Carboplatin is effective therapy for young children with progressive optic pathway tumors: A Pediatric Oncology Group phase II study¹

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The Pediatric Oncology Group conducted a phase II study to evaluate the activity of carboplatin in children 5 years or younger with progressive optic pathway tumors (OPTs). Of the 51 patients accrued to this study, 1 was not eligible because the child was older than 6 years. Fifty patients were eligible and had either neuro-imaging or symptomatic evidence of progressive OPTs. Twenty-one of 50 had evidence of neurofibromatosis type I (NF-1). Therapy consisted of carboplatin 560 mg/m² at 4-week intervals. Patients with stable disease or better after two courses were continued on therapy for 18 months or until progressive disease. Of the 50 eligible children, 39 had stable disease or better, and 34 completed the 18-month therapy. Our data are sufficient to conclude that the proportion of objective responses (complete, partial, or minor response or stable disease) exceeded 30% ($P < 0.00001$),

and the approximate 95% confidence interval estimate of the objective response rate was 0.665 to 0.895. Twenty-one patients went off protocol because of progressive disease. Fifteen patients progressed during the 18-month therapy, and 6 patients progressed after completing therapy. Six children died with progressive disease. Major toxicities were neutropenia and thrombocytopenia, and 3 children experienced allergic reactions. Carboplatin is active and safe for the treatment of young children with progressive OPTs. The addition of other potentially active drugs may further increase the event-free survival for these children. *Neuro-Oncology* 2, 213–220, 2000 (Posted to *Neuro-Oncology* [serial online], Doc. 00-022, September 6, 2000. URL <neuro-oncology.mc.duke.edu>)

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³Abbreviations used are as follows: EFS, event-free survival; NF-1, neurofibromatosis type 1; OPTs, tumors of the optic pathway; POG, Pediatric Oncology Group.

OPTs³ represent 1% to 5% of all tumors of the CNS in childhood (Alshail et al., 1997; Alvord and Lofton, 1988; Dutton, 1994; Rush et al., 1982). These tumors are usually glial derived and may involve the optic nerves alone, or invade the optic chiasm, adjacent hypothalamic structures, and posterior optic tracts. The age at presentation, symptom patterns, sex distribution, and usual sites of tumor location have been the subject of several reviews (Alvord and Lofton, 1988; Dutton, 1994). There is a well-established association with NF-1 (Dutton, 1994; Lewis et al., 1984; Lund and Skovby, 1991). The incidence of OPTs in patients with NF-1 has been reported to be as high as 15% to 21%

(Housepian and Chi, 1993; Listernick et al., 1989, 1994, 1997). For many patients with NF-1, the tumor may be asymptomatic at presentation and may progress slowly over years. In contrast, the incidence of NF-1 among all patients presenting with OPT has been estimated at 25% to 30% in large series (Dutton, 1994; Housepian and Chi, 1993) and may be higher because many reports fail to mention a search for features of the disease.

Controversy continues over the most appropriate treatment of progressive OPTs in children (Dutton, 1994; Hoffman et al., 1993; Hoyt and Baghdassarian, 1969; Jenkin et al., 1993). Tumors confined to the optic nerve with severe proptosis and vision loss have been successfully treated with surgery, with 85% to 100% long-term survival (Wright et al., 1980, 1989). However, surgical resection provides limited benefit for children with chiasmal tumors and is associated with the potential morbidity of blindness and hypothalamic damage (Dutton, 1994; Jenkin et al., 1993; Wisoff et al., 1990). Radiation therapy has been a treatment of choice for progressive OPTs for more than 3 decades. With irradiation doses over 4500 cGy, stabilization of vision and suppression of tumor growth have been reported in 65% to 90% of patients (Flickinger et al., 1988; Horwich and Bloom, 1985; Pierce et al., 1990). However, there are potential complications associated with CNS irradiation in very young children, including hypothalamic dysfunction, learning disabilities, and cerebrovascular disease (Dutton, 1994).

Recent reports suggest that chemotherapy may be a useful adjunctive therapy in progressive OPTs. Packer et al. reported a 62.5% progression-free survival among 24 patients (median follow-up of 4.3 years) with progressive OPT under 5 years of age at diagnosis when treated with vincristine and actinomycin-D (Packer et al., 1988). In a POG phase II study, carboplatin produced stable disease in 9 of 12 patients with recurrent low-grade astrocytic neoplasms for periods up to 68+ months (Friedman et al., 1992). Transient neutropenia and thrombocytopenia were the principal toxicities observed. Other investigators have also reported responses in low-grade gliomas treated with carboplatin (Charrow et al., 1993; Moghrabi et al., 1993). Based on these early results, POG-initiated a phase II trial of carboplatin in children less than 6 years of age with progressive OPTs. The objective of the study was to determine the response to treatment. We now report the long-term outcome for these patients.

Patients and Methods

Eligibility

All patients younger than 6 years with symptomatic or progressive OPTs were eligible for treatment. All patients were also enrolled on the natural history protocol (POG 8935) to assess symptom patterns and progression of OPTs in children younger than 21 years. Patients with NF-1 were eligible. Children with hypothalamic masses involving the postchiasmatic pathway were eligible, whereas those without involvement of optic pathway were ineligible. Progressive or symptomatic disease was defined according to criteria shown in Table 1.

Table 1. Eligibility criteria for Pediatric Oncology Group 8936

Progressive loss of vision, defined as doubling of octaves (20/40 to 20/80)
Visual acuity of 20/400 or less in one or both eye(s)
Increase in proptosis of >3mm
Papilledema or imaging signs of increased intracranial pressure
Hydrocephalus
<ul style="list-style-type: none"> • Change in neuro-imaging studies: 25% increase in the product of the maximum perpendicular diameters of tumor and/or • Increase in diameter of optic nerve of 2 mm and/or • Increased distribution of tumor involving posterior optic tract or radiations
Evidence of progressive disease was based on one or more of the above.

Before treatment, biopsy was required for any patient with a chiasmatic lesion that extended into the hypothalamus. For all other patients, surgery and biopsy were suggested but not required. All pathologic materials and results of surgery were reviewed centrally. Before study entry, patients were required to have a neurologic assessment, ophthalmologic evaluation, visual evoked response, audiograms, neurodevelopmental tests, and neuro-endocrine evaluation. Neuro-imaging with either CT scan, with and without contrast, or MRI scan, with and without gadolinium, was required. Myelograms and CSF cytology examination were not required. In addition, prechemotherapy studies included a complete blood count, electrolytes, serum calcium and magnesium, creatinine, and alanine aminotransferase.

The protocol was approved by individual institutional review boards, and all patients provided written informed consent.

Treatment Protocol (POG 8936)

Carboplatin was given by i.v. infusion at a dose of 560 mg/m² over 1 h. Chemotherapy was given in the outpatient setting every 4 weeks. For patients with stable disease or better, therapy was repeated every 4 weeks for a total of 18 cycles. If platelet count was less than 50,000/μl or absolute neutrophil count was less than 500/μl between treatment cycles, the next course of carboplatin was reduced by 25%. If neutrophil and platelet count nadirs recovered within the next 4-week cycle, attempts were made to escalate the next dose to 100%. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria.

Evaluation of Response

The principal objectives of this study were to assess response to therapy and to monitor the duration of EFS, which is measured from the beginning of treatment. Disease recurrence, disease progression, or death from any cause was regarded as a treatment failure. Neuro-imaging studies and visual acuity were performed before study entry and after two cycles (8 weeks) of chemotherapy. Responses were based primarily on CT or MRI results and were categorized as follows. A complete

Fig. 1. Kaplan-Meier plot of probability of event-free survival and survival for eligible patients.

response was the complete disappearance of the lesion. Partial response and minor response were defined to be at least a 50% decrease or at least a 25% to less than 50% decrease, respectively, in the product of the maximum perpendicular diameters of the lesion, with no evidence of progression and no new lesions. Stable disease was a less than 25% decrease or increase in the maximum perpendicular diameters of the lesion with no evidence of progression and no new lesions. Anything other than complete response, partial response, minor response, or stable disease was considered progressive disease and included any of the following: a 2-mm increase in the diameter of the optic nerve; an increase in tumor distribution involving the optic tract or optic radiations as indicated by CT or MRI scan using T1 with and without contrast and T2 imaging; contrast enhancement on CT or MRI; progressive visual loss; or increasing papilledema and/or hydrocephalus.

Patients with stable disease or better after 2 cycles of carboplatin were continued on study. Neuro-imaging was repeated every 3 months during chemotherapy. Patients completing 18 cycles were then imaged every 2 months for the first 6 months off therapy and then every 6 months thereafter.

Patients were considered to be off protocol or "off study" for purposes of analysis when there was evidence

of progressive disease after one or more courses of chemotherapy or if intolerable toxicity was observed.

Statistical Considerations

The primary objective of this phase II efficacy study was to determine whether the proportion of objective responses to this carboplatin-based chemotherapy regimen exceeded 0.30, where an objective response was defined to be one of the the following: complete response, partial response, minor response, or stable disease. Secondary objectives of this study were to provide a 95% confidence interval estimate of the objective response rate and to monitor the type and degree of the toxicities. On May 9, 1992, the original accrual objective of 25 evaluable patients was increased to 40 evaluable patients to help determine whether radiation therapy could be deferred by treatment with carboplatin. In fact, the study closed with 50 eligible and evaluable patients. Included in this report are Kaplan-Meier (Kaplan and Meier, 1958) EFS and survival curves with standard errors (Peto et al., 1977) for all eligible patients and all eligible neurofibromatosis patients (Figs. 1 and 2), and EFS curves for nonneurofibromatosis patients versus neurofibromatosis patients (Fig. 3). Because formal survival analy-

Fig. 2. Kaplan-Meier plot of probability of event-free survival and survival for eligible neurofibromatosis patients.

ses were not study objectives and, therefore, were not preplanned, these curves only provide anecdotal information. No statistical significance can be or is presented with them.

Results

Eligible Patients

Between June 1989 and March 1994, 50 patients with progressive OPTs were enrolled and eligible for study. All patients were younger than 6 years. The median age at diagnosis was 1.96 years (range, 4 months to 5.5 years). There were 30 females and 20 males. Neurofibromatosis was present in 21 of 50 patients. Thirty-three patients with signs and symptoms of progressive OPTs were eligible for immediate entry on the treatment protocol (POG 8936), whereas 17 patients were initially registered on the natural history protocol (POG 8935) and not treated with carboplatin until there was evidence of progression by visual changes or neuro-imaging.

Locations of OPTs are shown in Table 2. Tumors involved the chiasm and/or adjacent structures in 49 of 50 patients. In many patients, at presentation the tumor mass was large, measuring 3×3 cm or greater based on two-dimensional maximum perpendicular diameters. Twenty-five of 50 patients had disease extending into the

hypothalamus and 2 of 50 had leptomeningeal disease at diagnosis. Visual loss or other visual symptoms were a typical presenting complaint. Thirty of 50 patients had surgery. A biopsy alone was performed in 16 patients and a partial resection in 14 patients. In 27 patients, a diagnosis of pilocytic astrocytoma was confirmed by central review. Further details on the extent of these findings and changes after therapy are the subject of a separate report (POG 8935, Natural History Study).

Response to Treatment

Of the 50 eligible and evaluable patients, the overall best responses were 2 with partial response, 37 with stable disease, and 11 with no response or progressive disease after two courses of chemotherapy. Among the cohort of 39 patients with partial response or stable disease, 4 patients progressed before completing 18 months of treatment, and 1 patient with stable disease, who was treated off protocol with alternative therapy, remained progression-free. There were 34 patients who completed 18 months of therapy with partial response or stable disease. Six of these patients developed progressive disease posttherapy. Overall, 6 patients died secondary to tumor progression. These mortalities were observed in 5 nonneurofibromatosis patients with large chiasmatic tumors (4) and/or leptomeningeal dissemination (1).

Fig. 3. Kaplan-Meier plot of probability of event-free survival for nonneurofibromatosis versus neurofibromatosis patients.

Among the 21 neurofibromatosis patients, 14 patients had stable disease and 1 patient had partial response after two courses of chemotherapy. Overall, 9 neurofibromatosis patients went on to develop progressive disease, with one death. Twelve patients continue with stable disease off all chemotherapy.

The 39 objective responses among the 50 eligible and evaluable patients are sufficient to conclude that the proportion of objective responses to this therapy exceeded

0.30 ($P < 0.0001$), and the approximate 95% confidence interval estimate for the true objective response rate was 0.665 to 0.895.

Kaplan-Meier EFS and survival curves for all eligible patients and for all eligible neurofibromatosis patients are presented in Figs. 1 and 2. EFS curves for nonneurofibromatosis versus neurofibromatosis patients appear in Fig. 3. Because no formal survival analyses were planned for this study, no statistical comparisons are presented in conjunction with the curves, which only provide anecdotal information that may be useful in planning other studies.

Table 2. Sites of presentation of 50 patients with progressive optic pathway tumors

Sites ^a	Patients	
	Non-NF-1 (n = 29) ^b	NF-1 (n = 21) ^b
Orbit	0	1
Chiasm	29	20
Chiasm and nerve	13	17
Chiasm and optic tracts	8	7
Chiasm and hypothalamus	20	5
Leptomeninges	2	—

Abbreviations: NF-1, neurofibromatosis type 1.

^aOne or more observations may occur in each patient.

^bNumber of patients per group.

Toxicity

The significant toxicities reported during continuation of therapy with carboplatin are shown in Table 3. The principal toxicities were transient neutropenia, thrombocytopenia, and mild anemia. Allergic reactions were reported in 3 patients and resulted in discontinuation of therapy in 1 patient.

Discussion

This study represents the largest single series of children with progressive OPTs treated with single-agent chemo-

Table 3. Worst degree of toxicity reported among 50 patients evaluable for toxicity

Toxicity	None	Grade					
		1	2	3	4	5	Unknown
ANC	30	2	7	9	2	0	0
APC	47	0	1	2	0	0	0
Lymphs	49	0	1	0	0	0	0
Platelets	40	1	3	6	0	0	0
Hemoglobin	23	9	13	5	0	0	0
Fibrinogen	49	1	0	0	0	0	0
Calcium	49	0	0	1	0	0	0
Sodium	49	0	0	1	0	0	0

Abbreviations: ANC, absolute neutrophil count; APC, antigen presenting cell.

therapy. To prevent further progression of disease, 50 eligible children younger than 6 years were treated with a single infusion of carboplatin every 4 weeks for 18 cycles, or until progression of disease. Most of the children had large chiasmatic tumors, and 50% showed extension into the hypothalamus. Stabilization of disease was the common response to therapy. In total, 34 children who began therapy with carboplatin completed 18 months of planned treatment without progression. The EFS curves in Fig. 3 suggest that children with NF-1 fared as well or better than children without NF-1.

The primary rationale for using chemotherapy to treat young children who have progressive OPTs has been the desire to delay the need for radiotherapy or other forms of treatment that are potentially damaging. Radiation therapy has been the mainstay of therapy for children with progressive OPTs (Dutton, 1994; Horwich and Bloom, 1985; Jenkin et al., 1993; Kovalic et al., 1990; Pierce et al., 1990). However, significant complications frequently follow the use of such therapy in young children. Atrophy of normal brain parenchyma, growth hormone deficiencies, precocious puberty, diabetes insipidus, and neurodevelopmental disorders have all been associated with irradiation (Brauner et al., 1990; Davis et al., 1986; Duffner and Cohen, 1991; Dutton, 1994; Housepian and Chi, 1993; Okuno et al., 1985). Radiation-induced cerebral vasculopathy and second malignancy are also risks, especially for children with NF-1 (Grill et al., 1999; Imes and Hoyt, 1986; Sayli et al., 1993).

There are few published series on the role of chemotherapy for managing progressive OPTs. Packer et al. (1988) first reported on the efficacy of vincristine and actinomycin-D in delaying the need for radiation therapy in children younger than 5 years with OPTs. Prados et al. (1997) reported stabilization of chiasmal and hypothalamic gliomas in a mixed group of children between the ages of 4 months and 16 years after treatment with a 5-drug regimen. In this trial, the median time to tumor progression was 132 weeks (a 95% confidence interval was 106-186 weeks). Chamberlain and Grafe (1995) reported responses in 8 of 14 patients with recurrent chiasmatic-hypothalamic gliomas treated with 21-day courses of oral etoposide.

Recently, Packer et al. (1993) reported the results of a carboplatin and vincristine treatment in a series of children aged 3 months to 16 years with low-grade gliomas,

including OPTs. Using carboplatin 175 mg/m² for 4 consecutive weeks and vincristine 1.5 mg/m² for the first 3 weeks, and repeating each cycle every 7 weeks, the investigators obtained an estimated 3-year progression-free survival of 74% (SE 7%) for children 5 years or younger. It is difficult to compare outcome of Packer's series with that of our patients because we did not plan any survival analyses, his description of extent of disease at diagnosis was different, and the follow-up was shorter. In our series, 25 patients had evidence of hypothalamic invasion and 11 had hydrocephalus, clinical features associated with poorer prognosis.

Taken together, these clinical trials suggest that progressive OPTs may be successfully treated and stabilized with minimal toxicity for months or years with single-agent or multiagent chemotherapy.

Controversy remains as to what is the optimal treatment for young children with OPTs. We and others suggest that chemotherapy should be considered as the initial therapy in young children with progressive OPTs. The results of this trial with carboplatin suggest that this agent is active against OPTs and that patients failing chemotherapy can be salvaged with alternative treatments, including radiation, in most cases. Clinical trials that seek to add additional agents to a carboplatin backbone must carefully consider the risks for additional toxicity and second malignancy (as might be associated with procarbazine and etoposide) versus the potential for improved EFS. Future randomized clinical trials with single or multiagent chemotherapy may help to further resolve questions of safety and efficacy in this challenging group of patients.

Appendix 1

Participating Institutions and NCI Support

Institution	Grant No.
Baylor College of Medicine	CA-03161
Bergan-Passiac CCOP	
Hackensack Medical Center	
Boston Floating Hospital	
Carolinas Consortium	CA-69177
Medical University of South Carolina	
Children's Hospital Michigan	
	CA-29691

Institution	Grant No.
Children's Memorial Hospital (Chicago)	CA-07431
Dana-Farber Cancer Institute	CA-41573
Miami Children's	CA-41573
Duke University	CA-15525
Mount Sinai Medical School (N.Y.)	CA-69428
University of Massachusetts	CA-69428
Emory University	CA-20549
All Children's Hospital	
Florida CCOP	
Joe DiMaggio Children's Hospital	
Johns Hopkins University	CA-28476
Children's Hospital New Orleans/ LSU CCOP	
McGill University	CA-33587
Medical College of Virginia	
Midwest Children's Cancer Center	CA-32053
Massachusetts General Hospital	CA-29293
Rhode Island Hospital	CA-29293
POG Operations Office	CA-30969
Roswell Park Cancer Institute	CA-28383
University of Groningen	
Southwestern Medical School	CA-33625
Sainte-Justine	
St. Christopher's Hospital	
St. Jude Children's	CA-31566
St. Jude Midwest	CA-31566
POG Statistical Office	CA-29139
University of Alabama	CA-25408
Nemours Children's Clinic	
University of Miami	
Keesler AFB Hospital	CA-15898
University of Mississippi Medical Center	CA-15989
University of Rochester	
UC/Davis	
Children's Hospital (San Diego)	CA-28439
UT/San Antonio	
Tripler Army Medical Center	
Washington University	CA-05587

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