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REVIEW ARTICLE

Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape

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ABSTRACT

Pediatric neuro-oncology has undergone an exciting and dramatic transformation during the past 5 years. This article summarizes data from collaborative group and institutional trials that have advanced the science of pediatric brain tumors and survival of patients with these tumors. Advanced genomic analysis of the entire spectrum of pediatric brain tumors has heralded an era in which stakeholders in the pediatric neuro-oncology community are being challenged to reconsider their current research and diagnostic and treatment strategies. The incorporation of this new information into the next-generation treatment protocols will unleash new challenges. This review succinctly summarizes the key advances in our understanding of the common pediatric brain tumors (ie, medulloblastoma, low- and high-grade gliomas, diffuse intrinsic pontine glioma, and ependymoma) and some selected rare tumors (ie, atypical teratoid/rhabdoid tumor and CNS primitive neuroectodermal tumor). The potential impact of this new information on future clinical protocols also is discussed. Cutting-edge genomics technologies and the information gained from such studies are facilitating the identification of molecularly defined subgroups within patients with particular pediatric brain tumors. The number of evaluable patients in each subgroup is small, particularly in the subgroups of rare diseases. Therefore, international collaboration will be crucial to draw meaningful conclusions about novel approaches to treating pediatric brain tumors.

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INTRODUCTION

Despite improvement in the cure rates of pediatric brain tumors during the past two decades of the 20th century, which was largely a result of technologic advances in imaging, neurosurgery, and radiation oncology and the introduction of combination chemotherapy, outcomes have remained static for all of these tumors except medulloblastoma.[1] This article summarizes key collaborative group protocols and institutional studies that advanced the science of pediatric brain tumors and the survival of patients with these tumors. The lack of advances in treatment of pediatric brain tumors were hindered by our lack of knowledge about the molecular pathogenesis of brain tumors. This deficit is now being overcome by new technologies that facilitate our understanding of the genomic landscape of pediatric brain tumors, international cooperation among leading laboratory and clinical investigators, the availability of well-annotated tumor samples, and generous funding from government and philanthropic sources. The MAGIC (Medulloblastoma Advanced Genomics International Consortium) consortium instituted by the investigators at the Hospital for Sick Children in Toronto revolutionized international cooperation for studying medulloblastoma and set the stage for large-scale genomic studies.[2] Armed with this new genomic knowledge, we have renewed enthusiasm to develop novel therapeutic approaches that are tailored to each molecular subtype of disease under the broad umbrellas of medulloblastoma, high-grade glioma, low-grade glioma, ependymoma, and primitive neuroectodermal tumors.

MEDULLOBLASTOMA

Medulloblastoma is a highly malignant embryonal tumor that was first described as a distinct CNS tumor in 1925. Medulloblastoma occurs in infancy, childhood, or adulthood. Clinical heterogeneity has been documented in the clinical presentation, pathology, and cure rate.[3] By using combined-modality therapy that includes surgical resection, risk-adjusted irradiation, and adjuvant chemotherapy, approximately 70% of children and adolescents with medulloblastoma can be cured, albeit with debilitating long-term sequelae.[4]

Molecular Genetics of Medulloblastoma

One of the most important discoveries is that medulloblastoma is a heterogeneous disease that

consists of four core molecular subgroups identified via transcriptional profiling: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4.[5] These subgroups were defined by their unique clinical behavior and outcomes. The WNT-subgroup and SHH-subgroup medulloblastomas are characterized by aberrant activation of the WNT and SHH signaling pathways, respectively. Groups 3 and 4 were so named because of the absence of involvement of any clearly defined signaling pathway. Recently-developed genetic technologies, such as single nucleotide polymorphism gene-mapping arrays to identify somatic copy-number alterations and deep-sequencing studies, have exposed the genetic landscape of medulloblastoma, which thereby expanded our understanding of the molecular subgroups.[6] At least 30% to 40% of all medulloblastoma have been demonstrated to harbor somatic alterations (ie, single nucleotide variants, indels, and somatic copy number alterations) targeting a chromatin-modyfing gene, which confirms epigenetic deregulation as a major driver of medulloblastoma (Fig 1).[7]

WNT-subgroup medulloblastoma. The WNT subgroup accounts for approximately 10% of patients with medulloblastoma, and its cell of origin seems to arise from the lower rhombic lip.[8] Consequently, WNT medulloblastomas often develop in a central location, frequently abutting the brainstem. This subgroup generally occurs in older patients (median age, 10 years); almost all WNT tumors display classic histology and are rarely metastatic, and 80% to 85% of occurrences are associated with monosomy 6. Patients with WNT medulloblastoma experience excellent survival with contemporary therapy; their 5-year event-free survival (EFS) is greater than 90%.[9,10]

The most frequently mutated gene in WNT medulloblastoma is *CTNNB1*, which occurs in 85% of tumors analyzed. *DDX3X* mutations were enriched but not exclusive to the WNT subgroup; 11% of SHH tumors and 3% of group 3 tumors also express these mutations.[11-13] Approximately 15% of WNT tumors have *TP53* mutations, which are not associated with underlying Li-Fraumeni syndrome or a poor prognosis. This finding sharply contrasts with *TP53*-mutated SHH tumors.[14]

SHH-subgroup medulloblastoma. This subgroup comprises approximately 25% of medulloblastoma occurrences, most of which are of nodular desmoplastic (ND) histology. Indeed, all ND tumors are SHH medulloblastoma, but not all SHH medulloblastomas are ND; they also can have classic or large-cell/anaplastic (LCA) histology.[15] Cerebellar granule neuron precursors are the putative cells of origin of SHH medulloblastoma; therefore, these tumors frequently arise in a cerebellar hemisphere.[8] Three dominant subcategories prevail: infant SHH (0 to $<$ 4 years), childhood SHH ($\geq$ 4 to 17 years), and adult SHH ($>$ 17 years).[16]

PTCH1 mutations occur in all three SHH subcategories at approximately equal frequencies (42%, infant SHH; 36%, childhood SHH; and 54%, adult SHH tumors). Infant SHH tumors are the most likely to harbor *SUFU* mutations (32%). Childhood SHH is typified by *TP53* mutations (48%), which are frequently germline (80%) as part of Li-Fraumeni syndrome, and they rarely express *SUFU* (3%) mutations. This subgroup of SHH tumors with germline *TP53*-mutated tumors is more frequently associated with amplifications in *MYCN* (42%) and *GLI2* (30%). Adult SHH is characterized by mutations in *SMO* (30%) and aberrant activation of the phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (mTOR) –signaling pathway(30%).[16]

The prognosis of SHH medulloblastoma is quite variable: Patients who have infant SHH have an excellent prognosis when treated with chemotherapy alone[17]; those who have childhood SHH with *TP53* mutations have the worst outcome, especially when *MYCN* and *GLI2* are amplified. Patients with childhood SHH tumors that do not express *TP53* mutations and have average-risk features have a 5-year EFS of approximately 60%; those with adult SHH have a 5-year EFS of approximately 40% on the basis of retrospective data.[15,18]

Groups 3 and 4 medulloblastomas. Groups 3 and 4 account for 25% and 35% of medulloblastoma occurrences, respectively. They are molecularly distinct but share some overlap. Both have a male preponderance, and isochromosome 17q is confined to these subgroups, though it predominates in group 4 (80% *v* 26%). Groups 3 and 4 tumors demonstrate a relative paucity of recurrent driver mutations and are characterized by recurrent structural variants, including deletions, duplications, and inversions that place the growth factor–independent family of proto-oncogenes *GFI1* and *GFI1B* next to active enhancer elements, which results in their aberrant activation. This mechanism of enhancer hijacking activates *GFI1*/*GFI1B* in approximately 41% and 10% of group 3 and group 4 tumors, respectively.[19] The most frequently mutated gene in group 3 is *SMARCA4* (11%).

Continuing the theme of deregulated chromatin modifiers, inactivating mutations in the histone lysine (K) -specific demethylase 6A gene (*KDM6A*) encodes a protein that specifically demethylates the K27 residue of histone H3 (H3K27). Group 3 tumors are associated with LCA histology and metastatic disease (50%). They are also characterized by *MYCC* overexpression in most instances (approximately 17% have *MYCC* amplification). In the presence of metastatic disease, isochromosome 17q, or *MYCC* amplification, group 3 tumors confer a dismal prognosis. In addition to alterations of chromatin-modifying genes, copy number changes that target the transforming growth factor β–signaling pathway occur in 20% of patients with group 3 disease, most commonly through amplification of *OTX2* (8%).[2,7,20]

Group 4 tumors most commonly have classic histology, though some have LCA histology. Group 4 tumors are associated with *MYCN* amplification, which, in contrast to the SHH subgroup, is not associated with inferior outcome. Patients with group 4 medulloblastoma have an intermediate prognosis. However, those with metastatic disease have a higher risk of relapse, except in the presence of either whole chromosome 11 loss or chromosome 17 gain, which seem to identify a favorable prognostic subgroup. Group 4 has been found in a small number of infants who experience poor survival.[21]

Current Therapy for Medulloblastoma

During the past three decades, the use of empirically-based craniospinal irradiation (CSI) and chemotherapy after surgical resection has transformed a universally fatal disease into one in which the cure rate is approximately 70%. The application of clinical-risk stratification that is based on the extent of tumor resection and the presence of metastatic disease has refined treatment delivery. Children who are at least 3 years of age, have undergone gross-total resection ($<$ 1.5 cm^2 of residual tumor), and have no metastatic disease are classified with average-risk disease; the remainder are classified with high-risk disease. For children with average-risk disease, the introduction of chemotherapy has successfully demonstrated that addition of chemotherapy to CSI improved EFS. This finding has facilitated the

Fig 1. The genetic landscape of medulloblastoma. Recurrent genetic aberrations identified in medulloblastoma (derived from Northcott in 2012,[2,7] Robinson et al,[11] Pugh et al,[12] Jones et al,[13] and Northcott et al in 2014[19]) averaged and displayed proportionally by height of terrain peaks. The figure reveals the unique subgroup-specific molecular aberration and highlights chromatin remodeling mutations as the unifying theme among all four medulloblastoma subgroups. Wingless (WNT) medulloblastoma (left; blue icy landscape), the most molecularly homogenous group, consists of *CTNNB1* mutations in 85%, monosomy 6 in 80%, *DDX3X* mutation in 50%, *TP53* mutation in 13%, and mutations in chromatin remodeling genes in 49.5% (composed of mutations in *SMARCA4* [25%], *MLL2* [12.5%], *CREBBP* [6%], *TRAPP* [3%], and *MED13* [3%]). For the chromatin remodeling peaks (darker colored shading), only the most commonly mutated gene is labeled. Sonic hedgehog (SHH) medulloblastoma (bottom; red volcanic landscape) consists of *PTCH1* mutation/deletion in 29%, *TP53* mutation in 18%, *DDX3X* mutation in 11%, *GLI2* amplification/mutation in 8%, *MYCN* amplification in 6%, *SUFU* mutation in 6%, *SMO* mutation in 3%, *PTEN* deletion in 2.5%, *MYCL1* amplification in 2%, *CDK6* amplification in 1%, *MYCC* amplification in 0.7%, and mutations in chromatin remodeling genes in 21% (composed of mutations in *MLL2* [12%], *BCOR* [3%], *LBD1* [3%], *NCOR2* [1.5%], and *SMARCA4* [1.5%]). Group 3 medulloblastoma (top; yellow desert rocky terrain) is characterized by *GFI1/1B* structural variants (eg, inversions, duplications) in 41%, isochromosome (iso) 17q in 26%, transforming growth factor (TGF) -*β* signaling in 20%, *MYCC* amplification in 17%, *PVT1* alterations in 12%, *OTX2* amplification in 8%, *MYCN* amplification in 4%, *DDX3X* mutation in 3%, *CDK6* amplification in 1%, and mutations in chromatin remodelling genes in 28.5% (composed of mutations in *SMARCA4* [10.5%], other *KDM* family members [5%], *MLL2* [4%], *KDMA6A* [3%], *GPS2* [3%], *MLL3* [1%], *CREBBP* [1%], and *CHD7* [1%]). Group 4 medulloblastoma (right; green forest mountain terrain) is characterized by iso 17q in 80%, *GFI1/1B* structural variants in 10%, *SNCAIP* tandem duplications in 10%, *OTX2* amplification in 5.5%, *MYCN* amplification in 5%, *CDK6* amplification in 5%, *TP53* mutation in 1%, *MYCC* amplification in 1%, and mutations in chromatin remodeling genes in 30% (composed of mutations in *KDMA6A* [13%], other *KDM* family members [4%], *MLL3* [3%], *CHD7* [3%], *ZMYM3* [3%], *MLL2* [2%], *GPS2* [1%], and *BCOR* [1%]).

reduction of CSI from 36 Gy to 23.4 Gy without adversely affecting outcome.[22] Patients with average-risk disease have a 5-year EFS of approximately 80% after 23.4-Gy CSI, with a posterior fossa (PF) boost to 55.8 Gy in conjunction with platinum-based chemotherapy.[23] The recently completed Children's Oncology Group (COG) trial for average-risk medulloblastoma investigated the additional reduction of CSI to 18 Gy for children age 3 to 7 years, the age group that is most vulnerable to neurocognitive sequelae. In contrast, patients with high-risk disease have a 5-year EFS between 60% to 70% after they receive various treatment regimens centered on increased radiotherapy (RT) doses and intensified chemotherapy.[9,24] A recently published randomized study documented that there is no difference in the outcome for patients with high-risk medulloblastoma who get chemotherapy before RT versus chemotherapy after RT. Infants comprise a distinct risk group, in whom the outcome varies from 20% for those with macrometastatic disease to 90% for those with average-risk features and ND histology who received intensive chemotherapy-only regimens.[25]

Future Therapies for Medulloblastoma

WNT-subgroup medulloblastoma. Patients with WNT medulloblastoma are ideal candidates for therapy reduction to minimize the long-term effects of current therapy. However, given the potentially devastating consequences of reducing therapy in a patient incorrectly identified as having the WNT subgroup, accurate tumor assessment is paramount. International cooperative clinical trials are now underway or planned that incorporate molecular profiling to identify patients with WNT-subgroup disease and reduce not only their CSI dose but also their chemotherapy.

SHH-subgroup medulloblastoma. The potential effectiveness of *SMO* inhibitors in medulloblastoma was highlighted by the case report of a remarkable initial response of an adult with multiple-relapsed metastatic medulloblastoma treated with the *SMO* inhibitor GDC-0449.[26] Early-phase clinical trials of GDC-0449 for recurrent, SHH-driven medulloblastoma in adults and children revealed that it is well tolerated and has promising efficacy in certain patients.[27] Recent evidence suggests that *SMO* inhibitors demonstrate differential sensitivities depending on SHH subtypes; only patients who harbor upstream SHH-pathway mutations (ie, *SMO* and *PTCH1* mutations) showed sensitivity, whereas those with downstream aberrations (ie, *SUFU* mutations or *GLI2* amplification) demonstrated primary resistance.[16] Preclinical studies revealed that arsenic trioxide and itraconazole inhibited SHH signaling in the context of primary and secondary *SMO* inhibitor–resistant SHH medulloblastoma, an approach that requires additional evaluation for these SHH subtypes.[28]

Groups 3 and 4 medulloblastoma. Given the bleak outcome of group 3 patients, therapies that specifically target this subgroup are being sought with murine models that recapitulate the human tumors. By using one of these models and high-throughput screening, investigators identified two cytotoxic drugs, pemetrexed and gemcitabine, as effective and specific for group 3.[29] These drugs now are being evaluated in a clinical trial for newly diagnosed patients with medulloblastoma. Bromodomain and extraterminal domain family (BET) bromodomain inhibitors, which suppress *MYC*-associated transcriptional activity, have emerged as promising compounds targeting group 3 medulloblastoma. BET bromodomain inhibitors modulate *GLI* transcription downstream of *SMO* and *SUFU*; therefore, they may be effective against SHH medulloblastoma that shows primary or secondary resistance to *SMO* inhibitors.[30,31] Group 4–specific therapies remain elusive to date. Epigenetic-based therapies that target chromatin remodeling enzymes, such as demethylating agents (decitabine and azacitidine) and histone deacetylase inhibitors (vorinostat and panobinostat), are currently under preclinical investigation.

HIGH-GRADE GLIOMA AND DIFFUSE INTRINSIC PONTINE GLIOMA

Pediatric high-grade glioma (HGG) and diffuse intrinsic pontine glioma (DIPG) are diffusely infiltrative, malignant glial neoplasms that comprise a spectrum of histologies, and the vast majority are consistent with either anaplastic astrocytoma (WHO grade 3) or glioblastoma (WHO grade 4). Some DIPGs are consistent with diffuse astrocytomas (WHO grade 2) on initial biopsy, which may reflect sampling error. Their molecular genetic signatures and clinical behavior are indistinguishable from histologically higher-grade lesions.

Molecular Genetics of Pediatric HGG and DIPG

Subgroups of pediatric HGG and DIPG have been distinguished on the basis of recurrent combinations of genomic and/or epigenomic features with distinct biologic and clinical characteristics.[32-37] Key findings include the discovery of novel oncogenic driver mutations in histones H3.1 (position K27) and H3.3 (positions K27 and G34) as well as in the activin A receptor, type I (ACVR1). Genome-wide methylation-profiling data from the German Cancer Research Center and the Cancer Genome Atlas study groups support six epigenetically distinct subgroups of glioblastoma, five of which include pediatric patients (younger than 21 years, in descending order of prevalence): K27, G34, receptor tyrosine kinase (M6), mesenchymal (M1/M2), and isocitrate dehydrogenase (IDH; CpG island methylator phenotype).[38] An additional subgroup with glioblastoma histology but a distinct methylation signature that resembles pleomorphic xanthoastrocytoma (PXA) with frequent BRAF V600E mutations and a more favorable outcome was recently described and termed PXA-like.[39]

The K27 subgroup is characterized by its midline location (midbrain, brainstem, spinal cord), whereas the G34 subgroup most commonly arises in the cerebral white matter. The IDH subgroup, which is common in secondary glioblastomas that arise in adults and is characterized by mutations in IDH (*IDH1* or *IDH2*) as well as longer survival, is rarely seen in children. Published retrospective data indicate that the IDH, PXA-like, and G34 subgroups are associated with longer overall survival (OS), whereas the K27, receptor tyrosine kinase inhibitor, and mesenchymal subgroups are associated with the shortest OS.[33,39] In addition, the presence of amplified oncogenes, such as *EGFR*, *PDGFR*, and *MYCN*, was associated with a particularly poor outcome across subgroups. These data confirm the considerable molecular, biologic, and clinical heterogeneity of pediatric HGG and provide invaluable information for designing future clinical trials that involve a rational selection and stratification of patients on the basis of molecular subgroups, which are summarized in Figure 2.[39]

Current Therapies for Pediatric HGG and DIPG

The outcome for children with HGG or DIPG remains dismal and has been virtually unchanged for decades. For pediatric HGG, the strongest clinical prognostic factors are extent of resection and histologic grade. Single-agent temozolomide, when administered during and after RT, significantly prolongs EFS and OS in adults with glioblastoma[40]; however, similar treatment strategies used in a COG phase

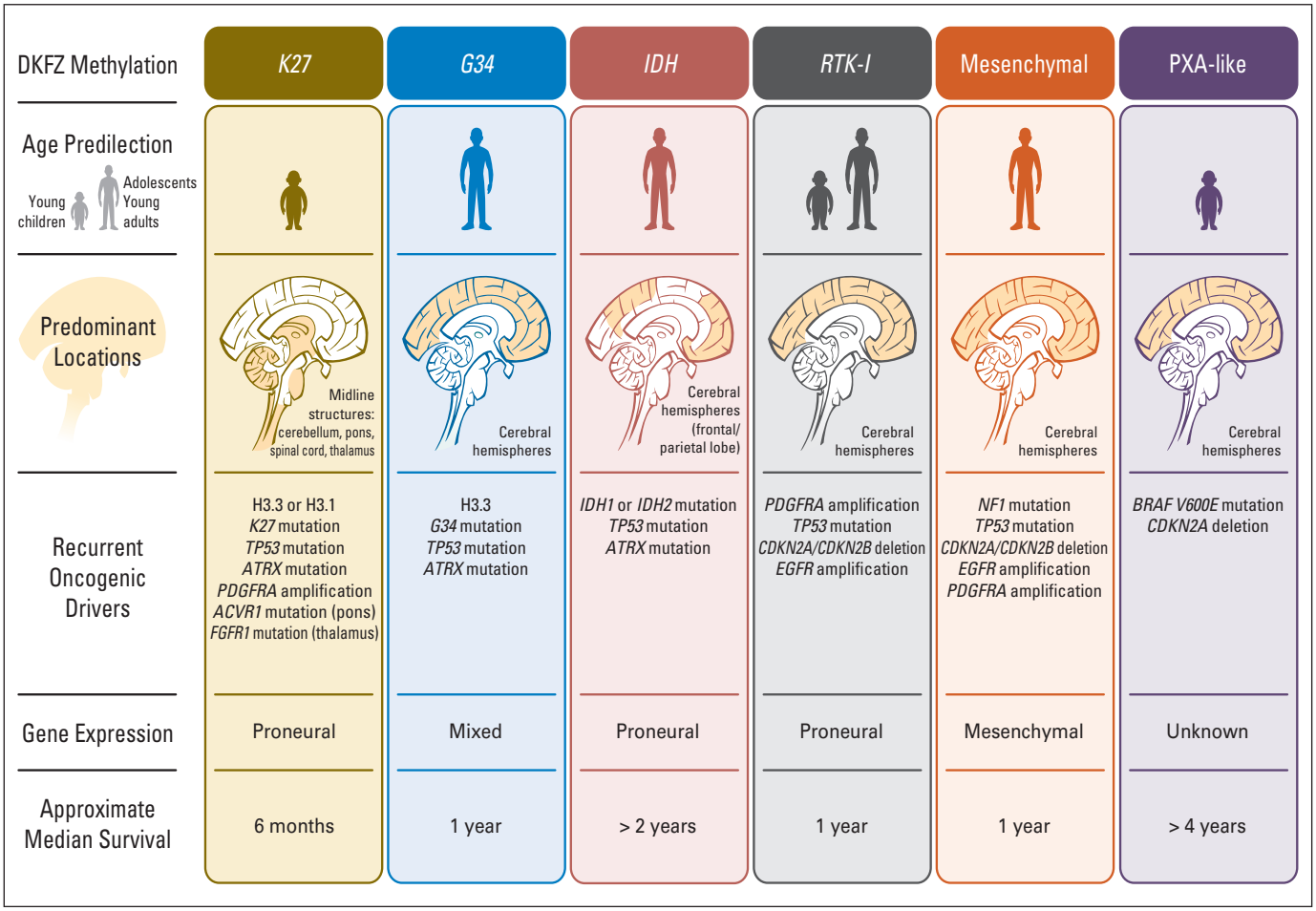

Fig 2. Subgroups of pediatric high-grade glioma that are based on German Cancer Research Center (DKFZ) methylation, age at onset, tumor location, oncogenic drives, gene expression, and median survival. IDH, isocitrate dehydrogenase; PXA, pleomorphic xanthoastrocytoma; RTK-I, receptor tyrosine kinase (subgroup 1).

II trial ACNS0126 (RT and temozolomide) did not improve the outcome in pediatric HGG compared with previous studies that used different adjuvant chemotherapy regimens.[41] Given the biologic heterogeneity of pediatric HGG, any clinical benefit of adjuvant chemotherapy may be confined to a particular subset. In pediatric patients with DIPG or HGG treated in arm C of the German Hirntumor cooperative group study for GBM (HIT-GBM-C) with intensive chemotherapy during and after RT, survival was better than that seen in prior HIT-GBM studies in the subgroup of patients with HGG who had undergone gross-total resection.[42] For DIPG, no improvement in outcome, compared with that achieved with RT alone, has been seen in any prospective clinical trial using RT plus adjuvant chemotherapy, including temozolomide and radiation sensitizers (ie, motexafin-gadolinium) and intensified chemotherapy regimens (Table 1). Thus, the standard of care for patients with DIPG remains RT alone.

The most recent COG HGG trial, ACNS0822, compared two combined-modality experimental arms that included either vorinostat or bevacizumab with standard therapy (ie, combined-modality that includes temozolomide). This study was recently closed after interim analysis showed that the predefined end point (ie, improved 1-year EFS compared with standard therapy) could not be met. In the context of the disappointing results of first-line therapy with bevacizumab in adults[47,48] and the lack of efficacy of bevacizumab-containing regimens in children with recurrent disease,[49,50] bevacizumab will probably not play a substantial role in future pediatric HGG and DIPG trials.

Future Therapies for Pediatric HGG and DIPG

The overarching theme that has emerged in pediatric HGG and DIPG biology is the disruption of multiple epigenetic regulatory processes by affecting histone modification, DNA methylation, and chromatin remodeling.[38] These data provide a foundation for the development of novel treatments that target the genetic and epigenetic drivers of pediatric HGG initiation and progression. Several agents that target specific chromatin modifiers are in preclinical and/or early clinical development, and such strategies will hopefully mature efficiently to enter clinical studies.[51,52]

The molecular heterogeneity of pediatric HGG and DIPG provides the impetus to stratify patients into biologically and clinically relevant molecular subgroups at the time of diagnosis.[39] It also motivates the identification of potentially actionable driver mutations, especially in the context of future clinical trials with novel, molecularly targeted drugs, including epigenetic modifiers. Preliminary data have demonstrated the efficacy of V600E inhibitors in recurrent HGG that harbors the mutation,

Table 1. Outcomes for Cooperative Group Studies

Protocol by Pediatric Brain Tumor Type	Study Hypothesis	Radiation Therapy	Chemotherapy	Planned Duration of Therapy	Accrual (No. of patients)	Age	EFS
Medulloblastoma							
Standard risk							
A 9961[23]	To determine efficacy of cyclophosphamide-based regimen versus standard regimen	23.4 Gy CSI; 55.8 Gy PF	Weekly VCR during RT; randomly assigned chemotherapy: CDDP/CCNU/VCR *v* CDDP/Cyclo/VCR	56 weeks	379	3-18 years	81% ± 2.1% (5 year); no difference between chemotherapy arms
SIOP III[43]	Randomized study to determine the efficacy of RT alone versus chemotherapy + RT	35 Gy CSI; 55 Gy PF	Weekly VCR during RT; carboplatin and VP16 alternating with cyclophosphamide and VP16	6 weeks for RT alone; 20 weeks for RT + chemotherapy	179	3-16 years	67% (5 year); 74.2% (chemotherapy + RT); 59.8%(RT alone)
High risk							
POG 9031[24]	Efficacy of pre-RT chemotherapy on the EFS of high-risk medulloblastoma	35.2-44.0 Gy CSI; 53.2-54.4 Gy PF	Three cycles of pre-RT chemotherapy with CDDP/VP16 followed by seven cycles of Cyclo/VCR *v* same chemotherapy given post-RT	47 weeks	224	3-18 years	68.1% ± 3% (5 year); no difference between the two arms
High-grade glioma							
ACNS0126[40]	Temozolomide administered during and after RT will improve EFS compared with historical controls	54.0 Gy	Temozolomide during RT and followed by RT for 10 cycles	50 weeks	107	3 to ≤ 22 years	11% ± 3% (3 year); no improvement
HIT-GBM-C[41]	Intensive chemotherapy during and after RT, followed by valproate maintenance therapy, will improve OS compared with historical controls	54 Gy	Two cycles of PEV and PEI, respectively, during RT, followed by six cycles of PEI alternating with monthly VCR, followed by continuous valproate maintenance therapy	30 weeks, followed by continuous valproate maintenance therapy	60	3-17 years	OS: 67% ± 10% (1 year) and 63% ± 12% (5 year) for patients with complete resection only; improvement compared with historical controls; no improvement for incomplete resection
Diffuse pontine glioma							
ACNS0126[44]	Temozolomide administered during RT and post-RT will improve EFS compared with historical controls	59.4 Gy	Temozolomide during RT and followed by RT for 10 cycles	46 weeks	63	3-21 years	14% ± 5.5% (1 year); no improvement
ACNS0222[45]	Motexafin-gadolinum administered during RT will improve EFS	54 Gy	Motexafin-gadolinium administered with daily RT	6 weeks	60	< 22 years	18% ± 5% (1 year); no improvement
HIT-GBM-C[41]	Intensive chemotherapy during and after RT, followed by valproate maintenance therapy will improve OS compared with historical controls	59.4 Gy	Two cycles of PEV and PEI, respectively, during RT, followed by six cycles of PEI alternating with monthly VCR, followed by continuous valproate maintenance therapy	30 weeks, followed by continuous valproate maintenance therapy	37	3-17 years	0.40 ± 0.07 years (median ± SD EFS); no improvement compared with control (0.55 ± 0.098 median ± SD EFS)
Low-grade glioma							
A 9952[46]	Compare the efficacy of two active chemotherapy regimens for LGG	—	Carbo/VCR *v* CCNU/procarbazine/TG/VCR	52 weeks	274	< 10 years	45% ± 3.2% (5 year); no difference in the two regimens
Ependymoma							
ACNS0121*	Efficacy of conformal RT in ependymoma	59.4 Gy (> 18 months)	Only for patients with subtotal resection	6 weeks	355	> 12 months to < 21 years	62.6 ± 2.7% (5 year); similar to highly selected single-institution series

Abbreviations: Carbo, carboplatin; CCNU, lomustine; CDDP, cisplatin; CSI, craniospinal irradiation; Cyclo, cyclophosphamide; EFS, event-free survival; HIT-GBM-C, arm C of Hirntumor study for GBM; LGG, low-grade glioma; OS, overall survival; PEI, cisplatin, etoposide, and ifosfamide; PEV, cisplatin, etoposide, and vincristine; PF, posterior fossa; RT, radiotherapy; SD, standard deviation; TG, thioguanine; VCR, vincristine; VP16, etoposide.
*T. Merchant, personal communication, July 2015.

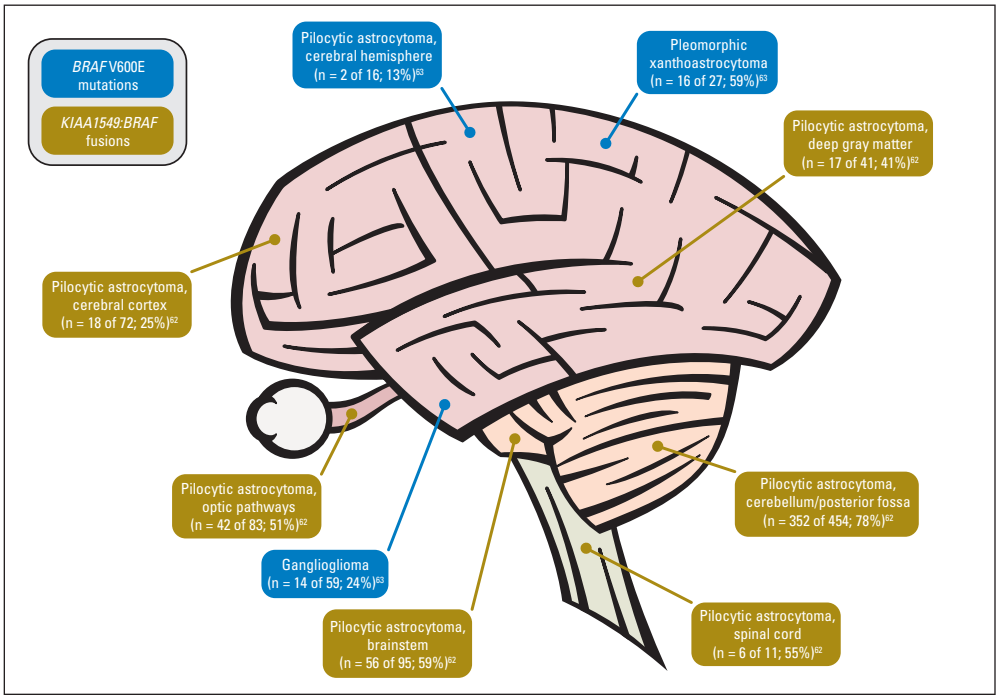

Fig 3. *BRAF* mutations and fusions by tumor histology and tumor location in pediatric low-grade gliomas.

which thus provides early proof of principal for treating HGG on the basis of molecular subgroups.[53]

LOW-GRADE GLIOMA

Low-grade gliomas (LGGs) represent multiple tumor subtypes and are the most common brain tumor of childhood. Two autosomal-dominant cancer-predisposition syndromes, tuberous sclerosis complex and neurofibromatosis type-1 (NF-1), are associated with an increased frequency of LGGs (subependymal giant cell astrocytomas and pilocytic astrocytomas of the optic pathways/hypothalamus, respectively). Despite many similarities, pediatric LGG subtypes have distinct predilections for specific locations within the CNS, which often correlate with specific genomic alterations and the ability to achieve gross-total resection (Fig 3).

BRAF oncogene mutations that activate the mitogen-activated protein kinase (MAPK) pathway represent the most frequent genomic alteration in pediatric LGGs.[54-56] Furthermore, *KIAA1549–BRAF* gene fusions are common among pilocytic astrocytomas in the cerebellum but not in the cerebral cortex,[56-62] whereas *BRAF* V600E mutations are more frequent among pleomorphic xanthoastrocytomas, gangliogliomas, and a subset of extracerebellar pilocytic astrocytomas.[63] Other alterations that activate the MAPK pathway, such as *SRGAP3–RAF1* and *FAM131B–BRAF* fusions and a 3-bp insertion at position 599 ($BRAF_{insT}$), have been identified in pediatric LGGs.[64,65]

Unlike LGGs among older adolescents and adults, childhood LGGs almost never express *IDH1* or *IDH2* mutations and rarely undergo malignant transformation into higher-grade neoplasms.[66,67]

Current Therapy for LGGs

Most children with LGGs undergo surgical resection followed by observation; carboplatin-containing chemotherapy and/or conformal RT are reserved for recurrent or progressive tumors.[68-71] Treatment decisions largely are based on the tumor's location and the patient's age at diagnosis rather than on the glioma histologic subtype or tumor biology. With such strategies, the 10- to 20-year OS for children with LGGs is 83% to 94%.[72-75]

Randomized, phase III clinical trials for children with LGGs have recently been conducted by COG and the International Society of Pediatric Oncology (SIOP). COG A9952 was a prospective, randomized trial for children younger than 10 years with LGGs. Enrolled patients without NF-1 were randomly assigned to receive carboplatin and vincristine (CV; n = 137) or thioguanine, procarbazine, CCNU (lomustine), and vincristine (n = 137). The 5-year EFS (± standard deviation) was 39% ± 4% for patients randomly assigned to CV and was 52% ± 5% for those who received thioguanine, procarbazine, lomustine, and vincristine ($P = .10$).[46]

The SIOP clinical trial LGG-2004 is a comprehensive treatment strategy for children with LGGs and includes a randomized chemotherapy trial for children without NF-1. The study compares CV versus CV plus etoposide. Results of the SIOP-LGG-2004 clinical trial are anticipated in the near future.

Future Therapies for LGGs

BRAF *duplication/MAPK pathway–targeting agents.* Considerable interest exists in the targeted inhibition of the MAPK pathway as therapy for pediatric LGGs. A recent phase II study of sorafenib was associated with an unexpected and unprecedented acceleration of LGG growth, irrespective of the tumor's *BRAF* status and most likely caused by paradoxical *ERK* activation, which led to early closure of this study.[76,77] In addition, an ongoing phase II study from the Pediatric Brain Tumor Consortium (NCT01089101) is examining the activity of selumetinib (AZD4266), an MEK1/2 inhibitor, against pediatric LGGs on the

basis of efficacy seen in a phase I study. As the results of the phase II study become available, *BRAF*/MAPK/*ERK* pathway inhibitors are expected to be examined in future trials designed for patients with newly diagnosed LGG.

BRAF *V600E–targeting agents.* Vemurafenib and dabrafenib are competitive small molecules that bind and inhibit the ATP-binding domain of mutant *BRAF* V600E but not other mutant forms of *BRAF*.[78] Vemurafenib and dabrafenib are approved by the US Food and Drug Administration for unresectable or metastatic melanoma with *BRAF* V600E mutations. Furthermore, trametinib, a MEK inhibitor, is also approved by the US Food and Drug Administration for *BRAF* V600E–mutated metastatic melanoma. Dabrafenib is currently being examined as therapy for *BRAF* V600E–mutant pediatric tumors, including LGGs (NCT01677741).

AKT/mTOR pathway–targeting agents. Subependymal giant cell astrocytoma, an LGG subtype found nearly exclusively among children with tuberous sclerosis complex, has an activated AKT/mTOR pathway. Clinical trials have demonstrated that mTOR inhibitors (eg, sirolimus and everolimus) have activity against this LGG subtype.[79,80] Everolimus has received approval as a treatment for subependymal giant cell astrocytomas that cannot be surgically resected.

Two clinical trials of mTOR inhibitors have demonstrated activity against progressive pediatric LGGs, regardless of NF-1 status. Yalon et al[81] reported the activity of sirolimus and everolimus against recurrent pediatric LGG. Among 19 evaluable patients, one experienced partial response (PR; > 50% decrease in tumor size), five experienced stable disease (SD), and 10 experienced progressive disease (PD); three patients discontinued the study therapy before being evaluated. Six patients (n =1, PR and n = 5, SD) experienced tumor stabilization for 12 months or greater, and two patients with PD experienced tumor control for at least 12 months after completion of therapy. Kieran et al[82,83] reported the activity of everolimus against pediatric LGGs. Of the 23 patients enrolled, four experienced PR, 13 had SD, and six experienced PD.[82,83] These responses justify additional exploration of mTOR inhibitors against pediatric LGGs.

EPENDYMOMA

Ependymoma is the second-most-common malignant brain tumor in childhood. Ependymoma can arise intracranially, in the supratentorial compartment (ST), and within the PF and spinal cord.[84] Despite our recent identification of driver oncogenes and molecular subtypes of ependymoma, the treatment of children and adolescents with the disease remains challenging. The outcome of ependymoma in children, especially in infants, is poor; almost half die as a result of their disease.[85]

In most pediatric ependymoma protocols, patients are stratified on the basis of the disease WHO grade and/or patient age at diagnosis. Histopathologic diagnosis, including WHO grading,[86] is still challenging and has been controversial with regard to classification and reproducibility.[87]

Several recent studies have provided reproducible evidence of distinct molecular subtypes of ependymomas.[88-93] Two molecular subtypes, although histologically similar within the PF, were discovered.[89] These distinct diseases differ on the basis of age at diagnosis, copy-number aberrations, gene expression, and outcome. Group-A PF ependymomas show flat genomes, occur predominantly in infants, and show activation of cancer-related signaling pathways (eg, vascular endothelial growth factor, platelet-derived growth factor receptor, integrin, MAPK). Group-B PF tumors occur in adolescents and young adults and frequently display large genomic aberrations. These ependymomas can be cured by RT alone.

Contemporary studies highlighted the genetic and epigenetic alterations as therapeutic targets of different subtypes of ependymoma.[92,93] By using whole-exome and whole-genome sequencing technologies, the researchers found that no single recurrent somatic mutations could be identified in PF ependymoma. The mutation rates in groups A and B were low (average, n = 5 somatic mutations per occurrence). Accentuating the DNA-methylation pattern, group-A ependymomas displayed a slightly higher proportion of methylated CpG islands within the promoter region than did group B ependymomas. Group-A tumors showed a greater extent of epigenetic silencing of targets of the polycomb repressive complex 2, including downregulation of differentiation genes through H3K27 trimethylation. In vitro preclinical studies that used epigenetic demethylating drugs have shown responses in isolated ependymoma cells. These results are promising treatment strategies that target DNA CpG methylation, polycomb repressive complex 2/enhancer of zeste homolog 2 (EZH2), and/or histone deacetylases (Fig 4).

Parker et al[93] recently discovered that greater than 70% of ST ependymomas express the *C11orf95–RELA* gene fusion within chromosome 11q, which was possibly caused by chromothripsis. *RELA* is a downstream target of nuclear factor-κB signaling that acts as a transcription factor and regulates cell maintenance.

A study that used data from 500 ependymal brain tumors presented a molecular-based classification scheme of nine molecular subgroups by using DNA methylation arrays. This molecular classification outperforms the current histopathologic grading in the risk stratification of patients[94] (Fig 4). Within each anatomic region, three subgroups were identified, including subependymomas (WHO grade 1) that can be diagnosed predominantly in adults, which affect the spinal cord, PF, and ST areas. Molecular subtypes of the spinal cord correlated with histologic diagnoses myxopapillary ependymoma and grade 2 ependymomas. Within the PF, previously described molecular subtypes could be confirmed, namely, group A (PF-EPN-A) and group B (PF-EPN-B). Tumors of the two remaining ST subtypes originate by tumorigenic gene fusions that affect the gene *RELA* (ST-EPN-RELA) and Yes-associated protein 1 (YAP1 [ST-EPN-YA]). The integration of molecular subtypes and clinical follow-up data revealed a strong association with poor OS of patients with ST-EPN-RELA and PF-EPN-A tumors, who are usually children.[94]

Current Therapy for Ependymoma

Treatment of all ependymomas consists of attempting complete neurosurgical resection and adjuvant RT. Study protocols differ in terms of eligibility criteria for RT; some centers start RT at 1 year of age or younger, and others start at 18 months. A recently concluded COG study that used adjuvant RT after surgical resection documented no improvement in outcome versus historical data, though the subset of patients with gross-total resection had an improved EFS (Table 1). The benefit of addition of adjuvant chemotherapy to surgical resection and RT is being investigated in the current COG trial for newly diagnosed ependymoma (NCT01096368).

The current European Ependymoma Study (SIOP Ependymoma II; EudraCT No. 2013-002766-39) will open for patient

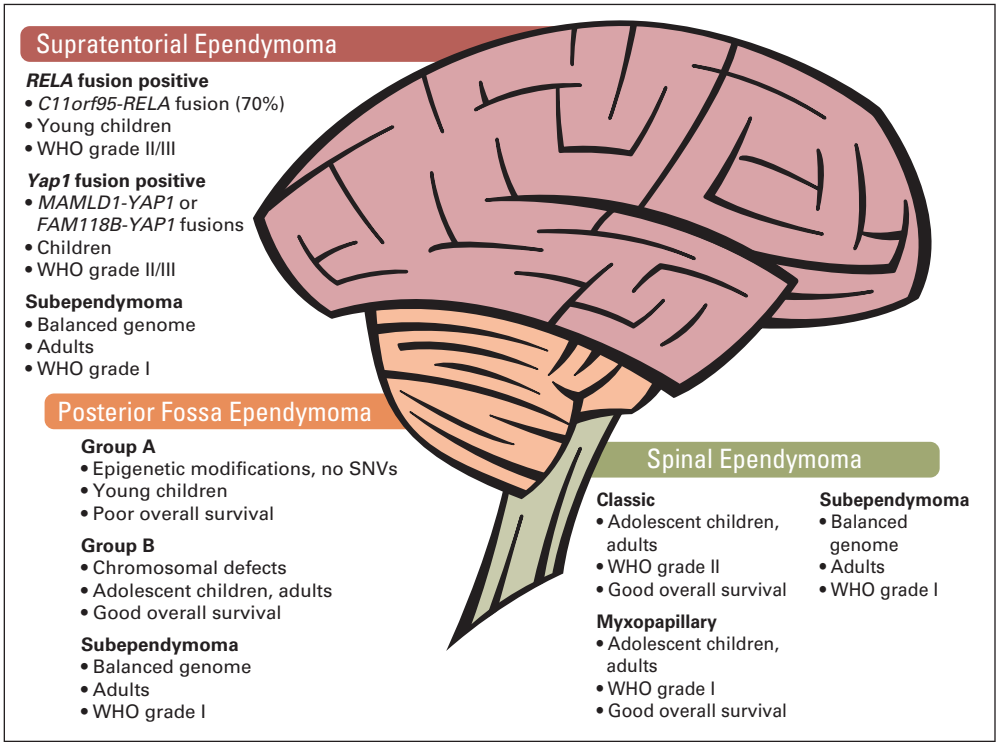

Fig 4. Several subtypes of ependymomas, including WHO grades 1 to 3 disease within all three compartments of the CNS—supratentorial (ST), posterior fossa (PF), and spinal (SP)—are illustrated. *RELA*-positive ependymomas, including *YAP1* fusion–positive ependymomas and subependymomas, arise within the ST region of the brain. Both fusion-positive subtypes display histopathologic features of WHO grades 2 and 3 ependymomas. In the PF, the majority of ependymomas belong to subtype group A, and group B tumors are more infrequent. Both subtypes display the histologic pattern of anaplastic and WHO grade 2 ependymomas; in contrast, subependymomas can be classified as WHO grade 1. SP tumors are diagnosed as classic ependymomas that are WHO grade 2 or 3; myxopapillary ependymoma and spinal subependymomas are WHO grade 1. In children, group A and *RELA*-positive tumors are diagnosed most often and are associated with poor overall survival. SNV, single nucleotide variant.

enrollment in late 2014. The study has three strata: Stratum 1 includes patients older than 1 year, who have had gross-total resection of a WHO grade 2 to 3 tumor. These children will receive conformal RT followed by random assignment with or without maintenance chemotherapy (vincristine, cyclophosphamide, etoposide, and cisplatin). Stratum II includes patients older than 1 year who have residual disease. These patients will receive chemotherapy (vincristine, cyclophosphamide, and etoposide), including random assignment with or without high-dose methotrexate, before a second resection and conformal RT. Stratum III includes patients younger than 1 year or those not eligible to receive RT. Patients in this group will be treated with standard chemotherapy (vincristine, cyclophosphamide, and cisplatin) and will be randomly assigned with or without treatment with the histone deacetylase inhibitor valproate.

Future Therapies for Ependymoma

Genetically engineered mouse models of ependymoma offer excellent opportunities for preclinical drug testing in vivo. The Ephb2 mouse model was used in a high-throughput screen that identified fluorouracil as an effective therapy for ST ependymoma.[95] Efficacy data in humans are currently being evaluated.

RARE EMBRYONAL TUMORS

Molecular subtyping of pediatric brain tumors revealed more than a decade ago that atypical teratoid/rhabdoid tumors (ATRTs) and other CNS primitive neuroectodermal tumors (CNS PNETs) are biologically distinct from medulloblastoma.[96] Because the next generation of clinical trials aims to stratify and treat tumors on the basis of molecular subtypes, it is of paramount importance to additionally characterize these rare embryonal tumors as distinct diseases.

ATRT

ATRT was initially described as a universally fatal tumor of young children (Table 2). It is associated with a deletion on chromosome 22 and, in addition, is characterized by the loss of *SMARCB1* expression.[97] ATRT arises in infratentorial or ST locations with an approximately equal proportion and rarely arises in the spine.[98-100] *SMARCB1* expression should be evaluated in all young patients with embryonal tumors to confirm the diagnosis of ATRT rather than medulloblastoma or other CNS PNETs.[101] The diagnosis of ATRT has implications for constitutional testing[102] and should lead to appropriately aggressive therapy that results in increased survival.[103]

Current therapy for ATRT. A significant proportion of ATRTs arise in children younger than 3 years. Treatment with conventional postoperative chemotherapy alone results in less than 20% survival.[104-106] Small cohorts of patients treated with regimens designed specifically for ATRT have achieved survival rates greater than 50%.[104,107] Treatment factors that predict survival have included the use of multimodality regimens containing RT, intrathecal chemotherapy, and/or high-dose therapy with stem cell rescue.[99,100,104,107,108] Ongoing, prospective studies will more precisely define the outcome of children with ATRT in the current era. Current curative therapy for ATRT is perhaps excessively toxic, including the acute toxicity of high-dose chemotherapy[108] and long-term toxicity of RT in young children. Novel therapy that improves outcomes while it decreases toxicity is greatly needed.

Future clinical trials for ATRT. The availability of ATRT cell lines and accurate preclinical mouse models have enhanced the discovery of novel therapeutic targets for ATRT. Current targets under consideration are aurora A kinase, cyclin D1, EZH2, and insulin-like growth factor-1. The availability of aurora A kinase inhibitors has facilitated the development of a phase II trial for patients with recurrent ATRT

Table 2. Patient Demographics and Molecular and Clinical Features of ATRT and CNS PNET

Feature	ATRT	ETMR*	CNS PNET	
			Group 2	Group 3
Median patient age	18 months	3 years	8 years	6 years
Sex ratio	Male > female	Female > male	Male > female	Male > female
IHC marker	*SMARCB1* negative	*LIN28* positive	*Olig2* positive	*LIN28* and *Olig2* negative
Metastatic disease at presentation, % of patients	30	25	15	50
Molecular marker	*SMARCB1*-inactivating genetic alteration (mutation, deletion, or insertion)	*C19MC* miRNA amplicon	*CDKN2A/B* loss; Chr 8p, 13, 20 gain	*CDKN2A/B* loss; Chr 14 loss

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; Chr, chromosome; CNS PNET, CNS primitive neuroectodermal tumor; ETMR, embryonal tumor with multilayered rosettes; IHC, immunohistochemistry.
*Also known as embryonal tumor with abundant neuropil and true rosettes, medulloepithelioma or ependymoblastoma.

and malignant rhabdoid tumor (NCT02114229). If this trial demonstrates the efficacy of this agent, it will most likely be incorporated into therapy for patients with newly diagnosed ATRT.

CNS PNETs

International collaboration and advanced genomics have supported the recent discovery of diagnostic and prognostic factors for CNS PNET. A comprehensive analysis of PNET tumors of cortical origin defined three distinct molecular subtypes, initially termed groups 1, 2, and 3.[109] Group 1 tumors, which have been the most well defined to date, are characterized by an amplification on chromosome 19q13.42 that contains a microRNA cluster that has a functional association with oncogenesis[110] and diffuse expression of the LIN28A protein, both of which may facilitate diagnosis by using standard pathology methods (ie, immunohistochemistry and fluorescent in situ hybridization).[111] The term embryonal tumor with multilayered rosettes (ETMR) has been proposed as a unifying diagnostic term for group 1 tumors, including the previously described embryonal tumor with abundant neuropil and true rosettes, ependymoblastoma, and medulloepithelioma, because genome-wide DNA methylation and copy-number analysis has demonstrated biologic similarity between these three histologic entities.[112]

ETMR occurs in the youngest age group and has been associated with the poorest prognosis of all CNS PNET in retrospective studies. However, our understanding of the biology of ETMR has rapidly facilitated preclinical modeling and evaluation of potential novel therapeutics; inhibitors of the insulin-like growth factor/phosphatidylinositol 3-kinase/mTOR pathway have shown early promise in a preclinical study.[113] Group 2 tumors may be defined by the expression of the Olig2 protein, and both groups 2 and 3 are associated with older age at diagnosis and frequent chromosome 9p loss centered on the *CDKN2A/B* locus.[109] Additional molecular study of these subtypes is warranted, as is additional study of CNS PNET that occurs in noncortical areas of the brain (Table 1).

Current clinical trials for CNS PNET. CNS PNETs can occur in any region of the CNS. Radiologically distinct tumors that arise in the pineal region are termed pineoblastomas. Although rare, CNS PNET can also arise in the brainstem.[114] The remaining CNS PNETs originate in other midline or, more commonly, cortical regions. Children with CNS PNET have been historically treated on medulloblastoma regimens but have had inferior outcomes. The 5-year survival of approximately 50% after conventional CSI and chemotherapy has not improved in two decades.[115,116]

Reports on whether survival of pineoblastoma is superior to that of other CNS PNETs are conflicting, which may be partially explained by the high likelihood of pineoblastoma to present or recur in a disseminated pattern.[116-118] A recent series has suggested that reduced CSI (23.4 Gy) followed by high-dose chemotherapy with stem-cell rescue offers an improved outcome in patients with localized surgically resected CNS PNET.[119]

Future clinical trials for CNS PNET. The molecular characterization of CNS PNET is an inspiring example of international cooperation and collaboration facilitating the study of the rarest diseases. There is an equally great clinical research challenge still before us: to conduct cooperative clinical trials that incorporate patients with newly diagnosed CNS PNET in appropriate studies of molecularly based therapy.

In conclusion, cooperation among investigators from around the globe has facilitated genomic analysis of pediatric brain tumors. This information has revolutionized our understanding of the underlying pathogenesis of pediatric brain tumors. Our laboratory-based research colleagues have done an admirable job in defining a path forward for the next generation of clinical studies. The challenge is now back to the clinicians and regulatory agencies to design and fund the next generation of clinical protocols that will facilitate rapid accrual of patients to protocols that promise to improve the cure rate while minimizing toxicities.[120]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pediatric Brain Tumors: Innovative Genomic Information Is Transforming the Diagnostic and Clinical Landscape

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