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ORIGINAL ARTICLE

Tandem high-dose chemotherapy with topotecan–thiotepa–carboplatin and melphalan–etoposide–carboplatin regimens for pediatric high-risk brain tumors

Jung Yoon Choi[1,2] · Hyoung Jin Kang[1,2] · Kyung Taek Hong[1,2] · Che Ry Hong[1,2] · Yun Jeong Lee[1] · June Dong Park[1] · Ji Hoon Phi[3] · Seung-Ki Kim[3] · Kyu-Chang Wang[3] · Il Han Kim[2,4] · Sung-Hye Park[5] · Young Hun Choi[6] · Jung-Eun Cheon[6] · Kyung Duk Park[1,2] · Hee Young Shin[1,2]

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Abstract

Background High-dose chemotherapy (HDC) and autologous stem-cell transplantation (auto-SCT) are used to improve the survival of children with high-risk brain tumors who have a poor outcome with the standard treatment. This study aims to evaluate the outcome of HDC/auto-SCT with topotecan–thiotepa–carboplatin and melphalan–etoposide–carboplatin (TTC/MEC) regimens in pediatric brain tumors.

Methods We retrospectively analyzed the data of 33 children (median age 6 years) who underwent HDC/auto-SCT (18 tandem and 15 single) with uniform conditioning regimens.

Results Eleven patients aged < 3 years at diagnosis were eligible for HDC/auto-SCT to avoid or defer radiotherapy. In addition, nine patients with high-risk medulloblastoma (presence of metastasis and/or postoperative residual tumor ≥ 1.5 cm^2), eight with other high-risk brain tumor (six CNS primitive neuroectodermal tumor, one CNS atypical teratoid/rhabdoid tumor, and one pineoblastoma), and five with relapsed brain tumors were enrolled. There were three toxic deaths, and two of which were due to pulmonary complications. The main reason for not performing tandem auto-SCT was due to toxicities and patient refusal. The event-free survival (EFS) and overall survival (OS) rates of all patients were 59.4% and 80.0% at a median follow-up with 49.1 months from the first HDC/auto-SCT, respectively. The EFS/OS rates of patients aged < 3 years at diagnosis, high-risk medulloblastoma, other high-risk brain tumor, and relapsed tumors were 50.0/81.8%, 87.5/85.7%, 66.7/88.9%, and 20.0/60.0%, respectively.

Conclusions Although tandem HDC/auto-SCT with TTC/MEC regimens showed promising survival rates, treatment modifications are warranted to reduce toxicities. The survival rates with relapsed brain tumors were unsatisfactory despite HDC/auto-SCT, and further study is needed.

Keywords Autologous stem-cell transplantation · Chemotherapy · Brain neoplasms · Medulloblastoma · Pediatrics

Abbreviations

ACTH	Adrenocorticotropic hormone
ANC	Absolute neutrophil count
ARDS	Acute respiratory distress syndrome
ATRT	Atypical teratoid/rhabdoid tumor
Auto-SCT	Autologous stem-cell transplantation

✉ Hyoung Jin Kang
kanghj@snu.ac.kr

[1] Department of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea

[2] Seoul National University Cancer Research Institute, Seoul, Republic of Korea

[3] Division of Pediatric Neurosurgery, Seoul National University College of Medicine, Seoul, Republic of Korea

[4] Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Republic of Korea

[5] Department of Pathology, Seoul National University College of Medicine, Seoul, Republic of Korea

[6] Department of Radiology, Seoul National University College of Medicine, Seoul, Republic of Korea

CE	Cyclophosphamide-melphalan
CPC	Chroid plexus carcinoma
CNS	Central nervous system
CR	Complete response
CSRT	Craniospinal radiotherapy
CTE	Carboplatin–thiotepa–etoposide
EFS	Event-free survival
GHD	Growth hormone deficiency
HDC	High-dose chemotherapy
MBL	medulloblastoma
MEC	Melphalan–etoposide–carboplatin
OS	Overall survival
PBL	Pineoblastoma
PBSCM	Peripheral blood stem-cell mobilization
PNET	Primitive neuroectodermal tumor
PR	Partial response
SNHL	Sensorineural-hearing loss
TRM	Treatment-related mortality
TTC	Topotecan–thiotepa–carboplatin

Introduction

Brain tumors are the most common malignant solid tumor in pediatric patients. The treatment outcome of pediatric brain tumors has improved with multimodal approaches involving surgery, chemotherapy, and radiotherapy (RT). However, the survival rates remain poor in patients with high-risk pathology, significant residual tumors after surgery, and relapsed tumors. High-dose chemotherapy (HDC) and autologous stem-cell transplantation (auto-SCT) has been used to improve the survival of children with brain tumors, who are expected to have a poor outcome and recurrence with standard treatment. The relapse rates in infants and young children are high, because it is difficult to implement RT due to late neurocognitive effects, which is one of the most important treatments in brain tumors [1]. HDC/auto-SCT has been used in infants and young children to avoid RT [2]. Some researchers have shown the possibility of improving survival rates by applying HDC/auto-SCT in pediatric brain tumor patients with high-risk pathology or for infants and young children [2–4].

The role of HDC/auto-SCT in relapsed pediatric brain tumors is controversial. Several studies did not show favorable results of HDC/auto-SCT in patients with relapsed brain tumors [5, 6]. Other studies presented different outcomes according to the characteristics of the relapsed brain tumors. Raghuram et al. reported that HDC/auto-SCT might improve survival in younger children with relapsed central nervous system primitive neuroectodermal tumor (CNS PNET), whereas it did not in older children and/or in children with pineoblastoma (PBL) [7]. Butturini et al. reported that HDC/auto-SCT in previously non-irradiated patients with relapsed medulloblastoma (MBL) and CNS PNET resulted in a chance for a cure [8]. The KSPNO-S-053 study suggested that tandem HDC/auto-SCT, especially for patients in partial response (PR) at HDC/auto-SCT, might be helpful to improve survival outcomes for those with relapsed MBL (3-year overall survival [OS] rate 33.3%, event-free survival [EFS] rate 26.7%) [9].

Although several studies on HDC/auto-SCT in pediatric brain tumors have been conducted, the optimal HDC/auto-SCT regimen is not defined. Carboplatin–thiotepa–etoposide (CTE) and cyclophosphamide–melphalan (CE) is one of the widely used HDC/auto-SCT regimens in pediatric brain tumors [10–13]. However, tandem HDC/auto-SCT of CTE and CE regimen showed relatively high treatment-related mortalities (TRMs) [13]. Myeloablative treatment containing topotecan–thiotepa–carboplatin (TTC) showed a satisfactory outcome in pediatric solid tumors including high-risk brain tumors [14, 15]. Thiotepa, which has abilities to penetrate CNS, but it has myelotoxicities, has been used in HDC/auto-SCT in brain tumors [16]. Topotecan, an inhibitor of topoisomerase I, is active against various neoplasms including brain tumors, also has good penetration into the CNS, and has little extramedullary toxicity [14]. Melphalan, etoposide, and carboplatin have been used previously and are known to be active against brain tumors [12, 17].

With this background, we applied TTC and melphalan–etoposide–carboplatin (MEC) as a tandem HDC/auto-SCT regimen in pediatric high-risk brain tumors. In the current study, we evaluated the outcome and toxicities of HDC and auto-SCT using TTC/MEC in high-risk brain tumors.

Patients and methods

Patients and study design

This was a retrospective study conducted at a single tertiary center, Seoul National University Children's Hospital. The medical records of 33 patients diagnosed with high-risk brain tumors and who underwent consecutive HDC and auto-SCT between September 2010 and October 2014 were reviewed. As patients were diagnosed before 2016, the 2007 WHO classification was used for histologic classification [18]. The patients underwent HDC and auto-SCT if they had the following indications: age < 3 years at diagnosis (infants and young children), with high-risk MBL (postoperative residual tumor ≥ 1.5 cm^2, leptomeningeal seeding at diagnosis or anaplastic histology), other high-risk brain tumors such as CNS atypical teratoid/rhabdoid tumor (ATRT), CNS PNETs, PBL, choroid plexus carcinoma (CPC), or relapsed brain tumor. According to the 2016 WHO classification, the CNS PNET in this study can be classified into the CNS embryonal tumor, NOS [19].

Surgery

For all patients, surgical removal was performed to a maximum extent when possible. The degree of resection was classified in two categories as significant residual tumor or not. Significant residual tumor was defined if the residual tumor size was ≥ 1.5 cm^2 in the operative record and/or in the postoperative MRI.

Radiation therapy

We applied reduced-dose craniospinal RT (CSRT) to reduce long-term side effects of RT. Patients aged ≥ 3 years at diagnosis received reduced-dose CSRT, local RT and boost RT to the seeding nodule (if present). The dose of RT was as follows: 30.6 Gy of CSRT and 23.4 Gy of local RT in patients aged ≥ 6 years with M 2–3 disease; 23.4 Gy of CSRT and 30.6 Gy of local RT in other patients.

For patients aged < 3 years at diagnosis, RT was omitted or deferred until after 3 years of age if patients achieved CR after HDC/auto-SCT and developed no relapse. However, early local RT was considered before HDC/auto-SCT if patients were diagnosed with CNS ATRT. If patients with M0 disease achieved CR after HDC/auto-SCT, RT was omitted. If patients with M+ disease achieved CR after HDC/auto-SCT, reduced-dose CSRT was planned after 3 years of age. If patients did not achieve CR after HDC/auto-SCT, they were planned to receive local RT (CSRT only for patients with M+ disease) after HDC/auto-SCT, irrespective of age.

Chemotherapy

Total treatment scheme is shown in Fig. 1.

For newly diagnosed high-risk brain tumors (≥ 3 years at diagnosis), the treatment scheme changed over the course of the study period. During the early study period (from January 2010 to October 2012), the treatment consisted of surgery, pre-RT chemotherapy (peripheral blood stem-cell mobilization [PBSCM] in the first cycle), RT, post-RT chemotherapy, and tandem HDC/auto-SCT. During the late study period (from November 2012 at diagnosis), surgery, followed by PBSCM, RT (within 4 weeks after surgery), and chemotherapy were performed. The combination of chemotherapeutic agents was the same regardless of the period. After six cycles of chemotherapy, tandem HDC/auto-SCT was performed.

For brain tumors in infant and young children (< 3 years at diagnosis), chemotherapy was started within 4 weeks after surgery (PBSCM in the first cycle). We added an intrathecal 3-drug (methotrexate, cytosine arabinoside, and hydrocortisone) infusion from November 2012 for patients with CNS ATRT and PNET. Tandem HDC/auto-SCT was performed after a total of 6 cycles of chemotherapy.

For relapsed brain tumors, surgery was conducted, if possible. HDC/auto-SCT was performed after four cycles of chemotherapy (PBSCM during the first cycle of chemotherapy). If the tumor progressed, salvage chemotherapy was administered.

Transplant conditioning regimen

The conditioning regimen for the first and second HDC/auto-SCT consisted of TTC and MEC (Fig. 1). A second HDC/auto-SCT was performed if toxicities after the first auto-SCT were resolved.

Assessment of engraftment and toxicity

Neutrophil engraftment was defined as the first day with an absolute neutrophil count (ANC) more than 1.0×10^9/L for three consecutive days. Platelet engraftment was defined as the first day with a platelet more than 20×10^9/L without platelet transfusion for at least 3 days. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events v4.0.

Response evaluation

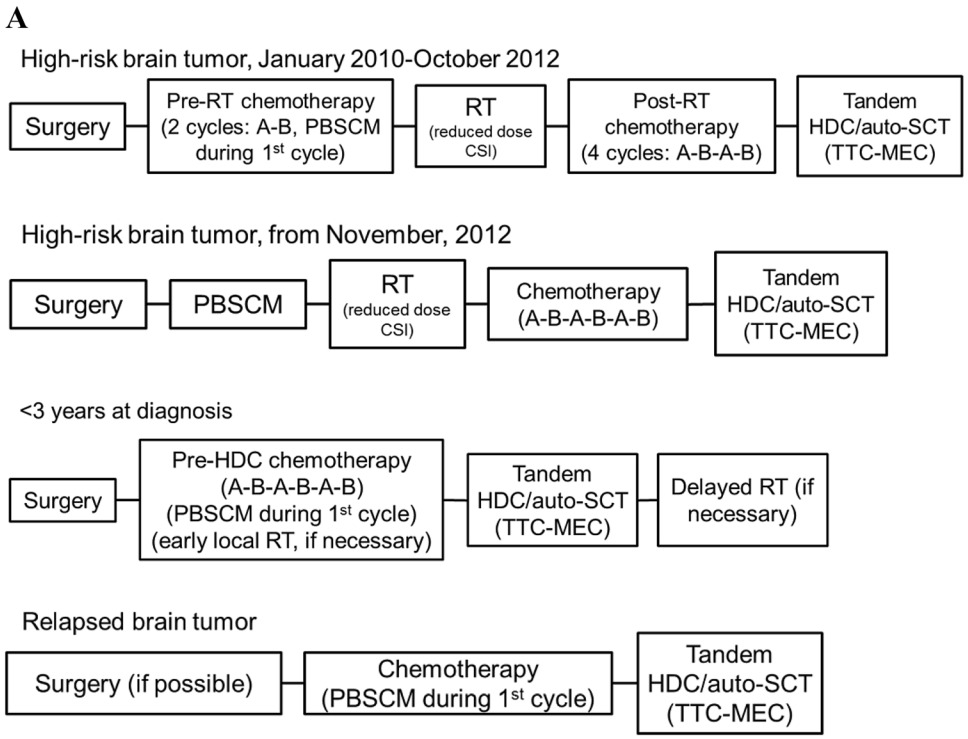
At diagnosis, disease status was assessed using MRI of the brain and spine and CSF examination. Evaluation was done at the following time points in the treatment protocol: after surgery, after RT, after every 3 cycles of chemotherapy, between the first and second HDC/auto-SCT, and every 3 months after tandem HDC/auto-SCT. Tumor response assessments were classified as complete response (CR), partial response (PR), progressive disease, and stable disease by the RANO criteria [20].

Endocrine late effects

According to the Children's Oncology Group long-term follow-up guidelines version 4.0, survivors were regularly evaluated for endocrine late effects including growth hormone deficiency (GHD), hypothyroidism, adrenocorticotropic hormone (ACTH) deficiency, and hypogonadism (primary ovarian failure or testicular dysfunction). Endocrine outcomes were determined by physical examination and laboratory tests including standard provocation tests.

Statistical analysis

The OS rate was calculated from the date of first auto-SCT to death or the date of last follow-up. The EFS rate was



B

1st: TTC (Topotecan-Thiotepa-Carboplatin)

Day	-8	-7	-6	-5	-4	-3	-2	-1	0
Topotecan (2 mg/m^2/day)	↑	↑	↑	↑	↑				
Thiotepa (300 mg/m^2/day)	↑	↑	↑						
Carboplatin (350 mg/m^2/day)				↑	↑	↑			

2nd: MEC (Melphalan-Etoposide-Carboplatin)

Day	-8	-7	-6	-5	-4	-3	-2	-1	0
Melphalan (140 mg/m^2/day, d-7) (70 mg/m^2/day, d-6)		↑	↑						
Etoposide (200 mg/m^2/day)	↑	↑	↑	↑					
Carboplatin (350 mg/m^2/day)	↑	↑	↑	↑					

Fig. 1 Total treatment scheme. **a** Regimen A consisted of cisplatin, cyclophosphamide, etoposide, and vincristine, and regimen B consisted of carboplatin, ifosfamide, etoposide, and vincristine. In patients with relapsed brain tumors, carboplatin, ifosfamide, etoposide, and vincristine were administered. **b** Conditioning regimen for tandem HDC/auto-SCT: The first cycle of HDC consisted of topotecan, thiotepa, and carboplatin (TTC), and the second cycle consisted of melphalan, etoposide, and carboplatin (MEC), *auto-SCT* autologous stem-cell transplantation, *CSI* craniospinal irradiation, *HDC* high-dose chemotherapy, *PBSCM* peripheral blood stem-cell mobilization

calculated from the date of first auto-SCT to the date of the event or the date of the last follow-up if the patient did not have events. Events were defined as relapse, TRM. The OS and EFS rates were estimated by Kaplan–Meier analysis, and were compared with the log-rank test. The cumulative incidence of relapse and TRM was estimated by competing risk analysis [21]. Statistical analyses were performed using R version 3.3.1.

Ethics statement

All patients and their parents provided informed consent for the treatments and procedures of HDC/auto-SCT. This retrospective study was approved by the institutional review boards (IRB number: 1608-070-784).

Results

Baseline characteristics

The baseline characteristics are summarized in Table 1. Thirty-three patients (21 male and 12 female patients) with high-risk brain tumors received HDC/auto-SCT. Although tandem HDC/auto-SCT was initially intended, only 18 of the 33 patients underwent tandem HDC/auto-SCT. The remaining patients underwent single HDC/auto-SCT: five patients due to parental refusal, four patients due to relapse before the second HDC/auto-SCT, three patients due to serious treatment-related complications after the first HDC/auto-SCT, two patients due to TRM, and one patient due to accidental death (brain hemorrhage after trauma) after the first HDC/auto-SCT (Fig. 2). The median interval between the first and second auto-SCT was 99 (range 90–135) days.

Engraftment

The median number of infused $CD34^+$ cells for the first and second auto-SCT was 24.63 (range 1.31–136.10) $\times 10^6$/kg and 13.98 (range 5.75–61.89) $\times 10^6$/kg, respectively ($p = 0.463$). All patients had engraftment for neutrophils, and only 1 patient died before platelet engraftment after the second auto-SCT. The median day for neutrophil engraftment for the first and second auto-SCT was 10 (range 8–13) days and 11 (range 9–12) days, respectively ($p = 0.429$). The median day for platelet engraftment for the first and second auto-SCT was 14 (range 10–69) and 16 (range 10–118) days, respectively ($p = 0.286$).

Toxicity and treatment-related mortality

Frequent toxicities greater than grade 3 included febrile neutropenia, oral mucositis, sensorineural-hearing loss (SNHL), and elevated liver enzymes (Table 2). Eleven patients were diagnosed with SNHL (10 patients after first HDC/auto-SCT, and one patient after second HDC/auto-SCT). Seven of the 11 patients with SNHL are alive to date, and six of them are in need of hearing aids. The median cumulative dose of carboplatin until the first and second auto-SCT was 2886.2 (range 2126.7–5696.5) mg/m^2 ($n = 33$) and 4182.9 (range 3447.1–7093.9) mg/m^2 ($n = 18$), respectively. Cytomegalovirus retinitis occurred in one patient after second auto-SCT.

Grade 3–5 acute respiratory distress syndrome (ARDS) occurred in 6 patients (four patients after first HDC/auto-SCT, and two patients after second HDC/auto-SCT). Three of the four patients who developed ARDS after first HDC/auto-SCT were diagnosed as idiopathic pneumonia syndrome according to the diagnostic criteria in the previous literatures, and two of them survived [22, 23]. The other patient died of ARDS caused by influenza pneumonia. After the second HDC/auto-SCT, one patient suffered from ARDS, presumably due to transplantation associated thrombotic microangiopathy. The other patient died of multi-organ failure due to aggravation of ARDS and hepatic veno-occlusive disease.

Three patients died of TRMs: ARDS in two patients after first auto-SCT and multi-organ failure in one patient after second auto-SCT. The cumulative incidence of TRM was 9.4%.

Relapse/progression and secondary malignancy

Relapse occurred in eight patients (five patients after the first and three patient after the second auto-SCT) at a median 3.6 (range 1.7–32.5) months after the first auto-SCT. The cumulative incidence of relapse was 28.1%. Two of the five patients who showed recurrence after first HDC/auto-SCT died of disease, two patients were lost to follow up at the state of progressive disease, and one patient is alive after receiving surgery and chemotherapy. Three patients with recurrence after completing tandem HDC/auto-SCT experienced a relapse after 4.4, 25.7, and 32.0 months after first auto-SCT, respectively. One patient had no evidence of disease after gamma knife surgery, and the other patients started chemotherapy followed by CSRT. One patient was diagnosed with renal cell carcinoma after 27.3 months after first auto-SCT.

Survival

Overall, 27/33 (single 10/15, tandem 17/18) patients who underwent HDC and auto-SCT survived. One patient died of traumatic brain injury after the first auto-SCT. Currently, 25 (single 8, tandem 17) patients are disease free and 20 (single 7, tandem 13) patients are event-free. The EFS and OS rates of all 33 patients were 59.4% and 80.0%, respectively, with a median follow-up duration of 49.1 (range 1.7–83.7) months (Fig. 3). The EFS rates by indication for HDC and auto-SCT were 50.0% in infant and young children, 87.5% in high-risk MBL, 66.7% in other high-risk brain tumors, and 20.0% in relapsed tumors ($p = 0.017$). The OS rates by indication for HDC and auto-SCT were 81.8% in infant and young children, 85.7% in high-risk MBL, 88.9% in other high-risk brain tumors, and 60.0% in relapsed tumors ($p = 0.27$) (Fig. 3). The EFS rates by histologic diagnosis were 56.1% in MBL, 100% in ATRT, 87.5% in PNET, 50.0% in PBL, and 50.0% in CPC ($p = 0.46$). The OS rates by histologic diagnosis were 47.4% in MBL, 100% in ATRT, 100% in PNET, 50.0% in PBL, and 100.0% in CPC ($p = 0.23$). The EFS rates by pre-HDC status were 69.3% in CR and 16.7%

Table 1 Characteristics of the 33 patients receiving HDC and auto-SCT

Characteristics	First HDC/auto-ASCT ($n=33$)	Second HDC/auto-SCT ($n=18$)
Age, y, median (range), at diagnosis	5.6 (0.7–15.3)	3.7 (1.0–15.3)
Age, y, median (range), at transplantation	6.4 (1.5–16.3)	4.9 (1.0–16.0)
Gender, No. (%)		
Male	21 (63.6)	10 (55.6)
Female	12 (36.4)	8 (44.4)
Diagnosis, No. (%)		
Medulloblastoma	17 (51.5)	7 (38.9)
CNS PNET	8 (24.2)	6 (33.3)
Pineoblastoma	2 (6.1)	2 (11.1)
CNS ATRT	4 (12.1)	1 (5.6)
Choroid plexus carcinoma	2 (6.1)	2 (11.1)
Indication for HDC/auto-SCT, No. (%)		
< 3 years of age at diagnosis	11 (33.3)	5 (27.8)
Medulloblastoma	4 (36.4)	1 (20.0)
CNS ATRT	3 (27.3)	0 (0.0)
CNS PNET	3 (27.3)	3 (60.0)
Chroid plexus carcinoma	1 (9.1)	1 (20.0)
High-risk medulloblastoma	9 (27.3)	5 (27.8)
Postoperative residual tumor ≥ 1.5 cm^2	4 (44.4)	1 (20.0)
Leptomeningeal seeding at diagnosis	6 (66.7)	5 (100.0)
Anaplastic histology	1 (11.1)	1 (11.1)
Other high-risk brain tumor[a]	8 (24.2)	7 (38.9)
Relapsed brain tumor	5 (15.2)	1 (5.6)
M stage		
M0	22 (66.7)	12 (66.7)
M1	1 (3.0)	0 (0.0)
M2	3 (9.1)	2 (11.1)
M3	7 (21.2)	4 (22.2)
Surgery		
Newly diagnosed patients		
< 1.5 cm^2	20 (60.6)	13 (72.2)
≥ 1.5 cm^2	8 (24.2)	4 (12.1)
Relapsed patients		
< 1.5 cm^2	2 (6.1)	0 (0.0)
Not done	3 (9.1)	1 (3.0)
RT		
CSRT + local RT at primary site	16 (48.5)	9 (50.0)
CSRT + local RT at primary site + boost	4 (12.1)	3 (16.7)
Local RT	5 (15.2)	2 (11.1)
No RT	5 (15.2)	4 (22.2)
CSRT + local RT at primary site before relapse	3 (9.1)	0 (0.0)

ATRT atypical teratoid/rhabdoid tumor, *auto-SCT* autologous stem-cell transplantation, *CNS* central nervous system, *CSRT* craniospinal radiotherapy, *HDC* high-dose chemotherapy, *PNET* primitive neuroectodermal tumor

[a]CNS PNET, ATRT, pineoblastoma

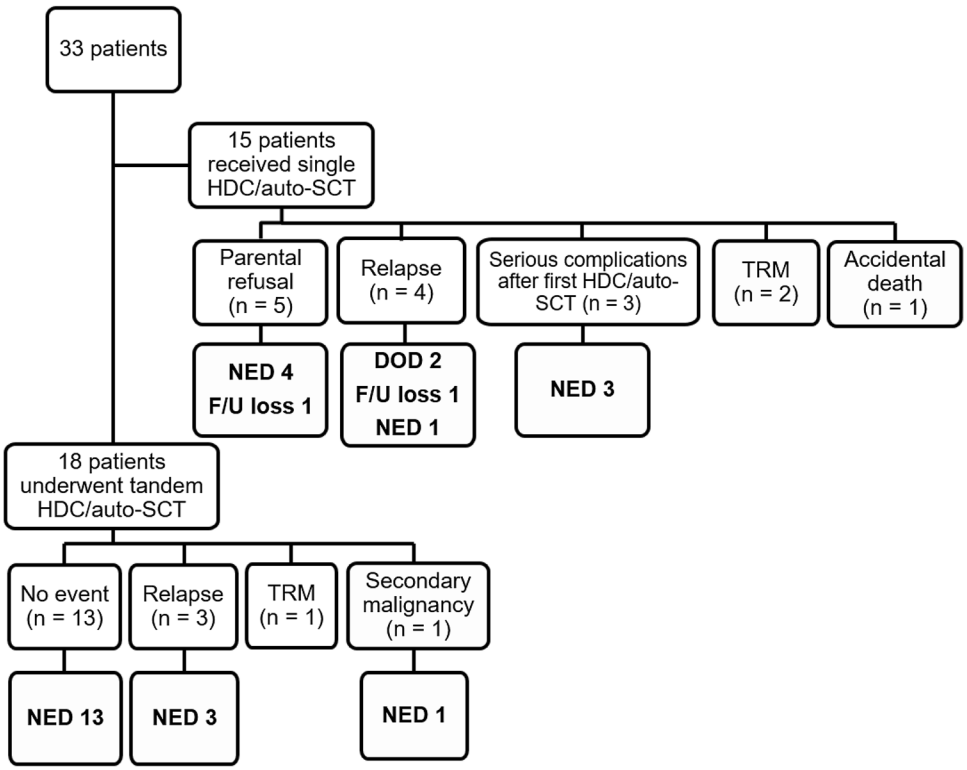


Fig. 2 Patient outcomes. *DOD* died of disease, *HDC/auto-SCT* high-dose chemotherapy and autologous stem-cell transplantation, *NED* no evidence of disease, *TRM* treatment-related mortality

in PR ($p = 0.0059$). The OS rates by pre-HDC status were 92.4% in CR and 33.3% in PR ($p < 0.001$) (Fig. 3).

Endocrine late effects

Among the 27 surviving patients, 24 patients were evaluated for endocrine late effects, except for two patients who were lost to follow up and one patient with secondary malignancy. The median follow-up time was 5.8 (range 2.8–8.3) years after last auto-SCT. In total, 87.5% ($n = 21$) patients were diagnosed as at least one endocrine disease. GHD was observed in 71.4% ($n = 15$) among 21 patients who underwent provocation tests. Primary hypothyroidism and ACTH deficiency were observed in 45.8% ($n = 11$) and 8.3% ($n = 2$)

Table 2 Toxicity profile of tandem HDC/auto-SCT

Parameters	First HDC/ASCT ($n = 33$)	Second HDC/ASCT ($n = 18$)
Grade 3, 4, 5 toxicity		
Febrile neutropenia	33 (100.0%)	17 (94.4%)
Oral mucositis	22 (66.7%)	2 (11.1%)
Sensorineural-hearing loss (SNHL)	10 (30.3%)	1 (5.6%)[a]
Elevation of liver enzyme	9 (27.3%)	15 (83.3%)
Hyperbilirubinemia	1 (3.0%)	0 (0.0%)
Acute kidney injury	1 (3.0%)	1 (5.6%)
Acute respiratory distress syndrome	4 (12.1%)	2 (11.1%)
Multi-organ failure	0 (0.0%)	1 (5.6%)
Hepatic veno-occlusive disorder	1 (3.0%)	2 (11.1%)
Peri-engraftment respiratory distress syndrome	0 (0.0%)	1 (5.6%)
Thrombotic microangiopathy	0 (0.0%)	1 (5.6%)
Bacteremia	1 (3.0%)	1 (5.6%)
CMV infection	13 (39.4%)	7 (38.9%)
CMV disease	0 (0.0%)	1 (5.6%)

auto-SCT autologous stem-cell transplantation, *CMV* cytomegalovirus, *HDC* high-dose chemotherapy

[a]This indicates the patient who newly developed SNHL after the second HDC/ASCT

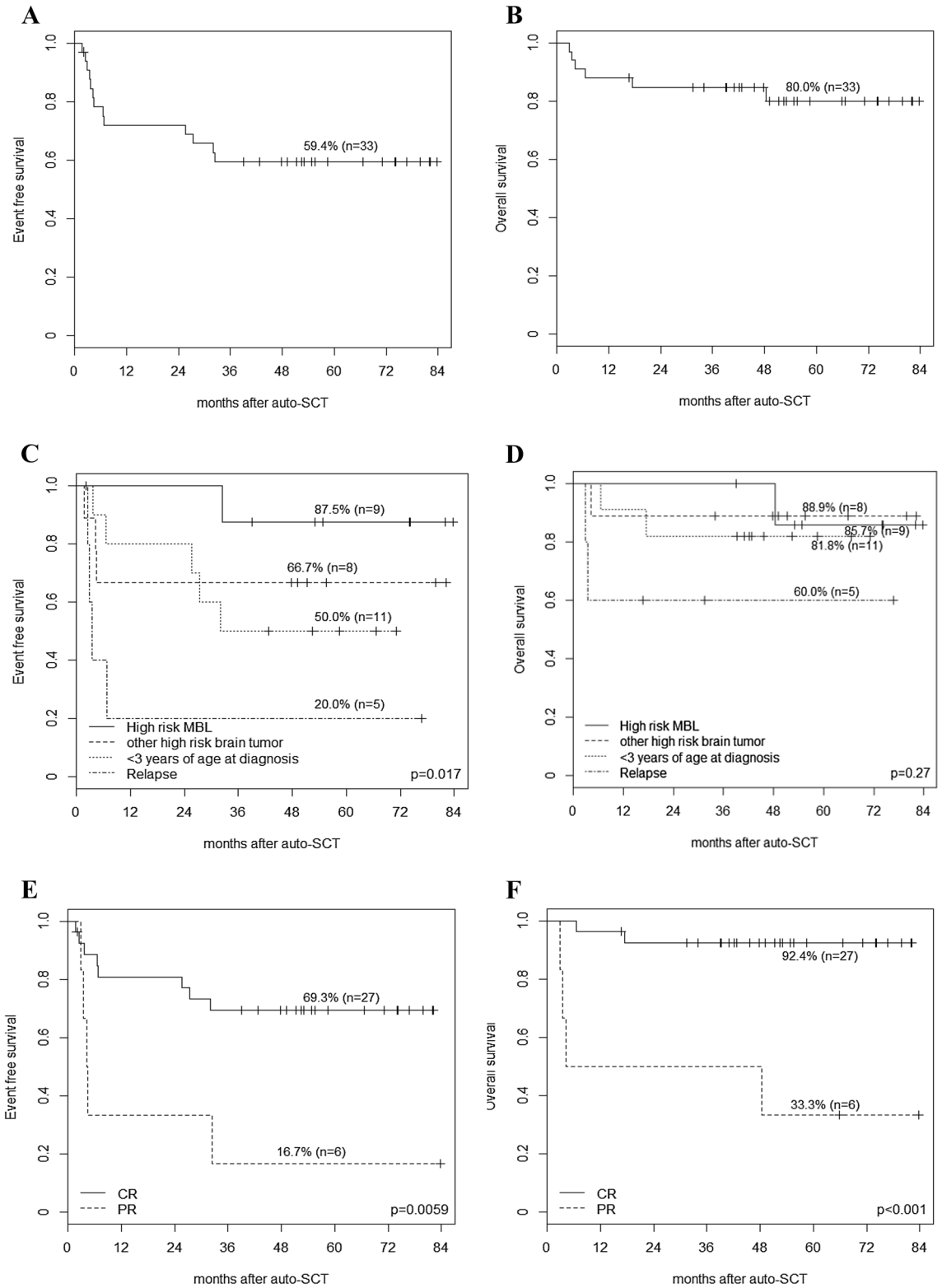


Fig. 3 Patient survival. **a** Event-free survival (EFS) rate of all the patients. **b** Overall survival (OS) rate of all the patients. **c** EFS rates of the patients by indication for HDC/auto-SCT. **d** OS rates of the patients by indication for HDC/auto-SCT. **e** EFS rates of the patients in complete remission (CR) and partial remission (PR) at the first high-dose chemotherapy and autologous stem-cell transplantation (HDC/auto-SCT). **f** OS rates of the patients in CR and PR at the first auto-SCT

of the 24 patients, respectively. Gonadal dysfunction was evaluated in patients who reached pubertal age (8 males, 5 females). Primary hypogonadism was diagnosed in 6 patients (1 male, 5 females). There was no significant difference of the incidence of GHD, primary hypothyroidism, ACTH deficiency, and gonadal dysfunction among patients treated with CSRT or not.

Discussion

This is the first study that applied tandem HDC and auto-SCT with a TTC/MEC conditioning regimen in pediatric high-risk brain tumors. According to data from the literature, patients with high-risk brain tumors who underwent HDC and auto-SCT using the TTC regimen showed favorable results and reasonable toxicities with 40–80% survival rates [14, 15]. We added the MEC with different combinations and doses as the second conditioning regimen to improve the outcomes. Sung et al. reported a 70.0% 5-year EFS rate in newly diagnosed patients with high-risk MBL who received tandem HDC/auto-SCT using the CTE and CE regimen [24]. With similar indications for HDC/auto-SCT, our study also showed a promising outcome of 87.5% EFS rate.

Brain tumors in infants and young children (< 3 years at diagnosis) are known to be associated with a poor outcome due to the limited use of RT. In our study, among the 8 infants and young children with brain tumors other than CNS ATRT, 4 did not receive RT after tandem HDC/auto-SCT. Two of the 4 patients relapsed after 32.0 and 25.7 months after first HDC/auto-SCT. Although the patients relapsed, they live without disease after performing surgery, RT, and chemotherapy after 3 years of age. Zaky et al. reported that infants and young children with CNS ATRT have a dismal outcome, with a 3-year EFS and OS rates of 21% and 26%, respectively [11]. Sung et al. reported that early RT prevented early progression in young patients with ATRT. Early RT with or without intrathecal chemotherapy might allow for avoiding CSRT in young children [25]. We applied early local RT in infants and young children with ATRT due to their poor prognosis. All 3 infants and young children who were diagnosed with CNS ATRT were alive after surgery, systemic and intrathecal chemotherapy, local RT, and HDC/auto-SCT. Therefore, HDC/auto-SCT might play a role in avoiding CSRT in patients with ATRT and deferring RT in patients with other embryonal tumors to achieve long-term survival.

The prognosis of patients with relapsed brain tumors remains very poor with survival rates of less than 20% in several reports [6, 26]. The EFS rate (20.0%, median follow-up duration 3.4 months, range 2.4–76.7 months) for patients with relapsed brain tumors was not satisfactory in our study. However, 50% (2/4) of TRM (ARDS) occurred in those with relapsed brain tumors, and only 1 of the 5 patients with recurrence completed tandem HDC/auto-SCT. Therefore, we could not conclude the effectiveness of HDC/auto-SCT in patients with relapsed brain tumor due to the limited numbers of our study.

Tandem HDC/auto-SCT using different drug combinations enables maximizing the effectiveness of chemotherapy and avoiding drug resistance and overlapping toxicities. To assess the feasibility of tandem HDC/auto-SCT, it is necessary to analyze toxicities of the treatments. SNHL occurred in 33.3% of the patients, and some of the patients denied a second auto-SCT due to this. Since SNHL was often not reversible in most patients, we should make more efforts to prevent it. SNHL can occur after administration of platinum compounds (cisplatin and high-dose carboplatin) and cranial RT [27]. To decrease and prevent accumulating ototoxicity due to repetitive administration of carboplatin, patients should undergo routine auditory examinations before and after HDC/auto-SCT. Another option might be to change the second HDC/auto-SCT regimen, and a busulfan-based conditioning regimen might be an option based on the previous studies [28, 29]. It is important to identify SNHL at an early stage to reduce further progression. In addition, hearing aids are recommended at an appropriate time to enhance speech and language in patients with irreversible SNHL.

Two of the three cases of TRM were due to pulmonary complications. TRM due to pulmonary complications developed in patients with relapsed brain tumors, who were heavily pretreated. Compared with the previous literature, there is no significant difference in the incidence of TRM after HDC/auto-SCT with TTC regimen. However, it is unusual that pulmonary complications were the main cause of TRM in our study. Patients with pulmonary complications had a higher mortality rate than did those without complications [30]. Yadav et al. reported that ARDS developed in 5.0% (15.6% in allogeneic SCT, 2.7% in auto-SCT) of patients undergoing hematopoietic SCT [31]. Because of the high mortality rate of pulmonary complications, it is necessary to identify the etiologies. Although pulmonary complications occur more often in allogeneic SCT than in auto-SCT, RT is one of the risk factors of pulmonary complications [32]. All six patients with ARDS in our study had received RT before HDC/auto-SCT. However, ARDS did not occur in all patients receiving RT, and this suggests that there may be unknown risk factors. Several studies have reported that patients with pulmonary complications such as ARDS and idiopathic pulmonary syndrome after hematopoietic SCT have a higher mortality, but some patients survive after early treatment with glucocorticoids [33, 34]. Five of the

six patients who developed ARDS were administered glucocorticoid pulse therapy, and three of the five patients with glucocorticoid pulse therapy survived. Therefore, clinicians should pay attention to pulmonary complications when performing HDC/auto-SCT for patients with brain tumors, especially those with relapsed disease. Early intervention, lung biopsy (if needed), and glucocorticoids pulse therapy are required.

Endocrine disorders are the most common late effects in pediatric brain tumors, as reported prevalence ranges from 22.1 to 50% differed by age of diagnosis, follow-up duration, or use of RT [35–37]. In this study, we found high prevalence of endocrine disorders up to 87.5% which may be associated with high-risk traits such as their young age or receiving CSRT. Although we could not conclude whether late effects of HDC/auto-SCT are higher than usual due to small number and heterogeneity of cases, close monitoring for endocrine dysfunction is needed.

This study has some limitations. First, the survival rates calculated was for patients who have reached HDC/auto-SCT. It is impossible to assess the survival rates of patients including those who have not reached HDC/auto-SCT. Second, each group consists of small number of patients because of patients' heterogeneous diagnoses and various indications. Third, the long-term effects of treatments other than endocrine dysfunction were not assessed. Despite these limitations, this study played an important role in evaluating outcomes and toxicities by attempting the uniform treatment regimens in all patients with pediatric high-risk brain tumor in a single center.

In conclusion, tandem HDC/auto-SCT with TTC/MEC might improve survival rates in patients with high-risk brain tumors including infants and young children. However, it is necessary to reduce toxicities such as SNHL and pulmonary complications to perform tandem HDC/auto-SCT successfully. Treatment modifications and efforts to identify the clinical and genetic risk factors of serious treatment -related complications are needed. Future study is also needed on the sub-analysis of the group in which favorable outcome is expected according to the molecular status. Further study is also considered to improve the survival rates of patients with relapse and to reduce late effects.

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Compliance with ethical standards

Conflicts of interests The authors declare that they have no conflict of interest.

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