TARGETING SHH-SUBGROUP MEDULLOBLASTOMA

Mini Review

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Abstract

Medulloblastoma (MB) is the most common malignant brain tumor in children. While most patients with MB can be cured, current treatments often require broad base therapies, such as radiation and chemotherapy, which can have devastating and long-term effects. Molecular classification of MB into distinct subgroups (WNT, SONIC HEDGEHOG (SHH), Group 3, and Group 4) has provided a template with which to identify and better target these specific tumor subtypes. Aberrant activation of the HEDGEHOG (HH) pathway is implicated in a third of all MB cases, and small-molecule inhibitors have already been developed that target these tumors. Many of such inhibitors specifically target the transmembrane protein SMOOTHENED (SMO), a key rate-limiting step of the HH pathway. Although SMO inhibitors have proven successful in preclinical studies and clinical trials are still ongoing, various mechanisms of treatment resistance have emerged despite initial favorable response. In this review, we focus on the SHH-subgroup MB and discuss recent advances in its clinical management.

ABBREVIATIONS

APC: Adenomatous Polyposis Coli; ATO: Arsenic Trioxide; BCC: Basal Cell Carcinoma; BET: Bromodomain And Extra-Terminal; CSF: Cerebrospinal Fluid; FDA: Federal Drug Administration; GLI-R: GLI truncated Repressor form; HAT: Histone Acetyltransferase; HH: HEDGEHOG; IDH1: Isocitrate Dehydrogenase 1; MAPK: Ras/Mitogen-Activated Protein Kinase; MB: Medulloblastoma; PATCHED1: PTCH1; PI3K: Phosphoinositide 3-Kinase; PKA: Protein Kinase A; PTEN: Phosphatase and Tensin Homolog; SHH-MB: Sonic HEDGEHOG Medulloblastoma; SMO: SMOOTHENED; SUFU: SUPPRESSOR OF FUSED; TERT: TELOMERASE REVERSE TRANSCRIPTASE; TRPS3: TRANSFORMATION RELATED PROTEIN 53; YAP1: Yes Associated Protein 1 (YAP1)

INTRODUCTION

Medulloblastoma (MB) is the most common malignant brain tumor in children, accounting for 15-20% of all pediatric brain tumors [1]. The American Cancer Society estimates that between 250 and 500 children are diagnosed with MB each year in the United States [2]. Adult MB is much less common and accounts for only 25-30% of all MB cases [3]. MB starts in the cerebellum, the part of the brain that controls balance, coordination, and other complex motor functions, and can spread to other parts of the brain and spinal cord through the cerebrospinal fluid (CSF). These tumors are fast growing and frequently compress (or grow into) the fourth ventricle, impeding normal CSF flow and causing hydrocephalus [4]. As a result, most patients present with symptoms of increased intracranial pressure such as headaches, nausea, and vomiting. In infants and children, symptoms may also include walking and visual problems, tilted head, neck stiffness, and fontanelle bulging [5].

The exact cause of MB is unknown and most cases are sporadic; however, there are a few rare genetic syndromes that have been linked to increased risk of developing this type of cancer, such as Gorlin, Turcot, and Li-Fraumeni syndrome [6]. Most Gorlin syndrome patients harbor mutations in the tumor suppressor gene PATCHED1 (PTCH1), a key regulator of the HEDGEHOG (HH) pathway. Patients with this syndrome develop multiple basal cell skin cancers (BCC) throughout their lifetime and have an increased risk of developing MB [7,8]. Turcot syndrome patients harbor mutations in a different tumor suppressor gene called ADENOMATOUS POLYPOSIS COLI or APC. APC is an essential negative regulator in the WNT signaling pathway and mutations have been shown to increase the risk of developing colorectal cancer as well as MB [9]. Patients with Li-Fraumeni syndrome have mutations in the gene that codifies for the TRANSFORMATION RELATED PROTEIN 53 (TRPS3 or P53), which predisposes them to several different types of cancer including MB [10]. These heritable syndromes have helped to uncover some of the pathways involved in MB development and highlight the fact that not all MB tumors are driven by the same mutations and thus should not be considered as one uniform malignancy.

CURRENT TREATMENTS

In treating MB, the first step is almost always surgery, the goal being to remove as much of the tumor as possible [11].
This is especially crucial, as multiple studies have shown that survival depends on how much of the tumor is left after resection [12,13]. Surgery is usually followed by radiation to the brain and spinal cord, combined or not with chemotherapy, and followed by several months of chemotherapy [14]. The use of radiation in young children is controversial, and some physicians choose to treat the tumor in another way or restrict radiation to only one part of the brain [4,15]. The treatment regimen varies according to the risk classification of the tumor patient. Average risk patients (older than 3 years, residual tumor after resection smaller than 1.5 cm² and/or no metastasis) are treated with radiation with or without vincristine, followed by adjuvant chemotherapy including vincristine, cisplatin, cyclophosphamide and/or lomustine. For high risk patients (younger than 3 years old, with residual tumor bigger than 1.5 cm² and/or metastasis) radiation is given at higher dose and is followed by cisplatin, cyclophosphamide and vincristine chemotherapy [16,17]. While most patients with MB can be cured, the cost in terms of long-term side effects can be very high [18]. One of the most common side effects is posterior fossa or cerebellar mutism syndrome; this is a postoperative complication related to disruption of the cerebellar vermis or dentate nuclei [19]. Moreover, younger patients are especially vulnerable to radiation and may develop neurocognitive impairments, hearing loss, growth failure, endocrine abnormalities, ataracts, fertility problems and/or cerebrovascular disease as a result of exposure [20-23]. In addition, radiation and chemotherapy increase the risk of developing secondary cancers or malignancies later on [24-26]. Physicians are working towards reducing these long-term effects, either by limiting the amount of radiation, using proton beams for example [27], offering stem cell transplantation prior to radiation [17] or making use of more targeted drugs with less toxicity. However, in spite of these drawbacks, surgery followed by radiotherapy/chemotherapy remain the standard of care for MB patients [28]. As it stands, current therapies are unlikely to significantly improve MB survival rates, as recurrent disease remains common with such therapies. Recurrent MB is almost uniformly fatal, with less than a 10% chance of survival after radiation [29]. Radiation and cytotoxic chemotherapy unintentionally select for treatment resistant cells, and these escapers drive leptomeningeal dissemination of metastatic clones [30]. For this reason, metastatic tumors have much more in common with each other than to the primary tumors from which they originally came [31].

**MOLECULAR CLASSIFICATION**

In patients with MB, prognosis depends heavily on the molecular makeup of the tumor [32]. Traditionally, classification schemes were based primarily on histopathology: classic vs. desmoplastic/nodular vs. extensive nodularity vs. large-cell/anaplastic. However, over the last decade, new genomic approaches have enabled the WHO classification of MB into four molecular subgroups based on differences in their transcriptome: WNT, SHH, Group 3, and Group 4 [33,34]. In addition, these molecular subgroups seem to be better predictors of patient outcome [35]. WNT subgroup patients have the best long-term prognosis, with 90% of patients surviving past five years, while Group 3 subgroup patients, which frequently harbor MYC amplifications, have the worst prognosis. The SHH subgroup is the most common in infants and adults overall, representing a third of all MB cases [36]. More recently, genome-wide DNA methylation and gene expression analyses have further stratified MB classification, identifying 12 distinct MB subtypes that are both biologically and clinically relevant: two WNT, four SHH, three Group 3, and three Group 4 [37]. Scientists have been able to take advantage of these stratified classifications by developing subgroup specific small-molecule inhibitors, with those targeting the HH pathway among some of the most advanced.

**SHH-SUBGROUP MB**

SHH-subgroup MB (SHH-MB) was named after the signaling pathway thought to drive tumor formation in that particular subgroup: the HH signaling pathway. HH proteins are powerful signaling molecules that act as morphogens, mitogens, and survival factors depending on the context. In vertebrates, there are three HH ligands: SONIC, DESERT, and INDIAN HEDGEHO [38]. These are synthesized as precursor proteins and then doubly lipid-modified before being secreted from the cell [39]. SHH signaling in vertebrates (Figure 1) depends on the primary cilium, an antenna-like organelle that extends from the surface of almost every cell type [40]. The primary cilium functions as a focal point for enrichment of SHH signal transduction, with various signaling components trafficking through the primary cilium in a microtubule dependent manner [39]. HH signaling begins when a HH ligand binds to the transmembrane receptor PTCH1 at the base of the primary cilium. This binding releases PTCH1-mediated inhibition of SMO, a G-protein-coupled transmembrane protein [41]. Once activated, SMO is trafficked to the tip of the cilium and binds to SUPPRESSOR OF FUSED (SUFU), relieving its repression of the GLI family of transcription factors. Activated GLI can then translocate to the nucleus and promote expression of downstream targets, such as GLI1, PTCH1, CCND1, and MYCN [42]. In the absence of HH ligand, PTCH1 prevents SMO from moving into the cilium, and SUFU targets GLI for proteosomal cleavage. This leads to the conversion of full-length GLI proteins into truncated repressors, GLI-R. GLI-R can then enter the nucleus and inhibit transcription of HH target genes [43-45].

During normal cerebellar development, SHH signaling stimulates the division of cells in the outermost layer of the cerebellum, also known as the external granular layer, and ultimately dictates the size and pattern of the organ [46,47]. In SHH-MB, this pathway is permanently turned on and the cells keep growing and dividing, SHH-driven tumors frequently possess mutations or amplifications in PTCH1, SMO, SUFU, and/or GLI2, all key regulators of the HH pathway. Further, SHH-MB can be further classified into three subtypes based on age group: infant (0-3 years), childhood (3-16 years), and adult (>16 years). PTCH1 mutations are found in more or less equal frequencies across all age groups. In contrast, SUFU mutations are found predominantly in infants; SMO mutations are found predominantly in adults [48]; and TRPS3 mutations, a poor prognostic indicator [49], are found more frequently in children [48]. Next generation sequencing studies of larger cohorts have also revealed the existence of certain genetic events specific to the SHH subgroup that go beyond the canonical HH pathway, some of which include ISOCITRATE DEHYDROGENASE 1 (IDH1) mutations, somatic alterations that affect histone acetyltransferase...
(HAT) complexes [50], PHOSPHATASE AND TENSIN HOMOLOG (PTEN) loss, TELOMERASE REVERSE TRANSCRIPTASE (TERT) promoter mutations, and/or YES ASSOCIATED PROTEIN 1 (YAP1) amplifications [37]. These findings suggest that in order for SHH-MB treatments to be effective they should target the SHH pathway in a manner consistent with the genetics behind each tumor.

TARGETED THERAPIES

The first identified inhibitor of HH signaling was Cyclopamine, a naturally occurring chemical that was discovered after causing birth defects in sheep [51]. Although it failed to translate clinically, Cyclopamine sparked the idea of using HH pathway inhibitors in cancer. Today, numerous HH inhibitors have been developed and many are undergoing clinical trials for a broad spectrum of HH-driven tumors (Table 1). The majority of these inhibitors target SMO, a key rate-limiting component of the HH pathway, and a few have also been evaluated in MB clinical trials, such as Vismodegib (GDC-0449) and Sonidegib (LDE-225) [52] (Table 2). Of these, Vismodegib became the first to receive FDA approval for advanced basal BCC patients [53], and clinical trials are already underway for other HH-driven malignancies, including several phase I and II trials for SHH-MB patients.

Vismodegib has garnered a lot of excitement as the first SMO antagonist to receive FDA approval, and while there have been favorable responses recorded; these are usually only transient, with tumor regrowth and metastasis commonly observed [52]. In a pioneering case study, treatment with Vismodegib in an adult patient with metastatic SHH-MB resulted in rapid tumor regression, decreased reported pain, and notable weight gain [54]. However, despite this promising response, the patient quickly relapsed after just three months of treatment. Further analysis of the tumor specimen before and after treatment revealed that it had acquired a secondary mutation in SMO that likely drove treatment resistance [55]. Since this study, a variety of other HH inhibitors have been investigated in the clinic, but SMO antagonists remain the most popular mode of intervention.

In a related study, Vismodegib showed efficacy against adult recurrent SHH-MB with longer progression-free survival when compared with non-SHH-MB patients. However, among those with SHH-MB, prolonged disease stabilization occurred in only 41% of patient cases [56,57]. Interestingly, a recent genomic profiling study of SHH-MB patients identified mutations in SUFU, GLI2, and MYCN as drivers of primary resistance to SMO inhibitors [48]. Furthermore, genomic analyses of relapsed BCC tumors also showed that resistance to Vismodegib is associated with HH pathway reactivation via mutations in SMO that prevent drug binding and/or SUFU or GLI2 amplifications [58].

Primary and acquired resistance to Vismodegib stress the need for novel targeted therapies. In turn, a number of molecules that target the HH pathway at distinct sites are currently being evaluated. Itraconazole and Saridegib (IPI-926) have shown great promise in pre-clinical MB models [59,60], including those resistant to Vismodegib [61], by binding to a different pocket on SMO. In addition, these compounds have already been assayed in clinical trials for BCC, prostate cancer, and advanced pancreatic adenoma among others [62]. The use of inhibitors that target the GLI family of transcription factors have also shown potential [63,64]. In particular, arsenic trioxide (ATO) has exhibited efficacy.
Table 1: 2017 clinical trials running for SHH inhibitors. Status as of April 2017.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target Type of Malignancy</th>
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<tbody>
<tr>
<td>Vismodegib (GDC-0449)</td>
<td>SMO</td>
</tr>
<tr>
<td>Sonidegib (LDE-225)</td>
<td>SMO</td>
</tr>
<tr>
<td>BMS-839323 (XL139)</td>
<td>SMO</td>
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<tr>
<td>Glasdegib (PF-0449913)</td>
<td>SMO</td>
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<tr>
<td>Saridegib (IPI-926)</td>
<td>SMO</td>
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<tr>
<td>Taladegib (LY2940680)</td>
<td>SMO</td>
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<tr>
<td>Arsenic Trioxide (ATO)</td>
<td>GLI</td>
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<tr>
<td>I-BET762 (GSK 525762A)</td>
<td>GLI/MYC</td>
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<tr>
<th>Compound</th>
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- **Vismodegib (GDC-0449)**: Metastatic Gastric & Esophageal Cancer, Small-Cell Lung Cancer, Acute Myeloid Leukemia, Castration-Resistant Prostate Cancer, Myelofibrosis, Chondrosarcoma, Advanced Pancreatic Cancer, Metastatic Gastric & Esophageal Cancer, Small-Cell Lung Cancer, Acute Myeloid Leukemia.
- **Sonidegib (LDE-225)**: Recurrent and Relapsed Medulloblastoma, Prostate Cancer, Castration-Resistant Prostate Cancer, Pancreatic Adenocarcinoma, Advanced Pancreatic Cancer, Refractory Multiple Myeloma, Recurrent Ovarian Cancer, Triple-Negative Breast Cancer.
- **BMS-839323 (XL139)**: Basal Cell Nevus Syndrome, Small Cell Lung Cancer, Esophageal Neoplasms, Stomach Neoplasms.
- **Glasdegib (PF-0449913)**: Myelodysplastic Syndrome, Acute Myeloid Leukemia, Primary Myelofibrosis, Myelodysplastic Syndrome, Acute Lymphoblastic Leukemia, Chronic Myelomonocytic Leukemia.
- **Saridegib (IPI-926)**: Primary Myelofibrosis, Basal Cell Carcinoma/Chondrosarcoma, Metastatic Pancreatic Cancer, Recurrent Head and Neck Cancer, Conventional Chondrosarcoma.
- **Taladegib (LY2940680)**: Esophageal Cancer, Advanced or Metastatic Solid Tumors.
- **I-BET762 (GSK 525762A)**: Relapsed, Refractory Hematologic Malignancies, Estrogen Receptor Positive Breast Cancer, NUT Midline Carcinoma.

**Abbreviations:** SMO: SMOOTHENED
Table 2: 2017 clinical trials running for medulloblastoma patients. Status as of April 2017.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Phase</th>
<th>Participant Population</th>
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<tbody>
<tr>
<td>Vismodegib (GDC-0449)</td>
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<td>I/II</td>
<td>Adult patients with recurrent, progressive, or refractory MB (NCT01601184)</td>
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<td>II</td>
<td>Children with newly diagnosed MB (NCT01878617)</td>
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<td></td>
<td></td>
<td>II</td>
<td>Adult patients with recurrent or refractory MB (NCT00939484)</td>
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<td>I</td>
<td>Children with recurrent or refractory MB (NCT01239316)</td>
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<td>Children with recurrent or refractory MB (NCT00822458)</td>
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<td>I</td>
<td>Patients with locally advanced or metastatic solid tumors (NCT00607724)</td>
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<tr>
<td>Sonidegib (LDE-225)</td>
<td>SMO</td>
<td>II</td>
<td>Patients with HH-pathway activated relapsed MB (NCT01708174)</td>
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<td>I/II</td>
<td>Children with recurrent or refractory MB, or other tumors potentially dependent on HH signaling pathway (NCT01125800)</td>
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<td>I</td>
<td>East Asian with advanced solid tumors (NCT1208831)</td>
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<td></td>
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<td>I</td>
<td>Patients with advanced solid tumors (NCT00880308)</td>
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Abbreviations: HH: HEDGEHOG; MB: medulloblastoma; SMO: SMOOTHENED

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REFERENCES


Cite this article