Autologous hematopoietic stem cell transplantation for high-risk brain tumors in children

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Abstract Autologous hematopoietic stem cell transplantation (AHSCT) has been advocated as a form of salvage therapy for children with high-risk or relapsed brain tumors but only limited data are available currently. We report the outcomes of pediatric brain tumors treated with AHSCT in a quaternary referral center in Hong Kong over 10 years (June 1996–May 2006). Thirteen patients with medulloblastoma (n = 9), cerebral primitive neuroectodermal tumor (n = 1), ependymoma (n = 1), germ cell tumor (n = 1) and cerebellar rhabdoid (n = 1) were transplanted because of tumor residual (n = 1) or recurrence (n = 12). Uniform upfront treatment protocols were adopted according to specific tumor types. Prior to AHSCT, 8 patients (61.5%) achieved complete remission and 5 (38.5%) were in partial remission. Conditioning employed thiotepa 300 mg/m², etoposide 250 mg/m² and carboplatin 500 mg/m² daily for 3 days. Toxicity included mucositis and neutropenic fever in all patients, grade 4 hepatic toxicity in 4 patients (including hepatic veno-occlusive disease in 2 patients) and grade 4 renal toxicity in 1 patient. The 5-year event-free survival was 53.9%. Five patients died of disease recurrence or progression 8–21 months after transplant with a median disease-free period of 8 months post-transplant. One died of transplant-related complications in the early post-transplant period. Seven survived for a median of 5.4 years (maximum follow-up of 9.8 years), with six having Lansky-Karnofsky performance score above 80. All survivors had complete remission before transplant though 2 had leptomeningeal spread. We conclude that AHSCT can achieve long-term survival in children with recurrent brain tumor. However, those with macroscopic residual tumor before transplant cannot be salvaged.

Keywords Autologous hematopoietic stem cell transplantation · Brain tumor · Children · Relapse

Introduction

Brain tumors are the second most common malignancy in children and the most common form of solid tumor. Multi-modality treatment involving surgery, radiotherapy and chemotherapy has drastically improved the survival of many children with brain tumors nowadays. However, the cure rate remains poor in some high-risk histological types, and for patients with residual, recurrent or disseminated disease. Therapeutic options in most of these patients are limited by previous chemotherapy and radiotherapy. Over the past decade, high-dose chemotherapy with autologous hematopoietic stem cell transplant (AHSCT) has been tried in patients with high-risk brain tumors in an attempt to eradicate residual neoplastic cells and improve cure rate. Alkylating agents have been the main class of drugs used because of their steep dose-response curve. Thiotepa, carmustine and melphalan are well suited for this approach because they can penetrate the blood-brain barrier and their primary dose limiting toxicity is bone marrow suppression. It has been found that the levels of thiotepa and its active metabolite TEPA are similar in plasma and cerebro-spinal fluid [1], and alkylating agents exhibit significant activity
against different brain tumors in cell cultures and animal models [2–4].

Up till now data are still limited in children concerning the efficacy and safety of the approach of high-dose chemotherapy with AHSCT to treat high-risk brain tumors. We began to adopt this approach since 1996 to treat children with high-risk brain tumors using a unified chemotherapy conditioning regimen across a variety of tumor types and disease status and here we report our findings, focusing on complications and disease outcomes.

Patients and methods

Study design and participants

This was a retrospective review of all pediatric AHSCT for brain tumors performed in Queen Mary Hospital, a University-affiliated quaternary referral center in Hong Kong, over the past 10 years (Jun 1996 to May 2006). The patients’ data on demographic and clinical characteristics, treatments and disease status before ASCT, complications after AHSCT and final outcomes were extracted. Apart from centrally stored hospital records, patients’ information was retrieved and verified from our Hematology-Oncology-Immunology database through our Departmental Computer Server. For patients admitted in or after 1997, relevant clinical information including laboratory results can also be retrieved by the Clinical Management System (CMS) of the Hospital Authority Server through the desk computers in the wards.

Treatment protocol

After initial diagnosis of brain tumors, patients were treated according to standard, internationally accepted multimodality treatment protocols according to tumor type and stage. All these upfront treatment protocols did not contain high-dose chemotherapy with AHSCT. Indications to proceed to high-dose chemotherapy with AHSCT were tumor recurrence or residual tumor after upfront treatment protocol. These patients were treated with second-line chemotherapy with or without surgery and additional radiotherapy first, aiming for complete remission before AHSCT. Patients with disease relapse must have at least partial response to re-treatments before proceeding to megatherapy and AHSCT. Those with progressive disease despite second-line treatments would be offered palliative care instead of AHSCT.

Conditioning chemotherapy regimens were the same for all patients indicated for AHSCT. Thiotepa 300 mg/m² (infused over 1 h at a concentration of 10 mg/ml normal saline), etoposide 250 mg/m² (infused over 6 h at a concentration of 0.4 mg/ml normal saline) and carboplatin 500 mg/m² (infused over 3 h at a concentration of 1–10 mg/ml 5% dextrose) were given once daily for 3 days from D-6 to D-4 [5–9]. No dose modification for carboplatin was made as all patients had normal renal function before transplant. Peripheral blood stem cells (PBSC) were used except in those who were too young with difficult vascular access, where bone marrow was used as the source of hematopoietic stem cells. Granulocyte colony stimulating factor (G-CSF) 10 µg/kg/day for 5 days was used for mobilization of PBSC, which was stored unmanipulated and reinfused after conditioning. Following AHSCT, patients received standard supportive care measures, including fluconazole, septrin and acyclovir for prophylaxis of fungal, Pneumocystis, and herpes virus and cytomegalovirus infections respectively. Transfusions of irradiated blood products were used to maintain hemoglobin level above 8 g/dl and platelet count above 20 × 10⁹/L. G-CSF was used if the patient had uncontrolled neutropenic sepsis or neutropenic fever not responsive to antimicrobial agents. No additional tumor-directed therapy would be given after AHSCT unless there was further residual or recurrent tumor.

Definitions

Neutrophil engraftment was defined as neutrophil count rising from trough to 0.5 × 10⁹/l or above for 2 consecutive days. Platelet engraftment was defined by 2 time points, with platelet count consistently and spontaneously rising above 20 × 10⁹/l and 50 × 10⁹/l respectively as indicators. Complete remission was defined as resolution of all initially demonstrable tumor without appearance of new areas of disease. Partial remission and stable disease were defined as greater or less than 50% decrease in the product of the two largest perpendicular diameters of the tumor respectively. Grading of toxicity was based on the National Cancer Institute common toxicity criteria. Event-free survival was assessed from the date of AHSCT to the date of disease relapse or progression or death, whichever came first. Overall survival was assessed from the date of AHSCT to the date of death. Both event-free and overall survivals were estimated by Kaplan-Meier method.

Results

A total of 13 pediatric patients with brain tumors had received high-dose chemotherapy with AHSCT in our center (Table 1). Nine of the patients were boys and the remaining 4 were girls. Medulloblastoma was the most
Table 1: Characteristics of brain tumor patients treated with autologous stem cell transplant

| Patient no. | Sex | Age at Dx (years) | Diagnosis | Location | CSF spread | Metastasis before transplant | Treatment before transplant | RT regimen | Resection of local recurrence before AHSCT | Chemotherapy after recurrence before AHSCT | Status before AHSCT | Site of relapse/residual |
|-------------|-----|-------------------|-----------|----------|------------|----------------------------|-----------------------------|-------------|-------------------------------------------|---------------------------------------------|---------------------|--------------------------|
| 1           | M   | 6.77              | Medulloblastoma | Cerebellum | No | Bone | OT<sup>a</sup>, CT<sup>b</sup>, RT<sup>c</sup> | 1<sup>st</sup> site: 54 Gy | Not applicable | POG<sup>d</sup> | PR2<sup>e</sup> | Multiple metastasis in lumbosacral vertebrae |
| 2           | M   | 12.47             | Medulloblastoma | Cerebellum | No | No | OT, CT, RT<sup>f</sup> | 1<sup>st</sup> site: 54 Gy | Yes | POG | CR2<sup>g</sup> | Posterior fossa (3.5 x 2.4 x 2.2 cm) |
| 3           | F   | 2.95              | Ependymoma    | Right parieto-occipital lobe | No | No | OT, CT, RT<sup>e</sup> | 1<sup>st</sup> site: 54 Gy | Yes | CCV<sup>h</sup> | CR2 | Occipital lobe (2.5 x 1.2 x 2 cm) |
| 4           | F   | 1.73              | Rhabdoid tumor | Cerebellum | No | No | OT, CT, RT<sup>i</sup> | 1<sup>st</sup> site: 54 Gy | Yes | Vincristine-ifosfamide and cisplatin-etoposide | PR2<sup>i</sup> | Posterior fossa (3x4x2.5 cm on relapse, 2.5 x 2.7 x 2.3 cm residual before ASCT) |
| 5           | F   | 5.15              | Medulloblastoma | Cerebellum | No | No | OT, CT, RT<sup>e</sup> | 1<sup>st</sup> site: 54 Gy | Yes | Cisplatin-etoposide | CR2<sup>i</sup> | Posterior fossa (0.6 x 1 x 1.3 cm) |
| 6           | F   | 4.40              | Medulloblastoma | Cerebellum | Yes | No | OT, CT, RT<sup>e</sup> | 1<sup>st</sup> site: 50.4 Gy | Not applicable | CCV | PR2 | Multiple brain and spinal deposits (all < 2 cm) |
| 7           | M   | 1.73              | Medulloblastoma | Cerebellum | Yes | No | OT, CT, RT<sup>e</sup> | 1<sup>st</sup> site: 50.4 Gy | Not applicable | CCV | CR2 | Multiple brain and spinal deposits (all < 2 cm) |
| 8           | M   | 10.37             | Medulloblastoma | Cerebellum | Yes | No | OT, CT, RT<sup>e</sup> | 1<sup>st</sup> site: 54 Gy | Not applicable | Not applicable | PR1 | Multiple deposits on spinal cord (all < 2 cm) |
| 9           | M   | 2.07              | Medulloblastoma | Cerebellum | Yes | No | OT, CT, RT<sup>e</sup> | 1<sup>st</sup> site: 50.4 Gy | Yes | CCV | CR2 | Posterior fossa (4.8 x 4.3 x 2.5 cm) |
| 10          | M   | 17.42             | Primitive neuroectodermal tumor | Right temporal lobe | Yes | No | OT, CT, RT<sup>e</sup> | 1<sup>st</sup> site: 57.9 Gy | Not applicable | CCV | CR2 | Multiple deposits on spinal cord (all < 2 cm) |
| 11          | M   | 9.45              | Germ cell tumor | Pituitary stalk | No | No | CT, RT<sup>e</sup> | 1<sup>st</sup> site: 39.6 Gy | Not applicable | BEP<sup>j</sup>, cyclophosphamide-topotecan | CR2 | Markedly increased in CSF #HCG, no gross tumor |
common tumor type \([ n = 9 \ (69.2\%)]\). Other brain tumors include cerebral primitive neuroectodermal tumor (PNET) \(( n = 1)\), ependymoma \(( n = 1)\), cerebellar rhomboid tumor \(( n = 1)\) and intracranial germ cell tumor \(( n = 1)\). All patients received upfront multi-modality treatments according to internationally accepted protocols which were the same in all hospitals treating pediatric brain tumors in Hong Kong. None of the patients were formally enrolled in clinical trials of these protocols. Medulloblastoma and cerebral PNET were treated with surgery and radiotherapy before 1997 and chemotherapy was added afterwards. For children before 3 years old, radiotherapy was withheld and chemotherapy was given according to the POG protocol \([10]\). For children above 3 years old, combined radiotherapy and chemotherapy with cisplatin-CCNU-vincristine (CCV) were given according to the CCG protocol \([11]\). Ependymoma was treated with surgery and radiotherapy; and intracranial germ cell tumor was treated with radiotherapy and chemotherapy according to the SFOP protocol \([12]\).

All patients received radiotherapy, 8 as upfront treatment and 5 as rescue treatment upon recurrence because these patients were too young at initial diagnosis \((<\ 2.5 \text{ years, } n = 4)\) or parents refused radiotherapy initially \((n = 1)\). For those 8 patients with upfront radiotherapy, 3 developed multiple craniospinal metastasis despite previous craniospinal irradiation; 1 developed multiple bone metastasis at lumbosacral spine; 2 developed local relapse at primary site; 1 (patient no. 11 with intracranial germ cell tumor) developed microscopic relapse detected by tumor marker (CSF βHCG); and 1 had gross residual disease at multiple spinal levels despite initial craniospinal irradiation. Thus it appeared that craniospinal irradiation with primary site booster had not prevented metastasis or relapse at primary site. For those 5 patients with rescue radiotherapy, 4 achieved complete remission before AHSCT and 1 had gross residual disease at primary site. Rescue radiotherapy in those without previous irradiation might help in achieving complete remission before megatherapy and AHSCT. Radiotherapy was not used as conditioning or adjuvant therapy post-transplant in any of the patients.

Six of the 13 included patients \((46.2\%\) had leptomeningeal spread and 1 patient \((7.7\%\) had bone metastasis. The remaining 6 patients \((46.2\%\) had resection of the locally recurrent tumor before transplant. The mean age at transplant was 8.5 years \((\text{SD } 5.1 \text{ years})\) with mean body weight 23.9 kg \((\text{SD } 11.3 \text{ kg})\). Indications for AHSCT were tumor recurrence in 12 patients, and residual tumor after upfront treatments in 1 patient \((\text{patient no. 8})\). The median time from initial diagnosis to AHSCT was 22 months \((\text{range, } 15–35 \text{ months})\). Prior to AHSCT, 8 patients \((61.5\%\) achieved complete remission and 5 \((38.5\%\) were
in partial remission. Out of the 8 patients who achieved complete remission before AHSCCT, 5 had done so by complete resection of the locally recurrent tumors, 1 by chemoradiation and 2 by chemotherapy alone. All the 12 patients with recurrent tumors were given additional chemotherapy before AHSCCT, even if they had complete resection of the recurrent tumors. All patients had normal or near-normal organ functions and free from systemic infections at the time of AHSCCT. The stem cell source was PBSC in 10 patients (76.9%) and bone marrow in 3 patients (23.1%). The mean nucleated cell, CD34 and CFU-GM cell doses were $4.55 \times 10^9/kg$, $3.10 \times 10^9/kg$ and $3.97 \times 10^5/kg$ respectively. Neutrophil engraftment occurred at a mean of 12 days (SD 2.3 days), while platelet engraftments occurred at means of 27.8 days (SD 9.3 days) and 47.3 days (SD 17.3 days) for platelets above $20 \times 10^9/l$ and $50 \times 10^9/l$ respectively. Twelve patients (92.3%) had neutrophil engraftment augmented by G-CSF.

All patients experienced neutropenic fever and mucositis after conditioning megatherapy in the early post-transplant period. Liver toxicity occurred in all patients. Although majority was mild in the form of asymptomatic elevation of liver parenchymal enzymes, grade 4 liver toxicity occurred in 4 patients, including 2 patients with hepatic veno-occlusive disease. Renal toxicity occurred in 7 patients, with grade 1 toxicity in 4 patients, grade 2 toxicity in 2 patients and grade 4 toxicity in 1 patient. Other important post-transplant complications are listed in Table 2. The mean duration of hospitalization for the transplant episode was 50.3 days (SD 14 days).

Six patients (46.2%) died at a median of 296 days post-transplant (range, 46–632 days). One patient (no. 10) died at a median of 249 days post-transplant. Table 2 Complications and outcomes of patients undergone autologous stem cell transplant

| Patient no. | Age at AHSCT (years) | Interval between Dx and recurrence | Stem cell source | Liver toxicity (grade) | Renal toxicity (grade) | Other complications | Disease status after AHSCT | Time to recurrence or progression (months) | Outcome LPS | LPSa |
|-------------|----------------------|-----------------------------------|-----------------|------------------------|------------------------|-----------------------|----------------------------|------------------------------------------|-------------|------|
| 1           | 8.6                  | 13                                | PBSCb           | 1                      | Nil                    | Neutropenic fever     | CRc                       | 13                                      | Died at D + 493 | N/A  |
| 2           | 14.3                 | 7                                 | PBSC            | 1                      | Nil                    | Pulmonary TB          | CR                        | N/A                                      | Survives for 9.8 years | 90   |
| 3           | 5.2                  | 18                                | PBSC            | 4                      | 2                      | Bacillus cereus sepsis, Cl. difficile colitis, VODc | CR                        | N/A                                      | Survives for 9.4 years | 80   |
| 4           | 3.9                  | 6                                 | PBSC            | 1                      | Nil                    | Otitis externa        | SDf                       | 8                                        | Died at D + 299 | N/A  |
| 5           | 6.4                  | 13                                | PBSC            | 1                      | 1                      | E. coli UTIf          | CR                        | N/A                                      | Survives for 6.0 years | 90   |
| 6           | 6.9                  | 25                                | PBSC            | 1                      | 1                      | Upper GIBg            | SD                        | 4                                        | Died at D + 293 | N/A  |
| 7           | 3.4                  | 11                                | BMi             | 2                      | Nil                    | Upper GIB             | CR                        | N/A                                      | Survives for 5.4 years | 80   |
| 8           | 11.7                 | N/Ad                             | PBSC            | 4                      | 2                      | Acute sensorineural hearing loss, subdural hematoma, Cl. difficile colitis, enterococcus UTI | CR                        | 11                                      | Died at D + 632 | N/A  |
| 9           | 4.4                  | 9                                 | BM              | 2                      | 1                      | Pseudomonas aeruginosa UTI | CR                        | N/A                                      | Survives for 5.0 years | 50   |
| 10          | 20                   | 16                                | PBSC            | 4                      | 4                      | E. coli sepsis, engraftment syndrome with ARDS, pleural effusion, pneumonia, pneumothorax, GIB, acute renal failure | CR                        | N/A                                      | Died at D + 46 | N/A  |
| 11          | 11.2                 | 14                                | PBSC            | 4                      | 1                      | Transient visual loss, VOD, seizure | CR                        | N/A                                      | Survives for 1.8 years | 90   |
| 12          | 11.8                 | 29                                | PBSC            | 3                      | Nil                    | Norovirus GEi, pneumonia, early CMV infection | SD                        | 4                                        | Died at D + 249 | N/A  |
| 13          | 2.7                  | 9                                 | BM              | 2                      | Nil                    | Cl. difficile colitis  | CR                        | N/A                                      | Survives for 1.2 years | 80   |

Note: LPSa, Lansky-Karnofsky performance score; bPBSC, Peripheral blood stem cell; cCR, Complete remission; dN/A, Not applicable; eVOD, Hepatic veno-occlusive disease; fSD, Stable disease; gUTI, Urinary tract infection; hGIB, Gastro-intestinal bleeding; iBM, Bone marrow; jGE, Gastro-enteritis.
died of transplant-related complications of sepsis and multi-organ failure in the early post-transplant period. The other 5 patients died of disease recurrence or progression 8–21 months after transplant with a median disease-free period of 8 months post-transplant (range, 4–13 months). Seven patients (53.8%) survived without disease for a median of 5.4 years (follow-up period: 1.2–9.8 years). The 5-year overall and event-free survival rates were 51.9% and 53.9% respectively (Fig. 1). The majority of survivors (85.7%) had satisfactory functional status with a Lansky-Karnofsky performance score of 80 or 90.

All 7 survivors had achieved complete remission before transplant. The 5-year overall and event-free survivals for those who achieved complete remission before AHSCT were 87.5% (Fig. 2a). Two patients with partial remission before AHSCT achieved complete remission post-transplant which lasted for 11–13 months before recurrence; and 3 other patients with residual disease before AHSCT had stable disease for 4–8 months before progression. Mortality was similar in boys (55.6%) and girls (50%). However, the survivors were younger (mean age 6.8 vs. 10.5 years) at the time of transplant. The chance of survival was lower in patients with a history of leptomeningeal spread compared to patients with localized recurrence only (33.3% vs. 83.3%). The only patient with bone metastasis before AHSCT eventually died of disease progression although he did not experience major complications from the transplant. The 5-year survivals for patients with or without metastatic relapse were 28.6% and 83.3% respectively (Fig. 2b). Patients who had relapsed or residual disease after irradiation at initial diagnosis appeared to have lower 5-year survival compared to those who relapsed without prior irradiation (37.5% vs. 80%) (Fig. 2c). No patient with leptomeningeal relapse and prior radiotherapy survived.

When analyses were confined to patients with medulloblastoma, the overall and event-free survival rates were 51.9% and 55.6% respectively (Fig. 3), similar to those for all types of brain tumors combined. There was no significant difference in clinical characteristics and transplant variables between patients with medulloblastoma and patients with other types of tumors, apart from a younger age at diagnosis for medulloblastoma (4.0 vs. 7.2 years) and a higher frequency of prior leptomeningeal spread in medulloblastoma (55.6% vs. 25.0%).
Survival of medulloblastoma patients after AHSCT

Discussion

High-dose chemotherapy with AHSCT has been tried in many different types of high-risk or recurrent brain tumors in children and different chemotherapy regimens were used in these studies with variable outcomes. Previous case series with more than 10 patients are summarized in Table 3. In these series, tumor response rates ranged from 0% to 71%, and transplant-related mortality ranged from 0% to 33%. The overall and event-free survival rates were also highly variable. Such variable results might be explained by significant heterogeneity in the underlying tumor type, pre-transplant treatment regimen, extent of disease, conditioning regimen and adjuvant treatments.

A variety of chemotherapeutic agents had previously been used in the preparatory phase of transplant and most employed a combination of 2 or 3 drugs. No existing data had clearly defined the most effective and safe conditioning regimen for pediatric brain tumors so far. We therefore applied the combination of thiotepa, etoposide and carboplatin as conditioning for all of our brain tumor patients who underwent autologous HSCT. This approach achieved a response rate, overall and event-free survivals comparable to previous reports with acceptable therapy-related toxicity.

In the study by Finlay, there were no long-term survivors after treatment with the combination of high dose thiotepa and etoposide for patients with cerebral PNET or medulloblastoma [13]. It appears that the addition of carboplatin to the conditioning regimen leads to a substantial improvement in outcome for this group of patients, with approximately 50% long-term survival in our cohort and 29–34% in other studies [5, 6]. Another conditioning regimen that results in similar long-term survival in patients with medulloblastoma is the combination of thiotepa and busulfan, which has also been reported to have 50% event-free survival at 3 years [20]. However, post-transplant adjuvant radiotherapy was used in a significant proportion of patients, which might have contributed to the favorable outcome. Although no severe adverse effects were reported in that series, busulfan is notorious for causing hepatic veno-occlusive disease, which occurred in up to two-thirds of patients in another series [21]. Therefore, in patients with medulloblastoma or PNET, the combination of carboplatin with thiotepa and etoposide appears to be one of the safest and most effective regimens. The morbidity and mortality associated with carboplatin could also be reduced with the use of the Calvert formula. From the literature, it seems that pineoblastoma, ependymoma, atypical teratoid rhabdoid tumor and diffuse pontine glioma had particularly poor outcomes after AHSCT. Better conditioning regimens or alternative approaches need to be devised for these types of tumors.

Despite having poorer prognosis, we found that patients with leptomeningeal spread could still be salvaged with megatherapy and AHSCT and achieved long-term survival. However, the single patient with bone metastasis eventually relapsed and died. It remains to be determined whether patients with bone or other extra-neural metastasis could benefit from this treatment approach.

Several studies have demonstrated that children with minimal residual disease or complete remission before AHSCT had better outcome [6, 7, 13, 14, 17–19, 23]. Gururangun found that 62.5% of patients with complete remission and 44.4% of patients with minimal residual disease < 2 cm survived, compared to 33.3% of patients with bulky disease [7]. Similarly, Fagioli found that patients with complete remission had better event-free survival (50.6%) at 3 years than those with measurable disease (19.6%) [14]; and Busca found that 100% of patients with complete remission survived but no patient with residual disease survived long-term [18]. Our study also concurred in that only patients who had achieved complete remission before AHSCT had long-term survival. For medulloblastoma and PNET, Fagioli, Perez-Martinez, and Graham found that patients with complete remission had better survival (80%, 45.5% and 41.7% respectively) than patients with measurable disease (16.7%, 37.5% and 30.8% respectively) [14, 17, 19]. Gururangun found that 100% of those with complete remission and 50% of those with minimal residual disease survived [7], while Broniscer found that 45.4% of patients with complete remission or minimal residual disease survived but none of patients with bulky disease survived [6]. For high grade glioma, Finlay found that patients with minimal residual disease < 2 cm had better survival (55.6%) than those with gross residual disease (0%) [13]; while Grovas found that patients with complete remission had the best chance of survival (50%), followed by those with minimal residual disease < 2 cm (20%) [23]. None of the patients with bulky disease survived [23]. In conclusion, it appears that cure is most likely in patients with complete remission, less likely in patients
**Table 3** Previous studies of autologous stem cell transplant for high-risk brain tumors in children

| Ref. | Number of patients | Tumor types | Conditioning* | Response rate (CR + PR) | Overall survival | Event-free survival | TRM** | Remarks |
|------|--------------------|-------------|---------------|-------------------------|------------------|---------------------|--------|---------|
| [13] | 45                 | Different tumors | TE            | 23                      | 40 (6 months)    | N/A                 | 16     | Survival was better in patients with minimal residual disease. |
| [14] | 27                 | Different tumors | TE            | N/A                     | 45 (3 years)     | 31 (3 years)        | 4      | Significant difference in survival for patients with complete remission compared to patients with measurable disease before AHSCT. |
| [15] | 20                 | Different tumors | TB            | 26                      | N/A              | N/A                 | 22     | Survival was better in patients with complete remission or minimal residual disease. |
| [16] | 19                 | Different tumors | CM            | 39                      | 39 (1 year)      | 17 (1 year)         | 10     | Survival was better in patients with complete remission or minimal residual disease. |
| [17] | 49                 | Different tumors | CM (n = 37) BM (n = 9) CE (n = 3) | 39 (1 year) | N/A | N/A | 2 | Survival was better in patients with complete remission or minimal residual disease. |
| [7]  | 20                 | Different tumors | TCE (n = 16) TE (n = 3) TEBcNU (n = 1) | 50 | 43 (3 years) | 47 (3 years) | 10 | Survival was better in patients with complete remission or minimal residual disease. |
| [18] | 11                 | Different tumors | TE (N = 6) TEBcNU (n = 5) | 0 | 45 (2 years) | 45 (2 years) | 0 | Only children without measurable disease before AHSCT survived. |
| [19] | 19                 | Medulloblastoma, supratentorial PNET | BM (n = 12) TBM (n = 3) BMTopo (n = 4) | 47 | N/A | N/A | 15 | Survival was better in patients with complete remission. |
| [5]  | 23                 | Medulloblastoma | TCE           | N/A                     | 61 (2 years)     | 44 (2 years)        | 13     | Hepatic VOD in 66.7% of patients. |
| [20] | 20                 | Medulloblastoma | TB            | 75                      | 50 (3 years)     | 5                   | 5      | Surgery at relapse, irradiation post-AHSCT and non-pineoblastoma were favorable prognostic factors. |
| [21] | 15                 | Medulloblastoma | TB            | 71                      | 13 (10 years)    | 27                  | 27     | Survival not better than conventional therapy. |
| [6]  | 17                 | Non-posterior fossa PNET | TCE           | 40                      | N/A              | 29 (5 years)        | 11     | Survival not better than conventional therapy. |

* Conditioning treatment details are not fully visible due to image resolution.

** TRM: Toxicity-related mortality.
with minimal residual disease and unlikely in patients with bulky disease before AHSCT. Those with partial remission before AHSCT probably could not eradicate their malignancies even with megatherapy and most died of disease progression eventually. However, 2 patients with partial remission before AHSCT in our study achieved complete remission post-transplant, which lasted for 11–13 months; and 3 other patients with residual disease before AHSCT had stable disease for 4–8 months before progression. The short-lasting response to high-dose chemotherapy in these patients might be related to intrinsic chemo-resistance of these tumors as evidenced by sub-optimal response to previous upfront and second-line chemotherapy. Other investigators have therefore tried to optimize the response by applying multiple sequential courses of megatherapy followed by repeated AHSCT [28–30]. Whether this intensive approach can result in better long-term survival without much added toxicity remains to be answered in future prospective long-term studies. Nevertheless, even a single course of megatherapy with AHSCT might be able to prolong survival for patients with gross residual disease. However, clinicians have to balance the definite risk of treatment-related mortality and toxicities against the potential benefit and modest gain in life expectancy; and detailed discussion with parents and patients are warranted before deciding to perform megatherapy and AHSCT. For curative intent, efforts should be made to achieve complete remission before AHSCT by further surgery and/or chemo-irradiation, since megatherapy with AHSCT works best as consolidation and cure is likely only in the absence of gross residual disease.

Furthermore, radiotherapy before or after AHSCT might have favorable impact at relapse in those young children not initially irradiated, as we found that 4 of 5 patients who received radiotherapy (full dose 36 Gy craniospinal irradiation with focal boost) following relapse but prior to transplant survived, with the only failure being the child with localized residual tumor immediately pre-transplant. Similar findings were reported by Gururangan [7] and Dupuis-Girod [20]. These groups irradiate children with 18 Gy with focal boost [7] or in the case of local recurrences, only focal boost without craniospinal irradiation [20].

Adverse effects from megatherapy were tolerable and manageable in most patients in the current study. Although all patients had profound cytopenia after conditioning chemotherapy which resulted in neutropenic fever, most patients responded to G-CSF and achieved neutrophil engraftment before 17 days. Renal toxicity was reversible in all patients except the one who died of multi-organ failure. In general, dose modification for carboplatin should be made according to the Calvert formula for patients with pre-existing renal impairment. Since all of our patients had normal renal function before transplant, no dose modification was made. We did not encounter severe neurological or pulmonary toxicity in our patients. Our conditioning

| Ref. | Number of patients | Tumor types | Conditioninga | Response rate (CR + PR) | Overall survival | Event-free survival | TRMb Remarks |
|------|--------------------|-------------|---------------|-------------------------|------------------|---------------------|--------------|
| [23] 11 | Glioblastoma multiciforme | TEBCU | 27 | 73 (1 year) 64 (2 years) | 46 (2 years) | 46 (2 years) | 18 | 45% severe pulmonary or neurological toxicities |
| [24] 13 | Malignant glioma | Tcy | 31 | 62 (1 year) 38 (1 year) | 27 (1 year) | 18 | 9 | For patients with bulky residual disease after surgery, survival with AHSCT is not better than conventional therapy |
| [25] 10 | Malignant glioma | TE (n = 5) TEBCU (n = 5) | 60 | N/A | N/A | N/A | 0 |
| [26] 36 | Malignant glioma | BCNU | 44 | N/A | N/A | 17 |
| [9] 15 | Ependymoma | TCE | 0 | 40 (6 months) 33 (1 year) 20 (2 years) | 27 (6 months) 27 (1 year) 0 (2 year) | 33 |
| [27] 16 | Ependymoma | TB | 0 | N/A | 19 (1 year) | 6 |

a T, Thiotepa; C, Carboplatin; E, Etoposide; B, Busulfan; M, Melphalan; Cy, Cyclophosphamide; BCNU, Carmustine; Temo, Temozolomide; Topo, Topotecan; bTRM, Transplant-related mortality; cN/A, Data not available
regimen of thiotepa, carboplatin and etoposide may be less likely to induce neurological toxicity than busulfan plus thiotepa [21], or pulmonary toxicity than carmustine plus thiotepa plus etoposide [23]. It is notable that our chemotherapeutic regimen had resulted in a relatively high frequency of hepatic veno-occlusive disease (15.4%), though not as high as that reported by Valteau-Cauanet (66.7%), who used busulfan and thiotepa as conditioning [21]. However, our two patients responded well to supportive treatment and eventually recovered. The single patient who died in the early post-transplant period was thought to have engraftment syndrome as he had developed adult respiratory distress syndrome at the time of rapid surge of neutrophils. He finally succumbed to sepsis with multi-organ failure. He was the oldest patient in our series. Whether we should reduce the doses of chemotherapeutic drugs in adolescent or young adult patients to minimize the risk of transplant-related mortality requires further studies.

The current study had several limitations. First, this is a retrospective review and not a prospective trial and therefore is subject to possible observation and selection biases. Nevertheless, we have included all patients who fulfilled the inclusion criteria and consented to AHSCT in our center to minimize bias and most data were organized and complete in the database of our departmental computer server. Second, the results of AHSCT might depend on efficacy of upfront treatments and therefore evolution of upfront treatments for pediatric brain tumors over time might have confounded the results. Third, the sample size is small limiting the statistical power of analyzing treatment outcomes in patients with different tumors and prognostic factors. Further multi-center studies of larger sample size are needed to confirm our findings and to determine the prognostic significance of various patient and disease characteristics. Given the heterogeneity of results in previous studies, a meta-analysis aiming at different subgroups of tumor types and treatment regimens. Fourth, we did not have formal neuropsychological testing or quality of life assessment for most patients and the Lansky-Karnofsky performance score we reported was just a very crude measure of functional status of the patients.

In conclusion, AHSCT can result in long-term survival with satisfactory functional status in children with recurrent brain tumors, especially for those who can achieve complete remission before transplant. Patients with leptomeningeal involvement may also be salvaged by this approach, although the survival in these patients is considerably lower. Those with gross residual tumor before transplant also had poor long-term survival. However, they might still respond to the treatment with temporary remission or stable disease for a meaningful period of time. Further studies are required to determine the most appropriate conditioning chemotherapy for different tumor types and modifications needed to minimize transplant-related mortality and morbidities.

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