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The future of targeted therapies for pediatric central nervous system tumors

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Abstract

Targeted therapies are changing the landscape of pediatric brain tumor management. They offer the opportunity of more effective and personalized treatment strategies, with reduced side effects and improved outcomes. This paradigm shift in pediatric neuro-oncology is still at an early stage, and this review summarizes ongoing research that aims at finding novel drugs or at improving the management of pediatric low- and high-grade gliomas, ependymomas, embryonal tumors, germ cell tumors, craniopharyngiomas, and choroid plexus carcinomas.

Key Points

- Targeted treatments are transforming the management of pediatric central nervous system tumors, particularly low-grade and a subset of high-grade gliomas.
- Still, many conditions do not benefit from targeted treatments, and there is an urgent need to find novel drugs for conditions associated with a poor outcome with current therapies.
- There is also a need to identify long-term side effects and potential toxicities of these new therapies and their impact on children.
- Integration of targeted therapies in pediatric neuro-oncology also presents an economic challenge that needs to be addressed globally.

Molecular targets for anti-neoplastic therapy include signal transduction pathways, tumor cell surface antigens, and intracellular kinases found in laboratory-based studies to be critical for oncogenesis and/or tumor progression.[1–3] Genetic alterations classically deemed "druggable" include somatic point mutations or small insertions or deletions within the coding region of an oncogene (or its epigenetic modifier) and gene fusions or translocations. Copy number gains of oncogenes leading to amplification may be targetable in some situations, though *MYC* and *MYCN* amplification have resisted attempts to be therapeutically targeted.[4–6] Unfortunately, many pediatric brain tumors are driven by genetic alterations that are challenging to target therapeutically, including chromosomal changes or inhibition of tumor suppressor gene function.[3,4]

Targeted therapeutics may work by inducing tumor cell apoptosis, inhibiting tumor angiogenesis, or inhibiting cancer proliferation.[2,3] The theoretical benefit of targeted therapy compared to traditional cytotoxic chemotherapy or radiation is specificity toward tumor cells, thus sparing healthy tissue, as well as a unique and often lower side-effect profile both acutely and long term.[1,2,7,8] However, with the exception of low-grade gliomas (LGGs), the impact of targeted therapies in the treatment of pediatric brain tumors has thus far remained limited, given these cancers' overall low tumor mutation burden, intratumor clonal heterogeneity, and rarity of recurrent interpatient genetic alterations.[1,9] Although the ability of the agent to penetrate the blood–brain barrier (BBB) may impact its efficacy,[10] a lack of correlation between preclinical data and clinical experience is not uncommon. For example, Mittapalli et al. have shown that the brain distribution of vemurafenib is severely restricted (with a distribution coefficient of 0.004) at the BBB due to active efflux by both P-gp and

breast cancer resistance protein.[11] Similarly, preclinical studies of dabrafenib have suggested minimal penetration of the intact BBB, measured by brain concentrations, pERK inhibition, and PET imaging.[12] Despite this, both vemurafenib and dabrafenib have shown excellent activity in BRAF V600 mutated low-grade and high-grade glioma (HGG).[13,14]

Several factors influence the success of targeted therapies. The presence of a primary oncogenic driver mutation, a homogeneous distribution of the driver mutation in the tumor, and a high therapeutic index of the targeted treatment are critical elements for successful therapy. Conversely, the targeting of secondary or nondominant alterations has shown disappointing results. Serial trials of targeted agents such as imatinib, gefitinib, tipifarnib, veliparib, or Panobinostat in patients with diffuse intrinsic pontine glioma illustrate the failure of such an approach.[15–19] In addition, many malignant pediatric brain tumors show extensive intratumoral heterogeneity and genetic instability that explains the frequent development of resistance.[20,21]

With the exception of pediatric gliomas, most targeted agents utilized for the treatment of pediatric central nervous system (CNS) tumors are administered at the time of disease recurrence or progression. Unfortunately, the genetic characterization of these tumors has primarily focused on alterations found at the time of diagnosis, with much more limited evaluations performed at recurrence or progression following upfront treatment; consequently, targeted agents are often used as second-line agents without awareness of post-treatment changes in the tumor genome.[4]

Of note, discussion of anti-neoplastic immunotherapeutics such as CART cells or tumor vaccines in the treatment of pediatric CNS tumors is outside the scope of this manuscript.

Pediatric Low-Grade Gliomas

The targeting of pediatric low-grade glioma (pLGG) with MEK, BRAF, and PanRAF inhibitors has been one of the most significant advances in pediatric oncology during the last 2 decades.[22] Several clinical trials have demonstrated the efficacy and tolerability of targeted therapy in patients. The combination of dabrafenib and trametinib has now been approved for the management of pLGG harboring the BRAF V600 mutation, following the results of the randomized trial comparing this combination to standard chemotherapy using vincristine and carboplatin.[14] Large multicenter randomized trials are ongoing to compare targeted therapies (selumetinib in NCT04166409 and NCT03871257 and tovorafenib in NCT05566795) to standard-of-care chemotherapy. One may expect from these trials a paradigm change in the front-line management of unresectable pLGG. This experience has also identified the limitations of these treatments, and several questions are still awaiting an answer.

Duration of Treatment and Risk of Progression

Certainly, one of the crucial concerns is the duration of treatment with MEK/BRAF and PanRAF inhibitors. Discontinuation of targeted therapy leads in many cases to rebound[23] or tumor progression, and there is no clear consensus regarding the duration of treatment when targeted therapy is initiated. While resuming targeted treatment is a logical approach, preliminary data on re-initiation of treatment suggest that the second response to MEKi and BRAFi is inferior when compared to initial therapy.[24] It seems, therefore, important to identify biomarkers that can reliably predict the risk of progression and tailor the duration of treatment according to these biomarkers. The risk of progression after discontinuation appears particularly important in patients with BRAF V600E-mutated LGGs.[25] The Canadian group has established recommendations for the discontinuation of treatment with MEKi + BRAFi in patients with BRAF V600 mutation glioma.[26] While the standard practice is a sudden discontinuation of targeted treatment, this group suggests a progressive weaning of the MEKi first, followed by a gradual weaning of the BRAFi with different durations of targeted treatment for patients with LGG (3 years) versus HGG (5 years). A prospective data collection is ongoing to assess the efficacy and safety of this approach.

Resistance to MEK/BRAF Inhibitors

The mechanisms involved in innate and acquired resistance to MEKi and BRAFi in pLGG are still poorly understood. Mechanisms of BRAF inhibitor resistance have been extensively studied in melanoma, lung cancer, and other adult malignancies, and vary within an individual type of cancer, as well as between different tumor types.[27–29] Why some patients with BRAF-fused LGG do not respond to MEK inhibition, and some patients with BRAF-mutated LGGs do not respond to BRAF inhibition, is still an enigma, and clinical trials in pLGG patients have shown a large heterogeneity in the response to targeted therapies.[14,30,31] Acquired resistance is also observed, with an initial response followed by subsequent tumor progression. This phenomenon is particularly concerning in tumors harboring a BRAF V600 mutation.[32,33] While data from colon cancer suggest that tumors becoming resistant to a drug or a combination of drugs, such as BRAF/MEK inhibitors, develop cross-resistance with other MEKi/BRAFi,[34] the evidence of cross-resistance is still lacking in pLGG. In the FIREFLY-1 trial of the PanRAF inhibitor tovorafenib, 60% of registered patients had received prior therapy with MEK or BRAF inhibitor, and previous exposure had no impact on the response rate.[31] PF-07799933 (RRY-440) is an orthosteric, pan-mutant BRAF inhibitor that has shown promising activity in the treatment of refractory BRAF-mutant solid tumors, including brain tumors, either alone or in combination with binimetinib. One patient with a BRAFV600E-mutant primary brain tumor refractory to 2 lines of BRAF + MEK inhibitors achieved a complete and sustained response with this agent.[35]

Several mechanisms of resistance have been identified across different tumor types. Concurrent mutations in genes involved in the PI3K/AKT pathway may be responsible for resistance to BRAF/MEK inhibition.[24] Loss of PTEN activates the PI3K/AKT pathway and may confer resistance against BRAF and MEK inhibitor.[36–38] It is

therefore important to extend molecular studies to identify patients who may benefit from alternative treatment options. Shreck et al. have analyzed paired samples of 15 patients with glioma (3 LGG, 12 HGG) to characterize mechanisms of resistance. They identified putative mechanisms of resistance in 60% of paired samples, involving RTK activity, RAS/ERK signaling, PI3K/mTOR signaling, or cell-cycle signaling, including 1 activating alteration in BRAF (L514V) in a patient with LGG treated with BRAF inhibitor.[38] An important mean of resistance to targeted therapies in glioma is autophagy. Mulcahy-Levy et al. showed that inhibition of autophagy could overcome resistance to BRAFi in vitro and the addition of the autophagy inhibitor chloroquine (CQ) in a patient with a BRAFV600E brainstem ganglioglioma who progressed while on vemurafenib induced a sustained response.[39] PBTC-055 is a Phase I/II trial of dabrafenib, trametinib, and hydroxychloroquine (HCQ) for BRAF V600E-mutant or trametinib and HCQ for BRAF fusion/duplication positive or neurofibromatosis type 1 (NF1)-associated recurrent or progressive gliomas in children and young adults.[40] In different tumor types, autophagy inhibition could be achieved through depletion of cellular copper levels and copper chelation with disulfiram or tetrathiomolybdate has shown interesting results in preclinical models, including gliomas.[41] Copper chelation appears to overcome the upregulation of autophagy that results from the inhibition of the MAPK pathway.[41–43] Other approaches need to be explored, and the role of the tumor microenvironment appears to be critical in the development of resistance. Sigaud et al. developed a class-specific MAPKi sensitivity score (MSS) that included the prediction of immune and stromal infiltration in order to evaluate whether the tumor microenvironment could have an impact on the predicted MAPKi sensitivity. They showed that the MSS was able to predict response to treatment in a subset of patients treated with trametinib, with a high MEK 1/2 MSS associated with better response, while a low MSS was predictive of a poorer response.[44] Levine et al. recently described the role of high inflammatory infiltrates as an important negative prognostic marker in BRAF-mutant LGG. They observed a frequent upregulation of immune checkpoints in pLGG, which suggests that immune checkpoint inhibitors may be an effective strategy to explore in resistant tumors.[45] Studies in Murine $BRAF^{V600E}$ HGG models showed that the combination of BRAFi + MEKi with PD-1 and CTLA-4 immune checkpoint inhibitors reactivates T cells and overcomes resistance.[46]

Combination Studies

Early results of clinical trials of MEK and BRAF inhibitors have already shown limitations with heterogeneity in the response rate and evidence of progression or rebound after discontinuation.[23] This has triggered an interest in combination studies. Following the results of NCT02684058, the combination of BRAF and MEK inhibitors has been FDA approved for the treatment of BRAF V600-mutated LGG and BRAF V600-mutated recurrent HGG.[14,47] Clinical trials are ongoing to study the potential benefit of the combination of targeted treatment with chemotherapy. NCT04576117 is a randomized trial that compares selumetinib alone to a combination of selumetinib and vinblastine in patients with recurrent pLGG. Another trial, NCT06381570, is studying the combination of vinblastine and tovorafenib in pediatric patients with recurrent/progressive RAF-altered LGG. The combination of mTOR and MEK inhibitors has prevented the development of resistance in a BRAF-fused pLGG model. PNOC021 is a Phase I trial evaluating the combination of trametinib and everolimus in pediatric and young adult patients with recurrent LGGs.

ERK Inhibitors and Senolytic Agents

The proteins extracellular signal-regulated kinase 1 (ERK1) and ERK2 are the downstream targets of MEK and play an important role in cell proliferation, survival, growth metabolism, and differentiation.[48] Ulixertinib is an ERK1/2 inhibitor that has shown good preclinical activity in patient-derived pLGG models.[49] The MATCH trial of Ulixertinib (NCT01781429) enrolled 11 patients with glial tumors (4 BRAF V600-mutated HGG, 1 NF1-mutated HGG, 1 BRAF V600-mutated LGG, 4 BRAF-fused LGG, and 1 BRAF-mutated glioneural tumor) and reported stable disease in 3 LGG patients.[50] Further development of this agent is under discussion.

Another area of interest concerns senescence and the potential interest of senolytic agents. Using patient-derived pilocytic astrocytoma (PA) cell lines, Selt et al. demonstrate the critical role of BCL-XL in the survival of senescent PA tumor cells, an observation that suggests a potential role for targeting BCL-XL with senolytic agents.[51]

Overall, despite major advances in the targeted treatment of pLGG, many questions remain unanswered. For example, should targeted treatment become standard of care for all patients, should they show a significant advantage in terms of response rate and/or progression-free survival? The experience accumulated over the last 3 decades has shown that 40%–50% of LGG patients experience sustained control with 1 line of chemotherapy. The pros and cons of each approach should be taken into account, including the short and long toxicity of MEK/BRAF/PanRAF inhibitors, their cost, and the financial burden on patients, families, and the healthcare system. The targeting of fibroblast growth factor receptor (FGFR)-altered tumor is another challenge. While early clinical trials and case reports have suggested activity,[52,53] the toxicity of these agents has raised major concerns in children,[54,55] and clinical trials have been put on hold in the pediatric age group.

Despite the recent FDA approval of vorasidenib for the treatment of IDH-mutated LGG (56)for patients above the age of 12,[56] data on the targeting of IDH1/2 mutation in LGGs in the pediatric and adolescent population remain limited. More information is needed to characterize the role of this agent in children and adolescents harboring this alteration[57]

Pediatric High-Grade Gliomas

Although they are histologically similar, there is a fundamental difference between infantile high-grade gliomas

(iHGGs) and HGGs in older children. iHGGs are mostly single-driver tumor and are particularly suitable for targeted treatment approaches.[58] Alterations in neurotrophic tyrosine receptor kinase (NTRK), anaplastic lymphoma kinase (ALK), and OS proto-oncogene 1, receptor tyrosine kinase (ROS1) are all targetable, and the efficacy of larotrectinib, entrectinib, lorlatinib, alectinib, and other inhibitors has been reported in clinical trials and case reports.[59–62] However, concerns have been raised regarding the long-term consequences of these agents, in particular the NTRK inhibitors in infants and young children.[63] TRK is essential for the development of the nervous system, and the impact of TRK inhibition on brain development is unknown. Preclinical experiments have shown that most mice with a germline mutation in the tyrosine kinase catalytic domain of the trkB gene die early, and postmortem examinations revealed major neuronal deficiencies in the central and peripheral nervous systems.[64] Therefore, the respective role of chemotherapy—that has shown interesting activity in iHGG[65,66]—and targeted therapies is still a matter of debate. Interestingly, the combination of larotrectinib and chemotherapy is currently investigated in the CONNECT trial 1903.[67]

BRAF mutations are observed in 5%–10% pHGGs, and the use of BRAF inhibitors has been associated with sustained response and improved survival. Following the results of NCT02684058, the combination of dabrafenib and trametinib has been FDA approved for patients with recurrent and refractory HGGs harboring a BRAF V600 mutation.[47] Anecdotal observations of patients successfully treated with BRAF inhibitors in combinations or not with MEK inhibitors and without irradiation suggest that a subset of patients with BRAF V600-mutated pHGG could be managed with a radiotherapy-sparing approach.[68] However, the rarity of this condition makes the development of large clinical trials challenging. A clinical trial is going on in the Children's Oncology Group in newly diagnosed patients with BRAF V600-mutated HGG combining trametinib and dabrafenib after radiation therapy (NCT03919071).

Bithalamic glioma has a uniformly dismal outcome and responds poorly to radiotherapy. Identification of a frequent EGFR exon 20 insertion may provide the opportunity to consider targeted therapies for this entity, as several agents with inhibitory activity against this alteration are currently being developed in lung cancer.[69–72] There are many FDA-approved (TKI) kinase inhibitors and monoclonal antibodies for targeting EGFR in various types of cancers, including several that have been investigated in treating pHGG patients.[19,73–75]

There is no drug that directly targets H3K27M, and the prognosis of patients with diffuse midline gliomas remains dismal.[76] ONC201 is a brain-penetrant imipridone recently identified as a dopamine receptor D2 antagonist.[77] This small molecule selectively binds to the G-protein-coupled dopamine receptor D2 (DRD2) and the mitochondrial protease ClpP and has shown promising activity in a Phase II study in adults where a patient with a recurrent secondary glioblastoma harboring an H3.3 K27M mutation achieved a sustained partial response.[78] Several trials of ONC201 have been inconclusive, mostly due to poor trial design.[79] The only future of ONC201 in pHGG harboring the H3K27M mutation will be through properly designed clinical trials such as BIOMEDE 2.0 (NCT05476939), an open-label randomized study of everolimus versus a hospital preparation of ONC201 in nonrecurrent brainstem H3K27M-DMG.

The main challenge in pHGG remains the targeting of the H3K27M. Early data on CAR T cell show promise.[80] The development of H3K27M inhibitors is still a major challenge and a priority for the present and the future.

Ependymomas

Ependymomas exhibit a poor response to chemotherapy, and no clinical trial has demonstrated a survival benefit associated with the addition of chemotherapy to adjuvant radiotherapy in the pediatric population.[81] Despite promising preclinical observations, the targeting of alterations of PI3K/Akt and EGFR pathways has been unsuccessful.[75,82] The paucity of genetic alterations and lack of druggable-driver alterations have prevented the application of precision medicine-based approaches. Recent advancements in animal models and single-cell studies have attempted to address some of these hurdles.[83] These studies have identified potential targets for supratentorial and infratentorial ependymomas. By matching transcriptomic signatures of ST-EPN-ZFTA with FDA-approved drugs, Ren et al. found that dasatinib selectively and potently inhibits ependymoma cell growth in vitro. They confirmed that dasatinib significantly prolonged survival of an orthotopic allograft model of ST-EPN.[84] In infratentorial ependymomas, the repurposing of metformin as a potential treatment for posterior fossa ependymoma group A (PFA) ependymoma has been suggested by Panwalkar et al.[85] Metformin is an activator of the AMP-activated protein kinase that lowers EZHIP and increases trimethylation at histone H3 lysine 27 (H3K27me3) and has shown therapeutic efficacy in patient-derived cell lines and patient-derived animal models. Clinical trials are needed to confirm these observations.

Medulloblastoma

It is important to remember that there is spatial heterogeneity of genomic alterations within individual medulloblastoma tumors, making the therapeutic targeting of these tumors difficult.[86] The most "druggable" medulloblastoma subgroup is Sonic Hedgehog (SHH), though the effect of smoothened (*SMO*) inhibition is entirely dependent on the location of the altered oncogene within the Hedgehog pathway (see below); in contrast, therapeutic targeting of WNT, Group 3, and Group 4 medulloblastoma subgroups has remained challenging.

WNT

The vast majority (90%) of WNT medulloblastoma are genomically characterized by activating somatic mutations (typically single-nucleotide variants) in exon 3 of *CTNNB1*, which codes for the β-catenin protein; the majority of

patients without somatic *CTNNB1* mutation will have an alteration in *APC* that is often germline.[4,7,87,88] The next common somatic mutation in this subgroup is the tumor suppressor gene *DDX3X*.[88–90]

Therapeutic targeting of the WNT/β-catenin pathway has been limited by its critical role in organogenesis during embryonal development and in adulthood for bone formation, skin and hair hemostasis, and hematopoiesis.[7,88,91] Additionally, given the fact that the excellent outcome of WNT subgroup medulloblastomas is at least in part due to a highly permeable BBB allowing improved penetration of chemotherapy in the CNS, there is concern that targeting elevated WNT signaling may make tumors less sensitive to chemotherapy by tightening the BBB.[88,92]

SHH

Pediatric SHH medulloblastoma is typically characterized by somatic mutations or deletions in *PTCH1*, *SUFU*, or *TP53, w*ith up to 40% of patients having a corresponding germline mutation (leading to Gorlin syndrome *PTCH1* and *SUFU* and Li Fraumeni for *TP53*).[7,93,94] Of all pediatric CNS embryonal tumors, the most experience in the use of targeted therapies is for SHH medulloblastomas. Importantly, however, SMO inhibitors are only efficacious for SHH medulloblastomas with genomic alterations upstream of *SMO* or of *SMO* itself, which are more common in adult rather than pediatric SHH medulloblastomas. *PTCH1* codes for a transmembrane protein that binds the SHH ligand, leading to activation of SMO; downstream effects of SMO activation include release of SUFU-induced inhibition of GLI proteins, which then activate SHH target gene transcription in the tumor cell nucleus. Consequently, SHH medulloblastomas with alterations in *SUFU* are resistant to SMO inhibitors, as are SHH medulloblastomas with MYCN amplification.[4,88,95–100]

The SMO inhibitor vismodegib has the most experience for the treatment of recurrent or progressive pediatric SHH medulloblastoma (including NCT00822458 and 01239316) and was recently utilized in a clinical trial as maintenance therapy in skeletally mature patients with newly diagnosed SHH medulloblastoma (NCT01878617).[98,100] The use of SMO inhibitors is limited in pediatric patients due to the drug class causing irreversible premature epiphyseal growth plate fusions.[101] Recent preclinical investigations have shown antitumor effects of vismodegib administered intraventricularly without the adverse effects on bones noted with systemic administration.[102]

Despite often notable disease responses to SMO inhibition in SHH medulloblastoma with alterations of *PTCH1* or *SMO*, resistance develops with prolonged drug exposure. Resistance may develop from the development of new genetic alterations downstream of *SMO*, new mutations of *SMO* leading to conformational changes in the protein preventing first-generation SMO inhibitors from successfully binding, or alterations of other signaling pathways, including PI3K. Direct GLI inhibitors as well as arsenic trioxide are under investigation for use in SHH medulloblastoma that have gained resistance to SMO inhibition or that are driven by mutations downstream of SMO.[4,7,97–100,103–106]

SHH medulloblastomas with *TP53* mutations (germline or somatic) have the poorest prognosis of all medulloblast omas.[93,107,108] Unfortunately, as in many other tumor types, *TP53* currently remains difficult to therapeutically target. Of note, *TP53*-mutant SHH medulloblastomas also appear to be resistant to SMO inhibition.[4,98,100]

Groups 3 and 4

Unfortunately, neither Group 3 nor 4 medulloblastomas have frequent targetable genetic alteration; those that are present are often associated with epigenetic regulation, including chromatin remodelers and histone modifiers. Around 10% of Group 3 medulloblastomas have alterations in *SMARCA4*; recurrent genetic alterations are rare in Group 4 medulloblastomas but include mutations of *KBTBD4*, *KDM6A, KMT2C*, *PRDM6*, and *ZMYM3*, all of which are involved in epigenetic regulation and currently not considered "druggable" alterations.[4,7,88,97]

The Group 3 medulloblastomas with the poorest outcomes are those with MYC amplification, which has proven extremely challenging to therapeutically target.[4,7,88,97] Numerous preclinical studies have attempted to therapeutically target *MYC* amplification in Group 3 medulloblastoma by inhibiting various downstream activated signaling pathways through targeting AURKA, BET, BRD4, FGFR, HDAC, mTOR, and PI3K; a clinical benefit has yet to be demonstrated, though many agents targeting these proteins are still in early-phase clinical trials in pediatrics.[88,103,109–114]

Overall, the targeting of MYC and TP53 are critical areas of focus in pediatric medulloblastoma. While traditional protocols have pooled together high-risk patients in a single category, specific clinical trials are needed to address these unique challenges.

Atypical Teratoid Rhabdoid Tumor

Atypical teratoid rhabdoid tumor (ATRT) is genomically characterized by alterations in either *SMARCB1* (>95%) or *SMARCA4*, components of the SWI/SNF chromatin remodeling complex.[115–118] Epigenetically, *SMARCB1*-altered ATRTs can be molecularly classified into 1 of 3 subgroups: MYC, SHH, or TYR, each with distinct mechanisms of *SMARCB1* loss, clinical characteristics, therapeutic vulnerabilities, and survival outcomes.[117,119,120]

Despite the genomic simplicity of ATRTs, targeted therapy for this tumor is of great interest, given its overall poor outcomes. The most clinical experience for this tumor is in the targeting of EZH2. With the loss of SMARCB1 or SMARCA4, polycomb repressive complex 2 (PRC2) becomes overly active; EZH2 is the catalytic subunit of PRC2. The EZH2 inhibitor tazemetostat has received FDA approved for the treatment of unresectable SMARCB1-deficient epithelioid sarcoma in patients ≥16 years and adult patients with relapsed or refractory (after at least 2 systemic therapies) *EZH2* mutant follicular lymphomas. Given extensive preclinical data suggesting in vitro and in vivo responses of rhabdoid tumors to EZH2 inhibition, tazemetostat has been evaluated in both Phase I and Phase II studies in children with relapsed or refractory *SMARCB1*

or *SMARCA4* altered tumors including ATRT.[121–127] In the Phase I study, 5/21 patients (24%) with ATRT had an objective response. In contrast, none of the 8 patients with ATRT on the Phase II study had an objective response to tazemetostat therapy, but 1 patient did have a prolonged progression-free survival of over 13 months.[128–132] A study combining tazemetostat with the PD-1 inhibitor nivolumab and CTLA-4 inhibitor ipilimumab is currently underway for patients with relapsed or refractory ATRT and other *SMARCB1* or *SMARCA4* altered tumors (NCT05407441).

Aurora kinase A inhibition using the small-molecule inhibitor alisertib has also been tested clinically in a Phase II study of patients with relapsed or progressive ATRT. After 12 weeks of therapy, 8/30 patients (27%) had a best response of stable disease, and only 1/30 (3%) had a partial response.[133] Given preclinical evidence demonstrating increased activity in CKD4/6 in this tumor, 13 pediatric patients with ATRT were treated with the CDK4/6 inhibition ribociclib on a Phase I study; the best response to treatment was stable disease seen in only 2/13 (15%), but this was maintained in both for >19 months.[128,134]

Other potential therapeutic targets for ATRT identified in preclinical studies include BET, BRD9, exportin-1, FGFR, HDAC, MDM2/MDM4, PARP, PDGFRα, PLK1, PTK7, and RRM2.[128,130,135–145] MYC subgroup ATRTs appear on preclinical testing to be uniquely sensitive to tyrosine kinase inhibition, while SHH subgroup tumors have sensitivity to gamma-secretase inhibitors.[119,130,146]

There have been very few collaborative clinical trials for ATRT.[131,133,147,148] There is an urgent need to systematically explore the potential of targeted agents for this condition that still has a guarded prognosis with intensive multimodal treatments.

Embryonal Tumor With Multilayered Rosettes

Embryonal tumor with multilayered rosettes (ETMR) is an embryonal tumor of infancy characterized in 90% of cases by copy number gain of a microRNA cluster on chromosome 19 (*C19MC*); the remaining cases typically have *DICER1* alterations (germline or somatic only).[149,150] Thus far, no clinical trials have been completed assessing the role of targeted agents either in newly diagnosed or recurrent ETMR, and preclinical studies have been limited by a lack of cell lines and animal models. However, there are some molecular targets of interest that have been identified.

Numerous signaling pathways are upregulated in ETMR, including the Hippo, mTOR, NOTCH, RAS, SHH, TGF-β, and WNT pathways. In vitro data have demonstrated synergy between topoisomerase 1 inhibitors such as topotecan or irinotecan with PARP inhibitors, as well as sensitivity of ETMR cells to treatment with chemical inhibitors of aurora kinase, BET, IGF1R, mTOR, PI3K, and polo-like kinase.[150–154] Additionally, proteosome inhibition was recently identified as a potential therapeutic vulnerability of ETMR cells.[155] Recent data suggest a potential role for FGFR inhibitors provide that their toxicity profile allows their use in infants and young children.[156]

CNS Neuroblastoma, *FOXR2*-Activated, and CNS Tumor With *BCOR* Internal Tandem Duplication

CNS neuroblastoma, *FOXR2*-activated (CNS NB-*FOXR2*), and CNS tumor with *BCOR* internal tandem duplication (ITD) are recent additions to the WHO classification of CNS tumors, having previously been grouped with several other tumor types under the umbrella term supratentorial primitive neuro-ectodermal tumor.[157,158] Given the recent characterization of these tumors, there is little data thus far regarding potential therapeutic targets for these pathologies. Recent data suggest that the MEK/ERK pathway may be a relevant target in CNS NB-*FOXR2*.[159] Similar to ATRT, CNS tumor with *BCOR* ITD has increased expression of PRC2 targets, suggesting a possible therapeutic role for EZH2 inhibition; other activated pathways in this tumor may include WNT and SHH, similar to ETMR.[160–162]

Pineoblastoma

Pineoblastoma is associated with both tumors, which can be molecularly classified into 1 of 4 subgroups: RB, MYC/FOXR2, 1/miRNA1, or 2/miRNA2. miRNA1 and 2 groups are associated with somatic and germline mutations in *DICER1* or somatic mutations in *DROSHA*, genes which are important in microRNA biogenesis, the RB group is associated with germline or somatic mutations in *RB1*, and the MYC/FOXR2 group has gain or amplification of *MYC*.[163–166] There has been very minimal published preclinical work investigating the role of targeted therapies for pineoblastoma. One investigation suggested a possible role for tricyclic antidepressants to disrupt intratumoral lysosomes and lead to pineoblastoma cell death; synergy was noted between nortriptyline, a tricyclic antidepressant, and the chemotherapeutic gemcitabine in vivo in pineoblastoma models.[167] The need to explore targeted therapy is particularly crucial in infant and young children who have a dismal outcome with radiation-sparing approaches.[168]

CNS Germ Cell Tumors

Pure germinomas frequently have mutually exclusive mutations of *KIT* or *RAS* (including *KRAS* and *NRAS)*; in contrast, alterations in these genes are rare in non-germinomatous germ cell tumors (NGGCT).[169–173] A small case series summarized the use of the KIT-targeted TKI dasatinib for the treatment of 6 pediatric patients with CNS germinomas. While the therapy was well tolerated and feasible, no objective responses were noted.[174]

Recurrent genomic alterations in the PI3K/AKT/mTOR pathway have also been noted in CNS germ cell tumors, including copy number gain of *AKT1*, loss-of-function mutations in *BCORL1*, and mutations in *mTOR* itself; this pathway is more likely to be altered in patients with basal ganglia or intraventricular germ cell tumors.[169–171,173,175]

Preclinical testing of the mTORC1/2 inhibitor torkinib in 2 *mTOR* mutant germinoma cell cultures demonstrated dose-dependent efficacy, suggesting a potential role for clinical evaluation.[171]

Meningioma

Meningiomas, primarily WHO grade 1, are associated with either germline or somatic *NF2* mutations. *NF2* wild-type meningiomas, again most commonly WHO grade 1, often harbor mutations in *AKT*, *KLF4*, *PI3KCA*, *SMO*, or *TRAF7*, though these predominate in adult rather than pediatric meningiomas.[176–184] Higher-grade meningiomas (grade 2 and 3) are often associated with alterations in the SWI/SNF complex or PRC2, including loss-of-function mutations in *SMARCE1* (either germline or somatic) in clear cell meningiomas.[178,179,182,184–186] Recent data focused on pediatric meningioma identified in-frame gene rearrangements leading to *YAP1* fusions in patients without somatic *NF2* alterations, leading to deregulation of the HIPPO pathway.[184] In addition to AKT/mTOR/PI3K, Hedgehog, HIPPO, and signaling pathways involved in meningioma pathogenesis include the MAPK and CDK-p16-Rb pathways, while overexpressed growth factors in this tumor include EGFR, PDGF, and VEGF.[176,177,179,183,187–190]

Many clinical trials targeting the variety of genetic alterations in meningioma have been completed or are ongoing in adult patients with recurrent tumors, including inhibitors of AKT1, CDK4/6, EGFR, FAK, MEK, mTORC1/2, PDGF, SMO, VEGF, and TEAD; unfortunately, the majority of completed studies did not significantly improve progression-free survival or lead to radiographic objective responses.[176–178,182,183,187–193] Plotkin et al. reported the results of a clinical trial of brigatinib in NF2-related schwannomatosis with progressive tumors that accrued 40 patients, including 12 patients aged 12–21 years old.[194] There were 20 patients with meningioma (53 meningiomas in total), and 3 patients (13/51 tumors) demonstrated a radiographic response to brigantinib. The annualized growth rate of meningiomas decreased from 139% to 9%. Preclinical data have shown that this antitumor effect is not mediated by ALK, but by nonreceptor TKI, including FAK and FAK2. In this context, the study the FAK inhibitor GSK2256098 for patients with *NF2* altered recurrent or progressive WHO grade 1–3 meningiomas met its 6-month progression-free survival efficacy endpoint.[195] The targeting of the Hippo pathway with transcriptional enhanced associate domain (TEAD) inhibitors that has shown promising results in preclinical studies and in early clinical trials.[196]

Adamantinomatous Craniopharyngioma

Adamantinomatous craniopharyngioma (ACP), the predominant histologic subtype of this tumor in pediatrics, is driven by somatic activating point mutations in *CTNNB1* (β-catenin).[197–199] Unfortunately, given the WNT pathways' roles in organ homeostasis, it has been difficult to safely therapeutically target.[197,200]

The MAPK pathway is active in ACP tumorigenesis, both at diagnosis and at recurrence; interestingly, this pathway is activated in a paracrine manner rather than secondary to mutations. As preclinical studies demonstrated antitumor effects of MAPK inhibition in ACP, 2 clinical trials are currently ongoing evaluating the role of targeting MEK (NCT05286788) or RAF (NCT05465174) in pediatric ACP.[197–199,201] While activation of the SHH pathway is well documented in ACP, inhibition of the pathway by the SHH inhibitor vismodegib paradoxically led to increased tumor growth and vascularization.[198–200,202]

ACP is also biologically characterized by high levels of inflammation, including IL-6, CXCL8 (IL-8), and CXCL1 in both the cystic and solid tumor components. Based on this data, the efficacy of the IL-6 inhibitor TOCILIZUMAB is currently being evaluated in a clinical trial for pediatric patients with ACP (NCT05233397).[197–199,202,203]

Choroid Plexus Carcinoma

Over half of choroid plexus carcinomas (CPC) are defined by deleterious mutations in *TP53*, which may be somatic or germline; CPC with *TP53* alterations have a significantly worse prognosis than wild-type tumors.[204–206] The Notch, PDGF, PI3K/mTOR, SHH, and WNT signaling pathways have also been shown to be involved in CPC pathogenesis.[205,207–213] Similar to ETMR, clinical translation of the genomic alterations that characterize CPC has been limited by the paucity of relevant cell lines and animal models. However, preclinical testing of the PDGF inhibitor imatinib in a choroid plexus epithelial cell line demonstrated dose- and time-dependent impairment in cell proliferation, while a patient-derived CPC cell line demonstrated sensitivity to the ATR inhibitor elimuser tib.[207,210,213]

The Emergence of Liquid Biopsies

Molecular alterations are currently identified from the analysis of tumor tissue obtained during tumor biopsy or resection. Confirmation of the type of alteration is required to access targeted treatment, with some exceptions, such as for mTOR inhibitors for patients with tuberous sclerosis or for MEK inhibitors for patients with NF1.

Liquid biopsies have emerged as a new tool for the diagnosis and management of several cancers. Liquid biopsies isolate and characterize cell-free DNA (cfDNA) from fluids such as plasma, cerebrospinal fluid (CSF), or urine.[38] In cancer patients, a small proportion of this cfDNA comes from dying tumor cells—called circulating tumor DNA (ctDNA). Liquid biopsy assays analyze the profiling of cell-free DNA (cfDNA) to detect molecular alterations that may aid in diagnosis and prognosis, detect relapse, and provide biologic targets for therapy. Liquid biopsies are routinely used in the management of patients with metastatic lung cancer and other solid tumors.[39]

In pediatric brain tumors, liquid biopsies may become an alternative to traditional tissue biopsies. Several studies have demonstrated the potential for this technique to detect alterations in the blood or the CSF. Early work by Miller et al. identified somatic alterations in 46.9% (30/64) of CSF samples of pediatric brain tumor patients.[40] Among pLGG, only disseminated low-grade tumors yielded positive results. Madlener et al. studied 78 liquid biopsies (44 from blood, 34 from CSF) in 34 pediatric glioma and 1 adult glioma patients (27 HGG, 8 LGG) with a focus on H3K27M and BRAF mutations. All patients had tumor tissue for comparison, and the sensitivity for 3K27M was 84.61% for CSF and 73.68% for plasma. For BRAF V600E, the sensitivity was 83.3% in plasma and 80% in CSF. The overall specificity was 100%. The ventricular CSF, taken via Ommaya Reservoir or shunt reservoir, showed a positive signal in 93%, versus 66% in lumbar punctures. However, they provided anecdotal evidence that tumor location may influence the result and 1 patient with a spinal cord tumor had negative ventricular CSF while the lumbar puncture yielded positive results. For BRAF, there was no significant difference in sensitivity between LGG and HGG.[41]

CSF liquid biopsies have also been studied in medulloblastoma and in germinoma, which are known to harbor frequent copy number alterations (CNAs) that can be inferred by panel sequencing or low-pass whole-genome sequencing and used as surrogate markers of measurable residual disease (MRD) at the molecular level. Nakano et al. used low-pass whole-genome sequencing in a series of 19 patients with germinoma and reported a detection rate of copy number alterations of 89% in baseline specimens.[214] In another study, Takayasu et al. used panel sequencing with a lower success rate of 33% only.[215] CSF cfDNA was assessed as a potential biomarker of minimal residual disease (MRD) in samples collected from 123 patients enrolled in the SJMB03 medulloblastoma trial. This work showed that patients with persistent MRD had a significantly higher risk of progression and that MRD detection preceded radiographic progression in half of the patients.[216]

Larger studies are necessary to determine the sensitivity of cfDNA at diagnosis, particularly in lower-grade tumors. In the future, incorporation of liquid biopsies into prospective clinical trials will be important to clarify their potential contribution in terms of diagnosis, eligibility for clinical trials, and importance during treatment. Technical advances in sequencing will certainly increase the sensitivity of this tool in the future.

Conclusions

While major advances have been made in understanding the complex biology of pediatric CNS tumors, effective targeted treatments have essentially influenced the management of pLGGs and pHGGs. Further research and clinical innovation are imperative to develop more effective and sustainable therapeutic options for other tumor types. There is a critical need to focus on challenging entities such as MYC-amplified or TP53-mutated SHH medulloblastoma, or ETMR, which still have a poor outcome despite the use of intensive multimodal treatment. The development of effective targeted therapies for diffuse midline gliomas is also a priority. There is a need to agree on the design of clinical trials that can effectively and rapidly evaluate the potential of new therapies. Furthermore, overcoming resistance to targeted therapies is a challenge that calls for continued innovation and research. The integration of targeted therapies in pediatric neuro-oncology also presents an economic challenge, and the high cost of these treatments prevents accessibility to all patients, particularly in low- and middle-income countries and in countries lacking universal health coverage. Lowering the cost of these lifesaving medications is also a critical priority. Finally, while the approval of targeted agents for pediatric CNS tumors has been primarily based on efficacy and short-term toxicity criteria, little is known regarding the long-term impact of these drugs. It is therefore critical to remain vigilant and carefully assess potential long-term toxicities in future research.

Keywords

BRAF | H3K27M | NTRK | pediatric central nervous system tumors | targeted treatments

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Conflict of interest statement

E.B. is member of advisory board with Novartis, Servier, Alexion, and Fore.

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