Strategy to minimize radiation burden in infants and high-risk medulloblastoma using intrathecal methotrexate and high-dose chemotherapy: A prospective registry study in Japan

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Abstract

Background: Most childhood medulloblastoma (MB) cases are curable using multimodal treatment, including craniospinal irradiation (CSI). However, late effects are a serious problem for survivors. This prospective registry study evaluated Japanese patients to determine whether a reduced radiation dose was feasible.

Patients and Methods: Patients with MB were classified as an infant group (<3 years old) and a high-risk (HR) group (≥3 years old with metastasis). The HR group received intrathecal methotrexate (IT-MTX) and high-dose chemotherapy (HDC) using thiotepa and melphalan, as well as concomitant radiotherapy with a recommended CSI dose of 18 Gy and a total local dose of 50 Gy. Radiotherapy was only considered for infants if residual tumors were present after the HDC.

Results: Between 1997 and 2006, we identified 28 HR patients (M1: 9, M2/3: 19) and 17 infant patients (M0: 11, M1: 3, M2/3: 3). During the median follow-up of 9.4 years for the entire HR group, the 5-year progression-free survival (PFS) rate was 82.1 ± 7.2% and the 5-year overall survival (OS) rate was 85.7 ± 6.6%. Subanalyses of the patients who received the recommended treatment revealed that the 5-year PFS and OS rates were both 90.5 ± 6.4%. In the infant group, the 5-year PFS rate was 52.9 ± 12.1% and the 5-year OS rate was 51.8 ± 12.4%. There were no serious adverse events associated with the IT-MTX and HDC treatments.

Conclusion: Intensified chemotherapy using HDC and IT-MTX might allow for a reduced prophylactic radiation dose in patients with MB with metastases. Further studies are needed to validate these findings.

KEYWORDS
chemotherapy, craniospinal irradiation, intrathecal methotrexate, medulloblastoma, radiotherapy, thiotepa

1 INTRODUCTION

Medulloblastoma (MB) is the most common malignant brain tumor in children and is sensitive to chemotherapy and radiotherapy, which makes it manageable in most patients using multimodal treatments. The development of intensive multiagent chemotherapy regimens has improved treatment outcomes, although radiation therapy, including craniospinal irradiation (CSI), remains important for managing...
recommended treatments

PATIENTS AND METHODS

Recommended treatments

Follow-up information was collected regarding the dates of all events, including recurrence, second neoplasms, relapse, and death. Grade 3 or higher adverse events (AEs; CTCAE ver. 2.0/3.0) were listed in the case report forms by the attending physicians, who were directly contacted to resolve any discrepancies or contradictions. Survival analyses were performed according to the intention-to-treat and per-protocol methods, with differences in overall survival (OS) and progression-free survival (PFS) evaluated using the Kaplan-Meier method. All statistical analyses were performed using EZR. AEs related to the chemotherapy were analyzed according to the induction regimen and HDC.

2.1 Definitions

The risk grouping was performed according to the presence of metastasis, which was staged using Chang’s classification. The extent of surgical resection at the primary site was classified as gross total resection (GTR), subtotal resection (STR), partial resection (PTR), or only biopsy. Although GTR was considered to be a case without residual tumor on the postoperative MRI images, the status of residual tumors was not clearly defined because it was not associated with risk stratification in this study. Classification as STR or PTR was decided on the discretion of the attending physician. Cases without metastasis were assigned to the standard-risk group, regardless of residual postoperative tumor status, and all cases with metastasis were assigned to the HR group. Patients who were <3 years old were assigned to the infant group and received a different recommended treatment, regardless of metastasis. Responses to chemotherapy were defined using the Response Evaluation Criteria in Solid Tumors version 1.0.

2.2 Recommended treatments

The recommended treatment for HR MB was four courses of induction chemotherapy alternating between regimen A and regimen B. Regimen A involved intravenous infusions of cisplatin (90 mg/m² for 1 day), cyclophosphamide (1 g/m² for 3 days), etoposide (100 mg/m² for 5 days), and vincristine (1.5 mg/m² for 1 day). Regimen B was the same regimen as regimen A except for the omission of etoposide. IT-MTX was concomitantly administered on day 1 of each course, with an added IT-MTX treatment on day 8 of the first course, which corresponded to a total of five IT-MTX treatments. The IT-MTX was administered at 12 mg/dose for children who were ≥3 years old. Radiation therapy was simultaneously administered from the beginning of the second chemotherapy course, with a recommended CSI dose of 18 Gy in 12 fractions and a local boost dose of 32 Gy in 20 fractions (total: 50 Gy), and the recommended field for local irradiation was defined as the posterior fossa. After the four courses of chemotherapy, an additional course of HDC with thiotepa and melphalan (the “double-conditioning regimen”) was recommended, based on a previous report (thiotepa at 200 mg/m² and melphalan at 70 mg/m² on days –12, –11, –5, and –4). An additional IT-MTX dose was administered once during the HDC. The details of the recommended regimens are summarized in Figure 1.

The recommended regimen for infants was not based on the metastatic status and did not include radiotherapy. In the infant group, the IT-MTX dose was adjusted according to age (10 mg/dose for patients who were 2 years old, 8 mg/dose for patients who were 1 year old, and 6 mg/dose for patients who were <1 year old). After three courses of regimen A and one course of regimen B, the infant group was recommended to receive the same double-conditioning regimen as the HR group but with dose modification for younger children. The HDC for patients who were <2 years old was calculated...
as thiotepa at 8 mg/kg/day and melphalan at 1.5 mg/kg/day. Radiation therapy (recommended local dose of approximately 50 Gy) was only considered at the physician’s discretion when a residual tumor was detected after the HDC.

3 | RESULTS

3.1 | Patient characteristics

Between November 1997 and November 2006, we identified 82 cases that were registered from 30 institutions. However, only 67 MB cases were included after excluding 13 cases with sPNETs/pineoblastomas, one case of relapsed MB, and one case of atypical teratoid rhabdoid tumor (ATRT) (Figure 2). The 67 MB cases included 18 patients who were <3 years old and 27 patients who were >3 years old with metastasis. In addition, one 2-year-old girl (MB49 in Table 1) received the regimen recommended for the HR group based on the physician’s decision. As a result, 17 patients were treated using the infant regimen and 28 patients were treated using the HR regimen. The median ages at the first surgery were 8.54 years in the HR group (range: 2.79-15.1 years) and 2.0 years in the infant group (range: 0.4-2.9 years). The male-female ratios were 1:0.9 in the HR group and 1.8:1 in the infant group. Nine HR patients had microscopic metastasis (M1) and 19 HR patients had macroscopic metastasis (M2/3). GTR of the primary tumor was achieved in 11 cases (M1: five cases, M2/3: six cases), with incomplete resection observed in the remaining 17 patients. There was no case involving only biopsy in the HR group. Six infant patients experienced metastasis at the initial staging, including three cases of M1 and three cases of M2/3 metastasis (Tables 1 and 2). GTR was achieved in six patients, and only two patients underwent biopsy.

3.2 | Outcomes in the HR cases

The median follow-up duration for the surviving HR patients was 9.4 years (range: 7.6-16.5 years), and seven of the 28 HR patients did not receive the recommended treatment. These nonrecommended treatments involved high-dose CSI (≥23.4 Gy) in five cases, including two cases with a dose of 36 Gy (MB43 and MB79), two cases with doses of 23.4-24 Gy (MB64 and MB76), and one case with a whole-brain irradiation dose of 24 Gy (MB52). Furthermore, the HDC was omitted in three cases, including two of the cases with high-dose CSI (MB76 and MB79). Local irradiation was not performed in one patient (MB20) for unknown reasons.

Survival analyses according to the intention-to-treat principle (n = 28) revealed 5-year rates of 82.1±7.2% for PFS and 85.7±6.6% for OS, with 10-year rates of 78.0±8.0% for PFS and 82.1±7.2% for OS (Figure 3A). Survival analysis based on the per-protocol method (n = 21) revealed that the 5-year PFS and OS values were both 90.5±6.4% (Figure 3B). Dose modifications were performed for the HDC in four of 25 patients, based on the physician’s discretion, which was most commonly related to decreased renal function. The resection status was not associated with significant differences in PFS and OS (P = .68).

3.3 | Outcomes in the infant group

Among the 17 infant cases, the median follow-up duration for surviving patients was 9.4 years (range: 3.6-14.2 years). Fourteen patients...
received HDC, including one patient who received thiotepa and busulfan as a conditioning regimen. Radiotherapy was added for six patients, including two cases with local irradiation for residual tumor and three cases with prophylactic CSI (Table 2). One patient whose tumor responded poorly to primary chemotherapy (MB23) received whole brain irradiation (45 Gy) and whole-spine irradiation (30 Gy).

In the infant group, the 5-year rates were 52.9 ± 12.1% for PFS and 51.8 ± 12.4% for OS (Figure 3C). Among the 16 patients with an evaluable treatment response after the first course of induction chemotherapy, eight patients achieved a complete response (CR), six patients achieved a partial response (PR), one patient achieved a mixed response, and one patient achieved no response.

### 3.4 Response to treatment

Twenty-three patients in the HR group had evaluable residual tumors after surgery. After the first course of chemotherapy, four patients achieved CR, 15 achieved PR, and three had stable disease. The response was not evaluated in one patient. Therefore, the response rate (CR + PR) for the first course of induction chemotherapy was 86.4% (19/22). Evaluable residual lesions remained before the HDC in 12 cases. Response to HDC was evaluable in 11 cases, and shrinkage of the residual lesions was observed in seven cases (63.6%). Over-all, 21 patients achieved CR after HDC and two patients subsequently experienced relapse. In addition, three of four cases with survival after HDC experienced relapse. The responses to HR treatment are summarized in Table 3. In the infant group, 12 patients had evaluable residual tumors after surgery. The response rate after the first course of induction chemotherapy was 81.8%. Tumor shrinkage after HDC was confirmed in three of four evaluable patients.

### 3.5 Toxicities

During the 178 courses of induction chemotherapy, 28 patients (62.2%) experienced 53 AEs that were considered grade 3 or greater. The highest incidence of severe AEs (20/45, 44.4%) was noted during the first chemotherapy course, and infections were the most frequent AEs, including 14 cases of sepsis (Table S1). One infant patient developed pneumonia after the first course of induction chemotherapy and subsequently died because of acute respiratory distress syndrome (MB15). Another patient in the infant group (MB25) died because of chemotherapy-related pulmonary toxicity after treatment for relapse. The frequency of severe AEs was not significantly different between the infant and HR patients. In the 39 cases that involved HDC, 11 patients (28.2%) experienced grade 3 or greater AEs, includ-
TABLE 1  Patient characteristics and treatment details of high-risk medulloblastoma

| No. | Age at onset (years) | Sex | Extent of resection | Metastases | Radiation field and dosage | HDC | Relapse | Location of relapse | EFS (days) | Outcome | Survival (days) |
|-----|----------------------|-----|---------------------|------------|---------------------------|-----|---------|---------------------|------------|---------|------------------|
| MB08 | 8                    | F   | STR/Ptr             | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 5112       | NED     | 5112             |
| MB14 | 12                   | M   | STR/Ptr             | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 4830       | NED     | 4830             |
| MB20 | 6                    | F   | STR/Ptr             | M2-3       | CSI 18 Gy only            | Yes | Yes  | Local + dissemination | 831        | DOD     | 1935             |
| MB21 | 13                   | M   | STR/Ptr             | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 3228       | NED     | 3228             |
| MB26 | 10                   | F   | STR/Ptr             | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 3942       | NED     | 3942             |
| MB34 | 11                   | M   | STR/Ptr             | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 4148       | NED     | 4148             |
| MB35 | 6                    | M   | STR/Ptr             | M1         | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 4264       | AWD     | 4264             |
| MB37 | 4                    | M   | STR/Ptr             | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 6007       | NED     | 6007             |
| MB43 | 4                    | M   | STR/Ptr             | M2-3       | CSI 36 Gy + local 50.4 Gy | Yes | Yes  | Spine               | 347        | DOD     | 420              |
| MB44 | 4                    | F   | STR/Ptr             | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 4047       | NED     | 4047             |
| MB48 | 8                    | M   | GTR                 | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 3256       | NED     | 3256             |
| MB49 | 2.8                  | F   | STR/Ptr             | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 3713       | NED     | 3713             |
| MB52 | 11                   | F   | STR/Ptr             | M2-3       | WBI 24 Gy + spine 18 Gy + local 50 Gy | Yes | No |                     | 3679       | NED     | 3679             |
| MB57 | 8                    | M   | GTR                 | M2-3       | CSI 18 Gy + local 50 Gy   | No  |      |                     | 938        | OCD     | 938              |
| MB60 | 5                    | M   | STR/Ptr             | M1         | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 3441       | NED     | 3441             |
| MB62 | 10                   | M   | GTR                 | M1         | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 3206       | NED     | 3206             |
| MB64 | 12                   | M   | STR/Ptr             | M2-3       | CSI 24 Gy + local 49.6 Gy | Yes | No   |                     | 4999       | NED     | 4999             |
| MB65 | 4                    | F   | STR/Ptr             | M1         | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 3357       | NED     | 3357             |
| MB66 | 7                    | F   | GTR                 | M2-3       | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 3229       | AWD     | 3229             |
| MB67 | 7                    | M   | GTR                 | M1         | CSI 18 Gy + local 50 Gy   | Yes | Dissemination |                     | 408        | DOD     | 618              |
| MB73 | 11                   | F   | GTR                 | M1         | CSI 18 Gy + local 56 Gy   | Yes | No   |                     | 2997       | NED     | 2997             |
| MB74 | 9                    | F   | GTR                 | M1         | CSI 18 Gy + local 56 Gy   | Yes | No   |                     | 3201       | NED     | 3201             |
| MB75 | 7                    | M   | GTR                 | M2-3       | CSI 18 Gy + local 46 Gy   | Yes | Dissemination |                     | 314        | DOD     | 357              |
| MB76 | 15                   | M   | STR/Ptr             | M2-3       | CSI 23.4 Gy + local 55.8 Gy | No |      |                     | 2789       | NED     | 2789             |
| MB77 | 5                    | F   | GTR                 | M1         | CSI 18 Gy + local 50 Gy   | Yes | No   |                     | 2857       | NED     | 2857             |
| MB79 | 9                    | F   | STR/Ptr             | M2-3       | CSI 36 Gy + local 55.8 Gy | Yes | Dissemination |                     | 2810       | NED     | 2810             |

Abbreviations: AWD, alive with disease; CSI, craniospinal irradiation; DOD, died of disease; EFS, event-free survival; GTR, gross total resection; HDC, high-dose chemotherapy; MB, medulloblastoma; NED, no evidence of disease; OCD, other cause of death; PTR, partial resection; STR, subtotal resection; WBI, whole brain irradiation.

3.6 Patterns of relapse

Relapse was observed in five HR patients, with four patients experiencing dissemination. Local recurrence was not observed in the HR group, although isolated metastatic recurrence was observed in the spinal cord of one patient (MB43). Three of the 21 patients who completed the recommended treatment relapsed, and two out of seven patients who did not receive the recommended treatment relapsed. In addition, only one of five patients treated using CSI doses >18 Gy relapsed. Three of the relapses occurred within 2 years and four patients died because of their primary disease. Only one patient with a late relapse was able to achieve a CR for a second time and survived for a short disease-free period after the relapse (MB81).

In the infant group, seven relapses were observed, including five metastatic relapses (dissemination: two cases, spinal lesion: three cases), one local relapse, and one primary progression. All relapses in the infant group occurred within 2 years and all of these patients died because of their primary disease.
| No. | Age at onset (months) | Sex | Extent of resection | Metastases | HDC | Radiation field and dosage | Relapse | Location of relapse | EFS (days) | Outcome | OS (days) |
|-----|----------------------|-----|---------------------|------------|-----|--------------------------|---------|---------------------|------------|---------|----------|
| MB02 | 2.4                  | M   | GTR                 | M0         | TEPA + Mel | No RT                   | Yes     | Local + spine       | 706        | DOD     | 1691     |
| MB06 | 1.0                  | M   | STR/ PTR            | M0         | TEPA + Mel | No RT                   | No      |                    | 4880       | NED     | 4880     |
| MB07 | 0.4                  | F   | STR/ PTR            | M0         | TEPA + Mel | Local 49.5 Gy           | No      |                    | 5174       | AWD     | 5174     |
| MB12 | 0.6                  | M   | Biopsy              | M0         | TEPA + Mel | No RT                   | Yes     | Local              | 443        | DOD     | 749      |
| MB15 | 1.3                  | M   | STR/ PTR            | M0         | NA         | No                      | No      |                    | 40         | TRD     | 40       |
| MB16 | 1.7                  | M   | STR/ PTR            | M0         | TEPA + Mel | No RT                   | No      |                    | 1295       | NED     | 1295     |
| MB18 | 2.2                  | M   | GTR                 | M0         | TEPA + Mel | No RT                   | No      |                    | 2164       | NED     | 2164     |
| MB19 | 1.8                  | M   | STR/ PTR            | M0         | TEPA + Mel | No RT                   | No      |                    | 4443       | NED     | 4443     |
| MB22 | 2.9                  | M   | GTR                 | M0         | TEPA + Mel | No RT                   | Yes     | Dissemination       | 415        | DOD     | 1505     |
| MB23 | 0.6                  | M   | Biopsy              | M2/3       | No         | WBI 45 Gy + spine 30 Gy | Yes     | Refractory          | 223        | DOD     | 223      |
| MB25 | 2.5                  | M   | STR/ PTR            | M1         | TEPA + Mel | No RT                   | Yes     | Spine              | 264        | TRD-PTR | 315      |
| MB32 | 2.0                  | F   | STR/ PTR            | M1         | TEPA + Mel | Local 50 Gy            | Yes     | Dissemination       | 540        | DOD     | 673      |
| MB42 | 2.8                  | F   | GTR                 | M2/3       | TEPA + Mel | CSI 18 Gy + local 50 Gy | Yes     | Spine              | 378        | DOD     | 563      |
| MB46 | 2.9                  | F   | STR/ PTR            | M0         | No         | CSI 18 Gy + local 50 Gy | No      |                    | 4031       | NED     | 4031     |
| MB54 | 0.7                  | F   | GTR                 | M1         | TEPA + Mel | No RT                   | No      |                    | 2976       | NED     | 2976     |
| MB63 | 2.8                  | M   | STR/ PTR            | M2/3       | TEPA + Bu  | CSI 30.6 Gy + local 49.3 Gy | No |            | 3433       | NED     | 3433     |
| MB72 | 2.7                  | F   | GTR                 | M0         | TEPA + Mel | No RT                   | No      |                    | 3042       | NED     | 3042     |

Abbreviations: AWD, alive with disease; Bu, busulfan; CSI, craniospinal irradiation; DOD, died of disease; EFS, event-free survival; GTR, gross total resection; HDC, high-dose chemotherapy; MB, medulloblastoma; Mel, melphalan; NA, not available; NED, no evidence of disease; OS, overall survival; PTR, partial resection; RT, radiation therapy; STR, subtotal resection; TEPA, thiotepa; TRD, treatment-related death; TRD-PR, treatment-related death post relapse; WBI, whole brain irradiation.

**DISCUSSION**

In the HR group, most patients received a reduced radiation dose (CSI: 18 Gy, total local: 50 Gy) plus intensified chemotherapy using IT-MTX and HDC (thiotepa and melphalan). This approach provided a 5-year PFS rate of 90.5% for HR patients, which is encouraging when compared to the previously reported 5-year event-free survival rates of 36-71% for HR MB.22-31 Although this study has several limitations, which are described below, this encouraging result suggests that an intensified chemotherapy regimen is effective, especially as the HR group only included patients with metastasis.
During the last 20 years, there have been various attempts to develop HDC using thiotepa, although the results in childhood MB have been limited. Moreover, the efficacy and safety of our unique HDC regimen, which we have named the “double-conditioning regimen,” have been reported for pediatric solid tumors but not for MB. For example, the HDC regimen from the present study included various beneficial characteristics, such as the use of a combination with melphalan, the 5-day rest between drug administrations, and the continuous infusion of thiotepa. These characteristics may have contributed to the good results in the HR group of patients with MB.

Postoperative residual tumor is a well-known poor prognostic factor. In most prospective clinical trials, residual tumors larger than 1.5 cm\(^2\) have been stratified as HR. In contrast, only patients with metastases were treated as the HR group in our study, regardless of residual tumors, because it would have been difficult to accurately evaluate the volume of residual tumors at all institutions. Although the effect of resection extent on the prognosis remains controversial, residual tumors larger than 1.5 cm\(^2\) are known to have a negative effect even in cases with metastases. In our study, the extent of resection did not affect the prognosis, which was probably due to inaccuracies in the definition of resectability, but might also have been so because the negative effect of residual tumors was offset by the HDC.

The 5-year PFS rate for infants was only approximately 50%, which agrees with the unsatisfactory results from previous reports. This may be because the treatment regimen is effective for desmoplastic MB (DMB) and medulloblastoma with extensive nodularity (MBEN), but not effective for non-DMB/MBEN cases. Nevertheless, HDC is reportedly effective for infant MB. The Head Start III trial examined intensive induction chemotherapy followed by HDC (thiotepa, carboplatin, and etoposide), and revealed an excellent 5-year PFS rate of 93% for 15 patients with DMB and MBEN. The Children’s Cancer Group 99703 trial also evaluated infant MB cases (<3 years old) that were treated using tandem HDC (thiotepa and carboplatin), which provided 5-year rates of 78.6% for event-free survival and 85.7% for OS in DMB cases, relative to 5-year rates of 50.5% and 60.6% for non-DMB cases. This result is extremely favorable for non-DMB cases, and suggests that HDC including thiotepa may be effective for both DMB and non-DMB cases.

The regimen from the present study incorporated IT-MTX, and previous studies have indicated that IT-MTX is effective in infant MB and ATRT cases. While the present study was unable to specifically evaluate the contribution of IT-MTX, we did not identify any cases of leukoencephalopathy. Given that the incidence of IT-MTX-induced leukoencephalopathy is related to the subsequent radiation dose, it appears that IT-MTX may be safe in regimens involving doses of 18 Gy for CSI and 50 Gy for total local irradiation.

Previous studies have indicated that a CSI dose of 36 Gy was associated with progressive impairment of neurocognitive function and elevated risks of pituitary dysfunction, hypothryoidism, late cardiac events, and premature ovarian failure. Furthermore, the risk of nonrelapse mortality is known to increase in the years after the treatment of brain tumors. Moreover, a study of neurocognitive function after prophylactic cranial irradiation in children with leukemia revealed that a radiotherapy dose of 24 Gy was associated with more adverse effects than a dose of 18 Gy, which only induced relatively minor effects during a follow-up of several decades.

Two strategies are currently being explored to improve the prognosis and decrease the late sequelae in patients with MB. The first strategy involves the introduction of a risk classification system based on molecular findings, while the second strategy involves treatment intensification using HDC that contains thiotepa for HR cases. In cases with low risks of relapse (eg, Wnt, Shh, and Group 4 cases), a reduced radiation dose can easily be achieved, although more effective treatments are still needed for HR cases. The Japan Children’s Cancer Group is currently exploring the feasibility of this HDC regimen and intrathecal chemotherapy in these HR cases.

This study has several critical limitations. The first limitation is the lack of pathological and biological information. In this registry, only categorical information regarding the institutional diagnosis was collected, and the detailed pathological subtypes of the MBs are unknown. Moreover, a central pathological review was not performed and it is possible that other brain tumors were included. For example, ATRT might have been included, especially in the infant group, as no molecular analysis was performed. The second limitation is the relatively small sample of patients and the multiple cases of non-compliance with the recommended regimen, which might have led to overestimated results, based on the small number of events. The third limitation is that this study did not assess the late effects of the recommended treatment, and further studies are needed to evaluate these late effects, even if the survival outcomes are considered acceptable after CSI with a dose of 18 Gy.

In conclusion, intensified chemotherapy with HDC and IT-MTX provided promising results in cases of metastatic MB. However, further trials are needed to confirm the efficacy and long-term safety of HDC in these cases.

### TABLE 3 Disease status of high-risk medulloblastomas in each treatment phase

| Disease status | After first induction chemotherapy | Before HDC | After HDC |
|----------------|-----------------------------------|------------|-----------|
| Without targetable lesion (n = 5) | CR 5 | 5 | 5 |
| With targetable lesion (n = 23) | CR, n (%) 4 (18.2) | 8 (40.0) | 16 (80.0) |
| PR, n (%) 15 (68.2) | 10 (50.0) | 3 (15.0) |
| SD, n (%) 3 (13.6) | 2 (10.0) | 1 (5.0) |
| PD 0 | 0 | 0 |
| NA 1 | 3 | 3 |

Abbreviations: CR, complete remission; HDC, high-dose chemotherapy; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease.
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CONFLICT OF INTEREST
None of the authors have any financial conflict of interest to disclose.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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