Curr Pediatr Rep (2014) 2:38–49
DOI 10.1007/s40124-013-0033-5

HEMATOLOGY/ONCOLOGY (Z FADOO, SECTION EDITOR)

Chemotherapy in Childhood Brain Tumors

John-Paul Kilday · Eric Bouffet

Published online: 14 November 2013

Abstract Over time, the systematic evaluation of conventional chemotherapy for the treatment of childhood malignant brain tumors has revealed subtype-specific effectiveness. While having a pivotal role in improving survival for medulloblastoma patients, its activity against other tumors, such as pediatric high-grade glioma, remains disappointing. Today's clinician faces a dilemma when trying to improve patient outcomes further; escalating traditional treatment is likely to produce only additional morbidity without improving cure, particularly for the very young. The current evolution of genetic and molecular brain tumor research brings with it the hope of establishing novel targeted agents that can either supplement or replace standard chemotherapy to improve patient outcome and minimize toxicity. This article reviews literature from the past year evaluating both conventional chemotherapy and molecular agents for the three most common tumor subgroups; medulloblastoma, glioma (low/high-grade) and ependymoma. Future treatment strategies across North America and Europe are also highlighted.

Keywords Pediatric brain tumor · Childhood brain tumor · Chemotherapy · Novel agents, targeted therapy

J.-P. Kilday (✉)
Department of Haematology/Oncology, Royal Manchester Children's Hospital, Oxford Road, Manchester, Greater Manchester M13 9WL, England, UK
e-mail: john-paul.kilday@cmft.nhs.uk

E. Bouffet
Division of Haematology/Oncology, Hospital for Sick Children, University of Toronto, Toronto, ON M5G 1X8, Canada
e-mail: eric.bouffet@sickkids.ca

Introduction

Brain tumors represent the most common solid malignancy of childhood, accounting for over 20 % of all pediatric cancers with an incidence of 2.5–4.0 per 100,000 in industrialized society [1]. Comprising several distinct histological entities, brain tumors collectively remain the leading cause of cancer-related death and long-term morbidity in this age group [2]. Current treatment strategies therefore aim to maintain or improve survival outcomes, while minimizing toxicity and subsequent long-term side effects.

Over the past 3 decades, chemotherapy has helped to improve cure rates for certain pediatric brain tumor groups, notably medulloblastoma [3–6]. However, using chemotherapy and irradiation to achieve such survival success is often achieved at a significant burden to the survivor, with most experiencing neurocognitive and neuroendocrine morbidities, leading to challenges with social reintegration [7, 8].

By contrast, significant improvements in outcome for other childhood brain tumors, such as high-grade gliomas (HGGs), have not been observed despite a spectrum of multimodal therapies including several conventional chemotherapeutic agents [9]. Likewise, most refractory or recurrent malignant brain tumors continue to have dismal outcomes [10, 11]. Chemotherapy is also the primary adjuvant treatment for many infant brain tumors, since potentially effective irradiation is impractical because of its overwhelming toxicity at this developmental stage [12]. A paucity of alternative therapies undoubtedly contributes to the generally poorer survival results observed for this age group [13].

Clinicians now face a therapeutic impasse; intensifying available treatment is unlikely to confer survival progress,

instead only producing additional toxicity. To address this, attention has now focused on the biological research of childhood brain tumors, identifying critical genetic pathways responsible for neoplastic formation and maintenance. In turn, this has generated novel targeted molecular therapies that are hoped to improve efficacy while reducing toxicity [14].

This article reviews the principal literature from the past year evaluating both conventional chemotherapy and novel targeted agents for the three most common tumor subgroups: medulloblastoma, glioma (low- and high-grade) and ependymoma. Given the evolving landscape of biological research, current pharmacotherapeutic clinical trials and future treatment strategies for these tumor groups across North America and Europe are highlighted.

Medulloblastoma

Medulloblastomas are the most common malignant pediatric brain tumor, comprising 15–20 % of all cases [15]. Over 80 % of children with average-risk disease can expect cure with consequences from contemporary adjuvant strategies [4, 16, 17•]. However, this percentage drops to ~50–70 % for high-risk, metastatic cases [18] and is lower still for most infant disease and at recurrence [10, 13]. Recent publications in the field reflect the distinct dilemmas facing each risk group.

Average-Risk Disease

Retrospective cohort analyses continue to raise concern regarding the deleterious effects of adjuvant therapy, including chemotherapy, for average-risk medulloblastoma. Long-term follow-up data for 379 such patients treated with 23.4 Gy craniospinal radiotherapy (CSRT) followed by vincristine, lomustine (CCNU) and either cyclophosphamide or cisplatin, according to the Children's Oncology Group (COG) trial A9961, were recently published [17•, 19]. Despite cure rates over 80 % with a relatively lower CSRT dose, progressive intellectual and academic decline over 5 years from therapy was observed in 110 evaluated cases, and was significantly worse for younger patients, those with higher initial IQ scores and cases of posterior fossa mutism [17•]. The 10-year cumulative incidence of secondary malignancy for the entire cohort was 4.2 % [19]. Cisplatin-induced ototoxicity was also highlighted in an analysis of 22 average-risk children by the Toronto group, reporting high-frequency hearing loss at a median cumulative dose of 412 mg/m^2, necessitating cisplatin reduction in over 80 % of the group and hearing support for a third of patients [20]. These findings advocate further therapeutic dose reduction, particularly of CSRT, while aiming to maintain current survival rates, and have provided the basis for the current COG ACNS0331 trial.

High-Risk Disease

The focus of high-risk medulloblastoma studies has been to improve on current, unsatisfactory survival rates by adjusting the chemotherapy agents, intensity and/or scheduling, together with CSRT dosing and fractionation.

A randomized North American study (POG9031) of 224 high-risk children compared pre-irradiation chemotherapy (etoposide and cisplatin) to scheduling post-CSRT. No survival advantage was conferred by pre-radiation chemotherapy [5-year event-free survival (EFS) of 66 vs. 70 % ($p = 0.54$) and 5-year overall survival (OS) of 73 vs. 76 % ($p = 0.47$)] [21•]. This result is in keeping with other studies where no difference or indeed worse cure rates were observed with pre-irradiation chemotherapy [22–24]. Survival results for M2-3 patients on POG9031 are favorable when compared to other high-risk medulloblastoma trials [22, 24, 25]. This may reflect a higher dose of CSRT (40 Gy with 4.8 Gy boosts to disease sites) given to M2-3 cases. However, the long-term toxicity of this approach remains unclear.

To avoid these higher radiation doses, Korean colleagues have reported their experience using high-dose chemotherapy (carboplatin/thiotepa, cyclophosphamide/melphalan) in 20 high-risk patients (17 M+ cases) with autologous stem cell rescue after reduced dose CSRT (23.4 or 30.6 Gy with disease boosts) and induction chemotherapy [26]. The estimated 5-year EFS for metastatic patients was 70 %. However, the study's limited size and follow-up period, together with a relatively high incidence of post-transplant veno-occlusive disease, prohibit definitive conclusions on its comparative benefit.

Chemotherapeutic radiosensitizers have emerged as another feasible alternative to high-dose irradiation in this setting. A phase I/II COG trial (COG99701) of concurrent carboplatin alongside vincristine and conventional CSRT (36 Gy with disease boosts) followed by maintenance chemotherapy for 81 high-risk children has reported promising results [27••]. Five-year EFS and OS rates (71 and 76 %) for M+ disease compared favorably with regimens that have used either higher doses of radiation or more intensive chemotherapy [4,21•,28]. This approach is now being assessed in a prospective, randomized COG trial (ACNS0332). Concomitant cyclophosphamide with CSRT has also been described, although reports are less encouraging with 5-year OS results of 40 % in five metastatic cases [29].

Infant Medulloblastoma

Survival for this age group remains hindered by the inability to administer effective CSRT because of its unacceptable neurocognitive toxicity. Since the 1980s, protocols have relied on chemotherapy-only regimens to delay or avoid irradiation [30–32], although outcomes remain poorer than for older counterparts, and neurocognitive concerns persist.

Recent published studies have evaluated the use of chemotherapeutic strategies incorporating focal radiotherapy [33, 34]. The COG trial P9934 analyzed 74 M0 patients treated with adjuvant posterior fossa/tumor bed radiotherapy, sandwiched between induction and maintenance chemotherapy cycles (vincristine, etoposide, cisplatin, cyclophosphamide) [33]. Survival data appeared encouraging (4-year EFS and OS rates of 50 and 69 %) and improved when compared to a historical chemotherapy-only cohort (POG9921; EFS 25 %, OS 46 %). However, the number of complete resections was considerably higher in the COG P9934 trial, as was the proportion of desmoplastic/nodular tumors, an established favorable prognostic marker in infant medulloblastoma [35]. Indeed, when stratifying patients according to desmoplastic/nodular histology, no outcome difference was appreciated between either strategy. Other chemotherapy-only trials have also shown excellent survival rates for this patient subgroup that are comparable with average-risk older children [36•], bringing into question radiotherapy's value in this context.

A similar approach, incorporating focal radiotherapy with adjuvant chemotherapy and intrathecal mafosfamide for 71 infants with embryonal brain tumors, was recently reported by the Pediatric Brain Tumor Consortium (PBTC) [34]. Survival results were not significantly improved compared to historical studies, once more bringing into question the beneficial role of irradiation (5-year EFS and OS rates of 33 and 51 %). However, the ability to administer IT therapy at least appeared a feasible future strategy. Across the cohort, a nodular histology conferred a favorable prognosis and a subset of infant medulloblastoma cases achieved excellent survival outcomes, reinforcing the likelihood that histological and biological stratification will guide future treatment protocols for this age and tumor group.

Recurrent/Refractory Disease

Studies continue to address the dismal prognosis of recurrent/refractory medulloblastoma. A European phase II study of irinotecan and temozolomide in combination failed to meet its primary efficacy endpoint [37]; nevertheless, it was well tolerated, and its objective response rate (32 %) after four cycles compared favorably with contextual chemotherapy studies (discussed in [37]), suggesting its suitability as a 'backbone' regime for supplemental targeted therapy. Indeed, the addition of bevacizumab to this regime has been reported in nine children by American colleagues [38]. After 6 months, the objective response rate was 55 %, and two children were disease free at 15 and 55 months from treatment. The current COG ACNS0821 trial is now evaluating this combination in a prospective, randomized manner.

Other studies have assessed multi-agent chemotherapy in this context [39, 40], although the longer-term toxicity of this strategy in already heavily pre-treated children remains uncertain and thereby warrants caution. Nevertheless, encouraging results have been observed with a novel metronomic anti-angiogenic multi-drug combination (bevacizumab, thalidomide, celecoxib, fenofibrate, etoposide and cyclophosphamide), producing 2-year EFS and OS rates of almost 70 % across seven medulloblastoma cases. An Austrian phase II investigation of this regime is now in progress (Table 1).

Future Strategies

As stated above, the immediate aim of studies will be to maintain cure but reduce morbidity in good prognostic groups via therapeutic de-escalation, whilst continuing to improve prognosis for high-risk groups and recurrent disease. Eventually, medulloblastoma trial designs are likely to stratify patients according to both clinical risk factors and the molecular subgroups now established from transcriptional profiling (SHH, Wnt, group 3, group 4) [41••], targeting subgroups with appropriate therapy. Indeed, the identification of these molecular subsets has triggered great interest in the identification of subgroup-specific novel agents. Efforts to date have focused on the development of SHH inhibitors, with two agents (GDC-0449 and LDE225) currently being evaluated in phase II and III trials (Table 1).

Low-Grade Gliomas

Low-grade gliomas (LGGs) account for most brain tumors in the pediatric population. Surgery is typically curative for accessible lesions, but is often not feasible for enlarging or symptomatic midline LGGs of the hypothalamus/optic pathway. For such cases, chemotherapy has now become the therapy of choice in children aged below 10 years or any patient with neurofibromatosis-type 1 (NF1), in order to delay or avoid radiotherapy and its sequelae. While response rates of up to 60 % have been reported [42], the current challenge is to control tumor recurrence or progression, observed in up to two-thirds of cases [2].

Table 1 Molecular targeted agents currently being evaluated in childhood malignant brain tumor trials

Agent	Mechanism/ pathway	Brain tumor	Phase	Trial ID code	Trial overview
Bevacizumab	Anti-VEGF mAb	HGG/DIPG	II	NCT00890786[b]	RT with bevacizumab ± temozolomide, followed by bevacizumab, irinotecan ± temozolomide
		HGG	II/III	COG ACNS0822[a]/ NCT01236560[b]	RT with temozolomide, bevacizumab or SAHA, followed by bevacizumab and temozolomide
		ST HGG	II	ITCC-019[c]	RT with temozolomide ± bevacizumab, followed by temozolomide ± bevacizumab
		HGG	II	NCT00879437[b]	RT with valproic acid, followed by valproic acid and bevacizumab
		MBL (r)	II	NCT01356290[a]	With thalidomide, celecoxib, fenofibric acid, etoposide, cyclophosphamide, etoposide, cytarabine
		MBL (r)	II	COG ACNS0821[a]/ NCT01217437[b]	Randomized addition to temozolomide and irinotecan
Vandetanib	VEGFR/EGFR inhibitor	DIPG	I	NCT00996723[b]	RT with vandetanib and dasatinib, followed by vandetanib and dasatinib
Cediranib	VEGFR inhibitor	Non-specific (r)	I	NCT00326664[b]	Cediranib only
Sunitinib	VEGF inhibitor	HGG/ ependymoma (r)	II	NCT01462695[b]	Sunitinib only
Pazopanib	VEGF inhibitor	Non-specific (r)	I	COG ADVL0815[a]/ NCT00929903[b]	Pazopanib only
Nimotuzumab	Anti-EGFR mAb	DIPG	II	NCT01145170[b]	RT with nimotuzumab
Cetuximab	Anti-EGFR mAb	HGG/DIPG	II	NCT01012609[b]	RT with cetuximab, followed by cetuximab and irinotecan
Dasatinib	PDGFR inhibitor	DIPG	I	NCT00996723[b]	RT with vandetanib and dasatinib, followed by vandetanib and dasatinib
Crenolanib	PDGFR inhibitor	HGG (r)/DIPG	I	NCT01393912[b]	RT with crenolanib, followed by crenolanib
Cixutumumab	IGFR mAb	Non-specific (r)	I	COG ADVL0813[a]/ NCT00880282[b]	Cixutumumab and temsirolimus
Cilengitide	Integrin inhibitor	DIPG	I	NCT01165333[b]	RT with cilengitide
		HGG (r)/DIPG (r)	II	NCT01517776[b]	Cilengitide with temozolomide
MK2206	AKT inhibitor	Non-specific (r)	I	COG ADVL1013[a]/ NCT01231919[b]	MK2206 only
AZD6244	MEK inhibitor	LGG (r)	I/II	NCT01089101[b]	AZD6244 only
Temsirolimus	mTOR inhibitor	Non-specific (r)	I	COG ADVL0813[a]/ NCT00880282[b]	Cixutumumab and temsirolimus
		Non-specific (r)	I	COG ADVL0918[a]/ NCT01141244[b]	Temsirolimus with temozolomide and irinotecan
SAHA	HDAC inhibitor	DIPG	I/II	COG ACNS0927[a]/ NCT01189266[b]	RT with SAHA, followed by SAHA
		HGG	II/III	COG ACNS0822[a]/ NCT01236560[b]	RT with temozolomide, bevacizumab or SAHA, then bevacizumab and temozolomide
Valproic acid	HDAC inhibitor	HGG	II	NCT00879437[b]	RT with valproic acid, then valproic acid and bevacizumab
ABT-888	PARP inhibitor	Non-specific (r)	I	NCT00994071[b]	ABT-888 with temozolomide
Lenalidomide	Anti-angiogenic	HGG/DIPG	I	NCT01222754[b]	RT with lenalidomide
Capecitabine	Anti-metabolite	HGG/DIPG	I	NCT00357253[b]	RT with capecitabine
5-FU	Anti-metabolite	Ependymoma (r)	I	NCT01498783[b]	5-FU only
Tivantinib	c-Met inhibitor	Non-specific (r)	I	COG ADVL1111[a]/ NCT01725191[b]	Tivantinib only

Table 1 continued

Agent	Mechanism/ pathway	Brain tumor	Phase	Trial ID code	Trial overview
Imetelstat	Telomerase inhibitor	Non-specific (r)	II	NCT01836549[b]	Imetelstat only
Crizotinib	ALK/ROS1 inhibitor	Non-specific (r)	I/II	COG ADVL0912[a]/ NCT00939770[b]	Crizotinib only
Dendritic cell vaccine	Immunotherapy	HGG	I	NCRN code pending	With temozolomide post RT
GDC-0449	SHH inhibitor	SHH MBL (r)	II	NCT01239316[b]	GDC-0449 only
LDE225	SHH inhibitor	SHH MBL (r)	III	NCT01708174[b]	LDE225 versus temozolomide. Two subgroup analysis: Children ≤6 years not treated with RT ± temozolomide and older patients who may have been treated with RT ± temozolomide

VEGFR vascular endothelial growth factor receptor, *mAb* monoclonal antibody, *SAHA* suberoylanilide hydroxamic acid (SAHA), *HDAC* histone deacetylase inhibitor, *COG* Children's Oncology Group, *5-FU* fluorouracil, *VEGFR* vascular endothelial growth factor receptor, *EGFR* endothelial growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *ST* supratentorial, *HGG* high-grade glioma, *DIPG* diffuse intrinsic pontine glioma, *LGG* low-grade glioma, *SHH* Sonic hedgehog pathway, *MBL* medulloblastoma, *(r)* recurrence/refractory cases only, *IGFR* insulin-like growth factor receptor, *RT* radiotherapy

[a] As per the Children's Oncology Group

[b] As per ClinicalTrial.gov (US National Institutes of Health, ClinicalTrials.gov; http://www.clinicaltrials.gov. Accessed August 2013)

[c] As per the Innovative Therapies in Children with Cancer group, *NCRN* National Cancer Research Network

Recently published factors for progression from the HIT-LGG group include patient age, disseminated disease, non-pilocytic histology and concurrent diencephalic syndrome [43]. Both conventional chemotherapy and molecular targeted therapy continue to be evaluated in this context for efficacy at minimal toxicity.

Conventional Agents

The COG has published the first randomized evaluation of two chemotherapy regimens for 274 patients with progressive or symptomatic pediatric LGGs (trial ACNS 9952): vincristine/carboplatin (VC) versus thioguanine/procarbazine/lomustine/vincristine (TPCV). While the 5-year EFS rates were not significantly different between groups (VC 39 %, TPCV 52 %, $p = 0.10$), TPCV appeared to confer a longer-term advantage [44••]. Objective tumor response was reported in ~50 % of both cohorts. While the results were potentially superior to preceding chemotherapy trials [45, 46], significant grade III/IV toxicities were reported, including allergy with VC (7 %), seizures/weakness with TPCV (18 %) and myelosuppression or peripheral neuropathy in both strategies. Certain late effects, including subfertility from TPCV, were not reported.

To reduce this toxicity burden, the Toronto group also published their experience of single-agent vinblastine in 50 evaluable children with recurrent LGG [47•]. Tumor response was observed in 36 % of patients, with a 5-year EFS of 42 %, similar to the COG study. In contrast, toxicity was primarily only hematological.

This metronomic vinblastine regime additionally produced sustained tumor response in two infants with diencephalic syndrome caused by optic pathway pilomyxoid astrocytomas, together with resolution of emaciation [48]. Italian colleagues also reported the successful treatment of diencephalic syndrome in eight infants with optic pathway LGGs using a combination of cisplatin/etoposide [49]. After a median follow-up of 3 years, all patients were alive with tumor response reported for 75 % of the group. However, cisplatin-induced ototoxicity in developing infants already at risk of visual impairment represents a significant concern. Nevertheless, these results imply a role for chemotherapy in managing this rare but potentially fatal co-morbid condition that has historically been treated aggressively with radiotherapy [50].

Targeted Agents

The most common biological alterations so far identified in LGGs involve aberrations in *BRAF*, a downstream gene in the RAS/REF/MEK/MAPK pathway. Pilocytic astrocytomas frequently demonstrate chromosome 7q34 duplication, resulting from a tandem duplication of *BRAF* and *KIAA1549*, producing a fusion oncogene [51]. This fusion appears to confer a less aggressive clinical phenotype and is associated with better outcome [52•]. However, whether it represents a potential target remains unclear. A phase II

study of sorafenib (a multi-kinase BRAF inhibitor) in children with refractory LGGs actually reported frequent early progression, potentially due to paradoxical ERK activation inducing tumor growth [53]. Other *BRAF* alterations are observed in pediatric LGG histological subtypes, albeit less frequently. A recent report on the successful management of a ganglioglioma patient harboring the *BRAFV600E* mutation illustrates the importance of identifying those likely to benefit from BRAF inhibitors promptly [54•].

Two recent studies have evaluated bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF) receptor, for refractory pediatric LGG disease either alone for a median duration of 12 months or in combination with irinotecan [55, 56]. Sustained tumor reduction was recorded in over 85 % of all patients, with manageable toxicity, primarily hypertension and proteinuria. While promising, progression occurred rapidly for 13/14 children on discontinuation of therapy, although re-treatment proved feasible and effective [55].

The non-surgical treatment of subependymal giant cell astrocytomas (SEGAs), ventricular-associated LGGs that arise in ~15 % of patients with the genetic disorder tuberous sclerosis complex (TSC), represents a recent triumph for targeted therapy in pediatric brain tumors. Characteristic TSC lesions arise from overactivity of the mammalian target of the rapamycin (mTOR) pathway, which can be targeted by mTOR inhibitors [57, 58]. Indeed, a double-blind, placebo-controlled randomized study has been published, comparing the oral mTOR inhibitor everolimus to placebo. The trial enrolled 117 patients (78 in the everolimus stratum and 39 in the placebo). Patients in the everolimus arm ($n = 27$) demonstrated a reduction in the total volume of the target SEGA of 50 % or more versus none in the placebo group [59••]. Again, tumor re-growth occurred on stopping therapy, but re-treatment was successful. However, the benefit of mTOR inhibitors appears restricted to TSC-associated SEGA; current evidence of activity in other LGGs remains elusive [60].

Future Strategies

It is likely that future clinical trials will incorporate novel agents, such as bevacizumab, with conventional chemotherapy in an attempt to overcome the persisting difficulty of refractory disease in pediatric LGGs. Recent work has suggested significant biological differences among LGGs, including new targetable alterations in several different signaling pathways [61•]. In the meantime, other inhibitors of the RAS/RAF/MEK/MAP kinase signaling cascade are also in LGG clinical trials (Table 1), including a phase I study of the MEK inhibitor AZD6244 in children with recurrent or refractory disease. Chemotherapy as first-line therapy in refractory adolescent optic pathway/hypothalamic LGGs, historically treated with irradiation, may also be evaluated further following promising data from Canada, where 11 LGG patients treated with chemotherapy had a progression-free survival comparable with a matched cohort aged below 10 years [62].

High-Grade Glioma

High-grade gliomas (HGGs) [primarily anaplastic astrocytoma (AA), glioblastoma multiforme (GBM) and diffuse intrinsic pontine glioma (DIPG)] account for ~10 % of pediatric brain tumors. Despite recent therapeutic advances, the outcome for children with HGGs remains extremely poor, with fewer than 20 % of patients achieving long-term cure [63]. While gross excision confers a survival advantage [64], no prognostic or therapeutic stratification currently exists for this group, and the role of chemotherapy remains ill-defined. The current standard of care for pediatric HGGs is postoperative focal radiotherapy combined with concomitant and adjuvant temozolomide as a result of encouraging adult work [65]. Unfortunately, this regime has not translated into significantly improved survival for affected children when compared to historical strategies [63, 66], but continues to be used because of its favorable toxicity profile and, more importantly, a lack of alternative effective strategies.

HGG Studies

The most recent published phase II pediatric HGG studies, assessing novel therapies for activity in refractory disease to identify those warranting inclusion in a primary setting, continue to generate disappointing results.

In a PBTC evaluation of lapitinib [an inhibitor of epidermal growth factor receptor (EGFR) and ERBB2] in ten recurrent HGGs, patients failed to show anti-tumor activity [67]. This may not be unsurprising as recent molecular classification work has shown EGFR overexpression to predominate in adult HGGs, whereas pediatric counterparts often demonstrate high platelet-derived growth factor (PDGFR alpha) expression [68•]. Likewise, poor results were found by a retrospective institutional evaluation of combining irinotecan and bevacizumab (a monoclonal antibody against VEGF) in 12 children with refractory HGG, with progression on therapy observed in all cases [56]. This reinforces the disappointing findings of a preceding PBTC HGG study using both agents [69], yet contradicts promising response rates observed in adults [70, 71], again implying biological diversity between HGGs from different age groups and suggesting other

growth factors may be more important in childhood HGG pathogenesis. Phase II evaluations of PDGFR inhibitors in pediatric HGGs are now being planned following feasible phase I results (Table 1) [72].

Drug analyses in pediatric DIPGs published in the past year have also failed to yield effective candidates. A COG evaluation of combining metoxafin and gadolinium, a potent radiosensitizer, to standard fractionated radiotherapy in 60 eligible DIPG patients failed to improve survival compared to historical controls [73], while another study of subcutaneous pegylated interferon alpha-2b in 32 DIPG children reported no improvement in patient survival [74].

Other than age-related biological diversity, another explanation for the lack of current pharmacotherapy in pediatric HGGs reflects an inability to penetrate the blood-brain barrier, with chemotherapy efflux occurring secondary to inherent drug transporter molecules, thereby conferring apparent resistance [75, 76]. The feasibility of convection-enhanced drug delivery to bypass the blood-brain barrier has recently been reported in two cases of childhood DIPG [77] and could offer exciting opportunities for chemotherapeutic success in pediatric HGG.

Future Strategies

Due to advancing knowledge of pediatric HGG biology from molecular and pre-clinical research, several targeted therapies are being evaluated across this childhood tumor group.

A multi-center international randomized study of additional bevacizumab therapy to standard postoperative radiotherapy and temozolomide in children with supratentorial HGG is now open (Table 1). The present HGG COG trial (ACNS0822) is analyzing three agents for radiosensitivity (vorinostat, temozolomide, bevacizumab) before proceeding to a bevacizumab/temozolomide adjuvant chemotherapy regime. In Europe, the next HIT-GBM trial will evaluate high-dose methotrexate prior to radiochemotherapy, building on previous experience with this approach [75]. For DIPG, the current COG ACNS0927 trial is also adopting a combined modality strategy, using a histone deacetylase (HDAC) inhibitor to replace temozolomide both during and post-radiotherapy (Table 1).

Several other molecular therapeutic agents are under evaluation in early phase trials, often in refractory or recurrent disease settings (Table 1). These include inhibitors of telomerase, PARP inhibitors, integrins, c-MET, ALK and the RAS/AKT pathway, agents targeting a range of tyrosine kinases and growth factor receptors, antimetabolites, proteosome inhibitors, angiogenic agents and immunotherapy.

Clearly, research elucidating innovative drug targets remains paramount for improving outcome in pediatric HGG and DIPG. This can only be achieved by obtaining tumor tissue for biological analysis, a controversial topic in DIPG. Brainstem biopsies have historically been deemed dangerous and redundant for such a dismal condition, yet recent publications have disputed this view, reporting success in 90 children with DIPG using a stereotactic approach [78–80]. Indeed, recent biological DIPG studies from tissue obtained by diagnostic biopsy or on post-mortem cases have identified potential targetable biological mutations in DIPG [80, 81], generating hope for future therapies.

Ependymoma

Intracranial ependymomas account for ~10 % of childhood brain tumors [2]. Thought to arise from the neuroepithelial lining of the ventricular system, most occur in children aged below 5 years [82]. The extent of tumor excision is accepted as a critical prognostic factor [82, 83]. Postoperative survival rates have improved with the introduction of irradiation such that, with the exception of infants and localized, lower-grade supratentorial lesions [84], the current therapeutic standard of care is maximal surgical resection followed by conformal involved-field radiotherapy, a strategy with reported cure rates of up to 70 % [83]. While the efficacy of adjuvant chemotherapy in this tumor group has generally proven disappointing, there are reports at least one-quarter of very young children with intracranial ependymomas can achieve cure with surgery and chemotherapy alone [85, 86], thereby avoiding radiotherapy, although this remains to be validated in randomized cohorts.

Primary Tumor

Although the precise role of chemotherapy in pediatric intracranial ependymoma remains controversial, recent evidence from the COG's phase II CCG-9942 trial suggests a benefit of administering pre-irradiation chemotherapy in cases of postoperative residual disease [87•]. In the study, 35 evaluable children with residual disease were treated with four, month-long cycles of cisplatin, vincristine, cyclophosphamide and etoposide. Of these, 20 (57 %) responded to treatment. The 5-year EFS for the chemotherapy group was comparable with 43 enrolled patients without residuum who received irradiation only (55 ± 8 vs. 58 ± 9 %, $p = 0.45$). However, any overall survival benefit appeared limited to those with an initial near-total resection, as cases of significant subtotal resection continued to demonstrate inferior outcome. Moreover, 15 % of patients progressed on chemotherapy, suggesting that the scheduled duration of chemotherapy may need to

be curtailed to prevent radiation delay. This finding is supported by preliminary data from the first SIOP trial of multimodality therapy in pediatric intracranial ependymoma [88]. Here, 30 children with incomplete resection also underwent a 4-month schedule of vincristine, etoposide and cyclophosphamide prior to involved-field radiotherapy. While 60 % demonstrated an objective treatment response, the 5-year OS rate (53.5, 95 % CI 37.5–67.1 %) remained inferior to that for 33 children treated with radiation alone following gross total resection (76.2, 95 % CI 56.1–88.0 %).

Recurrent Disease

In most series, recurrent ependymoma still has a dismal outcome [11, 89]. However, the course of progression is often protracted, enabling the study of multiple approaches. Radiotherapy for those not previously irradiated has the potential to be curative alongside surgery [85, 89], while re-irradiation has also been shown to be safe and effective at improving outcome [90]. Due to its indolent course, several chemotherapeutic regimens and novel agents have also been assessed in recurrent childhood ependymoma [91], including two recent PBTC phase II studies of lapitinib and the combination of bevacizumab and irinotecan [67, 92]. Unfortunately neither strategy resulted in significant tumor control or change in patient outcome.

Future Strategies

Based on infant data reporting long-term response in certain ependymomas with adjuvant chemotherapy [85, 86], the current COG ACNS0831 trial aims to definitively address the survival impact of conventional chemotherapy through its randomized administration to children with localized ependymoma already treated with postoperative focal radiotherapy. The next European/SIOP strategy will be to assess several adjuvant approaches depending on tumor location, resection status and patient age. Three randomized studies will assess the role of chemotherapy for residual disease, post-irradiation maintenance chemotherapy for completely resected ependymomas and the addition of HDAC inhibition to conventional postoperative chemotherapy in infants.

Additional targeted therapies that have shown promise in pre-clinical research are now being evaluated in early-phase clinical trials (Table 1). These include a PBTC study of the telomerase inhibitor imetelstat [93] and an institutional phase II study of 5-fluorouracil (5-FU), which has shown in vitro and in vivo efficacy against supratentorial ependymoma following molecular characterization and drug screening work [94••]. Likewise, the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) has also shown in vitro activity against subgroup-specific ependymoma [95], and dose escalation studies have now been published [96].

As current patient-risk stratification systems are inaccurate, future trial work must also prospectively assess new staging systems that incorporate recent molecular subgrouping advances [97•, 98•, 99•] in order to tailor therapy more appropriately.

Conclusion

Conventional chemotherapy has played a key role in the improved survival of certain childhood brain tumors, but ongoing progress is hampered by a lack of alternatives. While novel methods of administration and scheduling remain under investigation, much hope rests with the evolving, biologically driven era of targeting specific brain tumor pathways and mutations to improve efficacy with a reduced toxicity. Eventually, the ‘one drug fits all’ paradigm could be replaced by individualized therapy packages for specific brain tumors, a concept already under development [100].

While the future of tumor management is undoubtedly exciting, it is unlikely that these novel, cytostatic agents will be able to completely replace conventional cytotoxic therapy. Additional matters to consider include the as yet unknown long-term toxicity profiles and impact on normal development of these agents, the consequential increased demand for tumor tissue diagnoses for previously surgically naïve tumors (DIPG and optic pathway gliomas) and the cost implications of these therapies in today’s economic climate.

Disclosure John-Paul Kilday and Eric Bouffet declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have beenhighlighted as:
- • Of importance
- •• Of major importance

1. Stiller CA, Blyer WA. Epidemiology. In: Walker DA, Perilongo G, Taylor RE, editors. Brain and spinal tumors of childhood. London: Arnold; 2004. p. 35–46.
2. Heath JA, Zacharoulis S, Kieran MW. Pediatric neuro-oncology: current status and future directions. Asia Pac J Clin Oncol. 2012;8:223–31.

3. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol. 2006;24:4202–8.
4. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol. 2006;7: 813–20.
5. Evans AE, Jenkin RD, Sposto R, et al. The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. J Neurosurg. 1990;72:572–82.
6. Tait DM, Thornton-Jones H, Bloom HJ, Lemerle J, Morris-Jones P. Adjuvant chemotherapy for medulloblastoma: the first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). Eur J Cancer. 1990;26:464–9.
7. Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol. 2004;5:399–408.
8. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. J Clin Oncol. 2008;26:1112–8.
9. Gajjar A, Packer RJ, Foreman NK, et al. Children's Oncology Group's 2013 blueprint for research: central nervous system tumors. Pediatr Blood Cancer. 2013;60:1022–6.
10. von Hoff K, Hinkes B, Gerber NU, et al. Long-term outcome and clinical prognostic factors in children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91. Eur J Cancer. 2009;45:1209–17.
11. Zacharoulis S, Ashley S, Moreno L, et al. Treatment and outcome of children with relapsed ependymoma: a multi-institutional retrospective analysis. Childs Nerv Syst. 2010;26:905–11.
12. Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: biology, therapy, and late effects. Semin Radiat Oncol. 2010;20:58–66.
13. Lafay-Cousin L, Strother D. Current treatment approaches for infants with malignant central nervous system tumors. Oncologist. 2009;14:433–44.
14. Nageswara Rao AA, Scafidi J, Wells EM, Packer RJ. Biologically targeted therapeutics in pediatric brain tumors. Pediatr Neurol. 2012;46:203–11.
15. Klesse LJ, Bowers DC. Childhood medulloblastoma: current status of biology and treatment. CNS Drugs. 2010;24:285–301.
16. Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol. 2012;30: 3187–93.
17. • Ris MD, Walsh K, Wallace D, et al.: Intellectual and academic outcome following two chemotherapy regimens and radiotherapy for average-risk medulloblastoma: COG A9961. Pediatr Blood Cancer. 60: 1350–7, 2013. *This study highlighted the significant long-term neurocognitive sequelae of current therapy for a large clinical trial cohort of pediatric standard-risk medulloblastoma patients.*
18. Varan A. Risk-adapted chemotherapy in childhood medulloblastoma. Expert Rev Anticancer Ther. 2011;11:771–80.
19. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. Neuro Oncol. 2013;15:97–103.
20. Lafay-Cousin L, Purdy E, Huang A, et al. Early cisplatin induced ototoxicity profile may predict the need for hearing support in children with medulloblastoma. Pediatr Blood Cancer. 2013;60:287–92.
21. • Tarbell NJ, Friedman H, Polkinghorn WR, et al.: High-risk medulloblastoma: a Pediatric Oncology Group randomized trial of chemotherapy Before or after radiation therapy (POG 9031). J Clin Oncol. 31: 2936–41, 2013. *This randomized clinical trial study found no survival advantage for pre-CSRT chemotherapy scheduling compared to post-CSRT chemotherapy for high-risk medulloblastoma.*
22. Kortmann RD, Kuhl J, Timmermann B, et al. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. Int J Radiat Oncol Biol Phys. 2000;46:269–79.
23. Massimino M, Cefalo G, Riva D, et al. Long-term results of combined preradiation chemotherapy and age-tailored radiotherapy doses for childhood medulloblastoma. J Neurooncol. 2012;108:163–71.
24. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: the International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol. 2003;21: 1581–91.
25. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. J Clin Oncol. 1999;17:832–45.
26. Sung KW, Lim do H, Son MH, et al. Reduced-dose craniospinal radiotherapy followed by tandem high-dose chemotherapy and autologous stem cell transplantation in patients with high-risk medulloblastoma. Neuro Oncol. 2013;15:352–9.
27. •• Jakacki RI, Burger PC, Zhou T, et al.: Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. J Clin Oncol. 30: 2648–53, 2012. *This study is the first to report improved survival for high-risk medulloblastoma patients treated with 36 Gy CSRT (plus boost) and concomitant radiosensitizing chemotherapy, thereby avoiding the need to employ either higher doses of radiotherapy or chemotherapy. Prospective evaluation of this promising finding forms the basis for the current COG high-risk medulloblastoma clinical trial (ACNS0332).*
28. Gandola L, Massimino M, Cefalo G, et al. Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma. J Clin Oncol. 2009;27:566–71.
29. Campen CJ, Dearlove J, Partap S, et al. Concurrent cyclophosphamide and craniospinal radiotherapy for pediatric high-risk embryonal brain tumors. J Neurooncol. 2012;110:287–91.
30. Duffner PK, Horowitz ME, Krischer JP, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med. 1993;328:1725–31.
31. Grill J, Sainte-Rose C, Jouvet A, et al. Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. Lancet Oncol. 2005;6: 573–80.
32. Geyer JR, Sposto R, Jennings M, et al. Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. J Clin Oncol. 2005;23:7621–31.

33. Ashley DM, Merchant TE, Strother D, et al. Induction chemotherapy and conformal radiation therapy for very young children with nonmetastatic medulloblastoma: Children's Oncology Group study P9934. J Clin Oncol. 2012;30:3181–6.
34. Blaney SM, Kocak M, Gajjar A, et al. Pilot study of systemic and intrathecal mafosfamide followed by conformal radiation for infants with intracranial central nervous system tumors: a Pediatric Brain Tumor Consortium study (PBTC-001). J Neurooncol. 2012;109:565–71.
35. Leary SE, Zhou T, Holmes E, Geyer JR, Miller DC. Histology predicts a favourable outcome in young children with desmoplastic medulloblastoma: a report from the children's Oncology Group. Cancer. 2011;117:3262–7.
36. • Rutkowski S, von Hoff K, Emser A, et al.: Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. J Clin Oncol. 28: 4961–8, 2010. *An important accumulation of clinical trial data from five national study groups evaluating therapy for infant medulloblastoma. The study established histopathology as a strong prognostic factor for this patient group.*
37. Grill J, Geoerger B, Gesner L, et al. Phase II study of irinotecan in combination with temozolomide (TEMIRI) in children with recurrent or refractory medulloblastoma: a joint ITCC and SIOPE brain tumor study. Neuro Oncol. 2013;15:1236–43.
38. Aguilera D, Mazewski C, Fangusaro J, et al. Response to bevacizumab, irinotecan, and temozolomide in children with relapsed medulloblastoma: a multi-institutional experience. Childs Nerv Syst. 2013;29:589–96.
39. Peyrl A, Chocholous M, Kieran MW, et al. Antiangiogenic metronomic therapy for children with recurrent embryonal brain tumors. Pediatr Blood Cancer. 2012;59:511–7.
40. Kim H, Kang HJ, Lee JW, et al. Irinotecan, vincristine, cisplatin, cyclophosphamide, and etoposide for refractory or relapsed medulloblastoma/PNET in pediatric patients. Childs Nerv Syst. 2013;29(10):1851–8.
41. •• Taylor MD, Northcott PA, Korshunov A, et al.: Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 123: 465–72, 2012. *Key consensus paper on the four molecular subgroups of pediatric medulloblastoma.*
42. Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg. 1997;86:747–54.
43. Gnekow AK, Falkenstein F, von Hornstein S, et al. Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and adolescents of the German Speaking Society of Pediatric Oncology and Hematology. Neuro Oncol. 2012;14:1265–84.
44. •• Ater JL, Zhou T, Holmes E, et al.: Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol 30: 2641–7, 2012. *This was the first published randomized clinical trial of two of the most frequently used chemotherapy regimens for progressive/refractory pediatric low-grade glioma.*
45. Laithier V, Grill J, Le Deley MC, et al. Progression-free survival in children with optic pathway tumors: dependence on age and the quality of the response to chemotherapy—results of the first French prospective study for the French Society of Pediatric Oncology. J Clin Oncol. 2003;21:4572–8.
46. Walter AW, Gajjar A, Reardon DA, et al. Tamoxifen and carboplatin for children with low-grade gliomas: a pilot study at St. Jude Children's Research Hospital. J Pediatr Hematol Oncol. 2000;22:247–51.
47. • Bouffet E, Jakacki R, Goldman S, et al.: Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. J Clin Oncol 30: 1358–63, 2012. *This institutional study of vinblastine monotherapy for progressive/refractory pediatric low-grade glioma revealed comparable efficacy with the regimens of Ater et al. (ref. 42) but with a potentially improved toxicity profile.*
48. Singh G, Wei XC, Hader W, et al. Sustained response to weekly vinblastine in 2 children with pilomyxoid astrocytoma associated with diencephalic syndrome. J Pediatr Hematol Oncol. 2013;35:e53–6.
49. Sardi I, Bresci C, Schiavello E, et al. Successful treatment with a low-dose cisplatin–etoposide regimen for patients with diencephalic syndrome. J Neurooncol. 2012;109:375–83.
50. Burr IM, Slonim AE, Danish RK, Gadoth N, Butler IJ. Diencephalic syndrome revisited. J Pediatr. 1976;88:439–44.
51. Pfister S, Janzarik WG, Remke M, et al. BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. J Clin Invest. 2008;118:1739–49.
52. • Hawkins C, Walker E, Mohamed N, et al.: BRAF-KIAA1549 fusion predicts better clinical outcome in pediatric low-grade astrocytoma. Clin Cancer Res 17: 4790–8, 2011. *This analysis reported that the presence of the BRAF-KIAA1549 gene fusion can be used as a favorable prognostic marker in pediatric low-grade glioma.*
53. Karajannis MFM, Milla SS, Cohen KJ, Legault G, Wisoff JH, et al. Phase II study of Sorafenib in children with recurrent/progressive low-grade astrocytomas. Neuro-oncology. 2012;14:vi101–5.
54. • Rush S, Foreman N, Liu A: Brainstem ganglioglioma successfully treated with vemurafenib. J Clin Oncol 31: e159–60, 2013. *This was the first report of therapeutic response to targeted inhibitor therapy for a glial tumor harboring the BRAF V600E mutation.*
55. Hwang EI, Jakacki RI, Fisher MJ, et al. Long-term efficacy and toxicity of bevacizumab-based therapy in children with recurrent low-grade gliomas. Pediatr Blood Cancer. 2013;60:776–82.
56. Couec ML, Andre N, Thebaud E, et al. Bevacizumab and irinotecan in children with recurrent or refractory brain tumors: toxicity and efficacy trends. Pediatr Blood Cancer. 2012;59:34–8.
57. Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol. 2006;59:490–8.
58. Krueger DA, Care MM, Holland K, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med. 2010;363:1801–11.
59. •• Franz DN, Belousova E, Sparagana S, et al.: Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 381: 125–32, 2013. *This international randomized placebo-controlled study revealed a significant tumor shrinkage using the mTOR inhibitor everolimus for SEGAs in TSC patients.*
60. Yalon M, Rood B, MacDonald TJ, et al. A feasibility and efficacy study of rapamycin and erlotinib for recurrent pediatric low-grade glioma (LGG). Pediatr Blood Cancer. 2013;60:71–6.
61. • Zhang J, Wu G, Miller CP, et al.: Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. Nat Genet 45: 602–12, 2013. *This large-scale genetic sequencing study discovered novel genetic alterations and potential therapeutic targets across the entire range of pediatric LGGs.*
62. Chong AL, Pole JD, Scheinemann K, et al. Optic pathway gliomas in adolescence—time to challenge treatment choices? Neuro Oncol. 2013;15:391–400.
63. 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;13:317–23.
64. 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;89:52–9.
65. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987–96.
66. Cohen KJ, Heideman RL, Zhou T, et al. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group. Neuro Oncol. 2011;13:410–6.
67. Fouladi M, Stewart CF, Blaney SM, et al. A molecular biology and phase II trial of lapatinib in children with refractory CNS malignancies: a Pediatric Brain Tumor Consortium study. J Neurooncol. 2013;114:173–9.
68. • 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 28: 3061–8, 2010. *This international molecular profiling analysis showed substantial differences in the molecular features underlying pediatric and adult HGG.*
69. Gururangan S, Chi SN, Young Poussaint T, et al. Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study. J Clin Oncol. 2010;28:3069–75.
70. Ali SA, McHayleh WM, Ahmad A, et al. Bevacizumab and irinotecan therapy in glioblastoma multiforme: a series of 13 cases. J Neurosurg. 2008;109:268–72.
71. Bokstein F, Shpigel S, Blumenthal DT. Treatment with bevacizumab and irinotecan for recurrent high-grade glial tumors. Cancer. 2008;112:2267–73.
72. Broniscer A, Baker SD, Wetmore C, et al. Phase I trial, pharmacokinetics, and pharmacodynamics of vandetanib and dasatinib in children with newly diagnosed diffuse intrinsic pontine glioma. Clin Cancer Res. 2013;19:3050–8.
73. Bradley KA, Zhou T, McNall-Knapp RY, et al. Motexafin-gadolinium and involved field radiation therapy for intrinsic pontine glioma of childhood: a Children's Oncology Group phase 2 study. Int J Radiat Oncol Biol Phys. 2013;85:e55–60.
74. Warren K, Bent R, Wolters PL, et al. A phase 2 study of pegylated interferon alpha-2b (PEG-intron(R)) in children with diffuse intrinsic pontine glioma. Cancer. 2012;118:3607–13.
75. Agarwal S, Mittapalli RK, Zellmer DM, et al. Active efflux of Dasatinib from the brain limits efficacy against murine glioblastoma: broad implications for the clinical use of molecularly targeted agents. Mol Cancer Ther. 2012;11:2183–92.
76. Veringa SJ, Biesmans D, van Vuurden DG, et al. In vitro drug response and efflux transporters associated with drug resistance in pediatric high grade glioma and diffuse intrinsic pontine glioma. PLoS One. 2013;8:e61512.
77. Anderson RC, Kennedy B, Yanes CL, et al. Convection-enhanced delivery of topotecan into diffuse intrinsic brainstem tumors in children. J Neurosurg Pediatr. 2013;11:289–95.
78. 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;13:109–18.
79. Roujeau T, Machado G, Garnett MR, et al. Stereotactic biopsy of diffuse pontine lesions in children. J Neurosurg. 2007;107:1–4.
80. Grill J, Puget S, Andreiuolo F, et al. Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. Pediatr Blood Cancer. 2012;58:489–91.
81. Hawkins CE, Bartels U, Bouffet E. Molecular genetic approaches and potential new therapeutic strategies for pediatric diffuse intrinsic pontine glioma. J Clin Oncol. 2011;29:3956–7.
82. Kilday JP, Rahman R, Dyer S, et al. Pediatric ependymoma: biological perspectives. Mol Cancer Res. 2009;7:765–86.
83. Merchant TE, Li C, Xiong X, et al. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. Lancet Oncol. 2009;10:258–66.
84. Venkatramani R, Ji L, Lasky J, et al. Outcome of infants and young children with newly diagnosed ependymoma treated on the "Head Start" III prospective clinical trial. J Neurooncol. 2013;113:285–91.
85. Grundy RG, Wilne SA, Weston CL, et al. Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. Lancet Oncol. 2007;8:696–705.
86. Grill J, Le Deley MC, Gambarelli D, et al. Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. J Clin Oncol. 2001;19:1288–96.
87. • Garvin JH, Jr., Selch MT, Holmes E, et al.: Phase II study of pre-irradiation chemotherapy for childhood intracranial ependymoma. Children's Cancer Group protocol 9942: a report from the Children's Oncology Group. Pediatr Blood Cancer 59: 1183–9, 2012. *This COG study has identified a potential prognostic benefit of using pre-irradiation chemotherapy in cases of incompletely resected pediatric intracranial ependymoma. This finding is now being evaluated through randomization in the current ACNS0831 COG trial.*
88. Grundy R, Jaspin T, Macarthur D, Wilne S, Kilday JP, Mallucci C, et al. Outcome of children treated for intracranial ependymoma: the first SIOP trial. Pediatr Blood Cancer. 2012;59:992.
89. Messahel B, Ashley S, Saran F, et al. Relapsed intracranial ependymoma in children in the UK: patterns of relapse, survival and therapeutic outcome. Eur J Cancer. 2009;45:1815–23.
90. Bouffet E, Hawkins CE, Ballourah W, et al. Survival benefit for pediatric patients with recurrent ependymoma treated with re-irradiation. Int J Radiat Oncol Biol Phys. 2012;83:1541–8.
91. Bouffet E, Capra M, Bartels U. Salvage chemotherapy for metastatic and recurrent ependymoma of childhood. Childs Nerv Syst. 2009;25:1293–301.
92. Gururangan S, Fangusaro J, Young Poussaint T, et al. Lack of efficacy of bevacizumab + irinotecan in cases of pediatric recurrent ependymoma—a Pediatric Brain Tumor Consortium study. Neuro Oncol. 2012;14:1404–12.
93. Tabori U, Ma J, Carter M, et al. Human telomere reverse transcriptase expression predicts progression and survival in pediatric intracranial ependymoma. J Clin Oncol. 2006;24:1522–8.
94. •• Atkinson JM, Shelat AA, Carcaboso AM, et al.: An integrated in vitro and in vivo high-throughput screen identifies treatment leads for ependymoma. Cancer Cell 20: 384–99, 2011. *This study was the first reported in ependymoma to integrate drug screening methodology and molecular profile classification to identify drugs suitable for specific biological subgroups of ependymoma. Findings from this publication have been translated into current clinical practice.*
95. Milde T, Kleber S, Korshunov A, et al. A novel human high-risk ependymoma stem cell model reveals the differentiation-inducing potential of the histone deacetylase inhibitor Vorinostat. Acta Neuropathol. 2011;122:637–50.
96. Witt O, Milde T, Deubzer HE, et al. Phase I/II intra-patient dose escalation study of vorinostat in children with relapsed solid tumor, lymphoma or leukemia. Klin Padiatr. 2012;224:398–403.
97. • Johnson RA, Wright KD, Poppleton H, et al.: Cross-species genomics matches driver mutations and cell compartments to model ependymoma. Nature 466: 632–36, 2010. *Largest reported gene expression profile analysis of intracranial*

ependymoma that identified several molecular subgroups with novel driver mutations specific to each group.

98. • Witt H, Mack SC, Ryzhova M, et al.: Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. Cancer Cell 20: 143–57, 2011. *This large gene expression analysis in posterior fossa ependymoma highlighted two diverse groups with significant biological, demographic and prognostic profiles.*
99. • Korshunov A, Witt H, Hielscher T, et al.: Molecular staging of intracranial ependymoma in children and adults. J Clin Oncol 28: 3182–90, 2010. *A large genomic study of ependymoma in children and adults that showed that specific chromosomal imbalances influence disease activity and prognosis.*
100. Wolff JE, Brown RE, Buryanek J, et al. Preliminary experience with personalized and targeted therapy for pediatric brain tumors. Pediatr Blood Cancer. 2012;59:27–33.