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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

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Background. The survival of children with glioblastoma multiforme (GBM) remains poor. In an effort to improve the cure rate of children with this disease, high-dose chemotherapy followed by autologous stem cell rescue (ASCR) has been evaluated. We report the regimen-related toxicity (RRT) and survival seen in 11 children with newly diagnosed GBM treated with high-dose chemotherapy on a Children's Cancer Group study (CCG-9922). ***Procedures.*** This phase II pilot study, intended to treat 30 patients, accrued 11 patients from July, 1993, to April, 1995. The pre-ASCR preparative regimen included BCNU 100 mg/m^2 every 12 hr for a total of six doses on days −8, −7, −6; thiotepa 300 mg/m^2/day on days −5, −4, −3; and etoposide 250 mg/m^2/day on days −5, −4, −3. All patients received delayed radiotherapy at a dose of 5,400 cGy to the primary site commencing on approximately day +42 after ASCR. ***Results.*** Five patients (45%) developed significant, nonfatal (grade III or IV) pulmonary and/or neurological toxicities. Three patients developed signs and/or symptoms of idiopathic interstitial pneumonitis. Eight patients (73%) have died, two (18%) of toxicity, and six (55%) of disease progression. Three patients (27%) achieved and remain in complete radiographic remission 2.9, 3.9, and 5.1 years from ASCR. One of these three, developed a lymphoblastic nonhodgkins lymphoma (NHL) 3.5 years post-ASCR. The survival rates for these 11 children at 1 year and 2 years are 73% ± 13% and 46% ± 14%, respectively. The progression-free survival rates at 1 year and at 2 years are 64% ± 14% and 46% ± 14%, respectively. ***Conclusions.*** We conclude that high-dose chemotherapeutic regimens followed by ASCR is a feasible treatment of childhood GBM. The BCNU-based preparative regimen utilized in this study was associated with prohibitive pulmonary toxicity. Med. Pediatr. Oncol. 33:83–87, 1999. © 1999 Wiley-Liss, Inc.

Key words: carmustine toxicity; glioblastoma multiforme; high-dose therapy; stem cell rescue

INTRODUCTION

Brain tumors account for approximately one-third of all childhood malignant neoplasms. Children with newly diagnosed glioblastoma multiforme (GBM) have little hope of achieving long-term disease-free survival despite modern, multimodality therapy [1,2]. To improve treatment results for children with these malignant brain tumors, protocols that include high-dose chemotherapy followed by autologous bone marrow rescue have been investigated [3]. The increased treatment intensity of protocols such as these, however, can be associated with significant, life-threatening toxicity [4]. In the present study, we report the toxicity encountered in 11 patients with GBM treated with high-dose BCNU, thiotepa, and etoposide, followed by autologous stem cell rescue and delayed, local radiation therapy in a Children's Cancer Group study (CCG-9922).

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PATIENTS AND METHODS

Patient Eligibility

Patients 5–18 years old with GBM of the brain were eligible. Histologic diagnosis was confirmed by a rapid-review process before study entry. Patients with neuraxis dissemination on radiographic evaluation were ineligible for this study. Patients were required to have adequate organ function and performance status >60 at study entry by Lansky or Karnofsky scales. All participating centers were required to have protocol review and approval by the individual institution's human rights committee. All patients and/or the patients' legally authorized guardians provided informed consent.

Patients

Eleven patients (seven males, four females) 5–18 years old (median age 12 years) were treated at participating institutions between 1993 and 1995. Ten patients had centrally reviewed diagnoses of GBM; in one, the consensus diagnosis was GBM arising in a background of pleomorphic xanthoastrocytoma (PXA).

Cytoreductive Chemotherapy

Patients were treated with a combination of BCNU (carmustine), thiotepa, and etoposide (VP-16). BCNU was administered at a dose of 100 mg/m^2 as a 1-hr infusion every 12 hr for a total of six doses on days −8, −7, −6. Patients not already receiving corticosteroids for control of tumor mass effect and/or cerebral edema were given dexamethasone 4 mg/m^2/day before the first dose of BCNU on day −8, which was continued for 3 consecutive days. Thiotepa, 300 mg/m^2/day, was given as a 3-hr continuous infusion on days −5, −4, −3. Etoposide, 250 mg/m^2/day, was administered as a 2.5-hr/continuous infusion daily on days −5, −4, −3 immediately after completion of the thiotepa infusion.

Stem Cell Harvest/Reinfusion

Autologous bone marrow (n = 9) or peripheral blood stem cells (n = 2) were harvested and cryopreserved according to the individual institution's protocol. The autologous stem cells were reinfused through a central venous line 72 hr after the last etoposide dose, on day 0. Six patients received granulocyte colony-stimulating factor (G-CSF) after stem cell infusion. One additional patient received G-CSF for peripheral blood stem cell mobilization.

Radiation Therapy

All patients received radiation therapy to the primary site as indicated by the original MRI and/or CT scan, plus a 2 cm margin beginning on approximately day +42 after stem cell rescue. One death occurred before radiation therapy was given, and one patient died on day +102 of nonradiation-related pulmonary toxicity while receiving radiation therapy. Thirty fractions of 180 cGy, once daily, were planned to a total dose of 5,400 cGy for primary tumor, with boost to a total dose of 5,940 cGy for residual tumor as demonstrated by poststem cell rescue CT and/or MRI. Eight of eleven patients were irradiated in 33 fractions; one received 5,220 cGy in 29 fractions.

Evaluation of Response

Patients were to be evaluated at study entry with head CT or MRI, then at days +21, +42, +100, and every 2 months until 1 year after autologous stem cell rescue (ASCR). Additional evaluations were to be made according to the individual institution's protocol. The imaging modality used initially was to be kept consistent after stem cell rescue for evaluation of response.

Statistical Considerations

This study was designed as a phase II pilot study intended to treat a total of 30 patients. The study design included safety monitoring, which called for accrual to be halted if 3 of the first 10 or 5 of the first 20 patients treated experienced either toxic death or grade IV pulmonary toxicity owing to biopsy-proven pulmonary fibrosis. Under these guidelines early stopping did occur after the first 10 patients; however, because of delayed reporting, 11 patients were enrolled prior to study closure. The CCG Operations Center coordinated actions to describe patient performance and compliance issues associated with treatment. The method of Kaplan-Meier [5] was used to estimate survival, and standard errors were calculated as suggested by Peto and coauthors [6]. Standard errors are reported exclusively in this manuscript.

RESULTS

Toxicity

The toxicities encountered in these 11 patients are shown in Table I. All patients experienced some degree of bone marrow suppression with associated neutropenia, with or without thrombocytopenia and anemia. Six patients had severe mucositis, and two had dermatitis attributed to thiotepa. Four patients experienced systolic and/or diastolic blood pressure instability during administration of the myeloablative chemotherapy. One patient had gram-positive sepsis associated with severe neutropenia on day +2.

Five of eleven patients (45%) developed severe, nonfatal (grade III or IV) organ-specific toxicity. Four patients had unacceptable pulmonary toxicity, one grade III (supplemental oxygen required) and three grade IV (two requiring assisted ventilation, one with severe dyspnea and hypoxia). Two patients experienced significant grade III neurotoxicity (one patient developed both grade IV

TABLE I. Toxicity

Toxicity	Number
Hematologic	
Grade III–IV	11
Mucositis	
Grade III	3
Grade IV	3
Dermatitis	
Grade III	2
Blood Pressure	
Grade IV	4
Sepsis	
Grade III	1
Pulmonary	
Grade III	1
Grade IV	3
Neurological	
Grade III	2
Interstitial pneumonitis	3
Second malignancy	1

pulmonary and grade III neurological toxicities); one had nonrecurring seizures following high-dose chemotherapy, and the second developed severe leukoencephalopathy characterized by intellectual decline 2 years after bone marrow stem cell rescue and local radiotherapy. Three patients had signs and/or symptoms consistent with idiopathic interstitial pneumonitis. One patient developed a lymphoblastic non-Hodgkin lymphoma (NHL) 3.5 years post-ASCR.

Two toxic deaths (18%) occurred within the first 110 days after stem cell infusion. One patient developed severe venoocclusive disease, which resulted in death on day +86; autopsy demonstrated characteristic fibrin deposition within central veins with outflow obstruction. The second patient developed multiple cardiorespiratory symptoms 2 months after hospital discharge and died on day +105. Autopsy demonstrated evidence of hyaline membranes, pulmonary hypertension, patchy interstitial fibrosis, and pulmonary emboli in association with a right atrial mural thrombus.

Engraftment

All patients had successful stem cell engraftment. Absolute neutrophil count $\geq$500/μl was reached in a median of 13 days (range 7–29 days). Transfusion-independent platelet count $\geq$20,000/μl was reached in a median of 21 days (range 1–32 days). One patient did not require platelet transfusion support, and data were not available for two patients. The average length of hospital stay for these patients was 45 days.

Surgery

Seven of nine patients (78%) evaluable for disease response had complete or >90% surgical resection of the primary tumor, resulting in <1.5 cm^3 residual tumor. (One patient required two surgical procedures to achieve gross total resection.) Three of these seven patients (43%) are alive and disease-free 2.9, 3.9, and 5.1 years after ASCR. Four of the seven (57%) have died of disease progression. Two of nine evaluable patients (22%) had subtotal tumor resections (51–90% resection) and died of disease progression. The impact of surgery on survival is detailed in Table II.

Survival

Three of eleven patients (27%) are alive and remain disease-free 2.9, 3.9, and 5.1 years after ASCR. Six of these eleven patients (55%) have died as a result of disease progression. There were two toxic deaths (18%). For these 11 patients, the survival rates at 1 year and 2 years are 73% ± 13% and 46% ± 14%, respectively. The progression-free survival rates at 1 year and 2 years are 64% ± 14% and 46% ± 14%, respectively (Fig. 1).

DISCUSSION

ASCR is an effective mechanism for dose escalation of efficacious chemotherapeutic agents. Significant nonhematologic toxicity, however, may still occur from individual chemotherapeutic agents or their combination. The most commonly occurring unacceptable toxicity encountered in our patient population was pulmonary, seen in four patients. BCNU given in both standard doses [7] and high doses [8,9] has been associated with pulmonary toxicity. Corticosteroids have been employed by several groups in an attempt to treat and/or prevent the pulmonary effects of BCNU [10]. The routine use of corticosteroid prophylaxis in this study, prior to high-dose BCNU, may have prevented additional fatal pulmonary toxicity. The next most common severe toxicity occurring in this patient cohort was neurotoxicity, seen in two patients. High-dose [11] and intracarotid [12] BCNU have previously been associated with the occurrence of leukoencephalopathy. Two patients died within the first 110 days after stem cell rescue. One death occurred as a result of venoocclusive disease [13]. The other death resulted from respiratory compromise on day +105 post-ASCR; the pulmonary findings at autopsy had many of the features seen in fatal BCNU pulmonary toxicity [14].

The use of high-dose chemotherapy with ASCR and delayed radiation therapy may be an effective treatment for children with GBM. Alternative preparative chemotherapy combinations may be associated with decreased nonhematologic toxicity. BCNU, an active chemotherapeutic agent in the treatment of malignant gliomas, might still be utilized by decreasing the maximal dose given or substituting another dose schedule. A previous study employed BCNU, 50 mg/m^2 every 8 hr for a total of 12 doses, and resulted in an identical cumulative dose of 600 mg/m^2 without significant pulmonary or hepatic toxicity

TABLE II. Surgery/Survival*

Postoperative residual tumor volume (cm^3) Surg/NRad	Current status—alive vs. dead (days post-ASCR)	Cause of death
≥1.5/≥3.0	Dead (day +334)	Disease progression
<1.5/≥3.0	Dead (day +86)	Venoocclusive disease of the liver
<1.5 (None)[a]/1.5–3 (none)[a]	Dead (day +775)	Disease progression
None/none	Alive, NED (3.9 years)	
None/<1.5	Dead (day +432)	Disease progression
None/none	Alive, NED (2.9 years)	
None/none	Dead (day +1,227)	Disease progression
<1.5/unk	Dead (day +594)	Disease progression
<1.5/<1.5	Alive, NED (5.1 years)	
None/<1.5	Dead (day +407)	Disease progression
<1.5/1.5–3	Dead (day +105)	Pulmonary toxicity

*NED, no evidence of disease; unk, unknown.
[a]Patient required two surgical procedures to achieve total resection (second surgery).

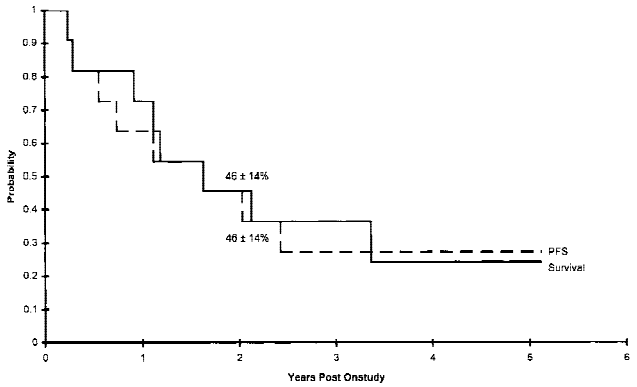

Fig. 1. Overall survival (solid line) and progression-free survival (dashed line).

[15]. Strategies that alter BCNU drug kinetics, resulting in an area under the curve (AUC) <600 (μg/ml) × 1 min, have been associated with decreased pulmonary toxicity [16]. Strategies such as these may be effective in decreasing BCNU regimen related toxicities.

Despite the prohibitive toxicity seen with the combination of high-dose BCNU, thiotepa, and etoposide, significant tumor response in this high-risk population was observed. Our results compare favorably to those of previous conventional chemotherapy trials in children with high-grade gliomas. In a prior conventional-dose study (CCG-945), 55 children were entered with reviewed diagnoses of GBM and had event-free survival rates of 38% ± 6%, 20% ± 5%, and 16% ± 5% at 1, 2, and 5 years, respectively. The extent of tumor resection has been shown to be an important outcome prognostic variable [1,17]. In CCG-945, patients with GBM having >90% resection vs. those with <90% resection had 1-year progression-free survival rates of 46% ± 9% and 30% ± 8%, respectively. The 5-year progression-free survival rates for this population were 25% ± 8% and 7% ± 5%, respectively [2]. Survival rates for children with bulky residual malignant gliomas after surgery, even when treated with aggressive chemotherapy and radiotherapy regimens, are no better than those seen with conventional dose therapy [18]. The limited number of patients entered in this study precludes a statistically meaningful evaluation of the impact of tumor resection on disease-free survival.

CONCLUSIONS

We conclude that our high-dose chemotherapy preparative regimen is a feasible treatment but is associated with significant nonhematologic toxicity, primarily BCNU-associated pulmonary toxicity. The use of alternative chemotherapeutic regimens is indicated for future studies.

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REFERENCES

1. Sposto R, Ertel IJ, Jenkin RDT, et al. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: Results of a randomized trial. A report from the Children Cancer Study Group. J Neurooncol 1989;7:165–177.
2. Finlay JL, Boyett JM, Yates AJ, et al. Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. J Clin Oncol 1995;13:112–123.
3. 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.
4. Klingemann HG, Shepherd JD, Reece, MJ, et al. Regimen-related acute toxicities: pathophysiology, risk factors, clinical evaluation and preventive strategies. Bone Marrow Transplant 1994;14:S14–S18.
5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
6. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585–612.
7. O'Driscoll BR, Hasleton PS, Taylor PM, et al. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. N Engl J Med 1990;323:378–382.
8. Wheeler C, Antin JH, Churchill WH, et al. Cyclophosphamide, carmustine, and etoposide with autologous bone marrow transplantation in refractory Hodgkin's disease and non-Hodgkin's lymphoma: A dose-finding study. J Clin Oncol 1990;8:648–656.
9. 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.
10. Mortimer JE, Hewlett JS, Bay J, et al. High-dose BCNU with autologous bone marrow rescue in the treatment of recurrent malignant gliomas. J Neurooncol 1983;1:269–273.
11. Burger PC, Kamenar E, Schold SC, et al. Encephalomyelopathy following high-dose BCNU therapy. Cancer 1981;48:1318–1327.
12. Kleinschmidt-DeMasters BK. Intracarotid BCNU leukoencephalopathy. Cancer 1986;57:1276–1280.
13. All-Nazir A, Garvin J, Kaplan L, et al. Hepatotoxicity in brain tumor patients undergoing myeloablative therapy with autologous bone marrow rescue. Med Pediatr Oncol 1995;25:307.
14. Mitsudo SM, Greenwald ES, Banerji B, et al. BCNU (1, 3-bis-(2-chloroethyl)-1-nitrosurea) lung drug-induced pulmonary changes. Cancer 1984;54:751–755.
15. Finlay JL, August C, Packer R, et al. High-dose multi-agent chemotherapy followed by bone marrow "rescue" for malignant astrocytomas of childhood and adolescence. J Neurooncol 1990;9:239–248.
16. Jones RB, Matthes S, Shpall EJ, et al. Acute lung injury following treatment with high-dose cyclophosphamide, cisplatin, and carmustine: Pharmacodynamic evaluation of carmustine. J Natl Cancer Inst 1993;85:640–647.
17. Ammirati M, Vick N, Liao Y, et al. Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas. Neurosurgery 1987;21:201–206.
18. Heideman RL, Douglass EC, Krance RA, et al. High-dose chemotherapy and autologous bone marrow rescue followed by interstitial and external-beam radiotherapy in newly diagnosed pediatric malignant gliomas. J Clin Oncol 1993;11:1458–1465.

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