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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

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Abstract

Purpose—Children and adolescents with malignant astrocytomas recurring after initial treatment have a dismal prognosis, with only rare patients surviving one year beyond recurrence. The purpose of this study was to attempt to improve their survival.

Methods—Twenty-seven children and adolescents with malignant astrocytomas (17 glioblastoma multiforme and 10 anaplastic astrocytoma) following initial tumor progression, received myeloablative chemotherapy followed by autologous marrow rescue with one of three thiotepa and etoposide-based chemotherapy regimens, administered alone (n=11) or combined with carmustine (n=5) or carboplatin (n=11). Time to progression and death following myeloablative chemotherapy for these patients was compared non-randomly with outcome of a contemporaneously treated cohort of similar patients who received only conventional chemotherapy following initial tumor progression. The two cohorts were compared for age, histology, prior therapies, extent of surgical resection at progression and time from initial diagnosis to progression.

Results—Five of 27 children (two with glioblastoma multiforme and three with anaplastic astrocytoma) survive event-free from 8.3 to 13.3 years (median of 11.1 years) following myeloablative chemotherapy. Of 56 children with recurrent malignant astrocytoma who received

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conventional chemotherapy following initial progression, no patient survives. Differences in distributions of survival were not significant when stratified by surgical debulking (p=0.39). However, for patients who were surgically debulked, the survival distributions are significantly different (p=0.017).

Conclusions—Myeloablative chemotherapy with autologous marrow rescue can produce durable remissions in children and young adults with recurrent malignant gliomas, in the setting of minimal residual tumor burden achieved surgically.

Keywords

Myeloablative chemotherapy; autologous bone marrow rescue; recurrent malignant astrocytoma

INTRODUCTION

The prognosis for children and adolescents with newly diagnosed malignant astrocytomas is poor despite surgical extirpation, irradiation and conventional chemotherapy. Patients with glioblastoma multiforme (GBM) usually develop disease progression within 12 months of diagnosis and die shortly thereafter [1]. The time to progression as well as the proportion of patients who survive is somewhat more favorable for patients with anaplastic astrocytoma (AA) [2]. In an effort to improve the outcome for patients with recurrent malignant astrocytomas, myeloablative chemotherapy with autologous bone marrow rescue (ABMR) has been evaluated in several studies, the majority using carmustine alone, with generally disappointing results [3,4,5,6]. Children with recurrent brain tumors, including malignant astrocytomas, have been shown to radiographically respond to myeloablative regimens of thioTEPA and etoposide with or without the addition of carmustine, followed by marrow rescue [7,8,9,10]. We now report upon our initial cohort of 27 consecutive patients less than 21 years of age with malignant astrocytomas treated with myeloablative chemotherapy following initial tumor progression. Within an attempt to put these results into context of outcome in similar patients, the survival of patients in this review was non-randomly compared to the outcome of patients enrolled on a contemporaneous Children's Cancer Group (CCG) malignant glioma study (CCG-945), who were treated with “conventional” chemotherapy at relapse [1].

METHODS

Myeloablative Chemotherapy Regimens

Twenty-seven patients aged 5 months - 21 years (median of 10.3 years) at date of treatment, received marrow rescue following myeloablative chemotherapy with one of three regimens: thioTEPA (900 mg/m^2 over three days) with etoposide (750 or 1500 mg/m^2 over three days) either alone (n=11), or preceded by either carmustine (600 mg/m^2 over 3 days), (n=5), or carboplatin (1500 mg/m^2 over three days or dosed daily by the Calvert formula [11] with an area under the curve of 7 mg/ml/min/day) (n=11). Previously cryopreserved (n=26) or refrigerated (n=1) autologous bone marrow was infused approximately 72 hours following completion of the chemotherapy. A single patient received irradiation following treatment prior to documented tumor progression.

Conventional Chemotherapy Strategies

In the comparison group, of all patients less than 21 years of age enrolled on CCG-945 who relapsed, 60 patients received conventional chemotherapy regimens at disease progression, including: ifosfamide-containing regimens plus etoposide (n=17), etoposide plus mannitol (n=13), the “8-in-1" regimen (n=12), thioTEPA (n=7), carboplatin-containing regimens

(n=9), nitrosourea-containing regimens (n=2), 5-fluorouracil/leucovorin (n=2), beta-interferon (n=1), and unspecified regimens (n=7).

Patient Characteristics

The characteristics of the patients undergoing either myeloablative or conventional chemotherapy following initial tumor progression are summarized in Tables I, II and III. All patients had radiographic documentation of recurrence. Pathological documentation of recurrence was not mandated, but was undertaken in 26 of 27 (96%) patients undergoing myeloablative chemotherapy; all patients had recurrent tumor confirmed as malignant astrocytoma, centrally reviewed by one of three neuropathologists in 26 of 27 cases. Eligibility for myeloablative chemotherapy required documentation of adequate organ function, as well as adequate hematological parameters.

A significantly smaller proportion of the CCG-945 study patients had pathological confirmation of relapse. Four of the 60 patients on the CCG-945 study who received conventional chemotherapy at initial progression had pathological confirmation of low-grade glioma at the time of progression, and have been excluded from this present analysis. Ten of the 27 patients were included in prior preliminary publications of toxicity and response [7,8,9,10].

Response Criteria

Radiographic responses to treatment were analyzed between four and eight weeks following myeloablative chemotherapy. A complete response (CR) indicated disappearance of all measurable disease on magnetic resonance or computed tomography imaging (with and without contrast); a partial response (PR), reduction of at least 50% in tumor size (assessed as the product of the two longest tumor diameters); a minor response (MR), reduction of between 25% and 50% in tumor size; stable disease (SD), less than 25% decrease in tumor size and less than 25% increase in tumor size; progressive disease (PD), greater than 25% increase in tumor size. The designation ‘continuing complete response (CCR)’ indicated that no evidence of residual disease was identified radiographically at the time of study entry, with no evidence of disease progression at the time of follow-up evaluation.

Biostatistics

Survival distributions were estimated by the Kaplan-Meier method and tests for equality by stratified Mantel-Haenszel or stratified exact log rank statistics [12,13]. Time at risk for both survival and event-free survival (EFS) was calculated from the date of recurrence for the conventional chemotherapy group and the date of myeloablative chemotherapy for the ABMR group. In estimating event -free survival (EFS), toxic deaths, tumor progression or death from other causes, whichever developed first, were identified as events. Tumor recurrence or progression was determined radiographically. Cox Proportional Hazards models [14] were used to estimate the hazard ratio and associated 95% confidence intervals. The hazard ratio reported is the risk of death of the conventional chemotherapy group relative to the myeloablative chemotherapy patients. The data in this report reflect follow-up information updated in 2003. The significance levels (based on Fisher's exact or Wilcoxon rank-sum tests) in Tables I, II and III are not adjusted for multiple comparisons and are provided for descriptive purposes. All p-values are for two-sided tests. While this comparison suffers from the many known weaknesses of non-random historical controls and the potential biases of getting patients to transplantation, we have conservatively identified a control group for assessing outcome. Only those patients with initially confirmed malignant astrocytoma who received conventional chemotherapy following progression on CCG-945 were included.

Informed Consent for Myeloablative Chemotherapy Regimens

Informed consent was obtained for all patients prior to undergoing myeloablative chemotherapy. The options of conventional chemotherapy, surgery, irradiation, or no further therapy were particularly emphasized. Informed consent was obtained for patients treated on CCG-945 according to institutional guidelines.

RESULTS

Response to Myeloablative Chemotherapy

Five of the treated patients had no radiographically evident residual tumor, and are therefore not evaluable for assessment of response to therapy; however, they are evaluable for assessment of toxicity and tumor progression. Out of these five patients, one patient demonstrated PD 15 days following marrow rescue and four patients are CCRs. One patient is inevaluable for tumor response, having received focal re-irradiation in the immediate post-treatment period. Of the 21 patients with radiographically evident residual tumor prior to starting myeloablative chemotherapy, there were four CRs (19%; 95% CI (0.06 to 0.37)), one PR and 10 SD. One patient with residual disease demonstrated radiographic tumor progression 25 days following autologous marrow transplant. The remaining five patients with residual tumor died of toxicity. The numbers of patients with responses were evenly distributed between the three regimens.

Toxicity of Myeloablative Chemotherapy

Overall toxic mortality of the regimens was 19% (five of 27 patients; 95% CI (0.06–0.38)), toxic deaths occurring between one and 68 days (median of 17 days) following marrow rescue. A single toxic death (9%) occurred amongst the 11 patients treated with the thioTEPA/etoposide regimen. There were two toxic deaths amongst the five patients treated with the carmustine-containing regimen, due to acute renal failure with or without neurological deterioration. There were two toxic deaths (9%) amongst 11 patients treated with the carboplatin-containing regimen. The grade III/IV acute toxicity profile is similar to the previously published results on a partial cohort of patients by Gururangan et al [9]. Of the patients surviving beyond the first two months following treatment, there has been no patient with significant organ function sequelae, no patients lost their hematopoietic grafts post-treatment or developed a second malignancy. Occasional patients previously treated either with cisplatin or irradiation to the auditory apparatus developed mild to moderate sensorineural hearing loss.

Comparison of Characteristics of Patients Receiving Myeloablative and Conventional Chemotherapy

Table I shows the two groups to have similar distributions of ages at initial diagnosis, of patients less than three years of age at initial diagnosis, of sex ratios, and of patients with primary spinal cord primary tumors. There is a higher frequency of GBM in the myeloablative treated group than in the conventionally treated group; however, this did not reach statistical significance (p=0.25). The conventionally treated group had a higher prior exposure to chemotherapy, specifically to nitrosoureas. Three patients undergoing myeloablative chemotherapy had received prior irradiation without chemotherapy as compared to none of the patients in the “conventional” chemotherapy group (Table II). The two groups have similar distributions of age and of time from diagnosis to initial progression. Sixteen percent of patients receiving conventional treatment at initial progression underwent irradiation in addition to chemotherapy, while three patients receiving myeloablative chemotherapy at initial progression underwent irradiation (two prior to and one following treatment). The percentage of patients undergoing surgical debulking

was significantly different between the two treatment groups (p=0.003); 41% underwent debulking in the ABMR group compared with 11% in the conventional chemotherapy group (Table III).

Event-free Survival and Survival

Of the 27 patients who received myeloablative chemotherapy, five died of toxicity and 17 developed disease progression. The Kaplan-Meier estimates of event-free survival (EFS) and overall survival (OS) for the myeloablative chemotherapy with ABMR and "conventional" chemotherapy control groups are shown in Figure 1. Based on these data, all subsequent comparisons of the two treatment groups are based on the primary outcome of survival. Conclusions would remain the same if EFS were the outcome of interest (data not shown). Differences in distributions of survival are significant at the p=0.010 levels when stratified for pathology (Fig. 2). For patients with GBM the survival distributions are not significantly different [p=0.16, hazard ratio=1.6 (95% confidence interval .83 – 3.1)], with four-year estimates of 12±6% with myeloablative chemotherapy and 0% with conventional chemotherapy. For patients with AA the survival distributions are significantly different [p=0.017, hazard ratio=2.7 (95% confidence interval 1.1 – 6.6)], with four-year estimates of 40±14% with myeloablative chemotherapy and 7±4% with conventional chemotherapy. Differences in distributions of survival are not significant when stratified by surgical debulking (p=0.39). However for patients who were surgically debulked, the survival distributions are significantly different (p=0.017), with four-year estimates of 46±14% with myeloablative chemotherapy and 0% with conventional chemotherapy. Two of the five survivors were infants and three survivors are more than three years of age.

Variables predictive of Survival Following Myeloablative Chemotherapy

Eleven patients survived longer than one year and five remain alive at a median of 11.1 years after transplant (range: 8.3 – 13.3 years). The single characteristic that most strongly distinguishes the surviving patients is minimal residual disease (MRD) status, as defined by less than 3 cm tumor diameter at the time of myeloablative chemotherapy (Fig. 3, unadjusted p=0.003). For patients with non-bulky tumor, the survival at four years is 46±14% *versus* 6±4% for those patients with bulky disease. Other potential prognostic factors were evaluated univariately and after stratifying for MRD. Patient age at diagnosis (p=0.46), age under three years at relapse (p=0.59), pathology (p=0.29), prior nitrosourea exposure (p=0.97), platinum exposure (p=0.20) and exposure to irradiation prior to undergoing myeloablative chemotherapy (p=0.11) did not impact upon survival following myeloablative chemotherapy.

DISCUSSION

Several therapeutic trials, in both adults and children with recurrent malignant astrocytoma, have demonstrated that the prognosis for such patients, irrespective of the therapeutic modality under evaluation, remains dismal [1–8,15]. Agents such as carboplatin, cisplatin, ifosfamide, thiotepa, idarubicin, etoposide, topotecan, irinotecan and temozolomide have shown minimal activity with ≤10% of children demonstrating objective responses [16–24]. Although combination chemotherapy has been slightly more effective in treating recurrent malignant gliomas in children, few studies if any have shown long-term disease control [25,26,27]. Because of this failure of "conventional" chemotherapy, the ability of myeloablative chemotherapy in both adults and children has been explored with variable results.

Several studies dating back to the early 1980s, using high-dose carmustine alone followed by marrow rescue, failed to impact favorably upon survival, both in recurrent and newly-

diagnosed patients with malignant astrocytoma [3,4,5,6]. The myeloablative regimen used in this study has evolved in a stepwise fashion. In 1986, a pilot study of thioTEPA and etoposide in recurrent malignant brain tumors was initiated. Subsequently, carmustine was added at a dose of 600 mg/m^2 and resulted in a 38% toxic mortality in recurrent patients [10]. Due to this toxicity, a third regimen was developed, substituting carboplatin for carmustine [16,28,29]. With the implementation of the Calvert formula for basing carboplatin dosage on renal and non-renal clearance rather than body surface area or body weight, the use of hematopoietic growth factors in the post-treatment period, interventional means to prevent and ameliorate veno-occlusive disease, the recognition of importance of early harvesting of bone marrow prior to exposure of myelotoxic chemotherapy, and the replacement of bone marrow by leukapheresed peripheral blood stem cells, there has been a seeming decrease in toxic mortality in the carboplatin-containing regimen [11,30,31,32]. The number of responses was similar with each regimen. However, a definitive conclusion about the efficacy of each regimen cannot be drawn due to the small number of patients.

Even with these advances, in this series there were five toxic deaths, including three in 22 patients treated with non-carmustine-containing regimens. However, the major positive finding of this study is that in comparison to other published studies utilizing either conventional or higher-dose chemotherapy regimens, five of 27 children have experienced long term event-free survival, at a median of 11 years from progression, including two with GBM. Only one of the long-term survivors also received additional radiotherapy.

Overall patients treated with non-myeloablative retrieval therapies, including 16% who received additional radiotherapy had a survival rate of 23±5% at one year, as compared to 41±9% for those treated with high-dose chemotherapy and ABMR. These results compare favorably to a group of contemporarily treated patients entered on the CCG randomized clinical trial performed between 1985 and 1992. Comparing the two groups of patients is difficult and there are likely inherent biases in patient selection that cannot be overcome, even with careful retrospective analysis. Patients with GBM were, if anything, more likely to be referred for myeloablative therapy than those with anaplastic tumors. The apparent major difference in the two groups is that those undergoing myeloablative chemotherapy were more likely to undergo a major surgical debulking than those who went on to receive “conventional” chemotherapy with or without further radiotherapy. Despite all these issues, the fact remains that over 20% of children with malignant astrocytoma undergoing myeloablative therapy at the time of recurrence are long-term survivors compared to none who failed initial treatment and were subsequently treated with “conventional” chemotherapeutic strategies.

It is difficult to ascertain the relative contributions of myeloablative chemotherapy and surgical re-resection towards the salvage rate observed in this study. Re-resection of malignant glioma alone at recurrence, while of some palliative benefit, has never been associated with improved cure rate. Future studies should seek to determine the potential role of focused re-irradiation as an adjunct to myeloablative chemotherapy, particularly in patients unable to achieve minimal tumor burden surgically. Additionally, the effectiveness of single *versus* tandem sequential myeloablative chemotherapy courses can be evaluated. . This current report demonstrates that with aggressive therapy some children and adolescents can have prolonged survival following relapsed malignant astrocytoma, and a nihilistic approach in such patients will retard progress. If confirmed in prospective clinical trials, this approach could then be further investigated for the treatment of children with newly diagnosed malignant astrocytoma as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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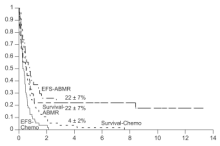

Fig. 1.

Event-free survival and survival distributions for patients with recurrent malignant astrocytomas treated with either conventional chemotherapy (Chemo, n=56) or myeloablative chemotherapy with autologous bone marrow rescue (ABMR, n=27). Chemo *versus* ABMR unstratified comparison of event-free survival: p=0.014 [*hazard ratio=1.9 (95% confidence interval 1.1–3.2)*]. Chemo *versus* ABMR unstratified comparison of survival: p=0.018 [*hazard ratio=1.9 (95% confidence interval 1.1–3.1)*]

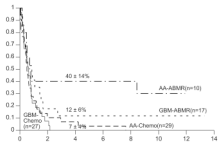

Fig. 2.

Survival distributions by histology for patients with recurrent malignant astrocytomas treated with either conventional chemotherapy (Chemo) or with myeloablative chemotherapy with autologous bone marrow rescue (ABMR). Chemo *versus* ABMR comparison stratified by histology: p=0.010.

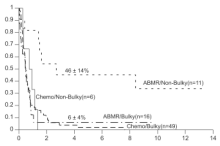

Fig. 3.

Survival distributions by surgical debulking for patients with recurrent malignant astrocytomas treated with either conventional chemotherapy (Chemo) or with myeloablative chemotherapy with autologous bone marrow rescue (ABMR). Chemo *versus* ABMR comparison stratified by surgical debulking: p=0.39. Chemo/Non-Bulky *versus* ABMR/Non-Bulky unstratified exact comparison: p=.017 [*hazard ratio=9.1 (95% confidence interval 1.7–47.2)*].

Table 1

Patient characteristics at initial diagnosis

	Standard-dose Chemotherapy	Myeloablative Chemotherapy	P-value
Numbers of patients	56	27	
Characteristics			
Median age in years (range)	11.1 (0.1–19.3)	8.5 (0.2–20.9)	.25
Age ≤ 3 years	7 (12%)	6 (22%)	.33
Females	27 (48%)	12 (44%)	.82
Spinal Cord Primaries	2 (4%)	3 (8%)	>0.3
Neuropathology			0.25
Glioblastoma Multiforme	27 (48%)	17 (63%)	
Anaplastic Astrocytoma	29 (52%)	10 (37%)	

Table 2

Initial treatment received by the patients in both groups

	Standard-dose Chemotherapy	Myeloablative Chemotherapy	P-value
Numbers of patients	56	27	
Treatment modality			
Chemotherapy	56 (100%)	22 (81%)	0.003
Platinum compounds	30 (53%)	17 (63%)	0.48
Nitrosoureas	56 (100%)	20 (74%)	0.0002
Procarbazine	30 (53%)	11 (41%)	0.35
Cyclophosphamide	0 (0%)	3 (11%)	0.032
Etoposide	0 (0%)	5 (18%)	0.003
Irradiation Only	0 (0%)	3 (11%)	0.032

Table 3

Patient characteristics at initial progression

	Standard-dose Chemotherapy	Myeloablative Chemotherapy	
Numbers of patients	56	27	
Characteristics			P-value
Median age in years (range)	12.0 (0.4–22.1)	10.3 (0.4–21.1)	.35
Interval from diagnosis to progression in months (range)	9.7 (0.7–65.1)	6.8 (1.1–65.2)	.77
Irradiation/re-irradiation on progression	9 (16%)	*1 (4%)	0.16
Standard-dose chemotherapy	56 (100%)	*2 (8%)	<0.0001
Surgical debulking of tumor			.003
Debulked**	6 (11%)	11 (41%)	
Non-debulked***	49	16	

* Prior to undergoing myeloablative chemotherapy;

** Extent of resection was not available for one patient;

*** <3 cm tumor diameter for the myeloablative and gross total resection or at least 90% (≥90%) resection for the chemo control group.