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Carboplatin and Etoposide With Hyperfractionated Radiotherapy in Children With Newly Diagnosed Diffuse Pontine Gliomas: A Phase I/II Study

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Background. Diffuse pontine gliomas remain one of the most lethal of pediatric malignancies despite the use of increasingly intensive therapies. We delivered intensive chemotherapy during and following 70.2 Gy of hyperfractionated radiation therapy in an attempt to improve survival.

Procedure. Nine consecutive children with diffuse pontine gliomas were treated on this single arm study. Carboplatin, given in combination with fixed dose etoposide, was escalated in successive cohorts to determine its maximum tolerated systemic exposure (AUC). Outcome was coded based on imaging characteristics and clinical status.

Results. Eight of the nine children on this study died of their disease at a median of 44 weeks, essentially the same survival as those treated on a previous Pediatric Oncology Group study using hyperfractionated radiation therapy alone. Toxicity was almost exclusively hematologic and not associated with significant morbidity.

Conclusions. The use of concurrent carboplatin and etoposide with hyperfractionated radiation therapy did not appear to improve the survival in this group of children with diffuse pontine gliomas. The toxicity of this chemotherapy during radiation therapy was primarily hematologic and well tolerated. New approaches to the treatment of these tumors need to be investigated. Med. Pediatr. Oncol. 30:28–33, 1998.

Key words: brainstem; glioma; brain neoplasms; antineoplastic agents; child

INTRODUCTION

Diffuse pontine gliomas represent 5–10% of brain tumors in children and are among the most refractory to therapy. The outcome of these patients with standard treatment remains poor; the use of conventionally fractionated radiation therapy, with or without chemotherapy, is associated with a median survival of less than one year and a 2-year survival rate of no more than 10–20% [1,2]. Attempts to improve survival have focused largely on the use of increasing doses of radiation therapy employing hyperfractionated schedules [3–9]. Serial studies over the past decade have suggested that hyperfractionated radiation therapy in the range of 70.2–72 Gy may be associated with a marginal improvement in imaging response and survival [7–10]. However, dose escalation beyond 70–72 Gy has shown no benefit in response or survival [8–12].

Even though adjuvant chemotherapy has not been shown to improve survival in this tumor [2], limited responsiveness to such therapy has been demonstrated in some phase II studies [13,14]. Building on these observations, we investigated the simultaneous use of 70.2 Gy hyperfractionated radiation therapy and a carboplatin/etoposide regimen in an attempt to improve response and overall survival. Carboplatin was chosen on the basis of phase II data, indicating prolonged disease stabilization and progression-free intervals in up to 25% of patients with recurrent brainstem tumors [13,15–19]. Further, the observation that intra-arterial platinum compounds potentially improved the objective response rate in adult malignant gliomas suggested that the use of this drug in higher than conventional doses might also be useful in brainstem gliomas, which are often histologically identified as malignant gliomas [20–23]. These factors, together with the ability to dose escalate systemically administered carboplatin using hematologic growth factor

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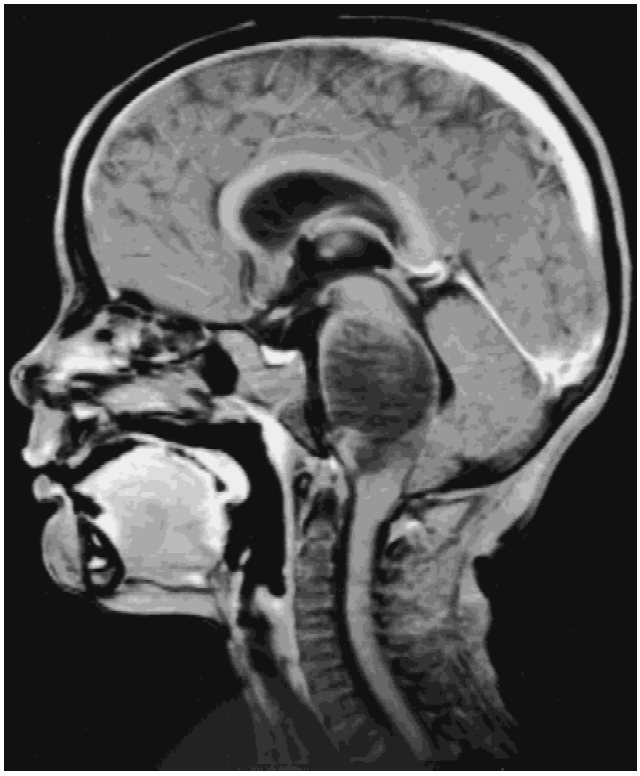

Fig. 1. A midline, sagittal, T1-weighted MRI of the brain following the intravenous injection of gadolinium contrast. This scan illustrates a typical, diffuse, nonenhancing pontine gliomas as seen in one of the patients in this series

support, led us to consider carboplatin as a rational drug to investigate in the setting of newly diagnosed brainstem tumors. The rationale for using concomitant etoposide was based on in vitro as well as clinical evidence of its anti-tumor synergy with platinating agents [24–26].

Here we present the results of higher than conventional dose carboplatin with etoposide given during and after hyperfractionated radiation therapy to a group of newly diagnosed diffuse pontine gliomas. Overall survival was compared with that noted following similar dose hyperfractionated radiation therapy alone.

MATERIALS AND METHODS

Patient Characteristics and Eligibility

Only patients with diffusely infiltrating, intrinsic pontine gliomas were eligible for this protocol; cystic, dorsally exophytic, or focal pontine lesions were ineligible as were brainstem lesions centered outside the pons. (Fig. 1) The eligibility criteria included: MRI evidence of a diffuse pontine lesion occupying $\geqslant$75% of the pons, symptoms of less than 6 months duration and at least two of the following three clinical signs: cranial nerve deficit(s), long tract signs, and/or cerebellar dysfunction.

Between November 1992 and January 1994, nine consecutive and newly diagnosed patients (3 male, 6 female) with diffuse pontine gliomas were treated on this study. The median age at diagnosis was 6.9 years (range: 4.2–12.8 years). The median duration of symptoms prior to diagnosis was 7 weeks (range: 1–15 weeks). At diagnosis, 9/9 patients had cranial nerve palsy(s), 8/9 had cerebellar signs, and 7/9 had long tract signs. No patient had a biopsy. Informed consent was obtained from each patient and/or parent/guardian prior to therapy. This protocol was approved by the Institutional Review Board at St. Jude Children's Research Hospital.

Therapy

Chemotherapy began coincident with radiation therapy and consisted of carboplatin on day 1 and etoposide (120 mg/m^2/day) on days 1–3. The carboplatin dose was individually determined to achieve a predetermined area under the plasma concentration × time curve (AUC) based on the use of a modified Calvert formula [27,28]. The carboplatin AUC was escalated by 2 mg/mL × min from 8 to 12 mg/mL × min in successive cohorts of three patients each based on tolerance, using conventional phase I criteria [29]. Cycles were repeated every 21 days for up to ten cycles. No intrapatient dose escalation was attempted. Granulocyte-colony stimulating factor (G-CSF) was given subcutaneously for 10–14 days starting 24 hours after the last dose of etoposide and was given for at least 10 days. G-CSF was stopped when the absolute neutrophil count (ANC) was >5,000/mm^3 or 14 days were administered, whichever came first.

Hyperfractionated radiation therapy to a dose of 70.2 Gy was delivered over 6 weeks using twice daily 117 cGy fractions with a minimum 6-hour interfraction interval. The treatment volume was based upon the tumor volume as determined by both T1 and T2 MRI sequences plus a 2-cm dosimetric margin.

Toxicity

Systemic toxicity was defined using National Cancer Institute common toxicity criteria. Hematologic toxicity was separately defined as follows: grade 4 neutropenia, an ANC <500/mm^3 for 6 or more consecutive days and grade 4 thrombocytopenia, a platelet count <50,000/mm^3 for 6 or more consecutive days. For patients with grade 4 hematologic toxicity, the carboplatin AUC was reduced by 20% in subsequent cycles. If hematologic toxicity persisted despite adjustment of the carboplatin dose, days 2 and 3 of etoposide were omitted in later cycles. Subsequent grade 4 toxicity mandated stopping therapy. The maximum tolerated dose (MTD) was defined on the basis of tolerance to the first two courses of therapy. The MTD was the dosage level immediately below that at which two patients of a cohort of 3–6 patients experienced grade 4 toxicity as defined above.

Response

Response was evaluated by clinical and MRI criteria after the completion of radiation therapy and two cycles

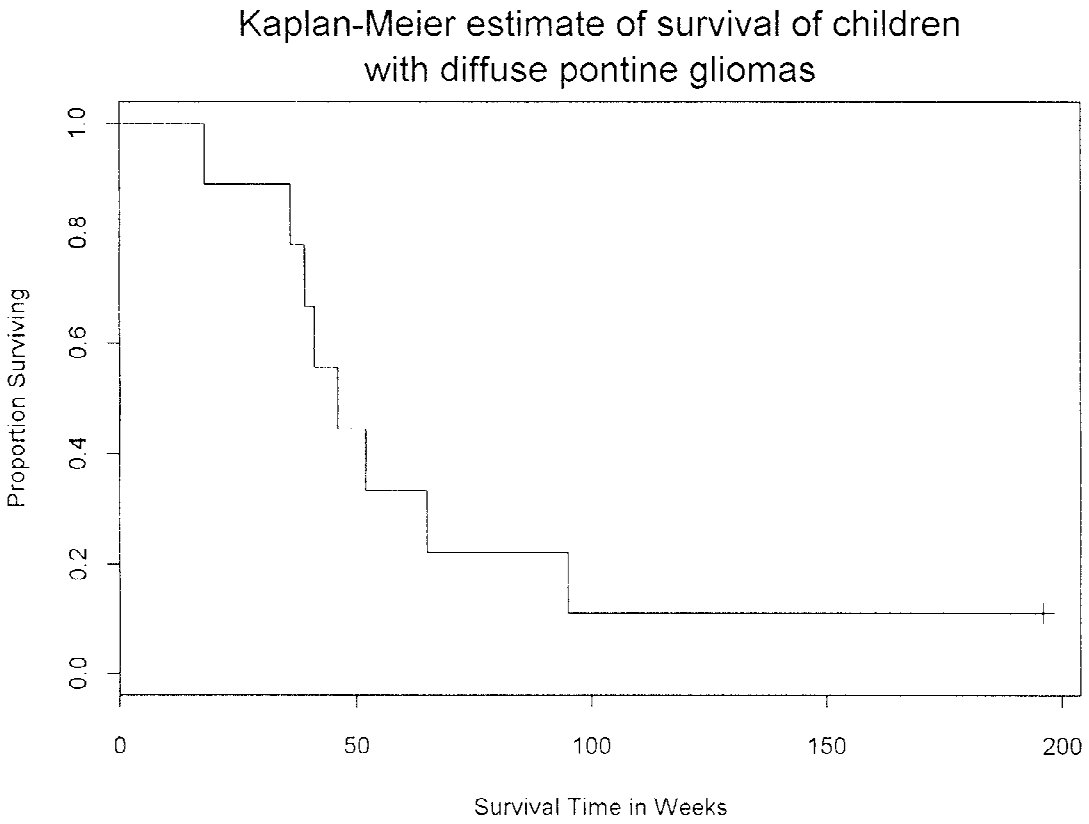

Fig. 2. Survival curve of children with diffuse pontine gliomas.

of chemotherapy. Tumor response was determined by changes in the clinical exam and by imaging changes. Imaging response was coded using the following guidelines with tumor size approximated by calculating the product of the maximum perpendicular diameter of all measurable lesions: progressive disease: ⩾25% increase in measurable lesions and/or the appearance of new lesions; stable disease: <25% decrease to a <25% increase in measurable lesions with at least stable neurological status; minor response: ⩾25% but <50% decrease in the lesions with stable or improved neurological status; partial response: ⩾50% decrease in the lesions with at least stable neurological function.

Statistical Considerations

The major objectives of this study were to evaluate the toxicity and feasibility of concomitant high dose carboplatin and etoposide during hyperfractionated radiation therapy, and to estimate the efficacy of the above on survival. Survival was estimated using a Kaplan-Meier estimate.

RESULTS

Therapy Delivered and Initial Response

Patients received a median of six cycles (range 4–10) of chemotherapy at carboplatin AUCs of 8, 10, and 12 mg/mL × min. All nine patients completed radiation therapy and at least two cycles of concomitant chemotherapy. MRI evaluation at that point revealed five patients with stable disease, two with a minor response, and two with a partial response. Only one patient received all ten scheduled cycles of chemotherapy. Three patients stopped chemotherapy after 5, 6, and 9 cycles due to hematologic toxicity; two of these patients were treated at an AUC of 12 and one at an AUC of 10. The remaining five patients stopped chemotherapy early due to progressive disease.

Outcome

All patients demonstrated progressive disease at a median of 32 weeks (range 14–70 weeks). Eight of nine patients eventually died of their disease a median of 44 weeks (range 18–95 weeks) following diagnosis. The overall survival was 44% at 1 year (95% confidence interval, 7–70%) and 11% at 2 years (95% confidence interval, 0–48%; Fig. 2) These results do not differ from the outcome of a similar population treated with 70.2 hyperfractionated radiation therapy alone on POG 8495 [7].

Five patients went on to receive other therapy (interferon, n = 2; topotecan, n = 3) following the determination of progressive disease; four of these subsequently

died of their disease. One patient continues with clinically stable disease at week 190+. The remaining four children died without further treatment.

Toxicity

No dose-limiting, nonhematological toxicity was seen at any carboplatin AUC. Serial glomerular filtration rate studies revealed no consistent or sustained decrease in renal function. Two patients had an allergic reaction to carboplatin during course #1 characterized by facial flushing in both cases and wheezing in one case. These symptoms were mild and reversible. Further courses of carboplatin were successfully given following premedication with diphenhydramine and/or hydrocortisone and prolongation of the infusion time. One patient suffered an acute increase in intracranial pressure during i.v. hydration associated with transient neurologic deterioration. A ventriculoperitoneal shunt was placed as a result. Subsequent courses were given without difficulty.

All patients were started on dexamethasone prior to beginning radiation therapy. Six patients were weaned to a total daily dose of 2 mg or less during irradiation; three patients were off steroids completely by the end of irradiation. Only three patients could not tolerate a significant wean, requiring between 3 and 8 mg of daily dexamethasone during radiation therapy.

At an AUC of 8 mg/mL × min, no patient had grade 4 hematologic toxicity. At AUCs of 10 and 12 mg/mL × min, 1/3 and 2/2, respectively, had grade 4 thrombocytopenia; no patient had grade 4 neutropenia. Because of the thrombocytopenia at AUCs 10 and 12 mg/mL × min, the carboplatin dose was de-escalated in a further patient cohort. An AUC of 8 mg/mL × min was subsequently determined to be the MTD. Six of nine patients required a reduction in chemotherapy dose following a median of four courses [3–8]. There was no apparent neurotoxicity associated with the use of hyperfractionated radiation therapy. There was no ototoxicity as documented by serial audiograms.

DISCUSSION

Diffuse pontine gliomas remain one of the most lethal tumors of childhood. Many different therapeutic approaches have been tried in an attempt to increase time to progression and overall survival with little success. The initial enthusiasm for hyperfractionated radiation therapy has not resulted in a substantial improvement in outcome [4–7,30]. Sequential trials suggest a dose level of 70.2–70 Gy may be marginally superior to higher dose levels using hyperfractionated radiation therapy [10–12]. Attempts at surgical resection or biopsy are not indicated in this subgroup of brainstem gliomas [31,32].

The addition of adjuvant chemotherapy has likewise not improved patient survival. The Children's Cancer Group randomized 74 eligible children with pontine and/or medullary brainstem gliomas to receive radiation alone (about 50 Gy) vs. radiation with concomitant chemotherapy consisting of prednisone, CCNU and vincristine. The addition of chemotherapy did not improve the survival as compared to those treated with irradiation alone: the 5-year survival of this patient group was 20%. This survival rate in part reflects less stringent eligibility criteria and the treatment of a less uniformly high-risk patient population than in more modern series [2,9,30].

The use of neo-adjuvant, pre-irradiation chemotherapy has some theoretical advantages in the treatment of patients with aggressive, malignant tumors. The Pediatric Oncology Group studied the use of four cycles of pre-irradiation cis-platinum and cyclophosphamide in a prospective fashion between 1988 and 1989. Following chemotherapy, or with clinical and/or imaging evidence of progressive disease during any of the first four cycles of chemotherapy, patients were treated with 66 Gy radiotherapy using a hyperfractionated technique. Thirty-two evaluable patients were treated but only half completed all four cycles of pre-irradiation chemotherapy. Despite the fact that 81% of patients had stable disease or partial response during chemotherapy, the median survival was 9 months, no different from the results following 66 Gy hyperfractionated radiation therapy alone [33].

Biological response modifiers have been used in patients with brainstem gliomas with a similar lack of efficacy. Packer administered β-interferon to 34 children with newly diagnosed brainstem gliomas during treatment with 72 Gy hyperfractionated radiation therapy. Treatment on this protocol resulted in a median survival of 9 months, a duration of survival which does not differ from that of other current series [34].

As a result of the failure of standard therapeutic approaches in improving outcome, more intensive therapies have been tried as well. High-dose chemotherapy with either bone marrow or peripheral blood stem cell support has been used as part of the therapy for this group of patients. In one series, six children with newly diagnosed brainstem gliomas were treated with high-dose cyclophosphamide and thiotepa followed by autologous bone marrow infusion. Five of the six survived long enough to receive 75.6 Gy of scheduled hyperfractionated radiation therapy at week 7. The median survival in this group was approximately 12 months; only one patient remained alive without evidence of disease at the time of the report. There were two toxic deaths out of the cohort of nine patients [35].

The current study combined 70.2 Gy hyperfractionated radiation therapy with concomitant intensive carboplatin and etoposide. As with prior studies, this treatment had little impact on survival; overall survival following this therapy was not better than that observed by others with hyperfractionated radiation therapy alone [7]. Non-

hematologic toxicity was minimal. Thrombocytopenia, not neutropenia, was responsible for dose-limiting toxicity in most cases. This observation may reflect the safety and efficacy of administering G-CSF during radiation therapy as described in other reports [36,37].

To date, there is no evidence to suggest that therapy beyond the use of radiation therapy has a significant clinical impact on the survival of children with diffuse pontine gliomas. Progress in the treatment of these tumors must rely on the continued evaluation of new and innovative therapeutic strategies.

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