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CLINICAL STUDY

An intrathecal limited postoperative chemotherapy regimen for the treatment of young children with nodular/desmoplastic medulloblastoma and medulloblastoma with extensive nodularity

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Abstract

Purpose Therapy for medulloblastoma in patients < 4 years old omits radiotherapy due to anticipated neurocognitive deficits. The German Pediatric Brain Tumor Study Group described a chemotherapy regimen (HIT-SKK' 92 and HIT-SKK 2000) without radiation which yielded a 5-year progression-free survival (PFS) rate of 85% in children with nodular/desmoplastic medulloblastoma (NDMB) and medulloblastoma with extensive nodularity (MBEN). We modified the HIT-SKK regimen to reduce the total number of intrathecal methotrexate (IT MTX) doses from 12 to 2 doses/cycle and obviate Ommaya reservoir implantation through the use of lumbar administration. We report the outcomes of five patients treated with our approach.

Methods IT MTX was eliminated altogether on weeks when high-dose intravenous methotrexate was administered. On weeks when no systemic methotrexate was administered, a single dose of lumbar-administered IT MTX was substituted in place of multiple intra-Ommaya doses. Cumulative dosing of MTX was 16–24 mg/cycle (age-based) compared to 24 mg/cycle in the HIT-SKK regimen. Following chemotherapy, patients were monitored with interval imaging, observation for acute and late effects, and survival.

Results Four children remained in remission 3, 5, 9, and 10 years post-treatment respectively, without observed learning difficulties. One child had recurrent tumor and metastasis 6 months post-treatment. She failed the attempted salvage regimen and continued to deteriorate, dying of disease at 3 years old.

Conclusions Review of existing literature supported our modifications well. While this report is limited by the small number of children treated, we believe there is encouraging evidence that our approach warrants further evaluation in a larger population of young children with NDMB and MBEN.

Keywords Desmoplastic medulloblastoma · Intrathecal methotrexate · Medulloblastoma with extensive nodularity (MBEN) · Infant medulloblastoma

Introduction

Medulloblastoma is the most common malignant pediatric brain tumor and accounts for roughly 10% of all brain tumors in children [1]. When stratifying by age, data from the Central Brain Tumor Registry of the US (CBTRUS) finds that 32.8% of medulloblastoma cases in the US between 2011 and 2015 were in children less than 4 years of age [2]. Initial therapy for this younger group generally involves surgical resection and chemotherapy, but omits radiotherapy in an effort to mitigate neurocognitive deficits [1]. The German Pediatric Brain Tumor Study Group has reported on a chemotherapy regimen (HIT-SKK'92 and HIT-SKK 2000) specifically designed for younger children with medulloblastoma. Their research has yielded a promising 5-year progression-free survival (PFS) rate of 85% in those with nodular/desmoplastic medulloblastoma (NDMB) and medulloblastoma with extensive nodularity (MBEN), characterized based on their histological appearance and molecularly classified as part of the sonic hedgehog (SHH) mutated subgroup of medulloblastoma [3–5].

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One logistical challenge with the HIT-SKK regimen is the frequent administration (12 doses/cycle) of intrathecal methotrexate (IT MTX) that requires the insertion of an Ommaya reservoir to facilitate this frequency of dosing. We postulated that such frequent administration of small doses of IT MTX could be omitted by making two modifications to the HIT-SKK regimen. We excluded IT MTX on weeks when patients received high-dose systemic methotrexate (HD MTX). We presumed that HD MTX would provide sufficient cerebrospinal fluid (CSF) exposure in the absence of added IT MTX. For weeks that did not include systemic MTX administration, we opted for a single higher dose of IT MTX on day 1. These modifications reduced the frequency of IT MTX from 12 doses/cycle in the HIT-SKK regimen to 2 doses/cycle in our modified regimen, obviating the need for Ommaya placement. In this paper, we present the care and outcomes of 5 young patients with NDMB or MBEN treated with this approach.

Materials and methods

The HIT-SKK systemic chemotherapy regimen was adopted as our institutional standard of-care with modifications to the IT MTX as detailed below. All children less than 4 years of age and newly diagnosed with NDMB or MBEN by histology were treated with this regimen following standard institutional informed consent. All children were staged to assess for evidence of disseminated (M+) disease at the time of diagnosis, but M+ disease did not exclude participation provided there was no suggestion of limited CSF flow as a result of a metastatic deposit. Chemotherapy commenced 3–4 weeks following best upfront surgical resection. All cases reported predate the use of molecular diagnostics for confirmation of SHH pathway mutations at our institution.

The protocol (see Table 1, row 1), was identical to the HIT-SKK regimen previously reported with the following modifications to the IT MTX dosing [3, 4]. On weeks 1 and 7, one dose of IT MTX was administered. The dose was age-dependent and mirrored the standard IT MTX dosing utilized in in the treatment of acute lymphoblastic leukemia (ALL) therapy with an administered dose of 8 mg (ages < 2 years), 10 mg (ages 2–2.99 years), or 12 mg (age > 3 years) [6]. On weeks 3 and 5, when the patient received HD MTX at 5 g/m^2 via a 24-h infusion, IT MTX was omitted. Three cycles of therapy were planned. Following completion of planned chemotherapy, all patients were followed with interval imaging assessments and standard monitoring for acute and late effects per institutional standards.

Results

Four of the five children remain in remission at time of last follow-up, which were 3, 5, 9, and 10 years post-treatment respectively. Table 2 summarizes the treatment, outcomes, and follow-up for each patient. No child had any acute toxicity attributable to the IT administration of MTX including the absence of leukoencephalopathy or arachnoiditis. We further describe each case below.

Patient 1

A 9-month-old female presented with uncontrollable vomiting of 2 weeks and strabismus. MRI revealed a large, enhancing mass in the right cerebellar hemisphere. Spinal MRI demonstrated leptomeningeal dissemination (LMD). Initial surgery resulted in subtotal resection (STR) prompting a second surgery approximately 1 month later resulting

Table 1 Comparison of chemotherapy regimens

Protocol		Week 1	Week 3	Week 5	Week 7
HIT-SKK	IO therapy	Methotrexate (2 mg/day, IO), day 1–4	Methotrexate (2 mg/day, IO), day 1–2	Methotrexate (2 mg/day, IO), day 1–2	Methotrexate (2 mg/day, IO), day 1–4
	Systemic therapy	Cyclophosphamide 800 mg/m^2/day, IV), day 1–3 Vincristine (1.5 mg/m^2, IV), day 1	Methotrexate (5 g/m^2, IV), 24 h Vincristine (1.5 mg/m^2, IV), day 1	Methotrexate (5 g/m^2, IV), 24 h Vincristine (1.5 mg/m^2, IV), day 1	Carboplatin (200 mg/m^2/day, IV), day 1–3 Etoposide (150 mg/m^2/day, IV), day 1–3
Johns Hopkins	IT therapy	Methotrexate (age-based[a], IT), day 1	None	None	Methotrexate (age-based[a], IT), day 1
	Systemic therapy	Same as HIT-SKK	Same as HIT-SKK	Same as HIT-SKK	Same as HIT-SKK
ACNS1221	IT therapy	None	None	None	None
	Systemic therapy	Same as HIT-SKK	Same as HIT-SKK	Same as HIT-SKK	Same as HIT-SKK

IO intraventricular/Ommaya, *IV* intravenous, *IT* intrathecal (lumbar injection)

[a]Age-based dosing: 8 mg (ages < 2), 10 mg (ages 2–2.99), 12 mg (ages 3–8.99)

Table 2 Patient summaries

Patient	Age of diagnosis	Diagnosis	Tumor location	Surgical resection Residual disease post-operation	Treatment	Last follow-up
1	9 months	NDMB, M+	Right cerebellar hemisphere	NTR (2 surgeries) 7 mm mass	4 cycles	11yo, NED
2	33 months	NDMB, M0	Left cerebellar hemisphere	NTR Peripheral nodular rim of resection cavity	3 cycles	7 yo, NED
3	8 months	NDMB, M0	Vermis and cerebellar hemisphere	STR 4 × 4.3 × 5.2 cm mass	3 cycles	10 yo, NED
4	17 months	NDMB, M0	Vermis and right cerebellar hemisphere	STR 4.7 × 5.1 × 4.8 cm mass	3 cycles followed by alternative chemo for recurring tumor	3 yo, DoD
5	23 months	MBEN, M0	Right cerebellar hemisphere	GTR None	3 cycles	5 yo, NED

NDMB nodular/desmoplastic medulloblastoma, *MBEN* medulloblastoma with extensive nodularity, *M+* metastasis, *M0* no metastasis, *STR* subtotal resection, *NTR* near total resection, *GTR* gross total resection, *NED* no evidence of disease, *DoD* dead of disease

in near total resection (NTR). Pathology was consistent with NDMB.

The patient received 3 cycles of chemotherapy with subsequent restaging demonstrating spinal imaging equivocal for resolving LMD vs. residual spine disease. One additional cycle of chemotherapy was administered with post-cycle 4 staging demonstrating a complete response (CR). Therapy was well tolerated with transient fever and neutropenia as acute toxicities. At 4 years of age, routine surveillance imaging demonstrated a new arachnoid cyst located in the lower ventral spinal canal, a possible complication of her prior intrathecal chemotherapy. This cyst was monitored and fenestrated at age 10 due to patient complaints of right leg and back pain/weakness. The patient's last imaging follow-up at age 11 showed no evidence of disease. Patient was referred for formal neurocognitive testing but did not follow up. Per her parents, she was doing well in school and showed no sign of learning difficulties. She is currently 14 years of age and no longer seen in oncology clinic but remains in good health according to her other healthcare providers. At age 14, she is in the 10th percentile for both stature and weight.

Patient 2

A 33-month-old female presented with several-month history of unstable gait and an episode of vomiting following a fall. MRI revealed a large cystic, centrally enhancing mass in the left medial cerebellar hemisphere. Spinal MRI was negative. Surgery resulted in NTR and pathology was consistent with NDMB.

The patient received 3 cycles of chemotherapy with subsequent staging demonstrating CR. Therapy was well tolerated with transient fever, neutropenia, and thrombocytopenia as acute toxicities. The patient's last imaging follow-up at age 7 showed no evidence of disease. Patient was referred for formal neurocognitive testing but did not follow up. Per her parents, she was doing well in school and showed no sign of learning difficulties. She is currently 13 years of age and no longer seen in oncology clinic but remains in good health according to her other healthcare providers. At age 13, she is in the 25th percentile for stature and 50th percentile for weight.

Patient 3

An 8-month-old female presented 1-month post fall with abnormally large head circumference, trouble lifting head, disconjugate gaze, and irritability. MRI showed a heterogeneous, cystic mass situated in the vermis and cerebellar hemispheres. Spinal MRI was negative. Surgery resulted in a STR and pathology confirmed NDMB.

The patient received three cycles of chemotherapy with subsequent MRI demonstrating a CR. Therapy was well tolerated with transient fever and neutropenia as acute toxicities. 8 months after finishing treatment, the patient's MRI showed a new small enhancing lesion (7 mm) along the inferior portion of the left cerebellar hemisphere. This lesion was monitored every 2–3 months by MRI for the following year and remained unchanged. The patient's last imaging follow-up at age 10 (she is currently 11) showed no evidence of returning disease. Patient was referred for formal neurocognitive testing but did not follow up. Per her parents, she was doing well in school and showed no sign of learning difficulties. At age 11, she is in the 50th percentile for both stature and weight.

Patient 4

A 17-month-old female presented with 10 days of vomiting, ataxia, and lethargy. MRI showed a heterogeneous, cystic, solid mass situated in the vermis and right cerebellar hemisphere. Spinal MRI was negative preoperatively. Surgery resulted in a STR and pathology confirmed NDMB.

The patient received three cycles of chemotherapy. Therapy was well tolerated with transient fever and pancytopenia as acute toxicities. The MRI which followed showed increased linear and nodular thickened enhancements within the operative bed, concerning, but not definitive for progressive disease (PD) No drop metastases were detected in the spinal MRI. Six months post-treatment, a restaging MRI demonstrated recurrent tumor in several places in both the brain and spine. A salvage regimen was undertaken but the tumor progressed and the patient continued to deteriorate, dying of disease at 3 years of age.

Patient 5

A 23-month-old female presented with head tilt, unsteady gait, vomiting, and lethargy. MRI revealed an enhancing, cystic mass in the right cerebellar hemisphere. Spinal MRI indicated no metastases. Surgery yielded gross total resection (GTR) and pathology indicated diagnosis of MBEN.

The patient received 3 cycles of chemotherapy and post-treatment staging revealed CR. Therapy was well tolerated with transient fever and pancytopenia as acute toxicities. During treatment, the patient developed left mild high frequency hearing loss as a complication and underwent ongoing speech therapy. The patient's last follow-up was at age 5 (she is currently 6) with MRI showing no evidence of disease and the patient presenting as healthy aside from her hearing issue. Patient has been referred for formal neurocognitive testing and plans to follow up in the near future. Per her parents, she was doing well in preschool and has met all milestones. At age 6, she is in the 50th percentile for both stature and weight.

Discussion

We have detailed 5 cases of children with NDMB/MBEN treated with modified IT MTX in which 4 of 5 children were successfully treated. The four children who remain alive have no active disease, healthy follow-ups, and no observed learning difficulties.

In eliminating IT MTX on weeks when we administered HD MTX, we postulated that given the CSF penetration of HD MTX, IT MTX administration was unnecessary. The literature on CSF penetration of intravenous methotrexate and subsequent therapeutic effect on various CNS diseases supports our claim. Early research on leukemic blasts in vitro and mouse models determined a minimum effective concentration of methotrexate in the CSF for robust cytotoxic effect to be between 10^{-8} and 10^{-6} M, with 10^{-6} M becoming the standard threshold [7, 8]. Multiple studies on pediatric patients with a range of CNS diseases (ALL, Non-Hodgkin's lymphomas, brain tumors, and meningeal metastases) found that HD MTX at a dose of 5 g/m^2 resulted in CSF concentrations of methotrexate greater than 10^{-6} M for the duration of the infusion and often longer [9–17]. Other research has looked more closely at clinical outcomes in patients given certain HD MTX dosages as opposed to measuring CSF levels. In those with brain tumors, primary CNS lymphoma, CNS metastases, and other CNS diseases (Erdheim-Chester Disease, inflammatory syndromes), studies show moderate to high response to HD MTX at doses between 0.5 and 8 g/m^2 with 3–24 h infusions [18–26]. Effect on the CNS is also confirmed by reports of acute and chronic neurotoxicity in leukemia patients, who typically receive the same dosage of 5 g/m^2 for 24 h [27, 28].

The change from multiple doses of IT MTX (2 mg/day for 4 days, 8 mg total) to one dose (8–12 mg, age-based) on weeks 1 and 7, was selected to ensure that adequate CSF levels of MTX were obtained. In addition, from a convenience perspective, this approach obviated the need for an Ommaya reservoir placement and subsequent removal. This dosing frequency also lessened the impact on the pharmacy and other staff members. One disadvantage to the IT MTX dosing utilized in our series was the need for sedation/anesthesia for administration in the absence of an Ommaya reservoir. We also acknowledge that some studies have shown less consistent methotrexate spread into brain ventricles via lumbar injection versus Ommaya [9, 29]. However, we mirrored our IT MTX dosing from the work that has been conducted in leukemia, a field in which IT MTX is routinely utilized and in which such dosing has been shown to be safe and effective in children of similar age and size [6].

In comparing our regimen versus HIT-SKK, the outcomes for patients are quite similar. HIT-SKK reported its main acute toxicities as neutropenia and fever, often requiring multiple admissions [3]. All of our patients also experienced these toxicities, as is common with the use of these systemic chemotherapy agents. Thus, there appears to be no distinction in the type and severity of toxicities from HIT-SKK's Ommaya reservoir approach versus our lumbar puncture approach.

The patient who failed treatment warrants further discussion. Further studies by the German HIT group have confirmed excellent survival (93% 5-year PFS) in SHH subgroup patients [5]. Recently, SHH-mutated medulloblastoma has been further stratified into two subtypes, SHH-I and SHH-II, based on gene methylation profiles [5]. Studies comparing these two subtypes, including one by the German group,

have found inferior survival in SHH-I patients, although statistically insignificant [5, 30]. It is possible that our patient fell into this category, resulting in non-effective treatment. Rarely, it has been shown that non-SHH subtypes of medulloblastoma can exhibit a level of desmoplasticity/nodularity [1]. Thus, it is also possible that our patient did not fall into the SHH category altogether and had a subtype of medulloblastoma less amenable to our treatment. We ultimately cannot confirm this patient's subtype, because her treatment predates the use of molecular analyses for diagnosis at our institution. Patients were diagnosed between 2007 and 2016, prior to the 2016 WHO restructured classification which recommended molecular testing and necessitated SHH mutation for NDMB and MBEN diagnosis [5].

Given our encouraging findings, one question raised is whether any IT MTX is required for successful treatment of such children. Minimizing IT MTX is ideal, as it is invasive and can cause neurotoxicity, with the HIT-SKK'92 study reporting cases of leukoencephalopathy associated with treatment [3]. We did not observe leukoencephalopathy or other neurotoxicity in our patients, possibly due to less overall IT MTX use. Complete exclusion of IT MTX was tested in a study conducted by the Children's Oncology Group (ACNS1221) in which the HIT-SKK regimen was utilized with the omission of all IT MTX (Table 1, row 3). The study closed early because the relapse rate was higher than expected with a 2-year PFS of 52%, with both local and disseminated relapses [30]. This pattern of early failure suggested that some amount of IT MTX was needed for long-term disease control.

In comparing our regimen versus HIT-SKK, the outcomes for patients are quite similar, though at different scales and levels of generalizability. HIT-SKK reported its main acute toxicities as neutropenia and fever, often requiring multiple admissions [3]. All of our patients also experienced these toxicities, as is common with use of methotrexate. Thus, there appears to be no distinction in the type and severity of acute toxicities from HIT-SKK's Ommaya reservoir approach versus our lumbar puncture approach. In qualifying long term toxicity, HIT-SKK assessed neurocognitive function via several standardized tests and found that patients who received intrathecal chemotherapy performed worse than cohorts who only received systemic chemotherapy, but better than cohorts who received radiotherapy [3]. We acknowledge the lack of formal neurocognitive testing in our surviving four patients that inhibits us from comparing our patients to HIT-SSK in this regard. Patients 1, 2, and 3 were referred for testing, but parents did not pursue such a route due to no observed learning difficulties. Patient 5 was treated most recently and will undergo testing in the future. Though standardized measures of neurocognition would have bolstered our conclusions on neurological outcomes, we believe it encouraging that all patients have performed well in school and parents have not observed any developmental delays.

While this report is limited by the small number of children treated, we feel there is sufficient evidence supporting continued study of this modified intrathecal approach in a larger population of young children with NDMB and MBEN.

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Declarations

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

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