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REVIEW ARTICLE

Medulloblastoma: Current Standard of Care and Future Treatment Opportunities

Lisa Mayr[1,2,3] · Amedeo A. Azizi[1,2,3] · Johannes Gojo[1,2,3] · Andreas Peyrl[1,2,3]

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Abstract

Medulloblastoma, the most common malignant brain tumor of childhood, is an aggressive embryonal tumor that arises from the posterior fossa. On the molecular level, four clinically relevant subgroups have been established, which have already been integrated into routine diagnostic procedures and treatment stratification. The initial step in treating medulloblastoma typically involves maximal safe surgical resection, followed by craniospinal irradiation in most patients (except very young children) and chemotherapy. Efforts to improve cure rates and reduce long-term detrimental effects led to the reduction in radiotherapy and adaptation of chemotherapy. Gradually, over the past decades, these strategies have resulted in significant improvements in treatment outcomes. However, patients with a medulloblastoma recurrence still fare badly, especially those children who already had radiotherapy as part of their initial treatment. Whereas there is no universal treatment strategy at relapse and the outcome remains poor, recently, the administration of anti-angiogenic metronomic therapy led to sustained long-term survival in a quarter of patients. Nonetheless, there remains an unmet need to improve survival and mitigate therapy-induced morbidity by developing new treatment strategies. Promising new approaches include targeting the Sonic Hedgehog pathway, addressing transcriptional and epigenetic drivers, improving drug delivery, and overcoming treatment resistance. Although the most common malignant brain tumor of childhood, the number of novel approaches in addition to a molecularly subdivided entity renders it difficult to form large clinical trials.

Key Points

Medulloblastoma is the most common malignant brain tumor of childhood.

The initial step of treatment typically involves maximal safe surgical resection, followed by radiotherapy (in children who are old enough) and chemotherapy.

Over the past decades, diagnosis and therapy of medulloblastoma have steadily improved, resulting in better treatment outcomes.

1 Introduction

Medulloblastoma is an aggressive embryonal tumor that arises from the posterior fossa (Fig. 1). The standard-of-care treatment includes maximal safe resection, craniospinal irradiation (CSI), and systemic chemotherapy. Very young children less than 3 years of age, who cannot safely receive craniospinal radiation, are treated instead with conventional chemotherapy, augmented with intraventricular chemotherapy, or high-dose chemotherapy followed by autologous stem cell transplantation. Despite the advances in multimodal therapy, the treatment of high-risk medulloblastoma remains challenging, especially in the setting of recurrence. We review the current state of medulloblastoma diagnosis and therapy, with a focus on new evolving therapeutic approaches.

✉ Andreas Peyrl
andreas.peyrl@meduniwien.ac.at

[1] Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

[2] Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna, Austria

[3] Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

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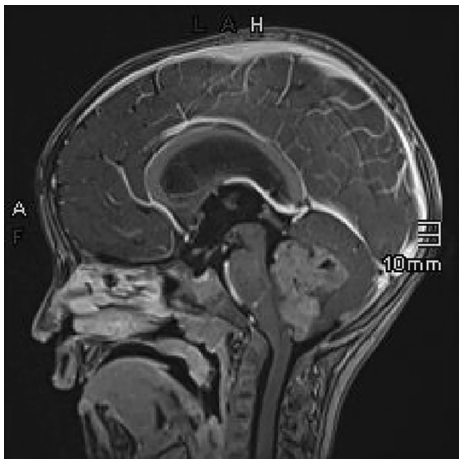

Fig. 1 Magnetic resonance imaging of the initial tumor in a patient with medulloblastoma (courtesy of the authors)

2 Epidemiology

Medulloblastoma is the most common malignant brain tumor of childhood and rarely occurs in adulthood. In children and adolescents, the annual incidence rate of all primary brain and other central nervous system (CNS) tumors is 6.02 per 100,000 population. Medulloblastomas account for 6.3% of all CNS tumors in individuals aged 0–19 years [1].

3 Early Clinical and Radiographic Diagnosis

Medulloblastoma was first recognized as a distinct entity by Cushing and Bailey in 1925, who described a series of densely cellular brain tumors of the posterior fossa [2]. Early diagnosis relied entirely on clinical features. Later, indirect methods such as pneumoencephalography were used to diagnose brain tumors. The introduction of computed tomography revolutionized brain tumor diagnosis in the 1970s, and magnetic resonance imaging quickly became the gold standard of care from the 1980s onward [3].

Most patients with medulloblastoma present with headache, nausea, vomiting, and ataxia. The symptoms are attributed to the localization in the posterior fossa on the one hand, and reflect increased intracranial pressure on the other hand. The first step in the diagnostic process is imaging of the brain. Current standard of care is magnetic resonance imaging of the entire CNS compartment, brain and spine, which is sensitive for the detection of solid metastases and leptomeningeal dissemination.

4 Histopathological Classification Evolution

Definitive diagnosis has always required histology. Early on, medulloblastomas were simply categorized as a type of primitive neuroepithelial cerebellar tumor (PNET). Developments in neuropathology led to the recognition of histological variants. Four classic morphological patterns were defined: (1) classic; (2) desmoplastic/nodular; (3) medulloblastoma with extensive nodularity; and (4) large cell/anaplastic; [4].

In the 21st century, genomic studies revolutionized medulloblastoma diagnosis. There has been a long controversy, whether medulloblastoma is a PNET localized in the cerebellum, or if it was an identity on its own. Using DNA microarray gene expression data in the early 2000s, it could be proved that medulloblastoma can be clearly distinguished from supratentorial PNETs [5]. Later on, the term PNET was even removed from the World Health Organization classification, because on the molecular level, it could be demonstrated that this term encompasses a variety of different tumor entities [6, 7].

Four clinically relevant molecular subgroups, WNT, Sonic hedgehog (SHH), Group 3, and Group 4, have been established. WNT tumors harbor *CTNNB1* (β-catenin) mutations and have a favorable prognosis. SHH tumors involve mutations in SHH pathway genes (*PTCH1, SUFU, SMO*) and *TP53* in some cases, and have a bimodal occurrence in infants and adults. Group 3 (often *MYC* amplified) affects infants and young children, with the worst overall survival, while Group 4 has an intermediate prognosis [8]. The four subgroups have recently been differentiated into further subtypes [9, 10].

The latest World Health Organization classification has incorporated these diagnostic developments. Medulloblastomas remain under one umbrella, but now have subgroup distinctions, integrating imaging, morphology, and molecular data into a unified diagnosis [11].

These four molecular subgroups have already been integrated into routine diagnostic procedures. To date, further subtyping has not led to the development of more effective targeted treatments.

5 Treatment

Maximal safe resection is a cornerstone of medulloblastoma management, serving key roles in diagnosis, relieving intracranial pressure, and local tumor control. Advances in surgical techniques, particularly the use of intraoperative imaging and neuromonitoring, have significantly improved the likelihood of achieving a gross

total resection while minimizing the risk to neurological function [12].

In the early days, medulloblastomas were seen as having a consistently unfavorable prognosis [13]. In a series in England published in 1953, some patients could be cured by adequate irradiation of the entire brain and cord. This principle is based on postmortem findings from untreated medulloblastoma cases, which almost universally revealed tumor deposits throughout the brain and spinal cord, which have seeded from the primary cerebellar tumor [14].

In a larger series in Toronto, published in 1969, complete CSI led to durable 5-year survival in a subset of children [15]. These early data established surgery plus high-dose CSI of 36 Gy with posterior fossa boosts of 50–54 Gy as the backbone of curative therapy.

Although staging was established universally according to Chang et al. [16], clinical studies are somewhat difficult to compare regarding residual tumors, age, histological variants, and metastases, which differ from study to study. Efforts to improve cure rates and reduce long-term side effects led to the reduction in radiotherapy and the addition of chemotherapy. Gradually, over the past decades, these strategies have resulted in significant improvements in treatment outcomes.

In the beginning of these efforts with large multicenter studies, a reduction in radiotherapy to a dose of 23.4 Gy neuroaxis irradiation compared with the standard dose of 36 Gy without additional chemotherapy was associated with an increased risk of recurrence [17]. Likewise, chemotherapy did not prove to be beneficial early on. In a randomized trial, adjuvant chemotherapy with vincristine, CCNU, and prednisone did not benefit patients with low-stage medulloblastoma compared with patients receiving radiotherapy only [18]. Similar results were revealed with a randomized trial comparing CSI only with CSI and adjuvant chemotherapy with vincristine and CCNU [19].

Another study to improve the outcome with chemotherapy was comparing vincristine, CCNU and prednisone (VCP) plus radiotherapy with an "eight-drugs-in-one-day" (8-in-1; vincristine, methylprednisolone, CCNU, hydroxyurea, procarbazine, cisplatin, cyclophosphamide, and cytarabine) and radiotherapy. VCP was the superior combination compared with 8-in-1 chemotherapy, maybe in part because in the 8-in-1 arm radiotherapy was delayed [20]. The addition of cisplatin to CCNU and vincristine and standard radiation therapy with 36 Gy CSI led to improved cure rates and proved that chemotherapy plays an important role in children with medulloblastoma [21].

Comparing maintenance chemotherapy after initial radiotherapy with cisplatin, CCNU and vincristine to neoadjuvant chemotherapy (cyclophosphamide, vincristine, methotrexate, etopside, carboplatin), maintenance chemotherapy was more effective in low-risk medulloblastoma. Moreover, neoadjuvant chemotherapy increased the myelotoxicity associated with subsequent radiotherapy, leading to more frequent treatment interruptions and prolonged overall treatment duration. Delayed and/or protracted radiotherapy was found to have a negative impact on the outcome [22].

A landmark study that long defined the standard of care for children with non-disseminated medulloblastoma demonstrated that treatment with reduced-dose CSI (23.4 Gy), followed by a 30 Gy boost to the posterior fossa and adjuvant chemotherapy with CCNU, cisplatin, and vincristine, resulted in a 5-year progression-free survival rate of 80% [23].

The immature brain has a high sensitivity to radiotherapy-induced cognitive deficits [24–26], which can increase for years after radiotherapy [27, 28]. These findings have set age limitations on the use of radiotherapy, and especially CSI in children. To avoid the devastating effects of irradiation of the neuroaxis in very young children, a study investigated intensive postoperative chemotherapy alone in children under 3 years of age. After surgery, children received intravenous chemotherapy (cyclophosphamide, vincristine, methotrexate, carboplatin, and etoposide), augmented with intraventricular methotrexate. This approach revealed encouraging survival rates, proving that postoperative chemotherapy alone is a promising treatment for medulloblastoma in young children, although those patients with visible metastases in magnetic resonance imaging seldom survive [29]. Recently, the addition of high-dose methotrexate to intensive chemotherapy including high-dose consolidation chemotherapy with hematopoietic stem-cell infusion led to significant improvements especially in group 3 medulloblastoma [30]. Another important finding using molecular stratification in high-risk medulloblastoma was that in group 3 medulloblastoma the addition of carboplatin led to significant improvement in survival [31].

Craniospinal irradiation is associated with a significant cognitive risk in all patients treated for pediatric medulloblastoma [24]. In recent decades, there was the attempt to modulate radiotherapy on the technical side to decrease the often devastating late effects.

Hyperfractionated radiotherapy divides the total dose of radiation into small doses and treatment fractions are given more than once a day. Hyperfractionated radiotherapy potentially permits a dose escalation to improve local tumor control, thereby increasing the biologic effective dose to the neuroaxis, without a concomitant increase of the biologically effective dose to the normal CNS. This strategy was applied in a European randomized controlled trial. Unfortunately, hyperfractionated radiotherapy was not superior to standard radiotherapy regarding survival, and overall cognitive ability was not significantly different in standard risk medulloblastoma [32, 33]. The situation is not so clear-cut in metastatic medulloblastoma. Intensive chemotherapy

including intraventricular chemotherapy before hyperfractionated radiotherapy and intensified maintenance therapy thereafter in metastatic medulloblastoma conferred overall favorable survival in this difficult-to-treat group of children [34]. The Milano strategy with a hyperfractionated accelerated radiotherapy regimen after surgery in high-risk medulloblastoma with intensive chemotherapy achieved improved survival that exceeded previously reported outcomes in all high-risk categories [35].

Proton beam therapy is a type of radiotherapy that uses a beam of high-energy protons, particles found in the nuclei of atoms, rather than high-energy electromagnetic rays (called "photons"). Proton radiotherapy is an advanced treatment option compared with conventional photon radiotherapy, delivering much lower doses of radiation to healthy tissues surrounding the tumor. After proton radiotherapy entered the field, its use and importance continue to grow steadily around the world. This led to a worldwide exponential increase in the number of centers using proton radiotherapy [36]. To achieve the same target clinical dose, proton radiotherapy deposits a smaller dose to healthy tissue compared with photon radiotherapy [37]. Even in the context of CSI, patients treated with proton radiotherapy experienced significantly better long-term outcomes in global intelligence quotient, perceptual reasoning, and working memory compared with patients treated with photon radiotherapy [38].

5.1 Trials with Discouraging Results

Not all trials had the expected and desired outcome in being less toxic while improving or at least maintaining the cure rates. Nonetheless, these trials, although disappointing, helped to move the field forward.

A pilot study aimed to treat children with WNT-activated medulloblastoma omitting radiotherapy completely and using surgery followed by chemotherapy alone. Unfortunately, the first enrolled children experienced early relapses, with both local and leptomeningeal recurrences. Because of these early relapses, the study had to be closed for safety concerns. A major takeaway is that radiotherapy is required to effectively treat children with WNT-altered medulloblastoma [39]. As a result, subsequent trials with WNT-altered medulloblastoma focused on reducing radiation doses rather than eliminating radiotherapy completely. Results of a COG study (NCT02724579) and a SIOP study (NCT02066220) are pending.

A prospective phase II study in children less than 4 years of age with non-metastatic nodular desmoplastic or medulloblastoma with extensive nodularity examined omitting intraventricular methotrexate from its chemotherapy backbone. The omission of intraventricular methotrexate resulted in unacceptably high relapse rates in this infant SHH-driven subgroup. The study had to close early as well, confirming that in the case of conventional chemotherapy, serial intraventricular chemotherapy is required for adequate disease control in children who are too young to receive CSI [40].

In average-risk medulloblastoma, a trial tested reducing the boost volume (posterior fossa vs involved-field tumor bed) and reducing the CSI dose (23.4 Gy vs 18 Gy) in younger children. Involved-field radiotherapy was non-inferior to whole posterior fossa radiotherapy. However, reducing CSI to 18 Gy significantly worsened the outcome and showed that CSI should not be lowered below 23.4 Gy in unselected average-risk patients, proving the importance of molecular stratification [41]. A list of trials with encouraging results and discouraging results can be found in Table 1 of the Electronic Supplementary Material.

5.2 Recruiting Trials for Initial Treatment of Medulloblastoma

Currently, there is a small number of actively recruiting trials for the initial treatment of medulloblastoma in children. NCT04474964 is investigating low-dose CSI followed by adjuvant chemotherapy in WNT medulloblastoma. NCT05535166 explores the use of molecular and clinical risk-adapted therapy in young children with newly diagnosed patients, testing the use of HD-MTX chemotherapy only in very young children with SHH-2 medulloblastoma and in infants with group 3 and group 4 medulloblastoma, treating with systemic chemotherapy and delayed risk-adapted CSI augmented with carboplatin. Additionally, there will be a comparison in infants and young children treated with systemic chemotherapy only to patients treated with systemic chemotherapy and intra-ventricular chemotherapy, or delayed risk-adapted irradiation.

Taken together, treatment of pediatric medulloblastoma has evolved from surgery and radiotherapy alone to highly stratified, multi-modal regimens. Contemporary therapy is risk-adapted, incorporating both clinical stage and molecular subgroup, to maximize cure while limiting late effects. Current trials continue to refine CSI dosing and chemotherapy, especially for WNT and SHH subtypes, novel targeted and immune-based therapies are being tested to improve outcomes in high-risk groups.

6 Recurrent Pediatric Medulloblastoma

While at initial tumor diagnosis multi-modal therapy proved to be highly effective in the majority of patients with medulloblastoma, approximately 30% of patients experience disease relapse, which is often metastatic at the time of recurrence (Fig. 2). Most patients with recurrence

Table 1 Ongoing trials of emerging therapies in medulloblastoma

Agent	Trial number	Title
CX 4945	NCT03904862	Testing the Safety and Tolerability of CX-4945 in Patients With Recurrent Medulloblastoma Who May or May Not Have Surgery
Difluoromethylornithine	NCT04696029	DFMO as Maintenance Therapy for Molecular High/Very High Risk and Relapsed Medulloblastoma
CDK4/6 inhibitor	NCT06959979	Novel Molecular Targets and Innovative Therapeutic Perspective in Medulloblastoma
Digoxin	NCT06701812	Digoxin Medulloblastoma Study
Apatinib	NCT04501718	Apatinib Combined with Temozolomide and Etoposide Capsules in the Treatment of Recurrent Medulloblastoma in Children
PLX038	NCT06161519	PLX038 in Primary Central Nervous System Tumors Containing MYC or MYCN Amplifications
TTRNA-DC vaccines; TTRNA-xALT; Td vaccine; pembrolizumab	NCT06514898	Adoptive T Cell Therapy, DC Vaccines, and Hematopoietic Stem Cells Combined With Immune checkPOINT Blockade in Patients With Medulloblastoma
Nivolumab	NCT06466798	Fourth Ventricular Administration of Immune Checkpoint Inhibitor (Nivolumab) and Methotrexate or 5-Azacytidine for Recurrent Medulloblastoma, Ependymoma, and Other CNS Malignancies
PEP-CMV; tetanus diphtheria vaccine	NCT05096481	PEP-CMV Vaccine Targeting CMV Antigen to Treat Newly Diagnosed Pediatric HGG and DIPG and Recurrent Medulloblastoma
BIOLOGICAL: IL13Ralpha2- CAR T cells	NCT04661384	Brain Tumor-Specific Immune Cells (IL13Ralpha2-CAR T Cells) for the Treatment of Leptomeningeal Glioblastoma, Ependymoma, or Medulloblastoma
Atovaquone	NCT06624371	Atovaquone Combined With Radiation in Children With Malignant Brain Tumors
Olaparib; 177Lu-DOTATATE	NCT06607692	Study in Children and Adolescents of 177Lu-DOTATATE (Lutathera®) Combined with the PARP Inhibitor Olaparib for the Treatment of Recurrent or Relapsed Solid Tumours Expressing Somatostatin Receptor (SSTR) (LuPARPed)
Multi-tumor antigen specific cytotoxic T lymphocytes	NCT06193759	Immunotherapy for Malignant Pediatric Brain Tumors Employing Adoptive Cellular Therapy (IMPACT)
iC9-GD2-CAR T cells	NCT05298995	GD2-CAR T Cells for Pediatric Brain Tumours
B7-H3-CAR T cells	NCT05835687	Loc3CAR: Locoregional Delivery of B7-H3-CAR T Cells for Pediatric Patients With Primary CNS Tumors
G207	NCT03911388	HSV G207 in Children With Recurrent or Refractory Cerebellar Brain Tumors

CAR chimeric antigen receptor

of their medulloblastoma will eventually succumb to their disease, especially those children who had previously undergone radiotherapy as part of their initial treatment strategy [42–48].

Historically, a standard salvage regimen was lacking, and treatment has relied on individualized combinations of surgery, radiotherapy, and chemotherapy. Multiple studies have shown that resection at relapse is associated with longer survival, especially for isolated local recurrences, albeit with limited long-term success [45, 48–50].

Over the decades, many cytotoxic regimens have been tried in relapsed medulloblastoma. None proved uniformly effective. Objective responses were typically transient, and 2-year survival remained below 25% [43, 44]. High-dose chemotherapy represents the most aggressive form of chemotherapy, adopted from other pediatric solid tumor protocols into the setting of relapsed medulloblastoma. High-dose chemotherapy was not generally successful in previously pre-irradiated patients, with only a small number of patients from these highly selected cohorts remaining alive [51–53].

Historically, clinicians were reluctant to re-irradiate patients with medulloblastoma because of the high risk of cumulative neurotoxicity, including brain necrosis. Presently, re-irradiation remains challenging, but might be an important salvage tool with disease control in a subset of patients [54, 55].

In children who were too young to be irradiated at diagnosis, a substantial proportion of these CSI-naive children with relapsed medulloblastoma were salvageable with subsequent CSI-based regimens [56]. A multicenter retrospective analysis evaluated outcomes in children with relapsed early-childhood SHH-subgroup medulloblastoma who had not

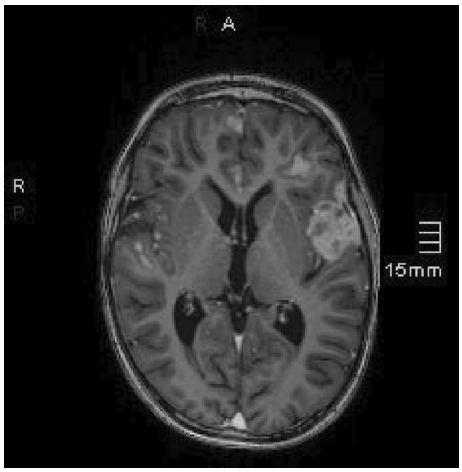

Fig. 2 Magnetic resonance imaging of a disseminated medulloblastoma at recurrence (courtesy of the authors)

received initial CSI, focusing on different salvage treatment approaches. Overall outcomes were poor, however, patients treated with combined chemo-radiotherapy demonstrated the longest post-relapse survival [57].

A commonly employed treatment approach for recurrent medulloblastoma is the combination of temozolomide and irinotecan (TEMIRI) [58], which was additionally augmented with bevacizumab [59]. These treatments were generally well tolerated and demonstrated an acceptable response rate, but did not result in prolonged responses in previously irradiated patients.

The MEMMAT trial, an anti-angiogenic metronomic regimen, incorporated intravenous bevacizumab together with oral agents (thalidomide, fenofibrate, celecoxib, etoposide, cyclophosphamide), intravenous bevacizumab, and intraventricular chemotherapy (etoposide, cytarabine). This outpatient regimen produced a 45% response rate and disease control in 57.5% of patients with previously irradiated medulloblastoma. Moreover, a quarter of the patients had sustained long-term survival [60].

7 Neuropsychology and Late Effects

Childhood medulloblastoma survivors are at risk for cognitive and academic declines, unemployment, and impaired fertility [61–64]. The standard of care for survivors of childhood cancer is defined in the *"Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers"* [65].

Children treated for medulloblastoma often show a reduced capacity to acquire new information and skills compared with their peers. Declines in academic performance and overall intellectual functioning have long been recognized as significant consequences of the disease and its treatment. More recent studies have further highlighted deficits in critical cognitive domains, with particular susceptibility to impairments in processing speed [66]. The dose of CSI was strongly associated with neurocognitive outcomes, but also the tumor itself and the surgical resection lead to low psychomotor abilities and decreased processing speed [67]. Hearing loss may develop in patients receiving CSI and the platinum-based agent cisplatin owing to its ototoxic effects, with children being particularly susceptible [68].

Posterior fossa syndrome, a complication associated with surgery in the posterior fossa region, affects up to 29% of patients with medulloblastoma. Posterior fossa syndrome presents variably but is typically characterized by reduced speech or mutism, and commonly occurs alongside ataxia, hypotonia, emotional lability, and other neurocognitive impairments. Patients who experience posterior fossa syndrome experience more severe neurocognitive deficits with minimal improvement over time [69].

8 Future Perspectives

8.1 Liquid Biopsy

Currently, physicians primarily depend on tumor biopsies to determine the neuropathological classification and detect the potential presence of a specific druggable (genetic) alteration. A liquid biopsy has the advantage of being less invasive, rapidly accessible, and can be performed sequentially when compared to standard tissue biopsies. The possibility of serial sampling of cerebrospinal fluid (CSF) and blood enables real-time monitoring of the treatment response, allowing earlier intervention and a more dynamic treatment management [70, 71].

The field is only at the beginning and rapidly evolving. Initial experience has already been gained in some areas. A longitudinal analysis of serial CSF-derived cell-free DNA revealed that a minimal residual disease assessment is a useful method of predicting disease relapse in medulloblastoma [72]. Droplet digital polymerase chain reaction has demonstrated high sensitivity and specificity for detecting MYC amplification in the CSF of patients with medulloblastoma [73]. Low-pass whole genome sequencing of CSF-derived cell-free DNA has proven to be feasible, with a higher sensitivity for detecting tumors than a conventional CSF cytologic analysis [74]. In the near future, a liquid biopsy will help us with minimal invasive techniques not only to correctly diagnose a medulloblastoma and its subtype, but also to predict the survival probability, monitor the treatment, and detect early signs of recurrence within the routine workflow.

8.2 Emerging Therapies

Nonetheless, there remains a great need to improve survival and mitigate therapy-induced morbidity by developing novel treatment approaches. The core principle of precision medicine is to tailor therapy based on predictors of response or resistance to specific molecularly targeted treatments. Advancements in the understanding of medulloblastoma biology raises the hope for the development of more selective, effective, and less toxic therapeutic agents. However, significant challenges remain. Many of the molecular alterations in medulloblastoma are difficult to therapeutically target, and conducting clinical trials that use pathway-specific biomarkers for patient selection is particularly difficult in the context of a rare disease. A list of ongoing clinical trials of emerging therapies in medulloblastoma is provided in Table 1.

We consider new and potential approaches, beginning with the SHH pathway, then move to transcriptional and epigenetic drivers, enhancing drug delivery and overcoming resistance, early-phase pediatric combination trials, and finish with novel immunotherapy studies.

8.3 Hedgehog (SHH) Pathway-Directed Strategies

The tumor molecular subgroup currently has the ability to guide some salvage decisions. For example, SHH medulloblastomas harbor mutations in the SHH pathway. Smoothened (SMO) is a critical component of the SHH pathway, regulating the suppressor of fused. SMO inhibitors prevent suppressor of fused activation, thereby blocking the nuclear translocation of GLI transcription factor proteins [75].

Vismodegib is a ligand-specific, brain-penetrant inhibitor of SMO. Even though SHH tumors are sensitive to this drug, no long-lasting responses have yet been described with vismodegib as a single agent, both in adult and pediatric medulloblastoma [76–78].

Two strategies for further development of inhibition of the SHH pathway are realized. Discovery of a drug that can synergize with vismodegib to improve its resistance in patients and enhance its efficacy, and targeting the SHH pathway further downstream.

The incorporation of SMO inhibitors into rational drug combinations designed to prevent resistance was further evaluated. In a clinical study, the addition of temozolomide to vismodegib did not cause significant additional toxicity, but failed to extend the duration of responses of vismodegib in patients with SHH-activated recurrent medulloblastoma [79].

EZH2 (Enhancer of Zeste Homolog 2) primarily trimethylates histone H3 on lysine 27 (H3K27me3), a key epigenetic mark associated with gene silencing. In medulloblastoma cells and orthotopic SHH models, the combined use of an EZH2 inhibitor and vismodegib demonstrated a remarkable synergistic effect in suppressing medulloblastoma growth. The dual blockade more effectively suppresses GLI transcriptional activity, presenting a promising treatment option for medulloblastoma [80].

Cancers driven by mutations downstream in the SHH pathway do not respond to SMO inhibition, and thus there is a strong need for the identification of compounds that act downstream of SMO, thereby overcoming resistance. A series of benzoindolone derivatives that inhibit GLI-mediated transcription downstream of SMO blocked SHH pathway readouts in cultured medulloblastoma cells resistant to SMO inhibitors. This epigenetic targeting of the SHH pathway through modulation of BET bromodomains might serve as an attractive strategy towards combating SHH pathway-driven cancers [81].

OLIG2-expressing tumor stem cells have been identified as drivers of recurrence in SHH medulloblastoma [82]. CT-179, a small-molecule OLIG2 inhibitor, targets SHH-medulloblastoma stem-like cells that drive recurrence. The brain-penetrant orally bioavailable OLIG2 inhibitor CT-179 combined efficiently with the CDK4/6 inhibitor palbociclib, and in combination with radiotherapy significantly slowed medulloblastoma progression in mouse models and organoids [83].

Using an unbiased high-throughput screen with a library of 172 compounds with known targets, the ribosomal S6 kinase 1 was identified as essential for SHH-MB cell survival. Pharmacological blockade of S6 kinase 1 induced apoptosis and impaired tumor growth in orthotopic xenografts, suggesting that inhibition of S6 kinase 1 specifically affects tumor growth in SHH medulloblastoma [84].

8.4 Targeting Transcriptional and Epigenetic Drivers

The highest-risk tumors are driven by recurrent MYC amplifications and experience poorer outcomes despite intensive multi-modal therapy. Therapeutic targeting of MYC directly has proven difficult so far, but inhibiting its transcriptional cofactors could offer a promising alternative.

MYC-driven Group 3 medulloblastomas rely on the elongation factor P-TEFb for aberrant transcriptional circuits. Inhibiting CDK9, a core component of P-TEFb, selectively impairs tumor cell proliferation and induces apoptosis in vitro and in orthotopic xenograft models. Inhibition of transcriptional CDKs interfered with enhancer-promoter activity in MYC-medulloblastoma and downregulated MYC-driven transcriptional programs, demonstrating robust anti-tumor activity, and might be a promising strategy for the treatment of MYC-medulloblastoma [85].

Histone deacetylases and phosphoinositide 3-kinases are two important classes of enzymes that regulate key cellular

processes. CUDC-907, which simultaneously inhibits histone deacetylases and phosphoinositide 3-kinases, reduced the viability of MYC-driven Group 3 medulloblastoma cells, patient-derived organoids, and xenograft models. Furthermore, when CUDC-907 was combined with cisplatin, the G0/G1 phase blocking effect was further improved. CUDC-907 in combination with radiotherapy inhibited DNA damage repair and boosted DNA damage. Dual inhibition targeting the MYC upstream pathway (histone deacetylase/phosphoinositide 3-kinase) exhibited significant anti-tumor effectiveness [86].

MYC has demonstrated the capability to bind directly to the EZH2 promoter and activate EZH2 transcription. EZH2 inhibition downregulates NUPR1, a stress-response factor that facilitates DNA repair, thereby sensitizing medulloblastoma cells with high MYC expression to PARP inhibitors. PARP inhibitors reportedly lead to replication stress in MYC-overexpressing cancers. EZH2 inhibition with tazemetostat considerably increased the sensitivity of MYC-high medulloblastoma tumor cells to the PARP inhibitor niraparib in MYC-high medulloblastoma tumor cells. This epigenetic-DNA-repair axis provides a rationale for dual-targeted therapy in aggressive medulloblastoma [87].

8.5 Enhancing Drug Delivery and Overcoming Resistance

Treatment of medulloblastoma is complicated by the tendency to leptomeningeal dissemination. Two non-receptor tyrosine kinases, ABL1 and ABL2, are key drivers of medulloblastoma dissemination. The allosteric ABL1/2 inhibitor, asciminib, and the multi-tyrosine kinase inhibitor nilotinib were combined with tariquidar, a third-generation P-glycoprotein inhibitor. Tariquidar increased the brain concentrations of asciminib and nilotinib, and increased cytotoxicity in medulloblastoma cells. The work supports the inhibition of P- glycoprotein as a potential possibility to improve CNS penetration of targeted agents [88].

Administration of substances directly into the CSF is a possible strategy to bypass the blood–brain barrier and the delivery of drugs to the site of the tumor, which is frequently used in the clinical setting [60]. Drugs suitable for intrathecal administration and prolonged exposure time are urgently needed. PLA-HPG nanoparticles that encapsulate the PARP inhibitor talazoparib were developed for intrathecal administration, achieving high CSF concentrations and selective uptake by leptomeningeal medulloblastoma cells. This has led to sustained drug retention in the tumor when delivered intrathecally. It demonstrates the feasibility of local nanoparticle-mediated therapy for CNS metastases [89].

Recent advances in nanoparticle-based drug-delivery systems allow for precise modulation of specific molecular pathways, thereby enhancing therapeutic efficacy while reducing off-target toxicities [90]. As stated above, current Hedgehog inhibitors are effective initially to treat SHH-MB but acquire resistance often after a short time. Systemic administration of the Hedgehog inhibitor MDB5 and SF2523, a BRD4/PI3K dual inhibitor, loaded on a COG-133 nanocarrier for enhanced drug delivery to the brain, was used to effectively deliver these drugs to medulloblastoma tumor sites and significantly inhibited medulloblastoma progression compared with non-targeted nanoparticle (NP) formulations [91]. An overview of targeted therapeutic approaches as well as the underlying mechanisms of resistance across all molecular subgroups of medulloblastoma is reviewed here [92, 93].

8.6 Early-Phase Pediatric Combination Trials

The presence of molecular alterations in recurrent tumors can be potentially addressed by targeted therapies. The WEE1 kinase is a negative regulator of the G2-M checkpoint. Inhibition of WEE1 disrupts cell-cycle control, inducing replication stress and premature mitotic entry. Inhibition of the WEE1 kinase by adavosertib (AZD1775) increases the replicative stress from chemotherapy, using the sensitizing effect of chemotherapy-induced DNA damage. Patients with defined genetic alterations und recurrent medulloblastoma were included in a pediatric phase I study to define the recommended dose and activity of adavosertib in combination with carboplatin. Unfortunately, the regimen proved to be too toxic for these heavily pretreated patients, moreover, none of the patients with recurrent medulloblastoma showed an objective response [94]. Combining adavosertib with irinotecan had a better tolerability, but did not meet the efficacy endpoint in recurrent medulloblastoma [95].

Nifurtimox is a nitrofuran compound that has been employed for over 50 years as a primary treatment for Chagas disease, a parasitic infection. Nifurtimox induces the formation of reactive oxygen species and increases oxidative stress. In combination with topotecan and cyclophosphamide, the regimen was well tolerated, but again, the responses in the subset of patients with medulloblastoma were not durable [96].

8.7 Novel Immunotherapy Studies

Immunotherapies aim at inducing anti-tumor immune response (e.g., immune checkpoint inhibitors) or by targeting tumor-specific features (e.g., chimeric antigen receptor T cells). While these therapies have shown very positive results in certain adult cancers, their effectiveness in pediatric solid tumors remains limited.

Chimeric antigen receptor T cells are genetically modified to equip T cells with the ability to recognize and target a specific antigen. Chimeric antigen receptor T-cell therapy

is a promising novel treatment and proved to be effective in various hematological malignancies [97]. Gangliosides are surface antigens that are expressed by pediatric tumors, including medulloblastoma. An early-phase clinical trial of GD2-chimeric antigen receptor T cells in patients with GD2-positive medulloblastoma demonstrated the safety and evidence of CNS trafficking [98].

Immunotherapy using checkpoint inhibitors represents a promising option in several solid tumors in adults, especially melanoma [99]. The checkpoint inhibitors nivolumab and ipilimumab were administered in pediatric patients with refractory hypermutated cancer and mismatch repair deficiency, and resulted in durable responses and prolonged survival [100]. Unfortunately, in recurrent medulloblastoma, nivolumab alone or in combination with ipilimumab showed discouraging survival [101].

9 Conclusions

Treatment of pediatric medulloblastoma has evolved from surgery and radiotherapy alone to highly stratified, multimodal regimens. Our rapidly expanding knowledge of medulloblastoma biology is expected to drive the development of an increasing array of diagnostic molecular technologies and treatment approaches. Contemporary therapy is risk adapted—incorporating both clinical stage and molecular subgroup—to maximize cure while limiting late effects. Current trials continue to refine CSI dosing and chemotherapy, especially for WNT and SHH subtypes, and novel targeted and immune-based therapies are being tested to improve outcomes in high-risk groups. Yet, the small number of patients in each stratum may hamper clinical trials and large international efforts are needed to successfully test novel treatment strategies.

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Authors' contributions AP and LM conceptualized the content, drafted the initial manuscript, and critically reviewed the manuscript. AA and JG critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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