Gliomas in Children

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Abstract

Gliomas are the most common primary central nervous system (CNS) neoplasms in children and adolescents and are thought to arise from their glial progenitors or stem cells. Although the exact cells of origin for most pediatric gliomas remain to be identified, our current understanding is that specific cell populations during CNS development are susceptible to particular oncogenic events during certain time windows and thus give rise to pediatric gliomas with distinct histological, molecular, and clinical features. These may be roughly segregated into low-grade gliomas (WHO grades I or II; including most mixed glial–neuronal tumors) and high-grade gliomas (WHO grades III or IV) according to their clinical course when untreated, even though this is not yet entirely clear for some of the recently emerging groups. The genetic and epigenetic characterization of pediatric gliomas across ages and histologies has facilitated the delineation of biologically relevant subgroups and have revealed potentially targetable alterations in some of them. This review outlines diagnostic features and molecular alterations in pediatric low- and high-grade gliomas and how the latter might be exploited with future targeted therapeutic strategies.

Keywords
- CNS
- brain tumor
- pediatric glioma
- astrocytoma
- genetics
- epigenetics
- targeted therapy

Low-Grade Gliomas

Diagnosis

Low-grade gliomas (LGGs) in children and adolescents comprise a heterogeneous spectrum of histological entities including both low-grade glial and mixed low-grade glial–neuronal tumors (LGGNTs). According to their nonmalignant features and slow-growing radiographic behavior, these tumors are classified into grade I or grade II by the WHO Classification of Tumors of the Central Nervous System (CNS).[1] Taken together, they represent the most common primary CNS neoplasms in this age group (~30%), with pilocytic astrocytomas (PAs; WHO grade I) accounting for the vast majority (~20%) of brain tumors in patients < 20 years of age.[1] Although neuropathological features to discriminate pediatric LGG entities from each other have been established, overlapping morphology may sometimes render an exact diagnosis challenging.

PAs mainly arise in infratentorial regions, such as the cerebellum, as well as in the optic nerves/chiasm or less frequently in the cerebral hemispheres and, upon imaging, usually appear as circumscribed lesions with mixed solid as well as cystlike components. Histologically, PAs present with a biphasic pattern with compacted bipolar cells with Rosenthal fibers alongside loose textured multipolar cells with microcysts; a PA variant with a prominent myxoid

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background matrix is called pilomyxoid astrocytoma.[1] Optic pathway PAs occur in approximately 20% of patients affected by germline mutations in the *neurofibromin 1* gene, causing the tumor predisposition syndrome neurofibromatosis type 1 (NF1).[2] At a slightly lower rate (~15%), patients with tuberous sclerosis syndrome (TSC), an autosomal dominant genetic disease (caused by inactivating germline mutations in *TSC1/2*) predisposing to benign tumor growth, develop subependymal giant cell astrocytomas (SEGAs; WHO grade I) before reaching adulthood.[3] SEGAs typically present as solid, partially calcified masses in the wall of the lateral ventricles and are composed of large ganglionic astrocytes arranged in sweeping fascicles, sheets, and nests.[1]

Among the other less frequent histopathological entities of pediatric LGGs, pleomorphic xanthoastrocytomas (PXAs; WHO grade II) arise almost exclusively in supratentorial regions, often involving the leptomeninges and superficial cortex. Radiographic appearance typically reveals a tumor mass with cystic portions and moderate contrast enhancement, while the overall variable histology of PXAs contains large pleomorphic as well as spindle and lipidized cells in a dense pericellular reticulin network.[1] Anaplastic features in PXA ($\geq$5 mitoses per 10 high-power fields; anaplastic PXA; WHO grade III) are associated with worse overall survival compared with PXA WHO grade II. In the absence of histological patterns typical for PA or PXA and in the presence of a diffusely infiltrating component, some pediatric LGGs are also diagnosed as pediatric-type diffuse astrocytomas (WHO grade II), but with differences compared with their adult counterparts, as they rarely ($<$ 10%) undergo malignant transformation and are associated with an overall better prognosis.

The group of pediatric LGGs extends to mixed glial–neuronal tumors, including dysembryoplastic neuroepithelial tumors (DNTs; WHO grade I), which typically occur in pediatric patients with early onset epilepsy. They are predominantly located in the cortical regions of the temporal lobe and do not show significant mass effect or edema upon imaging. The histological diagnosis is usually established by characteristic columns made up of bundles of axons oriented perpendicular to the cortical surface.[1] Also, often located in the temporal lobe and associated with seizures, gangliogliomas (WHO grade I) mostly present as circumscribed solid or mixed solid and cystic masses with variable contrast enhancement and occasional calcification. They are well-differentiated glial–neuronal neoplasms and are typically composed of mature, dysplastic ganglion cells in combination with neoplastic glial cells, which, in rare cases, may undergo malignant transformation to an anaplastic ganglioglioma (WHO grade III).[1]

Rare but overrepresented in early childhood (~15% of CNS tumors of infancy) are desmoplastic infantile astrocytoma and ganglioglioma (DIA/DIG; WHO grade I), which are always located supratentorially and often involve more than one cerebral lobe. Upon imaging, there is often a solid, superficial, enhancing component that extends to the leptomeninges, as well as a cystic part extending into the brain. Both variants share a prominent desmoplastic stroma in combination with either a neoplastic glial (DIA) or neoplastic glioneuronal (DIG) component.[1]

Molecular Biology

While the 2016 WHO classification system allows most pediatric LGGs to be aligned with a specific histopathological diagnosis, recent molecular genetic and epigenetic profiling studies suggest some overlap between various LGG entities as well as with pediatric high-grade gliomas (HGGs) (►**Fig. 1**). Genetic alterations activating the Ras-mitogen-activated protein kinase (MAPK) signaling pathway have been established as a hallmark of pediatric LGGs as well as some LGGNTs. Most prominently, single-hit MAPK aberrations were found in essentially all PAs, leading to the recognition of PA as a single-pathway disease.[4,5]

Approximately 70 to 80% of PAs carry a tandem duplication in chromosome band 7q34 resulting in a *KIAA1549:BRAF* fusion gene, leading to a loss of the autoinhibitory N-terminal region of BRAF while retaining its then constitutively active kinase domain.[6] Over the years, several alternative, less frequent fusion events involving *BRAF* and various other fusion partners (*SRGAP3*, *FAM131B*, and others) have also been described.[4,5] Taken together, *BRAF* fusion genes are detected in approximately 90% of cerebellar PAs and a majority (~50%) of supratentorial midline PAs (and only a few cases with non-PA histology), whereas they are rarely observed in hemispheric/cortical LGGs. The *BRAF* gene is also the target of a hot-spot mutation (BRAF V600E) recurring in a high fraction of gangliogliomas (~50%) and PXAs (50–80%), as well as a minority of supratentorial PAs.[7,8]

Next-generation sequencing studies across LGG histologies have revealed several additional genetic alterations beyond the *BRAF* gene. For example, constitutive fibroblast growth factor receptor (FGFR) activation has been observed through several molecular mechanisms, including fusion events involving *FGFR1* or *FGFR3* (previously observed in adult HGGs),[5] duplications of the whole kinase domain (internal tandem duplication, ITD),[4,5,9] and *FGFR1* hot-spot mutations (at p.N546 or p.K656),[4,5] suggesting a role for FGFR activation driving a majority of DNTs and some supratentorial PAs. Further rearrangements recently discovered across pediatric LGGs involve receptor tyrosine kinase genes *NTRK2* or *NTRK3* (previously observed in infantile HGGs),[4,5,9] as well as the *MYB* and *MYBL1* oncogenes, which seem to be most common in pediatric-type diffuse astrocytomas and angiocentric gliomas.[5,9–12] Angiocentric gliomas are a rare, slow-growing variant of diffuse gliomas with prominent angiocentric growth of tumor cells.[1] The most frequently detected variant so far is a *MYB:QKI* fusion gene.[12]

Although certain histologically defined LGG entities are clearly enriched for recurrent genetic alterations, there is no 1:1 match between specific histologies and individual mutations. For example, *BRAF* gene fusions seem to predominate in cerebellar (and supratentorial midline) PAs but have also been reported in gangliogliomas and PXAs, albeit at a considerably lower frequency. Conversely, BRAF V600E hot-spot mutations are mostly found in supratentorial hemispheric (and midline) gangliogliomas and PXAs (in the latter often

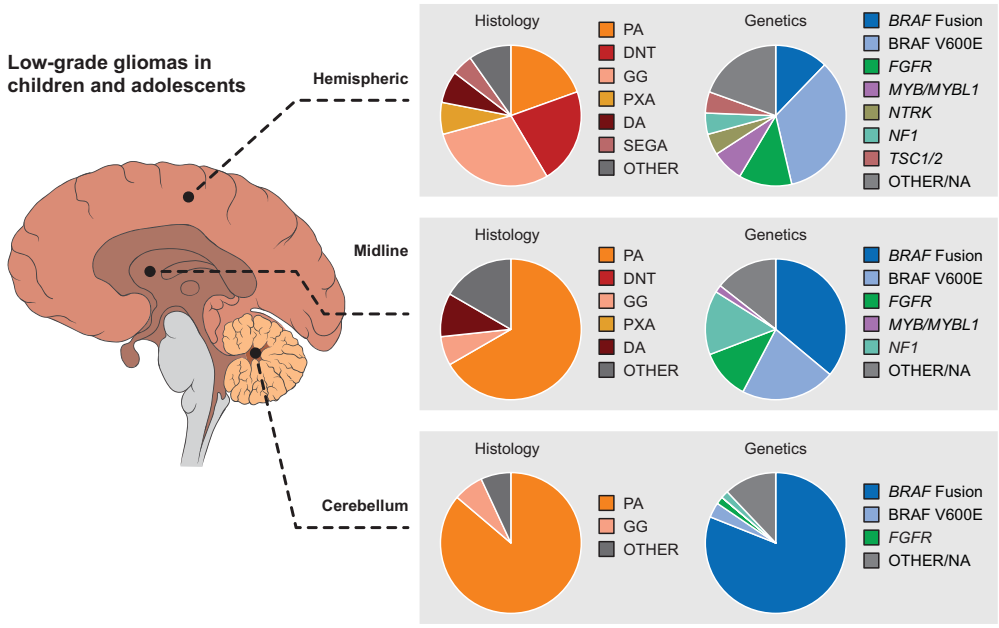

Fig. 1 Low-grade gliomas in children and adolescents.

co-occurring with *CDKN2A/B* deletions) but are also detected in rarer cases of PAs. Further, nonexclusive, enrichments include *FGFR1* alterations in DNT, and *MYB* alterations in angiocentric gliomas. The observation of *NTRK* and *FGFR* gene family rearrangements in a small fraction of HGGs (see in the following) also suggests some overlap in the underlying biology between histologically defined pediatric LGGs and HGGs.

Classification schemes that are solely based on the histopathological appearance of a tumor will therefore likely fail to capture the full spectrum of molecular LGG variants. As introduced by the WHO for some other CNS tumor entities, a more accurate classification will therefore require establishing an integrated histopathological/molecular diagnosis in a multilayered fashion. In LGGs, future categories may therefore molecularly discriminate *BRAF* fusion-positive, BRAF V600E-positive, and *BRAF* wild-type LGG/LGGNTs, from pediatric-type diffuse gliomas driven by *MYB*/*MYBL1*, *FGFR*, and *NTRK* abnormalities, being followed by a second layer describing the histopathological variant (►**Fig. 1**). This will help to determine the prognostic or predictive value of these markers as well as to identify patients who may potentially benefit from targeted therapeutic approaches.

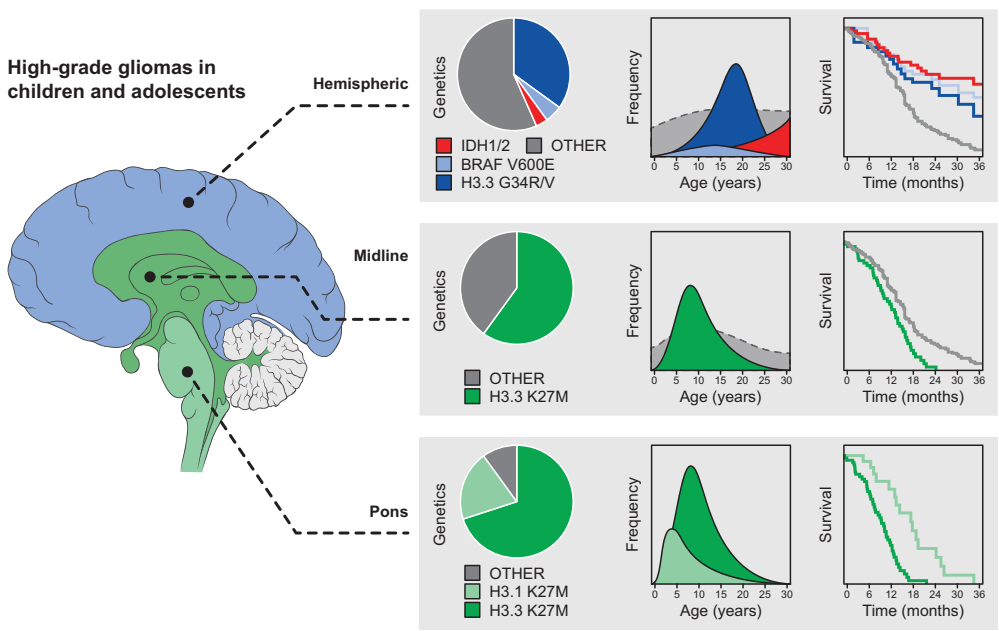

Fig. 2 High-grade gliomas in children and adolescents.

Current Treatment Strategies

Given the slow-growing natural history of pediatric LGGs and their low incidence of spontaneous malignant transformation, the majority of children with LGGs are long-term survivors well into adulthood.[13,14] Therefore, the ultimate treatment goal is to minimize long-term morbidity for patients. This is a fine balance between achieving tumor control and minimizing long-term treatment-related morbidity.

The mainstay of current LGG therapy is surgical resection where feasible followed by close surveillance thereafter. In tumors that can be resected, this initial therapy is oftentimes curative. However, when surgical resection is not feasible given the location of the tumor, or the tumor progresses, or tumor-related symptoms worsen after initial surgical resection, additional treatments are warranted. Options include chemotherapy, radiation therapy, and additional surgical procedures.

While focal radiotherapy was widely used in the past to achieve tumor control, several reports have stressed the increased risk for long-term treatment-related morbidities, including secondary malignancies, vasculopathies, endocrinopathies, and cognitive deficits.[15–17] This consideration is especially important for children with germline mutations predisposing to tumor formation, for example, NF1 patients, in whom the risk for radiation-induced secondary malignancies is particularly high.[18] Hence, radiation therapy is avoided for children with NF1 and is frequently reserved for non-NF1 patients in whom tumor control is not achievable with surgery and chemotherapy alone.

For chemotherapy, multiple regimens are being used (reviewed in Bergthold et al[13]). Combination regimens of vincristine plus carboplatin or monotherapy with vinblastine are most commonly used as first-line therapy and are associated with good overall survival.[19–21] However, long-term treatments over several years, oftentimes including multiple consecutive regimens, also lead to significant treatment-related morbidity, and more targeted approaches are therefore needed to improve the overall quality of life for these patients.

Targeted Therapeutic Approaches

Our recent increase in understanding the molecular and genomic alterations in pediatric LGGs has facilitated excitement to integrate and translate these findings into clinical practice to ultimately benefit our patients.

On the diagnostic side, recent consensus work has stressed the importance of integrating standardized molecular analysis, especially for BRAF fusions and the BRAF V600E mutation, into histologically based classifications at the time of initial resection or biopsy whenever possible.[22] These integrated diagnostics can then form the basis for well-stratified clinical trials with molecularly targeted therapies. On the therapeutic side, the molecular landscape of LGGs seems to be ideally suited for targeted therapies because of the paucity of mutations per tumor and availability of targeted drugs for many of the pathways involved.[5]

One of the first success stories in LGGs was the use of mammalian target of rapamycin (mTOR) inhibitors for treating SEGAs, tumors that arise in patients with hereditary activation of the mTOR pathway due to mutations in upstream TSC1/2; mTOR inhibitor everolimus led to a marked reduction or stabilization of tumor volume in patients with SEGAs.[23,24] In non-TSC LGG patients, everolimus has been studied for treating patients with recurrent LGGs, leading to promising preliminary results (ClinicalTrials.gov NCT00782626;[25]). A subsequent study of everolimus in recurrent LGGs is currently underway to evaluate the association of molecular features with outcome (ClinicalTrials.gov NCT01734512).

Based on the growing evidence that the MAPK pathway is the most frequently altered pathway in LGGs, several early phase clinical trials designed to target different components of the MAPK pathway have recently been completed or are underway. The first-generation BRAF inhibitor dabrafenib has led to encouraging results in patients with recurrent LGGs harboring the BRAF V600E mutation: most patients had either partial responses or stable disease.[26] Another first-generation BRAF inhibitor, vemurafenib, is currently being evaluated in clinical trials for recurrent BRAF V600E mutated LGGs as well (ClinicalTrials.gov NCT01748149). However, caution is warranted in patients with unknown BRAF status of their tumors: another first-generation BRAF inhibitor, sorafenib, accelerated growth in LGGs with the common KIAA1549:BRAF fusion.[27] Type II BRAF inhibitors are supposed to overcome this paradoxical stimulation of tumor growth in the context of a KIAA1549:BRAF fusion. One of them, MLN2480 (also known as TAK-580), has recently shown promising results in preclinical studies, and clinical trials are planned.[28] Another way to block the MAPK pathway regardless of the BRAF alteration is to use MEK inhibitors, which act downstream of BRAF. The MEK inhibitor selumetinib has recently completed phase I trials with promising results in recurrent LGGs and plexiform neurofibromas in NF1 patients[29,30] and is currently the subject of a phase II study. Other MEK inhibitors, binimetinib (ClinicalTrials.gov NCT02285439) and trametinib (ClinicalTrials.gov NCT02124772), are currently in early phase clinical trials. Trametinib is also being evaluated in combination with the type I BRAF inhibitor dabrafenib (ClinicalTrials.gov NCT02124772) for tumors harboring the BRAF V600E mutation.

Besides targeting the MAPK pathway at the level of BRAF or MEK, frequently found mutations in FGFR1 and NTRK kinases might represent additional opportunities for targeted therapies. A clinical trial with FGFR inhibitor AZD4547 is currently underway for patients with malignant gliomas harboring FGFR:TACC fusions (ClinicalTrials.gov NCT02824133). Larotrectinib and entrectinib (RXDX-101) are drugs targeting NTRK mutations and fusions and are also currently in early phase clinical trials (NCT02576431 and NCT02650401) in a wide range of solid tumors including gliomas.

In summary, the hope is that targeted treatment strategies will lead to long-term tumor control in patients with

LGGs, while less negatively impacting their healthy developing brain versus conventional genotoxic therapies. However, as most clinical studies with targeted therapeutics in LGGs are still underway or early in follow-up, we will have to learn how to integrate promising preliminary results into clinical practice while waiting for long-term toxicity, resistance, and outcome data.

High-Grade Gliomas

Diagnosis

HGGs are diffusely infiltrating malignant CNS neoplasms with very aggressive clinical behavior and are therefore classified as grade III or grade IV tumors by the WHO. They may occur anywhere in the CNS but most often arise in the cerebral hemispheres or midline structures of the brain, where the pons and thalamus are more commonly affected than the cerebellum or spine. Some HGGs arise in patients with cancer predisposition syndromes such as constitutional mismatch repair deficiency, Li–Fraumeni's syndrome, or NF1, but the majority present as sporadic tumors with unknown etiology.[31] Symptoms usually develop over a short period of time (i.e., months).

Supratentorial hemispheric HGGs typically appear as a poorly defined, irregularly shaped tumor upon imaging. Ringlike contrast enhancement around a central core of necrosis may be present, especially in grade IV lesions, and tumor-surrounding edema is frequent. Histologically, hemispheric HGGs are usually diagnosed as anaplastic astrocytoma (WHO grade III), characterized by increased cell density, nuclear atypia, and mitotic activity, or as glioblastoma (GBM; WHO grade IV), with additional microvascular proliferation and/or necrosis.[1] Diagnostically relevant mutations in *IDH1/2* genes are absent in children and only rarely detected in adolescents, resulting in "anaplastic astrocytoma, IDH wild type" or "GBM, IDH wild type" as the most common WHO-based diagnoses in this group.[1]

HGGs located in the midline CNS structures are often difficult to access for biopsy or surgery. Therefore, diagnosis of diffuse midline gliomas in children has long been based on the combination of characteristic clinical symptoms and radiological parameters without the necessity to acquire material for neuropathological evaluation. The most prominent example of this group is diffuse intrinsic pontine gliomas (DIPGs; WHO grade IV), typically presenting on magnetic resonance imaging (MRI) as a large, expansile, often asymmetric brainstem mass occupying more than two-thirds of the pons. In contrast to hemispheric HGGs occurring across all ages, there is a peak incidence of DIPGs between 4 and 7 years of age at diagnosis.[1] When biopsied, diffuse midline gliomas show low- to high-grade histologies, which do not correlate with differences in clinical outcomes, that is, almost all children succumb to their disease within 1 year after diagnosis.[32] The reintroduction of safe stereotactic biopsies in diffuse midline gliomas and following molecular profiling studies of the collected tumor tissue over recent years revealed highly specific and recurrent hot-spot mutations in histone genes occurring in diffuse gliomas across midline structures, leading to a newly established WHO category termed "diffuse midline glioma, H3 K27M-mutant" (WHO grade IV).[1] Therein, pathognomonic mutations at position K27 of histone 3 variants, detectable by various techniques, serve as robust molecular markers for neuropathological diagnosis and may even be used for disease monitoring by measuring their abundance in circulating tumor DNA (deoxyribonucleic acid) from patient blood samples.[33]

Independent of their primary location, pediatric HGGs may initially manifest as a diffuse, infiltrative phenotype, affecting most of one cerebral hemisphere (three lobes or more) or both cerebral hemispheres with additional involvement of the brainstem, cerebellum, and spinal cord. Originally called "gliomatosis cerebri" (GC), the overlap in the molecular genetic makeup discovered in GC with known HGG variants suggests that it rather represents an extremely invasive HGG phenotype than being a distinct biological CNS tumor entity, and therefore the term *gliomatosis cerebri* was eliminated as its own distinct entity in the 2016 revision of the WHO classification of tumors of the CNS.[1,34]

Molecular Biology

Histologically indistinguishable from their adult counterparts, large-scale genomic and epigenomic profiling studies have revealed fundamental differences in the molecular biology underlying pediatric HGGs. Moreover, recent international collaborative efforts to analyze increasing numbers of tissue samples identified molecular subgroups of the disease, each with distinct genetic characteristics as well as clinical features (►**Fig. 2**).

Pediatric HGGs were the first human cancer in which recurrent hot-spot mutations in histone genes were discovered.[35,36] Supratentorial hemispheric HGGs (including a fraction of tumors previously diagnosed as CNS primitive neuroectodermal tumors [37]) are highly enriched for G34R (or rarely G34V) mutations (~30%) in the histone gene *H3F3A* encoding for histone protein variant H3.3. The exact molecular consequences of glycine replacement by arginine or valine have yet to be elucidated, but the mutation may interfere with posttranslational modification of the H3.3 histone tail at position K36. The H3.3 G34 mutation is further associated with mutations in *ATRX* and/or *DAXX*, and affected tumors display marked subtelomeric DNA hypomethylation, which is why telomerase-independent telomere maintenance mechanisms (i.e., alternative lengthening of telomeres) may also play a role.[38] Mutations in *TP53* are very frequent.[38] Patients diagnosed with H3.3 G34R/V-mutated HGGs are typically in adolescence or early adulthood and seem to have a better outcome when compared with other pediatric HGG subgroups.[38]

Diffuse gliomas arising in the midline CNS structures carry a high rate of K27M mutations in histone genes *H3F3A* (~three-fourths; coding for histone variant H3.3) or *HIST1H3B/C* (~one-fourth; coding for H3.1).[35,36] While H3 K27 mutations can be detected in almost all diffuse pontine gliomas (> 90%), they are found at slightly lower frequency in the thalamus or spinal cord (50–60%). Rare variants of this

lysine by methionine substitution occurring in *HIST2H3C* or as H3 K27I have also been reported.[39] The K27M-mutant H3 protein sequesters EZH2, thereby inhibiting polycomb repressive complex 2, leading to a global decrease of H3 K27 trimethylation.[40] Up to 50% of diffuse midline gliomas harbor additional recurrent mutations targeting the receptor tyrosine kinase/RAS (Rat Sarcoma)/PI3K (Phosphatidylinositol-4,5-bisphosphate 3-kinase) pathway (e.g., *PDGFRA*, *PIK3CA*, *PIK3R1*, or *PTEN*), or the p53 pathway (e.g., *TP53*, *PPM1D*, *CHEK2*, or *ATM*; ~70%), and/or display recurrent focal gene amplifications of *PDGFRA*, *MYC/MYCN*, *CDK4/6*, *CCND1–3*, *ID2*, or *MET*.[41–44] Mutations in histone variant H3.3 are found in diffuse gliomas across the midline structures, and affected patients are typically aged 7 to 10 years, facing a very poor prognosis. Tumors with mutations in histone variant H3.1 develop at an earlier age (4–6 years) and exclusively in the pons. They are associated with a slightly better outcome and recurrent mutations in *ACVR1*.[39]

Only a small number of hemispheric HGGs in older adolescents (<5%), representing the lower age spectrum of gliomas in young adults, share their molecular characteristics with secondary GBMs and lower grade diffuse gliomas from which they develop, that is, hot-spot mutations in *IDH1/2* genes. Accordingly, affected patients have comparably good outcomes.[38]

There is a remaining fraction of approximately 50% of pediatric HGGs in which hot-spot mutations in histone variant genes or *IDH1/2* are absent. Further subclassification of these H3-/IDH-wild-type pediatric HGGs recently revealed significant molecular intertumoral heterogeneity and identified further molecularly and prognostically distinct subtypes with associated oncogenic drivers, namely, *MYCN*, *PDGFRA*, and *EGFR*.[45] However, the group of H3-/IDH-wild-type pediatric HGGs may include further increasingly smaller biologically relevant subgroups, each with very rare but potentially targetable alterations, such as *BRAF* mutations, or fusion events involving, for example, *NTRK* or *FGFR* genes.[46] As some of these have also been identified in pediatric LGGs, there may also be some overlap between LGGs and HGGs, underlining the need for an integrated molecular/histopathological analysis at the time of primary diagnosis.

Current Treatment Strategies

While our knowledge about molecular and biological features of pediatric HGGs has exponentially increased in a remarkably short period of time, its translation into clinical applications is lagging behind. Despite a multitude of clinical trials internationally, there has not been much improvement in patient survival in the last few decades, and most HGG patients still succumb to their disease within 1 to 3 years after diagnosis, depending on the location and molecular signature of their tumors.[47]

The standard therapy for diffuse midline gliomas including DIPG—tumors unresectable due to their location—is still focal radiotherapy. Many trials over the last few decades have tried different drugs and drug combinations for adjuvant chemotherapy, including temozolomide (TMZ), pCV (prednisone, lomustine [CCNU], vincristine), bevacizumab, irinotecan/cetuximab, and others, but have not been able to show survival benefits beyond radiotherapy alone, whereas some regimens added substantial toxicity.[48–52] Even higher doses of radiotherapy (70–78 Gy given in a hyperfractionated regimen) failed to prolong survival but increased neurotoxicity.[53,54] However, efforts to re-irradiate children with DIPG at first and even second progression have recently gained popularity and have led to clinical improvements and median survival increases of a few months without adding significant toxicity.[55,56]

Hemispheric HGG patients have also seen little clinical improvement over the last few decades. As discussed previously, this group of tumors seems to be an even more molecularly diverse disease than midline HGGs. This is important to keep in mind when evaluating and comparing studies conducted before molecular prognostic groups were recognized. The inclusion and proportion of certain pediatric HGG molecular subtypes with better (or worse) prognosis might affect trial outcomes,[57] many studies analyzed both grade III and grade IV gliomas together,[58,59] and in some studies, frequent misdiagnoses and the inclusion of LGGs was revealed upon central histopathological review.[60] The current standard of care for hemispheric HGGs is maximal, safe surgical resection followed by radiation therapy. While many clinical studies have added different adjuvant chemotherapy regimens during and after radiation, most of them have failed to lead to significant survival benefits for patients. Even the addition of TMZ, which has led to significantly improved progression-free survival and overall survival in adult patients with GBM, unfortunately failed to show a similar improvement of outcomes in the pediatric glioma population.[48] However, the addition of CCNU to TMZ in maintenance therapy in Children's Oncology Group study ACNS0423 increased event-free survival and overall survival in HGG patients, especially in those without gross total resection, grade IV HGGs, and MGMT (O6-alkylguanine DNA alkyltransferase) overexpression.[61]

Going forward, molecular diagnostics will be incorporated into clinical trials whenever possible to allow for more accurate diagnoses, better trial design, and association of biomarkers with outcome.

Targeted Therapeutic Approaches

Molecular characterization of pediatric HGGs at diagnosis has recently become more common and is now even the standard of care in some academic centers.[62,63] When done in a standardized way, these data can be used to either enroll patients in clinical trials with targeted therapies or identify actionable targets for personalized therapy approaches. The BRAF V600E mutation was one of the first genetic alterations identified in pediatric LGGs and was later also found in HGGs. In pediatric HGGs,[64] the mutation is associated with a better prognosis compared with other molecular subclasses,[57] and clinical trials are underway to assess the impact of the first generation BRAF inhibitors vemurafenib and dabrafenib as single agents, or dabrafenib in combination with the MEK inhibitor trametinib on disease outcomes (clinictrials.gov,

NCT01677741, NCT01748149, NCT02684058, NCT02124772). Another actionable target is platelet-derived growth factor receptor alpha (PDGFRA), which is commonly amplified or activated by somatic mutations in HGGs, including DIPGs.[65,66] Small molecule PDGFR inhibitors, including crenolanib and dasatinib, are being tested in clinical trials for pediatric HGGs, and the results are pending (ClinicalTrials.gov NCT01393912, NCT01644773, NCT02233049). Dasatinib is also being tested in combination with the c-MET (MET protooncogene) and ALK (anaplastic lymphoma kinase) inhibitor crizotinib (ClinicalTrials.gov NCT01644773). This is particularly interesting, as both MET and ALK-2/ACVR1 mutations have been described in pediatric HGGs,[42–44,61,67] and preliminary evidence for clinical benefit of the MET inhibitor crizotinib has been reported.[61] For tumors with ACVR1 mutations, which commonly co-occur with Histone 3.1 K27M mutations in diffuse midline gliomas, clinical trials with ACVR1 inhibitors have yet to be opened. However, there is increased interest to evaluate this target further, and early phase clinical trials are in planning phases. Other actionable targets include EGFR, which is amplified in a smaller subset of pediatric HGGs[45] and has led to the incorporation of EGFR inhibitors, including erlotinib into clinical trials (ClinicalTrials.gov NCT01182350, NCT02233049). Unfortunately, adding erlotinib to focal radiation alone did not improve patient outcomes.[68] However, patients were not assigned to erlotinib treatment based on activation of the EGFR pathway in their tumors, which could have negatively affected study results.

Another interesting aspect of pediatric HGGs is that tumor formation is strongly and frequently associated with dysregulation of epigenetic mechanisms caused by mutations in histones, DNA and histone methylation enzymes, and chromatin remodelers.[69,70] Unlike genetic mutations,[71,72] these epigenetic changes are potentially reversible and have therefore sparked interest in developing drugs against epigenetic enzymes. First successes in hematologic malignancies have led to approval of several epigenetic drugs for patient treatment and have increased interest in using these drugs in gliomas.

Panobinostat (LBH589) is an oral inhibitor of several histone deacetylases (HDACs) and has recently been shown to decrease proliferation of preclinical H3 K27M-mutant diffuse midline gliomas models.[73] Panobinostat has since moved into clinical trials and is currently being tested in patients with DIPG (ClinicalTrials.gov NCT02717455). As one of the hurdles for targeted therapies to reach their respective targets is the blood–brain barrier, new approaches to deliver drugs have emerged in parallel. Panobinostat, among other drugs, is being currently considered for early stage clinical trials facilitating drug delivery by convection-enhanced delivery—a catheter-based method in which the study agent is directly infused into the target tissue.[74,75] Another HDAC inhibitor that has been studied in the context of HGGs is vorinostat (SAHA); early studies in children with HGGs demonstrated good tolerability and have now moved to phase II studies in combination with radiation and TMZ[76] (ClinicalTrials.gov NCT01189266). A combination of vorinostat and the mTor inhibitor temsirolimus (NCT02420613) is also currently ongoing. Additional epigenetic drugs are currently further away from clinical use but nevertheless have produced interesting preclinical results: GSK-J4 (a small-molecule inhibitor of histone H3K27 demethylase JMJD3),[77] as well as EZH2 inhibitors and BET bromodomain inhibitors have all inhibited growth of preclinical H3 K27M diffuse glioma models.[78,79] The feasibility of testing some of these drugs in humans, their toxicity, brain penetration, and respective mechanisms of action must be elucidated before moving into clinical trials.

Discussion

The exponential growth of our knowledge of the molecular characteristics across pediatric gliomas has led to much excitement in the field. Gliomas can be subclassified based on their molecular alterations, and their signatures are being linked to particular locations, patient ages, and patient outcomes. As outlined previously, using state-of-the-art technologies for distinguishing molecular glioma subtypes at the time of primary diagnosis is becoming increasingly important in routine neuropathological diagnostic settings. Although the array-based assessment of DNA methylation patterns for molecular subclassification of pediatric gliomas (and other CNS tumors) has been shown to be a powerful tool, at the same time allowing for the detection of copy-number variations,[37,38,45,57] many of the currently known pediatric glioma classes are tightly linked to individual, recurrent, and specific alterations detectable by various alternative techniques. Refining existing classification histopathological systems by integrating these alterations is one of the next steps to improving clinical patient management and clinical trials.

However, there are also several challenges to overcome as the field moves forward. First, as "one-size-fits-all" trials become less and less attractive, international teams will have to collaborate and combine their patients into adequately powered trials for increasingly smaller tumor subgroups. Second, to correctly assign patients to such trials, upfront molecular diagnostics need to be integrated into classical histopathological and radiological diagnostics. These efforts will also need to be coordinated to allow for safe surgical procedures (especially for DIPGs) on the one hand and for standardized, comparable molecular diagnostics across different countries on the other. Third, efforts to investigate how new targeted therapies can overcome the blood–brain barrier will have to be developed in parallel. Fourth, studying acquired resistance to targeted therapies as well as testing combinatorial targeted therapies will be key to get closer to the goal of long-term tumor control in patients. Fifth, as the extent of tumor heterogeneity becomes more clear, especially in HGGs, it may be necessary to target cellular programs that are shared by all cells across different subclones, for example by discovering programs based on the developmental origin of the tumor. Sixth, immunotherapy represents another opportunity for improving patient outcomes and will need to be integrated with existing and new targeted therapies.

Some of these issues are already being addressed by the community involved in the care of children with brain tumors worldwide. After many decades of minimal clinical improvements, there is certainly reason for optimism that all these efforts will lead to meaningful clinical impact in the foreseeable future.

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