Targeted Therapies for Pediatric Central Nervous System Tumors

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Abbreviations

CNS	Central nervous system
HGG	High-grade glioma
LGG	Low-grade glioma
MAPK	Mitogen-activated protein kinase
MEK	Mitogen-activated extracellular signal-regulated kinase
mTOR	Mammalian target of rapamycin
NF1	Neurofibromatosis type 1
PN	Plexiform neurofibroma
PTCH1	Patched 1
SEGA	Subependymal giant cell astrocytoma
SHH	Sonic hedgehog
SMO	Smoothened
SUFU	Suppressor of fused
TSC	Tuberous sclerosis complex
WHO	World Health Organization

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Introduction

Central nervous system (CNS) tumors are the most common solid tumors in childhood and can be malignant or nonmalignant. Primary malignant CNS tumors represent approximately 20% of all childhood cancers yet account for 30% of all childhood cancer deaths in the United States, having superseded leukemia as the leading cause of death from childhood cancer [1, 2].

The prognosis for patients with CNS tumors is based on many factors, including the tumor type, its location and histologic grade, and the available treatment options. Historically, pediatric CNS tumors were diagnosed, classified, and treated based on their location and histologic criteria. Recent discoveries in pediatric neuro-oncology have greatly enhanced our understanding of the biology of these tumors, including their molecular and genetic characteristics. The molecular characterization of CNS tumors has led to improved diagnostic accuracy and risk stratification. In 2016, these advances resulted in a revised classification of CNS tumors by the World Health Organization (WHO), in which molecular parameters and histology define many tumor entities [3].

Based on our recent understanding of molecular markers, the use of targeted therapies has begun to transform our approach to treating many pediatric CNS tumors. Currently, a few targeted therapies are being used to treat subgroups of pediatric CNS tumors, mostly in the setting of clinical trials. The

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Table 33.1 Pediatric central nervous system tumors with molecularly defined therapeutic targets

Tumor type	Molecular subgroup	Therapeutic target	Molecular pathway	Clinically tested agents
Medulloblastoma	Sonic Hedgehog	SMO	SHH	Sonidegib (Odomzo®), Vismodegib (Erivedge®)
Subependymal giant cell astrocytoma	–	mTOR	mTOR	Everolimus (Afinitor®)
Low-grade glioma	*BRAF* V600E	BRAF V600E	MAPK	Dabrafenib (Tafinlar®), vemurafenib (Zelboraf®)
High-grade glioma	*BRAF* V600E	BRAF V600E	MAPK	Dabrafenib (Tafinlar®), vemurafenib (Zelboraf®)
Pilocytic astrocytoma	*KIAA1549:BRAF* fusion	KIAA1549:BRAF fusion	MAPK	Selumetinib (AZD6244), trametinib (Mekinist®)
Plexiform neurofibroma	–	MEK 1/2	MAPK	Selumetinib (AZD6244)

SHH sonic hedgehog, *mTOR* mammalian target of rapamycin, *MAPK* mitogen-activated protein kinase, *MEK* mitogen-activated extracellular signal-regulated kinase, *SMO* smoothened

tumors being treated by this approach include sonic hedgehog (SHH) medulloblastoma, subependymal giant cell astrocytoma (SEGA), *BRAF* V600E-mutated low-grade and high-grade gliomas (LGG, HGG), *KIAA1549:BRAF* fusion-positive pilocytic astrocytoma, and plexiform neurofibroma (PN).

For many patients, including patients with recurrent or refractory disease, the use of targeted therapies for these tumor subtypes has resulted in significant tumor regression and improved survival. In this chapter we provide an overview of pediatric CNS tumors for which key driver mutations and targeted therapies have created a paradigm shift in the treatment approach (Table 33.1).

Medulloblastoma

Medulloblastoma is a heterogeneous disease consisting of four main molecularly defined subgroups: wingless (WNT; group 1), sonic hedgehog (SHH; group 2), group 3 (characterized by *MYC* amplification and *GFI* activation), and group 4 (characterized by *MYCN* and *CDK6* amplifications and alterations in *SNCAIP*) [4]. To date, targeted therapy is only applicable to the SHH subgroup, which represents approximately 25% of all medulloblastomas. Nodular desmoplastic histology is pathognomonic for the SHH subgroup, although SHH tumors also exhibit classic or large-cell/anaplastic histology. SHH medulloblastoma affects patients of all ages, but it primarily occurs in children younger than 5 years and in individuals older than 16 years. The 5-year overall survival for patients with tumors of this subgroup is 70%; however, the current treatment often results in significant morbidity, and the prognosis in recurrent or refractory disease is dismal [5].

SHH medulloblastoma most frequently arises from a cerebellar hemisphere, and cerebellar granule neuron precursors are its imputed cells of origin. This tumor subtype is characterized by aberrant activation of the SHH signaling pathway (Fig. 33.1). In a normal cell, binding of a SHH ligand to the patched 1 (PTCH1) receptor releases its inhibition of smoothened (SMO), the main upstream activator in the pathway. Activated SMO then releases suppressor of fused (SUFU) inhibition of GLI proteins, which can then translocate to the nucleus and activate transcription of SHH target genes (*GLI1*, *GLI2*, *PTCH1*, and *MYCN*). In SHH medulloblastoma, a ligand-independent pathway disruption occurs as a result of somatic or germline mutations involving one of several genes in the SHH pathway. This disruption leads to aberrant expression of SHH target genes, which allows cell proliferation and tumorigenesis [5].

The activating mutations most commonly found to occur in SHH medulloblastoma and to disrupt the SHH signaling pathway include mutations of *PTCH1*, *SMO*, *SUFU*, and *TP53*, as well as *GLI2* and *MYCN* amplification. Patients who harbor upstream SHH-pathway mutations (e.g.,

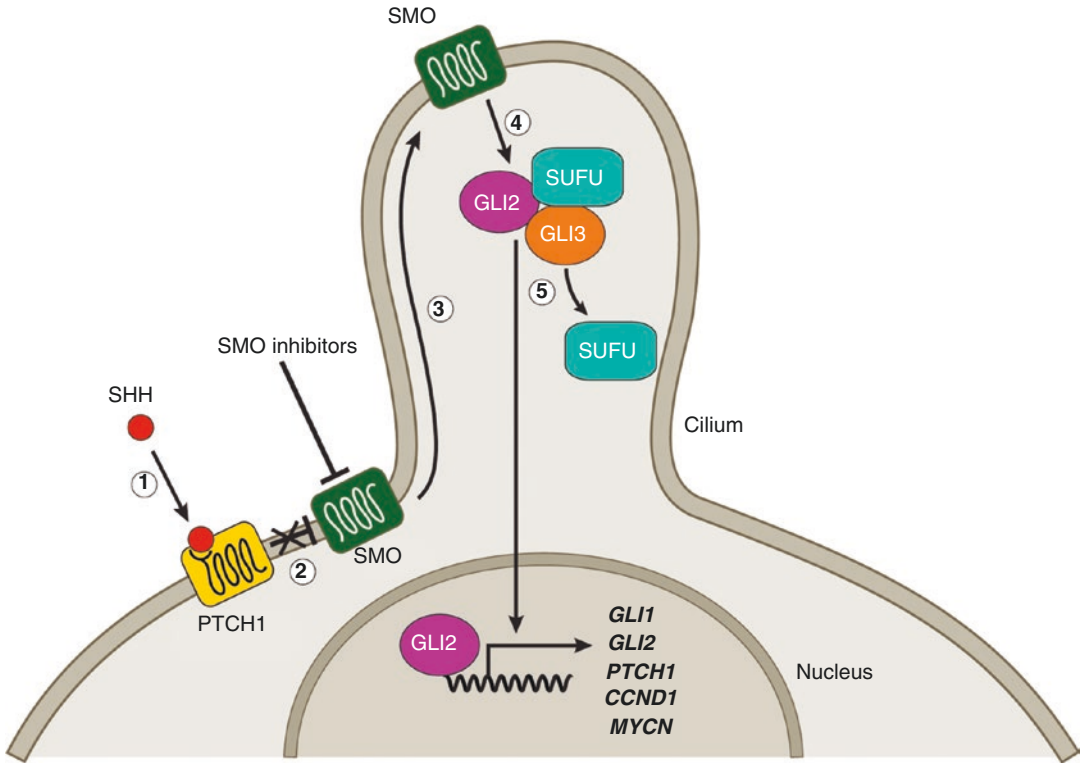

Fig. 33.1 Illustration of sonic hedgehog (SHH) signaling pathway. (1) SHH ligand binds to PTCH1 transmembrane protein. (2) Binding of SHH to PTCH1 relieves inhibition of smoothened (SMO). (3) Activated SMO localizes to cilium. (4) SMO releases suppressor of fused (SUFU) inhibition of GLI proteins. (5) Activated GLI proteins translocate to nucleus and activate transcription of SHH target genes (i.e., GLI1, GLI2, PTCH1, and MYCN). In SHH-subgroup medulloblastoma, disruptions to SHH pathway occur through mutation of PTCH1, SMO, or SUFU and/or amplification of GLI2 or MYCN. (Robinson et al. [5]. Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved]

PTCH1 and *SMO* mutations) have shown sensitivity to SMO inhibitors, which first emerged as a potentially effective targeted therapy for SHH medulloblastoma after an adult with relapsed metastatic disease was treated with vismodegib and experienced a profound initial response [6]. Agents in this class of targeted inhibitors act as competitive antagonists of the SMO receptor, inhibiting signaling downstream of SMO. Unfortunately, patients with SHH medulloblastoma who harbor downstream mutations (e.g., *SUFU* mutations or *GLI2* amplification) are resistant to these agents.

In several pediatric and adult clinical trials for recurrent SHH medulloblastoma, the SMO inhibitors vismodegib and sonidegib have been well tolerated and have demonstrated promising efficacy [5, 7]. Objective tumor responses were seen in as many as 33% of reported cases, with the responses in several patients being sustained for 4–8 months [5, 7]. Two clinical trials are currently investigating the effectiveness of vismodegib in treating this tumor subgroup [8, 9]. Children treated with SMO inhibitors should be closely monitored for premature physeal closure, as the SHH pathway plays a role in bone development [10, 11].

Subependymal Giant Cell Astrocytoma

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with an estimated prevalence of 1 in 6000 live births. In more than

85% of affected individuals, TSC is caused by mutations in the tumor suppressor genes TSC1 (hamartin) or TSC2 (tuberin). These mutations cause hyperactivation of the mammalian target of rapamycin (mTOR) signaling pathway and upregulation of mTOR complex 1, which results in abnormal cellular growth and proliferation and the development of benign tumors (hamartomas) in multiple organ systems, including the brain, kidneys, lungs, and skin. Subependymal giant cell astrocytomas (SEGAs) are slow-growing low-grade glioneuronal tumors that typically arise near the foramen of Monro and occur in up to 20% of patients with TSC. Generally, half of all patients will become symptomatic, usually in adolescence or young adulthood. Although non-malignant, SEGAs carry a clinically significant risk of morbidity and mortality, including seizures and sudden death from acute hydrocephalus, because of their progressive volume increase and lack of spontaneous regression [12]. For many years, surgical resection was the only standard therapy available. Unfortunately, not all tumors are resectable because of their location, and numerous postoperative complications have been reported, including intraventricular hemorrhage, cognitive impairment, and eventual recurrence if gross total resection is not achieved.

Targeted inhibition of the mTOR pathway has significantly improved outcomes in patients with TSC. Everolimus was the first mTOR inhibitor to be approved for treating SEGA associated with TSC, after clinical trials demonstrated a rapid, marked reduction in tumor volume (over 50% in some cases) and improved quality of life after only a few months of therapy [12]. Everolimus functions by inhibiting mTOR complex 1, thereby correcting the molecular defect responsible for TSC and tumor development. There are numerous reports of cases in which treatment with everolimus led to the resolution of tumor-associated ventricular dilation, a reduction in seizure frequency, and a decrease in tumor size in organ systems other than the brain. Treatment with sirolimus (formerly called rapamycin) has demonstrated similar results [12, 13].

Long-term follow-up of patients being treated with everolimus continues to demonstrate the sustained efficacy of mTOR inhibition with respect to SEGA tumor reduction after more than 5 years of continuous therapy; no patients receiving continuous treatment with everolimus have required surgical intervention for tumor progression [13]. However, because SEGAs do not completely resolve with therapy, continuous use of everolimus may be necessary to maintain reductions in tumor volume and prevent lesions from regrowing. The studies performed to date have shown everolimus to be safe and effective, with no limiting toxicities and no adverse effect on patient growth or maturation.

Consensus guidelines recommend targeted mTOR inhibition with everolimus as the standard of care for treating symptomatic, unresectable SEGAs in patients with TSC. In addition, everolimus is recommended as an alternative to surgery in cases of asymptomatic SEGAs that show signs of growth on serial imaging.

Gliomas

Low-grade gliomas (WHO grade 1 and grade 2 tumors) are the most common CNS tumors in children. Based on their histology, they are categorized in three major classes: astrocytic tumors, oligodendroglial tumors, and neuronal and mixed neuroglial tumors. LGGs are characterized by slow growth and are often considered a chronic disease. They commonly arise in the cerebral hemispheres or posterior fossa and are frequently cured via gross total resection. Tumors arising from midline structures (e.g., the hypothalamus, basal ganglia, and brainstem) and the optic pathway are less amenable to resection and typically require alternative treatment approaches. Some cancer predisposition syndromes, such as tuberous sclerosis and neurofibromatosis type 1, are associated with an increased frequency of LGGs [14, 15].

Although they rarely undergo malignant transformation, LGGs can cause significant morbidity, including headaches, seizures, vision loss, endocrine dysfunction, and impaired cognition. Chemotherapy is the initial approach for treating unresectable or subtotally resected tumors.

Carboplatin, vincristine, temozolomide, vinblastine, thioguanine, procarbazine, lomustine, and Avastin are among the agents most commonly used, with variable response rates being reported in the medical literature. Radiation therapy is generally reserved for individuals who experience treatment failure after chemotherapy. However, these standard therapeutic approaches are not always successful [14, 15].

Recent genomic discoveries have altered the landscape of pediatric LGG therapy by identifying key driver mutations in the mitogen-activated protein kinase (MAPK) pathway that contribute to cellular proliferation and tumorigenesis. Duplication or mutation of the *BRAF* gene is the main molecular alteration in pediatric LGGs. The *BRAF* V600E mutation and *KIAA1549:BRAF* fusion (caused by duplication of the 7q34 region) are the two *BRAF* aberrations most frequently identified and result in constitutive activation of the MAPK pathway [14–16]. The prognostic implications of these genetic alterations in pediatric LGGs have not been determined [15, 16]. Recent use of therapies that target these alterations and inhibit the MAPK pathway has demonstrated that such approaches hold considerable promise for treating LGGs, including tumors that are refractory to conventional therapy. These personalized, selective approaches to therapy offer an alternative to the "one treatment fits all" strategy [14].

Approximately 90% of pilocytic astrocytomas (mostly extracerebellar tumors) harbor the *KIAA1549:BRAF* fusion; the prevalence of this fusion in other pediatric LGGs has not been determined [15]. Inhibitors of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and activity, of which selumetinib and trametinib are two examples, have been studied in *KIAA1549:BRAF* fusion-positive LGGs in preclinical and clinical settings, and sustained responses have been demonstrated, with a reduction in tumor size exceeding 60% in some cases [17, 18].

As many as 70% of pleomorphic xanthoastrocytomas, 20% of gangliogliomas, and 10% of pilocytic astrocytomas harbor the *BRAF* V600E mutation, and other LGG subtypes have also been found to carry the mutation [16]. Dabrafenib and vemurafenib are competitive small molecules that inhibit the ATP-binding domain of mutant BRAF V600E and have shown efficacy at slowing tumor growth and inducing tumor regression in a variety of *BRAF* V600E-mutated LGGs, including numerous tumors that were refractory to conventional therapy. BRAF inhibition has been reported to induce a reduction in tumor size of up to 70%, with the responses being sustained for up to 1 year. Those patients treated by this method, including infants as young as 2 months, have experienced clinical improvements in their neurodevelopment, ambulation, and vision in cases involving hypothalamic/chiasmatic tumors [19–21]. Retreatment with vemurafenib after tumor progression has been shown to induce tumor regression, which suggests that some patients will benefit from continuous therapy [19].

Agents that target BRAF can be easily administered orally, cause minimal myelosuppression, and are often less toxic than conventional agents. However, BRAF V600E inhibitors have been reported to induce proliferation of malignant cutaneous lesions [22]. Regular comprehensive assessments by a dermatologist should be part of the routine monitoring of pediatric patients with LGGs being treated with dabrafenib or vemurafenib, especially as the duration of therapy required in these cases has yet to be determined.

The *BRAF* V600E mutation and *KIAA1549:BRAF* fusion are valuable diagnostic markers and should be considered part of the standard workup in cases of pediatric LGG, especially when the tumors are refractory to conventional therapy. Clinical trials are currently being conducted to further investigate the efficacy of BRAF-targeting therapies for pediatric LGGs.

High-grade gliomas (WHO grade 3 and grade 4 tumors) are the least common malignant brain tumors in children, but as a group they remain the most lethal and difficult to treat, with an overall survival rate of less than 10% [15]. They arise most frequently from the brain or brainstem and are typically characterized by rapid growth. Diffuse intrinsic pontine gliomas are considered an incurable pediatric cancer type and significantly decrease the overall survival rate of pediatric HGGs.

Current treatment approaches for pediatric HGGs include surgical resection followed by radiation therapy and/or chemotherapy. As with most tumor types, the extent of resection is a strong clinical prognostic factor. To date, no chemotherapeutic regimen has proven highly effective in treating this class of tumors. For this reason, clinical trials continue to investigate ways to improve survival, including through the use of novel therapies. The biologic and molecular subgrouping of these tumors is expected to alter the treatment landscape by identifying actionable driver mutations.

Although less commonly seen than in LGGs, *BRAF* V600E mutations have been detected in pediatric HGGs, including glioblastoma multiforme, anaplastic astrocytoma, anaplastic pleomorphic xanthoastrocytoma, and anaplastic ganglioglioma. Vemurafenib has been reported to induce tumor regression in a few cases of recurrent or progressive *BRAF* V600E-mutated HGG [23–25]. Most notably, vemurafenib induced complete clinical regression of a recurrent glioblastoma multiforme in a 9-year-old patient within 4 months of treatment initiation. Clinical and radiographic response has now been maintained for more than 6 months, with the patient remaining on therapy [25]. Similarly, vemurafenib induced a partial response in a 2-year-old patient with anaplastic ganglioglioma; this patient was reported to have maintained significant clinical and neurological improvement at 20 months after treatment initiation [23]. BRAF inhibition has important therapeutic potential in pediatric HGGs; it may extend survival, improve quality of life, allow for a safer surgical resection, or increase the time to radiation treatment in order to preserve neurocognitive development. Diagnostic workup for the *BRAF* V600E mutation should be considered in cases of pediatric HGG, especially when the tumors are refractory to conventional therapy.

Plexiform Neurofibroma

Neurofibromatosis type 1 (NF1) is an autosomal dominant condition that affects 1 in 3000 live births. It is the most common human cancer predisposition syndrome and is characterized by multiple clinical manifestations, including tumors of the nervous system. Plexiform neurofibromas (PNs) are benign peripheral nerve sheath tumors characterized by differentiated Schwann cells. The tumors develop in 20–50% of individuals with NF1, generally during childhood, and are often characterized by rapid growth during this period. They can grow to be quite large and cause significant morbidity, including pain, disfigurement, functional impairment, and various other neurologic complications. Because of their location and tendency to extend through multiple layers of tissues and involve multiple nerves or nerve plexuses, complete surgical resection of PNs (historically, the most effective treatment) is often not feasible [26, 27]. An additional concern is that PNs can transform into malignant peripheral nerve sheath tumors, which affect approximately 10% of individuals with NF1 [27].

The development of PNs is a consequence of mutations in the NF1 gene, a tumor suppressor gene that encodes a protein called neurofibromin. Neurofibromin is a negative regulator of RAS activity that is nonfunctional in patients with NF1. The lack of functional neurofibromin leads to dysregulated RAS, tumorigenesis, and the development of PNs [26, 27]. It has been demonstrated in preclinical mouse models that targeted MEK inhibition can induce regression of PNs by suppressing the RAS/MAPK signaling pathway [26]. These data prompted a recent phase I clinical trial of selumetinib in NF1-related PNs, in which selective inhibition of MEK 1 and MEK2 produced profound, sustained tumor regression in children. Among the 24 patients enrolled on the trial, 71% experienced a partial response (a tumor volume decrease from baseline of at least 20%), and all patients experienced some decrease in tumor volume. The median decrease in tumor volume from baseline was 31%, with the largest decrease being 47%. Nearly all patients receiving long-term selumetinib therapy have experienced a sustained reduction in tumor volume and minimal toxic effects [26].

MEK inhibition has important therapeutic potential for pediatric PNs, particularly inoperable tumors. By reducing the tumor volume, treatment

with selumetinib may improve the patient's quality of life by decreasing disfiguration and increasing motor function. Because PNs did not completely resolve with selumetinib therapy, continuous targeted MEK inhibition may be necessary to maintain the reductions in tumor volume. It is uncertain if MEK inhibition has the potential to decrease the incidence of malignant transformation of PNs.

Conclusions and Future Directions

Although the field of targeted therapy for pediatric CNS tumors is still in its infancy, it has the potential to revolutionize the care of children with primary CNS tumors by improving survival and limiting treatment-associated toxicity. The recently revised classification of CNS tumors by the WHO has enhanced our understanding of the underlying pathogenesis of pediatric brain tumors and highlighted the importance of molecular characterization in the identification, risk stratification, and treatment of CNS tumors.

Just as everolimus has become the standard of care for treating subgroups of patients in which SEGA has been diagnosed, targeted therapy based on molecular markers may become standard practice in subgroups of patients with other tumor types. Most notably, targeted therapy may play an increasingly significant role in treating patients with SHH medulloblastoma, *BRAF* V600E-mutated gliomas, *KIAA1549:BRAF* fusion-positive pilocytic astrocytoma, or plexiform neurofibroma (Table 33.1). Clinicians should actively pursue additional diagnostic testing in patients being treated for tumors that commonly harbor targetable molecular aberrations, especially when the tumors are recurrent or refractory to conventional therapy.

Laboratory-based research will continue to elucidate key driver mutations, expand our understanding of their associated molecular pathways, and lead to the use of additional targeted agents in other tumor subtypes, as well as to the development of novel agents. The challenge for clinicians and neuro-oncology consortiums will be to design the next generation of clinical trials to investigate the clinical potential of molecularly defined targeted therapies.

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