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Proceedings of the Comprehensive Oncology Network Evaluating Rare CNS Tumors (NCI-CONNECT) Adult Medulloblastoma Workshop

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†NCI-CONNECT Adult Medulloblastoma Workshop, please see full list of workshop participants at the end of the manuscript.

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Abstract

Background. Medulloblastoma (MB) is a rare brain tumor occurring more frequently in children in whom research has been primarily focused. Treatment recommendations in adults are mainly based on retrospective data and pediatric experience; however, molecular features and treatment tolerance differ between the 2 age groups. In adults, prognostic tools are suboptimal, late recurrences are typical, and long-term sequelae remain understudied. Treatment has not adapted to molecular classification advances; thus, the survival rate of adult MB has not improved.

Methods. In 2017, the National Cancer Institute (NCI) received support from the Cancer Moonshot℠ to address the challenges and unmet needs of adults with rare central nervous system tumors through NCI-CONNECT, a program that creates partnerships among patients, health care professionals, researchers, and advocacy organizations. On November 25, 2019, NCI-CONNECT convened leading clinicians and scientists in a workshop to review advances in research, share scientific insights, and discuss clinical challenges in adult MB.

Results. Working groups identified unmet needs in clinical trial design, tissue acquisition and testing, tumor modeling, and measurement of clinical outcomes.

Conclusions. Participants identified opportunities for collaboration; discussed plans to create a working group of clinicians, researchers, and patient advocates; and developed specific action items to expedite progress in adult MB.

Key Points

- A diagnosis of medulloblastoma in adults is less common than in children, and the disease differs in multiple clinical, molecular and therapeutic aspects.
- A multidisciplinary panel convened by NCI-CONNECT met to review clinical and research challenges to elaborate an action plan and help expedite progress.
- The path forward includes updating the NCCN guidelines, launching prospective trials for adults with newly diagnosed and recurrent tumors, and creating a working group to continue these efforts.

Developing therapies for rare central nervous system (CNS) cancers is a formidable task.[1] The mission of NCI-CONNECT, housed in the National Cancer Institute's (NCI's) Center for Cancer Research, Neuro-Oncology Branch, and supported by the Cancer Moonshot℠, is to address this challenge and expedite progress for adults with rare CNS tumors (see https://www.cancer.gov/rare-brain-spine-tumor/tumors).[2–4] On November 25, 2019, NCI-CONNECT convened a workshop on adult medulloblastoma (MB). This manuscript summarizes the workshop proceedings, which included presentations on challenges of clinical care and ongoing clinical research projects, followed by in-depth working group discussions. Participants recognized the critical need for collaborative efforts to advance care and developed an action plan to address challenges and expedite progress for adults with MB.

The Patient Perspective: What Are the Specific Needs of Adults With MB?

Nicole Willmarth, PhD; Brittany Cordeiro

The workshop opened by highlighting the needs of adults with MB in a joint presentation by the American Brain Tumor Association (ABTA), a patient advocacy organization, and NCI-CONNECT. ABTA's mission is to advance the understanding and treatment of brain tumors, with the goals of improving, extending, and ultimately saving the lives of those impacted by a brain tumor diagnosis. The organization hosts *ABTA Connections*, an online support community with more than 27 000 members; however, between 2011 and 2019 only 12 postings were specific to adults with MB (age 18 or older). Most were between ages 20 and 24, and most postings were by caregivers. The adults who posted needed help coping with what is traditionally believed to be a pediatric tumor, expressed a desire for more guidance on treatment decisions (eg, whether to receive chemotherapy at diagnosis), and reported feeling lonely and uncertain about the future. Participants reported it was upsetting learning their oncologist had never seen an adult with MB. *ABTA Careline* is another resource providing patient information by email and phone about varied topics such as financial assistance and second opinions. From 2001 to 2019, 31 individuals inquired about adult MB with most contacts initiated by caregivers. Resources and information were provided depending on individual need and included online support networks or local support groups, financial resources, and printed educational materials, such as the ABTA Medulloblastoma Brochure.

Through social media outreach, NCI-CONNECT also gathers input on the experience of adults with MB. Twitter and Facebook users were encouraged to describe finding care, how they felt during treatment, quality-of-life (QoL) issues and challenges, and their experience trying to find information about adult MB. Similar to the ABTA findings, patients expressed confusion about the treatment decisions and a need for support to process information. Both groups expressed a consensus that connecting adults with MB with each other would be beneficial as this population feels isolated and in need of support.

Introduction to Adult MB: Challenges and Opportunities

Marta Penas-Prado, MD

MB is a malignant primary CNS tumor that accounts for less than 1% of brain tumors in adults. In patients age 15 and older, less than 150 new cases are diagnosed each year in the United States and an estimated 450 in Europe.[5,6] While MB is more common in children age 14 and younger, patients between ages 15 and 39 represent about 30% of all cases.[6] For the purpose of this workshop, "adult MB" refers to those diagnosed at age 18 or older, although the biology of the disease in late adolescents seems similar to that of adults, and MB is recognized as one of the cancers occurring in the adolescent and young adult (AYA) population.[7] Patients age 40 and older account for less than 8% of all MB cases, but represent an important therapeutic challenge. Research priorities have been skewed toward pediatric MB and treatment recommendations in adults are frequently based on retrospective data and the pediatric experience due to limited clinical trial data and lack of randomized studies.[8,9] However, the molecular features of MB in adults[10,11] and their tolerance to treatment[12] differ from pediatric patients, warranting research focused on adults.

Despite advances in molecular classification there has been little change in treatment and, as expected, no significant improvement in survival for adult MB over the last 2 decades. Currently, approximately 30% of cases recur after therapy and survival rates are dismal.[13,14] As discussed

later, the introduction of smoothened (SMO) inhibitors in clinical trials for patients with recurrent MB who have the Sonic Hedgehog (SHH) subgroup (SHH-MB) has produced some modest responses but, when given as a single agent in the recurrent setting, has failed to improve survival.[15] Risk stratification in adults still depends exclusively on clinical factors and is adapted from pediatric data, classifying patients in 2 disease categories: *standard* or *average risk* (gross total resection defined as ≤1.5 cm^2 postoperative residual tumor and absence of metastatic dissemination inside or outside the CNS), and *high risk* (>1.5 cm^2 residual and/or presence of metastatic dissemination at diagnosis).[8] Strikingly, most adults present with standard-risk disease, but some still experience recurrence (often with extraneural dissemination) and succumb to the disease.

Although the understanding of molecular markers that can determine prognosis in pediatric MB has advanced considerably,[11,16] these markers are either infrequent in adults (eg, *TP53* mutations, *MYC* and *MYCN* amplification), or their association with specific molecular subgroups and prognosis is unclear. For example, monosomy 6 is almost exclusively seen in pediatric WNT MB, but is present in both SHH and Group 4 tumors in adults; furthermore, monosomy 6 was found not to be a positive prognostic marker in adult MB. Unlike in children, 50% of adult MBs with loss of 6q and nuclear beta catenin positivity had no *CTNNB1* mutations.[17] *TP53* mutations seem to be highly enriched in childhood SHH MB (SHH-α) and confer prognostic significance within this subtype, but are infrequent in adults (SHH-δ) and were not found to be associated with prognosis in non-α SHH subtypes.[11] Thus, clinical and molecular prognostic tools in adults remain suboptimal and late recurrences with dissemination both inside and outside the CNS are typical but unpredictable based on clinical factors alone, which is further obscured by heterogeneous upfront therapies, as discussed later.[14,18] Moreover, long-term sequelae in survivors are understudied and therefore, poorly understood.[19,20]

Lack of a standard approach based on randomized prospective trials is a major impediment to improving treatments. Upfront treatment typically includes surgical resection to achieve a gross total resection (if safe) and obtain tissue for diagnosis and determination of molecular subgroup and risk factors, followed by craniospinal irradiation (CSI). While available data in children support the use of upfront postirradiation chemotherapy in all risk groups,[21] this approach has not been tested in randomized trials in adults. However, cumulative evidence from a prospective observational multicenter study,[22] a prospective pilot trial,[12] and 2 large retrospective studies (a meta-analysis and a National Cancer Data Base analysis),[23,24] among others,[13,25,26] have indicated feasibility and benefit of first-line chemotherapy on survival, albeit with associated toxicity. Furthermore, an optimal chemotherapy regimen that balances toxicity and benefit on survival has not been defined. Due to this limited evidence, treatment of adults is still highly variable within and across institutions and internationally.[27] To better understand treatment variability and outcomes, a retrospective review collected data on 200 adults with MB seen at The University of Texas MD Anderson Cancer Center (MDACC) (Nazanin Majd et al., unpublished observations).[18] This study showed substantial heterogeneity in treatment approach and documentation of staging and other clinical data when patients were seen at multiple institutions, which is common for adults with MB. In fact, a subset of standard-risk patients whose records contained detailed clinical and treatment data corroborating their correct risk classification and receipt of appropriate treatment had better outcomes compared with the whole standard-risk cohort whose clinical documentation often precluded verification of risk classification. This highlights the limitation and bias of using retrospective, nonstandardized clinical data, highly prone to incompleteness and inaccuracies, in large molecular studies and as a benchmark for trial design. Further, it supports the collection of comprehensively annotated clinical information in well-designed registries when clinical trials data are not available.

Another major challenge to improving treatment is the lack of a standard tumor subgroup assignment method. The 2016 World Health Organization (WHO) CNS tumor classification does not make specific recommendations regarding the various methods for assessing histological and molecular groups or genetic alterations, leaving the choice of methodology to the end user. A new edition, in progress, will likely incorporate new data suggesting existence of subtypes within the classically defined subgroups.[11,28] According to the 2016 WHO classification, MB can be defined histologically or genetically (Table 1), but no biomarkers determining prognosis are included beyond *TP53* mutation in SHH-MB, which is very rare in adults.[29] The International MB Working Group has recommended molecular classification algorithms combining different immunohistochemistry (IHC) and molecular testing methods, although these are based primarily on pediatric populations.[30]

The molecular profiles differ between adults and children,[10] indicated by 70% incidence of SHH-MB in adults versus 30% in children and other features such as an increased somatic mutation frequency in adults.[31] SHH is comprised of at least 4 subtypes, with δ (relatively devoid of *TP53* mutations and strongly enriched for *TERT* promoter mutations) being the most common in older patients.[11] Other unique molecular feature of adult SHH MB includes the presence of occasional *IDH* mutations and highly recurrent hotspot noncoding somatic mutations of U1 spliceosomal small nuclear RNAs (snRNAs) in almost all adults.[32,33] Group 4, the second most common subgroup in adults, comprises approximately 20% of all cases and carries a worse prognosis in adults than in

Table 1. Current WHO Classification of Medulloblastoma (2016)[21]

MB, histologically defined[a]	MB, genetically[b] defined
Classic	WNT-activated
Desmoplastic/nodular	SHH-activated, *TP53* mutant
Extensive nodularity (MBEN)	SHH-activated, *TP53* wild type
Large cell/anaplastic (LCA)	Non-WNT/Non-SHH (Group 3, Group 4[c])

[a]The 5 histological variants are not evenly distributed among molecular subgroups.
[b]Based on transcriptome or methylome profiling.
[c]Provisional variants.

children. WNT is third in frequency and may also be associated with worse prognosis in adults, whereas Group 3 is rare. Importantly, given the retrospective nature of the data, it is unclear why Group 4 and WNT tumors are associated with worse prognoses in adults. In addition to possible differences in tumor biology, other possible factors include incorrect or insufficient staging (including suboptimal imaging); insufficient first-line therapy (adults are often treated with CSI alone or receive less chemotherapy due to worse tolerance); chemotherapy-related deaths; delays in starting CSI after resection (in pediatric MB trials it has generally been mandated to start within 30 days of resection); and failure to identify the few known high-risk molecular features.

In conclusion, the lack of prospectively validated tools for risk stratification beyond clinical factors in adults limits the ability to ascertain prognosis and identify optimal treatment. Development of risk-adjusted upfront treatment based on molecular risk factors, long-term follow-up, and better rescue treatments are all critical needs for optimal care.

Clinical Trials for Adults With MB

An overview of upcoming upfront trials (European Organisation for Research and Treatment of Cancer [EORTC], Alliance) and ongoing trials (St. Jude, PBTC) enrolling adults with MB was provided during the workshop. All trials focused on the use of SMO inhibitors for patients with newly diagnosed or recurrent SHH-MB. The typical presence of SHH pathway mutations at the level or upstream of SMO in adolescents and adults makes therapy with SMO inhibitors attractive for testing and is supported by preclinical and clinical data. In SHH-δ tumors, *PTCH* and *SMO* mutations are present in 50% and 20% of cases, respectively.[34,35] Mouse models treated with SMO inhibitors show impressive effects in targeting and downregulating the SHH pathway.[36,37] Although clinical trials have shown a high proportion of responders to single-agent SMO inhibition among patients with recurrent SHH-MB,[38] development of resistance is common[39] and typically related to SMO mutations conferring resistance or downstream aberrations (eg, *SUFU* mutations, *MYCN* amplification, or *GLI2* amplification) and *TP53* mutations.[40] Importantly, trials of SMO inhibitors in newly diagnosed pediatric patients had to be terminated because of growth plate toxicities in young children on prolonged therapy.[41] Therefore, skeletally mature patients (postpubertal and adults) are the ideal population to test SMO inhibitors to reduce relapse in newly diagnosed disease and also in recurrent disease as combination therapy, given the rapid development of resistance when used as a single agent.

EORTC Trial: Personalized Risk-Adapted Therapy in Postpubertal Patients With Newly Diagnosed MB (PersoMed-I, EORTC-1634-BTG)

Peter Hau, MD.—The EORTC has developed an international trial for adults with newly diagnosed MB to be launched in 2020, incorporating comprehensive translational studies. The main objective is to determine if the addition of the SMO inhibitor sonidegib to upfront therapy with maximal safe resection, reduced-dose CSI (23.4 Gy) and multiagent chemotherapy (vincristine, lomustine, and cisplatin), improves progression-free survival (PFS) in patients age 16 or older with SHH-MB, *TP53* wild type, stage M0 or M1, as compared with full-dose CSI (35.2 Gy) combined only with chemotherapy. Though not included in the primary objective, adults with MB of all other subgroups will be randomized to full-dose or reduced-dose CSI with the same upfront chemotherapy, minus sonidegib (Supplementary Figure 1). This trial is modeled on the recent multicenter NOA-07 pilot feasibility trial, in which adults (age 21 and older) with newly diagnosed MB (Chang stage T1–4 and M0 or M1) received full-dose photon CSI with concomitant weekly vincristine, followed 6 weeks later by maintenance chemotherapy with lomustine, cisplatin, and vincristine for up to 8 cycles.[12] Radio-polychemotherapy was proven feasible with 70% of patients receiving at least 4 cycles, but also led to considerable toxicity, and patients older than age 45 experienced a significantly higher rate of severe adverse events. Based on these findings, the chemotherapy regimen in the upcoming EORTC trial will be modified to decrease the amount of vincristine and the total number of cycles, with detailed guidelines for dose modification and discontinuation of drugs in case of toxicity.

This study will recruit approximately 205 patients (postpubertal in the SHH arms and age 18 and older in all other arms). Neuropathology review will be performed centrally before initiation of therapy and will be based on integrated histopathological and molecular subclassification through DNA methylation-based brain tumor classifier and next-generation gene panel sequencing. This will allow for detection of high-risk molecular features, stratification in molecular subgroups, and assignment to the experimental arm. Secondary objectives and translational studies will include short- and long-term health-related QoL, neurocognitive function and social outcome, endocrine function, correlation of molecular markers with measures of clinical benefit, and protons versus photons toxicity. Circulating tumor DNA in cerebrospinal fluid (CSF) obtained via lumbar punctures will be evaluated longitudinally to monitor response and resistance and to discover biomarkers for response prediction. A radiomics and radiogenomics subproject will noninvasively observe changes over time that might be associated with genotype changes, which could shed further light on treatment resistance or responsiveness. A radiotherapy subproject will monitor quality assurance within the protocol, clinical outcomes including toxicity, patterns of failure, dose–response effects, and identify image-based and clinical risk factors determining outcomes. Projected accrual is 36 months, with primary endpoint analysis expected in 2028.

Alliance Trial: Comprehensive Management of AYA and Adult Patients With MB or Pineal Embryonal Tumors With a Randomized Placebo Controlled Phase II Trial Focusing on SHH Pathway Inhibition in SHH Subgroup Patients (the AMBUSH Trial: Adult and Adolescent MB Using Sonic Hedgehog Trial)

Anita Mahajan, MD.—This trial, currently in development, focuses on determining the role of SHH pathway inhibition to improve the outcome of AYA and

adults with standard-risk, newly diagnosed SHH-MB. The primary blinded randomized objective is to determine whether the SMO inhibitor sonidegib versus placebo as maintenance therapy after reduced-dose CSI and chemotherapy prolongs PFS for AYA and adults with standard-risk SHH-MB. In addition, this study aims to obtain prospective data for future studies of all subgroups and pineal embryonal tumors, a rare group of CNS tumors, since the treatment platform is similar. Establishing a prospectively and rigorously collected set of data on a cohort treated with the current standard of care facilitates its potential use as external or synthetic controls when evaluating experimental regimens in these rare tumors.

AYA and adults with standard-risk SHH-MB (defined per this protocol as M0 with gross total, near total, or subtotal resection and absence of high-risk histological or molecular markers) will be treated with reduced-dose CSI using 23.4 Gy and a total tumor bed dose of 54 Gy, and randomized after radiation to multiagent chemotherapy (cisplatin, vincristine, and cyclophosphamide) followed by maintenance with sonidegib for 1 year, versus the same chemotherapy followed by placebo. Randomization will be unblinded at relapse, and patients who had been on placebo maintenance will be allowed to cross over to sonidegib. AYA and adults with standard-risk non-SHH MB will be treated in a nonrandomized arm with reduced-dose CSI followed by the same multiagent chemotherapy. Finally, adults with pineal embryonal tumors or high-risk MB (defined as any of the following: M1-3, *MYC* amplification, SHH with *TP53* mutation, anaplastic features) will be treated with full-dose CSI (36 Gy with a tumor bed boost of 18 Gy) with concurrent chemotherapy and the same regimen of adjuvant multiagent chemotherapy (Supplementary Figure 2). Secondary objectives will include: overall survival (OS) and event-free survival (EFS) in all treatment arms; the impact of stratification factors on survival (proton vs. photon-based CSI, residual disease vs. complete resection, age <25 vs. ≥25, and Karnofsky Performance Score [KPS] 50–70 vs. ≥80), acute toxicities, therapy tolerance, late effects, long-term outcomes, and relationship with CSI doses and modality; QoL; neurocognitive, auditory, visual, and neuroendocrine effects; and evaluation of molecular diagnostics and outcomes. This study will recruit approximately 160–170 patients, of which 92 will be included in the primary randomized cohort (ie, standard-risk SHH-MB); 30–40 will be patients with standard-risk non-SHH MB, and 20–30 will be patients with high-risk MB or pineal embryonal tumors.

Ongoing Trials for Newly Diagnosed and Recurrent MB Including Adult Patients (SJMB12, NCT01878617; SJDAWN, NCT03434262)

Giles W. Robinson, MD.—There are 2 ongoing clinical trials at St. Jude Children's Research Hospital that include adults with MB. The SJMB12 multisite upfront trial is the first stratified MB trial based on combined molecular (WNT, SHH, non-WNT/non-SHH) and clinical risk groups (presence of metastatic disease and/or residual disease). It launched in 2013 and is enrolling patients in Australia, Canada, New Zealand, and the United States. It originally included patients ages 3–25 but was later amended to include adults with SHH-MB up to age 39. This nonrandomized trial modifies the CSI and chemotherapy backbone tested in previous studies based on the presence of molecular and clinical risk factors.[42,43] For skeletally mature SHH-MB patients, maintenance with the SMO inhibitor vismodegib for 1 year after completion of chemotherapy is added, with the goal of investigating if SMO inhibitors given upfront can reduce relapse. As of April 2020, more than 480 patients were enrolled across all arms (5%–10% adults).

The SJDAWN trial treats a multitude of recurrent CNS tumors but focuses on recurrent MB and opened in 2018. The objective is to determine the safety, tolerability, dose, and preliminary efficacy of ribociclib, a CDK4/6 inhibitor, in combination with 1 of 3 other drugs: gemcitabine for Group 3/4 MB; trametinib for SHH-MB and WNT-MB; or sonidegib for SHH-MB in skeletally mature patients with *PTCH1* mutations or 9q loss who have been off SMO inhibitor therapy for at least 6 months. Similar to SJMB12, SJDAWN includes adults with SHH-MB up to age 39. Extensive exploratory molecular studies will evaluate if any efficacy signal can be matched to a tumor biomarker or characteristic. By using the combination of a SMO inhibitor and a CDK4/6 inhibitor in patients with activated SHH pathway due to *PTCH1* mutations, the aim is to target the pathway downstream from SMO and increase the length of responsiveness to treatment.[44]

Phase I/II and Surgical Study of CX-4945 in Patients With Recurrent SHH MB (PBTC-053; NCT03904862)

Ira J. Dunkel, MD.—This multisite Pediatric BrainTumor Consortium (PBTC) trial led by Ralph Salloum, MD studies CX-4945, an orally bioavailable small-molecule selective inhibitor of protein kinase CK2, which is overexpressed in several tumor types and is downstream of SMO in the SHH pathway. Inhibition of CK2 results in inhibition of Gli.[45] Work by Purzner et al. found CK2 activity is required for multiple terminal components of the SHH pathway.[46] CK2 inhibition results in mouse and human MB cell death in vitro. In addition, CK2 inhibition results in decreased SHH-MB tumor growth in vivo and increased survival in mice with vismodegib-resistant cerebellar SHH-MBs. CX-4945 has been studied in adults in a Phase I trial in solid tumors and a Phase II recommended dose trial with an established 21 days on/7 days off schedule.[47]

The PBTC-053 clinical trial includes 3 arms. Study participants must have a diagnosis of SHH-MB that is recurrent and confirmed both histologically and by Clinical Laboratory Improvement Amendments (CLIA)-certified methylation-based subgroup testing. Prior exposure to SMO inhibitors is allowed. The first arm is a Phase I study in skeletally immature children that will determine the maximum tolerated dose and a recommended Phase II dose of CX-4945 administered orally daily. The second arm is a Phase II study of skeletally mature adolescents and adults and will involve continuously administered drug to test safety and tolerability and estimate an objective response rate. Finally, an arm including patients for whom surgical resection is clinically indicated will characterize the concentrations of CX-4945 in tumors. Correlative

studies include PK, Western blot analysis of Ser129-p-Akt, Ser473-p-Akt, and Gli1 in tumor tissue, and optional genomics. This clinical trial was activated in 2019 and is expected to be completed in 2.5–3.5 years.

Working Group Reports

Workshop participants met in 4 multidisciplinary groups to discuss focused topics and create a list of action items to build collaborations and advance care for adults with MB. Working group topics were clinical trials, tissue acquisition and testing, tumor modeling, and measurement of clinical outcomes.

Clinical Trials

Adults with MB have limited access to clinical trials. This group discussed the following needs: selecting homogeneous inclusion and exclusion criteria among upcoming trials for newly diagnosed adults to allow for comparable populations between studies; collaborating to share data worldwide and to design optimal trials for recurrent MB of all subgroups; combining efforts in the pediatric and adult communities; and collecting data from patients unable to participate in clinical trials in natural history or registry studies.

Two decades after the first prospective trial designed specifically for adult MB was published,[13] 2 large multicenter randomized trials for newly diagnosed adult MB are in preparation and were presented during this workshop. Given their complexity and long duration, with final analyses expected in about a decade from trial activation, the scientific community has the ethical obligation to find ways to collaborate and work synergistically to answer pending questions as these studies progress. Determining if SMO inhibitors are effective in increasing cure rates or achieving long-term control of SHH-MB when given during CSI and adjuvant chemotherapy (EORTC trial), or as maintenance after completing adjuvant chemotherapy (Alliance and SJMB12 trials) is the main objective of these trials. Whereas each trial has sufficient patients to address their primary objective, individually they will be insufficient to conclusively answer other important questions facing the collective adult MB community. Therefore, the principal investigators of the EORTC and Alliance trials have agreed to harmonize as many endpoints as possible to facilitate combined analyses. Examples of questions needing answers include: What are the differences between proton and photon CSI in terms of acute, subacute, and late toxicities and their respective impact on bone marrow reserve, and what is the tolerance of adults to post-CSI cytotoxic chemotherapy depending on the use of protons or photons? What are their comparative effects on long-term cognitive function?[48,49] What is the optimal upfront cytotoxic chemotherapy regimen and the relative efficacy and tolerability of different regimens in adults?[21] Finally, can adults with non-SHH tumors (Group 4 and WNT), together representing about 30% of adult MB,[10] achieve equivalent outcomes with lower CSI dose than historic higher dose of 36 Gy? Many clinicians have evolved their practice to reflect their best clinical judgment, but prospective data related to these questions are lacking.

Several specific recommendations emerged from the discussion to better align these upfront trials: selection of primary endpoint; inclusion and exclusion criteria; diagnostic criteria for participation; chemotherapy regimen (including doses and rules for monitoring of toxicity and dose reductions/discontinuation); and need for tumor tissue and CSF banking for correlative studies.

Since a prolonged survival is expected, an OS primary endpoint would make trials for newly diagnosed patients extraordinarily long. Other alternative endpoints such as EFS or PFS at 3 years (or 5 years) from diagnosis are more feasible in this population. PFS is typically defined as the interval from the date of histological diagnosis to the first radiological evidence of disease progression, or date of last follow-up or death, whichever is earlier. An EFS endpoint typically also includes death resulting from any cause and development of secondary malignancies. It was noted that the ongoing SJMB12 trial and previous prospective trials in adult MB have used PFS as an endpoint[12,14] and therefore this endpoint would be more appropriate to allow for comparisons across previous and current studies.

Trialists should consider which inclusion and exclusion criteria provide a clear justification for excluding patients from clinical trial participation. For example, an appropriate functional status requirement should be considered. Most neuro-oncology clinical trials are designed for malignant gliomas and typically enroll patients with a functional status at or above a KPS of 70% due to concerns about rapid resistance to therapy, neurological decline, and short survival. In contrast, patients with newly diagnosed MB are expected to have a more substantial tumor response to therapy, higher chances of a long survival or potential cure, and therefore a higher potential for recovery or stabilization of their deficits over time, especially once therapy is completed. Functional criteria that could provide more permissive trial inclusion are a KPS of 50% or greater, or an Eastern Cooperative Oncology Group (ECOG) status of 0–2. Regarding appropriate organ function, it was recommended that investigators rely on existing recommendations from the Friends of Cancer Research, the American Society of Clinical Oncology, and the Society for Neuro-Oncology (SNO) to make trials more permissive, thereby including more patients.[50,51]

Standard diagnostic criteria for eligibility across trials are important, for example, uniform use of the DNA methylation classifier for tumor subgrouping. A first neuropathological review at trial entry could establish the diagnosis histologically based on hematoxylin and eosin (H&E) stain and IHC markers. A second review including DNA methylation and targeted sequencing panel for detection of mutations could establish the molecular subgroup and the presence of known molecular risk factors such as *TP53* mutations (although their frequency in adults is low and its prognostic significance remains uncertain). Importantly, timely testing should be performed to ensure patients start therapy without delay. Delays in starting CSI have been shown to worsen prognosis in MB,[52,53] thus the working group recommended that CSI start within 42 days of diagnosis.

Chemotherapy regimens used for adults with MB in clinical trials and in standard practice are highly

heterogeneous. A meta-analysis determining the relationship between prescribed dose-intensity of chemotherapy and survival in children with MB pooling data on more than 2000 patients found a positive relationship between dose-intensity and outcome for cyclophosphamide and cisplatin, but a very weak 1 for vincristine, and a negative relationship for lomustine (lomustine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea).[54] Even though these data cannot be directly extrapolated, it is clear that chemotherapy tolerance is worse in adults, particularly beyond cycle 4, and that vincristine and cisplatin toxicities such as polyneuropathy and ototoxicity are also worse in older adults.[12] For these reasons, the working group recommended to limit the total cumulative dose of cisplatin to 300 mg/m^2, 8 mg/m^2 for vincristine and 12 g/m^2 for cyclophosphamide, as well as to include strict guidelines for dose modifications and discontinuation. Of note, the upcoming EORTC trial will use a regimen including concurrent vincristine during CSI, and adjuvant lomustine, cisplatin, and vincristine for a total of 6 cycles, based on previous experience with the prospective NOA-07 trial and HIT 2000 protocol.[12,22] As a prior Phase III trial in children compared both cyclophosphamide and lomustine-based regimens without finding a difference in outcome,[21] trialists concluded using different chemotherapy regimens in the EORTC versus the Alliance trial would be acceptable and could even lead to a better understanding of toxicities in adults as inclusion criteria and endpoints will be comparable between trials.

Finally, it is imperative that clinical trials collect tumor tissue, blood, and sequential CSF for future testing and correlation with outcome, response, and resistance to therapy. The working group also recognized the benefits of well-designed prospective registries or natural history studies to collect data on patients who cannot participate in clinical trials, as such data will also contribute to increase knowledge about the disease, and ultimately, improve therapies and outcomes.

Tissue Acquisition and Testing

This working group discussed the types of samples to be obtained in routine practice, clinical trials, and registries; optimal methods for subgrouping and risk stratification; and collaboration on repositories and registries to share data.

An immediate goal identified by this working group was the incorporation of best practices for diagnosis of adult MB in the National Comprehensive Cancer Network (NCCN): Guidelines for Central Nervous System Cancers.[55] Pathological standardization would limit discrepancies among institutions. Every tumor should be assigned a molecular subgroup as this provides valuable prognostic data and may inform targeted therapy options. IHC markers (beta-catenin, YAP1, and GAB1)[30] have the advantage of being rapid, but is difficult to standardize across all centers, and currently no readily available IHC marker can distinguish between Group 3 and Group 4 tumors. Genome-wide DNA methylation testing with application of the CNS tumor classifier is emerging as a reliable and reproducible method to classify MB. It is performed for most MB cases in some European countries (Germany, France, and United Kingdom)

and is also increasingly performed at centers in the United States.[11,56–58] Beyond its utility in subgrouping, the methylation classifier has the important advantage of reducing diagnostic error, which occasionally occurs when a clinically and histopathologically suspected MB is revealed by the methylation classifier to, in fact, represent another tumor entity, or vice versa.[56] Accurate diagnosis is essential because posterior fossa tumors such as glioblastoma variants, diffuse midline glioma, highly anaplastic glioma, Atypical Teratoid Rhabdoid Tumor, or metastatic tumors may mimic the clinical and pathological presentation of MB. DNA methylation should be established as the gold standard of diagnostic confirmation and subgrouping for MB and included in eligibility for clinical trials. However, methylation analysis raises challenges related to timing, cost, and availability. The group consensus was that a reasonable standard is full pathological testing completed within a month from tissue acquisition. Clinical trials could incorporate methylation testing in their design to accommodate for patients whose insurers will not provide reimbursement in health systems where this is an issue. Alternatively, advocacy groups and philanthropic organizations could be engaged to assist with methylation testing costs. Further, because methylation testing provides a plethora of data relevant to MB such as copy number profile, *MYC* and *MYCN* amplification, and focal *PTCH1* deletions, its widespread use in combination with targeted gene sequencing could result in an overall absolute value gain and composite cost–benefit analysis might demonstrate that it is superior to IHC and other ancillary tests, thus saving health care costs and duplicated efforts from laboratory testing.

Finally, availability of methylation analysis has increased over time, but many centers currently do not yet have this capacity, or they lack the required CLIA certification to report test results. When this testing becomes commercialized it will be more available to geographically distant providers, increasing processing time related to sample transfer. A resolution of these logistical issues is a pressing need to advance the accurate classification of tumors and ultimately patient care. Alternatively, other testing techniques for MB exist and without methylation analysis can be considered to make as accurate a diagnosis as possible. A prospective study comparing DNA methylation and sequencing to IHC results would confirm the accuracy and correlation of these techniques for subgrouping of adult MB.

It was also proposed to conduct a survey of SNO and European Association of Neuro-Oncology (EANO) members and possibly other cooperative groups to better understand their real-world experiences with adult MB patients seen at community care centers. Such survey would query: (1) the standard pathological assessment of adult MB at individual institutions; (2) the availability of specialized IHC and molecular testing via genome-wide DNA methylation for diagnostic confirmation and subgrouping, and next-generation sequencing for detection of actionable mutations; and (3) whether IHC, DNA methylation results, or other specialized testing was used in determining prognosis and treatment plan. An additional challenge not addressed at this workshop but worth of future discussion is the limited availability of tumor testing in low- and middle-income countries.

A central tumor repository will be essential to move the field forward. The NCI-CONNECT program may serve as the best starting point as it has established a repository of clinically annotated tumors, using work originally established with CERN (The Collaborative Ependymoma Research Network). NCI-CONNECT is mandated to share data to promote discovery and improve understanding of rare CNS tumors and can accommodate up to 600 new patients per year, far exceeding the incidence of MB. Referring centers could submit tumor tissue and in a timely manner receive an integrated diagnosis that incorporates next-generation sequencing and DNA methylation. CSF, blood collections, and clinical and imaging data could also be included. Although international regulations pertaining to transfer of tissue and patient information are a potential obstacle to collaboration, a possible solution would be to establish a European center of excellence to spearhead collection and tissue analyses from European centers. EORTC has established a platform (SPECTA) that could be the bridge for that purpose.

Tumor Modeling

There is limited availability of tumor models resembling non-SHH adult tumors. Moreover, there are insufficient data on tumor evolution due to limited availability of tumor tissue and other biological samples (blood, CSF) obtained throughout the course of the disease. This working group discussed collaboration to create animal, patient-derived xenograft (PDX) or bioinformatic models that recapitulate adult MB of all subgroups.

The most common preclinical models of MB actually recapitulate adult tumors, particularly those that rely on perturbation of the PTCH/SMO/SHH pathway. Thus, this is an underutilized resource and should be leveraged to study adult MB. Furthermore, there are not enough models for Group 4, the second subgroup in frequency in adults.[59] Genetically engineered murine models of MB also recapitulate the developmental nature of the tumor in that they often develop in the immediate postnatal period. Presently, there are about 45 MB cell lines for adults, but only about 18–20 have been sufficiently characterized in terms of their molecular profile (eg, DAOY-SHH, D283-Group 3).[60] Prospectively creating PDX models in the poorly defined adult MB tumors is a first step to better profile subtypes and determine how well they recapitulate the adult patient. However, these models would lack the impact of a functioning immune system and its relevance to the tumor microenvironment. MB represents a relatively homogeneous cancer and thus synthetic lethality may be particularly attractive to discover new vulnerabilities of the cancer cells that can be targeted therapeutically.[61] Bioinformatic modeling may also be helpful but requires a preponderance of data. Use of pediatric MB data (the most analogous disease), combined with radiomic data may yield clinically actionable targets. Immunophenotyping, network analysis, RNAseq, copy number analysis, and drug screens are also potentially insightful investigations to discover actionable targets. Single-cell sequencing can be of importance for SHH-MB given the resistant populations that arise with SMO inhibitors, as well as for Group 3 given its homogeneity, although Group 3 is underrepresented in adults.

Preclinical models that recapitulate the clinical experience with use of SMO inhibitors, where a rapid response is frequently observed but is not durable, are an important area under development.[62] Recent studies comparing primary to recurrent tumor samples in childhood MB have noted that the subgroup was retained at recurrence.[63] It has also been shown that new mutations are acquired downstream of SHH at recurrence, such as *SMO* mutations,[64] *MYC* amplification, or *TP53* mutations.[65] Single-cell analysis has confirmed, as previously stated, that MB is more homogenous than glioblastoma and that Group 4 is more differentiated than Group 3.[66]

Genetic syndromes with a predisposition for MB may also be insightful for elucidating underlying molecular mechanisms of resistance. These include Li–Fraumeni, Gorlin, Familial Adenomatous Polyposis (FAP), Neurofibromatosis type 1, Constitutional Mismatch Repair Syndrome (CMMR), Rubinstein–Taybi, Fanconi anemia, and germline mutations in *BRCA2*, *PALB2*, and *ELP1*.[67,68] These syndromes could potentially be of use in establishing a model for adult MB.

Table 2. Action Items: Clinical Trials

	Timing	Task/recommendations
Group 1—clinical trials	Immediate	1.1. Harmonize newly diagnosed protocols (EORTC, Alliance) to facilitate future analysis: • Endpoint selection: PFS preferred. • Chemotherapy backbone: limit total number of cycles, limit total dose of cisplatin, and total dose of vincristine, introduce clear guidelines for treatment modification and discontinuation based on toxicity. • Incorporate acquisition of CSF for correlative studies. • Use common scales to measure clinical outcomes.
	Short-term	1.2. Establish collaborations to launch clinical trials for recurrence: • SHH-MB: tackling and/or preventing resistance to SMOi; approach for patients without PTCH1 or SMO mutations. • Establish experimental approach for patients with non-SHH MB.

Table 3. Action Items: Tissue Acquisition and Testing

	Timing	Task/recommendations
Group 2—tissue acquisition and testing	Immediate	2.1. Standardize molecular diagnosis and subgrouping: include recommendation for DNA methylation as current first choice in NCCN guidelines
	Short-term	2.2. Standardize molecular diagnosis and subgrouping: launch SNO survey on current practice regarding testing for diagnosis and subgrouping; expand to other cooperative societies (Alliance, NRG Oncology) to get more input from oncology practices
		2.3. Educate patients/caregivers/care providers/3rd party payers regarding the need to be seen at centers with expertise and need for DNA methylation as standard of care
		2.4. Create central repositories (deceased and lost to follow-up patients: tumor, clinical data)
	Long-term	2.5. Standardize molecular diagnosis and subgrouping: launch prospective study to compare IHC and DNA methylation, including cost analysis
		2.6. Explore possibility of philanthropy payment for DNA methylation in clinical trials
		2.7. Create central repositories (alive patients: tumor, blood, CSF, clinical data)

Table 4. Action Items: Tumor Modeling

	Timing	Task/recommendations
Group 3—tumor modeling	Short-term	3.1. Create prospective bank of PDX models with collaboration among sites
		3.2. Generate tumor models from genetic syndromes
		3.3. Subtype available MB cell lines
		3.4. Incorporate RNAseq to look for potential targets by bioinformatic analysis (SL trials); incorporate pediatric data
	Long-term	3.5. Collect advanced imaging data

Table 5. Action Items: Measuring Clinical Outcomes

	Timing	Task/recommendations
Group 4—measuring clinical outcomes	Immediate	4.1. Recommendations for inclusion in NCCN guidelines: • consideration of clinical trials and registries in newly diagnosed and recurrent setting; • language for 3D post contrast T1 MRI as with glioma guidelines; • consideration of proton for craniospinal radiation; • recommendations regarding baseline evaluations (fertility, stem cell collection, support group, neurorehabilitation)
		4.2. Consensus recommendations regarding data to be collected: use of steroids, neurosymptoms (hearing, dysarthria, ataxia, mood disturbance, vision, cognition, fatigue)
	Short-term	4.3. Improve care for patient with limited geographical mobility: web-based tumor board
		4.4. Create and distribute education materials for radiation oncologists (may be best specialty group to refer patients for trial participation)
	Long-term	4.5. Develop educational coping material and psychological intervention/evaluation specific for adults (return to work or education)
		4.6. Create central registries for non-trial participants (see also Group 2; 2.4, 2.7)

Measuring Clinical Outcomes

Acute and long-term effects of the tumor and subsequent therapy on symptom burden, QoL, neurocognitive function, and social outcome have not been studied systematically in adults with MB. This group was charged with discussing which data and instruments should be used to collect outcomes data and how to include such evaluations in upcoming clinical trials and practice.

Ideally, data collection and services to be offered at baseline for adults with newly diagnosed MB should include fertility counseling and preservation, germline testing to identify disorders with high risk of second malignancies and need for family genetic counseling, stem cell collection, participation in patient and caregiver support groups, and neurological rehabilitation postsurgery and at other necessary times. Clinical data of importance to collect through the disease course include use of steroids and neurological symptoms such as hearing impairment, dysarthria, ataxia, neuropathy, mood disturbance, vision impairment, neurocognitive dysfunction, and fatigue. The group recommended collecting these data at baseline, 6 months after diagnosis, and annually thereafter for patients who remain without evidence of recurrent or progressive tumor after initial therapy. Such data will inform the development of educational and support resources that are symptom-specific and psychological interventions to assist with personal and social functioning; for example, counseling regarding returning to work or education. This group also recommended that adults should be referred to clinical centers of excellence at the time of new diagnosis or recurrence for specialized diagnosis, consideration of proton CSI,[48] and enrollment to clinical trials and/or registries. Because patients with limited resources or living in remote areas might not have access to such a center, a web-based tumor board could be used to provide expert advice. Radiation oncologists were identified as health care providers routinely involved in the care of these patients who could serve as a bridge between patients and needed expertise.

To ensure reproducible imaging outcomes, the group supported the MRI standards proposed by the Response Assessment in Pediatric Neuro-Oncology (RAPNO) committee.[69] In particular, the use of 3-D postcontrast T1-weighted imaging for tumor size, diffusion-weighted imaging for tumor detection, and postcontrast FLAIR for CSF dissemination was stressed.[70] RAPNO incorporates evaluation of brain MRI, spinal MRI, CSF cytology, neurological examination, steroid use, and status of extra-CNS disease to determine response. Imaging the spine is recommended at the time of diagnosis, at recurrence, and at the time of new neurological symptoms.

Action Items and Future Directions

The discussions of each working group were organized into a list of immediate, short-term, and long-term actionable items to achieve the workshop's mission to expedite progress for adults with MB. A summary of these action items is provided in Tables 2–5. Importantly, an identified high priority need was to recommend incorporation of the following into the adult MB algorithms of the NCCN guidelines: facilitating referral of patients to centers of excellence; promoting patient participation in clinical trials or registries; encouraging use of DNA methylation for confirmation of diagnosis and subgrouping; offering counseling on contraception and fertility preservation; evaluating patients for symptoms and medical management of endocrine, vision, hearing, and neurocognitive deficits; providing psychosocial support and referral to neurorehabilitation; minimizing

delays in therapy; and incorporating imaging standards and criteria for progression (manuscript in preparation). Two new randomized clinical trials for newly diagnosed MB led by EORTC and Alliance will explore the role of SMO inhibitors and obtain preliminary data about the benefit and toxicity of cytotoxic chemotherapy regimens in adults. These prospective data, along with the comprehensive correlative studies planned in both trials will be of immense value as benchmark for future trials both in newly diagnosed and recurrent disease. Several recommendations emerged from this workshop to better align these upfront trials, such as harmonizing endpoints to facilitate combined analyses. Finally, there was consensus to create an adult MB Working Group to actualize these items and organize future meetings to continue this work.

Supplementary Data

Supplementary data are available at *Neuro-Oncology Advances* online.

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