Current Oncology Reports (2020) 22:90
https://doi.org/10.1007/s11912-020-00953-4

NEURO-ONCOLOGY (Y UMEMURA, SECTION EDITOR)

Medulloblastoma: an Old Diagnosis with New Promises

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Abstract

Purpose of Review Molecular subtyping in medulloblastoma (MB) has diagnostic and prognostic values which impact therapy. This paper provides guidance for the clinician caring for pediatric and adult patients with medulloblastoma in the modern era.

Recent Findings Medulloblastoma comprises four molecularly distinct subgroups: wingless activated (WNT), sonic hedgehog activated (SHH), group 3, and group 4. Risk stratification before and after the discovery of molecular subgroups aims at minimizing toxicity by reducing radiation and chemotherapy doses in low-risk patients while maintaining favorable overall survival (OS). The mainstay of newly diagnosed medulloblastoma treatment is surgery, radiation therapy, and chemotherapy, except for children under 6 years of age, where high-dose chemotherapy with autologous stem cell rescue is used to avoid or delay radiotherapy, preventing neurocognitive sequelae. Management of recurrent/refractory medulloblastoma remains a challenge with immunotherapy and small-molecule inhibitors forming the backbone of novel strategies.

Summary Recent innovations in medulloblastoma research allow us to better understand pathogenesis and molecular characteristics resulting in advanced risk stratification models, new therapeutic approaches, and overall improved survival and quality of life.

Keywords Medulloblastoma · Molecular subtyping · Genomics · Neurosurgery · Radiation therapy · Chemotherapy · Targeted therapy · Clinical trials

Introduction

In 1925, Harvey Cushing, MD and Percival Bailey, MD coined the term medulloblastoma after reviewing a series of cases of central nervous system (CNS) tumors and identifying a subtype of posterior fossa tumors seen in younger children [1]. They also recognized that more extensive tumor excision correlated with longer survival. In the 1950s, the introduction of craniospinal irradiation (CSI) with a posterior fossa boost further improved outcome, but at a price: increased risk of neurocognitive impairment, endocrine disfunction, and secondary malignancies were commonly seen [2]. In the 1970s, adjuvant chemotherapy was introduced in an effort to improve survival, decrease radiation dose, and subsequently reduce deleterious late effects [3]. While surgery, external beam radiation therapy (in patients over 6 years of age), and chemotherapy continue to be the mainstay of medulloblastoma treatment, the discovery of molecular subtyping in 2000, led to the identification of four distinctive subgroups of medulloblastoma incorporated into the 2016 WHO classification of CNS tumors [4]. The advent of newer technologies to further subclassify tumors has set the stage for novel therapeutic approaches.

Epidemiology

CNS tumors are the most common form of solid tumors in children and adolescents [5] and the leading cause of cancer-related death in this age group [6]. Embryonal tumors account for 10%, with medulloblastoma being the most common, representing 63%. In children age 0–19 years, the incidence is 0.39 per 100,000 population, and it decreases with age [7]. As with most childhood cancers, medulloblastoma is more common in

This article is part of the Topical Collection on *Neuro-oncology*

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Published online: 09 July 2020

males [8], though there may be variability depending upon MB subtypes as discussed below [9•]. While much is known about the MB biology including molecular characteristics and genetic syndromes, to date, the role of environmental factors is unknown.

Genetic Syndromes

The association between certain hereditary cancer predisposition syndromes and medulloblastoma is well recognized. Table 1 summarizes the most important familial cancer predisposition syndromes associated with medulloblastoma. In 2018, Waszak et al. reported that germline mutations accounted for 6% of medulloblastoma diagnoses [10••]. The investigation also found that the risk of medulloblastoma is highest in carriers of *SUFU* and *TP53* mutations and *BRCA2* and *PALB2* biallelic mutations [10••]. In over half of the cases, where an underlying genetic predisposition syndrome was identified after germline testing had been performed, medical and family histories were unrevealing emphasizing the need of new guidelines for genetic counseling and testing. Understanding the molecular characteristics of these tumors played a significant role in the identification of the medulloblastoma subgroups.

Subgroups—Signal Pathways

Pomeroy et al. demonstrated in 2002 that medulloblastomas are molecularly distinct from other brain tumors [11]. Further investigation by Taylor et al. defined four distinct molecular entities: wingless activated (WNT 10%), sonic hedgehog activated (SHH 30%), group 3 (20–25%), and group 4 (35–40%) [12, 13]. It has been shown that the molecular subgroup is defined at the time of tumor initiation and is not affected by genetic evolution, therapy, or other factors [14]. Figure 1 summarizes the characteristics of each MB subgroup.

WNT Subgroup

Ten percent of all medulloblastomas belong to the WNT subgroup and occur in children over 3 years of age with a 1:1 M:F ratio. If diagnosed before age 16 years, prognosis is excellent [15, 16].

The Wnt/β-catenin pathway plays a central role during embryonal development, regulating stem cell pluripotency and driving cell growth and proliferation. Nearly 90% of WNT medulloblastomas harbor mutations in exon 3 of the *CTNNB1* gene, resulting in reduced cytoplasmic degradation and nuclear accumulation of the transcription factor co-activator β-catenin [17••]. Other commonly mutated genes in the WNT subgroup include *DDX3X*, *SMARCA4*, *TP53*,

Table 1 Cancer predisposition syndromes in medulloblastoma

Mutated gene	Cancer predisposition syndrome	Clinical features	Role of mutated gene	Subgroup association
APC	Turcot syndrome	Multiple adenomatous colon polyps, increased risk of colorectal cancer and CNS tumors	Negative regulator that controls β-catenin concentrations	WNT, rarely SHH
PTCH1	Gorlin syndrome	Developmental abnormalities, bone cysts, increased risk of basal cell carcinoma and medulloblastoma	Receptor for sonic hedgehog	SHH
SUFU			Negative regulator in the hedgehog/smoothened signaling pathway	
TP53	Li Fraumeni syndrome	Multiple cancer types and primary sites (breast, sarcomas, brain tumors, adrenocortical carcinoma) at an early onset	Tumor suppressor protein regulates genes involved in cell cycle arrest, apoptosis, senescence, DNA repair, and changes in metabolism	SHH
BRCA2/*FANCD1*	Fanconi anemia	Developmental abnormalities, bone marrow failure, predisposition to medulloblastoma	Double-strand DNA-break repair, vital in homologous recombination	SHH if compound heterozygous, groups 3 and 4 if heterozygous mutation
PALB2			Partner and localizer of BRCA2	SHH, rarely group 3 and group 4
CREBBP	Rubinstein Taybi syndrome	Microcephaly, growth deficiency, dysmorphic features, intellectual disability, increased risk of brain tumors	CREB binding protein—co-activator of transcription factors	

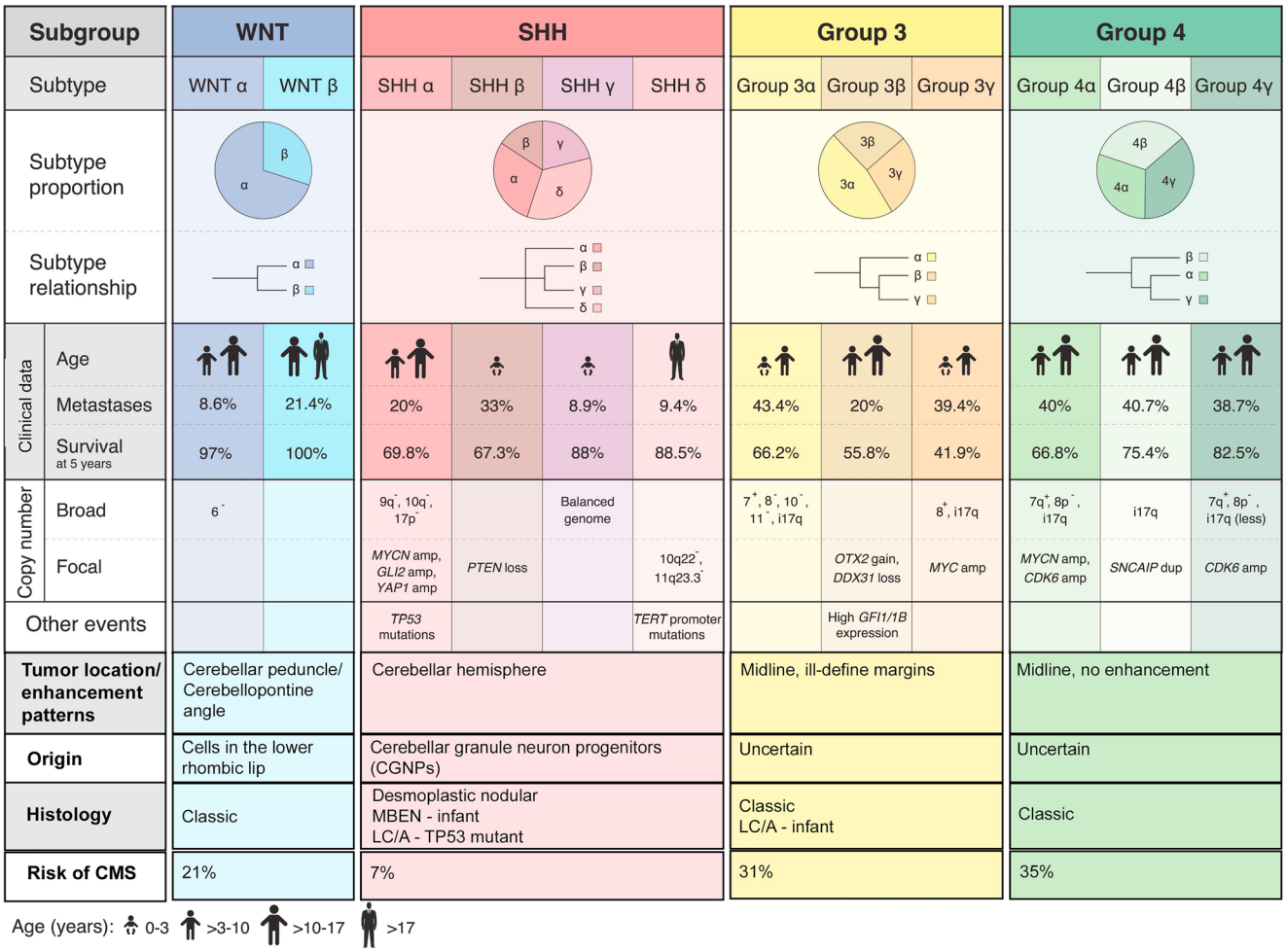

Fig. 1 Summary of medulloblastoma subgroups adapted from Cavalli et al. Intertumoral Heterogeneity within Medulloblastoma Subgroups. Cell 2017;31:75 [12]

and *CSNK2B*, which also contribute to tumorigenesis. Gibson et al. developed a transgenic mouse model of WNT MB using constitutively active Ctnnb1 and absent p53 expressions [18]. The addition of constitutively active Pik3ca increased tumor development from 20 to 100% and reduced the latency of tumor onset in the mice from 6 to 3 months of age [19]. The 10–15% of WNT MB lacking *CTNNB1* mutations often harbor pathogenic variants of the *APC* gene [10••]. Another hallmark of WNT-driven MB is monosomy 6, found in about 85% of the cases. A small-subset WNT medulloblastomas acquire subclonal genetic alteration which secondarily activate the SHH pathway [20]. The prognostic and therapeutic significance of this finding remains unclear.

SHH Subgroup

The sonic hedgehog pathway regulates cellular differentiation, organ formation, and post-embryonic tissue regeneration and repair in multicellular organisms [21]. The key components of the pathway include the transmembrane receptor Patched1 (PTCH1), the signal transducer Smoothened (SMO), GLI transcription factors, and Suppressor of fused homolog (SUFU), which normally suppresses GLI [22]. SHH binds PTCH1, which releases SMO resulting in the dissociation of the GLI transcription factors from SUFU. The unbound GLI translocates to the nucleus turning on gene transcription. [23].

Disruption of this pathway may result in SHH-driven medulloblastoma as follows: loss of function mutations or deletions in *PTCH1* (43%) and *SUFU* (10%), activation of mutations in *SMO* (9%), or amplifications of *GLI1* or *GLI2* (9%) [17••]. Wetmore et al. demonstrated that germline deletion of *PTCH1* generated MB in 15–20% of mice, and the additional deletion of *TP53* produced tumors in 100% [24].

More recent studies identified four SHH MB subtypes, each with a specific phenotype and different prognosis [12]. For example, SHHα with germline or somatic *TP53* mutations occurs in older children and adolescents and predicts poor outcome. Both SSHβ and SSHγ tumors develop primarily in infants, with SSHγ conferring a better prognosis [25]. Finally, SSHδ, commonly seen in adults, has a prognosis

somewhere in the middle and is almost always associated with somatic *TERT* promoter mutations [26].

Group 3 Subgroup

Group 3 medulloblastoma, seen primarily in infants and older children with a male predominance, has a 40–65% OS depending upon the subtype. These patients may present with disseminated disease, which have a guarded prognosis [13], especially in the setting of *MYC* amplification, representing 15–20% of the cases [27]. Other cytogenetic features include the presence of isochromosome 17q and gain of chromosome 8q [12]. Gene-level mutations are rare, primarily occurring in *SMARCA4*, *KBTBD4*, *CTDNEP1*, and *KMT2D* [17••]. Enhancer hijacking is a well described epigenetic phenomenon, whereby regulatory elements are translocated close to coding genomic regions, resulting in gene overexpression and tumor formation. Northcott et al. observed that enhancer hijacking occurs in one-third of group 3 MB (resulting in *GFI1*/*GFI1B* oncogene activation) and in 17% of group 4 MB as described next [28, 29].

Group 4 Subgroup

Group 4 is most commonly driven by the enhancer-hijacking-mediated overexpression of *PRDM6*, strongly associated with focal tandem duplication of *SNCAIP*. Mutations in histone-modifying genes *KDM6A*, *ZMYM3*, *KMT2C*, and *KBTBD4* have also been described [17••]. Cytogenetic aberrations are frequent in this subgroup, with gain of chromosome 7 (40%) or 17q (> 80%), and deletion of chromosome 8 (40%), 11 (> 30%) or 17p (> 75%), and the most common, isochromosome 17q (80%). High-level amplifications of *MYCN* and *CDK6* are also observed [27].

Its prognosis is intermediate: patients with metastasis have a higher risk of relapse, while those tumors with loss of chromosome 11 or gain of chromosome 17 are associated with good outcome [30•].

Clinical Presentation

Medulloblastoma typically originates from the posterior fossa, and most clinical symptoms at presentation result from increased intracranial pressure (ICP) due to obstructive hydrocephalus and cerebellar dysfunction. In a study from 2012 by Brasme et al., the most frequent symptoms leading to a MB diagnosis were vomiting, headache, ataxia, and neuropsychological symptoms depending upon age at presentation [31]. In this report, psychomotor regression was seen early in children under 3 years of age, while declining school performance often prompted investigation in older patients. The median time from symptom onset to definitive diagnosis was 65 days; however, survival and neurological outcome were independent in this report, which predates molecular risk stratification [31]. Despite medulloblastoma being a rapidly growing tumor, obtaining a final diagnosis can be challenging due to non-specific symptoms or a completely normal neurological exam.

Diagnosis

Once symptoms are recognized, neuroimaging is obtained; typically, a non-contrast head CT scan, which does not require anesthesia, can be safely performed on critically ill children and is widely available. In most instances, a hyperdense mass in the posterior fossa surrounded by vasogenic edema and hydrocephalus is seen.

Thereafter, confirmatory magnetic resonance imaging (MRI) is performed to provide further detail and identify metastases. Tumors are typically hypointense to grey matter on T1-weighted imaging with heterogenous gadolinium enhancement. A recent article by Perreault et al. demonstrated a correlation between tumor location/enhancement patterns and molecular subgroups [32•]. Most WNT tumors occurred along the cerebellar peduncle/cerebellopontine angle, while SHH medulloblastoma occurred in the cerebellar hemisphere. Group 3 and group 4 tumors were found in the midline, occupying the fourth ventricle. Group 3 tumors had ill-defined margins, and group 4 MB did not enhance (Fig. 2). Differential diagnosis of a posterior fossa mass includes pilocytic astrocytoma, ependymoma, atypical teratoid/rhabdoid tumor, exophytic brainstem glioma, embryonal tumor with multi-layered rosettes, and choroid plexus papilloma. In adults, metastatic disease of an extracranial primary site should be considered. Spectroscopy can be helpful in distinguishing high- from low-grade tumors; tractography may help surgeons minimize postoperative morbidity [33].

Staging

In 1969, Chang proposed the following staging criteria for medulloblastoma: 1) M0: no evidence of metastatic disease; 2) M1: positive cerebrospinal fluid (CSF) cytology without gross tumor visible on MRI; 3) M2: intracranial metastasis; 4): M3: metastasis within the spinal subarachnoid space and; and 5) M4: disease outside of the neuraxis, most common in the bone and bone marrow [34].

Ideally, extent of disease evaluation should be performed preoperatively and include pre- and post-contrast brain and spine MRI and lumbar puncture (LP) only if the patient is stable without signs or symptoms of increased

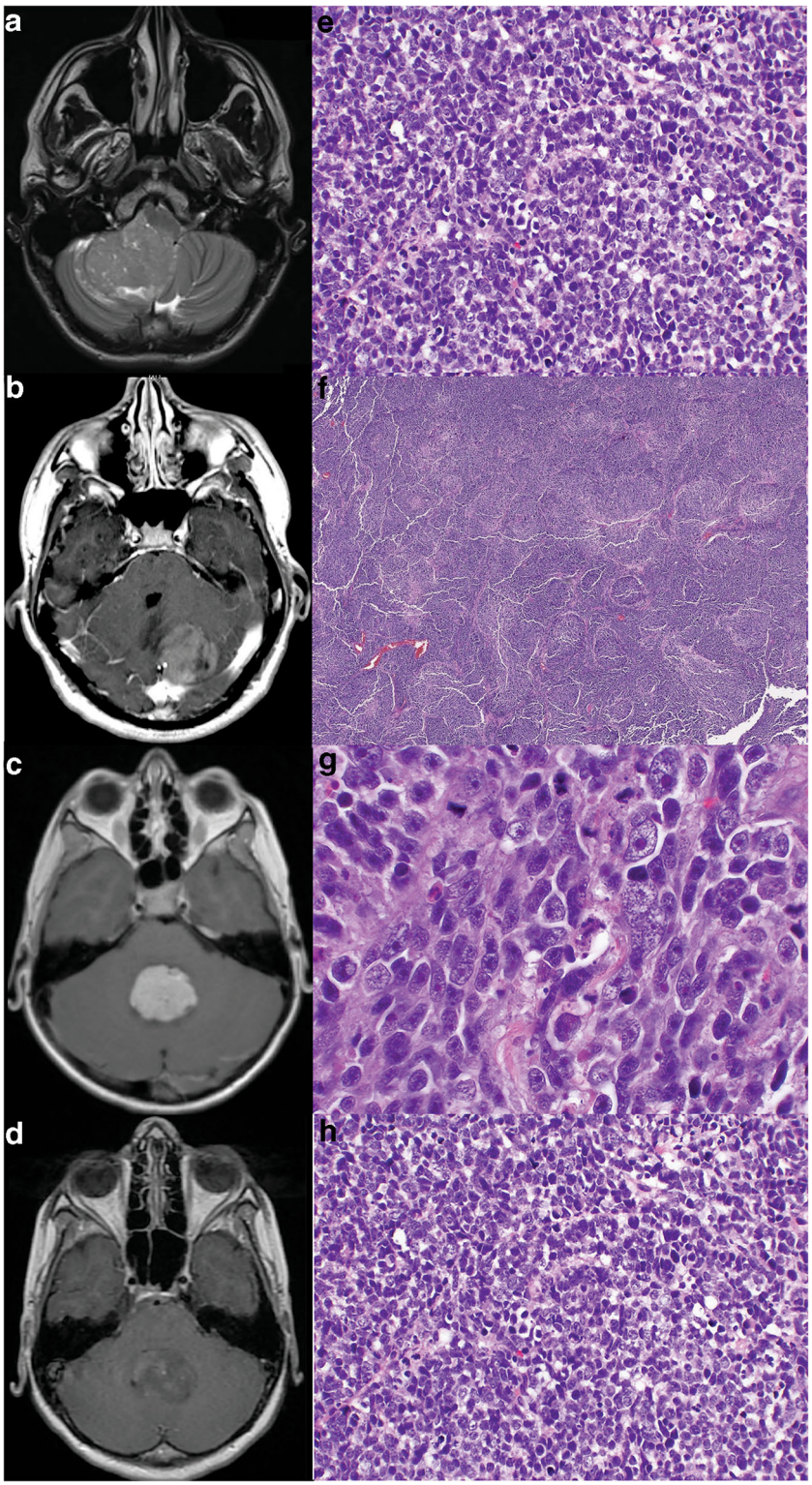

Fig. 2 Characteristic MRI images of medulloblastoma subgroups and the histopathological variants commonly associated with them. **a** Characteristic location of WNT MB in the cerebellopontine angle region showing **e** classic histology. **b** SHH MB in a hemispheric location with **f** desmoplastic nodular histology. **c** Group 3 MB with contrast enhancement in the midline/fourth ventricle showing **g** large cell/anaplastic features. **d** Group 4 MB showing no enhancement in the midline/fourth ventricle, often associated with **h** classic histology

ICP. If deferred, LP should be performed no sooner than 14 days postoperatively to avoid false-positive results, but prior to the initiation of therapy, preferably 30 days from diagnosis.

Histopathology

The 2016 edition of the WHO CNS classification recognizes that both histology and genetic signature are important in

defining MB subgroups, all of which are grade IV and characterized by small round blue cells usually of cerebellar origin. Histopathologic variants of MB include: 1) classic with minimal or no differentiation; 2) desmoplastic/nodular (DNMB) which has nodules of differentiated cells with internodular fibrosis; 3) medulloblastoma with extensive nodularity (MBEN) with more significant nodularity; and 4) large cell/anaplastic (LC/A-MB) characterized by bizarre atypical polymorphic cells, nuclear molding, high mitotic rate, and apoptotic bodies (Fig. 2) [4]. Classic histology is seen in almost all WNT medulloblastomas [35], the majority of Group 3 and 4 tumors [13], and occasionally in SHH-driven tumors which are largely desmoplastic/nodular [36]. MBEN, typically seen in very young children with SHH/TP53WT, can be associated with Gorlin syndrome [37]. LC/A-MB is most often seen in SHH/TP53 mutant and infant group 3 MB [38, 39] (Fig. 2).

The origin of medulloblastoma cells has long been debated. Gibson et al. has shown that WNT subgroup tumors derive from cells in the lower rhombic lip, while cerebellar granule neuron progenitors (CGNPs) are the probable cell of origin for SSH medulloblastoma [18]. As of today, it is still uncertain where group 3 and group 4 tumors originate from.

Risk Stratification

Risk stratification guidelines include age, extent of resection, presence of metastasis, and histological subtypes. Average-risk patients are older than 3 years of age and have M0 disease with less than 1.5 cm^2 of residual tumor after resection. High-risk children have microscopic or macroscopic metastasis, more than 1.5 cm^2 of mass present after surgery, and/or large cell anaplastic histology. Children under 3 years of age represent a distinctive-risk group and require a different treatment approach, which omits upfront radiation due to the unacceptable risk of neurocognitive impairment.

Experts convened at a consensus conference in 2015 in Heidelberg to refine risk stratification in the context of molecular subtypes [40••]. The low-risk group (> 90% survival) includes non-metastatic WNT medulloblastoma diagnosed before age 16 years, and non-metastatic group 4 tumors with loss of chromosome 11 or gain of chromosome 17. The standard-risk group (75–90% survival) consists of non-metastatic SHH medulloblastoma without *TP53* mutation or *MYCN* amplification; non-metastatic group 4 tumors without chromosome 11 loss; and non-metastatic, non-*MYC*-amplified group 3 tumors. The high-risk group (50–75% survival) includes metastatic non-infant TP53 wild type and non-metastatic MYCN-amplified SHH medulloblastoma, and metastatic group 4 medulloblastoma. The very high–risk group (< 50% survival) is comprised of *TP53*-mutated SHH medulloblastoma and metastatic group 3 tumors.

The transcriptome of adult medulloblastomas differs considerably from pediatric counterparts, both in tumor biology and prognostic impact [41]. Therefore, age-specific classification is necessary when designing clinical trials for adult medulloblastoma.

Treatment

Surgery

The first step in the management of medulloblastoma is maximal safe surgical resection, which is usually performed by posterior craniotomy. A recent retrospective analysis of almost 800 medulloblastoma patients found a progression-free survival benefit between gross total and subtotal resection, but not between gross total and near total resection, which questions the role of second-look surgeries to remove small residual tumors (less than 1.5 cm^2), especially when the risk of neurological sequelae is increased [42•]. For increased extent of resection, the study did not observe significant survival benefit in WNT, SHH, group 3, or M0 group 4 patients.

While extensive neurosurgical procedures carry inherent risks, cerebellar mutism syndrome (CMS) is a complication unique to posterior fossa surgery. One to two days postoperatively, patients develop speech impairment, oral apraxia, emotional lability, hypotonia, and ataxia. Neuropsychologic testing reveals difficulty with executive function, linguistic processing, visual spatial abilities, and affective modulation [43]. In 2006, the Children's Oncology Group (COG) reported an incidence of 25% in all patients with medulloblastoma; risk factors included younger age, larger tumor volume, and midline tumor location [44]. Tractography reveals disruption of cerebrocerebellar pathways [33]. Most recently, Jabarkheel et al. found that independent of tumor volume and location, subgroup of MB is predictive of CMS as follows: group 4 tumors (35%), group 3 (31%), WNT (21%), and SHH (7%) [45]. Patients with moderate to severe CMS often have long-term neurocognitive effects, which may be compounded by other effects of treatment for medulloblastoma [46].

Radiation

Because survivors of medulloblastoma treated with radiation therapy (RT) are often left with neurocognitive, neuroendocrine, and auditory sequelae, decreasing radiation dose and volume while maintaining survival is crucial [47]. Average-risk patients over 6 years of age receive 23.4-Gy craniospinal irradiation (CSI), a tumor bed boost to 55.8 Gy, and weekly vincristine during radiotherapy, beginning roughly 30 days post-resection [48, 49]. Initiating RT sooner than 3 weeks pos-operatively, delaying treatment, or attempting to further reduce the CSI dose to 18 Gy resulted in inferior OS [50, 51],

while hyperfractionation had no effect [52]. For high-risk patients, 36-Gy CSI and additional boost to metastatic sites besides the tumor bed are standard. Concomitant carboplatin as a radiosensitizer did not alter outcomes for this patient population [53].

While RT has improved overall survival in MB patients, dose-dependent late effects primarily related to CSI and seen typically 5 years post-treatment need to be monitored. The COG has published long-term follow-up guidelines to aid the clinicians [54•]. Radiation to the hypothalamic-pituitary axis, associated with hypothyroidism, growth hormone and ACTH deficiency, and altered metabolism, may result in obesity and delayed puberty [55, 56].

A systematic review in 2015 by Hanzlik et al. found that even with reduced-dose RT, pediatric medulloblastoma survivors had lower IQ, memory, and executive function scores with ongoing decline compared with normal population and patients receiving only focal radiation [57].

The advent of proton beam RT has significantly improved both acute and long-term morbidity associated with photons without reducing OS [58•]. Acute toxicities (fatigue, esophagitis, and nausea) and late effects (neurocognitive and ototoxicity) are reduced with proton beam RT. However, alopecia and radiation necrosis may occur more often with proton radiation. [59, 60]. Other late effects including cavernomas, meningiomas, and high-grade second malignancies may also develop following radiation (from either CSI or the boost), but risk factors, other than familial cancer predisposition syndromes, require further investigation [61, 62].

Chemotherapy

Chemotherapy was first added to medulloblastoma treatment in the 1970s, significantly improving both progression-free survival (PFS) and OS rates, allowing reduction of CSI dose for average-risk patients [63]. All studies investigating optimal time for chemotherapy concluded that surgery-radiation-chemotherapy sequence is favored over "sandwich chemotherapy," or pre-radiation chemotherapy only [64–67]. Alkylators [68] represent the backbone of maintenance chemotherapy, and currently, the "Packer regimen" (vincristine and cisplatin plus either lomustine or cyclophosphamide) is the standard of care for standard-risk patients [48]. For patients with high-risk disease, maintenance chemotherapy includes higher cumulative dose cyclophosphamide [69]. The incorporation of high-dose chemotherapy with autologous stem cell transplantation (thiotepa-containing regimens) did not improve outcomes for high-risk patients but was associated with significant neuro- and hepatotoxicity [70, 71]. Acute and long-term side effects of chemotherapy are well described. While both pediatric and adult MB protocols traditionally include vincristine, adults may develop neuropathy sooner, with more severity, requiring dose reduction or complete omission of the drug [72]. Patients receiving alkylating agents are at risk of developing secondary malignancies; the cumulative 10-year incidence of treatment-related tumors was 4.2% on the standard-risk COG protocol A9961 [73]. Grade 3 or 4 ototoxicity due to both radiotherapy and the use of cisplatin affects 20–25% of the patients [48].

Infant Medulloblastoma

The Head Start group of protocols have shown that chemotherapy improves survival while avoiding or delaying radiotherapy to preserve the intellect of young children [74, 75]. In 2005, Rutkowski et al. showed that the addition of intrathecal methotrexate improved survival in infants with desmoplastic variants of MB [76]. Several subsequent studies confirmed that infants with DNMB and MBEN have outcomes around 80% [74, 77, 78]. A recently closed COG study included systemic high-dose methotrexate during induction plus three cycles of thiotepa and carboplatin followed by stem cell rescue in children less than 3 years of age. Incorporating molecular subgroups as part of risk stratification (as in the Head Start 4 protocol) is being investigated.

Adult Medulloblastoma

Medulloblastoma accounts for less than 1% of adult intracranial tumors [79]. Seventy percent of cases are classified as SHH (desmoplastic/nodular or extensive nodularity histology), followed by group 4 and WNT, each around 15%, and rarely group 3 [39]. WNT is the most favorable subtype, with an 80% 5-year OS, slightly lower than 90% observed in children younger than 16 years [16•]. This difference is largely unexplained due to the rarity of the tumor and the heterogeneity of the treatment. Craniospinal irradiation with a boost to the tumor bed is considered the standard of care, and while maintenance chemotherapy is feasible, its role has not yet been investigated in a prospective randomized study [80–82].

Refractory and Recurrent Disease

Refractory and recurrent medulloblastomas are responsible for 95% of medulloblastoma-associated death [83]. Aside from the very young patients who can be salvaged with radiation therapy following a treatment with a chemotherapy-only approach, survival after relapsed medulloblastoma is grim [84]. The combination of temozolomide and irinotecan has been utilized in the relapsed medulloblastoma setting due to its favorable toxicity profile and the feasibility in heavily pretreated patients, and showed a 30% response rate with a median survival of 16 months [85, 86]. The most recent COG

Table 2 Ongoing clinical trials for newly diagnosed medulloblastoma and ongoing clinical trials for relapsed/progressive medulloblastoma

ClinicalTrials.gov Identifier	Phase	Treatment	MB subgroup (if applicable)	Sponsor
Ongoing clinical trials for newly diagnosed medulloblastoma				
NCT01878617	II	Clinical and molecular risk-directed therapy for newly diagnosed MB	WNT: 3 treatment arms SHH: 2 treatment arms Non-WNT/non-SHH: 3 treatment arms	St. Jude Children's Research Hospital
NCT02875314	IV	HeadStart4: newly diagnosed children (< 10 years old) with medulloblastoma	Non-WNT/non-SHH	Nationwide Children's Hospital
NCT02724579	II	ACNS 1422: reduced CSI and chemotherapy in younger patients with newly diagnosed WNT-driven medulloblastoma	WNT	Children's Oncology Group
NCT02066220	II/III	SIOP PNET 5 medulloblastoma	WNT	Universitatsklinikum Hamburg-Eppendorf
NCT02025881	I/II	Study of sequential high-dose chemotherapy in children with high-risk MB (HR MB-5)	N/A	Gustave Roussy, Cancer Campus, Grand Paris
NCT01857453	II	Dose decrease for RT associated with chemotherapy for treatment of standard-risk adult medulloblastoma	N/A	Central Hospital, Nancy, France
Ongoing clinical trials for relapsed/progressive medulloblastoma				
NCT01356290	II	Metronomic and targeted anti-angiogenesis therapy (MEMMAT)	N/A	Medical University of Vienna
NCT03904862	I/II	CX-4945 (silmitasertib), casein kinase II inhibitor	SHH	Pediatric Brain Tumor Consortium
NCT03936465	I	BMS-986158 bromodomain (BRD) and extra-terminal domain (BET) inhibitor	MYC or MYCN amplification or translocation, or high copy number gain, BRD3 or BRD4 translocation	Dana-Farber Cancer Institute
NCT02359565	I	Pembrolizumab	N/A	National Cancer Institute
NCT03173950	II	Nivolumab	N/A	National Cancer Institute
NCT03389802	I	APX055M monoclonal antibody binding to CD40	N/A	Pediatric Brain Tumor Consortium
NCT00089245	I	Intrathecal radiolabeled monoclonal antibody against B7-H3 (I-8H9–omburtamab)	N/A	Y-mAbs Therapeutics
NCT03911388	I	G207–oncolytic herpes simplex virus 1	N/A	University of Alabama at Birmingham
NCT02962167	I	MV-NIS–modified measles virus	N/A	Sabine Muller, MD, PhD
NCT03043391	I	PVSRIPO–oncolytic poliovirus	N/A	Istari Oncology, Inc.
NCT03299309	I	PEP-CMV–cytomegalovirus-specific peptide vaccine	N/A	Gary Archer, PhD
NCT03500991	I	HER2-specific CAR T cell locoregional immunotherapy	N/A	Seattle Children's Hospital
NCT03638167	I	EGFR806-specific CAR T cell locoregional immunotherapy	N/A	Seattle Children's Hospital
NCT03387020	I	Ribociclib (cyclin D1/CDK4 and CDK6 inhibitor and everolimus	N/A	Pediatric Brain Tumor Consortium
NCT03434262	I	Ribociclib and gemcitabine Ribociclib and trametinib Ribociclib and sonidegib	Groups 3 and 4 MB WNT and SHH MB SHH	St. Jude Children's Research Hospital
NCT03598244	I	Volitinib–c-Met inhibitor	N/A	National Cancer Institute
NCT02095132	I/II	Adavosertib (MK-1775)–WEE1 inhibitor and irinotecan	N/A	National Cancer Institute
NCT03213678	II	Samotolisib (LY3023414)–PI3K/mTOR inhibitor Pediatric MATCH Treatment Trial	TSC or PI3K/mTOR mutations	National Cancer Institute
NCT03213665	II	Tazemetostat–EZH2 inhibitor	EZH2, SMARCA4, or SMARCB1 mutation	National Cancer Institute
NCT03233204	II	Olaparib–Pediatric MATCH Treatment Trial	Defect in DNA damage repair pathway	National Cancer Institute
NCT04023669	I	Prexasertib (LY2606368)–CHK1/2 inhibitor and cyclophosphamide Prexasertib (LY2606368)–CHK1/2 inhibitor and gemcitabine	SHH, groups 3 and 4, indeterminate MB Groups 3 and 4 MB	St. Jude Children's Research Hospital
NCT02644291	I	Mebendazole	N/A	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

phase II trial is investigating the synergistic effect of bevacizumab when added to temozolomide and irinotecan (ACNS 0821), with preliminary results showing a median event-free survival (EFS) of 9 months vs. 6 months and a median OS of 19 months vs. 16 months when compared with the standard arm [87].

New Approaches

The recent refinement of risk stratification provides an opportunity to personalize therapy, while the use of targeted therapy allows dose reduction of cytotoxic chemotherapy, resulting in the mitigation of treatment-related toxicity and maintaining favorable OS. Table 2 summarizes ongoing trials for both newly diagnosed and recurrent/progressive medulloblastomas.

Phoenix et al. has shown that WNT medulloblastomas contain aberrant vascular networks and disrupted blood-brain-barrier (BBB), which allow for increased concentrations of systemic chemotherapy; de-escalation of therapy in low-risk patients is tested in multiple clinical trials [88].

In adult SHH medulloblastoma inhibiting SMO and blocking downstream signaling (e.g., vismodegib) can be a successful strategy, as these tumors frequently (80%) harbor *PTCH1* or *SMO* mutations. Of note, the use of these inhibitors is associated with disrupted bone homeostasis, limiting its use in skeletally immature patients. A current St. Jude upfront MB trial adds vismodegib as maintenance therapy for skeletally mature patients with SHH MB. Some tumors, however, present with inherent resistance to SMO inhibitors by harboring either certain SMO mutations, which impair drug binding or genetic alterations in the downstream effectors SUFU or Gli [89]. Alternatively, prolonged exposure to smoothened inhibitors may result in acquired resistance by reactivation of the hedgehog pathway. To overcome these limitations, silmitasertib, a casein kinase 2 inhibitor which blocks signaling at the most terminal component Gli, is currently in a phase I/II trial for patients over 3 years with recurrent/relapsed SHH medulloblastoma.

The aforementioned St. Jude trial includes strata for group 3 and group 4 intermediate- and high-risk medulloblastoma patients, adding pemetrexed and gemcitabine to the standard therapy. Based upon promising preclinical data, trials targeting the PI3K, mTOR, cyclin-dependent kinase (CDK), or BET bromodomain pathways are ongoing for recurrent and/or refractory group 3 MB [90–92].

Immunotherapy and small-molecule inhibitors form the backbone of novel strategies for many refractory tumors. The programmed cell death protein 1 (PD1) inhibitors pembrolizumab and nivolumab, successful at treating lung and breast cancer CNS metastases, are now being investigated in the treatment of refractory primary CNS tumors. Their therapeutic benefit in this population must be balanced with immune-related adverse events including encephalitis, meningitis, and myelitis [93]. Antibodies against the molecules of the co-stimulatory pathways represent the next generation of immune checkpoint inhibitors. APX005M, a monoclonal antibody against CD40, is currently in a phase I trial. Kramer et al. recently reported that intrathecal B7-H3, another immune checkpoint protein expressed in embryonal tumors, was well tolerated in patients with leptomeningeal disease including a subset of MB patients and possibly demonstrating improved outcome in the relapsed/refractory setting [94, 95].

Oncolytic viral therapy, whereby viruses selectively inhibit malignant cells by producing a robust immune response, is another promising strategy for recurrent/progressive MB [96]. These viruses, including the herpes simplex virus variant G207, a modified measles virus (MV-NIS), and the polio/rhinovirus recombinant PVSRIPO require local delivery and are under investigation in phase I trials. Cytomegalovirus (CMV) proteins, often selectively expressed in brain tumors, have been the target of numerous vaccine trials over the past several years. A PEP-CMV vaccine trial in pediatric patients with recurrent MB is underway [97].

Chimeric antigen receptor (CAR) T cells, an emerging therapeutic approach, has been particularly challenging for CNS tumors due to limitations in identifying tumor-specific antigens. Forty percent of medulloblastomas express human epidermal growth factor 2 (HER2), a poor prognostic indicator [98]. Patients aged 1–26 years may be eligible for a current trial, in which CAR T cells expressing various epidermal growth factor receptor (EGFR) antigens are infused locoregionally. Finally, because natural killer (NK) cells can recognize and eliminate cancer cells without antigen specificity, it became the focus of an ongoing study using intrathecal autologous NK cells [99].

Small molecular inhibitors are also being used to treat relapsed/refractory medulloblastoma, regardless of molecular subtypes. Several clinical trials currently use these agents including CDK4/6, c-Met, Wee1, PI3K/mTOR, EZH2, or CHK1/2, either as monotherapy or in combination with conventional chemotherapy.

Conclusion

Recent innovations in medulloblastoma research allowed us to better understand pathogenesis and molecular characteristics, resulting in advanced-risk stratification models, new therapeutic approaches, and overall improved survivals while preserving quality of life. Large multicenter, international trials, especially in adults with MB, are needed to further understand the biology and improve both short- and long-term outcomes.

Acknowledgments We thank Joseph Olechnowicz, MA for his help with editing the manuscript; Marc Rosenblum, MD for providing histopathology images; and Sofia Haque, MD for her help providing radiologic images.

Compliance with Ethical Standards

Conflict of Interest None of the authors has any potential conflicts of interest to disclose.

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