilot study, 2 doses of MTX (5 gm/m^2) were given prior to RT followed by simultaneous chemotherapy-RT and subsequent maintenance chemotherapy as per the HIT-GBM-C protocol. The toxicity profile was acceptable, with no deaths related to drug toxicity. Data from this study suggested that the HIT-GBM-D protocol is favorable for treating pHGG patients with a GTR.[22] The approach of giving 2 cycles of high-dose MTX prior to radiochemotherapy will be assessed in a phase III RCT, and results from the randomized study are pending. The German Society for Pediatric Oncology

conducted a randomized clinical trial to evaluate the efficacy of pre-RT intensive chemotherapy in pHGGs in 1991.[23] Participants were randomized post surgery to 2 different chemotherapy arms (sandwich chemotherapy [protocol S] and maintenance chemotherapy [protocol M]). Participants on protocol S received chemotherapy followed by RT, while those on protocol M received RT and vincristine followed by chemotherapy. The EOR was the most important prognostic factor, with a median survival of 5.2 years in participants with ≥90% resection compared with 1.3 years for those who underwent less than complete resection ($P < .0005$). Post GTR, participants who received sandwich chemotherapy had better OS when compared with protocol M (OS, 5.2y vs 1.9y, respectively;$P = .015$). Data from this study suggested that early, intensive chemotherapy increases survival rates in pHGG patients with GTR and that pre-RT chemotherapy is feasible and safe for these patients.[23] A French study from French Society of Pediatric Oncology evaluated pre-RT BCV chemotherapy (BCNU, cisplatin, and vincristine) in pHGG. Although the response rate was 20%, there was no improvement in EFS and there was unacceptable pulmonary toxicity.[24]

Temozolomide-based Regimens

Temozolomide is an oral pro-drug that undergoes in vivo spontaneous hydrolysis into its active metabolite and acts as an alkylating agent to induce DNA damage. In a landmark RCT, concurrent TMZ with RT was compared with RT alone for the treatment of newly diagnosed adults with GBM (aGBM). The study showed significant survival benefit in the TMZ arm compared with RT alone (2 y and 5y OS, 26.5% and 9.8%, respectively, when compared with 10.4% and 1.9%, respectively, for RT alone).[25] Although this study established the current standard of care for aGBM, few participants were long-term survivors. Resistance to TMZ is mediated via a DNA repair gene called O^6-methylguanine-DNA-methyltransferase (MGMT). Normally, MGMT removes methylated adducts (DNA damage) from the O^6-guanine position. MGMT promoter methylation results in silencing of the gene, which leads to reduced proficiency of DNA damage repair induced by alkylating agent chemotherapy.[26] Thus, MGMT methylation is used as a biomarker for predicting response to alkylating agents, especially TMZ in adults.[26] Although there are several methods for MGMT promoter methylation analysis (pyrosequencing [PSQ], methylation-specific polymerase chain reaction [MSP], and methylation-specific multiplex ligation-dependent amplification [MS-MLPA]), MSP appears to be the best method for use in routine clinical diagnostics.[27] MGMT promoter methylation is less frequent in pHGG (16%–50%) when compared with aGBM (45%); several studies consider MGMT promoter methylation to be a biomarker for predicting good response to alkylating agents in pHGG.[28–30] In one of the earliest clinical trials of TMZ in pHGG (UKCCSG/SFOP) children with relapsed or progressive, biopsy-proven HGG were treated with oral TMZ (200 mg/m^2 on 5 consecutive days) and monitored for response by serial MRI.[31] Prolonged myelosuppression (thrombocytopenia) leading to treatment delays/dose reductions and toxic deaths (sepsis, pneumonia) were the most common toxicities reported. The study concluded that TMZ as a single agent has no activity in relapsed or progressive pHGG.[31] In the COG ACNS0126 phase II study, participants received concomitant TMZ with RT followed by TMZ.[32] There was no improvement in participant survival when compared with historic controls (CCG945): 3 year EFS and OS of 11% ± 3% and 22% ± 5%, respectively. In a follow-up phase II study (ACNS0423) adjuvant lomustine (CCNU) was added to TMZ following concurrent TMZ with RT; preliminary results showed no significant difference in the 2-year OS rate (45% ± 5% vs 36% ± 5% in the ACNS0126 study; $P > .1$).[33] In an attempt to overcome resistance to TMZ, MGMT inhibitors (O^6-benzylguanine) in combination with TMZ have been offered in phase I trials. Although there is increased activity of this combination in pHGG patients, there is also more toxicity.[34,35] Although single-agent TMZ has not improved outcomes for pHGG, combination therapy of RT with concomitant and adjuvant TMZ is widely practiced by pediatric neuro-oncologists based on adult data and the lack of alternatives with superior clinical efficacy.[36] This could be due to the favorable toxicity profile and the ability to add to this chemotherapy backbone in current and future studies.

Angiogenesis Inhibitors

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor A (VEGF-A), has been used as both single agent[37] and in combination with RT and other drugs for the treatment of aGBM. The use of bevacizumab with irinotecan in recurrent GBM in adults has shown promising response rates, although the impact on OS has been debated.[37,38] However, results have not been replicated using the same combination in the pHGG population.[39,40] The Pediatric Brain Tumor Consortium (PBTC) conducted a phase II trial of bevacizumab and irinotecan in children with recurrent, progressive, or refractory HGG and DIPG. There was minimal efficacy in both cohorts, and no sustained objective response was observed despite evidence of target inhibition. However, half of the evaluable participants who had non-brainstem HGG showed stable disease for a long period of time (mean, 176 d; range, 86–546 d). These data suggest that this combination might produce more favorable results in newly diagnosed pHGG.[39] Similar results have been reported from another study using the same combination for progressive or recurrent GBM/DIPG in children. Toxicity and treatment tolerance were comparable with aHGG patients, but the radiological response rate and survival appeared inferior in pediatric patients.[40] The variable response to bevacizumab in children and adults may be explained by the fact that VEGF is not the only mediator of angiogenesis, and other growth factors (fibroblast growth factor [FGF] and platelet-derived growth factor [PDGF]) may play an important role in pHGG.[41] Although bevacizumab may not be effective in the setting of recurrent pHGG, it could be more effective in newly diagnosed cases, given the ability of antiangiogenics to normalize blood vessels and allow for better delivery of cytotoxic therapy as well as increase the effectiveness of RT.[42–44]

Bevacizumab as a Frontline Therapeutic Agent

Since the FDA approval of bevacizumab for the treatment of recurrent aGBM, 2 large RCTs have evaluated the clinical benefit of adding bevacizumab to the current standard of care (RT with concurrent and adjuvant TMZ) for newly diagnosed GBM in adults.[45,46] The 2 trials (AVAglio and Radiation Therapy Oncology Group RTOG0825) both showed prolongation of PFS by 3–4 months with the addition of bevacizumab, but there was no significant effect on OS. Of importance, there were differences in participant-reported outcomes (quality of life [QoL], neurocognitive

testing) between the 2 trials. Whereas the AVAglio trial showed improvement in or prolonged maintenance of performance status and QoL, the RTOG0825 trial demonstrated decreasing QoL and a decline in cognitive function. Subsequent trials will include refinement of clinical endpoints and use of new biomarkers (both clinical and imaging) to better assess the response and use of newer agents in combination with bevacizumab, especially agents that inhibit invasion in future clinical trials.[47] The current COG randomized phase II/III study ACNS0822 assigns participants to receive either TMZ, bevacizumab, or the HDAC inhibitor vorinostat (SAHA) as radiosensitizers with RT followed by TMZ and bevacizumab. A multicooperative group (ITCC/SIOP-E, Australian CCTG, Canadian C[17]) randomized phase II study (the HERBY trial, NCT-01390948) is comparing bevacizumab concurrent with TMZ and RT followed by TMZ and bevacizumab to chemoradiation with TMZ followed by adjuvant TMZ for children with newly diagnosed HGG.

In addition to bevacizumab, inhibitors of other proangiogenic factors including platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGFR) are under investigation in phase I-II trials in pHGG. However, it is important to note that these receptor tyrosine kinases (RTKs) have many biological functions beyond angiogenesis and that targeted therapies against RTK may exert therapeutic effects as well as toxicities through other downstream pathways. Although EGFR amplification is rare in pHGGs, it is overexpressed in more than 80% of these tumors.[48] In a recent phase II trial, erlotinib (an orally active and potent/selective inhibitor of EGFR and HER2) was combined with RT in treatment of newly diagnosed pHGG cases. Although therapy was well tolerated, there was no impact on the outcome.[49] Nimotuzumab (humanized IgG1 monoclonal antibody against EGFR), used either alone or in combination with RT and chemotherapy in pHGG, was also well tolerated and showed a median survival time of 32.66 months and a 2-year survival rate of 54.2%.[50] In this study, nimotuzumab was given for a prolonged period of time in some cases (4 years), was tolerated, and showed no disease progression after discontinuation of treatment.[50] Antiangiogenic agents, such as thalidomide and its analog lenalidomide, have been tried in small groups of children with some promising results.[51] There is an ongoing phase I trial testing lenalidomide in combination with RT for newly diagnosed pHGG (NCT-01222754).

The Present

Targeted Therapies

Although there is no standard of care based on a recent phase III RCT, the current accepted treatment for pHGG includes maximal safe surgical resection followed by RT with TMZ and/or bevacizumab.[36] Existing protocols have yet to demonstrate any significant survival advantage. Therefore, there is an urgent need to develop biologically relevant therapies in children with HGG. Recent insights regarding the biology and signaling pathways in pHGG and DIPG have led to studies using targeted therapies.[52–54] Broadly, these can be divided into RTK inhibitors, specific signaling pathway inhibitors (PI3K/AKT/mTOR, Ras/Raf/MEK, and CDK pathways), chromatin remodeling/posttranslational histone modification pathway inhibitors, antiangiogenic therapies, radiosensitizers, and immunotherapies (Tables 1 and 2).

RTKs play a pivotal role in cell signaling and have been shown to be deregulated (mutated, amplified, deleted, or overexpressed) in malignant gliomas across the ages and anatomical sites. Most of these alterations are age and group specific.[54] Initial trials involving these biologically targeted therapies offered monotherapy in unselected patient populations (studies were not stratified based on the presence or absence of the target). The rationale for proceeding with these trials included lack of tissue (especially for DIPG) to test for the targets, lack of validated predictive biomarkers, and concerns regarding tissue sampling. Unfortunately, this approach has led to disappointing patient outcomes.[52] There are multiple activated signaling pathways in a given tumor and heterogeneity within different areas of the tumor, which lead to signaling redundancy and use of alternative pathways when one or more are inhibited. In order to overcome this resistance, pathways need to be targeted horizontally (vs more than one RTK) or vertically (vs a specific RTK plus its downstream pathways). Potential targets in pHGG are further elucidated in Jones et al.[52]

Platelet-derived Growth Factor Receptor Inhibitors

PDGFRA focal amplifications are most commonly found in the midline infratentorial (histone 3.1/3.3 K27M) subgroup (DIPG) and also in the RTK1 subgroup.[54–55] Although initial studies identified this recurrent focal amplification at a higher rate in DIPG,[56–58] subsequent data from treatment-naïve DIPG suggest that this amplification occurs at a slightly lower rate (<40%).[54]

Table 1. Molecular targets in pediatric high-grade glioma

Target	Agent	Recurrent/Relapsed	Median PFS (mo.)	PFS-6 (%)	Reference
VEGF	Bevacizumab (with irinotecan)	Recurrent/relapsed	4.5	42	39
EGFR	Erlotinib	Recurrent/relapsed	1.5	34	100,101
	Gefitinib	Recurrent/relapsed/newly diagnosed	NR	15 (1 year PFS)	102
	Nimotuzumab	Recurrent/relapsed	1.8	NR	103
PDGFR	Imatinib	Recurrent/relapsed	NR	18	60,104
mTOR	Temsirolimus	Recurrent/relapsed	1.9	NR	105
αV-Integrin	Cilengitide	Recurrent/relapsed	1.0	NR	68

Abbreviations: EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; NR, not reported; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; VEGF, vascular endothelial growth factor (adapted from ref. 52).

Table 2. Integrated biological approach in the management of pediatric high-grade gliomas: the future

Clinical Features at Diagnosis	Tumor Location	Subgroup-specific Mutations	Immuno-histochemistry Markers	Cytogenetics or Biomarkers	Potential Targets	Target-specific Therapies	Additional Comments/References
	Midline/Deep						
Child (rarely adolescent) with median age of 10.5 y (range 5–23 y) (**K27M group**)	(a) Thalamus, basal ganglia, and spinal cord	(a) H3F3A (K27M) (14%) (b) FGFR1	(a) H3.3K27M (b) FOXG1$^-$/OLIG2$^+$ (c) TP53-mut (70%). (d) ATRX-LOE (50%)	(a) NF-1 mutations	(a) BET bromodomains. (b) FGFR1	(a) BET bromodomain inhibitors: JQ-1, I-BET151. (b) BGJ398 (pan-FGFR inhibitor)	(a) BET Bromodomain inhibitors may be useful in all subgroups of HGGs. (b) JQ1 has good CNS penetration. (c) FGFR1 – gain of function mutations. (d) BGJ398 (NCT-01975701) Ref: 55,72,83,85
Child with mean age of 8.1 y, with insidious onset and rapid progression of typical symptoms (**K27M group**)	(b) Brainstem	(a) H3F3A (K27M) (71%)	(a) H3.3K27M (b) FOXG1$^-$/OLIG2$^+$ (c) TP53-mut	(a) PDGFRA (amp/mut/del) (40%) (b) MYC/PVT1	(a) BET bromodomains (b) PDGFRA	(a) BET bromodomain inhibitors: JQ-1, I-BET151. (b) PDGFRA inhibitors: Imatinib, Dasatinib, Nilotinib, etc.	(a) Dasatinib has better CNS penetration than imatinib Ref: 55,60,72,83,89
		(b) H3.1 (K27M)/ HIST1H3B/ HIST1H3C (12%–31%)	(a) TP53-mut (b) Increased levels of phosphorylated SMAD1/5/8		(a) BET bromodomains. (b) ACVR1	(a) BET bromodomain inhibitors: JQ-1, I-BET151. (b) ACVR1 inhibitors: K02288, LDN193189	(a) Usually associated with ACVR1 mutations. Ref: 55,72,85–88,90
		(c) ACVR1 (20–22%)	(a) Increased levels of phosphorylated SMAD1/5/8		ACVR1	(a) ACVR1 inhibitors: K02288, LDN193189 (b) RAR-γ agonists: NRX204647, R667(Palovarotene)	(a) ACVR1 – activating /gain of function mutations. (b) Inhibitors need further in vitro and in vivo validation in HGGs. Ref: 85–88,90
Child with median age of 6.3 y, with female preponderance, atypical clinical features (longer duration of symptoms, atypical radiology). Histology is grade-IV (100%)		(d) H3F3A (WT) (e) MYCN amplification	(1) TP53-mut (2) MYCN	(a) MYC-N upregulation (3%–5%). (b) Chromothripsis in Chr-2 (c) ASAP2	(a) BET bromodomains (b) MYC-N	(a) BET bromodomain inhibitors : JQ-1, I-BET151. (b) N-MYC destabilization: AURKA inhibitors-MK5108, MLN8054, MLN8237.	Ref: 55,75–77,83–84,89

	Cortical (hemispheric) tumors						
Typically adolescent or young adults with a median age of 18 y (range 9–42 y) (**G34 R/V group**)	(a) T>P>O	H3F3A (G34R/V) (12%–14%)	(a) FOXG1^{+}/ OLIG2^{-} (b) TP53-mut (100%). (c) ATRX-LOE (100%). (d) MYCN	(a) MYC-N up regulation (b) ALT +ve (c) 1q (single copy gain) (19%–29%). (d) 13q (single copy loss) (24%–34%)	(a) BET bromodomains (b) MYC-N. (c) CHK-1	(a) BET bromodomain inhibitors: JQ-1, I-BET151. (b) N-MYC destabilization: AURKA inhibitors- MK5108, MLN8054, MLN8237. (c) CHK-1 inhibitors: SB21807, TCS2312	(a) All inhibitors need further in vitro and in vivo validation in HGGs. (b) AURKA inhibitors in Phase I-II clinical trials. Ref: 55,75–78,83–84
Young adults with preponderance of tumors in the frontal lobes. Mean age of 40 y (range 13–71 y) (**IDH group**)	(b) F>>>T > P	(a) IDH1-R132H (0%–16%)	IDH1-R132H		IDH1-R132H	AGI5198	Ref: 82,93
		(b) IDH2-R140Q			IDH2-R140Q	AGI6780	Ref: 94
Adolescent/young adult, with another peak in adult/elderly. Mean age of 36 y (range 8–74 y) (**RTK1 group**)	(c) F>P>T	(a) SETD2 (15%) (b) NTRK1/2/3 mutations (40%)	FOXG1^{+}/ OLIG2^{+}	(1) ALT + (2) CDKN2A and CDKN2B (focal deletion) (10%–19%)	(a) BET bromodomains. (b) NTRK fusion genes	(a) BET bromodomain inhibitors: JQ-1, I-BET151 (b) NTRK inhibitors: Lestaurtinib (NTRK2), AZ64 (pan-NTRK inhibitor)	(a) NTRK mutations are fusion genes, seen more commonly in children < 3 years of age, in NBS-HGGs. (b) Inhibitors need further in vitro and in vivo validation in HGG. Ref: 54,83,90–92
		(c) RAS/AKT	YB-1 (nuclear stain +ve)		RAS/AKT/mTOR pathway		Inhibitors already in various phases of clinical trials. Ref: 52,61
	All Locations						
		(a) BRAF-V600E (10%–25%)	BRAF-V600E		(a) BRAFV600E (b) MEK	(a) BRAF-V600E inhibitors: Vemurafenib, Dabrafenib,PLX4720 (b) MEK inhibitors: Trametinib	(a) Inhibitors already in clinical trials for LGG and melanomas. (b) Combination of V600E and MEK inhibitors may be useful to overcome resistance. Ref: 97–99

Continued

Table 2. *Continued*

Clinical Features at Diagnosis	Tumor Location	Subgroup-specific Mutations	Immuno-histochemistry Markers	Cytogenetics or Biomarkers	Potential Targets	Target-specific Therapies	Additional Comments/References
		(b) MGMT methylation (16%–50%)	MGMT			Alkylating agents: Temozolamide	MGMT promoter methylation status best determined by MSP (methylation-specific polymerase chain reaction). Ref: 27–30
		(c) RAS/AKT	YB-1 (nuclear stain +ve)		RAS/AKT / m-TOR pathway		(a) Inhibitors already in various phases of clinical trials. Ref: 52,61,90

Abbreviations: A: ALT, alternative lengthening of telomeres; BET: bromo and extra C-terminal; F, frontal lobe; IT, infratentorial; O, occipital lobe; P, parietal lobe; ST, supratentorial; T, temporal lobe.

Hence, there may be a link between prior RT and PDGFRA amplification, as this oncogenic event is more commonly observed in radiation-induced gliomas.[59] Several clinical trials have been conducted targeting PDGFRA. A PBTC-sponsored phase I trial evaluated imatinib as a PDGFRA inhibitor.[60] Although a phase II dose was determined, further trials have not been pursued. An ongoing phase I trial is evaluating the oral PDGFR inhibitor crenolanib (CP-868596) in children with pHGG (NCT-01393912).

RAS/AKT Pathway Inhibitors

The RAS/AKT pathway is aberrantly activated in ~70% of aGBMs.[53] Faury et al. compared pediatric and adult GBM samples for activation of these pathways.[61] Assessment of the RAS/AKT pathway activation revealed a subset of pGBMs with pathway activation, a neural stem cell phenotype, and very poor prognosis. This pGBM subset was distinct from aGBM and showed nuclear overexpression of Y-box protein (YB-1). The authors hypothesized that active AKT contributes to gliomagenesis by relieving the translational repression of YB-1 on numerous oncogenic factors.[61] There are several ongoing or completed phase I-II clinical trials that target the RAS/AKT pathways. These include MK2206, a highly selective allosteric AKT inhibitor for treating younger patients with recurrent or refractory solid tumors or leukemia (NCT-01231919); enzaustarin, a PKC-β inhibitor used in treating young patients with refractory primary CNS tumors (NCT-00503724); an insulin-like growth factor receptor (IGF-1R) recombinant monoclonal antibody (cixutumumab) in combination with temsirolimus; an mTOR inhibitor used in treating unresponsive or recurrent solid tumors (NCT-00880282); and sunitinib (a pan-RTK inhibitor vs VEGFR, PDGFR, KIT, and FLT-3) to evaluate safety and efficacy in recurrent/ progressive/ refractory pHGG (COG-ACNS1021, Phase II completed).

Role of Megatherapy With Autologous Stem Cell Transplantation. High-dose myeloablative chemotherapy with autologous hematopoietic stem cell rescue (ASCR) has resulted in survival for selected groups of patients with pHGG (those with minimal or no residual disease prior to consolidation with myeloablative chemotherapy). The majority of reports are limited to small numbers of participants who were either newly diagnosed[62] or had recurrent disease.[63] However, overall long-term survival rates remain poor with significant long-term morbidity and mortality from the treatment regimen, and this therapeutic approach is not currently recommended for newly diagnosed pediatric patients with HGG.

Special Circumstances

Treatment of Infants With High-grade Glioma

Although HGG is rare in this age group, infants (children aged < 3 years) have a better outcome than older children. In order to avoid the long-term effects of RT to the developing brain, clinical trials have been designed to either delay or totally avoid RT. There is a subset of patients aged < 3 years who have shown improved outcomes with chemotherapy alone.[64–66] Whenever possible, RT should be omitted or delayed in the treatment of infants with HGG.

Recurrent High-grade Glioma. Relapse or progression of disease is very common in pHGG, and mortality approaches 100% in these cases. The tumor recurrence can be local or disseminated (especially in nonresponsive tumors). Treatment options for relapsed HGG are limited and depend on factors such as the patient's age, performance status, initial response to therapy, time since the original diagnosis, and whether tumor recurrence is local or diffuse. Limited therapeutic options include repeat resection, re-irradiation, and systemic chemotherapy. There is an ongoing randomized phase I/II clinical trial (CINDERELLA trial) evaluating carbon ion therapy in adult participants with recurrent HGG (NCT-01166308). We expect carbon ion therapy trials to be extended to selected pediatric patients with recurrent HGG.

A large number of single-agent phase I/II trials have been conducted in children with recurrent HGG, but the majority of agents tested have revealed minimal or no activity (range of response rates, 0%–23%; Table 1). The Pediatric Preclinical Testing Program, along with the PBTC, COG, and other cooperative groups, is developing a preclinical pipeline prior to testing these new agents in early phase clinical trials in children. Targeted therapies, such as bevacizumab as single agents or in combination with cytotoxic chemotherapy, have been used with some success in adults but have been disappointing in children. Recently completed phase II studies combining O^6BG with TMZ[67] and the anti-integrin agent cilengitide (ACNS0621)[68] for recurrent disease have not provided sufficient response data to proceed to phase III studies. Patients with no or minimal residual disease following re-resection of a recurrent tumor may benefit from myeloablative chemotherapy with ASCR; however, this approach remains experimental and is not recommended outside of participation in a clinical trial.

The Future

Integrated Biological Classification

Taken together, pediatric HGGs are not the same biologically as adult malignant gliomas. Recent studies have identified 6 different biological subgroups of GBM across all ages. The clinical and biological data clearly show that GBMs in adults and children have significant differences in their underlying biology.[55] Chromatin-remodeling defects are central to the pathogenesis of pediatric and young adult HGG. Recurrent somatic driver mutations in the H3F3A gene, which encodes the replication-independent histone 3 variant (H3.3), leads to amino acid substitutions at key residues, (namely lysine [K] 27 [K27M] [23%–43%] and glycine 34 [G34R/V] [12–14%]) and identifies distinct subgroups of pediatric GBM.[54,55,69] H3.3 K27M mutations are more frequent in subcortical regions such as the thalamus and brainstem, whereas H3.3 G34R/V lesions tend to be in hemispheric locations.[55,70] IDH1/2 mutations are typical of secondary GBM in young adults and are present in ~70% of cases with predominant localization in frontal and temporal lobes. However, IDH1/2 mutations are also seen in 0%–16% of childhood primary GBM.[54] Therefore, there is a possibility that these IDH-mutant primary GBMs in children may have progressed rapidly from clinically undiagnosed LGG.[54] Mutations in H3F3A and IDH1 are mutually exclusive anatomically and across specific age groups: in children (K27M mutations), adolescents (G34R/V mutations), and young adult patients (IDH1 mutations) locations.[70] Whole exome-sequencing studies of pediatric GBM have identified mutations in α-thalassemia/mental retardation syndrome X-linked (ATRX, 14%–29%)[54] and death domain-associated protein (DAXX, 34%) genes.[69] These genes act as histone chaperones and help in the chromosomal deposition of H3.3 protein in a replication-independent manner. ATRX and/or DAXX mutations have a strong association with TP53 mutations and alternative lengthening of telomeres (ALTs).[55,69] Recently, mutations were identified in SETD2, a H3K36 trimethyltransferase, in pediatric HGGs localized exclusively to the cerebral hemispheres. SETD2 mutations are specific to HGG in children (15%) and adults (8%).[54] These mutations are mutually exclusive with H3F3A mutations in HGG but sometimes overlap with IDH1 mutations.[71] Of interest, activating BRAF mutations, such as BRAF V600E, are also present in 10%–25% of pediatric HGGs.[54]

Mechanisms of Tumorigenesis

Recent studies have provided mechanisms to explain the consequences of several of these mutations found in younger patients with HGG. A gain-of-function K27M mutation in H3.3 or H3.1 leads to global downregulation of the repressive histone mark histone H3 lysine 27 trimethylation (H3K27m3) through inhibition of the polycomb repressive complex 2 via EZH2 (the K27M-mutant H3.3 binds to the catalytic unit of EZH2 and interferes with enzymatic activity).[72] Because the main function of H3K27m3 is to repress transcriptional activity, global loss of K27 methylation leads to upregulation of hundreds of genes, mainly those associated with neural development. This has been proposed as the main driver of gliomagenesis in K27M-mutant HGG.[72–74] Similarly, the H3.3 G34R/V mutations can interfere with the regulatory H3K36me3 modification, leading to upregulation of genes involved in stem cell maintenance, cell-fate decisions, and self-renewal.[75] MYCN is one of the most highly regulated genes in the G34R/V mutations and is a potential therapeutic target[75–78] in this subgroup of pHGG. SETD2 mediates H3K36me3 trimethylation, and mutations in this gene correlate with a global decrease in H3K36me3, leading to similar upregulation of genes as well as increased spontaneous mutation frequency and chromosomal instability.[79] This is reflected by a particularly high number of pGBMs that show ALT in this subgroup. IDH1/2 mutations lead to overproduction of 2-hydroxyglutarate (2-HG), which inhibits the demethylases (TET or Jumonji) required for modification of histones and DNA and may thereby block differentiation and tumorigenesis.[80,81]

Integration of Recent Advances Into Clinical Practice

Feasibility of Subgroup Identification. Subgroup identification of pHGGs is feasible both on a clinical and pathological basis. The characteristic age of presentation and neuroanatomic localization of subgroup-specific tumors should alert the clinician and the pathologist about the type of mutations. Commercially available antibodies against specific proteins should help further classify these tumors. OLIG2, FOXG1, ATRX, and R132H-IDH1 have been validated by immunohistochemistry using a tissue microarray in a subgroup-specific manner.[55] Recently, specific antibodies against H3.3 K27M-mutant[72] and R132H-IDH1[82] have been validated and should be helpful for specific subgroup identification. Additional surrogate markers, such as TP53 mutation, ALT,

MYCN, BRAF-V600E, phosphorylated SMAD1/5/8, and YB-1, should aid the neuropathologist in making a subgroup-specific diagnosis and identifying potential therapeutic targets (Table 2).

Subgroup Specific Targets and Therapies. Despite vast differences in the subgroups of pHGG, the one theme common to all is epigenetic deregulation due to specific mutations.

(1) *All subgroups:* bromodomains are protein motifs that primarily bind to acetylated lysine residues and regulate transcriptional regulation, DNA replication, and repair. Recent studies have shown that bromo and extra C-terminal (BET) bromodomain inhibitors are effective for treating genetically/epigenetically diverse GBM tumors both in vitro and in vivo.[83] Using JQ-1 (Jun Qi-1), a small molecule inhibitor against BRD4, the authors demonstrated that JQ-1 induced apoptosis, significantly repressed growth of orthotopic GBM tumors, and showed excellent brain-penetrating capacity. Bromodomain inhibitors may be useful in the MYCN-amplified childhood tumor, neuroblastoma. Bromodomain-mediated inhibition of MYCN impaired growth and induced apoptosis in neuroblastoma. BRD4 knockdown phenocopied these effects, establishing BET bromodomains as transcriptional regulators of MYCN.[84] This mechanism of action might be helpful in G34R/V tumors, in which MYCN is found to be upregulated.[75]

(2) *H3F3A (K27M) (supratentorial-midline/DIPG) subgroup:* There is an emerging consensus that biopsy of DIPG and other midline HGGs is relatively safe in specialized pediatric centers using modern neurosurgical techniques. Recent studies have shown that we can reliably identify the whole mutational landscape of pHGGs (especially midline tumors like DIPG) using tissue obtained by small-needle pretreatment biopsies.[85] The availability of an antibody against the H3.3 K27M-mutant[72] provides opportunities to improve diagnosis, assignment of prognosis, and identification of potentially druggable targets (PDGFRA, ACVR1, and FGFR1). Specific inhibitors of ACVR1 are available but require further in vitro and in vivo validation in pHGG.[86–88] Recent studies have described 3 molecularly distinct subgroups of DIPG (H3K27M, silent, and MYCN), thereby identifying novel therapeutic targets.[89]

(3) *H3F3A (G34R/V) (supratentorial-cortical) subgroup:* MYCN is one of the most highly regulated genes in the G34R/V mutations and is a potential therapeutic target[75–78] in this subgroup of pHGG. In addition to BET bromodomain inhibitors, N-MYC destabilizing agents like aurora kinase A (AURKA) inhibitors (MK5108, MLN8054, and MLN8273)[75–77] and CHK1 inhibitors (SB21807, TCS2312)[78] have shown promising results. However, further in vitro and in vivo validation is necessary. Recent genomic landscape studies (whole-genome, whole-exome, and/or transcriptome sequencing) of pHGGs have identified recurrent fusion genes involving the neurotrophin receptor genes (NTRK1, NTRK2, and NTRK3) in 40% of non-brainstem HGGs (NBS-HGGs) in infants.[90] These fusion genes result in aberrant activation of the PI3 K/AKT/MAPK pathways and HGG formation when transduced in primary mouse astrocytes.[90] There are small molecule inhibitors available for the neurotrophin receptors.[91,92] AZ64 is an active, orally available, small molecule kinase inhibitor with nanomolar potency against all 3 NTRK receptors shown to inhibit growth of NTRK-expressing neuroblastomas, both in vitro and in vivo in animal models.[91] AZ64 enhances the efficacy of conventional chemotherapy and RT. Lestaurtinib is a specific inhibitor of NTRK2 shown to enhance the efficacy of selective chemotherapeutic agents in animal models.[92]

(4) *IDH1/2 subgroup:* IDH1/2 mutations are highly prevalent in several cancers including HGG. AGI-5198, a small molecule inhibitor of R132H-mutant IDH1 reduced the level of 2-HG and substantially reduced the growth of glioma cells in vitro and human glioma xenografts in vivo.[93] AGI-6780, a small molecule inhibitor of R140Q-mutant IDH2 has been shown to induce differentiation of human AML cells in vitro.[94] However, further validation in pHGG is required. Recent advances in metabolic imaging have identified noninvasive methods for detecting the presence of 2-HG in glioma patients.[95,96] This approach could have valuable clinical and therapeutic implications, including longitudinal monitoring of treatment.

(5) *Others:* Activating BRAFV600E mutations are present in pHGG in about 10%–25% of patients.[54,97] Detection of this mutated protein by IHC is now available, and there are several V600E small molecule inhibitors undergoing clinical trials.[97–99]

Can We Learn From the Past to Help With the Design of Future Clinical Trials?

Identification of multiple new targets in specific patient subgroups does not necessarily translate into successful targeted therapies. The development of novel drugs in children requires rigorous preclinical and clinical validation (including pharmacokinetics and pharmacodynamics). When planning future clinical trials using targeted therapies, investigators will avoid pitfalls of the past, including signaling pathway redundancy leading to resistance, lack of biomarkers to assess response, lack of patient preselection, and single-agent testing. Inhibiting multiple targets using synergistic combinations will provide more effective and durable therapies, especially in the setting of progressive/recurrent disease. Clinical/cytogenetic/molecular subgroup-based patient stratification will be incorporated for future pHGG clinical trials. However, this will require extensive collaboration among all stakeholders involved in the treatment of children with malignant gliomas.

Summary

HGGs in children are biologically distinct from adult GBMs. Recent integrated genomic studies have identified biological subgroups of pHGG. The complex interaction of genetic and epigenetic factors at specific times of brain growth and development contribute to the pathogenesis of pediatric and young adult HGG. Historically, treatment protocols for pHGG have been derived from adult therapies and have had poor outcomes. Future molecularly driven classifications and treatment strategies will take into account distinct biological differences, including genetic drivers of gliomagenesis, and identify relevant therapeutic targets and design appropriate preclinical model systems to test these targets in the pediatric setting . Once validated, these targets can be used in combination with existing therapies to maximize therapeutic efficacy and improve outcomes.

Acknowledgments

Dr. Issai Vanan is a Father Peter J. Mckenna St Baldrick's Cancer Research Scholar, supported by the St. Baldrick's Foundation (USA). Dr. Eisenstat holds the Muriel and Ada Hole Kids with Cancer Society Chair in Pediatric Oncology, University of Alberta (Canada).

References

1. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007; 114(2):97–109.
2. Dolecek TA, Propp JM, Stroup NE, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. *Neuro Oncol*. 2012;14:v1–v49.
3. Kaderali Z, Lamberti-Pasculli M, Rutka JT. The changing epidemiology of paediatric brain tumours: a review from the Hospital for Sick Children. *Childs Nerv Syst*. 2009;25(7):787–793.
4. Drappatz J, Schiff D, Kesari S, et al. Medical management of brain tumor patients. *Neurol Clin*. 2007;25:1035–1071.
5. Recht L, Mechtler LL, Wong ET, et al. Steroid-sparing effect of corticorelin acetate in peritumoral cerebral edema is associated with improvement in steroid-induced myopathy. *J Clin Oncol*. 2013;31:1182–1187.
6. Well EM, Gaillard DW, Parker RJ. Pediatric brain tumors and epilepsy. *Semin Pediatr Neurol*. 2012;19:3–8.
7. Weller M, Stupp R, Wick W. Epilepsy meets cancer: when, why and what to do about it?. *Lancet Oncol*. 2012;13:e375–e382.
8. Peet AC, Arvanitis TN, Leach MO, et al. Functional imaging in adult and pediatric brain tumors. *Nat Rev Clin Oncol*. 2012;9(12): 700–711.
9. Wisoff JH, Boyett JM, Berger MS, et al. Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. *J Neurosurg*. 1998; 89(1):52–59.
10. Kramm CM, Wagner S, Van Gool S, et al. Improved survival after gross total resection of malignant gliomas in pediatric patients from the HIT-GBM studies. *Anticancer Res*. 2006;26:3773–3780.
11. Gaspar LE, Fisher BJ, Macdonald DR, et al. Supratentorial malignant glioma: patterns of recurrence and implications for external beam local treatment. *Int J Radiat. Oncol Biol Phys*. 1992;24:55–57.
12. Wild-Bode C, Weller M, Rimner A, et al. Sub lethal irradiation promotes migration and invasiveness of glioma cells: implications for radiotherapy of human glioblastoma. *Cancer Res*. 2001;61: 2744–2750.
13. Fitzek MM, Thornton AF, Rabinov JD, et al. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. *J Neurosurg*. 1999;91:251–260.
14. Mizumoto M, Tsuboi K, Igaki H, et al. Phase I-II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. *Int J Radiat Oncol Biol Phys*. 2010;77(1):98–105.
15. Mizoe JE, Tsujii H, Hasegawa A, et al. Phase I-II clinical trial of carbon ion radiotherapy for malignant gliomas: combined x-ray radiotherapy, chemotherapy and carbon ion radiotherapy. *Int J Radiat Oncol Biol Phys*. 2007;69(2):390–396.
16. Coombs SE, Kieser M, Rieken S, et al. Randomized phase II study evaluating carbon ion boost applied after combined radiochemotherapy with temozolomide versus a proton boost after radiochemotherapy with temozolomide in patients with primary glioblastoma: the CLEOPATRA trial. *BMC Cancer*. 2010;10:478–486.
17. Sposto R, Ertel IJ, Jenkin RD, et al. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial-a report from the Childrens Cancer Study Group. *J Neurooncol*. 1989;7(2):165–177.
18. MacDonald TJ, Arenson EB, Ater J, et al. Phase II study of high dose chemotherapy before radiation in children with newly diagnosed high-grade astrocytomas: final analysis of Children's Cancer Group Study 9933. *Cancer*. 2005;104(12):2862–2871.
19. Wolff JE, Molenkamp G, Westphal S, et al. Oral trosfosfamide and etoposide in pediatric patients with glioblastoma multiforme. *Cancer*. 2000;89(10):2131–2137.
20. Wolff JE, Wagner S, Reinert C, et al. Maintenance treatment with interferon-gamma and low-dose cyclophosphamide for pediatric high-grade gliomas. *J Neurooncol*. 2006;79(3):315–321.
21. Wolff JE, Driever PH, Erdlenbruch B, et al. Intensive chemotherapy improves survival in pediatric high-grade glioma after gross total resection: results of the HIT-GBM-C protocol. *Cancer*. 2010;116(3): 705–712.
22. Wolff JE, Kortmann RD, Wolgg B, et al. High dose methotrexate for pediatric high grade glioma: results of the HIT-GBM-D pilot study. *J Neurooncol*. 2011;102(3):433–442.
23. Wolff JE, Gnekow AK, Kortmann RD, et al. Preradiation chemotherapy for pediatric patients with high-grade glioma. *Cancer*. 2002;94:264–271.
24. Chastagner P, Kalifa C, Doz F, et al. Outcome of children treated with preradiation chemotherapy for a high-grade glioma: results of a French Society of Pediatric Oncology (SFOP) pilot study. *Pediatr Blood Cancer*. 2007;49:803–807.
25. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
26. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005; 352(10):997–1003.
27. Christians A, Hartmann C, Benner A, et al. Prognostic value of three different methods of MGMT promoter methylation analysis in a prospective trial on newly diagnosed glioblastoma. *PLoS ONE*. 2012;7(3):e33449.
28. Donson AM, Addo-Yobo SO, Handler MH, et al. MGMT promoter methylation correlates with survival benefit and sensitivity to temozolomide in pediatric glioblastoma. *Pediatr Blood Cancer*. 2007;48:403–407.
29. Srivastava A, Jain A, Jha P, et al. MGMT gene promoter methylation in pediatric glioblastomas. *Childs Nerv Syst*. 2010;26:1613–1618.
30. Pollack IF, Hamilton RL, Sobol RW, et al. MGMT expression strongly correlates with outcome in childhood malignant gliomas: results from the CCG-945 cohort. *J Clin Oncol*. 2006;24(21):3431–3437.
31. Lashford LS, Thiesse P, Jouvet A, et al. Temozolomide in malignant gliomas of childhood. *J Clin Oncol*. 2002;20:4684–4691.
32. Cohen KJ, Pollack IF, Zhou T, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. *Neuro Oncol*. 2011;13(3):317–323.
33. Jakacki RI, Burger P, Zhou T, et al. A phase II study of concurrent radiation and TMZ followed by TMZ and lomustine (CCNU) in the treatment of children with HGG: results of COG ACNS0423. *Neuro Oncol*. 2010;12(6):ii1–ii134 (Page-ii12, Abstract-HGG.10).

34. Broniscer A, Gururangan S, MacDonald TJ, et al. A phase I trial of single dose TMZ and continuous administration of O^6-benzylguanine in children with brain tumors: a pediatric brain tumor consortium report. *Clin Cancer Res*. 2007;13(22):6712–6718.
35. Warren KE, Aikin AA, Libucha M, et al. Phase I study of O^6-benzylguanine and TMZ administered daily for 5 days to pediatric patients with solid tumors. *J Clin Oncol*. 2005;23(30): 7646–7653.
36. Fangusaro J, Warren KE. Unclear standard of care for pediatric high grade glioma patients. *J Neuro Oncol*. 2013;113:341–342.
37. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009;27:4733–4740.
38. Vredenburgh JJ, Desjardins A, Herndon JE, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol*. 2007; 25(30):4722–4729.
39. Gururangan S, Chi SN, Young Poussaint T, et al. Lack of efficacy of bevacizumab and irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a PBTC study. *J Clin Oncol*. 2010;28(18):3069–3075.
40. Narayana A, Kunnakkat S, Chacko-Matthew J, et al. Bevacizumab in recurrent high-grade pediatric gliomas. *Neuro Oncol*. 2010;12(9): 985–990.
41. Ellis M, Hicklin DJ. Pathways mediating resistance to vascular endothelial growth factor-targeted therapy. *Clin Cancer Res*. 2008;14(20):6371–6375.
42. Gorski DH, Beckett MA, Jaskowiak NT, et al. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res*. 1999;59(14):3374–3378.
43. Lee CG, Heijn M, di Tomaso E, et al. Anti-vascular endothelial growth factor treatment augments tumor radiation response under normoxic or hypoxic conditions. *Cancer Res*. 2000;60(19): 5565–5570.
44. Goels S, Duda DG, Munn LL, et al. Normalization of the vasculature for treatment of cancer and other diseases. *Physiol Rev*. 2011;91(3): 1071–1121.
45. Chinot OL, Wick W, Mason M, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblstoma. *N Engl J Med*. 2014;370:709–722.
46. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:699–708.
47. Fine HA. Bevacizumab in glioblastoma--still much to learn. *N Engl J Med*. 2014;370:764–765.
48. Bredel M, Pollack IF, Hamilton RL, et al. Epidermal growth factor receptor expression and gene amplification in high-grade non-brainstem gliomas of childhood. *Clin Cancer Res*. 1999;5: 1786–1792.
49. Qaddoumi I, Kocak M, Pai Panindiker AS, et al. Phase II trial of erlotinib during and after radiotherapy in children with newly diagnosed high-grade gliomas. *Front Oncol*. 2014;4:67. Doi:10.3389/fonc.2014.00067.
50. Cabanas R, Saurez G, Rios M, et al. Treatment of children with high-grade gliomas with nimotuzumab- A - year institutional experience. *MAbs*. 2013;5(2):202–207.
51. Kim CY, Kim SK, Phi JH, et al. A prospective study of temozolomide and thalidomide during and after radiation therapy for pediatric diffuse pontine gliomas: preliminary results of the Korean Society for Pediatric Neuro-Oncology study. *J Neuro Oncol*. 2010;100: 193–198.
52. Jones C, Perryman L, Hargrave D. Paediatric and adult malignant glioma: close relatives or distant cousins?. *Nat Rev Clin Oncol*. 2012;9:400–413.
53. Tanaka S, Louis DN, Curry TW, et al. Diagnostic and therapeutic avenues for glioblastoma: no longer a dead end?. *Nat Rev Clin Oncol*. 2013;10(1):14–26.
54. Sturm D, Bender S, Jones DTW, et al. Paediatric and adult glioblastoma multiform (epi)genomic culprits emerge. *Nat Rev Cancer*. 2014;14:92–107.
55. Sturm D, Witt H, Hovestadt H, et al. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. *Cancer Cell*. 2012;22:425–437.
56. Paugh BS, Broniscer A, Qu C, et al. Genome-wide analyses identify recurrent amplifications of receptor tyrosine kinases and cell cycle regulatory genes in diffuse intrinsic pontine gliomas. *J Clin Oncol*. 2011;29:3999–4006.
57. Puget S, Phillip C, Bax DA, et al. Mesenchymal transition and PDGFRA amplification/mutation are key distinct oncogenic events in pediatric diffuse intrinsic pontine gliomas. *PLos ONE*. 2012;7: e30313.
58. Zhargooni M, Bartels U, Lee E, et al. Whole-genome profiling of pediatric DIPG highlights PDGFRA and poly (ADP-ribose) polymerase as potential therapeutic targets. *J Clin Oncol*. 2010; 28:1337–1344.
59. Paugh BS, Qu C, Jones C, et al. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol*. 2010;28:3061–3068.
60. Pollack IF, Jakacki RI, Blaney SM, et al. Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: a Pediatric Brain Tumor Consortium report. *Neuro Oncol*. 2007;9:145–160.
61. Faury D, Nantel A, Dunn SE, et al. Molecular profiling identifies prognostic subgroups of pediatric glioblastoma and shows increased YB-1 expression in tumors. *J Clin Oncol*. 2007;25(10): 1196–1208.
62. Massimino M, Gandola L, Luksch R, et al. Sequential chemotherapy, high-dose thiotepa, circulating progenitor cell rescue, and radiotherapy for childhood high-grade glioma. *Neuro Oncol*. 2005; 7(1):41–48.
63. Finlay JL, Dhall G, Boyett JM, et al. Children’s Cancer Group. Myeloablative chemotherapy with autologous bone marrow rescue in children and adolescents with recurrent malignant astrocytoma: outcome compared with conventional chemotherapy: a report from the Children’s Oncology Group. *Pediatr Blood Cancer*. 2008;51(6):806–811.
64. Geyer JR, Finlay JL, Boyett JM, et al. Survival of infants with malignant astrocytomas. A Report from the Childrens Cancer Group. *Cancer*. 1995;75(4):1045–1050.
65. Duffner PK, Krischer JP, Burger PC, et al. Treatment of infants with malignant gliomas: the Pediatric Oncology Group experience. *J Neurooncol*. 1996;28(2–3):245–256.
66. Dufour C, Grill J, Lellouch-Tubiana A, et al. High-grade glioma in children under 5 years of age: a chemotherapy only approach with the BBSFOP protocol. *Eur J Cancer*. 2006;42(17):2939–2945.
67. Warren KE, Gururangan S, Geyer JR, et al. A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: a Pediatric Brain Tumor Consortium study. *J Neurooncol*. 2012;106(3):643–649.

68. MacDonald TJ, Vezina G, Stewart CF, et al. Phase II study of cilengitide in the treatment of refractory or relapsed high-grade gliomas in children: a report from the Children's Oncology Group. *Neuro Oncol*. 2013;15(10):1438–1444.
69. Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature*. 2012;482(7384):226–231.
70. Fontebasso AM, Liu XY, Sturm D, et al. Chromatin remodeling defects in pediatric and young adult glioblastoma: a tale of a variant histone 3 tail. *Brain Pathol*. 2013;23(2):210–216.
71. Fontebasso AM, Schwartzentruber J, Khuong-Quang DA, et al. Mutations in SETD2 and genes affecting histone H3K36 methylation target hemispheric high-grade gliomas. *Acta Neuropathol*. 2013;125(5):659–669.
72. Lewis PW, Muller MM, Koletsky MS, et al. Inhibition of PRC2 activity by a gain-of-function H3 mutation found in pediatric glioblastoma. *Science*. 2013;340:857–861.
73. Yuen BTK, Knoepfler PS. Histone H3.3 mutations: A variant path to cancer. *Cancer Cell*. 2013;24:567–574.
74. Chan KM, Fang D, Gan H, et al. The histone H3.3K27M mutation in pediatric glioma reprograms H3K27 methylation and gene expression. *Genes Dev*. 2013;27(9):985–990.
75. Bjerke L, Mackay A, Nandhabalan M, et al. Histone H3.3 Mutations Drive Pediatric Glioblastoma through Upregulation of MYCN. *Cancer Discov*. 2013;3(5):512–519.
76. Brockmann M, Poon E, Berry T, et al. Small molecule inhibitors of Aurora-A induce proteasomal degradation of N-Myc in childhood Neuroblastoma. *Cancer Cell*. 2013;24:75–89.
77. Shimomura T, Hasako S, Nakatsure Y, et al. MK-5108, a highly selective Aurora-A kinase inhibitor, shows antitumor activity alone and in combination with docetaxel. *Mol Cancer Ther*. 2010; 9(1):157–166.
78. Cole KA, Huggins J, Laquaglia M, et al. RNAi screen of the protein kinome identifies checkpoint kinase 1 (CHK1) as a therapeutic target in neuroblastoma. *Proc Natl Acad Sci USA*. 2011;108(8): 3336–3341.
79. Gerges N, Fontebasso AM, Albrecht S, et al. Pediatric high-grade astrocytomas: a distinct neuro-oncological paradigm. *Genome Med*. 2013;5:66–77.
80. Kim W, Liau L. IDH mutations in human glioma. *Neurosurg Clin N Am*. 2012;23:471–480.
81. Ichimura K. Molecular pathogenesis of IDH mutations in gliomas. *Brain Tumor Pathol*. 2012;29:131–139.
82. Capper D, Zentgraf H, Balss J, et al. Monoclonal antibody specific for IDH1 R132H mutation. *Acta Neuropathol*. 2009;118:599–601.
83. Cheng Z, Gong Y, Ma Y, et al. Inhibition of BET bromodomain targets genetically diverse glioblastoma. *Clin Cancer Res*. 2013;19(7): 1748–1759.
84. Puissant A, Frumm SM, Alexe G, et al. Targeting MYCN in neuroblastoma by BET bromodomain inhibition. *Cancer Discov*. 2013;3:308–323.
85. Fontebasso AM, Papillon-Cavanagh S, Schwartzentruber J, et al. Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma. *Nat Genetics*. 2014;46(5):462–466.
86. Sanvitale CE, Kerr G, Chaikaud A, et al. A new class of small molecule inhibitor of BMP signaling. *PLoS ONE*. 2013;8(4):e62721.
87. Shimono K, Tung W, Macolino C, et al. Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor-γ agonists. *Nat Med*. 2011;17(4):454–462.
88. Cannon JE, Upton PD, Smith JC, et al. Intersegmental vessel formation in zebrafish: requirement for VEGF but not BMP signalling revealed by selective and non-selective BMP antagoists. *Br J Pharm*. 2010;161:140–149.
89. Buczkowicz P, Hoeman C, Rakopoulus P, et al. Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations. *Nat Genetics*. 2014;46(5):451–456.
90. Wu G, Diaz AK, Paugh BS, et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. *Nat Genetics*. 2014;46(5):444–450.
91. Iyer R, Varela CR, Minturn JE, et al. AZ64 inhibits TrkB and enhances the efficacy of chemotherapy and local radiation in neuroblastoma xenografts. *Cancer Chemother Pharmacol*. 2012;70:477–486.
92. Iyer R, Evans AE, Qi X, et al. Lestaurtinib enhances the antitumor efficacy of chemotherapy in murine xenograft models of neuroblastoma. *Clin Cancer Res*. 2010;16(5):1478–1485.
93. Rohle D, Popovici-Muller J, Palaskas N, et al. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. *Science*. 2013;340:626–630.
94. Wang F, Travins J, DeLaBarre B, et al. Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. *Science*. 2013;340:622–626.
95. Andronesi OC, Kim GS, Gerstner E, et al. Detection of 2-hydroxyglutarate in IDH-mutated glioma patients by in vivo spectral-editing and 2D correlation magnetic resonance spectroscopy. *Sci Transl Med*. 2012;4:116ra4.
96. Metellus P, Figarella-Branger D. Magnetic resonance metabolic imaging of glioma. *Sci Transl Med*. 2012;4:116ps1.
97. Dasgupta T, Haas-Kogan DA. The combination of novel targeted molecular agents and radiation in the treatment of pediatric gliomas. *Front Oncol*. 2013;3:110.
98. Nicolaides TP, Li H, Solomon DA, et al. Targeted therapy for BRAF-V600E malignant astrocytoma. *Clin Cancer Res*. 2011; 17(24):7595–7604.
99. Belden S, Flaherty KT. MEK and RAF inhibitors for BRAF-mutated cancers. *Expert Rev Mol Med*. 2012;14:(e17):1–10.
100. Geoerger B, Hargrave D, Thomas F, et al. Innovative therapies for children with cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors. *Neuro Oncol*. 2011;13:109–118.
101. Broniscer A, Baker SJ, Stewart CF, et al. Phase I and pharmacokinetic studies of erlotinib administered concurrently with radiotherapy for children, adolescents, and young adults with high-grade glioma. *Clin Cancer Res*. 2009;15(2):701–707.
102. Geyer JR, Stewart CF, Kocak M, et al. A phase I and biology study of gefitinib and radiation in children with newly diagnosed brain stem gliomas or supratentorial malignant gliomas. *Eur J Cancer*. 2010; 46(18):3287–3293.
103. Lam C, Bouffet E, Bartels U. Nimotuzumab in pediatric glioma. *Future Oncol*. 2009;5(9):1349–1361.
104. Baruchel S, Sharp JR, Bartels U, et al. A Canadian paediatric brain tumour consortium (CPBTC) phase II molecularly targeted study of imatinib in recurrent and refractory paediatric central nervous system tumours. *Eur J Cancer*. 2009;45(13):2352–2359.
105. Geoerger B, Kieran MW, Grupp S, et al. Phase II trial of temsirolimus in children with high-grade glioma, neuroblastoma and rhabdomyosarcoma. *Eur J Cancer*. 2012;48:253–262.