

Phase I Study of Tandem High-Dose Chemotherapy With Autologous Peripheral Blood Stem Cell Rescue for Children With Recurrent Brain Tumors: A Pediatric Blood and Marrow Transplant Consortium Study

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Background. High-dose chemotherapy with autologous stem cell rescue (HDC/SCR) has produced responses and prolonged survival for some children with recurrent brain tumors, but is associated with considerable morbidity and mortality. A Phase I trial of two cycles of HDC/SCR for recurrent brain tumors in children was performed to determine the maximum tolerated doses for a novel regimen. **Procedures.** Two cycles of HDC/SCR were given. Cycle 1 included thiotepa and carmustine given on days –5, –4, and –3. Four to six weeks later, patients received cycle 2 which included thiotepa and carboplatin given on days –5, –4, and –3. Autologous peripheral blood stem cells (PBSC) were infused on day 0 of each cycle. **Results.** Thirty-two patients were treated and 25 patients received both cycles of HDC/SCR. Common toxicities included mucositis, emesis, diarrhea,

anorexia, and pancytopenia. Eight of 32 (25%) assessable children died from regimen-related toxicity. Pulmonary failure occurred in seven patients. Seven patients had grade 3–4 neurotoxicity. The 3-year event-free survival (EFS) was 25%. **Conclusions.** We determined the maximum tolerated regimen to be thiotepa 600 mg/m² and carmustine 300 mg/m² followed by thiotepa 600 mg/m² and carboplatin 1,200 mg/m². Pulmonary toxicity was considerable. The toxic death rate was similar to other trials of HDC/SCR for children with recurrent brain tumors performed during the same time period. The regimen resulted in prolonged time to progression for a significant number of patients and long-term survival for some patients with recurrent medulloblastoma and rhabdoid tumor. *Pediatr Blood Cancer* 2011;57:506–513. © 2010 Wiley-Liss, Inc.

Key words: brain tumors; myeloablative therapy; Phase I clinical trials; stem cell transplantation

INTRODUCTION

Brain tumors are the most common solid tumor of childhood. The outcome of children with recurrent malignant brain tumors is dismal [1]. High-dose chemotherapy followed by autologous peripheral blood stem cell rescue (HDC/SCR) has been used for the treatment of recurrent brain tumors. Several chemotherapy combinations have been studied. While toxicities have been significant, this approach has resulted in long-term survival with good quality of life for some patients [2–7]. Patients with gross residual disease at the time of HDC/SCR and those with metastatic disease are much more likely to have disease progression despite this approach [8–13]. Radiation therapy prior to HDC/SCR may also be associated with a worse outcome [13–17]. There have also been several studies of 2–4 cycles of HDC/SCR reported for children with high-risk newly diagnosed brain tumors [18–20] or recurrent disease [6,21–23].

We report the results of a Phase I trial of tandem HDC/SCR for recurrent brain tumors in children. The goal was to improve outcomes with less toxicity by using two cycles of HDC/SCR at reduced intensity compared to a single cycle of HDC/SCR. The novel chemotherapy regimen used alkylating agents—thiotepa, carboplatin, and carmustine—which have activity against brain tumors [3,10,24]. Dose escalation of thiotepa in both cycles and of carmustine was planned. Table I compares the drug doses used for this study versus those reported for a single HDC/SCR approach by the Children's Cancer Group (CCG) [10,24].

METHODS

Patient Eligibility

Patients were eligible if they had a progressive or recurrent brain tumor including medulloblastoma (MB), ependymoma, high-grade (III/IV) astrocytoma (HGA), primitive neuroectodermal tumor (PNET), rhabdoid tumor, or pineoblastoma. Patients with brain stem tumors and those who had previous HDC/SCR were not eligible. Other eligibility criteria included: (1) age 1–21 years, (2) availability

of at least 4×10^6 CD34+ cells/kg of body weight available for SCR, (3) creatinine clearance >50 ml/min/1.73 m² or serum creatinine $<2 \times$ upper limit of normal, (4) bilirubin <1.5 mg/dl and SGPT $<5 \times$ upper limit of normal, (5) FEV₁, FVC, and DLCO (corrected) $\geq 60\%$ of predicted (no dyspnea on exertion and oxygen saturation $\geq 95\%$ by pulse oximetry on room air if unable to perform spirometry), (6) cardiac ejection fraction of $\geq 50\%$ (by echo or MUGA), (7) absolute neutrophil count $>1,000/\mu\text{l}$ and platelet count $>100,000/\mu\text{l}$, (8) performance score (Lansky or Karnofsky) of ≥ 50 , (9) no treatment (radiation or chemotherapy) within 3 weeks of protocol therapy, excluding steroid therapy for increased intracranial pressure. The study was approved by the Internal Review Committee of the Pediatric Blood and Marrow Transplant Consortium as well as by the Institutional Review Board of participating institutions and informed consent was obtained from the patient or guardian.

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TABLE I. Comparison of Drug Doses Between This Study and Prior Children's Cancer Group (CCG) HDC/SCR Studies

	CCG 9883 (mg/m ²)	CCG 9922 (mg/m ²)	Current regimen (mg/m ²)	
			Cycle 1	Cycle 2
Thiotepa	900	900	600	600–750
Etoposide	750	750		
BCNU		600	300	
Carboplatin	1,500			1,200–1,500

Patient Characteristics

Patient characteristics are presented in Table II. Thirty-three patients were enrolled on the study. One patient developed progressive disease prior to study therapy and no further information is reported. The median patient age was 7 years (range 1.75–18). The median time from diagnosis to progressive disease prior to HDC was 21 months (range 3–120). The median time from progressive disease to HDC was 3 months (range 1–10).

Eighteen patients had MB, 15 with a history of metastatic disease within the CNS, including 10 with spinal drop metastases. Chang staging for 17 patients for whom data are available were M0 (3), M2 (5), M3 (10). Other tumors included HGA (7), ependymoma (3), rhabdoid tumor (2), supratentorial PNET (1), and pineoblastoma (1). Twenty-five patients had residual disease at the time of HDC/SCR. Twelve patients had bulky tumor (defined as >1 cm in greatest diameter) at the time of HDC/SCR, including seven patients with MB.

Study Design

The study was a Phase I trial conducted by the Pediatric Blood and Marrow Transplant Consortium. Patients were enrolled from 1995 to 2002. Patients had collection of PBSC prior to study entry. PBSC containing $\geq 2 \times 10^6$ CD34+ cells/kg were infused on day 0 of each cycle. The first HDC cycle included thiotepa IV over 3 hr followed immediately by carmustine IV over 2 hr on days –5, –4, and –3. Dexamethasone 4 mg/m² daily PO or IV was given on days –5, –4, and –3 in an attempt to prevent pulmonary toxicity from BCNU. The second HDC cycle included thiotepa IV over 3 hr followed immediately by carboplatin IV over 2 hr on days –5, –4, and –3. For patients with a creatinine clearance of <100 ml/min/1.73 m², the dose of carboplatin was calculated using a modified Calvert formula [25,26]. The target AUC used was 7 and 5.5 mg min/ml for the corresponding doses of 500 and 400 mg/m², respectively. The lower of the dose calculated by per m² dosing or by the modified Calvert formula was used.

Cycle 2 commenced between 28 and 42 days after the PBSC infusion of cycle 1 if: (1) ANC was $\geq 500/\mu\text{l}$ and platelets were $\geq 20,000/\mu\text{l}$ (could be with transfusion support); (2) non-hematopoietic toxicity has resolved sufficiently; (3) study eligibility criteria for renal, hepatic, and pulmonary function were met at this time. Local radiotherapy was allowed after the second PBSC cycle when the platelet count reached 50,000/ μl .

Dose Escalation and Maximum Tolerable Regimen (MTR)

Dose escalation was planned as shown in Table III. Patients were treated in cohorts of three. Toxicity was graded according to the

Children's Cancer Group Toxicity scale. If none of three patients had dose-limiting toxicity (DLT), subsequent patients were enrolled at the next dose level. If one out of three had DLT, then an additional three patients were enrolled at the same dose level. If two patients at a dose level had DLT, then that level was deemed unacceptable and an additional three patients were treated at the previous level. If <2 out of 6 patients had DLT, the dose level was considered tolerable. DLT was defined as: (1) severe organ dysfunction according to Bearman criteria [27] lasting >7 days, or; (2) death attributable to regimen-related toxicity occurring before day 28 following SCR (day 100 for non-infectious pulmonary toxicity). Patients were considered not assessable for determination of the MTR and were replaced if they received only one HDC/SCR and did not have DLT.

When the protocol was amended to allow the enrollment of an additional six patients at the MTR in order to better define the pulmonary toxicity at this level and to modify the steroid dosing during the conditioning regimen, the following rule was added. For the six additional patients, if two experience DLT, the study will be closed and the previous MTR without the minor modification will be deemed the acceptable approach.

Clinical Monitoring and Intervention for Lung Disease

Because of pulmonary toxicity associated with high-dose carmustine, patients were monitored with handheld spirometry daily and pulse oximetry weekly starting with cycle 1 and continuing for 4 weeks following cycle 2. A decrease in spirometry volume by >10% or oxygen saturation (by >3% and/or to <95%) was followed by pulmonary function testing if the patient could comply. Significant decreases in lung volumes or diffusion capacity were treated with prednisone 1–2 mg/kg/day, which could be tapered over 2 months (as tolerated) following improvement.

Statistical Analysis

Overall and event-free survival was calculated from the day of SCR after the first HDC cycle. The survivor function was estimated by the method of Kaplan and Meier [28]. Survival curves were created using the program R (R Development Core Team, Vienna, Austria).

RESULTS

Therapy

Seven patients received only one cycle of HDC/SCR because of severe toxicity (1), toxic death (3), disease progression (1), and parental request without severe toxicity (2). Two patients received RT for residual disease after HDC/SCR (one craniospinal and one local RT) as allowed by the protocol. Two patients received temozolomide after recovery from HDC/SCR because of bulky residual disease.

Toxicity

Common toxicities included mucositis, emesis, diarrhea, anorexia, and pancytopenia. Mucositis was usually mild to moderate; 5/32 patients had grade 3–4 mucositis. Mucositis was usually more severe after the second cycle. Emesis and diarrhea were usually mild to moderate; 2/32 patients had grade 3–4 diarrhea and 1 patient had grade 4 emesis. Anorexia frequently required parenteral nutrition. Twelve bacterial infections occurred in nine patients, including

TABLE II. Patient Characteristics, Treatment, and Outcome

UPN	Age ^a (years)/ sex	Disease	Dose level	Treatment at Dx	Time from Dx to progression (month)	Treatment at progression	Time from progression to HDC (month)	Protocol treatment after HDC	Metastases		Disease status at HDC	Bulk ^b disease at HDC	TTP (month)	Current status
									Intracranial	Spinal				
1	10/M	MB	1	S, CS/L RT	9	C	5	—	—	Yes	CR2	—	—	135+ months, A&W
2	6/M	Epend	1 ^c	S, L RT	44	S	5	—	—	—	PR3	—	—	Toxic death—1.5 months
3	14/M	MB	1	S, C, CS/L RT	55	C	4	—	Yes	Yes	PR2	Yes	18	46 months, DOD
4	8/F	Epend	1 ^c	S, C/L RT	21	C, L RT	4	—	Yes	Yes	PR3	Yes	—	Toxic death—1.5 months
5	14/F	GBM	1 ^c	S, C, L RT	9	S, C	3	—	—	—	PR2	—	43	58 months, DOD
6	1.75/F	MB	1	S, C	5	—	1	CS/L RT	Yes	Yes	PR2	—	48	54 months, DOD
7	18/M	HGA	1	S, C, L RT	54	S	3	—	—	—	CR2	—	—	Toxic death—2 months
8	3/M	MB	1	S, C	9	C	7	—	Yes	Yes	PR2	Yes	—	Toxic death—0.5 months
9	11/F	MB	1	S, C, CS/L RT	17	C	3	—	—	—	CR2	—	13	25 months, DOD
14	6/F	MB	2a	S, C	30	C, CS/L RT	6	—	—	—	PR2	—	—	Toxic death—0.5 months
15	6/F	Pineo	2a ^c	C, L RT	28	C, L RT	10	—	Yes	Yes	PR2	—	2	3 months, DOD
16	14/M	GBM	2a ^c	S, C, C/L RT	N/A	S, C	N/A	—	—	—	PR2	Yes	23	32 months, DOD
17	1.5/F	Rhab	2a	S, C	12	C	9	L RT	—	—	PR2	Yes	—	90+ months, A&W
18	4/M	MB	2a	S, C	14	C, L RT	2	—	Yes	—	PR2	Yes	34	87+, A&W
19	6/F	MB	2a	S, C, CS/L RT	19	C	4	—	Yes	+ CSF	PR2	—	4	8 months, DOD
20	6/F	Epend	2a	S, L RT	17	S, C	6	—	—	—	PR2	—	12	18 months, DOD
21	10/M	sPNET	2a	S, C, CS/L RT	44	S, C	4	—	—	—	CR3	—	—	Toxic death—0.5 months
22	7/F	MB	2a	S, CS/L RT	120	S, C	2	—	Yes	—	CR2	—	—	83+ months, A&W
23	3/F	GBM	2a	S, L RT	66	S, C	5	—	Yes	—	PR2	Yes	12	18 months, DOD
10	12/M	Rhab	0	S, C, CS/L RT	18	C	3	—	Yes	—	PR2	—	—	100+ months, A&W
11	4/M	MB	0 ^c	S, C, CS/L RT	41	—	1	—	Yes	—	PR2	Yes	1	42 months, DOD
12	10/M	MB	0	S, C, L RT	21	C	4	—	Yes	Yes	PR2	—	—	92+ months, A&W
13	6/F	HGA	0	S, L RT	10	S	2	—	—	—	PR2	—	5	58 months, DOD
24	4/M	MB	0	S, C, CS/L RT	11	C	6	—	Yes	Yes	PR2	—	6	9 months, DOD
25	3/M	HGA	0	S	36	S, C, L RT	7	—	—	—	PR2	Yes	9	10 months, DOD
27	18/M	GBM	0	S, C	12	S, C, L RT	2	—	—	—	PR2	—	5	16 months, DOD
28	7/F	MB	0	S, C, CS/L RT	26	C	4	—	Yes	Yes	PR2	Yes	—	Toxic death—1 months
29	3/F	MB	0	S, C, L RT	3	—	1	—	Yes	Yes	PD	—	18	27 months, DOD
30	8/F	MB	0	S, C, CS/L RT	54	C	6	—	Yes	Yes	PR2	Yes	4	5 months, DOD
31	12/M	MB	0	S, C, CS/L RT	100	S, C	2	—	Yes	—	PR2	Yes	18	26 months, DOD
32	12/M	MB	0 ^c	S, C, CS/L RT	31	C	2	—	—	—	PR2	—	—	Toxic death—0.5 months
33	4/F	MB	0	S, C	9	C, CS/L RT	10	—	Yes	Yes	CR2	—	—	54+ months, A&W

UPN, unique patient identifier; Dx, diagnosis; HDC, high-dose chemotherapy; TTP, time to progression; MB, medulloblastoma; Epend, ependymoma; GBM, glioblastoma multiforme; HGA, high-grade astrocytoma; Rhab, rhabdoid tumor; Pineo, pineoblastoma; sPNET, supratentorial primitive neuroectodermal tumor; S, surgery; C, chemotherapy; CS RT, craniospinal radiation therapy; L RT, local radiation therapy; CR, complete remission; PR, partial remission; A&W, alive and well; DOD, dead of disease. Patients 6 and 17 received post-HDC/SCR radiotherapy as per the protocol. Patients 30 and 31 were treated with temozolomide off protocol soon after HDC/SCR because they had large residual masses. All patients listed as "Toxic death" under the "Current status" column were considered as DLT except for Patients 2 and 4 (see Dose Escalation Section in Results Section for details). ^aAge at start of protocol therapy and gender; ^bBulk disease defined as tumor with maximal diameter > 1 cm; ^cReceived only cycle 1. Patient 26 (not included in the table) had progressive disease and died prior to study therapy.

TABLE III. Dose Escalation Schema

Dose level	First cycle	Second cycle
Level 0	Thiotepa 600 mg/m ² BCNU 300 mg/m ²	Thiotepa 600 mg/m ² Carboplatin 1,200 mg/m ²
Level 1	Thiotepa 600 mg/m ² BCNU 300 mg/m ²	Thiotepa 600 mg/m ² Carboplatin 1,500 mg/m²
Level 2a	Thiotepa 600 mg/m ² BCNU 300 mg/m ²	Thiotepa 750 mg/m² Carboplatin 1,200 mg/m ²
Level 3a	Thiotepa 750 mg/m² BCNU 300 mg/m ²	Thiotepa 750 mg/m ² Carboplatin 1,200 mg/m ²
Level 4a	Thiotepa 750 mg/m ² BCNU 450 mg/m²	Thiotepa 750 mg/m ² Carboplatin 1,200 mg/m ²

The dose escalated at each level is shown in bold. The original dose of carboplatin for levels 2–4 was 1,500 mg/m². However, because of dose-limiting toxicity at level 1 (see text), the dose of carboplatin was decreased when therapy was de-escalated to dose level 0. The dose of carboplatin remained at 1,200 mg/m² for the amended dose levels 2–4.

bacteremia (8 gram positive and 3 gram negative) and one catheter-related *Pseudomonas* cellulitis.

Grade 3–5 toxicities and grade 2 pulmonary toxicity treated with steroids are shown in Table IV. No patient had non-fatal severe organ dysfunction lasting >7 days. Eight patients (25%) had regimen-related deaths. The cause of death was pulmonary failure (n = 4, including two with pulmonary hypertension), pulmonary and renal failure (n = 2), renal failure (n = 1), and severe hepatic veno-occlusive disease (VOD) with multi-organ failure (MOF) (n = 1). Fatal pulmonary toxicity was more common at dose level 1, occurring in 4/9 patients at this level compared to 2/23 patients at the other dose levels. Non-fatal pulmonary toxicity occurred in eight patients. Four patients had restrictive lung disease without an oxygen requirement and four patients required oxygen. One episode was associated with cytomegalovirus reactivation and one episode that occurred 5 months after HDC/SCR was associated with *Pneumocystis jirovecii* after craniospinal RT. The non-infectious cases resolved with steroid therapy. Three patients who required steroids for pulmonary toxicity after cycle 1, tolerated cycle 2 and did well long-term. Seven subjects had grade 3–4 neurotoxicity, one with concomitant VOD. Severe neurological toxicity included coma (2), seizures (3), ataxia (1), and weakness/lethargy (1). Three patients with pre-existing sensorineural hearing loss (SNHL) had worsening SNHL after HDC/SCR.

TABLE IV. Severe Toxicities by Dose Level

Dose level	Pulmonary	Hepatic	Renal	Neurological	MOF	Infection	Mucositis	GI	Skin
0	5/13 (1 Gr 2, 3 Gr 3, 1 Gr 5)	0/13	1/13 (1 Gr 5)	3/13 (2 Gr 3, 1 Gr 4)	0/13	7/13 (5 Gr 3, 2 Gr 4)	3/13 (2 Gr 3, 1 Gr 4)	2/13 (1 Gr 3, 1 Gr 4)	0/13
1	5/9 (1 Gr 3, 4 Gr 5)	1/9 (1 Gr 3)	1/9 (1 Gr 4)	2/9 (1 Gr 3, 1 Gr 4)	2/9	2/9 (2 Gr 3)	2/9 (2 Gr 3)	0/9	1/9 (1 Gr 4)
2a	4/10 (1 Gr 2, 1 Gr 3, 1 Gr 4, 1 Gr 5)	1/10 (1 Gr 5)	1/10 (1 Gr 4)	2/10 (1 Gr 3, 1 Gr 4)	2/10	1/10 (1 Gr 3)	0/10	1/10 (1 Gr 4)	1/10 (1 Gr 3)

MOF, multi-organ failure; GI, gastrointestinal. Severe toxicities include grade 3–5 toxicities and grade 2 pulmonary toxicities requiring steroid therapy; grade 5 toxicity is fatal. Multi-organ failure includes patients in whom the primary cause of death was hepatic (i.e., veno-occlusive disease) or pulmonary failure. Two of the four fatal pulmonary toxicities at dose level 1 were judged to not be related to study therapy (see text).

Dose Escalation

Two of six assessable patients at dose level 1 had DLT. Both had MOF, one with VOD. Three additional patients treated at dose level 1 were considered not assessable for the purpose of determining the MTR. One patient received only the first HDC/SCR cycle per parental request. Two patients had very complicated histories and clinical courses that confounded the role of HDC in their deaths. One patient died due to aspiration pneumonia and with refractory seizures presumed to be due to a familial seizure disorder that had also claimed the life of his sister. The second patient had pulmonary failure associated with aspiration 3 weeks following cycle 1 after esophageal dilatation for a chronic stricture.

The dose level was de-escalated to level 0 by reducing the carboplatin dose in cycle 2. As the fatal pulmonary toxicities seen at dose level 1 occurred soon after course 2 chemotherapy, we attributed them to the intensity of cycle 2 therapy and not to the nitrosourea. We therefore kept the nitrosourea dose the same in dose level 0 as in dose level 1. After 3/3 assessable patients tolerated dose level 0, the dose level was then escalated to dose level 2a (modification of the original dose level 2 using the reduced carboplatin dose of level 0 with an increase in the thiotepa dose during cycle 2). Only one of three assessable patients treated at dose level 2a had DLT, so an additional three patients were enrolled. Because of previous experience with some patients not being assessable, two additional patients were enrolled in anticipation of the need for replacement patients. When two of the first six had DLT (one VOD with MOF and one pulmonary failure), dose level 2a was deemed unacceptable. The additional two patients did not have DLT.

Dose level 0 was further evaluated with the enrollment of an additional three patients according to the study design. None of the first six patients at dose level 0 had DLT. Because 2/6 patients had non-fatal pulmonary toxicity requiring steroid therapy, an additional six patients were enrolled at dose level 0 to better define the risk of pulmonary toxicity. In addition, steroid therapy during carmustine administration was increased from dexamethasone 4 mg/m² daily on day –5 to day –3 to 4 mg/m² twice daily on day –5 to day –1 for these patients in an attempt to prevent pulmonary toxicity. Despite this change, two of these six children had DLT (one MOF and one pulmonary failure). Both patients with DLT had *Pseudomonas* infections; one episode was between cycles 1 and 2 and the other followed cycle 2. It is possible that the additional steroid therapy contributed to

the toxic deaths by causing increased immunosuppression. Overall, 2/12 assessable patients treated at dose level 0 had DLT and the toxic death rate was 17%.

Patient Outcome

Thirty-two patients received protocol therapy. Although the study was a Phase I study to determine an acceptable treatment regimen, long-term outcome data are available. Seven children remain alive and without disease, including 5/18 with MB (135, 92, 87, 83, and 54 months after HDC/SCR) and both patients with rhabdoid tumors (100 and 90 months after HDC/SCR). All five surviving patients with MB had metastatic disease prior to HDC/SCR, including three with spinal leptomeningeal disease. All of them had received RT prior to HDC/SCR—craniospinal (two at diagnosis and one at disease progression) or local (one at diagnosis and one at disease progression). Only one of them had bulk disease at the time of HDC. This patient is alive and well 87 months after HDC, despite progressive disease 34 months after HDC. The patient had resection of a large drop metastasis that confirmed relapsed MB. Following surgery, the patient was treated with chemotherapy and local radiotherapy. Eighteen patients had progressive disease at a median of 12 months after HDC/SCR (range 1–48).

Progression-free and overall survival curves are shown in Figure 1. The Kaplan–Meier estimates of EFS and overall survival at 3 years for all patients are 25% (95% CI 14–46%) and 38% (95% CI 24–59%). The Kaplan–Meier estimates of EFS and overall survival at 3 years for patients with MB are 28% (95% CI 13–58%) and 44% (95% CI 26–74%).

DISCUSSION

HDC/SCR has been shown to be beneficial for some patients with recurrent brain tumors, with 3-year EFS of ~30% in some reports [2]. We conducted a Phase I trial of tandem cycles of HDC. The intensity

of each myeloablative cycle was reduced to avoid excessive cumulative organ toxicity. The first cycle was intended to be cytoreductive, allowing the second cycle to be delivered at a time of minimal residual disease. Another unique feature of the regimen is that alkylating agents were given on the same days rather than on sequential days as in previous trials of HDC/SCR. The hypothesis was that efficacy would be increased by achieving higher peak alkylator levels and toxicity would be decreased (especially mucositis) due to the shorter duration of exposure. A dose-escalation study design was used to determine doses with acceptable acute and cumulative toxicities.

The use of two cycles of thiotepa allowed the total thiotepa dose to be escalated from 900 mg/m² as previously reported with HDC/SCR for brain tumors [8] to 1,200 mg/m². However, carboplatin dosing had to be reduced compared to that previously reported [10]. The incidence of pulmonary toxicity was higher than expected for carmustine at the dose given [29]. The latter two findings may have been related to giving the alkylating agents on the same day.

The tandem HDC/SCR therapy was associated with considerable toxicity. Pulmonary toxicity was a major limitation of this therapy, occurring in 44% of patients. It should be noted that our assessment for pulmonary toxicity is intentionally very inclusive and includes patients with aspiration pneumonia, infections, and post-infectious complications that likely were not directly due to the specific chemotherapy used. A similar 45% incidence of pulmonary toxicity was reported for a myeloablative regimen containing carmustine 600 mg/m², thiotepa, and etoposide for children with newly diagnosed HGA [24]. In our study, pulmonary toxicity occurred at all dose levels, but was most severe at dose level 1. There was only 1 fatal pulmonary toxicity out of 13 patients at the MTR (dose level 0) and this was due to pulmonary hypertension following *Pseudomonas* sepsis. An association between either gender or prior craniospinal irradiation and nitrosourea-related pulmonary toxicity has been previously described. We found no statistical association between pulmonary toxicity and either gender ($P = 1$) or prior spinal irradiation ($P = 0.5$).

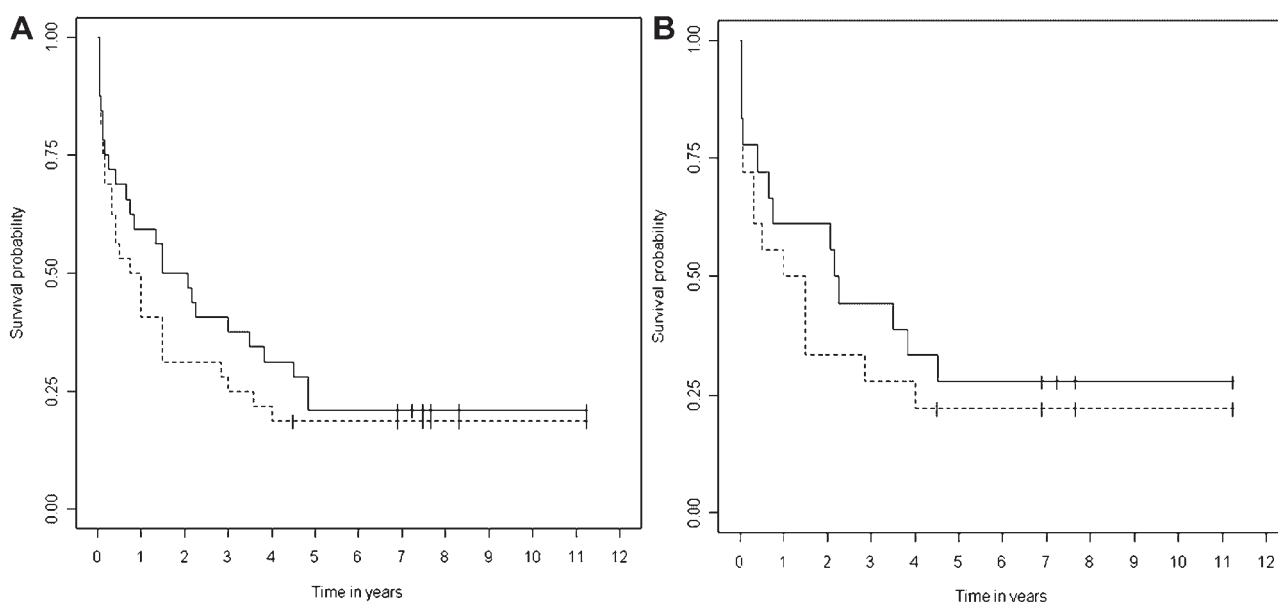


Fig. 1. A: Event-free survival (---) and overall survival (—) from the day of SCR after the first HDC cycle for all 32 patients and (B) for 18 patients with medulloblastoma.

Neurotoxicity occurred in 22% of patients and was similar at all dose levels. Neurotoxicity has been reported at similar frequencies with other regimens for brain tumors—30% with busulfan and thiotepa [30] and 22% with etoposide, thiotepa, and carboplatin [10]. Grade 3–4 hepatotoxicity occurred in 6% of patients, which compares favorably to 25% reported with busulfan and thiotepa [9] and 56% reported with etoposide, thiotepa, and carboplatin [10]. Severe renal toxicity occurred in 6% patients, similar to that reported with etoposide, thiotepa, and carboplatin [10]. Mucositis and gastrointestinal toxicity were less common than reported with other regimens for recurrent brain tumors [10,11]. This finding supports our hypothesis that fewer days of chemotherapy administration would reduce mucosal toxicity.

Three patients had worsening SNHL after HDC/SCR. All had medulloblastoma, had received craniospinal irradiation with posterior fossa boost, and had SNHL prior to HDC/SCR. The relationship to prior therapy has been reported with other high-dose carboplatin regimens [21].

Our tandem HDC/SCR regimen resulted in similar toxicities to a single cycle of etoposide, thiotepa, and carboplatin [3,10]. Possible advantages of the tandem regimen include less severe mucositis and less grade 3–4 hepatic toxicity. Unfortunately, the toxic death rate of 25% in our Phase I trial was similar to Phase II trials using one cycle of HDC which reported rates of 11–22% [10,12,18,31]. It should be noted that the toxic death rate in our study was 17% at the MTR and 0% for the six patients treated at the MTR without the additional steroid therapy (as discussed above). More recent studies have demonstrated toxic mortality rates declining to below 10% [32]. We would point out that our study was conducted between 1995 and 2002. As such we would attribute the discrepancy between the toxic death rates in contemporary studies and in ours to ongoing improvements in supportive care for such heavily pretreated patients. Also, the toxic death rate in our Phase I study and the toxic death rates from Phase II studies are difficult to compare because there are likely significant differences in the disease status and prior therapy between patients treated on these different types of studies.

A preliminary assessment of efficacy is possible although it must be noted that this is in the context of a Phase I trial that was not designed to look at efficacy. The 3-year actuarial event-free survival (EFS) for patients with MB was 28% (5/18). All five surviving patients with MB had metastatic disease prior to HDC/SCR, including three with spinal leptomeningeal disease. All of them had received RT prior to HDC/SCR—craniospinal (two at diagnosis and one at disease progression) or local (one at diagnosis and one at disease progression). Of course, the RT at disease progression could have contributed to the long-term disease control. Efficacy of our approach is also suggested by the prolonged progression-free interval experienced by a significant number of patients. In addition to the long-term survivors, 36% of patients had progression-free intervals of at least 1 year after SCR including 5/13 patients with MB (13, 18, 18, 18, 48 months), 3/6 with glioblastoma multiforme or HGA (12, 23, and 43 months), and 1/3 with ependymoma (12 months). Of note, only two of these patients received additional therapy during the progression-free interval. One patient received craniospinal RT with a local boost for residual disease as allowed per protocol. The other patient received temozolomide for residual bulky disease.

The discussion of efficacy is very complicated based on numerous factors. This study was one of the few Phase I dose escalation trials

performed for HDC/SCR in children. Most studies have used fixed doses of chemotherapy for pilot or Phase II studies. Because our study was a Phase I trial of a novel chemotherapy regimen, we had an extremely high-risk cohort of patients. For example, 15/18 MB patients had metastatic disease and 7/18 had bulky disease at the time of transplant. Also, of the five long-term survivors with MB, three did not have biopsy of recurrent disease or neurological symptoms at the time of recurrence. These three patients had recurrence at 9, 14, and 21 months after diagnosis. It is possible that some of the radiographic relapses represented imaging changes rather than disease. Of note, Dunkel et al. [15] did not find a statistically significant difference in EFS for patients with MRI evidence of recurrent MB versus those with tissue confirmation of recurrence. Interestingly, our results are remarkably similar to those of Dunkel for patients with recurrent MB [10,15].

Thirteen of 18 patients with MB had received radiotherapy as part of their initial treatment. Three of 13 (23%) previously irradiated patients and 2/5 (40%) non-irradiated patients survive. It should be noted that some studies have demonstrated similar survival rates in previously irradiated patients [13,15], whereas others have reported dismal results in such patients [16,17,33].

Tandem HDC/SCR did not overcome the impact of bulky disease. At dose level 0, the maximum tolerated regimen, disease-free survival is 3/5 patients without bulky disease compared to 0/4 with bulky disease at the time of HDC. Bulky disease has been correlated with poor outcome in most HDC/SCR studies [32].

Metastatic disease at HDC/SCR for patients with MB is another poor prognostic factor. In a study of etoposide, thiotepa, and carboplatin for recurrent MB, the 3-year EFS was 26% for patients with M1⁺ disease and 60% for patients with M0 disease [10]. Similarly, a report of melphalan and cyclophosphamide for recurrent MB had 4/4 patients surviving after HDC/SCR for patients with relapse isolated to the posterior fossa, but 0/14 survivors with M2⁺ disease [11]. In our study, 5/15 (33%) patients with M2⁺ disease remain alive with follow-up of 54–135 months.

The two long-term survivors with rhabdoid tumors are noteworthy in light of the very poor prognosis for such patients. One patient had intracranial metastases at the time of progression and had received craniospinal RT at initial diagnosis. The other patient had bulky disease at the primary site at the time of HDC. This patient received only local RT after HDC/SCR because of young age. Finally, despite prolonged time to progression in three patients with glioblastoma multiforme, the long-term survival for patients with HGA and other histologies was poor. This is similar to the experience for these tumors reported with other HDC regimens, although there is some suggestion of benefit in some reports.

In conclusion, we determined the maximum tolerated regimen for tandem HDC/SCR with carmustine and thiotepa for the first cycle and thiotepa and carboplatin for the second cycle. Although mucositis and hepatotoxicity were less common and less severe compared to reports of single cycle HDC/SCR, pulmonary toxicity was considerable and the toxic death rate was not improved compared to that of a single cycle of HDC/SCR in patients with recurrent disease performed during the same time period. If a Phase II study with chemotherapy at the MTR is performed in the future, it will be important to closely monitor pulmonary toxicity and to have appropriate stopping rules for toxicity. The tandem regimen appears to have significant activity against brain tumors, particularly medulloblastomas and rhabdoid tumors.

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REFERENCES

- Gillheeny SW, Khakoo Y, Souweidane M, et al. Thiotepa/topotecan/carboplatin with autologous stem cell rescue in recurrent/refractory/poor prognosis pediatric malignancies of the central nervous system. *Pediatr Blood Cancer* 2010;54:591–595.
- Dunkel IJ, Finlay JL. High-dose chemotherapy with autologous stem cell rescue for brain tumors. *Crit Rev Oncol Hematol* 2002;41:197–204.
- Gururangan S, Dunkel IJ, Goldman S, et al. Myeloablative chemotherapy with autologous bone marrow rescue in young children with recurrent brain tumors. *J Clin Oncol* 1998;16:2486–2493.
- Grodman H, Wolfe L, Kretschmar C. Outcome of patients with recurrent medulloblastoma or central nervous system germinoma treated with low dose continuous intravenous etoposide along with dose-intensive chemotherapy followed by autologous hematopoietic stem cell rescue. *Pediatr Blood Cancer* 2009;53:33–36.
- Kadota RP, Mahoney DH, Doyle J, et al. Dose intensive melphalan and cyclophosphamide with autologous hematopoietic stem cells for recurrent medulloblastoma or germinoma. *Pediatr Blood Cancer* 2008;51:675–678.
- Sung KW, Yoo KH, Cho EJ, et al. High-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk or relapsed medulloblastoma or supratentorial primitive neuroectodermal tumor. *Pediatr Blood Cancer* 2007;48:408–415.
- Finlay JL, Dhall G, Boyett JM, et al. Myeloablative chemotherapy with autologous bone marrow rescue in children and adolescents with recurrent malignant astrocytoma: Outcome compared with conventional chemotherapy: A report from the Children's Oncology Group. *Pediatr Blood Cancer* 2008;51:806–811.
- Finlay JL, Goldman S, Wong MC, et al. Pilot study of high-dose thiotepa and etoposide with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. *J Clin Oncol* 1996;14:2495–2503.
- Dupuis-Girod S, Hartmann O, Benhamou E, et al. Will high dose chemotherapy followed by autologous bone marrow transplantation supplant cranio-spinal irradiation in young children treated for medulloblastoma. *J Neurooncol* 1996;27:87–98.
- Dunkel IJ, Boyett JM, Yates A, et al. High-dose carboplatin, thiotepa, and etoposide with autologous stem-cell rescue for patients with recurrent medulloblastoma. *J Clin Oncol* 1998;16:222–228.
- Graham ML, Herndon JE, Casey JR, et al. High-dose chemotherapy with autologous stem-cell rescue in patients with recurrent and high-risk pediatric brain tumors. *J Clin Oncol* 1997;15:1814–1823.
- Broniscer A, Nicolaides TP, Dunkel IJ, et al. High-dose chemotherapy with autologous stem-cell rescue in the treatment of patients with non-cerebellar primitive neuroectodermal tumors. *Pediatr Blood Cancer* 2004;42:261–267.
- Butturini AM, Jacob M, Aguajo J, et al. High-dose chemotherapy and autologous hematopoietic progenitor cell rescue in children with recurrent medulloblastoma and supratentorial primitive neuroectodermal tumors—The impact of prior radiotherapy on outcome. *Cancer* 2009;115:2956–2963.
- Gajjar A, Pizer B. Role of high-dose chemotherapy for recurrent medulloblastoma and other CNS primitive neuroectodermal tumors. *Pediatr Blood Cancer* 2010;54:649–651.
- Dunkel IJ, Gardner SL, Garvin JH, et al. High-dose carboplatin, thiotepa, and etoposide with autologous stem cell rescue for patients with previously irradiated recurrent medulloblastoma. *Neuro-Oncology* 2010;12:297–303.
- Gururangan S, Krauser J, Watral MA, et al. Efficacy of high-dose chemotherapy or standard salvage therapy in patients with recurrent medulloblastoma. *Neuro-Oncology* 2008;10:745–751.
- Valteau-Couanet D, Fillipini B, Benhamou E, et al. High-dose busulfan and thiotepa followed by autologous stem cell transplantation (ASCT) in previously-irradiated medulloblastoma patients: High toxicity and lack of efficacy. *Bone Marrow Transplant* 2005;36:939–945.
- Strother D, Ashley D, Kellie SJ, et al. Feasibility of four consecutive high-dose chemotherapy cycles with stem-cell rescue for patients with newly diagnosed medulloblastoma or supratentorial primitive neuroectodermal tumor after craniospinal radiotherapy: Results of a collaborative study. *J Clin Oncol* 2001;19:2696–2704.
- Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): Long term results from a prospective, multicentre trial. *Lancet Oncol* 2006;7:813–820.
- Thorarinsdottir HK, Rood B, Kamani N, et al. Outcome for children <4 years of age with malignant central nervous system tumors treated with high-dose chemotherapy and autologous stem cell rescue. *Pediatr Blood Cancer* 2007;48:278–284.
- Foreman NK, Schissel D, Le T, et al. A study of sequential high dose cyclophosphamide and high dose carboplatin with peripheral stem-cell rescue in resistant or recurrent pediatric brain tumors. *J Neurooncol* 2005;71:181–187.
- Ozkaynak MF, Sandoval C, Levendoglu-Tugal O, et al. A pilot trial of tandem autologous peripheral blood progenitor cell transplantation following high-dose thiotepa and carboplatin in children with poor-risk central nervous system tumors. *Pediatr Hematol Oncol* 2002;21:635–645.
- Rosenfeld A, Kletzel M, Duerst R, et al. A phase II prospective study of sequential myeloablative chemotherapy with hematopoietic stem cell rescue for the treatment of selected high risk and recurrent central nervous system tumors. *J Neurooncol* 2010;97:247–255.
- Grovas AC, Boyett JM, Lindsley K, et al. Regimen-related toxicity of myeloablative chemotherapy with BCNU, thiotepa, and etoposide followed by autologous stem cell rescue for children with newly-diagnosed glioblastoma multiforme: Report from the Children's Cancer Group. *Med Pediatr Oncol* 1999;33:83–87.
- Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: Prospective validation of a simple formula based on renal function. *J Clin Oncol* 1989;7:1748–1756.
- Newell DR, Pearson ADJ, Balmanno K, et al. Carboplatin pharmacokinetics in children: The development of a pediatric dosing formula. *J Clin Oncol* 1993;11:2314–2323.
- Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol* 1988;6:1562–1568.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:451–481.

29. Ager S, Mahendra P, Richards EM, et al. High-dose carmustine, etoposide, and melphalan ('BEM') with autologous stem cell transplantation: A dose-toxicity study. *Bone Marrow Transplant* 1996; 17:335–340.
30. Kalifa C, Hartmann O, Vassal G, et al. High-dose busulfan and thiotepa with autologous bone marrow transplantation in childhood malignant brain tumors: A phase II study. *Bone Marrow Transplant* 1992;9:227–233.
31. Mahoney DH, Jr., Strother D, Camitta B, et al. High-dose melphalan and cyclophosphamide with autologous bone marrow rescue for recurrent/progressive malignant brain tumors in children: A pilot Pediatric Oncology Group study. *J Clin Oncol* 1996;14:382–388.
32. Marachelian A, Butturini A, Finlay J. Myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for childhood central nervous system tumors. *Bone Marrow Transplant* 2008;41: 167–172.
33. Massimino M, Gandola L, Spreafico F, et al. No salvage using high-dose chemotherapy plus/minus reirradiation for relapsing previously irradiated medulloblastoma. *Int J Radiat Oncol Biol Phys* 2009;73:1358–1363.