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Original Research

Current studies and future directions for medulloblastoma: A review from the pacific pediatric neuro-oncology consortium (PNOC) disease working group

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ABSTRACT

Medulloblastoma (MB) is the most common malignant central nervous system tumor of childhood, comprising a heterogenous group of tumors each with distinct biology, clinical behavior, and prognosis. Long-term survival remains unacceptable, and those who do survive face high late mortality risk, new chronic treatment-related medical conditions, neurocognitive impairments, and poor health-related quality of life. Up-front treatment strategies now integrate molecular subgrouping with standard clinico-radiological factors to more actually risk stratify newly-diagnosed patients. To what extent this new stratification will lead to improvements in treatment outcome will be determined in the coming years. In parallel, discovery and appreciation for medulloblastoma's inter- and intra-tumoral heterogeneity continues growing. Clinical trials treating relapsed disease now encompass precision medicine, epigenetic modification, and immune therapy approaches. The Pacific Pediatric Neuro-Oncology (PNOC) Medulloblastoma Working Group is committed to developing clinical trials based on these evolving therapeutic strategies and supports translational efforts by PNOC researchers and the multi-stakeholder medulloblastoma community at large.

Introduction

Medulloblastoma (MB) is the most common malignant central nervous system (CNS) tumor of childhood, with an annual incidence of ~5 cases per 1 million individuals and median diagnostic age of 6 years [1]. As an embryonal tumor of the cerebellum, MB has the propensity to disseminate through the brain and spinal cord. Our understanding of MB's biological heterogeneity has rapidly expanded within the last decade and continues to grow. The groundbreaking expression profiling discoveries of at least four molecular subgroups – Wingless-activated (WNT), Sonic Hedgehog-activated (SHH), and non-WNT/non-SHH (including Groups 3 and 4) [2] – with distinct molecular profiles, clinical presentation, and prognoses led to their incorporation within the 2016 WHO classification of CNS tumors [3] and further refinements in the 2021 WHO classification [4].

For MB, recent advances in molecular diagnostics are poised to translate into long-overdue clinical breakthroughs. Standard of care MB treatment has remained unchanged over the past several decades, utilizing clinico-radiological risk-stratification according to patients' age, residual post-resection disease, metastatic status, and tumor histology [5]. Therapy for children diagnosed at minimum 4 years or older consists of maximal safe surgical resection, craniospinal irradiation (CSI), and cytotoxic chemotherapy. Therapy for young children diagnosed with medulloblastoma is designed to avoid or delay craniospinal irradiation and preserve neurocognitive function, so consists of maximal safe surgery and intensive cytotoxic chemotherapy [6]. Such approaches have led to long-term survival of over 80% for average risk and 60% for high-risk disease in resourced countries [7-9].

In terms of global outcomes, the results from European and North American trials remain notably overrepresented in published literature. Lower MB survival rates have been reported from investigators in Iran and Malaysia [10-11], locations likely affected by resource constraints. Unifying national/international treatment guidelines and integrating pediatric oncologists within the care of children earlier in treatment are hopeful, evolving strategies for these countries [12]. Survival in India continues to improve as treatment intensification is achieved with less

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resources, with recent reporting of 5-year 62% survival for high-risk disease [13]. Furthermore, investigators have shown rapid, economical and effective means to molecularly subgroup, allowing for accurate diagnosis and prognostication [14]. Effort is ongoing from oncologists within low- and middle-income countries (LMIC) and across global consortia networks to better understand, recognize and improve medulloblastoma survival for children treated across the world, not just within European and North American borders.

Horrifically, once it has recurred, medulloblastoma is largely incurable [15,16]. Several studies report median survival times of 19-27 months post recurrence [17,18], while a recent single-institution review found a median survival of only 10.3 months in those whose initial therapy included craniospinal radiation [19]. Even those who do survive medulloblastoma beyond 5 years carry a 15-year mortality rate of at least 23.2%, owing largely to subsequent neoplasms and chronic treatment-related health conditions [20]. On top of increased long-term mortality, adult survivors of MB lead lives with pronounced risk of hearing and/or visual impairment, seizures, stroke, lower educational attainment and social independence in comparison to their siblings [21]. Thus, goals of novel interventions for medulloblastoma must be aimed towards improving not only the duration, but quality of survival across multi-faceted health domains.

The patient, family, and neuro-oncologic communities recognize the urgent need for better care and outcomes. With the mission to advance survival and quality of life outcomes for children with medulloblastoma and other pediatric CNS tumors, the Pacific Pediatric Neuro-Oncology Consortium (PNOC) was formed in 2012 and continues to grow as an international consortium with centers within the United States, Europe, Asia, and Australia. On behalf of the PNOC Medulloblastoma Working Group, we highlight the current trials for patients with medulloblastoma as well as emerging treatment strategies, with a special focus on studies conducted by PNOC.

Discussion

Up-front medulloblastoma trials

Clinical trials for newly diagnosed and relapsed medulloblastoma have historically treated patients based on their extent of disease (metastatic vs non-metastatic, volume of residual tumor following up-front surgical resection) and limited molecular information (e.g. MYC amplification), but are now evolving to incorporate molecular subgroup in addition to the above validated clinico-radiological risk factors. The recently published Children's Oncology Group (COG) trial for average-risk medulloblastoma, ACNS0331 (NCT00085735), randomly assigned young patients ages 3-7 years to either standard dose or reduced dose CSI; inferior results were obtained for the reduced dose cohort [7]. However, post-hoc analysis demonstrated excellent results for the WNT-activated subgroup, providing a rationale for therapy de-escalation that is being investigated in the actively enrolling COG trial ACNS1422 (NCT02724579) as well as the phase 2 trial FOR-WNT2 at Tata Memorial Centre in India (NCT04474964). These trials proceed with caution in providing reduced-dose craniospinal irradiation in effort to reduce long-term morbidity and mortality. Two prior prospective studies for WNT-MB that attempted to de-escalate therapy by providing chemotherapy without radiation (NCT02212574) [22] or providing focal conformal radiation without craniospinal [23] have failed due to unacceptably high risk of relapse.

The COG trial ACNS0332 for newly-diagnosed high-risk medulloblastoma (NCT00392327) tested the addition of carboplatin concomitantly with radiation as well as the role of isotretinoin as a pro-apoptotic agent. While isotretinoin did not affect patient outcomes, the study did include a subanalysis of molecular subgroups for both interventions; this subanalysis demonstrated a survival advantage with the addition of carboplatin to radiation in patients with group 3 medulloblastoma [24]. The recently published results from the St. Jude Children's Research Hospital SJMB03 trial for newly diagnosed medulloblastoma (NCT00085202) included an extensive subanalysis of the different molecular subgroups, further validating their clinical significance [8]. In the actively enrolling St. Jude SJMB12 clinical trial for newly-diagnosed medulloblastoma (NCT01878617) as well as the International Society of Paediatric Oncology (SIOP) medulloblastoma trials PNET 5 MB-LR and PNET 5 MB-SR, patients are risk-stratified according to both their clinical and molecular features including molecular subgroup.

Infant medulloblastoma has historically been considered high risk due to the necessary avoidance of radiation therapy [25]. We now know this population is enriched for SHH-activated tumors [26]. The currently enrolling HeadStart4 trial (NCT02875314) for children <10 years old with medulloblastoma incorporates histological subtypes, molecular subgroups, and clinical response into its risk-adapted therapy design. Early survival results for infants and young children with localized SHH MB are promising [27].

Emerging clinical trial strategies

Precision medicine

A major question at the forefront of clinical and biology research in medulloblastoma is whether the current consensus molecular subgroups are enough to predict clinical outcomes and guide treatment stratification. Modern analysis continues to show that medulloblastoma is an extremely heterogeneous disease [28-31]. Although initially four subgroups were recognized [3], studies now provide evidence of medulloblastoma comprising 8-12 subgroups with differing molecular signatures, response to therapy, and prognosis. In hindsight, we suggest that the frequent failure of treatments to provide long-term disease control or cure was in part due to the profound heterogeneity of this disease.

Another important research question is whether recurrent actionable mutations in medulloblastoma can be effectively targeted by the addition of molecular-driven therapies. Several studies have evaluated the use of the SHH inhibitors vismodegib or sonidegib in patients with relapsed SHH-MB [26,32,33]; these trials revealed that only a subset of patients will respond to targeted therapy, and those who do often do not have a sustained response. Sequencing and profiling of SHH medulloblastomas has shown intra-subgroup heterogeneity, with the response to SHH inhibitors found only in patients with mutations upstream of Smoothened (SMO) [34]. Even within the appropriate target populations, molecularly-targeted therapies will likely not achieve disease control unless used in combination to prevent resistance [35]. In addition, the use of targeted therapy in children requires exquisitely careful study. As vismodegib advanced into pediatric phase II trial development, irreversible growth plate fusions were found in several patients after prolonged exposure, consistent with preclinical evidence studies [36]. As mentioned above, SJMB12 (NCT01878617) now continues to enroll *skeletally mature* patients with newly-diagnosed SHH MB onto treatment with the SHH inhibitor vismodegib in combination with multi-agent chemotherapy. The efficacy of vismodegib in the up-front setting for a restricted population will become clear in the years ahead.

Investigators continue to look for subgroup-specific strategies. DNA sequencing, gene expression profiling and high-throughput drug screening of a panel of orthotopic patient-derived xenografts identified actinomycin D as an effective drug against the majority of group 3 medulloblastomas tested [37]. Of most significance, this study found that most RNA-based predictions were not validated by empirical drug testing, and that high-throughput drug screening could identify therapies for medulloblastoma that could not be predicted by genomic or transcriptomic analysis. MB's intra- and inter-patient heterogeneity may ultimately demonstrate the need for individualized therapy combined with a standardized chemotherapy backbone.

Fortunately, PNOC is investigating the role of precision medicine in the treatment of medulloblastoma. PNOC027 (NCT05057702) opened in 2022 as a pilot trial of real time drug screening and genomic testing to determine individualized treatment plans for patients with relapsed

medulloblastoma. The treatment plan will take into consideration each participant's successfully completed drug screening results, current clinical data, including prior history and treatment(s), clinical molecular testing using whole exome sequencing (WES) and RNAseq, other medical conditions and age of the participant. The trial is assessing the safety of this personalized treatment approach in these children, and within the limitations of a feasibility trial, determining whether participants gain clinical benefit.

Epigenetic modification

Mutations in chromatin remodeling proteins have been observed in medulloblastoma and histone methylation alterations have correlated with worse outcomes [38-40]. Of its many consequences, evidence suggests that chromatin remodeling aberrations can lead to upregulation of *MYC* [41]. These findings support interplay between alterations in chromatin remodeling and aberrant *MYC* expression as an important contributor to medulloblastoma oncogenesis.

Histone deactylase (HDAC) inhibitors have been pre-clinically studied across many pediatric CNS tumors as a means to rescue histone mutation induced genetic alterations. A high-throughput small-molecule screen using *MYC*-driven medulloblastoma cells found that HDAC inhibitors inhibited tumor cells *in vitro* without toxicity to normal cerebellar cells [42]. The intracellular signaling pathway PI3K/AKT in medulloblastoma associates with enhanced tumor growth, metastasis, and chemoresistance and is frequently activated by genetic and epigenetic alterations within this tumor type. Studies have shown *PI3K* inhibitors including GDC-0941 and BKM120 (buparlisib) target medulloblastoma stem cell subpopulations and decrease medulloblastoma growth *in vitro* and *in vivo* [43,44]. Combining the strategies, treatment with the HDAC inhibitor panobinostat and BKM120 showed a synergistic effect in the inhibition of MYC-driven medulloblastoma in vivo [42].

Supported by such pre-clinical evidence, PNOC016 (NCT03893487) opened in 2019 as a target validation study to investigate the tumor penetration of the pan-HDAC and PI3K inhibitor fimepinostat for newly-diagnosed diffuse intrinsic pontine glioma, recurrent high-grade glioma, and recurrent medulloblastoma. The study is now closed to accrual and allowing for data maturation.

Immune environment manipulation

Coinciding with genomic investigations, efforts to understand and manipulate the MB immune environment are underway. The use of replication-competent oncolytic viruses (OV) as anti-tumor therapy has grown in oncology, and measles virus specifically demonstrated efficacy against xenograft, immune-compromised and immune competent medulloblastoma murine models [45-47]. From this pre-clinical data emerged PNOC005 (NCT02962167), a phase 1 trial investigating the safety of modified measles virus (MV-NIS) in children and young adults with recurrent medulloblastoma or atypical teratoid rhabdoid tumor (ATRT). Trial enrollment is ongoing.

Chimeric antigen receptor (CAR) T cell strategies are rapidly developing as candidate targets are discovered and CAR-T manufacturing processes are refined. After investigators showed that a medium-length CAR spacer enhanced the therapeutic efficacy of human Erb-B2 receptor tyrosine kinase 2 (HER2)-specific CAR T cells in an orthotopic xenograft medulloblastoma model, they launched the phase 1, single-institution trial BrainChild-01 (NCT03500991) to evaluate the repeated locoregional delivery of HER2-specific CAR T cells for children with recurrent or refractory CNS tumors. The trial remains open and enrolling, with tolerability reported on the initial 3 patients [48]. B7-H3 CAR T cells also recently showed antitumor activity in orthotopic xenograft medulloblastoma models [49], and phase 1 testing is ongoing for children with recurrent or refractory CNS tumors (NCT04185038). As these trials continue, the need to develop CAR-T cells against multiple targets grows clearer. Recently, as EPHA2, HER2 and interleukin 13 receptor α2 were all identified as cell-surface targets expressed on medulloblastoma, investigators demonstrated efficacy of intrathecal delivery of EPHA2, HER2 and interleukin 13 receptor α2 CAR T cells in primary, metastatic and recurrent group 3 medulloblastoma xenografts models [50], with hopes to develop a clinical trial.

While CAR T cells hold promise for certain cancers, medulloblastoma efficacy will likely still be limited by antigenic heterogeneity and uncharacterized tumor-specific antigens. Pioneering efforts to create an adoptive cellular therapy platform using total tumor RNA (ttRNA)-pulsed dendritic cells led to the proven generation and expansion of polyclonal tumor-reactive T cells against a plurality of antigens in both human and murine medulloblastoma. In a patient with relapsed medulloblastoma receiving such therapy, an early and massive expansion of tumor-reactive lymphocytes as well as prolonged persistence in the peripheral blood was observed during an effective therapeutic response [51]. These efforts have led to the open and enrolling phase 2 Re-MATCH trial of autologous tumor-specific T cell immunotherapy plus ttRNA-loaded dendritic cell vaccine against recurrent medulloblastoma, as well as supratentorial primitive neuroectodermal tumor (NCT01326104).

Much immunotherapy research has focused on improving adaptive immune function, but the signal-regulatory protein (SIRP)α-CD47 pathway, a phagocytosis checkpoint in macrophages and other innate immune cells, holds therapeutic potential as well. Using anti-CD47 antibodies to block CD47 signaling and allow for macrophage-mediated phagocytosis has proven efficacious across various adult malignancies. A humanized anti-CD47 antibody, Hu5F9-G4, demonstrated therapeutic efficacy *in vitro* and *in vivo* in patient-derived, primary and metastatic orthotopic xenograft medulloblastoma models. Intraventricular administration of Hu5F9-G4 further enhanced its activity against disseminated medulloblastoma leptomeningeal disease [52], paving the way for PNOC clinical testing. PNOC025 (NCT05169944), a phase 1 trial of the anti-CD47 monoclonal antibody Magrolimab, opened in 2022 for children and adults with recurrent or progressive malignant brain tumors.

Immunotherapy, if harnessed effectively, could improve survival while reducing morbidity. While data emerge on the variability of the immune microenvironment by molecular subtype [53,54], how much predictive variability exists by anatomic compartment, tumor biology, treatment, and individual characteristics, and how to overcome this variability, remains to be seen.

PNOC Medulloblastoma trial evaluations

As detailed above, MB trials enacted through PNOC have built on the recent biological discoveries of the immune microenvironment, integrated stress response, targeted pathways, and individualized drug screening. While the primary objectives of phase 0/1 studies are to determine feasibility and safety, efforts are made within each PNOC trial to optimize comprehensive data collection for further understanding and translation.

Xenograft development

Given the heterogeneity of medulloblastoma, it is unlikely that one treatment modality will be effective against all forms of this disease. This argues for clinically relevant models of medulloblastoma that reflect the range of subgroups, molecular aberrations, patterns of invasion, proclivity to malignant progression, and patterns of chemotherapy responsiveness. PNOC027 attempts to establish patient derived xenograft models through an exploratory aim, and similar aims will likely be incorporated in future trials.

Liquid biopsy

Cell-free DNA (cfDNA) has emerged as a molecular tool for non-invasive diagnosis and disease monitoring in a variety of human cancers [55]. As cancer cells die, their DNA bearing the molecular signature of the tumor genome is released into the extracellular space [56]. Cell-free

DNA has been identified in plasma and cerebral spinal fluid (CSF) of brain tumors [57-59], and the detection rate within medulloblastoma specifically has ranged from 26-64% [60,61]. PNOC025 is currently investigating changes in cell free tumor DNA in peripheral blood and CSF, as efforts are ongoing to improve extraction rates and purification techniques. If a standardized clinical use for medulloblastoma could be achieved, cfDNA would afford the opportunity for real-time assessment of alterations in molecular burden and variant evolution to monitor and guide therapy [59].

Comprehensive participant reported outcomes (PROs)

Medulloblastoma survivors presently face high late mortality risk, new chronic medical conditions, and poor health-related quality of life (HRQOL) [20,21,62-66]. Novel interventions must be sought with the goals to improve mortality *and* morbidity, which can only be accomplished through more comprehensive examination of the effects of therapy on the patient's physical, psychological, social, and cognitive health. All PNOC medulloblastoma trials currently incorporate a core set of validated, participant-reported measures including the Pediatric Quality of Life Inventory (PedsQL), Patient-Reported Outcomes Measurement Information System (PROMIS), Behavior Rating Inventory of Executive Function (BRIEF), ADHD Rating Scale, and Adaptive Behavior Assessment System, Third Edition (ABAS-3). PNOC investigators are working to optimize what PROs can be built, included, and validated in future trials to better understand therapeutic effects, including social determinants of health.

Target validation

Despite PNOC016's successful enrollment, the role of tissue collection for the objective of target validation alone within pediatric trials remains controversial. Determining pharmacokinetic and pharmacodynamic endpoints early in the process clearly allows for more educated decisions that ultimately improve chances of therapeutic success and save resources [67,68]. Within early phase clinical trials, pharmacokinetics, pharmacodynamics, and efficacy are becoming increasingly more relevant in determining the recommended phase 2 dose (RP2D). It has been shown that RP2Ds for molecularly targeted agents found through nonclassical definitions compared with toxicity alone was significantly associated with higher likelihood of FDA approval [69].

Research biopsies occur commonly within early phase adult oncology trials, where they have been proven safe and feasible [70]. Not surprisingly, a higher percentage of patients undergo research biopsies when considered mandatory as compared to optional [71]. Up to 50% of adult patients have stated mandatory biopsy would not impact their willingness to enroll in a clinical trial, and if generally accepted this practice would significantly benefit the scientific community [70,72]. Adult patients' acceptance of biopsy risks is higher and anxiety regarding research biopsy less than that of providers and institutional review board members [73].

Consideration of research biopsies within the pediatric patient population adds further ethical and legal complexity. Work is needed to understand parental attitudes and perceptions towards their children's participation in medulloblastoma trials that would incorporate such design. Certainly, non-therapeutic tissue collection would represent a paradigm shift in this population. Support for research biopsies has accelerated for pediatric diffuse intrinsic pontine glioma [74], after our field recognized the necessity of determining drug candidate and neurosurgical biopsies of even the most eloquent areas, including brainstem and deep-brain, were proven safe [75]. Should the support of patient and family advocates, regulatory bodies, and treating providers happen, target validation measures may be incorporated more into future PNOC studies. However, thoughtful strategies will be required to evaluate target effects of novel therapies in the context of intra- and interpatient medulloblastoma heterogeneity.

PNOC Medulloblastoma community engagement

In Summer 2019, PNOC developed working groups to align basic scientists, clinical researchers, families and foundations in translational strategies for children, adolescents and young adults with CNS tumors. Soon after, PNOC partnered with the Children's Brain Tumor Network (CBTN) to grow collaborations and augment preclinical resources [76]. The PNOC Medulloblastoma Working Group holds monthly meetings to share new findings from research laboratories, clinical trial development updates (with real-time feedback and incorporation of trial endpoints and biomarkers), and advancements in medulloblastoma-related areas of interest from invited speakers. The group iteratively seeks perspectives from patient and family advocates to best inform future directions. Family-led sessions have included a lecture in 2021 on regulatory and industry strategies to fund pediatric trials and a discussion panel in 2022 of parents of medulloblastoma survivors. The medulloblastoma working group continues to advance translation of new therapies and biomarkers, develop pipelines for preclinical and clinical research, and build collaborations both within academia and across stakeholders.

To expand global outreach for the medulloblastoma community, the PNOC Foundation hosted a virtual medulloblastoma webinar in Fall 2021. A panel of trialists, clinicians and scientists discussed up-front and relapsed treatment strategies, survivorship care, and emerging science for live participants across North America, Central America, Europe, Asia, and the Middle East. Further efforts are ongoing to build iterative opportunities for information sharing and connection.

Conclusions

The complexity of medulloblastoma's heterogeneity continues to reveal itself. Early phase MB trials built on the recent biologic discoveries of the immune microenvironment, epigenetic modification, targeted pathways, and individualized drug screening have opened and continue to enroll within PNOC. As these therapies develop, efforts to comprehensively understand their effects in relation to intratumoral, intertumoral, and inter-individual heterogeneity are required to best understand their successes and failures.

Furthermore, medulloblastoma's complexity has begged the need for iterative refinement of risk stratification and trial design. As novel therapies develop, strategic decisions must be made about when and for whom to introduce them. Most innovative strategies presently involve enrolling medulloblastoma patients at recurrence, however patients with the most aggressive high-risk subgroups have the most to gain from up-front testing in effort to improve survival chances. Within currently lower-risk subgroups, selecting whom to trial treatment reduction, and how, remains a challenge. The future success of newer therapies will hopefully provide opportunity to reduce treatment burden and ultimately the significant late effects so many suffer from. Much study lays ahead to attain a cure for all medulloblastoma, through treatment that will allow for lives well lived.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Tab Cooney: Writing – original draft. **Holly Lindsay:** Writing – review & editing. **Sarah Leary:** Writing – review & editing. **Robert Wechsler-Reya:** Writing – review & editing.

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