Treatment of patients with recurrent gliomas with cyclophosphamide and vincristine

DARRYL C. LONGEE, M.D., HENRY S. FRIEDMAN, M.D., ROBERT E. ALBRIGHT, JR., M.D., PETER C. BURGER, M.D., W. JERRY OAKES, M.D., JOSEPH O. MOORE, M.D., and S. CLIFFORD SCHOLD, JR., M.D.

Departments of Pediatrics, Medicine, Pathology, and Surgery, Duke University Medical Center, Durham, North Carolina

Seventeen patients with recurrent gliomas were treated with the combination of cyclophosphamide and vincristine. All but one had previously received and failed chemotherapy. Cyclophosphamide was administered at doses ranging from 250 to 1000 mg/sq m by intravenous infusion on Days 1 and 2, and vincristine was given at a dose of 1.0 mg/sq m (2 mg maximal dose) intravenously on Day 1; cycles were repeated every 4 weeks. Clinical and radiographic improvement was observed in eight of 16 evaluable patients, and four other patients had stabilization of previously progressive disease. Four patients are alive and off treatment without evidence of recurrence for a median period of 37 months; these included an adult with a cerebral anaplastic astrocytoma now more than 51 months after therapy. Toxicity included moderately severe myelosuppression that required hospitalization in seven patients. These results indicate that the combination of cyclophosphamide and vincristine has activity in the treatment of recurrent gliomas, and warrant the use of these drugs in larger controlled studies, particularly if they can be used in conjunction with hematopoietic growth factors.

KEY WORDS  •  brain neoplasm  •  glioma  •  chemotherapy  •  cyclophosphamide  •  vincristine  •  colony-stimulating factor

The role of chemotherapy in the treatment of recurrent gliomas remains unclear. A variety of agents have been used either alone or in combination, with response rates of 20% to 45% in most studies. The median duration of response in these studies is between 3 and 6 months, and it is unusual for patients with recurrent gliomas to survive more than 12 months. Cyclophosphamide and vincristine have demonstrated activity as single agents and in combination in the treatment of recurrent central nervous system (CNS) tumors of childhood; cyclophosphamide is highly active against a human glioma xenograft in athymic mice. This report reviews the treatment results in 17 patients with recurrent gliomas treated with a combination of cyclophosphamide and vincristine.

Clinical Material and Methods

Patient Selection

To be eligible for treatment, patients must have had histological evidence of a primary CNS neoplasm or convincing clinical and radiographic evidence of such a neoplasm if tissue was unavailable. The histological diagnosis was confirmed by a single neuropathologist (P.C.B.). Radiographic evidence of persistent or progressive disease was required. Minimal hematological values for entry into study included a hemoglobin of more than 10 gm/dl, an absolute neutrophil count (ANC) of more than 1500 cells/µl, a platelet count of more than 100,000 cells/µl, a blood urea nitrogen level of less than 25 mg/dl, and a bilirubin level of less than twice normal values. The patient could not have received antineoplastic chemotherapy or radiotherapy, or have undergone surgical resection of tumor within 6 weeks of starting therapy.

Treatment Schedule

Cyclophosphamide was administered at doses ranging from 250 to 1000 mg/sq m body surface area intravenously over 1 hour for 2 consecutive days. The goal was to treat all patients with 1000 mg/sq m of cyclophosphamide; however, some patients had been heavily pretreated with other antineoplastic chemotherapy which necessitated initiating treatment with lower doses of cyclophosphamide (see Table 1). Intravenous
fluids were delivered in high volume (150 to 200 ml/hr) to prevent bladder toxicity. Most patients also received vincristine at a dose of 1.0 mg/sq m body surface area (maximum dose of 2 mg) intravenously on Day 1 of each cycle. The regimen was repeated every 3 to 4 weeks as permitted by the patient's hematological status. Treatment was continued for a minimum of 12 months or until there was evidence of tumor progression.

Response Evaluation

Patients were evaluated by neurological examination at least prior to every other course of therapy; at that time a clinical assessment of improvement, deterioration, or no change was made. Any change from the previous examination must have been independent of the dose of corticosteroids and must have been interpreted as due to the effects of the tumor itself.

Computerized tomography (CT) of the head was also performed prior to every other course of chemotherapy. Each patient had contrast-enhanced CT, receiving 200 ml of 60% iothalamate meglumine as a 100-ml bolus followed by a 100-ml intravenous drip. Sections through the tumor bed had a 5-mm interscan distance and were 5 mm thick. One neuroradiologist interpreted all studies and a judgment of increase, decrease, or no change in tumor size was made.

The CT studies were further analyzed by estimating the percentage reduction in the volume of the region of abnormal enhancement (enhancing tumor volume, or ETV), determined using a microcomputer-based planimetric method. Regional volume was quantitated by tracing the outline of defined regions on serial CT scan slices into a microcomputer system (IBM XT/AT computer system or compatible) using a backlit digitizing tablet.* To calculate a region's volume, the cross-sectional surface areas are summed, multiplied by the section thickness, and corrected for the magnification factor. Regions of abnormal contrast-enhancement ("total tumor"), intralesion low density ("core"), and perilesion low density ("edema") were traced and volumes were quantitated. The ETV is determined as the difference between the total tumor and the core volumes.

Responding patients were those who developed both clinical and radiographic improvement independent of the corticosteroid dose. Those patients who showed no clinical deterioration or increased steroid requirement and had a change in ETV of less than 25% were considered to have stable disease. Clinical deterioration, increase in corticosteroid requirement, or an increase in ETV of 25% or more indicated progressive disease. To be evaluable for response, patients must have received at least two cycles of therapy and have had a subsequent neurological examination and cranial CT scan.

Toxicity Evaluation

Complete blood counts, including differential leukocyte counts and platelet counts, were performed weekly or more frequently if indicated. Renal function, hepatic enzymes, and serum electrolytes were checked periodically to assess nonhematological toxicity. If hematological toxicity was severe (that is, with a hemoglobin nadir < 8 gm/dl, ANC < 500 cells/ul, or platelet count < 50,000 cells/ul), the subsequent dose of cyclophosphamide was reduced by 25%. If the nadirs were considered life-threatening (that is, with a hemoglobin < 7 gm/dl, ANC < 200 cells/ul, or platelet count < 20,000 cells/ul), the cyclophosphamide dose was reduced by 50%. Packed red blood cells, platelet transfusions, and intravenous antibiotics were administered as indicated. The minimum hematological values required before any treatment course was begun after the first course included hemoglobin greater than 9 gm/dl, ANC greater than 1500 cells/ul, and platelet count greater than 100,000 cells/ul.

Results

Patient Characteristics

Seventeen patients were treated in this study (Table 1). For purpose of review, the cases were separated by histology into one of three groups. Group 1 included six patients with recurrent glioblastoma. This group consisted of five men (median age 49.5 years) and one 6-year-old girl. Group 2 consisted of five patients with recurrent anaplastic astrocytoma (four men and one woman, median age 49 years). Group 3 included six cases with a variety of histological diagnoses: two oligodendrogliomas, one optic glioma, one malignant primary brain neoplasm which could not be classified, and two cases involving deep-seated lesions for which tissue diagnosis was unavailable. The patient ages in this group ranged from 6 months to 52 years; there were three females and three males. All 17 patients in the study had radiographic evidence of tumor activity. Fourteen had been previously treated with surgery, and 16 had received radiotherapy and other antineoplastic chemotherapy.

Treatment Response

Sixteen of the 17 patients were evaluable for response to chemotherapy. Case 6 was omitted from the study at the family's request after one course of therapy. A response was observed in one of the five evaluable patients with recurrent glioblastoma (Case 1). This patient, whose tumor had progressed despite treatment with diaziquone (AZQ) and procarbazine, improved clinically and demonstrated a 66% reduction in ETV on cranial CT scans. The duration of response was 8 months and the survival time from initiation of treatment was 27 months. Of the remaining four patients with recurrent glioblastoma, two were stabilized clinically and radiographically for brief periods of 3 to 4

* Digi-Pad digitizing tablet manufactured by GTCO, Rockville, Maryland.
Cyclophosphamide and vincristine for recurrent glioma

**TABLE 1**

*Clinical summary in 17 patients treated with cyclophosphamide/vincristine*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis &amp; Tumor Location</th>
<th>Age (yrs), Sex</th>
<th>Previous Therapy</th>
<th>Treatment</th>
<th>Response &amp; Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: glioblastoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>rt thalamus</td>
<td>49, M</td>
<td>resection, radiotherapy, AZQ, PCB</td>
<td>CTX 1000 mg/sqm + VCR 1 mg/sqm × 8 courses</td>
<td>improved, 66% reduction in ETV: 8 mos</td>
<td>died of progressive disease 19 mos later</td>
</tr>
<tr>
<td>2</td>
<td>rt temporal parietal</td>
<td>54, M</td>
<td>resection, radiotherapy, AZQ</td>
<td>CTX 500 mg/sqm + VCR 1 mg/sqm × 3 courses</td>
<td>stable: 3 mos</td>
<td>died of progressive disease 7 mos later</td>
</tr>
<tr>
<td>3</td>
<td>rt thalamus</td>
<td>45, M</td>
<td>resection, radiotherapy, AZQ</td>
<td>CTX 1000 mg/sqm × 4 courses</td>
<td>stable: 4 mos</td>
<td>died of progressive disease 1 mos later</td>
</tr>
<tr>
<td>4</td>
<td>rt parietal</td>
<td>51, M</td>
<td>resection, radiotherapy, AZQ</td>
<td>CTX 1000 mg/sqm + VCR 1 mg/sqm × 3 courses</td>
<td>no response</td>
<td>died of progressive disease 3 mos later</td>
</tr>
<tr>
<td>5</td>
<td>rt pons</td>
<td>6, F</td>
<td>biopsy radiotherapy, AZQ, carboplatin</td>
<td>CTX 750 mg/sqm + VCR 1 mg/sqm × 2 courses</td>
<td>no response</td>
<td>died of progressive disease 2 mos later</td>
</tr>
<tr>
<td>6</td>
<td>rt temporal parietal</td>
<td>47, M</td>
<td>resection, radiotherapy, AZQ, BCNU</td>
<td>CTX 750 mg/sqm + VCR 1 mg/sqm × 1 course</td>
<td>nonevaluable; permission to continue therapy denied after 1 course</td>
<td>died of progressive disease 3 mos later</td>
</tr>
<tr>
<td>Group 2: anaplastic astrocytoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>lt frontal</td>
<td>43, M</td>
<td>resection, radiotherapy, AZQ, PCB, CCNU</td>
<td>CTX 800 mg/sqm × 8 courses, CTX 530 mg/sqm + VCR 1 mg/sqm × 12 courses</td>
<td>improved, 43% reduction in ETV: completed therapy</td>
<td>alive &amp; well 51+ mos off therapy</td>
</tr>
<tr>
<td>8</td>
<td>rt thalamus</td>
<td>41, F</td>
<td>resection, radiotherapy, AZQ</td>
<td>CTX 500 mg/sqm + VCR 1 mg/sqm × 12 courses</td>
<td>improved, 79% reduction in ETV: completed therapy</td>
<td>died of recurrence 28 mos after beginning CTX/VCR therapy</td>
</tr>
<tr>
<td>9</td>
<td>lt parietal</td>
<td>58, M</td>
<td>resection, radiotherapy, AZQ</td>
<td>CTX 1000 mg/sqm + VCR 1 mg/sqm × 8 courses</td>
<td>improved, 51% reduction in ETV: 8 mos</td>
<td>died of progressive disease 11 mos later</td>
</tr>
<tr>
<td>10</td>
<td>lt temporal</td>
<td>49, M</td>
<td>resection, radiotherapy, AZQ, BCNU, PCB</td>
<td>CTX 1000 mg/sqm + VCR 1 mg/sqm × 4 courses</td>
<td>stable: 4 mos</td>
<td>died of progressive disease 10 mos later</td>
</tr>
<tr>
<td>11</td>
<td>cervical cord</td>
<td>49, M</td>
<td>resection, radiotherapy, AZQ, PCB</td>
<td>CTX 600 mg/sqm + VCR 1 mg/sqm × 3 courses</td>
<td>no response</td>
<td>died of progressive disease 4 mos later</td>
</tr>
<tr>
<td>Group 3: other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>lt thalamic glioma (presumed)</td>
<td>19, F</td>
<td>radiotherapy, AZQ, BCNU</td>
<td>CTX 750 mg/sqm + VCR 1 mg/sqm × 21 courses</td>
<td>improved, 36% reduction in ETV: completed therapy</td>
<td>alive &amp; well 30+ mos off therapy</td>
</tr>
<tr>
<td>13</td>
<td>optic glioma</td>
<td>½, M</td>
<td>biopsy</td>
<td>CTX 330 mg/sqm + VCR 1 mg/sqm × 28 courses</td>
<td>improved, 43% reduction in ETV: completed therapy</td>
<td>alive &amp; well 24+ mos off therapy</td>
</tr>
<tr>
<td>14</td>
<td>pontine glioma (presumed)</td>
<td>16, M</td>
<td>radiotherapy, AZQ, BCNU</td>
<td>CTX 700 mg/sqm + VCR 1 mg/sqm × 13 courses</td>
<td>improved, 42% reduction in ETV: completed therapy</td>
<td>alive &amp; well 39+ mos off therapy</td>
</tr>
<tr>
<td>15</td>
<td>oligodendroglioma, lt frontaltemporal</td>
<td>38, F</td>
<td>resection, radiotherapy, AZQ, BCNU</td>
<td>CTX 1000 mg/sqm + VCR 1 mg/sqm × 6 courses</td>
<td>improved, 60% reduction in ETV: 8 mos</td>
<td>discontinued therapy, lost to follow-up</td>
</tr>
<tr>
<td>16</td>
<td>oligodendroglioma, rt frontal</td>
<td>32, M</td>
<td>resection, radiotherapy, AZQ, PCB</td>
<td>CTX 500 mg/sqm + VCR 1 mg/sqm × 5 courses</td>
<td>stable: 4 mos</td>
<td>died of progressive disease 7 mos later</td>
</tr>
<tr>
<td>17</td>
<td>malignant neoplasm, rt parietal</td>
<td>52, F</td>
<td>resection, radiotherapy, AZQ, PCB</td>
<td>CTX 750 mg/sqm + VCR 1 mg/sqm × 2 courses</td>
<td>no response</td>
<td>died of progressive disease 1 mo later</td>
</tr>
</tbody>
</table>

* AZQ = Diaziquone; PCB = procarbazine; CTX = cyclophosphamide (daily dose on a daily × 2 schedule); VCR = vincristine (single dose); ETV = enhancing tumor volume; BCNU = carmustine; CCNU = lomustine.

† Malignant primary brain neoplasm that could not be classified.

months with survival times of 5 and 10 months. The other two patients failed to respond to chemotherapy and died within 6 months.

Responses were observed in three of five patients with recurrent, heavily pretreated anaplastic astrocytoma (Group 2). Case 7 demonstrated clinical improvement, with a 43% reduction in ETV. This patient remains alive and well off treatment for 51+ months (Fig. 1). Two patients (Cases 8 and 9) improved clinically and achieved greater than 50% reductions in ETV. One of these (Case 8) died of tumor recurrence 28 months after beginning therapy with cyclophosphamide and vincristine. The duration of response in Case 9 was 8 months and the survival time was 19 months. Of the
two remaining patients with recurrent anaplastic astrocytoma, one was clinically stable for 4 months and survived for 14 months and the other failed to respond and died 7 months after the initiation of therapy.

Responses were observed in four of the six patients with diagnoses other than glioblastoma or anaplastic astrocytoma (Group 3). Cases 12, 13, and 14 (with a thalamic, optic, and pontine glioma, respectively) improved clinically with less than 50% reductions in ETV. All three remain alive and well off therapy for 24 to 39+ months. One patient with recurrent oligodendroglioma (Case 15) demonstrated clinical improvement, with a 60% reduction in ETV; the duration of this response was 8 months. A second patient with oligodendroglioma (Case 16) was stabilized clinically and radiographically for 4 months and survived for 11 months after initiation of therapy. One patient failed to respond to treatment and died within 3 months.

Overall, eight of the 16 evaluable patients responded to the combination of cyclophosphamide and vincristine, with both clinical and radiographic improvement, and four remain alive without evidence of disease recurrence off therapy for a median of 37 months (range 24 to 51+ months). There was a positive correlation between improved neurological examination and reduction of enhancing tumor volume on CT scans. Each patient who improved clinically with this treatment regimen demonstrated at least 36% reduction of ETV. In contrast, of the four patients who were clinically stable for brief periods of time, none showed a reduction in ETV of more than 11%.

Toxicity

A total of 141 courses of chemotherapy were administered to the 16 evaluable patients. As can be seen in Table 2, the most significant hematological toxicity was granulocytopenia. Seven of the 16 patients had a total of 12 hospital admissions to receive intravenous antibiotics secondary to fever and neutropenia. Additionally, there were 10 dose reductions of cyclophosphamide among eight patients as a result of significant myelosuppression. There was no treatment-related mortality in this study. Nausea was moderately severe in some instances, but was controlled for the most part by premedicating the patients with antiemetics. There were no episodes of vincristine neurotoxicity or of cyclophosphamide-related hemorrhage cystitis.

Discussion

The response rate of 50% to cyclophosphamide and vincristine combined therapy in this small group of patients with recurrent gliomas compared favorably to the results reported in other Phase II studies.11,17 Of particular significance are the four patients who remain alive without evidence of recurrence a median of 37 months following completion of 1 to 2 years of chemotherapy. The histological diagnoses of these four patients included cerebral anaplastic astrocytoma, thalamic glioma, pontine glioma, and optic glioma. A fifth patient with a cerebral anaplastic astrocytoma died of
tumor recurrence 28 months after beginning therapy.

The rationale for the use of cyclophosphamide in the treatment of glioma is supported by the results of a therapeutic profile generated from a human glioma in the athymic mouse model. The extensively characterized human glioma cell line D-54MG was established as a serially transplantable subcutaneous xenograft in adult homozygous athymic BALB/c mice. Intraperitoneal cyclophosphamide at a dose of 517 mg/sq m on 2 consecutive days produced tumor regression in nine of 10 animals and a tumor growth delay of 16.9 days in comparison to control tumors. This tumor growth delay and number of tumor regressions exceeds that of most other forms of antineoplastic chemotherapy. In the same treatment model, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) produced a similar growth delay (16.7 days); however, there were no tumor regressions in the 10 animals treated.

Previous studies have demonstrated activity of vincristine and cyclophosphamide in recurrent CNS tumors of childhood. Rosenstock, et al., reported objective responses (without radiographic evaluation) in five of 10 children with recurrent gliomas who were treated with vincristine as a single agent. Responses were observed in cases of optic glioma, cerebral astrocytoma, malignant glioma with spinal cord metastasis, and two cases of pontine glioma; the median duration of response was 29 months. Toxicity was minimal with the exception of seizures in three patients.

Allen and Helson found high-dose cyclophosphamide (≥ 80 mg/kg) to have activity in a variety of recurrent CNS tumors in children. The study included seven glioma patients: two with posterior fossa ependymoma and five with brain-stem glioma. Of the two patients with ependymoma, one achieved a complete response with a duration of 24+ months and the other achieved disease stability for a period of 4 months. Four of the five patients with brain-stem glioma achieved partial responses for a median duration of 7 months (range 3 to 11+ months). However, hematological toxicity was considerable at this dosage. All patients in the study reached leukocyte nadirs of less than 1000 cells/cu mm within 7 to 10 days following chemotherapy as well as platelet nadirs, usually 75,000 cells/cu mm within 10 to 14 days. Ten of the 57 courses of treatment administered resulted in hospital admission for management of platelet production. It is possible that the ability to more safely administer aggressive chemotherapy may result in an augmented antitumor activity.

This study is also of interest in that several of the responding patients had previously failed therapy with nitrosoureas. The classical alkylating drugs, such as cyclophosphamide, produce their cytotoxicity through molecular mechanisms different from that of the nitrosoureas. As shown by Friedman, et al., several experimental medulloblastoma tumor lines that are resistant to nitrosoureas retain marked sensitivity to cyclophosphamide and other classical alkylating drugs. Since resistance to nitrosoureas is largely mediated by a deoxycytidine kinase (DNA) repair enzyme, O'-alkylguanine-DNA alkyltransferase, which does not repair DNA adducts produced by the classical alkylators, nitrosourea-resistant tumors may well retain sensitivity to cyclophosphamide.

The combination of high-dose cyclophosphamide and vincristine was found to be quite effective in the treatment of patients with recurrent and metastatic medulloblastoma in a Phase II study reported by Friedman, et al. Responses were observed in all four patients with extraneural disease and in four of eight patients with neuraxis disease, with response durations of 2 to 21+ months. The primary toxicity was neutropenia, and four of the 80 courses of chemotherapy were followed by hospital admission for management of fever with neutropenia.

Myelosuppression was the limiting factor in the administration of high-dose cyclophosphamide in the present study. The primary hematopoietic insult at this dosage level was seen in the neutrophil population. Seven of the 16 evaluable patients experienced severe life-threatening neutropenia (ANC < 500 cells/cu mm) within 7 to 10 days following chemotherapy. Dose reductions of cyclophosphamide were made 10 times among eight patients. Reduced doses of cyclophosphamide may have contributed to tumor progression in two of these patients. Two patients (Cases 9 and 15) achieved dramatic responses clinically and radiographically while receiving cyclophosphamide at a dosage of 1000 mg/sq m. However, severe myelosuppression necessitated two separate dose reductions for each patient. At the time of tumor progression, these patients were receiving only one-third of their starting doses of cyclophosphamide.

An intriguing possibility for circumventing the myelosuppression associated with aggressive chemotherapy might be the adjunctive use of recombinant human granulocyte and granulocyte-macrophage colony-stimulating factor. These growth factors serve to stimulate marrow production of granulocytes and macrophages as well as improve granulocyte function. Preliminary studies indicate that these factors, when given in conjunction with intensive doses of chemotherapy, can shorten the duration of neutropenia as well as accelerate the recovery of platelet production. It is possible that the ability to more safely administer aggressive chemotherapy may result in an augmented antitumor activity.

This study is also of interest in that several of the responding patients had previously failed therapy with nitrosoureas. The classical alkylating drugs, such as cyclophosphamide, produce their cytotoxicity through molecular mechanisms different from that of the nitrosoureas. As shown by Friedman, et al., several experimental medulloblastoma tumor lines that are resistant to nitrosoureas retain marked sensitivity to cyclophosphamide and other classical alkylating drugs. Since resistance to nitrosoureas is largely mediated by a deoxycytidine kinase (DNA) repair enzyme, O'-alkylguanine-DNA alkyltransferase, which does not repair DNA adducts produced by the classical alkylators, nitrosourea-resistant tumors may well retain sensitivity to cyclophosphamide.

These results clearly demonstrate the activity of cyclophosphamide and vincristine in some cases of recurrent gliomas in children and adults and warrant their consideration in larger controlled randomized trials in patients with an earlier stage of disease. Future studies will determine what role the colony-stimulating factors may play in extending the maximum safe dosage of.
myelosuppressive chemotherapy and whether this will translate into an increased therapeutic advantage.

Acknowledgment

The authors thank Martha Timmons for the expert secretarial assistance in preparing this manuscript.

References


Manuscript received April 21, 1989. Accepted in final form September 19, 1989. This work was supported in part by National Institutes of Health Grants NS-20023, CA-44640, and CA-15525, and American Cancer Society Award CH-403. Dr. Friedman is the recipient of National Institute of Neurological Disorders and Stroke (NINDS) Teacher Investigator Development Award 1K07-NS-00958. Dr. Albright is the recipient of NINDS Teacher Investigator Development Award SK07-NS-01004. Dr. Schold is the recipient of Jacob Javits Investigator Award NS-20581 from the NINDS. Address reprint requests to: S. Clifford Schold, Jr., M.D., Division of Neurology, Department of Medicine, P.O. Box 3963, Duke University Medical Center, Durham, North Carolina 27710.