High-Dose Thiotepa and Etoposide in Children with Poor-Prognosis Brain Tumors

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BACKGROUND. Outcome data were analyzed for 27 patients who were affected with recurrent or newly diagnosed high-risk brain tumors and who underwent high-dose chemotherapy with triethylenethiophosphoramide (thiotepa) and etoposide in addition to autologous stem cell transplantation between May 1992 and September 2002.

METHODS. Fifteen males and 12 females (median age, 11 years) were included in the study. Twelve patients had newly diagnosed high-risk brain tumors, and 15 patients had recurrent brain tumors. The conditioning regimen consisted of thiotepa 900 mg/m^2 and etoposide 1500 mg/m^2 over 3 days starting on Day −5. Stem cell rescue was performed using bone marrow (BM) in 8 patients, peripheral blood stem cells (PBSCs) in 18 patients, and BM and PBSCs in 1 patient.

RESULTS. For the BM group, neutrophil (PMN) engraftment was achieved on Day +14 (median value), whereas platelet (PLT) engraftment was achieved on Day +68 (median value). One patient did not achieve PLT engraftment. For the PBSC group, the PMN engraftment was achieved on Day +10.0 (median value), and the PLT engraftment was achieved on Day +15.5 (median value). Transplantation-related toxicity (evaluated using the Bearman score) included Grade 2–3 mucositis in 16 patients, Grade 1 kidney toxicity in 6 patients, Grade 1 liver toxicity in 6 patients, and Grade 2 liver toxicity in 1 patient. Transplantation-related mortality was observed in 1 patient (3.6%), who died of Candida pneumonia. The 3-year overall survival (OS) rate was 44.6%, and the 3-year event-free survival (EFS) rate was 31%. There was a statistically significant difference in OS and EFS rates for patients who underwent ASCT and achieved complete remission compared with patients who had measurable disease.

CONCLUSIONS. The results of the current study suggest that high-dose chemotherapy followed by ASCT may be beneficial for patients who achieve complete remission before ASCT, whereas for other patients, new strategies are required. ***Cancer* 2004;100:2215–21.** *© 2004 American Cancer Society.*

KEYWORDS: brain tumor, high-dose thiotepa, high-dose etoposide, autologous stem cell transplantation.

Children with high-risk and recurrent brain tumors currently have a poor prognosis.[1–5] To increase brain distribution of antitumor drugs that do not cross the blood-brain barrier at conventional dosages and to achieve higher concentrations within the tumor, high-dose chemotherapy (HDCT) followed by autologous hemopoietic stem cell rescue has been proposed. To date, different conditioning regimens have been used for heterogeneous groups of patients.[6–10]

Triethylenethiophosphoramide (thiotepa) and its active metabolite triethylenephosphoramide are able to achieve a 1:1 plasma-to–cerebrospinal fluid ratio after intravenous administration[11] and exhibit a steep dose-response curve against medulloblastoma and

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TABLE 1
Patient Characteristics

UPN	Dx	Disease site at Dx	Age at Dx	Mets at Dx	Site of mets	Time to Dx of first recurrence (mos)	Site of first recurrence
47	MB	PCF	3 yrs, 11 mos	No[a]	NA	18.9	Spine[b]
53	GBM	R temp-occ	15 yrs, 6 mos	No	NA	NA	NA
113	A-OLIGO	R sub-temp	6 yrs, 8 mos	No	NA	66	R subtemp[c]
115	GBM	L par-occ	12 yrs, 2 mos	No	NA	5.5	L par-occ
135	PNET	R temp-par-occ	1 yr, 9 mos	No	NA	13.2	R occ
140	GBM	Temp	2 yrs, 5 mos	No	NA	66.9	Temp
155	MB	PCF	8 yrs, 11 mos	No	NA	74.1	Cerebral hemispheres
162	AA	Thalamus, basal nuclei	13 yrs, 1 mo	No	NA	NA	NA
166	PNET	Par + splenium	13 yrs, 5 mos	No	NA	NA	NA
172	PNET	Thalamus	10 yrs, 6 mos	No	NA	NA	NA
187	PINEO	Pineal gland	8 yrs	Yes	CSF	22.4	Pineal gland, spine, CSF
196	MB	PCF	12 yrs	No	NA	19.3	Bone (S1–S4)
202	PINEO	Pineal gland	10 yrs, 6 mos	No	NA	NA	NA
203	MB	PCF	7 yrs, 10 mos	No	NA	17.9	PCF and spine
208	MB	PCF	10 yrs	No	NA	1.6	Midbrain, spine
212	MB	PCF	6 yrs, 4 mos	No	NA	19.7	Cerebral hemispheres
225	A-EPEND	PCF	5 yrs, 5 mos	No	NA	44.3	Fourth ventr[d]
228	GCT	Pineal region	12 yrs, 8 mos	Yes	Spine	NA	NA
260	AA	Cervicodorsal spine	5 yrs, 8 mos	No	NA	NA	NA
300	MB	PCF	10 yrs, 10 mos	Yes	Third ventr, CSF	NA	NA
306	A-EPEND	L lat ventr	6 yrs, 6 mos	No	NA	NA	NA
308	AA	R par-occ	7 yrs, 4 mos	No	NA	1.6	R par-occ, splenium
320	GBM	L temp	15 yrs, 5 mos	No	NA	NA	NA
333	MB	PCF	7 yrs	Yes	Third ventr, spine	NA	NA
338	MB	PCF	7 yrs, 11 mos	Yes	CSF	31.7	Ventr
349	MB	PCF	14 yrs, 8 mos	Yes	Leptomeninges	NA	NA
379	MB	PCF	10 yrs, 9 mos	No[a]	NA	19.1	Intraventricular

UPN: unique patient number; Dx: diagnosis; Mets: metastases; PCF: posterior cranial fossa; NA: not applicable; MB: medulloblastoma; GBM: glioblastoma multiforme; A-OLIGO: anaplastic oligodendroglioma; PNET: primitive neuroectodermal tumor; AA: Grade 3–4 anaplastic astrocytoma; PINEO: pineoblastoma; A-EPEND: anaplastic ependymoma; GCT: germ cell tumor; temp: temporal; occ: occipital; par: parietal; lat: lateral; ventr: ventricle; L: left; R: right; CFS: cerebrospinal fluid; S1–S4: sacral spinal segments 1–4.

[a] CSF was not evaluated.

[b] Patient 47 had a second recurrence (16.8 mos after the first recurrence) in the meninges, subarachnoid space, midbrain, and posterior cranial fossa.

[c] Patient 13 had a second recurrence (3 mos after the first recurrence) in the right subtemporal region and a third recurrence (8.1 mos after the second recurrence) in the right temporal-occipital region.

[d] Patient 225 had a second recurrence (19.1 mos after the first recurrence) in the third ventricle and the lateral ventricle.

glioma central nervous system (CNS) tumor cell lines. Etoposide also has shown adequate penetration into the brain parenchyma.[12] Both thiotepa and etoposide have demonstrated good activity against recurrent brain tumors at conventional doses.[13–15] In the current report, we present the results obtained using an etoposide/thiotepa-based conditioning regimen in 27 patients who were affected with recurrent or newly diagnosed high-risk brain tumors.

MATERIALS AND METHODS

Patients

Between May 1992 and September 2002, 27 patients affected with recurrent or newly diagnosed high-risk brain tumors underwent HDCT followed by autologous stem cell transplantation (ASCT). The characteristics of patients' disease status and previous treatments are listed in Tables 1 and 2. Twelve patients had newly diagnosed high-risk brain tumors, including 3 patients with medulloblastoma, 2 patients with glioblastoma multiforme, 2 patients with primitive neuroectodermal tumors (PNET), 2 patients with anaplastic astrocytoma, 1 patient with pineoblastoma, 1 patient with anaplastic ependymoma, and 1 patient with a germ cell tumor. Fifteen patients had recurrent brain tumors, including 7 patients with medulloblastoma in first recurrence, 1 patient with medulloblastoma in second recurrence, 2 patients with glioblastoma multiforme in first recurrence, 1 patient with anaplastic oligodendroglioma in third recurrence, 1 patient with a PNET in first recurrence, 1 patient with anaplastic astrocytoma in first recurrence, 1 patient with anaplastic ependymoma in second recurrence, and 1 patient with pineoblastoma in first recurrence. Fifteen

TABLE 2
Patient Characteristics: Disease Status, Previous Therapy, Disease Recurrence or Progression, and Survival

UPN	Dx	Prior therapy	No. of recurrences	Treatment before HDCT	Disease status at HDCT	Disease status after HDCT[a]	RT after HDCT	Time to recurrence/ progression (mos)	Survival	
									Status	Time (mos)
47	MB	S, RT, CT	2	CT	PR	SD	No	8.6	DOD	9.3
53	GBM	NA	Dx	S[b]	PR	CR	Yes	No	NED	127.1[g]
113	A-OLIGO	S, RT, CT	3	S[b], CT	PR	CR3	No	4.3	DOD	10.3
115	GBM	S	1	S[b], CT	CR2	CCR	Yes	No	NED	94.9[g]
135	PNET	S, CT	1	S[b], CT, RT	CR2	CCR	No	No	NED	82.1[g]
140	GBM	RT, CT	1	S[b], CT	CR1	NA	NA	NA	TRM	1
155	MB	S, RT	1	S[b], CT	CR2	CCR	No	29.8	DOD	55.6[g]
162	AA	NA	Dx	S[d], CT	SD	SD	Yes	4.5	DOD	8.7
166	PNET	NA	Dx	S[e], CT	PR	SD	Yes	5.3	DOD	11.2
172	PNET	NA	Dx	S[e], CT	CR1	CCR	Yes	9.6	DOD	14.6
187	PINEO	RT, CT	1	CT	SD	PD	No	1.9	DOD	7.8
196	MB	S, RT	1	RT, CT	PR	SD	No	32	DOD	59.4[g]
202	PINEO	NA	Dx	S[f], RT, CT	CR1	CCR	No	No	NED	59.6[g]
203	MB	S, CT, RT	1	CT	PR	CR	No	7.1	DOD	10.2
208	MB	S	1	S[f], RT, CT	PD	SD	No	4.5	DOD	6.8
212	MB	S, RT, CT	1	CT	PR	SD	No	7.3	DOD	17.3
225	A-EPEND	S, RT, CT	2	CT	PR	SD	No	9.8	DOD	13.3
228	GCT	NA	Dx	S[c], CT, RT	SD	PR	No	4.0	DOD	7.9
260	AA	NA	Dx	S[d], CT	PR	SD	Yes	No	SD	41.3[g]
300	MB	NA	Dx	S[d], RT, CT	CR1	CCR	No	No	NED	29.4[g]
306	A-EPEND	NA	Dx	S[f], CT	PD	SD	Yes	4.9	DOD	17.1
308	AA	S	1	S[b], CT	PR	SD	Yes	5.3	DOD	9.2
320	GBM	NA	Dx	S[d], CT	PR	SD	Yes	No	SD	23.4[g]
333	MB	NA	Dx	S[d], CT, RT	CR1	CCR	No	No	NED	19.7[g]
338	MB	S, CT, RT	1	CT	SD	SD	No	No	SD	16.1[g]
349	MB	NA	Dx	S[d], CT, RT	CR1	CCR	No	9.1	SD	12.6[g]
379	MB	S, CT	1	CT, RT	CR2	CCR	No	No	NED	7.3[g]

UPN: unique patient number; Dx: diagnosis; HDCT: high-dose chemotherapy; RT: radiotherapy; MB: medulloblastoma; S: surgery; CT: chemotherapy; GBM: glioblastoma multiforme; A-OLIGO: anaplastic oligodendroglioma; PNET: primitive neuroectodermal tumor; AA: Grade 3–4 anaplastic astrocytoma; PINEO: pineoblastoma; A-EPEND: anaplastic ependymoma; GCT: germ cell tumor; PR: partial remission; CR: complete remission; CCR: continuing complete remission; SD: stable disease; PD: progressive disease; DOD: died of disease; NED: no evidence of disease; TRM: transplantation-related mortality; NA: not applicable.

[a] Response to high-dose thiotepa and etoposide was evaluated at a median of 45.5 days after autologous stem cell transplantation.

[b] Total resection.

[c] Total resection of the primary site.

[d] Subtotal resection.

[e] Partial resection.

[f] Biopsy.

[g] Patients who attended school after high-dose chemotherapy.

males and 12 females were included in the study. The median age at transplantation was 11 years (range, from 3 years and 3 months to 19 years and 1 month).

Patients were eligible for the treatment regimen if they had normal cardiac, hepatic, renal, and pulmonary function. All patients and/or their parents provided informed consent.

Bone Marrow Harvesting And Reinfusion

Eight patients underwent bone marrow (BM) collection; seven underwent this procedure before early 1997, when peripheral blood stem cell (PBSC) harvesting was not yet used at our center. Eighteen patients had mobilized PBSCs collected, and 1 patient had both BM and PBSCs collected.

The mobilizing regimen consisted of cyclophosphamide 4 g/m^2 on Day 1 and etoposide 200 mg/m^2 per day on Days 2–4 (total dose, 600 mg/m^2) for 19 patients, and etoposide 420 mg/m^2, cisplatin 100 mg/m^2, ifosfamide 10 g/m^2 for 1 patient. All patients also received granulocyte-colony-stimulating factor (G-CSF) 10 μg/kg per day from Day 5 until the day of the last apheresis. One patient received a mobilizing regimen but did not have the required number of CD34-positive cells for PBSC harvesting. The median number of aphereses was 2 (range, 1–3).

The myeloablative regimen consisted of thiotepa 300 mg/m^2 per day on Days −5, −4, and −3 (total dose, 900 mg/m^2) and etoposide 500 mg/m^2 per day on Days −5, −4, and −3 (total dose, 1500 mg/m^2). Seventy-two hours after the end of chemotherapy, autologous stem cells were infused.

Supportive Care

Platelet (PLT) counts were required to be maintained at levels $>$ 25,000/μL to minimize the risks of intracranial hemorrhage. Hemoglobin was required to be maintained at levels $>$ 8 g/dL. Patients with febrile neutropenia were treated with antibiotic and antifungal agents when appropriate. G-CSF was used beginning on Day +8 after transplantation.

Post-ASCT Therapy

Radiotherapy (RT) was received by nine patients after ASCT, according to the therapeutic protocols (Table 2).

Response and Toxicity Criteria

Pretransplantation and posttransplantation gadolinium-enhanced and unenhanced magnetic resonance imaging (MRI) studies were compared for assessment of response. Responses were categorized as follows: complete remission (CR) was defined as the resolution of all initially demonstrable tumor without the appearance of any new areas of disease, partial remission (PR) was defined as a decrease of $>$ 50% in tumor size, stable disease (SD) was defined as an increase or decrease of $<$ 25% in tumor size, and progressive disease (PD) was defined as an increase of $>$ 25% in tumor size or the appearance of new lesions. Patients who had no radiologic evidence of disease at the time of ASCT and who remained without disease post-ASCT were categorized as having a continuing complete response (CCR). Measurable disease was defined as any cerebral and/or spinal MRI and/or cerebrospinal fluid cytology specimen that was positive for evidence of disease. HDCT toxicity was evaluated according to the scoring system of Bearman et al.[16]

Statistical Analysis

Survival analyses were carried out using the Kaplan–Meier method.[17] Overall survival (OS) was assessed from the date of ASCT to death, with censoring on the date of the most recent contact. Event-free survival (EFS) was assessed from the date of ASCT to the date of disease progression/recurrence or death due to toxicity, with censoring on the date of the most recent contact.

RESULTS

Engraftment

Neutrophil engraftment and PLT engraftment were defined by an absolute neutrophil count (PMN) $>$ 500/μL for 3 consecutive days and a PLT count $>$ 50,000/μL for 3 consecutive days without transfusion, respectively. When all patients were considered, the median time to PMN engraftment was 10 days (range, 9–21 days), and the median time to PLT engraftment was 19.5 days (range, 7–149 days). One patient who died of transplantation-related causes (TRM) on Day +29 did not achieve PLT engraftment.

Toxicity

Pancytopenia requiring broad-spectrum antibiotics for fever and neutropenia and requiring packed red blood cell and PLT transfusions was noted in all patients. Mucositis occurred in all patients except one. Grade 2–3 mucositis was noted in 16 patients (57%). Six patients developed mild renal toxicity (Grade 1), two patients developed Grade 1 gastrointestinal toxicity, six patients developed Grade 1 liver toxicity, and one patient developed Grade 2 liver toxicity. TRM was observed in 1 patient (3.6%), who died of Candida pneumonia on Day +29 after ASCT.

Response to High-Dose Thiotepa and Etoposide

Three patients who were experiencing PR achieved CR after HDCT; these patients included 1 patient with a newly diagnosed high-risk brain tumor (glioblastoma multiforme) who was alive with no evidence of disease 127.1 months after ASCT and 2 patients with recurrent brain tumors (1 anaplastic oligodendroglioma in third recurrence, with disease progression at 4.3 months, in a patient who died of disease 10.3 months after ASCT and 1 medulloblastoma in first recurrence, with disease progression at 7.1 months, in a patient who died of disease 10.2 months after ASCT) (Table 2). Two patients with PD who underwent HDCT (1 patient with medulloblastoma in first recurrence and 1 patient who had an anaplastic ependymoma at diagnosis) had SD until 4.5 months and 4.9 months after ASCT, respectively, at which time disease progression was documented; these patients died of disease at 6.8 months and 17.1 months after ASCT, respectively.

One patient who had SD before HDCT (germ cell tumor at diagnosis) achieved a PR that was maintained for 4 months, at which time disease progression was documented. This patient died of disease 7.9 months after ASCT. One patient who had SD before HDCT (pineoblastoma in first recurrence) had PD detected 52 days after ASCT and died of disease 7.8 months after ASCT.

Ten patients had no measurable disease at the time of ASCT (2 patients with glioblastoma multiforme in first recurrence, 1 patient with PNET at diagnosis, 1 patient with PNET in first recurrence, 3 patients with medulloblastoma at diagnosis, 2 patients with medulloblastoma in first recurrence, and 1 patient with pineoblastoma at diagnosis), and 6 patients continued to experience CCR after myeloablative chemotherapy (1 patient with glioblastoma multiforme in first recurrence, 1 patient with PNET in first recurrence, 1 patient with pineoblastoma at diagnosis, 2 patients with medulloblastoma at diagnosis, and 1 patient with medulloblastoma in first recurrence) and are alive with no evidence of disease at a median of 44.5 months after ASCT (range, 7.3–94.9 months). Three patients (1 patient with medulloblastoma at diagnosis, 1 patient with PNET at diagnosis and 1 patient with medulloblastoma in first recurrence) developed recurrent disease 9.1 months, 9.6 months, and 29.8 months after ASCT, respectively. The patient who had medulloblastoma at diagnosis was alive with SD 12.6 months after ASCT. The disease status of 1 patient was not evaluable due to toxicity-related death 1 month after ASCT.

Ten patients, including 8 patients experiencing PR (2 patients with medulloblastoma in first recurrence, 1 patient with medulloblastoma in second recurrence, 1 patient with PNET at diagnosis, 1patient with anaplastic ependymoma in second recurrence, 1 patient with anaplastic astrocytoma at diagnosis, 1 patient with anaplastic astrocytoma in first recurrence, and 1 patient with glioblastoma multiforme at diagnosis) and 2 patients with SD (1 patient with anaplastic astrocytoma at diagnosis and 1 patient with medulloblastoma in first recurrence), had no measurable response to HDCT. Seven of these patients developed recurrent disease at a median of 7.3 months (range, 5.3–32 months) and died of disease at a median of 11.2 months (range, 8.7–59.4 months) after ASCT, whereas the remaining 3 patients are alive with SD (1 patient with anaplastic astrocytoma at diagnosis, 1 patient with glioblastoma multiforme at diagnosis, and 1 medulloblastoma in first recurrence) at a median of 23.4 months after ASCT.

OS and EFS

The 3-year-OS rate was 44.6% after a median follow-up of 13.9 months (range, 1.0–127.1 months) (Fig. 1). The 3-year-OS rates were 77.1% and 27.5% for patients who underwent ASCT while experiencing CR and patients with measurable disease at the time of ASCT, respectively ($P = 0.03$) (Fig. 2). There was no statistically significant difference in OS and EFS rates between patients who underwent ASCT at diagnosis and patients who underwent ASCT at the time of recurrence (Fig. 3). The overall 3-year EFS rate was 31% (50.6% and 19.6% for patients who underwent ASCT during CR and patients with measurable disease at the time of ASCT, respectively; $P = 0.02$) (Fig. 4). The median time to disease recurrence/progression was 6.2 months (range, 1.9–32.0 months).

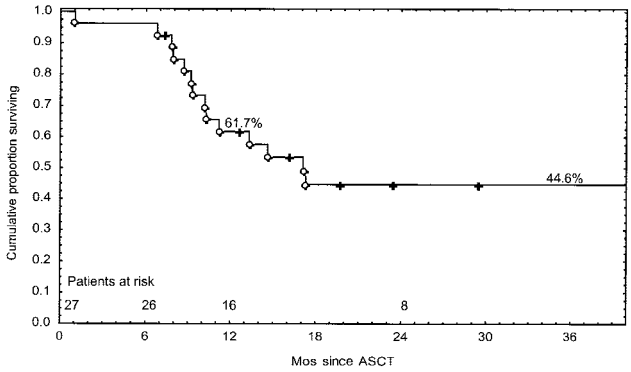

FIGURE 1. Overall survival curves (Kaplan–Meier) for children with brain tumors who underwent autologous stem cell transplantation (ASCT). Circles: dead; crosses: alive.

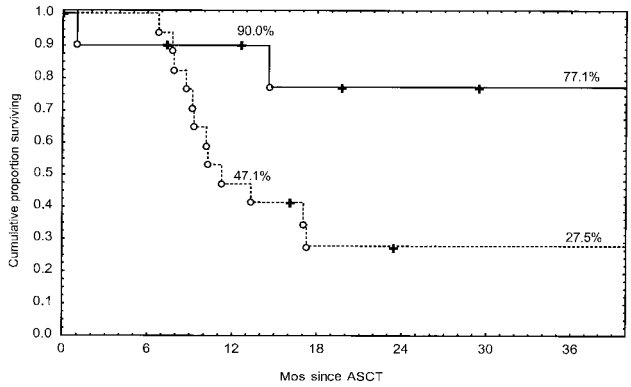

FIGURE 2. Overall survival curves (Kaplan–Meier) after autologous stem cell transplantation (ASCT) for patients experiencing complete remission (CR) compared with patients who had evidence of disease at the time of ASCT ($P = 0.03$). Solid line: CR; dashed line: with disease; circles: dead; crosses: alive.

DISCUSSION

The prognosis for children with standard-risk medulloblastoma or other PNETs has improved notably in recent years. Nonetheless, for many other children with newly diagnosed malignant brain tumors, especially in the absence of radical surgical resection, prognosis remains poor despite the use of irradiation and conventional chemotherapy. Recurrent and metastatic brain tumors continue to be associated with poor prognosis, and it should be noted that the therapeutic options for patients with such malignancies are limited by previous chemotherapy and RT.[18,19]

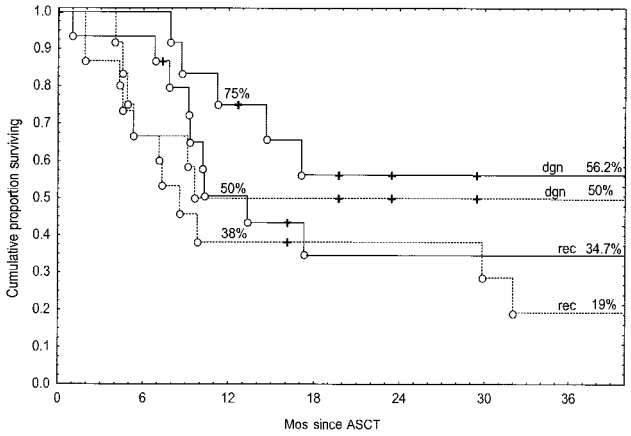

FIGURE 3. Kaplan–Meier overall survival (OS; solid lines) and event-free survival (EFS; dashed lines) curves for patients who underwent autologous stem cell transplantation (ASCT) and received high-dose chemotherapy either at the time of diagnosis (dgn) or at the time of disease recurrence (rec) ($P = 0.12$ and $P = 0.28$, respectively; not significant). Circles: dead (OS) or with recurrent/progressive disease (EFS); crosses: alive (OS) or alive without recurrent/progressive disease (EFS).

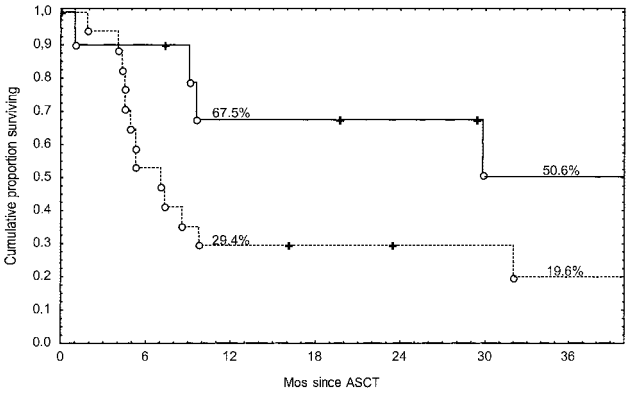

FIGURE 4. Kaplan–Meier event-free survival for patients who underwent autologous stem cell transplantation (ASCT) during complete remission (CR) compared with patients who had evidence of disease at the time of ASCT ($P = 0.02$). Solid line: CR; dashed line: with disease; circles: disease recurrence or progression; crosses: alive without disease recurrence or progression.

To increase brain distribution of antitumor drugs that do not cross the blood-brain barrier at conventional dosages and to achieve greater concentrations within tumors, the use of HDCT followed by autologous hemopoietic stem cell rescue has been proposed. An additional objective of HDCT is to delay or even eliminate the need for RT, which is one of the major causes of failure with respect to growth and development.

Alkylating agents, such as thiotepa, are the most appropriate drugs to use in this setting due to the steep linear logarithmic dose-response relation and activity against CNS tumors that they exhibit.[11] Etoposide has exhibited a good level of penetration into brain parenchyma as well,[12] and both of these agents have demonstrated good activity against recurrent brain tumors at conventional doses.[13–15]

Finlay et al.[20] treated 45 patients with high doses of etoposide (1500 mg/m^2) and thiotepa (900 mg/m^2) followed by autologous stem cell rescue; those investigators obtained a 23% CR + PR rate in heavily pretreated patients and a 16% toxicity-related death rate. Bouffet et al.[21] treated 22 patients with recurrent or newly diagnosed high-grade glioma and reported a 29% response rate (1 CR and 3 PRs) along with an OS rate no better than what had been achieved using conventional treatment.

Various thiotepa-based conditioning regimens involving busulfan or cyclophosphamide, with or without etoposide, have been reported elsewhere.[22–27] In the current study, we treated 27 patients with recurrent or newly diagnosed brain tumors. This group, which was heterogeneous with respect to histologic diagnosis and disease stage at study entry, had a 23% response rate to HDCT (Table 2).

HDCT was well tolerated: 1 patient (3.6%) died of Candida pneumonia on Day +29 after ASCT. Mucositis occurred in all but 1 patient, and severe mucositis (Grade 2–3) occurred in 16 patients (57%). Six patients developed mild renal toxicity (Grade 1), two patients developed Grade 1 gastrointestinal toxicity, six patients developed Grade 1 liver toxicity, and one patient developed Grade 2 liver toxicity. According to the study conducted by Heideman et al.,[24] no patient developed acute neurotoxicity due to HDCT. In contrast, some reports describe mild-to-severe adverse neurologic effects, including altered behavior with or without visual hallucinations, seizures, severe headache, intracranial hemorrhage, ataxia, hemiparesis, cranial nerve deficit, and herniation, which probably are related to the regimens used or to the glial swelling induced by tumor lysis.[13,22,28,29] In the current study, hematologic reconstitution was prompt and durable.

The observed 3-year OS rate was 44.6% (Fig. 1), and the 3-year EFS rate was 31%. There were statistically significant differences in OS and EFS for patients experiencing CR who underwent ASCT compared with patients who had measurable disease at the time of ASCT (Figs. 2, 4). No data on response rates according to tumor type could be obtained, due to the heterogeneity of the study group. Six months after HDCT, many patients (13 of 27) were able to attend school, although 1 patient (Patient 333) experienced problems with concentration and another (Patient 135) had difficulty with reading and writing. The results of the current study suggest that HDCT followed by ASCT

may be beneficial for patients who achieve CR before ASCT; however, for other patients, new strategies are required.

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