High-Dose Chemotherapy With Autologous Stem Cell Rescue for the Treatment of Patients With Brain Tumors

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ABSTRACT

Despite the use of surgery, irradiation, and standard-dose chemotherapy, the majority of patients with malignant brain tumors succumb to their disease. Over the past 15 years, investigators from several institutions have used high-dose chemotherapy with autologous stem cell rescue (ASCR) to try to improve survival in these patients. One of the earliest studies was a 2-drug regimen using thiotepa and etoposide in patients with recurrent brain tumors (Finlay JL, et al. *J Clin Oncol* 14:2495–2503, 1996). The overall response rate was 23% in 35 patients with radiographically measurable disease who survived at least 28 days after autologous bone marrow rescue. Subsequent studies have used several different combinations of chemotherapy, including thiotepa/etoposide with and without carboplatin, thiotepa/busulfan, thiotepa/cyclophosphamide, and cyclophosphamide/melphalan. Responses have been seen in patients with a variety of recurrent brain tumors including medulloblastoma, primitive neuroectodermal tumor (PNET), high-grade glioma, and central nervous system (CNS) germ cell tumors. Because of these encouraging results, high-dose chemotherapy with ASCR has more recently been used in young children newly diagnosed with brain tumors to avoid radiation therapy with its associated long-term sequelae in very young children. Responses with durable event-free survival were seen in children with medulloblastoma, PNET, and ependymoma. This approach is presently being examined by cooperative groups. There are 2 studies using sequential courses of high-dose chemotherapy with ASCR in children newly diagnosed with brain tumors currently under way within the Children's Oncology Group (COG). Future studies include examining the use of high-dose chemotherapy with ASCR vs. standard-dose therapy in a randomized setting and incorporating new agents such as temozolomide as part of the cytoreductive regimen. In addition, the use of high-dose chemotherapy with ASCR may be combined with other approaches including immunomodulation and gene therapy.

INTRODUCTION

Brain tumors are the second most common malignancy in children and the most common solid tumor. They occur with a frequency of 24.5 per million children per year.[1] In adults, the incidence of CNS tumors per 100,000 population is 6.5 at 35 years, increasing to 70 by 70 years of age.[2] In the past 10 years, the survival rates for many malignancies, particularly pediatric tumors, have significantly improved. However, the survival of many children and adults with malignant brain tumors remains poor.

Over the past 15 years, investigators from several different institutions have used high-dose chemotherapy with autologous stem cell rescue in the treatment of patients with malignant brain tumors. The drugs considered to have the best tumoricidal activity against brain tumors are alkylating agents such as thiotepa, melphalan, BCNU, cyclophosphamide, and the platinum compounds. These drugs are particularly well suited for use at high doses with autologous stem cell support because of their steep linear-log dose-response curve. In addition, the principal dose-limiting toxicity for many of these drugs is bone marrow suppression. These drugs are cell-cycle nonspecific and therefore are not schedule dependent. Furthermore, the addition of nonalkylating agents, such as etoposide, synergistically enhances tumor kill.

One of the earliest studies using combination chemotherapy at high doses was a 2-drug regimen using thiotepa and etoposide with autologous bone marrow rescue in patients with recurrent brain tumors.[3] The study was piloted at the University of Wisconsin–Madison in 1986 and became a cooperative group study in the Children's Cancer Group in 1988. Of 35 patients with radiographically measurable disease who survived at least 28 days after autologous bone marrow rescue, the overall response rate (complete and partial responses) was 23%. Objective responses were seen in 4 of 14 assessable patients with high-grade glioma and in 2 of 6 patients with PNET.

In 1988, a 3-drug regimen using BCNU in addition to thiotepa and etoposide was initiated. Although responses were seen, the toxic mortality rate as a result of multiorgan system failure was unacceptably high.[4] In 1989, a third study using carboplatin with thiotepa and etoposide was opened at Memorial Sloan Kettering Cancer Center. There have been approximately 70 patients with brain tumors recurrent or refractory after irradiation and/or conventional-dose chemotherapy treated with this approach. Because of encouraging results seen in patients with recurrent brain tumors, this approach has more recently been used in infants and young children newly diagnosed with malignant brain tumors in an attempt to limit and, if possible, avoid the use of irradiation because of its long-term effects on the growth and development of young children.

Preliminary results of the 3-drug regimen (carboplatin, thiotepa, and etoposide) in patients with recurrent brain tumors as well as the use of high-dose

chemotherapy with ASCR in infants and young children newly diagnosed with malignant brain tumors are presented. In addition, results of studies using high-dose chemotherapy performed by other investigators are discussed.

MATERIALS AND METHODS

Recurrent Malignant Brain Tumors in Children and Young Adults: Study of Carboplatin, Thiotepa, and Etoposide

Patients with high-risk brain tumors that had either recurred or proven resistant to conventional chemotherapy and radiation therapy were considered eligible for this study. Patients had to have minimal residual disease before undergoing the high-dose chemotherapy. This could be achieved with either surgery or standard-dose chemotherapy.

Cytoreduction consisted of carboplatin as a 4-hour infusion on days –8, –7, and –6. The carboplatin was initially administered at a dose of 500 mg/m^2 per day; it was subsequently dosed using the Calvert formula with an area under the curve of 7 per day calculated from the urine creatinine clearance collected before each dose of carboplatin.[5,6] Thiotepa was administered at a dose of 300 mg/m^2 per day as a 3-hour infusion on days –5, –4, and –3. The etoposide was administered on the same days as the thiotepa at a dose of 250 mg/m^2 per day over 3 hours each day. Autologous stem cells, initially from bone marrow and more recently from peripheral blood, were reinfused on day 0.

Newly Diagnosed Malignant Brain Tumors in Children ≤6 Years of Age: Intensive Induction Chemotherapy Followed by Consolidation With High-Dose Carboplatin, Thiotepa, and Etoposide With Autologous Stem Cell Rescue

Eligibility criteria included all children <3 years of age newly diagnosed with a malignant brain tumor irrespective of residual disease or neuraxis dissemination. In addition, children 3 to 6 years of age with poor-risk tumors, including 1) all high-grade gliomas, brain-stem tumors, and supratentorial PNETs, 2) medulloblastomas with neuraxis dissemination, and 3) ependymomas with residual disease and/or neuraxis dissemination, were eligible.

Patients received 5 cycles of induction chemotherapy including cisplatin, vincristine (first 3 cycles only), cyclophosphamide, and etoposide. Patients who had responsive disease or no evidence of disease after completion of the induction phase proceeded with consolidation chemotherapy. The consolidation phase consisted of high-dose carboplatin, thiotepa, and etoposide with autologous stem cell rescue as described above for patients with recurrent brain tumors. Children who had no

evidence of disease before consolidation did not receive any irradiation. Children with unresectable disease before consolidation received involved-field irradiation approximately 6 weeks after the high-dose chemotherapy.

RESULTS

Recurrent Malignant Brain Tumors in Children and Young Adults: Study of Carboplatin, Thiotepa, and Etoposide

Seventy patients with malignant brain tumors that had recurred or were refractory to irradiation and/or standard-dose chemotherapy were treated with carboplatin, thiotepa, and etoposide at Memorial Sloan Kettering Cancer Center or New York University Medical Center between 1989 and 2000. Diagnoses included medulloblastoma (n = 17), other PNET (n = 13), malignant glioma (n = 25), germ cell tumor (n = 6), ependymoma (n = 5), and other (n = 4). Ages ranged from 1 to 45 years (median, 14 years). Thirty-seven patients were rescued with bone marrow, 30 received peripheral blood, and 3 received both bone marrow and peripheral blood stem cells. Carboplatin was dosed using the Calvert formula in 22 patients who received bone marrow and in all patients who received peripheral blood stem cells. Overall, the toxic mortality rate was 11 of 70 (16%); however, in the past 5 years, the toxic mortality rate has been 1 of 33 (3%).

The 4-year event-free survival for patients with recurrent malignant glioma rescued with bone marrow was 10%. For patients with medulloblastoma and supratentorial PNET, the 4-year event-free survival was 35%. Five of 6 patients with recurrent CNS germ cell tumors are alive without evidence of disease, 4, 12, 15, 36, and 45 months after stem cell rescue.

Newly Diagnosed Malignant Brain Tumors in Children <6 Years of Age: Intensive Induction Chemotherapy Followed by Consolidation With High-Dose Carboplatin, Thiotepa, and Etoposide With Autologous Stem Cell Rescue

Between 1992 and 1997, 75 children <6 years of age were enrolled in Head Start I. Diagnoses included medulloblastoma (n = 17), other PNETs (n = 21), ependymoma (n = 12), high-grade glioma and rhabdoid tumors (n = 19), and brain-stem tumors (n = 6).

The median overall survival for the entire cohort was 25 months, with an estimated 6-year overall survival of 32%. The median event-free survival for the entire cohort was 14 months, with an estimated 3-year event-free survival rate of 29%. Patients with completely resected tumors had a better survival than those with incomplete resection (4-year overall survival of 57% vs. 30% [P=.03] and 2-year

event-free survival of 54% vs. 25% [*P*=.06], respectively). Survival in patients <3 years of age was not inferior to that in older children (median overall survival of 39 vs. 32 months, respectively; *P*1=.4). Prognosis varied greatly between histologic subtypes. The estimated 4-year overall survival was 57% for medulloblastoma, 38% for PNET, 47% for ependymoma, and 16% for brain-stem tumors.

DISCUSSION

Most patients with recurrent malignant brain tumors have a dismal outcome with standard-dose therapy. Not too long ago, some investigators suggested that routine surveillance scans in patients who had completed therapy for medulloblastoma were not even warranted, since no patients with recurrent disease survived.[7] However, the use of autologous bone marrow and, more recently, peripheral blood stem cells has allowed the administration of much higher doses of chemotherapy. In addition, improvements in supportive care and the use of autologous peripheral blood stem cells have significantly decreased toxicity associated with this therapy.

As expected, the best responses in the 3-drug regimen (carboplatin, thiotepa, and etoposide) were seen in patients with brain tumors, which tend to be more chemosensitive. These included medulloblastoma, supratentorial PNET, and germ cell tumors. Other investigators have found similar results. Mahoney et al.[8] reported the results of a pilot study from the Pediatric Oncology Group using escalating doses of cyclophosphamide and fixed doses of melphalan with autologous bone marrow rescue for children with recurrent or progressive malignant brain tumors. Responses were seen in 7 of 18 evaluable patients including 4 patients with medulloblastoma, 2 with germinoma, and 1 with ependymoma. The French have also seen responses in children using the combination of thiotepa and busulfan. Kalifa et al.[9] reported a 75% response rate in previously treated patients with medulloblastoma/PNET. Bouffet et al.[10] recently presented the results of the French Pediatric Oncology Society using high-dose etoposide and thiotepa for patients with refractory and recurrent malignant intracranial germ cell tumors. Six of 11 evaluable patients had responses (3 CR and 3 PR).

The treatment of very young children with malignant brain tumors is particularly challenging because of the aggressive nature of their tumors and also because of the potential long-term sequelae associated with treating these patients at such a young age. Preliminary results of the Head Start therapy indicate that a significant number of children newly diagnosed with malignant brain tumors can achieve durable remissions without the use of radiotherapy or prolonged maintenance chemotherapy.[11] This is particularly true for children with medulloblastoma, supratentorial PNET, and ependymoma. Additional studies are needed to confirm these results. At the present time there are 2 studies underway in COG for

children newly diagnosed with malignant brain tumors involving high-dose chemotherapy with autologous stem cell rescue.

Unfortunately, there are still patients with malignant brain tumors for whom the use of high-dose chemotherapy has not yet proven to be effective. These include patients with recurrent ependymoma or recurrent brain stem tumors and patients newly diagnosed with malignant gliomas. For these patients, modifications in the present high-dose regimens as well as other approaches are needed. Future studies include the use of other cytoreductive agents including the new oral alkylating agent temozolomide as well as intravenous busulfan. In addition, other approaches including the use of antiangiogenesis agents as well as immunomodulation and gene therapy, with and without high-dose chemotherapy, are being explored.

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