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Updates on Management of Adult Medulloblastoma

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Opinion statement

Medulloblastoma (MB) is a malignant embryonal tumor of the posterior fossa and is the most common type of brain cancer in pediatric patients. In contrast, adult MB is very rare with an incidence of 0.6 per million per year and mostly affects young adults below the age of 40. Recent molecular analyses of pediatric and adult MB have classified these tumors into at least four individual molecular subgroups (SHH, WNT, group 3, and group 4) with distinct demographics, histology, and prognosis. The discrete biological composition of these tumors likely explains the marked heterogeneity in responses seen to conventional therapies such as radiation and cytotoxic chemotherapies. Given the low incidence of adult MB, prospective studies are challenging and scarce, and management guidelines are largely derived from the pediatric MB patient population and retrospective data. However, adult MB is clinically and molecularly distinct from pediatric MB and a comprehensive review of published literature on adult MB highlighting their differences is warranted. Here, we review the management of adult MB focusing on recent studies exploring the effectiveness of upfront chemotherapy, clinical trials in the context of molecular subgroup-specific therapies, and the potential role of immunotherapy in treating this disease.

Introduction

Medulloblastoma (MB) is the most common CNS embryonal tumor of childhood, accounting for 25% of all intracranial neoplasms [1]. In contrast, adult MB is exceedingly rare and accounts for < 1% of intracranial tumors [2]. An estimated 140 new cases of adult MB are diagnosed in the USA

annually [3]. Median age of adult MB patients is about 30 with very few cases diagnosed above the age of 40, and the male to female ratio is approximately 3:2 [4••, 5, 6••].

Patients typically present with neurological symptoms attributable to the posterior fossa location of the tumor and/or hydrocephalus. Current conventional management of adult MB includes maximum safe resection [7], followed by craniospinal radiation (CSRT) with or without concurrent and/or adjuvant chemotherapy depending on clinical risk stratification (extent of resection, presence of metastatic dissemination inside and/or outside the CNS). Even though treatment of adult MB is very heterogeneous across (and even within) institutions, a common practice for the last several decades has been to treat patients with complete resection and non-metastatic dissemination with CSRT alone, whereas patients with incomplete resections and/or metastatic dissemination were treated also with upfront chemotherapy [5, 8]. However, this treatment approach poses at least three problems. First, the clinical risk stratification in which this treatment decisions are based is extrapolated from pediatric data and not sufficiently validated in adults, and whereas the presence of metastatic disease at diagnosis has been found to be a significant prognostic factor in both retrospective and prospective series of adult MB [8–10]; the role of extent of resection is less clear. Second, despite most adult MB being non-metastatic at diagnosis [10, 11], the role of upfront chemotherapy for adult non-metastatic MB has never been tested in a randomized prospective trial. Third, responses to conventional therapies are variable even in patients with similar clinical risk stratification. This is likely largely driven by underlying tumor biology, although variability in management—either due to perception of inadequate "fitness" of adult patients to receive aggressive therapy, or their actual limited tolerance to therapy—may also have an important role. The three major molecular subgroups in adults in order of frequency include Sonic Hedgehog (SHH), group 4, and Wingless (WNT) [12]. SHH subgroup is the most common form of adult MB accounting for 60% of cases with a 5-year overall survival (OS) rate of 76% [12]. Group 4 and WNT account for 25% and 15% of adult MB with 5-year OS rates of 47% and > 80% respectively in adults [12]. In contrast with pediatric MB in which group 3 represents 28 % of all MB, this subgroup is rarely seen in adults [12, 13].

Prospective studies in adult MB are scarce due to its low incidence. However, two recent large retrospective studies (a National Cancer Data Base analysis and a meta-analysis) [4••, 6••] and two prospective studies [8, 14, 15, 16••] have provided evidence supporting the use of upfront chemotherapy and demonstrated its feasibility in adult MB patients, including those with standard-risk or non-metastatic disease at presentation, which represent the majority of patients. In addition, the identification of molecular subgroups has resulted in the introduction of experimental therapies directed towards "actionable" targets such as SMO inhibitors in SHH and drugs that target β-catenin in WNT molecular subgroups. Varying prognosis of tumors belonging to different molecular subgroups have also provided the rationale for escalation and de-escalation trials in pediatric MB to intensify treatment for poor-prognosis patients and to reduce the risk of iatrogenic toxicity for those with excellent prognosis. However, the applicability of this approach to adult MB is still unclear due to more uncertainty regarding the molecular markers determining their prognosis.

Advances in immunotherapy have changed the landscape of treatment of many solid cancers, and its role in treatment of MB, as the most common pediatric CNS tumor, is a subject of intense investigation given the growing evidence of significant immunosuppression in malignant CNS tumors.

Here, we aim to review the literature pertaining to the role of conventional treatments, novel clinical trial designs, and immunotherapy in adult MB and to provide an algorithm that can be used to standardize the approach to management of this disease.

Clinical and radiographic presentation

MB arises from the cerebellum and the floor of the fourth ventricle. In adults, it is more common for MB to arise from the lateral cerebellar hemispheres than from midline structures [17], which reflects the higher proportion of SHH molecular subtype and its presumed cell of origin (granule neuron precursor

cells of the external granule layer of the cerebellum) [18]. The clinical symptoms and signs are associated with the location of the tumor in the posterior fossa, increased intracranial pressure, and/or obstruction of cerebrospinal fluid pathway. Adults typically present with headache, dizziness, nausea, ipsilateral cerebellar signs, and ataxia. Detailed general and neurological history and exam are essential in detecting spinal spread or extra-CNS dissemination. Adult MB rarely spreads outside of the CNS at the time of diagnosis; however, extra-CNS metastasis rates of as high as 35% in adult MB patients with distant recurrence have been reported [5].

MRI of the brain demonstrates iso to hypointense T1 and hyper to hypointense T2 lesions. The intensity and extent of contrast enhancement on T1 post-contrast imaging vary widely. Interestingly, MBs typically show a characteristic diffusion restriction with increased signal on diffusion-weighted imaging (DWI) sequence corresponding to decreased signal on apparent diffusion coefficient (ADC) sequence. One study including 21 MB pediatric patients with definitive disease recurrence has shown that DWI is more sensitive in detecting MB recurrence than gadolinium contrast enhancement [19]. In this study, only 76% of patients with definitive MB recurrence demonstrated gadolinium enhancement on T1 imaging and 100% of recurrent lesions demonstrated diffusion restriction. The authors therefore recommend routine use of DWI and ADC sequences for diagnosis of early MB recurrence. We have also anecdotally observed the benefit of using diffusion restriction imaging on detection of adult MB recurrence in some cases (unpublished data).

The differences in neuroradiological findings in adult vs. pediatric MB have been studied retrospectively [20]. Adult MB lesions are more likely to demonstrate inhomogeneous contrast enhancement, hyperintense signal on T1, and hypointense signal on T2 sequences and are less likely to demonstrate contrast enhancement when compared with the pediatric MB lesions. These differences in MRI appearance may be explained by substantial molecular differences that may influence neuroradiologic findings. Correlations between molecular subgroup and imaging findings have been reported in pediatric MB. Perreault et al. assessed MRI imaging features in 47 molecularly defined pediatric MB patients as the discovery cohort and confirmed their findings in 52 patients as the validation cohort [21]. They discovered that tumor location and enhancement pattern were predictive of molecular subgroups of pediatric MB, with group 3 and group 4 tumors mostly localizing to the midline and fourth ventricle and SHH and WNT tumors localizing to cerebellar hemispheres and cerebellopontine angle, respectively. In this study, while enhancement was common in SHH and group 3 tumors, it was not as common in group 4 tumors. Similarly, imaging biomarkers predicting adult MB molecular subgroups have been described [22]. Keil et al. assessed pre-operative MRIs from 29 adult MB patients enrolled into the Multicenter Pilot-Study for the Therapy of Medulloblastoma of Adults (NOA-7) and demonstrated that hydrocephalus, intraventricular macrometastases, and hemorrhage when combined could identify WNT MB with 100% sensitivity but a lower specificity of 88.3%. In addition, hemorrhage was exclusively seen in non-WNT/non-SHH MB in their cohort. These imaging biomarkers seem to be driven by tumor location and biological behavior of distinct subgroups.

All newly diagnosed MB patients should undergo staging including post-operative MRI of the brain, MRI of the entire spine with and without contrast, and lumbar puncture with cytology. The neurological exam and degree of

suspicious for spinal spread will determine the number of times lumbar puncture should be repeated to increase the diagnostic yield. Systemic staging is warranted if there are symptoms or signs of extra-CNS involvement, although is not routinely performed in the absence of clinical suspicion for spread. Recently, an international working group was established to develop consensus recommendations for response assessment in adult and pediatric MB—still to be prospectively validated—with the goal of achieving more reliable risk stratification and uniformity across clinical trials [23].

Histology

The World Health Organization (WHO) classification of CNS tumors from 2016 provided guidance for an "integrated diagnosis" of MB including both molecular characteristics and histopathological features. Histologically, MB is an embryonal neuroepithelial tumor arising in the cerebellum and dorsal brain stem and consists of densely packed small round undifferentiated cells with mild-to-moderate nuclear pleomorphism and a high mitotic count [24]. There are four major histological subtypes of MB: classic, desmoplastic/nodular, large cell/anaplastic (LCA), and extensive nodularity. The most common histologic variant is classic MB in both children and adults (70–80%) and the least common is MB with extensive nodularity (3%) [25]. In children, LCA histology has been shown to be an independent indicator of poor prognosis and desmoplastic/nodular variant is thought to impart an excellent outcome [26, 27]. However, differences in prognostic value of histological subtypes have been described in adults and children [25], and these differences are likely related to heterogeneity of the molecular substrate of each histological subtype.

Transcriptome profiling of MB has indicated at least 4 distinct molecular subgroups, which by consensus are designated as WNT-activated, SHH-activated, group 3, and group 4. These subgroups have prognostic value and have posed implications in the treatment of MB (discussed in detail below). The current WHO classification does not endorse a specific method for molecular subclassification of MB, although both transcriptome and methylome profiling and immunohistochemistry panels have been proposed. Of note, despite the identification of molecular subgroups, the histopathology classification is still retained due to its clinical utility in the absence of molecular subgroup determination, not feasible in all neuropathology laboratories worldwide. Interestingly, each molecular subtype contains histologically distinct categories. For example, WNT subtype mainly includes classic histologic subtype, and groups 3 and 4 contain classic as well as LCA subtypes. SHH includes all histologic subtypes (classic, desmoplastic/nodular, and LCA); however, all desmoplastic/nodular MB belong to the SHH subgroup, at least in adults [28]. Whether or not histologic categorization of MB retains prognostic value once molecular subgrouping is widely available for all patients remains to be determined.

Molecular subgroups

The discovery of distinct molecular subgroups in MB has greatly helped our understanding of the molecular drivers of this disease and is being incorporated

in prospective clinical trials in pediatric MB. The four major subtypes of MB are SHH, WNT, group 3, and group 4. The most common subgroup in adults is SHH accounting for 60% of adult MB patients [12]. This is followed by group 4 and WNT tumors. Group 3 adult MB is exceedingly rare. Below is a description of demographics, clinical features, cytogenetic, and gene expression profiles of each subgroup with emphasis on the difference between these subgroups in adults and children.

SHH

SHH ligand binds to its cell surface receptor PTCH1 (patch-1) and inhibits its interaction with its neighboring cell surface receptor, SMO (smoothened). SMO, no longer inhibited by PTCH1, in turn activates intracellular proteins MYC and GLI, which translocate to the nucleus and activate their target genes which induce cell proliferation. The SHH subgroup comprises tumors with activated SHH pathway. The WHO 2016 classification further subdivides SHH-activated tumors into *TP53*-wildtype and *TP53*-mutant subgroups. *TP53*-mutant is more common in childhood than in infancy and adults, and it is predominantly associated with large cell/anaplastic histological subtype [24]. About 50% of children with SHH/*TP53*-mutant tumors harbor germline *TP53* mutations which may lead to diagnosis of Li-Fraumeni syndrome [29]. SHH/*TP53*-mutant tumors have been shown to have dismal prognosis in contrast to SHH/*TP53*-wildtype tumors in the pediatric population (5-year OS rate of 41% ± 9% for SHH/*TP53*-mutant vs. 81% ± 5% SHH/*TP53*-wildtype ($P < 0.001$) [29]. In adult SHH MB, *TP53* mutations are rarely seen and their prognostic significance is unclear.

The most common genetic abnormalities in SHH/*TP53*-wildtype tumors are *PTCH1* loss in all ages, *SMO*, *TERT* promoter, and *DDX3X* mutations mainly in adults, and *SUFU* (suppression of the fused homologue) mutation in infants [18, 30]. The SHH subgroup has been of particular interest in the development of targeted therapies in MB given clinically available SMO inhibitors. Genome sequencing of SHH subtype and functional assays in different xenograft models has demonstrated that SHH tumors harboring a *PTCH1* mutation were responsive to SMO inhibition, whereas those harboring *SUFU* mutation were resistant to SMO inhibition, as SUFU is a downstream effector of SMO and PTCH1 [30].

SHH subtype comprises all histology types, with classic being the most frequent, but all desmoplastic/nodular tumors belong to SHH subtype, at least in adults [28]. The 5-year survival rate for both children and adult MB is intermediate and about 70%. Common chromosomal abnormalities include loss of chromosomes 9q and 10q and gain of chromosome 3q. Importantly, chromosomal alterations and their implications are different in children and adults. For example, chromosome 10q loss is restricted to the SHH subgroup in children, but is seen in all 3 subtypes in adults. Interestingly, whereas 10q loss is not prognostic in pediatric MB, it is a strong predictor of poor prognosis in adults [12].

WNT

WNT signaling is characterized by "Wingless/Integrated" (WNT) extracellular protein binding to its receptor, Frizzled (FZD), and downstream activation of

intracellular pathways. Upon binding of WNT to FZD, β-catenin binding to cytosolic proteins such as APC, GSK3β, and Axin is disrupted. This frees the transcription factor β-catenin to translocate to the nucleus and to induce the expression of its target genes, such as the oncogenes *MYC* and *MYCN*. Activation of WNT signaling pathway is seen in 15% of adult MB and 10% of childhood MB [12]. WNT-activated MB are typically of classic histologic subtype, rarely metastasize, and have the best prognosis when compared with other subgroups. Importantly, the 5-year survival rate of WNT-activated MB in adults is 80% vs. > 95% in children, suggesting either differences in biological behavior or differences in treatment provided to patients of different age. Mutation in the β-catenin gene, *CTNNB1*, is the most frequent mutation in WNT-activated MB. The common cytogenetic abnormality detected in this subgroup is loss of chromosome 6q [31]. Unlike in pediatric patients, adult MBs with nuclear β-catenin and chromosome 6q deletion do not have improved prognosis. Interestingly, chromosome 6q loss is not confined to WNT in adults and has been described in SHH and group 4 [28] and the prognostic value of 6q loss in pediatric patients can be attributed to its enrichment in pediatric WNT MB [32]. In addition, while *CTNNB1* mutations are common in pediatric WNT group, half of adult MB WNT lack *CTNNB1*-activating mutation suggesting that alternative *CTNNB1*-independent mechanisms may be in place for WNT pathway activation in adults [33].

Overall, the excellent prognosis of WNT MB in comparison with other subgroups provides the rationale for consideration of de-escalated treatment options to reduce the risks of iatrogenic toxicity from conventional methods of radiation and chemotherapy in this patient population. However, caution is warranted in adult patients given the challenges to correctly identify WNT subgroup and the observed differences in outcome when compared with pediatric population.

Group 3

Group 3 and group 4 indicate molecular subtypes of MB where distinct molecular and cytogenetic profiles have been identified, but activation of a single signaling pathway associated with these subgroups has not been discovered. Group 3 comprises 25% of infants and children MB, but has rarely been described in adults [12, 34]. Group 3 contains classic and LCA histologies and has the worse prognosis of all subtypes with a very high tendency to metastasize. The most common genetic abnormality in group 3 is *MYC* mutation and amplification. This group contains the most chromosomal abnormality with gain of chromosomes 7, 1q, 17q, and 18q and loss of chromosomes 8, 11p, 5q, 10q, and 16q.

Group 4

Group 4 is the most common molecular subgroup of MB overall. About 20–25% of all adult MB (second in frequency after SHH) and 35% of children with MB (most frequent subgroup) belong to this group [18]. Similar to group 3, group 4 contains both classic and LCA histologies. Prognosis is intermediate with 5-year survival rate of about 50% in adults and children [28]. Of note, prognosis of group 4 MB seems worse in adults as compared with children [34]. Common genetic mutations include *MYCN* and *CDK6* amplification as well

chromosomal abnormalities including gain of chromosomes 7, 17q, and 18q and loss of chromosomes X, 8, and 11p.

In order to improve subgroup classification and prognosis predictions, Schwalbe et al. retrospectively collected 426 MB samples of pediatric patients 0–16 years of age at diagnosis and performed comprehensive molecular profiling and unsupervised class discovery of test and validation cohorts. They further subdivided the 4 molecular subgroups into 7 molecular subgroups with distinct clinical outcome (MB_{WNT}, $MB_{SHH\text{-}infant}$, $MB_{SHH\text{-}child}$, $MB_{Grp3\text{-}HR}$, $MB_{Grp3\text{-}LR}$, $MB_{Grp4\text{-}HR}$, $MB_{Grp4\text{-}LR}$), where high risk (HR) and low risk (LR) refer to clinical risk stratification described below. This study identified additional patient population with excellent prognosis outside of WNT subgroup and very high-risk non-infant population who would benefit from optimization of treatment options based on their clinically significant subgroups [35]. Similar studies in adult MB are needed to further improve our knowledge of disease risk stratification and to inform treatment options.

The main 4 subgroups described above have been also further divided into 12 subtypes based on distinct somatic copy-number aberrations, activated pathways, and clinical outcomes [36•], which describe the unexplained variations that were seen in clinical behavior and response to therapy in the 4 subgroups.

Clinical staging

Clinical staging of MB has been used for decades for risk stratification and to determine the intensity of adjuvant treatments. Chang staging for MB takes tumor dimension and disease spread into consideration to determine low- vs. high-risk groups (Table 1). Patients with tumors larger than 3 cm with unequivocal spread into the brainstem or beyond the aqueduct of Sylvius and/or foramen magnum noted during surgery or on imaging, or any metastasis outside of the brain parenchyma are considered high risk [37]. Another more commonly used risk stratification tool used in both adults and children was introduced by Packer et al. in 1999 [38] (Table 2). In this staging system, high risk (HR) MB is defined as age less than 3 years, or > 1.5 cm^2 of residual tumor after resection, or presence of any metastasis (M+). Patients who do not meet any of these criteria are classified as standard risk (SR). Adult patients with HR MB have worse survival than the SR patients [5, 17]. However, unlike in children, in adults, the prognostic value of extent of resection is controversial [5]. In addition, metastatic disease at diagnosis is much less frequent in adults than in children (7% vs. 30%) [11], and metastases after diagnosis are found earlier in children than in adults (20 months vs. 36 months) [17]. These differences indicate that the clinical staging of MB may not be as relevant in adults as is in children, and prognosis is likely driven mostly by molecular subgroups and not the extent of the disease.

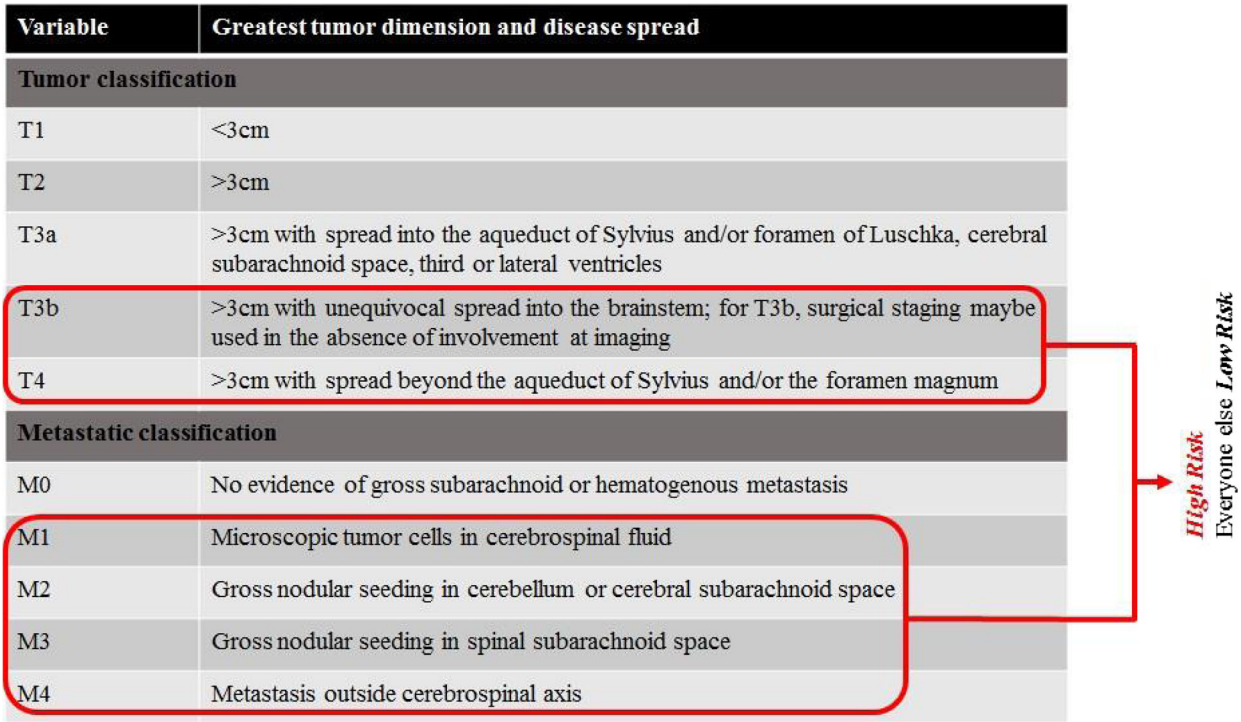
Treatment

Surgery

As extent of residual tumor has historically been shown to correlate with prognosis in children [7, 40], maximum safe resection has also been the goal of

Table 1. Chang Staging criteria for medulloblastoma. Reproduced from Chang CH et al. [37], with permission from the Radiological Society of North America

Variable	Greatest tumor dimension and disease spread
Tumor classification	
T1	<3cm
T2	>3cm
T3a	>3cm with spread into the aqueduct of Sylvius and/or foramen of Luschka, cerebral subarachnoid space, third or lateral ventricles
T3b	>3cm with unequivocal spread into the brainstem; for T3b, surgical staging maybe used in the absence of involvement at imaging
T4	>3cm with spread beyond the aqueduct of Sylvius and/or the foramen magnum
Metastatic classification	
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells in cerebrospinal fluid
M2	Gross nodular seeding in cerebellum or cerebral subarachnoid space
M3	Gross nodular seeding in spinal subarachnoid space
M4	Metastasis outside cerebrospinal axis



surgical resection in adult MB. More recently, the clinical importance of extent of resection in a subgroup-specific context has been studied retrospectively in the pediatric population [41]. Interestingly, no significant survival benefit was found for greater extent of resection (i.e., gross total resection or GTR vs. subtotal resection or STR) for patients with WNT, SHH, or group 3 tumors. However, there was a progression-free survival (PFS), but not OS, benefit of GTR over STR in group 4 tumors. In this study, the prognostic benefit of increased extent of resection was overall attenuated with consideration of molecular subgroups, questioning the benefit of "second-look" surgeries to remove small residual portions of tumor given the potential of neurological deficits associated with posterior fossa tumor resection. Nevertheless, current evidence suggests that maximum safe resection should remain the goal of initial surgery in both adult and pediatric MB patients. In addition to cytoreduction,

Table 2. Packer staging criteria for medulloblastoma [39]

	High risk	Standard risk
Residual disease	> 1.5 cm^2	< 1.5 cm^2 residual disease AND
Dissemination	Disseminated disease (M1–M4) OR	No metastasis (M0) AND
Age	Age < 3 years	Age > 3 years

third ventriculostomy or ventriculoperitoneal (VP) shunt placement may be needed to restore CSF flow. About 20% of adult MB patients in our retrospective cohort required VP shunts to relieve hydrocephalus (unpublished data).

Radiation therapy

Radiation is universally used for treatment of both SR and HR patients after resection of MB. In large retrospective studies and meta-analyses, 83–97.5% of adult patients had received radiotherapy [6, 42, 43]. Radiation is commonly delivered as CSRT with a boost to posterior fossa or the tumor bed. CSRT has been shown to be a favorable prognostic factor in large retrospective population-based studies [4••, 43] and a large meta-analysis of the literature [6••] in adult MB patients. A few prospective studies evaluating the role of CSRT in treatment of adult patients with MB have been reported. Friedrich et al. followed 70 adult patients ≥ 21 years of age with M0 MB treated with radiotherapy (35.2 Gy to the craniospinal axis and a boost to 55.2 Gy to the posterior fossa) in a prospective observational multicenter study [44]. Forty-nine of these patients received also maintenance chemotherapy, lomustine (CCNU), vincristine, and cisplatin, after radiation based on individual decisions by the patients or physicians. They reported a 4-year event-free survival (EFS) rate of 68% and OS rate of 89% after a median follow-up of 3.7 years. Silvani et al. reported on long-term outcome of 28 adult MB patients treated with cisplatin and etoposide followed by CSRT [45]. The median OS was 11.3 years and progression-free survival (PFS) and OS rates at 5 years were 57.6 and 80%, respectively. Several factors have been determined to be important in terms of benefit from radiation including dose of radiation, time from surgery to radiation, and type of radiation.

Radiation dose

Posterior fossa doses of above 54 Gy have been associated with improved 5-year disease control rate (91% vs. 30% in those receiving < 54 Gy) in the pediatric population [46]. However, higher radiation doses are also associated with significant neurocognitive and endocrinologic sequelae in long-term survivors in children [47]. The effect of radiation on neurocognitive function has not been studied prospectively in adults, but a recent retrospective study demonstrated frequent impairment in neurocognitive function in adult MB patients; 70% of whom had received radiation [48]. The dose delivered to the whole brain and spine and the use of a boost to the tumor bed vs. the posterior fossa vary depending on the risk groups. Given known neurocognitive effects of CSRT, reduced dose RT have been studied in childhood SR MB. Pediatric Oncology Group (POG) 8631 and Children's Cancer Group (CCG) 923 randomized 123 patients > 3 years of age with SR MB to CSRT of 36 Gy vs. 23.4 Gy, both followed by posterior fossa boost to 54 Gy, but the study was closed due to high relapse rate in the reduced dose arm [49]. Since reduced dose CSRT alone was insufficient, CCG 9892 treated 65 patients (ages 3–10) with non-disseminated MB with 23.4 Gy to the craniospinal axis with posterior fossa boost followed by 8 cycles of cisplatin, vincristine, and lomustine to determine if reduced dose RT can be complemented with chemotherapy [39]. The outcome compared favorably with those obtained in studies

using higher dose radiotherapy alone or standard dose chemotherapy plus RT [50]. These studies established the use of reduced dose CSRT and upfront chemotherapy in the pediatric population with SR MB. In HR pediatric population, there is consensus to delay RT for children < 3 years of age given high risk of severe neurologic impairment if their initial treatment incudes CSRT. HR pediatric population > 3 years of age are commonly treated with 36 Gy of radiation to the whole brain and spine with posterior fossa boost to a total dose of 55.8 Gy [51]. Depending on the degree of spinal dissemination, some may require higher spinal doses.

The exact radiation dose in adults is not well-established. Adults tolerate late CNS toxicities from CSRT better than children given their CNS developmental stage; however, their tolerance to acute and subacute radiation toxicity to their bone marrow and other organs exposed to radiation is not necessarily better [52] and they also suffer from cognitive sequelae [48]. Adopted from the pediatric literature, one of the following doses is typically delivered in adults; SR patients are typically treated with reduced dose (23.4 Gy) to the whole brain and spine with a posterior fossa boost of 30.6 Gy along with upfront chemotherapy as supported by two recent large retrospective studies [4••, 6••], or with full dose (36 Gy) to the whole brain and spine with a boost of 18.8 Gy to posterior fossa [14]. High-risk patients are treated with 36 Gy to the whole brain and spine with a posterior fossa boost of 18 Gy along with upfront chemotherapy. Earlier studies reporting leptomeningeal failure in the posterior fossa as the most common component of relapse in MB advocated for posterior fossa boosts [53]. However, given significant toxicity from boost to posterior fossa, particularly in children, conformal boost to the tumor bed was studied and was shown to allow for significant sparing of critical structures with similar posterior fossa failure rates similar to studies that had treated the entire posterior fossa [54]. Therefore, at some centers, CSRT is complemented with boost to the tumor bed as opposed to the entire posterior fossa, particularly in SR cases.

Time to radiation

Delaying the start of radiation after surgical resection and RT interruptions have been associated with poor survival in both children and adults. In a retrospective review, Abacioglu et al. showed that the 5-year disease-free survival rate for adult patients who started RT < 3 weeks, between 3–6 weeks and > 6 weeks after surgery was 0%, 85%, and 75%, respectively ($P = 0.002$) [55]. The PFS-5 of 0% for patients starting radiation less than 3 weeks from surgery is an unexpected finding, but it should not be over-interpreted given the small number of patients in each of these groups and the retrospective nature of the study, which may have introduced bias on the reason these patients started radiation earlier than others. In a pediatric prospective randomized study comparing neoadjuvant chemotherapy followed by RT with RT alone, a shorter time to RT completion was associated with improved EFS ($P = 0.01$)[56]. Based on these observations, efforts should be made to start RT 3–6 weeks after surgery with minimal disruptions, which should be a critical goal to keep in mind when referring patients to other institutions for a second opinion or to receive radiation therapy. We strongly recommend that both the referring and the accepting institution work diligently and in coordination to minimize any delays.

Type of radiation

The use of proton beam therapy is becoming more widespread both in children and adults with the goal to mitigate acute and late side effects of CSRT. Proton therapy provides adequate coverage of the target volume with reduced entrance dose and an abrupt dose cutoff leading to no exit dose compared with photon radiation [57]. Proton therapy has been shown to be superior to intensity-modulated x-rays (IMRT) in the pediatric population with MB with reduced risk of myelosuppression and ototoxicity [58, 59]. Similarly, proton radiation has been shown to result in less treatment-related morbidity including fewer acute gastrointenstinal and hematological toxicities when used in adults with MB [52]. An additional consideration is that proton beam CSRT may facilitate the use of upfront chemotherapy in adults due to better preservation of bone marrow reserve, although there is no prospective data at present to demonstrate or refute this potential benefit. Despite its advantages for treatment of patients with MB, proton radiation is not widely available, which limits its utility to the patients who are able to receive care at larger medical facilities.

Chemotherapy

Chemotherapy has an established role in treating pediatric MB patients, specifically in those < 3 years of age with the goal of delaying RT, in those with standard-risk disease treated with reduced dose CSRT, and in those with otherwise high-risk disease [56]. Exact cytotoxic agents and timing of upfront chemotherapy in relation to RT (prior to RT: neoadjuvant and after RT: adjuvant) have been controversial in both the pediatric and the adult population, although at present, adjuvant chemotherapy is favored in standard practice [60].

The adult MB literature suffers from paucity of prospective studies and treatment decisions are inferred from the pediatric literature. There are three prospective studies that have provided invaluable information about treatment of MB in adults and should serve as benchmarks for future prospective studies. Brandes et al. enrolled 95 patients ≥ 18 with adult MB from 1989 to 2001 and followed them longitudinally leading to publications in 2003, 2007, and 2010. In this study, low-risk (LR) patients received CSRT alone (36 Gy plus 18.8 Gy to posterior fossa) and high-risk (HR) patients received 2 cycles of chemotherapy prior to CSRT and up to 4 cycles of maintenance chemotherapy in metastatic patients after CSRT [14]. Patients received nitrogen mustard, vincristine, oral prednisone, and procarbazine between 1985 and 1995. After 1995, patients received cisplatin, etoposide, and cyclophosphamide. Followed from 1989 to 2009, the long-term survival outcomes of these patients were as follows: Survival at 5 and 10 years were 92% and 65% in LR vs. 58% and 45% in HR (P = 0.002 and 0.02, respectively). Survival at 5 and 10 years were 71% and 62% in M0 and 47% and 29% in M+ patients (P = 0.09 and 0.04, respectively). Residual disease had no impact on a 10-year PFS or OS [8]. Combination of cisplatin, etoposide, and cyclophosphamide is currently a widely used chemotherapy regimen to treat adult MB patient in many institutions. The second prospective study of adult MB evaluated feasibility and toxicity of chemoradiation in adult patients. The German Neuro-oncology Working Group (NOA)-7 performed a prospective single-arm phase II trial where 30 patients ≥ 21 with Chang Stage T1–T4 and M0 and M1 were treated with CSRT 35.2 Gy with a posterior fossa

boost plus concurrent vincristine followed by up to 8 cycles of cisplatin, lomustine, and vincristine. In this study, 70% of patients received more than 4 cycles of chemotherapy meeting the predefined feasibility goal of at least 45% of patients receiving at least 4 cycles of chemotherapy, but all patients needed dose reductions and only 12.5% of patients over 45 years received all 8 planned cycles. Sixty-seven percent of patients went off study due to toxicity under maintenance chemotherapy with polyneuropathy as the most common non-hematological toxicity and leukopenia as the most common hematological toxicity [16••]. This study points out the feasibility but poor tolerance of cytotoxic chemotherapy by adult patients and raises concerns about the utility and toxicity of concurrent vincristine. Polyneuropathy, a well-established side effect of vincristine, was a foremost reason for discontinuing the chemotherapy regimen in this study. The third prospective study was one conducted by Moots et al. which closed early due to poor accrual. Moots et al. treated 11 patients from 1998 to 2004 with neoadjuvant chemotherapy (cisplatin, etoposide, cyclophosphamide, and vincristine) followed by craniospinal radiation. Neoadjuvant chemotherapy did not impair the ability of patients to complete radiation; however, the outcome was worse than expected; overall response rate was 45% (5/11), with PFS-5 of 27% and OS-5 of 55% [61•].

Given a perceived (but poorly studied) better tolerance of RT in adults than in children, and poor tolerance of cytotoxic chemotherapy in adults, until recently, upfront chemotherapy was generally reserved for adults with high-risk disease only, although with high variability of care within and among different institutions. In addition, the benefit of chemotherapy in M0 patients who had received high-dose CSRT was uncertain. Two recent large retrospective studies have demonstrated the benefit of upfront chemotherapy in LR adult MB patients [4••, 6••]. Kann et al. performed a retrospective study evaluating the role of adjuvant chemotherapy in adult MB patients ≥ 18 using the National Cancer Data Base registry. The 5-year OS rate in propensity-matched patients who received radiation and chemotherapy upfront was 84% vs. 74% in those who had received radiotherapy alone ($P = 0.01$). On subgroup analysis, 5-year OS for patients who had received radiation and chemotherapy upfront vs. radiation only was improved for M0 patients, for patients who had received high CSRT doses, and for M0 who had received high-dose CSRT. Similar benefit from chemotherapy at diagnosis was seen in a recent meta-analysis. Kocakaya et al. performed a meta-analysis of 277 publications from 1969 to 2013 in adults ≥ 15 years of age. They identified 907 patients; 94% and 71% of which had received radiotherapy and chemotherapy, respectively. Patients who received chemotherapy at diagnosis (neoadjuvant or adjuvant) performed significantly better than those receiving only radiotherapy and those who received chemotherapy only at recurrence. These large retrospective studies have provided data in support of upfront chemotherapy use in adult MB patients, including SR patients. This data suggests that chemotherapy at diagnosis improves long-term survival; however, neither of these retrospective studies addressed the timing of upfront chemotherapy (neoadjuvant vs. adjuvant) or the type of chemotherapy to use, or the relative role of upfront chemotherapy depending on molecular subgroup.

The three prospective studies in adults used different timing of chemotherapy in relation to radiation: combination of neoadjuvant and adjuvant chemotherapy in Brandes et al. [14], neoadjuvant chemotherapy in Moot et al.

[61•], and combination of concurrent chemotherapy and adjuvant chemotherapy in Beier et al. [16••] studies. Even though timing of chemotherapy was not tested head-to-head in these trials, similar to the pediatric patients [60], survival outcome of neoadjuvant chemotherapy in Moot et al. study was worse than expected in adults [61•], and current available data does not support the use of neoadjuvant chemotherapy. In our practice, we typically treat patients with CSRT alone followed by adjuvant chemotherapy.

The prospective studies mentioned above favor the use of cisplatin-based chemotherapy along with etoposide and cyclophosphamide [14, 61•] or with lomustine and vincristine [16••]. Similar to adults, cisplatin and vincristine have been the backbone of chemotherapy trials in pediatric population. The use of lomustine vs. cyclophosphamide in a cisplatin-based regimen did not result in significant difference in PFS or OS rates in 5 and 10 years between treatment arms in children with SR disease [50]. Ototoxicity was seen in 25% of children, and cumulative cisplatin dose was not associated with EFS or OS, suggesting that lower doses of cisplatin can likely be used to help reduce ototoxicity without affecting survival outcome. Substitution of cisplatin for carboplatin has been studied in treatment of infants and young children with CNS tumors (20 out of 53 total patients had MB) and carboplatin had similar activity to cisplatin in otherwise similar regimens [62]. In our practice, we favor the use of the Carbo-CV (carboplatin, CCNU (lomustine) and vincristine) as adjuvant chemotherapy in adult patients after CSRT, with the substitution of carboplatin for cisplatin. In a case by case basis, we may use concurrent vincristine in younger patients without comorbidities with a low threshold to eliminate vincristine if symptoms of neuropathy develop. Unfortunately, no prospective data is available at present to determine the comparative efficacy and safety of these treatment modifications (carboplatin vs. cisplatin; removal of concurrent and/or adjuvant vincristine), and well-designed registry of natural history studies would be a reasonable alternative to investigate this further, given the challenges of obtaining prospective data [63].

Recurrent disease

Late relapse is more common in adult MB patients than in the pediatric population [15, 64]. This was apparent in Brandes et al.'s study particularly for low-risk patients with prolonged follow-up. Despite MB being a potentially curable disease, recurrent MB is difficult to treat, there are no curative treatments, and most patients succumb from the disease in less than 2 years [5]. With the discovery of distinct molecular subgroups mentioned above, identifying the particular molecular subgroups is crucial and highly recommended for consideration of clinical trials.

Conventional treatments

Conventional approach to treatment of recurrent MB includes consideration of re-resection, re-radiation, and conventional chemotherapy. The goal of re-resection is cytoreduction, symptom control, and obtaining new tumor tissue for histological confirmation and molecular analyses. Whereas MBs are known to preserve their molecular subgroup at recurrence, their specific molecular alterations do differ [65, 66]. Additionally, long-term survivors of MB are at risk of developing second CNS malignancies that can be indistinguishable from

recurrent MB in imaging studies [67–69]. Re-resection has not been studied in prospective studies, but anecdotal reports point to re-resection as a valid treatment alternative for a recurrent disease [70]. However, re-resection, the same as resection at original diagnosis, is not enough for disease control if used alone and should be followed by additional therapies.

The benefit from re-radiation is uncertain as it has not been formally evaluated in prospective studies. In a retrospective study, re-radiation in 38 pediatric patients with recurrent MB resulted in a statistically significant improvement in OS from initial diagnosis with a 5- and 10-year OS rates 55% ± 14% and 33% ± 16% vs. 46% ± 14% and 0% for re-irradiated SR patients vs. others, respectively ($P = 0.036$), with the caveat of increased rate of necrosis in the re-irradiated patients [71]. In addition, a non-statistically significant difference in EFS favoring re-radiation was seen in a prospective pediatric MB population who underwent re-radiation after high-dose chemotherapy with autologous stem cell rescue [72]. In a study by Bakst et al., re-radiation provided the most benefit to patients with no evidence of disease after surgical resection [73]. Potential benefits from re-radiation should be weighed against the risk of cumulative toxicity, radiation necrosis, and cognitive impairment. It is also important to keep in mind that radiation may provide local control, but significant rates of out-of-field metastasis after re-radiation for MB have been reported [71]. Consideration of systemic treatments in recurrent disease is crucial given potential benefit of improved systemic control and lower risk of radiation toxicity.

The exact chemotherapy regimen to be used at the time of recurrence is unclear. In the case of prior durable response (> 2 years in adults), consideration of cytotoxic platinum or cyclophosphamide-based regimens is reasonable. In addition, chemotherapies with better tolerance profile such as single-agent temozolomide or various combinations of temozolomide, irinotecan, and bevacizumab have shown some activity in the recurrent setting [74–77].

Stem cell transplant

Given the promising outcome of stem cell transplant in recurrent pediatric MB [78–80], high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) has also been studied for treatment of adult MB patients [81]. Zia et al. treated 6 recurrent adult MB patients with surgical debulking followed by HDCT/ASCT and radiotherapy when possible. They demonstrated median duration response of 13.5 months and median survival of 21.5 months after first ASCT. No treatment-related mortality was observed, but one patient developed severe multiorgan dysfunction and multiple enhancing cerebral lesions thought to be related to therapy. Similarly, Dunkel et al. treated 25 previously irradiated MB patients (median age 13.8 years; 7–44.7 years) with HDCT followed by autologous stem cell rescue. Median survival was 26.8 months, but 3/25 (12%) died of treatment-related toxicities within 30 days of stem cell rescue [72]. In a retrospective study, the outcome of adult patients treated with HDCT and ASCT ($n = 10$) was compared with those who had received conventional chemotherapy ($n = 13$). In this study, HDCT/ASCT was associated with increased survival ($P = 0.044$) and a longer time to disease progression ($P = 0.028$) with the HDC/ASCT having median survival of 3.47 vs. 2.00 years in the conventional chemotherapy group [82]. These results are promising;

however, the retrospective nature of this study, the small number of patients, and the risk of selection bias should be considered when interpreting the data.

Ongoing clinical trials

Molecularly targeted trials

The discovery of various molecular subgroups has been the incentive for the development of novel molecularly targeted trials in MB. SHH MB comprising the most common molecular subgroup of MB in adults best exemplifies the use of small molecular inhibitors of activated signaling pathways in MB. Vismodegib and sonidegib are two SMO inhibitors that are currently in clinical trials for treatment of MB. Vismodegib, FDA-approved in 2012 for treatment of basal cell carcinoma, was shown to be well-tolerated and have anti-tumor effect in a pediatric MB phase I trial [83]. Vismodegib was studied in a phase II trial in children and adults 22 years or older with recurrent or refractory medulloblastoma (NCT00939484). Prolonged stabilization was seen in 41% of patients in the SHH subgroup. Four out of 4 non-responders' tumor tissue tested demonstrated mutations in SHH pathway downstream of SMO, and 2 out of 4 responders' tumor tissue tested showed mutation upstream of SMO consistent with the mechanism of action of vismodegib [84]. Interestingly, vismodegib has been shown to result in a sustained response in a case of unresectable multifocal MB, which likely belonged to group 4 based on iso 17q chromosome and *TP53* mutation indicating that vismodegib may block alternate forms of downstream SHH-activated pathways outside of the classical SHH subgroup [85]. Sonidegib was tested in a phase I trial in adult patients with MB and basal cell carcinoma and was shown to have anti-tumor activity in those with SHH-activated pathway. In addition, in a phase II study of sonidegib in patients with SHH pathway–activated relapsed MB (NCT01708174), overall response rate was similar to other investigational agents at about 18%. Durable responses were observed in three responders; however, detailed genetic makeup of the responders vs. non-responders was not described [86]. As it is commonly the case with inhibition of signaling pathways, intrinsic and acquired resistance to these inhibitors has been described. *SMO-D437H* mutation has been shown to disrupt the ability of vismodegib to bind SMO, but has no effect on downstream SHH signaling [87]. In addition, upregulation of GLi2 and PI3K has been shown to confer resistance to SMO inhibitors [87, 88]. To overcome resistance mechanisms, BET bromodomain inhibitor which modulates GLi expression downstream of SMO/SUFU has been proposed as a strategy for treating SHH-driven tumors with intrinsic or acquired resistance to SMO inhibitors [89].

WNT-activated MB characterizes a second subgroup of MB with potential benefit from molecular-targeted therapies. Despite the discovery of the WNT pathway more than 30 years ago, therapeutic agents targeting WNT pathway are not in clinical use yet. Challenges involved in successful clinical development of WNT-targeted therapies include extensive crosstalk with other signaling pathways and significant role of the WNT signaling in normal development [90]. Norcantharidin, a protein phosphatase inhibitor which promotes loss of nuclear β-catenin, has been shown to have anti-tumor effects in MB cell lines and to promote neuronal differentiation in xenograft mouse models [91]. Interestingly, Zinke et al. have shown that lithium chloride which leads to β-catenin

stabilization reduces growth of SHH-driven MB tumor spheres by downregulating GLi1 [92]. As these two pre-clinical agents with opposing roles on β-catenin indicate, there are likely interactions between the SHH and the WNT pathway which need to be further explored. Zinke et al. proposed that β-catenin stabilization increases its physical interaction with GLi1, leading to GLi1 degradation and inhibition of SHH signaling.

Unlike the SHH and WNT subgroups, there are no well-defined signaling pathways activated in groups 3 and 4. Elevated MYC expression has been found in about 10–20% of patients within group 3 [93]. In addition, *MYC* paralog, *MYCN* is amplified in 6% of patients within group 4 [94]. Pemetrexed and gemcitabine, FDA-approved cytotoxic chemotherapy agents, were identified as compounds that preferentially inhibited group 3 MB in a high-throughput cell-based assay. They also increased survival of xenograft mice bearing human group 3 MB that overexpress MYC while having little effect on mouse SHH MB [95]. Pemetrexed and gemcitabine are amongst agents that are being tested in a risk-directed therapy trial in newly diagnosed MB (NCT01878617) for patients 3–21 years of age stratified based on both clinical and molecular risks.

Given the growing knowledge of molecular risk factors and their impact on prognosis, there have been efforts in escalating and de-escalating treatments for MB patients with the goal of treatment optimization based on expected prognosis. The pediatric trial mentioned above (NCT01878617) is a prototypical trial of treatment based on risk stratification where patients' clinical risk (low, standard, intermediate, and high) as well as molecular subtypes (WNT, SHH, non-WNT/non-SHH) will be determined prior to enrollment into the various arms. The goal of this trial will be to determine (1) whether patients with low-risk WNT tumors can be treated with a lower dose of radiation and lower dose of cyclophosphamide as compared with prior trials, (2) if adding targeted therapies after standard chemotherapy will benefit SHH-activated tumors, (3) if addition of new chemotherapy agents to the standard chemotherapy will improve outcome for intermediate and high-risk non-SHH/non-WNT patients, and (4) whether standard-risk non-WNT/non-SHH tumors can be treated with reduced dose of cyclophosphamide. A similar study is addressing low-dose radiation without concurrent vincristine followed by fewer cycles of chemotherapy (7 as opposed to 9) alternating between cisplatin/lomustine/vincristine and cyclophosphamide/vincristine in WNT-activated average risk medulloblastoma (ACNS1422) in patients 3 years of age or older. These studies attempt to test the use of targeted agents and reduce the risk of iatrogenic-induced morbidity in patients with otherwise good prognosis. However, it is not yet clear if good prognosis of certain subgroups such as WNT subgroup is explained by tumor intrinsic factors or by responsiveness to current standard of care [96]. Treatment de-escalation should therefore only be practiced within the context of clinical trials.

Ongoing clinical trials

Immunotherapy has changed the landscape of treatment of metastatic melanoma [97], non-small cell lung cancer (NSCLC) [98], and renal cell carcinoma (RCC) [99], and its FDA approval indications are on the rise for various types of solid cancers [97]. Immunotherapy has been a subject of intense investigation

in treatment of CNS tumors given profound immunosuppressive microenvironment in malignant CNS tumors such as glioblastoma (GBM) [100].

However, immune checkpoint inhibitors (CPI), the forefront of immunotherapy modalities, have failed as monotherapy in recurrent GBM studies [101, 102]. Lack of success of CPI treatment is thought to be due to lack of tumor T cell infiltrates in GBM, and similar findings have been reported in MB [103, 104]. In a recent immune profiling study of pediatric MB tissue, Vermeulen et al. have shown that cytotoxic T cells infiltrate MB tissue with variable activation status and show no correlation with overall survival [104]. In addition, MB cells were shown to have impaired antigen presentation due to downregulated MHC-1 expression and lack of expression of the T cell inhibitory ligand, PD-L1. This raises the question whether the PD-1/PD-L1 axis has a role in immune escape by MB. The PD-1 blocker, nivolumab, is currently under investigation in adult patients with rare CNS tumors to include MB (NCT03173950).

Active transfer of immune cells such as T cells, dendritic cells (DCs), and NK cells into the tumor microenvironment is another form of immunotherapy with potential anti-tumor effect which can overcome lack of cytotoxic T cell infiltration and impaired antigen presentation seen in MB. CAR T cells target specific antigen(s) on tumor cells and mount T cell–mediated anti-tumor immune responses. Durable regression of MB after regional and intravenous delivery of anti-HER2 CAR T cell has been demonstrated in xenograft mice models of MB [105]. DCs are considered to be the most potent antigen-presenting cells of the immune system and are engineered to target a plethora of tumor antigens specific to a patient's tumor or to target a common antigen presented by most tumors in treatment of cancer. Autologous DCs loaded with a personalized cohort of total tumor messenger RNA amplified from a personalized cDNA library have been developed [106] and are currently in clinical trials in children and adult patients ≤ 30 years of age with recurrent medulloblastoma and primitive neural ectodermal tumors (Re-MATCH trial; NCT01326104).

The main challenge of DC vaccine generated by exposure to entire tumor antigen load (autologous DC vaccines) is that it requires tumor collection from each individual patient and prolonged processing times. Alternative strategies that are not dependent on tumor antigen with focusing on the innate immune system can be beneficial. NK cells are large lymphocytes of the innate immune system that are able to lyse infected cells directly, without specific immunization, via secreting granules containing perforin and granzymes or by inducing antibody-dependent cellular cytotoxicity of antibody-coated cells [107]. MB cells have been shown to express ligands for triggering NK cells receptors and to be susceptible to NK-mediated cytotoxicity in pre-clinical models [108]. A phase I dose escalation trial of NK cells in pediatric MB where NK cells are delivered to the posterior fossa via the fourth ventricle catheter after surgery is currently ongoing at MD Anderson Cancer Center (NCT02271711). Pre-clinical data suggests that SHH inhibition in SHH-activated MB cell lines raises the expression and secretion of chemokines involved in NK cell migration [109], suggesting that combination of targeted therapy and immunotherapy may have heightened effectiveness in particular MB subtypes.

Even though immune cell signatures of the MB subgroups have not demonstrated independent prognostic value to date [110], knowledge of specific antigenic profile of the tumor and immune cell composition of tumor

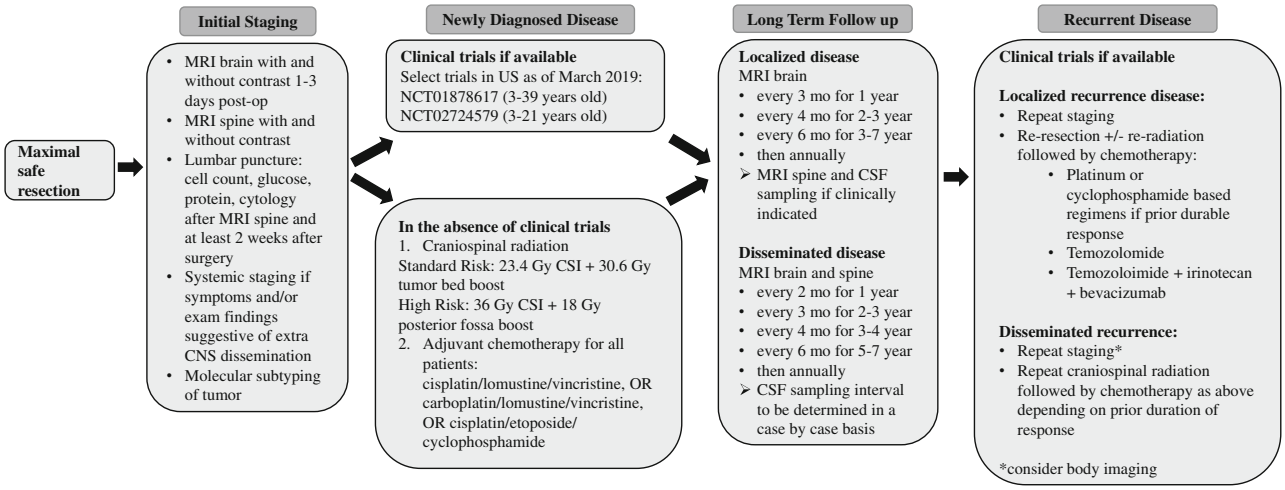


Fig. 1. Adult medulloblastoma management algorithm. CSI craniospinal radiation, CSF cerebrospinal fluid.

microenvironment in various subtypes is essential for successful implementation of immunotherapy in treatment of MB. Subgroup-specific immune microenvironment profiling in MB tumors has shown that SHH MB displays strong signatures of fibroblasts, T cells, and macrophages, while markers of cytotoxic lymphocytes are enriched in group 4 tumors [110]. In addition, immunologic characterization of pre-clinical models of molecular subtypes of MB in mice have shown higher percentages of DCs, infiltrating lymphocytes, myeloid-derived suppressor cells, and tumor-associated macrophages in murine SHH tumors compared with group 3. Interestingly, PD-1 blockade showed superior anti-tumor efficacy in animals bearing group 3 intracranial tumors compared with SHH tumors [111]. These results indicate that immunologic differences in various molecular subgroups likely dictates response to immunotherapy.

Immunoprofiling of adult MB tissue and understanding of MB tumor microenvironment with attention to molecular subgroups is needed in determining which immunotherapy modality may be most effective in treatment of MB. However, rarity of adult MB limits performing such studies within single institutions. Therefore, access to multi-institutional tumor repositories is needed to aid our understanding of immune cell composition of adult MB and to implement successful immunotherapy strategies to treat this disease.

Summary

Treatment of adult MB has been evolving over the past few years. Management of adult MB is largely inferred from pediatric MB trials as prospective studies in adults are scarce due to the rarity of the disease in adults. Despite this, large retrospective studies have been instrumental in providing rationale for our current treatment regiments. Upon clinical and molecular risk group identification after diagnosis, clinical trials such as NCT01878617, a clinical and molecular risk-directed therapy trial, and

ACNS1422, a reduced therapy trial for SR WNT–driven patients, should be considered for patients who meet the age cutoff. However, caution is warranted with de-escalation approach in adult patients given the challenges to correctly identify WNT subgroup and the observed differences in outcome when compared with pediatric population.

In the absence of available clinical trials, we recommend that the treatment of newly diagnosed MB in adult patients includes CSRT followed by platinum-based combination cytotoxic chemotherapy regimens such as a modified Packer's regimen (Carbo-CV; carboplatin, lomustine (CCNU), and vincristine). Long-term surveillance is indicated in adult MB patients as late recurrences are common (median time to first recurrence of ~ 8 years in our unpublished case series). We recommend restaging with MRI spine and CSF analysis when recurrence is suspected. At recurrence, targeted therapy and immunotherapy clinical trials should be considered followed by re-resection or biopsy and consideration of re-challenge with cytotoxic chemotherapies depending on prior responses. In addition, temozolomide has shown some activity in recurrent MB. We favor delaying re-radiation if possible to avoid risk of radiation-induced necrosis and myelotoxicity which may hinder future use of cytotoxic chemotherapy. See Fig. 1 for a proposed adult MB management algorithm.

With the discovery of molecular subgroups with distinct demographic, clinical, and prognostic characteristics, our knowledge of molecular drivers of MB has dramatically increased. This has led to the introduction of targeted therapy for treatment of MB, most notably the use of SMO inhibitors for SHH-driven tumors. In addition, pre-clinical data indicate that there may be subgroup-specific susceptibility to already FDA-approved drugs such as the use of gemcitabine and pemetrexed for group 4 MB. Furthermore, varying prognosis of the molecular subgroups have introduced the concept of de-escalation therapies to reduce the risk of iatrogenic toxicities. Combination of targeted therapies and de-escalation/intensification therapies is being tested in NCT01878617, a clinical and molecular risk-directed therapy trial, in patients 3–21 years of age. Similar trials in adult patients older than 21 and additional studies to identify and validate a high-risk molecular signature are needed to optimize management of adult MB patients. Given the rarity of adult MB, multi-institutional clinical trials are needed to achieve meaningful accrual. In addition, such multi-institutional trials will aid in developing tumor repositories for future molecular and immunoprofiling of adult MB tumor which will lay the foundation for future next-generation clinical trials and improved outcome of these patients.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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