Medical and Pediatric Oncology 31:16–18 (1998)

Treatment of Adults With Progressive Oligodendroglioma With Carboplatin (CBDCA): Preliminary Results

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Background. Exploration of the role of chemotherapy in the treatment of low grade glioma, including oligodendroglioma, has been limited to the pediatric population, reflecting the sensitivity of young patients to radiation-induced toxicity and a desire to avoid this intervention (7–12). ***Procedure.*** Nine adults with progressive oligodendroglioma were treated with carboplatin at a dose of 560 mg/m^2 administered at 4 week intervals. ***Results.*** Eight patients have demonstrated stable disease as determined by serial MRI imaging at 2–3 month intervals with neither tumor regression nor growth noted. The ongoing duration of tumor control ranges between 6–22 months. Three patients have completed therapy with carboplatin and continue with stable dis-ease off chemotherapy. One patient progressed after 1 year of therapy with histologic confirmation of growth of well differentiated oligodendroglioma. Toxicity was limited to grade 3 thrombocytopenia in 3 patients and grade 3 neutropenia in 2 patients. ***Conclusions.*** Carboplatin appears to be active in the treatment of adults with progressive oligodendroglioma. Further trials are warranted to more precisely define the role of carboplatin in the treatment of these tumors. Med. Pediatr. Oncol. 31:16–18, 1998.

Key words: oligodendroglioma; carboplatin; brain tumors; glioma

INTRODUCTION

Oligodendrogliomas are low grade gliomas that are morphologically benign but can display an aggressive biological course with infiltration and destruction of normal brain. Surgical resection is the treatment of choice, but infiltration of brain frequently precludes substantial tumor removal. Radiotherapy is considered conventional adjuvant treatment for incompletely resected newly diagnosed oligodendroglioma. Although adjuvant radiotherapy may increase short-term disease control, it does not produce an ultimate increase in survival [1–3]. Leighton et al [4] reviewed the outcome of patients with low grade glioma, including a subset with oligodendroglioma, comparing the patients who received radiotherapy following a subtotal resection with those who were irradiated at the time of disease progression. No difference in outcome was observed, which is consistent with prior reports suggesting that radiotherapy of incompletely resected oligodendroglioma should be withheld until tumor growth is noted [5,6].

Exploration of the role of chemotherapy in the treatment of low grade glioma, including oligodendroglioma, has been limited to the pediatric population, reflecting the sensitivity of young patients to radiation-induced toxicity and a desire to avoid this intervention [7–12]. However, radiotherapy produces toxicity in adults as well [13], warranting definition of the role of chemotherapy in this age group. We now report our initial experience using carboplatin therapy in adults with progressive oligodendroglioma.

CLINICAL MATERIAL AND METHODS

Patient Eligibility

To be eligible for treatment, patients were required to: 1) have histological confirmation of an oligodendroglioma ($\leq$2 years since tissue diagnosis), and 2) have demonstrated radiographic evidence of tumor progression. Patients previously treated with chemotherapy or radiotherapy were eligible for enrollment.

Chemotherapy Protocol

Carboplatin (560 mg/m^2) was given intravenously in 5% dextrose in one-half normal saline over one hour,

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Received 10 November 1997; Accepted 4 February 1998

TABLE I. Patient Demographic Response

PT	Gender	Age (yrs)	Tumor Site	Prior Therapy	Start Date	Response	Toxicity[a]	# Cycles
1	M	55	R parieto-temporal	surgery (1986); XRT (1986); surgery (3/96)	4/96	SD	neut (3)	7
2	M	22	R frontal	surgery (10/95)	5/96	SD	N/V	10
3	M	45	L frontotemporal	surgery (8/89); XRT (8/89); bx (7/96)	8/96	SD	fatigue	10
4	M	40	R parieto frontal	surgery (8/90); bx (7/96)	8/96	SD	thromb (3)	11
5	M	30	R frontal + corpus callosum	surgery (10/93); surgery (9/96)	1/97	SD	NA	9[b]
6	M	48	Bifrontal	surgery (12/96)	2/97	SD	thromb (4);neut (3)	9
7	F	52	R temporofrontal	surgery (2/89); bx (11/96)	4/97	SD	hypokalemia;neut (3); anemia (3)	9
8	M	52	L temporal	biopsy (1/93); PCV × 8; bx (3/97)	4/97	SD	—	6
9	F	45	L paratrigonal white matter	biopsy (6/97)	8/97	SD	—	6

[a](grade).
[b]PD noted 2/98.

preceded and followed by one hour of intravenous hydration (total fluid over three hours 900 ml/m^2). Carboplatin was given at four-week intervals and was continued in successive cycles until the disease progressed, unacceptable toxicity supervened, or 12 months of stable disease had been documented. Patients were treated as outpatients.

Prior to therapy, the following parameters were examined: complete blood cell count, and serum creatinine, hepatic transaminase, and bilirubin levels. Retreatment with chemotherapy was not begun until the absolute granulocyte count was greater than 750/μl, the platelet count was greater than 100,000/μl, and the creatinine level was less than 1.5 mg/dl. Patients received a 25% dose reduction if the prior course resulted in a platelet count nadir of less than 30,000/μl. A 25% dose escalation was instituted if the prior course resulted in or a platelet count nadir of more than 100,000/μl.

Evaluation of Toxicity and Response to Therapy

A neurological examination was carried out before each course of therapy. Magnetic resonance (MR) imaging or CT was performed before therapy started, after the initial two cycles, and then after every three cycles. After completion of treatment, images were obtained every three months. Audiograms were performed prior to the first course and every six months thereafter. Complete blood cell counts were obtained weekly during treatment and prior to every course. Also serum creatinine, hepatic transaminase, and bilirubin levels were measured prior to each treatment. Toxicity was graded and recorded using the common toxicity criteria.

Response criteria were defined objectively on MR or CT imaging as follows: complete response (CR), complete disappearance of disease; partial response (PR); a decrease of more than 50% in tumor size; minimal disease (MR); a decrease of <50% in tumor size, stable disease (SD); no change in tumor size; and progressive disease (PD). Tumor size was assessed using the product of the longest measured perpendicular diameters of the tumor.

Patient Characteristics

Nine patients were treated with carboplatin. There were 7 males and 2 females with a median age of 45 years (range 22–55) (Table I).

Prior therapy included biopsy in 2 patients, partial resection in 7 patients, radiation in 2 patients prior to progression and chemotherapy in 1 patient prior to carboplatin. All 9 patients demonstrated a 25–50% increase in tumor size over a 2–4 month period of time immediately preceding enrollment on this protocol.

RESULTS

Response

All nine patients received a minimum of two cycles, ranging between 6–10 cycles. Several patients had delays in repeat cycles due to prolonged marrow recovery following treatment that did not meet criteria for dose reduction.

Eight patients have demonstrated stable disease as determined by serial MRI imaging at 2–3 month intervals with neither tumor regression nor growth noted. The ongoing duration of tumor control ranges between 6–22 months. Three patients have completed therapy with carboplatin and continue with stable disease off therapy (Table I). One patient demonstrated progressive disease after 1 year of therapy with histologic confirmation of growth of well differentiated oligodendroglioma.

Toxicity

Nine patients have received 77 cycles of carboplatin to date. Two patients developed thrombocytopenia <50,000 cells/μl, 3 patients developed neutropenia with an absolute neutrophil count <500 cells/μl and 1 patient exhib-

ited anemia (hgb < 10g/dl). No nephrotoxicity, ototoxicity, hypersensitivity reactions or fever and neutropenia were noted in any patient (Table I). No dose modifications were required.

DISCUSSION

The critical questions regarding the treatment of adults with oligodendroglioma are: 1) what, if any, intervention should follow initial surgery of a newly diagnosed tumor and 2) what is the optimal therapy of a progressive or recurrent tumor. The Duke Brain Tumor Center does not offer further treatment of patients with newly diagnosed oligodendroglioma following surgery, acting on the belief that the toxicity and lack of ultimate disease control favor withholding further treatment until disease progression is noted [4]. However, disease progression ultimately occurs in the vast majority of patients and treatment with an additional non-surgical modality becomes necessary. The toxicity of radiotherapy in adults motivated our current attempts to use chemotherapy in lieu of radiotherapy for adults with progressive oligodendroglioma [13]. The current results with carboplatin revealed that this agent produced disease control in all 9 patients with progressive oligodendroglioma although the duration of follow-up is still relatively short. Four patients continue to demonstrate disease control for 18–22 months with three patients off chemotherapy. This cessation of tumor growth in these patients, all with actively growing tumors at the time chemotherapy was initiated, proves that carboplatin has anti-glioma activity. The duration of control will be defined with more prolonged observation of these patients.

The decision to use chemotherapy, in lieu of radiotherapy, for adults with progressive oligodendroglioma requires a selection of agent(s) based both on activity and toxicity. Carboplatin produced trivial toxicity in our adult patients, similar to our observations in pediatric patients [10,11]. Although alternative regimens have been explored in the pediatric population [8,9,12], carboplatin produces disease control equal to any other regimen with a patient-friendly, every four week, outpatient schedule and less toxicity. Although other investigators have proposed trials for adults with low-grade gliomas using ''PCV'' (procarbozine, CCNU, and vincristine), this regimen is far more toxic than carboplatin. The degree of progressive and severe myelosuppression, as well as neurotoxicity seen with PCV, is not seen with carboplatin, which produces only mild myelosuppression and no neurotoxicity. Furthermore, ototoxicity, a known complication of high dose carboplatin, was not noted at the dose employed in this trial.

Our results suggest that carboplatin is active in the treatment of adults with progressive oligodendroglioma. Expanded trials with this agent in adults with these tumors, as well as astrocytoma and mixed glioma, are warranted, both to defer or prevent use of radiotherapy and for tumors which recur after radiotherapy.

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