Carboplatin treatment of progressive optic pathway gliomas to delay radiotherapy

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Six patients with optic pathway gliomas who were previously managed with surgery and/or chemotherapy were treated with carboplatin (560 mg/sq m) after radiographic evidence of disease progression. The median age at diagnosis was 2 years (range 4 months to 7 years), and the interval between diagnosis and carboplatin therapy ranged between 7 months and 6.5 years (median 1.8 years). Treatment was given at 4-week intervals and continued until unacceptable toxicity supervened, the disease progressed, or the disease was stable for 12 months. All patients demonstrated disease stability at the outset of the third cycle and continued to do so at the time of this writing. Two patients were 16 and 32 months from initial carboplatin therapy and have been off treatment for 5 and 14 months, respectively; two patients are still receiving therapy at 7 and 11 months after their initial treatment. During the study, two patients developed hypersensitivity to the drug, requiring its discontinuation. Toxicity was minimal, consisting mainly of thrombocytopenia, requiring a one-dose reduction in four of the six treated patients. No platelet transfusions were needed. These results suggest that carboplatin can arrest growth of progressive optic pathway gliomas in children and allow delay of radiotherapy. A larger trial will be required to define the optimal use of carboplatin in the treatment of low-grade gliomas in children.

KEY WORDS: carboplatin • chemotherapy • low-grade glioma • astrocytoma • optic pathway • children

THE optimum treatment of optic pathway gliomas in children remains controversial. Despite their benign morphological appearance, these tumors can demonstrate a striking biological heterogeneity ranging from indolent local progression to fulminant metastatic spread.6,7,8,20,38,46 Prediction of their clinical behavior on an individual basis is currently not possible.

Low-grade gliomas in children are initially treated with surgery, with the degree of resection dependent on the primary tumor site.23,24 Those children who undergo a gross resection, as is frequently seen with cerebellar juvenile pilocytic astrocytomas, are often cured, with a 10-year progression-free survival rate of more than 80%.18,19,31,40 Unfortunately, gliomas situated at more crucial sites, such as the optic pathway, are less amenable to resection, with postsurgical residual tumor frequently left. Although adjuvant radiotherapy can delay tumor progression following surgery, it may not produce an ultimate increase in survival time.11,12,13,18,23,30,38,59,47

Several clinical investigators have suggested that children with partially resected low-grade gliomas should not routinely receive irradiation, but instead should be carefully followed until there is radiographic or functional evidence of tumor progression.3,10,36,46 This argument has been strengthened by the development of increasingly sensitive neuroimaging techniques that allow earlier detection of tumor growth.7,8,25,42,48 The current Pediatric Oncology Group (POG) and Children’s Cancer Study Group (CCSG) protocol, which randomly assigns children older than 5 years of age having incompletely resected low-grade gliomas to an observation versus a radiotherapy protocol, may help to determine whether there is a survival benefit associated with giving radiotherapy immediately versus deferring it until tumor progression. Nevertheless, the toxicity associated with irradiating a developing central nervous system can be profound, and that fact supports efforts to delay radiotherapy in these children.4,10,12,13,18,24,26,29,31,43

Chemotherapy using a combination of vincristine and actinomycin D or a nitrosourea-based therapy has been used to delay irradiation in children with newly diagnosed low-grade gliomas of the optic pathway.3,32,35,37 Although this approach is successful in deferring radiotherapy, ultimate tumor progression appears to be the usual outcome. Nevertheless, carboplatin (cis-diam-
mindicarboxylato-1,1-cyclobutaneplatinum), a second-generation cisplatin analog, has produced prolonged stabilization of tumor growth in children treated for low-grade gliomas that recurred after radiotherapy.\(^4\) We now report the results of carboplatin therapy for progressive optic pathway low-grade gliomas in six children who have never received radiotherapy.

**Clinical Material and Methods**

**Patient Eligibility**

To be eligible for this study, patients were required to: 1) be less than 18 years of age; 2) have histological confirmation of a low-grade glioma (except for one patient with a "typical" tumor of the optic nerves, chiasma, and optic tracts); 3) have never received radiotherapy; 4) demonstrate radiographic evidence of tumor progression; and 5) have an informed consent from a parent or legal guardian. Patients previously treated with chemotherapy were eligible for enrollment.

**Chemotherapy**

Carboplatin (560 mg/sq m) was given intravenously in 5% dextrose in one-half normal saline over 1 hour, preceded and followed by 1 hour of intravenous hydration (total fluid over 3 hours 900 ml/sq m). Carboplatin was given at 4-week intervals and was continued in successive cycles until the disease progressed, unacceptable toxicity supervened, or 12 months of stable disease had been documented. All 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 50,000/µl. A 25% dose escalation was instituted if the prior course resulted in an absolute granulocyte count nadir of more than 1500/µl and/or a platelet count nadir of more than 100,000/µl.

**Evaluation of Toxicity and Response to Therapy**

A neurological and ophthalmological examination was carried out before each course of therapy. Magnetic resonance (MR) imaging was performed before therapy was started and prior to every other course. After completion of treatment, MR images were obtained every 3 months. Audiograms were performed prior to the first course and every 6 months thereafter. Neuropsychological examinations were carried out before the first course and repeated yearly. Complete blood cell counts were obtained weekly during treatment. Prior to every course, serum creatinine, hepatic transaminase, and bilirubin levels were measured. Toxicity was graded and recorded following the POG toxicity criteria.

Response criteria were defined objectively on MR imaging as follows: complete response, complete disappearance of disease; partial response, a decrease of more than 50% in the product of the longest measured perpendicular diameter of the tumor; stable disease, less than 50% decrease or less than 25% increase in said product; and progressive disease, greater than 25% increase in said product.

**Results**

**Patient Characteristics**

Six patients (four girls and two boys) were enrolled in the protocol (Table 1). The median age at diagnosis was 2 years (range 4 months to 7 years). A diagnosis of low-grade glioma (pilocytic astrocytoma) confirmed histologically in five patients. The sixth patient (Case 2) was enrolled with MR imaging evidence of a tumor involving the optic nerves, the chiasma, and the optic tracts; we believed that she did not require histological confirmation of her disease. The tumors were located in the optic pathway in five cases and in the hypothalamus in one. Two patients had neurofibromatosis.

The interval between diagnosis and carboplatin therapy ranged between 7 months and 6.5 years (median 1.8 years). In four patients carboplatin was the initial therapy; two patients had received chemotherapy 6 and 46 months prior to carboplatin, and one patient had undergone a subtotal resection 14 months earlier.

**Drug Toxicity**

Six patients received a total of 69 cycles of carboplatin. Two patients developed an allergic reaction to the drug, manifested as urticaria, requiring its discontinuation; one patient was in her ninth cycle and the other in his 12th and last course. The former was switched to cyclophosphamide, after which she also developed urticaria.

In four patients, dose levels were lowered following thrombocytopenia, but the dose was subsequently increased for one patient to the original level. No patient required platelet transfusions. There were no episodes of fever or neutropenia, and nausea and vomiting were mild; no neurological or renal toxicity was present.

**Response to Therapy**

All patients were evaluable for response. All patients demonstrated stable disease when evaluated following two cycles of carboplatin and, at the time of this writing, remain in a stable condition. Two patients are 16 and 32 months from initial carboplatin therapy and have spent 5 and 14 months off treatment, respectively. Two patients are still receiving therapy at 7 and 11 months. Two patients developed hypersensitivity to the drug, requiring its discontinuation. One of these patients, however, was in his 12th and last course. He is now alive with stable disease 22 months from his initial carboplatin therapy, 10 months off treatment. The other patient was followed expectantly and given cyclophosphamide 2 months later for decreased vision. She developed urticaria in response to that drug and was then treated with radiotherapy. She is now 9 years of age with stable disease 18 months after her initial carboplatin therapy and 6 months following radiotherapy.
Carboplatin treatment of optic pathway gliomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Diagnosis, Sex</th>
<th>Site of Glioma</th>
<th>Histological Diagnosis</th>
<th>Prior Therapy</th>
<th>Interval From Diagnosis to Prior Therapy</th>
<th>Interval From Diagnosis to Carboplatin</th>
<th>Duration of Carboplatin Therapy</th>
<th>Reponse</th>
<th>Duration of Response (mos)</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4mos. M</td>
<td>optic pathway</td>
<td>pilocytic astrocytoma</td>
<td>biopsy; CY/VCR</td>
<td>2 mos</td>
<td>77 mos</td>
<td>12 mos</td>
<td>SD</td>
<td>24+</td>
<td>hypersensitivity to carboplatin, off therapy 12 mos on therapy</td>
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<tr>
<td>2</td>
<td>6mos. F</td>
<td>optic pathway</td>
<td>not done</td>
<td>none</td>
<td>---</td>
<td>42 mos</td>
<td>11 mos</td>
<td>SD</td>
<td>11+</td>
<td></td>
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<tr>
<td>3</td>
<td>1yr. F</td>
<td>optic pathway</td>
<td>consistent with pilocytic astrocytoma (small fragment)</td>
<td>biopsy; CDDP/VP16/VCR/CY/BCNU × 12 mos</td>
<td>13 mos</td>
<td>31 mos</td>
<td>7 mos</td>
<td>SD</td>
<td>7+</td>
<td>on therapy, neurofibromatosis</td>
</tr>
<tr>
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<td>3 yrs. M</td>
<td>hypothalamic</td>
<td>pilocytic astrocytoma</td>
<td>biopsy</td>
<td>---</td>
<td>7 mos</td>
<td>11 mos</td>
<td>SD</td>
<td>16+</td>
<td>off therapy 5 mos</td>
</tr>
<tr>
<td>5</td>
<td>4 yrs. F</td>
<td>optic pathway</td>
<td>pilocytic astrocytoma</td>
<td>biopsy</td>
<td>---</td>
<td>9 mos</td>
<td>18 mos</td>
<td>SD</td>
<td>32+</td>
<td>off therapy 14 mos</td>
</tr>
<tr>
<td>6</td>
<td>7 yrs. F</td>
<td>optic pathway</td>
<td>pilocytic astrocytoma</td>
<td>biopsy</td>
<td>---</td>
<td>12 mos</td>
<td>9 mos</td>
<td>SD</td>
<td>9</td>
<td>hypersensitivity to carboplatin → stopped, progression off therapy → CY, hypersensitivity to CY → RT, off therapy 8 mos, neurofibromatosis</td>
</tr>
</tbody>
</table>

*CY = cyclophosphamide; VCR = vincristine; CDDP = cisplatin; SD = stable disease; VP16 = etoposide; BCNU = carmustine; RT = radiotherapy.

Discussion

No consensus exists regarding the optimum therapy for children with optic pathway gliomas because of the uncertainty of the tumor's biological behavior following diagnosis. Although radiotherapy can delay tumor progression, both lack of evidence for increased survival time and the fact that toxicity is associated with radiotherapy have led to the recent POG/CCSG trial. We hope that the trial will define the merits of immediate versus deferred radiotherapy for children with incompletely resected low-grade gliomas.

Although this clinical trial may facilitate selection of the optimum time to initiate radiotherapy, no consideration of an alternative intervention will be addressed.

The role of chemotherapy in the treatment of children with brain tumors has been increasing, with promising clinical trials reported for medulloblastoma, high-grade glioma, and germinoma. Recent reports have demonstrated the chemosensitivity of low-grade gliomas, including optic pathway gliomas and oligodendrogliomas. Carboplatin, a second-generation cisplatin analog, has produced prolonged stable disease and occasional frank tumor regression in children with previously irradiated, progressive low-grade gliomas. This study extended our observations to patients with nonirradiated progressive optic pathway gliomas.

The results from our current study suggest that carboplatin may be beneficial in the therapy of pilocytic astrocytomas of the optic pathway in children with progressive disease that has only been treated with surgery or other forms of chemotherapy. Despite the small number of patients and the relatively short period of observation, all patients demonstrated stabilization of disease and, in several cases, symptomatic improvement. Toxicity was minimal, consisting of thrombocytopenia, requiring a dose reduction in four of the six treated patients (with one patient's treatment subsequently increased back to the initial dose). Two patients developed hypersensitive reactions requiring discontinuation of carboplatin therapy. This type of reaction has been reported previously.

These results suggest that carboplatin can arrest growth of progressive optic pathway gliomas and produce symptomatic improvement. Although the precise duration of tumor stabilization or the optimum duration of chemotherapy is unclear, all patients treated demonstrated cessation of tumor growth, obviating the need for immediate intervention with radiotherapy. Therefore, it is possible that, with carboplatin, radiotherapy may be deferred in children with progressive optic pathway gliomas and possibly in those with other low-grade gliomas. Postponement of radiotherapy to an older age would potentially decrease radiation-associated toxicity. Larger trials such as POG Protocol 9035, which evaluates carboplatin therapy in children younger than 5 years of age with progressive optic pathway tumors, will be needed to define the percentage of patients who will demonstrate arrest of tumor growth, the duration of stable disease, the duration of treatment required, and the optimum choice of chemotherapeutic agents.

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References


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