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Treatment strategies for relapsed medulloblastoma in the pediatric population: illustrative case

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BACKGROUND Relapsed medulloblastoma (MB) remains a significant cause of pediatric cancer mortality, accounting for approximately 10% of all childhood cancer deaths. Despite advances in molecular characterization and treatment of primary MB, no standardized protocol currently exists for managing recurrence. This case highlights a novel approach to treating relapsed MB and aims to contribute to the evolving understanding of optimal strategies in this setting.

OBSERVATIONS The authors describe the case of a pediatric patient with relapsed MB, characterized as group 4 MB, managed with a personalized treatment approach involving repeat craniospinal irradiation, chemotherapy, and bone marrow transplant. In parallel, they review current literature and ongoing clinical trials to contextualize this strategy within the broader landscape of relapsed MB management. The case underscores the heterogeneity in treatment approaches and the lack of consensus regarding best practices. At the time of this report, the patient is approximately 6 months post–bone marrow transplant and continues to be monitored for signs of disease recurrence.

LESSONS This case illustrates the importance of an individualized, multidisciplinary approach to relapsed MB, accounting for prior therapies, tumor biology, and patient goals. Ongoing research and collaboration are essential to establishing more effective, evidence-based standards of care for this challenging diagnosis.

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KEYWORDS relapsed medulloblastoma; pediatric brain tumor; recurrence; medulloblastoma management

Medulloblastoma (MB) is the most common embryonal tumor in children. Treatment typically involves resection followed by radiation therapy (RT) and chemotherapy, resulting in a median long-term survival rate of approximately 70%–80%.[1,2] However, outcomes vary significantly among patient subsets. In particular, individuals with recurrent or metastatic MB face a poor prognosis, with a median survival of less than 6 months.[3]

Extensive research has focused on the molecular mechanisms driving MB recurrence and metastasis, with substantial research into the impact of MB subgroups on disease progression. The four primary MB subgroups include Wingless-activated (WNT) (MB_{WNT}), Sonic Hedgehog–activated (SHH) (MB_{SHH}), and non-WNT–/non-SHH–expressing tumors including group 3 ($MB_{group\ 3}$) and group 4 ($MB_{group\ 4}$) MB. Specific molecular subgroups of MB are associated with a greater risk of metastasis and recurrence, with MB_{SHH} (TP53 mutant type) and $MB_{group\ 3}$ tumors demonstrating the highest risk, and MB_{WNT} subgroup demonstrating the lowest risk.[4] Despite a growing understanding of mechanisms behind relapsed MB, no standardized treatment protocol exists. The poor prognosis of these tumors, coupled with the lack of clear therapeutic guidelines on how to treat recurrent/metastatic disease, underscores the need for further research into effective management strategies of these tumors.

This report aims to offer insights into the characteristics of relapsed MB, including both metastatic and local recurrences, summarize current treatment approaches, and provide evidence-based recommendations for optimizing the management of these recurrent tumors, drawing on both existing literature and the illustrative case.

Illustrative Case

Case Description

An 11-year-old male presented with a 2-month history of intermittent headaches, 2 weeks of diplopia, and 1 week of eye deviation. Additional symptoms included early morning nausea and vomiting,

ABBREVIATIONS CSI = craniospinal irradiation; GVT = graft versus tumor; MB = medulloblastoma; OS = overall survival; PFS = progression-free survival; re-RT = reirradiation therapy; RT = radiation therapy; SHH = Sonic Hedgehog–activated; TMZ = temozolomide; WNT = Wingless-activated.

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along with significant weight loss (30 pounds) over 8–10 months. On examination, he exhibited bilateral cranial nerve VI palsy without other neurological deficits. MRI revealed a metastatic MB with leptomeningeal enhancement (Fig. 1A). Biopsy confirmed grade 4 MB with both intracranial and intraspinal metastases, and methylation profiling confirmed the tumor as $MB_{group\ 4}$.

The patient underwent a successful gross-total resection of the primary tumor via suboccipital craniotomy, placement of an external ventricular drain, and subsequent placement of a ventriculoperitoneal shunt for hydrocephalus management. Postresection, the patient was started on chemotherapy as per ACNS0332 regimen A, combined with proton beam craniospinal irradiation (CSI) therapy. This treatment course consisted of weekly vincristine alongside concurrent CSI therapy with multiple boosts to the resection cavity and gross disease (36-Gy whole brain and spinal axis, 39.6-Gy focal spinal irradiation, and 54-Gy cranial tumor bed boosts); and maintenance chemotherapy including cisplatin, vincristine, and cyclophosphamide. The treatment course was complicated by several adverse events, including grade I high-frequency hearing loss, necessitating a 25% cisplatin dose reduction; colitis and proctitis secondary to pancytopenia with subsequent sepsis requiring intravenous antibiotics; and significant anemia necessitating routine blood transfusions.

The patient returned to his baseline functional status 3 months posttreatment, and follow-up imaging showed no evidence of disease (Fig. 1B).

Twelve months after completing therapy, routine surveillance MRI detected a new focal enhancing nodule within the supramarginal gyrus (Fig. 1C). Lumbar puncture was negative for tumor cells. Resection of the new lesion revealed rapid tumor growth between detection and surgery, indicative of the aggressive phenotype characteristic of relapsed MB. Of note, molecular profiling remained consistent between the primary and secondary tumors, and methylation profiling confirmed the relapsed tumor as $MB_{group\ 4}$.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Epidemiology of MB

CNS tumors account for approximately 25% of all childhood cancers, and of these tumors, 15% are MB.[5] MB is an embryonal tumor arising from the cerebellum that primarily affects the pediatric population (70% of cases), with peak incidence between ages 5 and 7 years.[6]

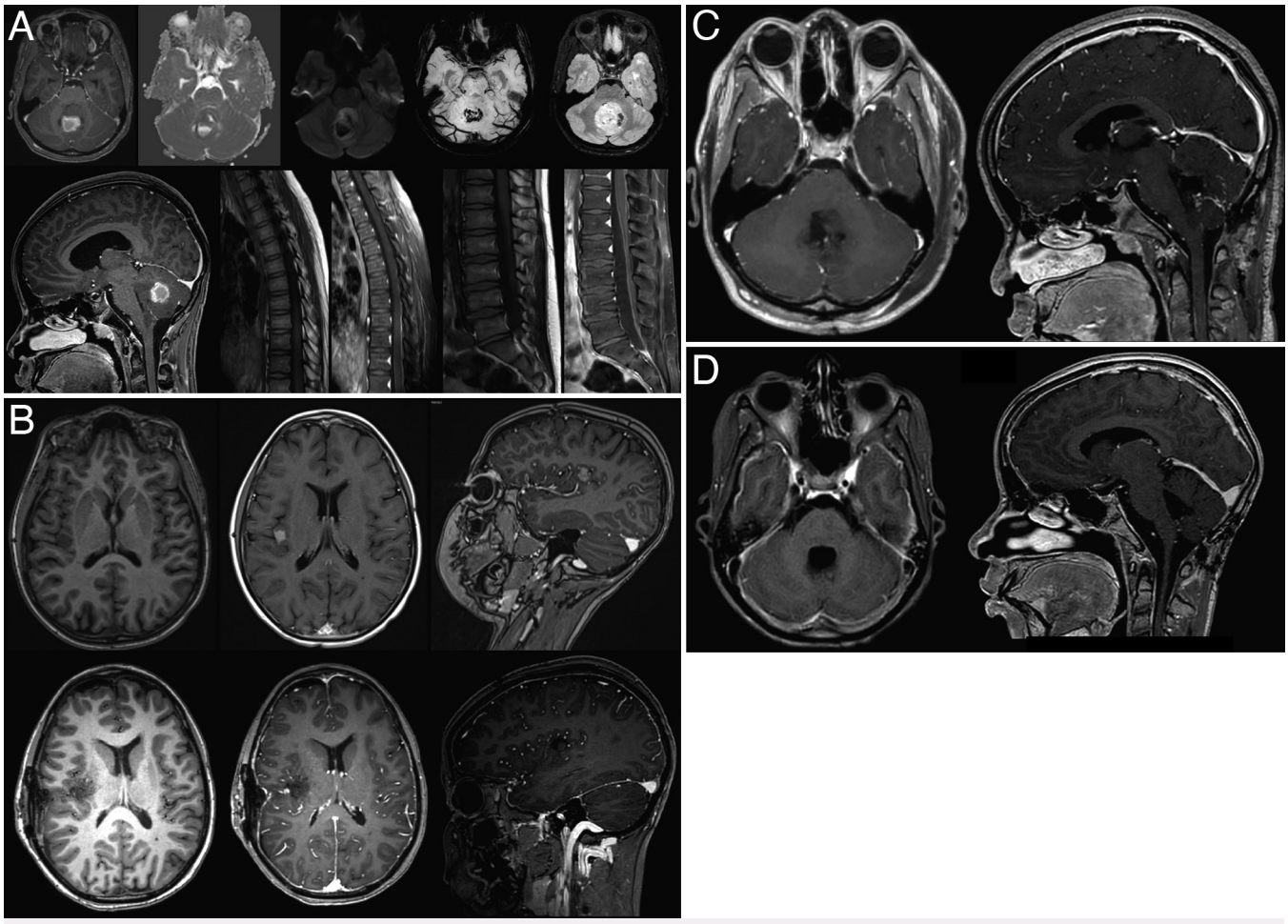

FIG. 1. MR images obtained preoperatively (**A**), postoperatively (**B**), at an interval follow-up showing tumor progression (**C**), and at the most recent posttransplant study (**D**).

There are around 0.74 cases per 100,000 children per year, and the disease is more prevalent in males than females.[7]

Approximately one-third of pediatric MB becomes recurrent/metastatic.[8] In 20%–30% of affected patients, metastasis is evident at initial presentation, while rates of metastasis are significantly higher in MB relapse compared to primary diagnosis.[9] In contrast to the 5-year survival rates for primary MB, recurrent/metastatic MB carries a high mortality rate, accounting for around 10% of all pediatric cancer deaths.[1]

Correlations Between MB Characteristics and Metastasis

Subtype

Tumor characteristics, prognosis, and likelihood of metastasis vary by molecular subgroup (WNT, SHH, $MB_{group\ 3}$, and $MB_{group\ 4}$), which tends to remain consistent at time of recurrence. Briefly, $MB_{group\ 4}$ is the most common MB subtype (> SHH > $MB_{group\ 3}$ > WNT); $MB_{group\ 3}$ and SHH (TP53 mutant type) have the poorest prognosis (> $MB_{group\ 4}$ > SHH (wildtype) > WNT); and $MB_{group\ 3}$ and $MB_{group\ 4}$ have the highest rates of metastasis (> SHH > WNT).[10,11]

Location

Primary MB tumors commonly arise in the posterior fossa, and more specifically within the cerebellar vermis.[12] Metastases most commonly (33% of the time) localize to the leptomeninges via hematogenous dissemination, although extraneural metastases can occur on the bone (78% of extraneural metastases), lymph nodes (33%), liver (15%), and lungs (11%).[2,13]

Residual Disease

Studies have shown that patients who have > 1.5 cm of residual disease postresection are at higher risk of recurrence.[14]

Imaging Studies

Several imaging findings are characteristic of MB. Broadly, MB appears hyperdense on CT imaging and demonstrates reduced diffusion on diffusion-weighted imaging. Tumors are isointense or hypointense on T1-weighted imaging and hyperintense on T2/FLAIR imaging. Metastases may appear as nodular leptomeningeal enhancement with nerve root thickening on MRI.[13]

Imaging can also be used to distinguish MB subtypes based on tumor location (e.g., MB_{SHH} tumors are frequently found in the lateral cerebellum); enhancement patterns (e.g., minimal or no enhancement of midline/fourth ventricle is characteristic of $MB_{group\ 4}$); and apparent diffusion coefficient, which is higher with large cell/anaplastic variants (associated with $MB_{group\ 3}$ and $MB_{group\ 4}$) compared to classic variants (associated with MB_{WNT}).[15] While imaging can help differentiate subtypes, thereby helping to further predict prognosis and likelihood of relapse, it cannot replace surgical biopsy.

Symptoms

Symptoms of MB can differ between initial presentation and recurrence. At initial presentation, common symptoms are typically related to elevated intracranial pressure, including headache, nausea, vomiting, and diplopia, or to mass effect, such as ataxia. These clinical features often reflect obstructive hydrocephalus caused by the tumor, in addition to its direct effects. In contrast, relapsed MB is frequently asymptomatic and detected incidentally on routine surveillance imaging, although some patients may present with new or progressive neurological symptoms.[16]

Observations

Treatment for primary MB tumors is well delineated and commonly involves resection followed by a combination of CSI therapy and chemotherapy.[2] Unlike primary MB, no standardized treatment protocol exists for relapsed MB. Current management strategies include re-resection, reirradiation therapy (re-RT), conventional and high-dose chemotherapy, and metronomic antiangiogenic multiagent therapy (Tables 1 and 2).[17] Unfortunately, many of these salvage therapies have proven to be ineffective and relapsed MB remains highly fatal in the pediatric population. Current research and clinical trials are ongoing to uncover novel therapies that may effectively treat these recurrent tumors.[18]

Utilizing the case at hand, and informed by the existing literature, this paper aims to synthesize evidence-based recommendations for improving management of relapsed MB, in hopes that it can help further guide treatment approaches and serve as a basis for future research into these lethal childhood tumors.

Treatment Strategies Used in This Case

Following identification and resection of the recurrent MB, the patient was restarted on CSI (18 Gy) with a boost to the resection cavity (54 Gy). He tolerated this treatment well aside from minimal cytopenia not requiring transfusions and mild nausea/anorexia that resolved with supportive care. The decision to reinitiate CSI was guided by existing literature supporting the efficacy and relative safety of re-RT in relapsed MB. Compared to focal re-RT or no retreatment, many retrospective studies have demonstrated improved survival outcomes with repeat CSI, along with acceptable toxicity profiles and a low incidence of symptomatic radionecrosis.[19,20] While no standardized guidelines exist for the optimal interval between radiation courses, a nearly 2-year gap in this case was considered sufficient for neural recovery, based on evidence from prior reports. Given that the patient had previously received a higher than standard spinal dose during his initial treatment (39.6 Gy), the repeat course was delivered at a reduced CSI dose (18 Gy) to mitigate the risk of long-term radiation-related complications while maintaining therapeutic efficacy.

Re-RT was followed by a course of chemotherapy according to protocol ACNS0821,[21] which involved the administration of three cycles of irinotecan 50 mg/m^2 and temozolomide (TMZ) 150 mg/m^2 over the course of 5 days per cycle. Guided by current literature, the oncology team considered adding bevacizumab to the patient's regimen as it has been shown to significantly reduce mortality in children with recurrent MB, when compared to irinotecan and TMZ and without bevacizumab.[22] However, it was omitted from this patient's treatment due to a paucity of safety data in the setting of re-RT and potential future allogeneic stem cell transplant, in addition to provider concerns regarding the associated risk of intracranial hemorrhage in patients with brain metastases. The decision to provide 3 months of therapy was made to bridge the patient between repeat CSI and transplant with systemic therapy.[23]

Following completion of chemotherapy and RT, repeat imaging showed no evidence of disease recurrence and the patient was deemed to be in radiographic remission.

Given the poor outcomes associated with standard therapies for recurrent MB, the neuro-oncology team determined that enrollment in a clinical trial was warranted. At present, a curative approach is being pursued. The patient was enrolled in two tandem clinical trials, Reduced Intensity Conditioning and Partially HLA-Mismatched (HLA-Haploidentical) Related Donor Bone Marrow Transplantation

TABLE 1. Overview of re-RT approaches for treatment of relapsed MB

Authors & Year	No. of Patients	Age, yrs	Re-RT Dose/Protocol	CSI/ Focal RT	Outcomes
Iribas et al., 2024[30]	27	<18	Unknown	19/8	1- & 2-yr PFS rates of 57% & 33% & 1- & 2-yr OS rates of 67% & 44%, respectively
					Relapse significantly higher in males, those who relapsed 24 mos after diagnosis, & those who received chemotherapy after re-RT
					No difference in survival btwn focal RT & CSI
Adolph et al., 2024[31]	293	<18	Patients stratified by whether they had had RT, initial irradiation (of primary tumor), & re-RT; outcomes were assessed	NA	Re-RT improved median PFS & OS, but had minimal effects on long-term survival
					Re-RT improved survival in most w/o re-resection
					CSI greatly improved median & long-term survival in RT-naive patients
					In patients too young to receive RT as 1st-line treatment, primary RT at recurrence associated w/ markedly improved survival
Massimino et al., 2023[6]	25	Median 11.4	Re-RT was administered at median 32 mos after 1st RT	5/20	Median PFS post–re-RT 8.2 mos; OS 23.9 mos
					Metastatic status at diagnosis/relapse negatively affected outcomes
Baroni et al., 2021[19]	24	<18	Re-RT field & dose were not systematic & were determined based on disease characteristics	15/9	3-yr post–1st failure & post–re-RT PFS & OS higher for children who received re-CSI compared w/ children who received focal re-RT
Tsang et al., 2019[32]	14	<18	Median total doses of 58.5 (range 50.5–82.9) Gy & 60.6 (range 51.8–82.9) Gy at spinal level & brain, respectively	7/7	Overall median survival 12.4 mos
					Those w/ focally recurrent disease had better OS
Gupta et al., 2019[33]	28	Median 18 at index diagnosis	Dose & vol of re-RT based on site & patterns of relapse, w/ median cumulative biologically effective dose of 117 (range 78–132) Gy; all patients received platinum-based salvage chemotherapy either before or after re-RT	7/21	2-yr post–re-RT PFS & OS rates 46% & 51%, respectively
					Younger age (<18 yrs) at initial diagnosis, primary risk stratification (SR), & molecular subgrouping (group 4) associated w/ significantly better post–re-RT outcomes
Farnia et al., 2016[34]	12	<18	Median total dose of 40 (range 20–54) Gy (RBE)	5/7	Median PFS 22.7 mos from last day of 2nd radiation course
Wetmore et al., 2014[20]	14		Median dose of 36 (range 18–54) Gy & median cumulative dose of 91.9 (range 73.8–109.8) Gy	8/6	For relapsed SR & HR patients (SR > HR), use of additional irradiation resulted in statistically significant improvement in OS from initial diagnosis
					5- & 10-yr OS rates of 55% ± 14% vs 33% ± 16% & 46% ± 14% vs 0%, respectively, for re-RT patients vs others
Bakst et al., 2011[35]	13		Median dose of 30 (19.8–45) Gy & median cumulative dose of 84 (range 65–98.4) Gy; intensity-modulated RT used in 54% of cases	1/12	Overall disease-free survival of 46% 5 yrs after initial recurrence
					Median survival since time of initial recurrence 45 (range 13–186) mos
Padovani et al., 2011[36]	5	Range 10–27	Re-RT focused on relapsed disease w/ median dose of 28 Gy (20–36 Gy; 1.8 Gy/fraction) & concomitant TMZ (75 mg/m/day) alone or as part of multidrug metronomic regimen	—	5-yr event-free survival ranged from 70% to 83%

HR = high risk; NA = not applicable; SR = standard risk.

for High-Risk Solid Tumors (NCT01804634) and Nivolumab Therapy Following Partially HLA Mismatched (Haploidentical) Bone Marrow Transplant in Children and Young Adults with High Risk, Recurrent or Refractory Sarcomas (NCT03465592).[24,25] As part of these protocols, the patient received a haploidentical bone marrow transplant intended to reconstitute the immune system and induce a graft versus tumor (GVT) response. While the "graft versus leukemia" effect has been well documented in hematological malignancies, there is emerging

TABLE 2. Overview of chemotherapy/alternative approaches for treatment of relapsed MB

Authors & Year	No. of Patients	Age, yrs	Protocol	Outcomes
O'Halloran et al., 2024[37]	9	<18	Novel reinduction chemotherapy regimen consisting of irinotecan, cyclophosphamide, TMZ, & etoposide	Overall response rate after 2 cycles 78%
Peyrl et al., 2023[38]	40	<20	Metronomic antiangiogenic regimen consisting of daily oral thalidomide, fenofibrate, celecoxib, & alternating 21-day cycles of low-dose (metronomic) oral etoposide & cyclophosphamide, supplemented by intravenous bevacizumab & intraventricular therapy consisting of alternating etoposide & cytarabine	57.5% of patients achieved disease control after 6 mos of treatment, w/ a response detected in 45% of patients
				Median OS 25.5 (10.9–40.0) mos & median PFS 8.5 (1.7–15.4) mos
				Mean (SD) PFS at both 3 & 5 yrs 24.6% (7.9%), while mean (SD) OS at 3 & 5 yrs 43.6% (8.5%) & 22.6% (8.8%), respectively
				In patients demonstrating a response, mean (SD) overall 5-yr PFS 49.7% (14.3%), & for patients who remained progression free for the 1st 12 mos of treatment, mean (SD) 5-yr PFS 66.7% (16.1%)
				No significant differences in PFS or OS were evident based on molecular subgroup analysis or no. of prior recurrences
Slavc et al., 2022[39]	29	<18	MEMMAT-like metronomic antiangiogenic approach: modified 5-drug oral regimen that includes daily oral thalidomide (3 mg/kg), daily oral fenofibrate (90 mg/m^2), twice daily oral celecoxib (dosed by weight), & alternating 21-day cycles of low-dose oral etoposide (35–50 mg/m^2) & cyclophosphamide (2.5 mg/kg); supplemented by IV bevacizumab (10 mg/kg) every 2 wks & intraventricular therapy consisting of alternating etoposide (0.5 mg daily for 5 days, <1 yr 0.25 mg) & liposomal cytarabine (0–3 yrs: 25 mg, 3–9 yrs: 35 mg, >9 yrs: 50 mg)	This treatment approach may increase median OS & PFS
				Median OS after recurrence 29.5 mos w/ OS of 48.3% ± 9.3% at 3 yrs & PFS of 42.0% ± 9.5% at 3 yrs
				When broken down by subgroup, OS at 5 yrs was 60.0% ± 21.9% for $MB_{group\ 3}$ & 31.3% ± 11.6% for $MB_{group\ 4}$, & PFS at 5 yrs was 80.0% ± 17.9% for $MB_{group\ 3}$ & 22.6% ± 11.3% for $MB_{group\ 4}$
Levy et al., 2021[23]	105	<21	Protocol ACNS0821: TMZ (150 mg/m^2 PO for 5 days) & irinotecan (50 mg/m^2 IV for 5 days) w/ or w/o bevacizumab (10 mg/kg IV on days 1 & 15); repeated every 28 days for a total of up to 12 cycles	Addition of bevacizumab to TMZ/irinotecan significantly reduced risk of death in children w/ recurrent MB
				Median OS 13 mos in standard arm & 19 mos w/ addition of bevacizumab; median event-free survival 6 mos in standard arm & 9 mos w/ addition of bevacizumab
ClinicalTrials.gov, NCT05057702[40]	Currently recruiting		Clinical trial PNOC027 (NCT05057702): utilizes genomic testing & real-time drug screening to come up w/ individualized treatment plans for patients	Trial ongoing
Prados, 2023[18]; Robinson et al., 2015[41]; Kieran et al., 2017[42]	—		Subgroup-specific treatments: several studies looking at subgroup-specific small-molecule targeted strategies	Currently no studies have successfully demonstrated the efficacy of these treatments
Vitanza et al., 2021[43]; Gholamin et al., 2017[44]; Fernández et al., 2013[45]	—		Immune modulation strategies: studies looking at the efficacy of CAR T cells, modified measles virus (MV-NIS), monoclonal antibodies, intratumoral injections, NK cells, & TGFβ	Research ongoing w/ anecdotal reports of success

MV-NIS = measles virus encoding the human thyroidal sodium iodide symporter; IV = intravenous; PO = by mouth; RBE = relative biological effectiveness.

theoretical and preclinical evidence to support a similar GVT effect in solid tumors.[25,26] The patient then received maintenance nivolumab following his haploidentical bone marrow transplant to reduce relapse in the posttransplant setting. Although nivolumab, a PD-L1 inhibitor, has shown limited efficacy in relapsed MB, likely due to low PD-L1 expression in these tumors, its use has not been previously evaluated in the context of posttransplant immunological modulation.[26]

Our patient is approximately 6 months posttransplant at the time of this report and is clinically doing well. The treatments utilized in his case likely worked both individually and in combination to treat his condition through precise targeting of the tumor itself, as well as through immunomodulation, although the efficacy of these treatments will continue to be assessed over the next few months and years. He will continue to be monitored over the coming months. The trials

are actively enrolling patients, and complete results will be published separately. No definitive conclusions can be drawn regarding the efficacy of these treatments based on a singular case, and outcomes may only be evaluated following completion of these trials. Permission to include clinical trial information in this report was granted by the research team.

Enrollment in both clinical trials occurred sequentially and was approved by the institutional IRB, with each trial addressing distinct therapeutic arms. Data reporting was conducted per trial protocol to prevent overlap or bias. The treatment approach utilized in this case contrasts with those described in the current literature and highlights a novel strategy under investigation.

Case Reports

To conduct this review, we searched the PubMed database for articles published between 1999 and 2024, with an emphasis on more recent publications containing up-to-date information on relapsed MB. Search terms included "relapsed medulloblastoma," "radiation therapy," "chemotherapy," "pediatric medulloblastoma," "salvage therapy," and "clinical trials." A total of 25 papers were identified and included in the review, consisting of 4 case reports and 21 studies or trials.

There are few case reports on relapsed MB in the pediatric population. Of these, several case reports have studied the administration of both re-RT and chemotherapy for relapsed MB. Kline et al. discussed the case of a patient with a WHO grade 4 MB_{SHH} who at the time of recurrence received repeat CSI alongside chemotherapy, as per protocol ACNS0332.[12] They concluded that existing salvage therapy strategies may be inadequate for long-term disease control, except for patients with an isolated primary site relapse and in those who have not received upfront RT.[12] A case series from Yue et al. presented 4 patients who at the time of recurrence each received local RT and TMZ chemotherapy, with all 4 patients dying from tumor metastasis or regrowth.[27] In contrast, a case report by Giakoumettis et al. on a patient treated with concurrent re-RT and TMZ chemotherapy found that a combination of approaches and re-RT may lead to good survival outcomes in patients with relapsed MB.[28] Another case series from Dominari et al. found that resection of the recurrent lesion and repeat irradiation may benefit patients, with satisfactory short-term results.[29]

Studies and Ongoing Trials

Current management protocols and ongoing trials for relapsed MB can be divided into two categories: RT and chemotherapy/alternative strategies (Tables 1 and 2).

Re-RT options involve either repeat CSI or focal RT, with dosages and timing based on individual disease characteristics. Many studies have shown promising results of re-RT, showing marked improvement in progression-free survival (PFS) and overall survival (OS) rates in relapsed MB patients. Multiple factors have been implicated in the efficacy of re-RT, including but not limited to biological sex, type of RT (CSI vs focal RT), prior RT, and disease qualities (stage, subgroup, and risk profile).

Several notable salvage chemotherapy or alternative approaches include protocol ACNS0821 (used in this case study) and a metronomic antiangiogenic regimen or MEMMAT (Medulloblastoma European Multitarget Metronomic Anti-Angiogenic Trial)–like approach, both of which have shown some promise in improving survival rates in patients with relapsed MB. Research into alternative approaches involving genomics, subgroup-specific treatments, and immune modulation is ongoing.

Lessons

The patient received a sibling haploidentical bone marrow transplant as a participant in clinical trial NCT01804634 and continues to receive maintenance nivolumab while enrolled in clinical trial NCT03465592. He is approximately 6 months posttransplant at the time of this report. Repeat brain and spine imaging have continued to show no evidence of disease, and he is in sustained remission. Although follow-up MRI revealed a FLAIR abnormality in the right ventral thalamus, the abnormality overlapped with the re-RT field and was deemed to be a treatment effect from RT rather than recurrence. His posttransplant course was complicated by seizures during engraftment, multipathogen viremia (cytomegalovirus, Epstein-Barr virus, adenovirus, and human herpesvirus 6 [HHV-6]), herpes simplex virus 1 gingivostomatitis, and medication or infection-related renal toxicity. These complications have since resolved, and the patient is doing well and at his neurological baseline. He will continue to be monitored over the coming months.

Summarizing the current literature, individualized, multimodal strategies are central to managing relapsed MB. High-dose chemotherapy followed by autologous or allogeneic stem cell transplant and post-transplant checkpoint inhibition remains a key component in appropriately selected patients. When feasible, re-RT can offer additional local control. Metronomic antiangiogenic regimens, such as the MEMMAT protocol, have demonstrated potential in prolonging PFS. Molecular profiling now plays an increasing role in guiding targeted therapy, and checkpoint inhibitors (e.g., PD-1 blockade with nivolumab) are gaining traction as maintenance or salvage options. While these approaches continue to evolve, clinical trial participation remains essential to optimize outcomes in this heterogeneous and challenging disease.

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Disclosures
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Conception and design: Lockhart, Ruiz, Kirnaz, Martin, Kobets. Acquisition of data: Lockhart, Ruiz, Jabbar Dar, Abbas, Oriko, Loeb, Fox, Martin, Kobets. Analysis and interpretation of data: Lockhart, Ruiz, Abbas, Loeb, Martin, Kobets. Drafting the article: Lockhart, Ruiz, King, Kirnaz, Oriko, Cohen, Fox, Kobets. Critically revising the article: Lockhart, Ruiz, King, Kirnaz, Cohen, Loeb, Fox, Martin, Kobets. Reviewed submitted version of manuscript: Lockhart, King, Kirnaz, Cohen, Loeb, Fox, Kobets. Approved the final version of the manuscript on behalf of all authors: Lockhart. Statistical analysis: Lockhart. Administrative/technical/material support: Lockhart, Kirnaz, Jabbar Dar. Study supervision: Lockhart, Kobets.

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