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Phase II study of reduced-dose craniospinal irradiation and combination chemotherapy for children with newly diagnosed medulloblastoma: A report from the Japanese Pediatric Brain Tumor Consortium

Keiko Okada[1] | **Toshinori Soejima**[2] | **Hiroaki Sakamoto**[3] | **Junko Hirato**[4] | **Junichi Hara**[1]

[1] Department of Pediatric Hematology/Oncology, Osaka City General Hospital, Osaka, Japan

[2] Department of Radiation Oncology, Kobe Proton Center, Kobe, Japan

[3] Department of Pediatric Neurosurgery, Osaka City General Hospital, Osaka, Japan

[4] Department of Pathology, Gunma University Hospital, Maebashi, Japan

Correspondence
Keiko Okada, Department of Pediatric Hematology/Oncology, Osaka City General Hospital, 2-13-22 Miyakojima-Hondori, Miyakojima-ku, Osaka 534-0021, Japan.
Email: keiko-okada@med.osakacity-hp.or.jp

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Abstract

Background: Standard doses of craniospinal irradiation (CSI) are 23.4 Gy for patients with average-risk and 36 Gy for those with high-risk medulloblastoma (MB). We investigated whether intensified chemotherapy including intrathecal chemotherapy with simultaneous irradiation is able to reduce CSI dose to 18 Gy.

Methods: Newly diagnosed average-risk patients aged 3-11 years and high-risk patients aged 3-18 years were eligible. Patients with Stage M1-4 disease were classified as high-risk MB and the others, including M0 patients with >1.5 cm^2 postoperative residual tumor, were classified as average-risk MB. Patients received chemotherapy consisting of cyclophosphamide, etoposide, cisplatin, and vincristine. Radiotherapy was started concomitantly with the second course of chemotherapy. Radiation doses were 50 Gy to the primary site and 18 Gy to the craniospinal axis. Average-risk patients received five courses of chemotherapy. High-risk patients received high-dose chemotherapy consisting of thiotepa and melphalan following four courses of chemotherapy. All patients received intrathecal methotrexate.

Results: From 2006 to 2014, 48 patients (35 average and 13 high risk) who met the eligibility/exclusion criteria were enrolled. The 3-year progression-free survival (PFS) and 3-year overall survival (OS) were 90.5% (standard error 5.2%) and 93.9% (4.2%), respectively, for average-risk patients, and 100% and 100%, respectively, for high-risk patients. There was no leukoencephalopathy or treatment-related deaths. Two patients experienced secondary cancer.

Conclusions: These results suggest that CSI 18 Gy is adequate at least in a proportion of patients with MB treated with intensified chemotherapy including intrathecal methotrexate and simultaneous irradiation, though the results in high-risk patients were only exploratory.

KEYWORDS
high-dose chemotherapy, intrathecal methotrexate, medulloblastoma, reduced-dose craniospinal irradiation

Abbreviations: Ccr, creatinine clearance; CR, complete response; CSF, cerebrospinal fluid; CSI, craniospinal irradiation; G-CSF, granulocyte colony-stimulating factor; GTR, gross total resection; HDC, high-dose chemotherapy; MB, medulloblastoma; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; STR, subtotal resection

1 | INTRODUCTION

Medulloblastoma (MB) is a common malignant brain tumor occurring in children.[1] Conventional treatment involves a combination of surgery, radiotherapy, and chemotherapy. Children > 3 years of age at diagnosis with residual tumor < 1.5 cm^2 and no metastasis (average risk) have a predicted 5-year progression-free survival (PFS) of 80%.[2-4] High risk is defined by >1.5 cm^2 residual tumor or M+ disease; high-risk children > 3 years of age have a 5-year PFS of 50-70%.[3,5,6] Standard doses of craniospinal irradiation (CSI) for patients with MB are 23.4 Gy for average-risk and 36 Gy for high-risk patients. CSI induces cognitive decline, growth failure, and endocrinologic sequelae, so a reduction in CSI dosage is required.

We have treated MB patients using CSI 18 Gy since 1997. Our group has performed a prospective registry study that showed promising results with intensified chemotherapy including high-dose chemotherapy (HDC) and intrathecal methotrexate plus simultaneous irradiation, which might permit CSI dose reduction to 18 Gy in high-risk MB patients.[7] Based on that result, we planned a phase II clinical trial to investigate whether multidrug-intensified chemotherapy including intrathecal chemotherapy plus simultaneous irradiation, without HDC, is able to reduce the dose of CSI to 18 Gy in average-risk MB patients. Average-risk patients ≥ 12 years were excluded because the degree of their cognitive decline after cranial irradiation was small and their benefit from dose reduction was limited. We also included high-risk MB patients following the strategy of our previous registry study.[7]

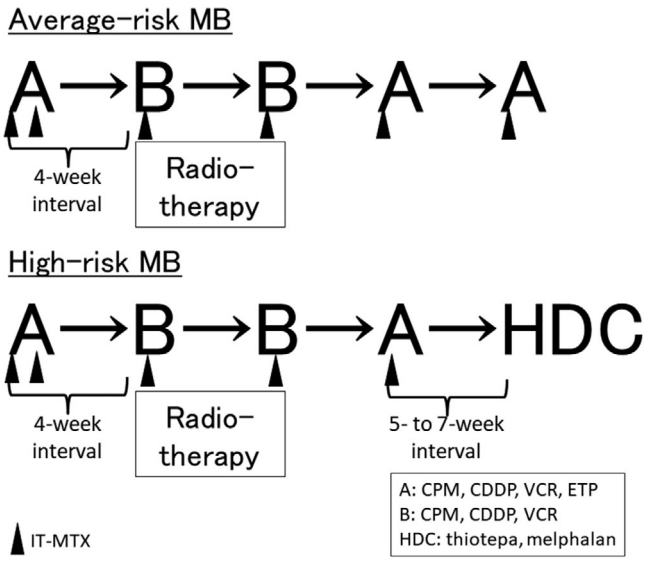

FIGURE 1 Treatment schema for average-risk and high-risk medulloblastoma patients. Abbreviations: CDDP, cisplatin; CPM, cyclophosphamide; ETP, etoposide; HDC, high-dose chemotherapy; IT-MTX, intrathecal methotrexate; MB, medulloblastoma; VCR, vincristine

2 | METHODS

2.1 | Patients

Patients with a histologically confirmed medulloblastoma were eligible. They had to be 3-18 years of age at diagnosis and to have received no previous chemotherapy or radiotherapy other than corticosteroids. Other eligibility criteria included: normal bone marrow function (white blood cell count ≥ 2×10^9/L, absolute neutrophil count ≥ 1×10^9/L, and platelet count ≥ 100×10^9/L); normal liver function (alanine aminotransferase ≤ 100 IU/L and total bilirubin < 1.5 mg/dL); normal renal function (serum creatinine less than the upper limit of normal by age); and Eastern Cooperative Oncology Group performance status score 0-3. After enrollment, patients ≥ 12 years of age who were classified as average risk were excluded. Treatment had to start within 35 days of surgery. All institutions participating in the study received approval from their respective review boards. Written informed consent was obtained from patients, parents, or legal guardians. The trial was conducted in accordance with the Declaration of Helsinki and was registered at the University Hospital Medical Information Clinical Trials Registry (UMIN000000545).

All patients were assessed before surgery or at least 7 days after surgery by gadolinium-enhanced magnetic resonance imaging (MRI) of the head and spine, bone scintigraphy, bone marrow aspiration, and lumbar cerebrospinal fluid (CSF) examination. The extent of surgery was defined as follows: gross total resection (GTR) if no visible tumor remained on postoperative MRI; subtotal resection (STR) if most of the tumor was resected but there was slight residual tumor; partial resection if not GTR, STR, or biopsy; and biopsy if surgical removal was <10% of the total tumor mass. We defined the extent of resection using operative notes and MRI assessed within 72 h of surgery.

Patients were classified as average risk or high risk according to the Chang staging system alone.[8] We defined patients as average risk if they had no evidence of metastatic disease (M0), including patients with residual tumor > 1.5 cm^2. We defined patients as high risk if they had metastatic disease (M1-4).

Pathologic review was not performed prior to study enrollment. Pathology slides were centrally reviewed at Gunma University Hospital and classified according to the most current World Health Organization criteria.

2.2 | Treatments

Average-risk patients received five cycles of chemotherapy. High-risk patients received four cycles of chemotherapy followed by HDC. The chemotherapy regimen consisted of cyclophosphamide (1000 mg/m^2/day) with mesna on days 1, 3, and 5; cisplatin (90 mg/m^2) on day 2; vincristine (1.5 mg/m^2) on day 1; etoposide (100 mg/m^2/day) on days 1-5; and intrathecal methotrexate (12 mg/body) on day 1 (and day 8 on the first course only). Granulocyte colony-stimulating factor (G-CSF) was administered from day 6 until neutrophil recovery. As shown in the treatment schema (Figure 1), all patients received simultaneous radiotherapy from the beginning of the second course

of chemotherapy. During radiotherapy (the second and third courses), etoposide administration was omitted to avoid severe mucositis and myelosuppression. Chemotherapy cycles were administered every 28 days. A new cycle started once the absolute neutrophil count reached $\geq 0.75 \times 10^9$/L $\geq$24 h after the last administration of G-CSF, the platelet count reached $\geq 50 \times 10^9$/L, nonhematologic toxicity recovered to grade 0 or 1, and there was no infection. Peripheral blood stem cells were harvested after the first or second course of chemotherapy. A minimum of 2×10^6 CD34+ cells per kg were collected and cryopreserved.

Radiation doses were 50 Gy (32 fractions) to the primary site and 18 Gy (12 fractions) to the craniospinal axis.

High-dose chemotherapy with autologous stem cell rescue was started within 35-49 days of the initiation of the fourth course and consisted of thiotepa (200 mg/m^2/day, 24-h continuous infusion) on days −12, −11, −5, and −4; and melphalan (70 mg/m^2/day, 1-h infusion) on days −12, −11, −5, and −4. According to the previous study,[9] doses of thiotepa and melphalan were reduced based on creatinine clearance (Ccr) measured before days −12 and −5. When Ccr was 70-100 mL/min/1.73 m^2, the doses of thiotepa and melphalan were reduced to Ccr/100 × standard doses. We abandoned HDC if a patient's Ccr was <70 mL/min/1.73 m^2. G-CSF was administered from day 5 until neutrophil recovery.

2.3 | Pathology review

Histological review was not performed prior to study enrollment. Central pathologic review was subsequently performed on 39 of 48 specimens by a single neuropathologist (Junko Hirato).

2.4 | Endpoints and statistical analysis

The primary endpoint was to estimate 3-year PFS. The secondary endpoints were overall survival (OS) and toxicity rate. Toxicity was graded according to Common Terminology Criteria for Adverse Events v4.0. All grade 3 and 4 toxicities and all unexpected toxicities were reported.

The study design required 30 average-risk patients and 37 high-risk patients based on the binomial distribution with the α level of 0.1 and statistical power of 90%. The expected PFS and the threshold event-free survival were 80% and 60% for average-risk patients, and 60% and 40% for high-risk patients, respectively. However, high-risk patient recruitment was stopped early as thiotepa has not been available in Japan since 2009.

Kaplan-Meier analysis was used to estimate the distribution of PFS and OS. PFS was calculated from the date of study enrollment to date of progressive disease. OS was calculated from the date of study enrollment to the date of last follow up or date of death from any cause. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[10]

TABLE 1 Patient demographic and clinical characteristics

Characteristic	Average-risk patients (n = 35)	High-risk patients (n = 13)
Sex, n (%)		
Male	26	11
Female	9	2
Median age, y (range)	7.6 (3.1-11.6)	6.6 (3.9-14.3)
Metastatic status, n (%)		
0	35 (100)	0
1	0	3 (23.1)
2	0	2 (15.4)
3	0	8 (61.5)
Extent of resection, n (%)		
Gross total resection	22 (62.9)	5 (38.5)
Subtotal resection	9 (25.7)	6 (46.2)
Partial resection	4 (11.4)	1 (7.7)
Biopsy only	0	1 (7.7)
Histology, n (%)		
Classic	24 (85.7)	10 (90.9)
Desmoplastic/nodular	1 (3.6)	0
Large cell/anaplastic	3 (10.7)	1 (9.1)
Not examined	7	2

3 | RESULTS

3.1 | Patients

From 2006 to 2014, 48 patients (35 average risk and 13 high risk) were enrolled. Table 1 shows the characteristics of the 48 patients. Ten patients with metastatic disease (M2-3) and three with positive CSF tumor cells (M1) were classified as high risk. CSF was collected before surgery in all of M1 patients. Central pathological review confirmed that the diagnoses of all reviewed patients (39/48) were correct. There were almost no major treatment deviations except for two average-risk patients who received HDC and two high-risk patients who received CSI 24 or 36 Gy, respectively. The treating physicians of these patients decided to provide treatment intensification because of refractory tumors in a high-risk patient and tumor masses that did not shrink during treatment in the other three patients.

3.2 | Outcome

To estimate the distribution of PFS and OS, the four patients with treatment deviations were censored at the time of the major treatment deviation. The 3-year PFS and OS were 90.5% (standard error 5.2%) and 93.9% (standard error 4.2%), respectively, for average-risk patients, and 100% and 100%, respectively, for high-risk patients (Figure 2A,B). The median follow up for surviving patients was

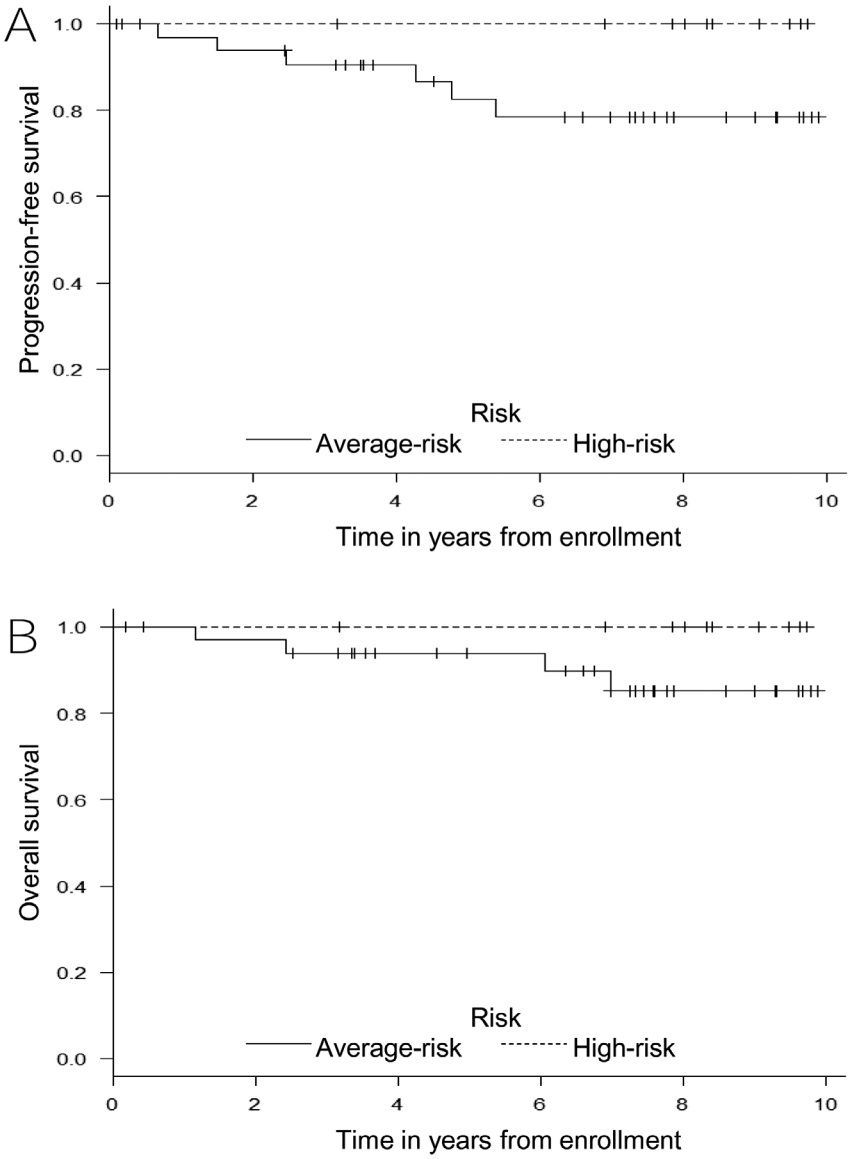

FIGURE 2 Progression-free survival (A) and overall survival (B) for patients with average-risk and high-risk medulloblastoma

89 months for average-risk patients and 98 months for high-risk patients. PFS and OS were not significantly different between those with and without residual tumor > 1.5 cm^2 in average-risk patients ($P = .49$ and .29, respectively).

No patients experienced disease progression during treatment. Thirteen average-risk patients and eight high-risk patients had residual tumor at the start of chemotherapy and were evaluable for response to chemoradiotherapy. Table 2 shows their responses. Eight of 13 evaluable average-risk patients achieved complete response (CR) at the end of induction therapy (two were not evaluable). Four of eight evaluable high-risk patients achieved CR at the end of induction therapy (one was not evaluable). Among the remaining high-risk patients (one stable disease and two partial response), one was not able to receive HDC because of severe anorexia and one of other two patients achieved CR after HDC. Two high-risk patients had residual tumors at the end of all treatments and one of them survived. The remaining patient had refractory tumors and received CSI 36 Gy and thiotepa/melphalan/busulfan for HDC, which was a treatment deviation. However, he died of systemic fungal infection after HDC, and viable tumors were detected on autopsy.

Relapse occurred in six average-risk patients (Table 2). Three of them developed disease dissemination; the times to progression of these patients were 8, 18, and 29 months that were earlier than the other relapsed patients (51, 57, and 64 months). In particular, the progression pattern of two patients with large cell/anaplastic histology was aggressive and they died of the disease. Two high-risk patients who were not able to receive HDC because of the toxicity, mentioned later, were alive without relapse at the time of the data cutoff.

3.3 | Toxicity

There was no major unexpected toxicity. Expected hematologic grade 4 toxicity was observed among all patients. The median neutropenic periods (absolute neutrophil count < 0.5×10^9/L) of courses 1, 2, 3, and 4 were 8.5, 10, 11, and 14 days, respectively. Expected nonhematologic

TABLE 2 Treatment outcome

Outcome	Average-risk patients (n = 35)	High-risk patients (n = 13)
Response after induction therapy among 21 evaluable patients, n (%)		
CR	8 (61.5)	4 (50)
PR	2 (15.4)	2 (25)
SD	1 (7.7)	1 (12.5)
PD	0	0
Not evaluated	2 (15.4)	1 (12.5)
Status at last follow up, n (%)		
Alive with CCR	29 (82.9)	12 (92.3)
Dead with CCR	0	0
Alive after relapse	2 (5.7)	0
Dead after refractory disease	0	1 (7.7)
Dead after relapse	4 (11.4)	0
Relapse site among 6 patients, n (%)		
Posterior fossa	2 (33.3)	0
Ventricle	1 (16.7)	0
Dissemination	3 (50.0)	0

Abbreviations: CCR, continuous complete remission; CR, complete response; PD, progressive disease; PR, partial response; SD, standard disease.

grade 4 toxicities were observed in six patients: aminotransferases increased (n = 2), and varicella zoster virus encephalitis, hemolytic uremic syndrome, hemorrhagic ileum ulcer, and constipation (each n = 1). One average-risk patient who suffered from varicella zoster virus encephalitis was subsequently treated with reduced-intensity chemotherapy. Two high-risk patients were not able to receive HDC because of grade 3 renal dysfunction and grade 3 anorexia, respectively. Frequent grade 3 toxicities during the chemotherapy and HDC phases, respectively, included febrile neutropenia (79% and 100%), aminotransferases increased (36% and 10%), oral mucositis (30% and 100%), and diarrhea (13% and 50%).

Late adverse events were reported in eight patients. Six patients experienced grade 3 toxicities including hearing loss (n = 3), and ataxia, cognitive dysfunction, and anorexia (each n = 1). A secondary neoplasm occurred in two patients: acute lymphoblastic leukemia developed 2 years after the end of chemotherapy in an average-risk patient and thyroid cancer 4 years after the end of chemotherapy in another average-risk patient. There was no leukoencephalopathy or treatment-related deaths.

4 | DISCUSSION

The results of this study of reduced-dose CSI 18 Gy for children with newly diagnosed MB, which was based on a previous phase II trial prospective registry study,[7] showed a promising 5-year PFS rate of 83.9 ± 6.7% for average-risk patients. Simultaneous radiotherapy with the second and third courses of chemotherapy may raise the antitumor effect of treatment. Intrathecal methotrexate also may have enabled us to reduce the CSI dose. This would be similar to the HIT-SKK'92 study, which showed that chemotherapy including intraventricular methotrexate allowed radiotherapy to be avoided in the treatment of young children with MB.[11] In addition, a metaanalysis of atypical/teratoid rhabdoid tumors has shown the advantage of intrathecal chemotherapy.[12] Concern has been raised about neurotoxicity and leukoencephalopathy with intrathecal methotrexate[13-15]; however, neither neurotoxicity nor leukoencephalopathy were reported in our study, which was probably related to low-dose radiotherapy.

Having residual tumor > 1.5 cm^2 in average-risk patients was not related to outcome. Our chemotherapy regimen was more intensive than conventional chemotherapy,[2,4] and the strong intensity of chemotherapy may have eliminated an influence of the degree of tumor resection on the outcome.

High-risk patient recruitment was stopped early due to the lack of availability for thiotepa in Japan since 2009. The results of our study for high-risk MB patients were therefore only exploratory, as the sample size was small, only 15 patients. However, it still gave promising results since there were no disease recurrences during a long-term follow up. We have previously reported that HDC consisting of thiotepa and melphalan demonstrated antitumor activity against several types of tumors including MB,[7,9] and the registry data previously reported by us showed excellent results (5-year PFS 82.1 ± 7.2% and 5-year OS 85.7 ± 6.6%) in 28 high-risk MB patients. Taken together, this strongly suggests that HDC not only allows the radiation dose to be reduced to 18 Gy but also significantly improves survival. Thiotepa became available again in Japan in 2019. We are therefore planning a new study using HDC consisting of thiotepa and melphalan for MB.

As of 2016, the World Health Organization proposed an integrated phenotypic and genotypic classification system for central nervous system tumors.[16] Further, it has been suggested that molecular genetic findings should be utilized for risk stratification.[17-19] We were not able to diagnose tumor samples genetically in this study as there were few specimens available. We will adopt molecular classification in the future. We will also estimate whether irradiation dose reduction is possible in patients with good prognosis and in the standard prognosis group by adding HDC in our next study.

Detailed neuropsychological outcomes have been assessed in only a part of the patients in this study. We are evaluating neuropsychological outcomes as secondary endpoints in our next study.

In conclusion, these results suggest that multidrug intensified chemotherapy including intrathecal chemotherapy with simultaneous irradiation, which adds HDC to some selected patients, is able to reduce dose of CSI to 18 Gy in a high proportion of patients with MB.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Keiko Okada https://orcid.org/0000-0003-0825-2985

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