Chiasmatic optic glioma treated with chemotherapy

A preliminary report

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Chiasmatic optic glioma is a rare tumor with an erratic natural history, usually seen in young children. A prior study from this institution demonstrated that these lesions were frequently lethal, despite initial clinical stabilization following radiation therapy, and that visual, intellectual, and late endocrinological disabilities were prevalent. A novel approach was developed in 1977, when an initial clinical response to vincristine was recorded in a child with a recurrent optic glioma. Since then, all children with recurrent optic glioma and all children aged 6 years old and under with newly diagnosed optic glioma have been offered a program of initial therapy with vincristine and actinomycin D for six cycles over 18 months. The four children with recurrent tumor who were treated with that regimen remain clinically stable 13 to 115 months after chemotherapy. Twelve children (eight under 24 months old) with newly diagnosed optic glioma have been treated with this program, and three are still on therapy. Four developed progression while on therapy, and five remain stable from 1 to 60 months posttherapy. The four children who developed progressive disease have been treated with radiation therapy and remain stable. Six of the 12 children showed shrinkage of their tumor on computerized tomography while receiving chemotherapy. This program may serve as an alternative to initial radiation therapy in young children.

KEY WORDS ~ optic nerve glioma □ chemotherapy □ radiation therapy □ glioma □ children

Chiasmatic optic gliomas represent 2% to 5% of all childhood brain tumors. They remain enigmatic and controversial lesions. Information concerning the natural history of these tumors and the outcome of the children afflicted with them is usually limited to series reviewing a small number of patients evaluated over a long period of time by one subspecialty group. In a recent review of our experience at The Children's Hospital of Philadelphia of children with optic gliomas treated over a 20-year period, we found that: 1) these tumors may act aggressively despite being histologically low-grade gliomas; 2) vision rarely improves after x-ray treatment; 3) progressive disease may occur years after treatment with radiation therapy (RT); and 4) significant late sequelae affecting intellect and hormonal function are frequent, and may in part be secondary to RT.

The standard therapeutic approach for chiasmatic optic gliomas has been by biopsy or subtotal resection followed by RT. The role of chemotherapy in the treatment of these childhood tumors is unknown. Over the past 7 years, we have treated children harboring chiasmatic optic gliomas with vincristine and actinomycin D without concomitant RT. These agents were chosen because of 1) our initial success with vincristine in the treatment of a child with an optic glioma that recurred following RT; 2) the efficacy of these agents in the treatment of low-grade fibromatosis outside the central nervous system; 3) the lack of significant long-term effects attributed to these agents, which have been in common use for over 20 years; and 4) the concern that the late neuropsychological sequelae seen in our prior patients may be partly due to cranial irradiation, especially in the very young children who represent a significant proportion of our patients. This report summarizes our early results with these drugs in patients with newly diagnosed and recurrent optic gliomas of childhood.
Chemotherapy for childhood optic glioma

TABLE 1
Clinical summary of four cases of recurrent optic glioma*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (mos) at Diagnosis</th>
<th>Initial Treatment</th>
<th>Age (mos) at Recurrence</th>
<th>Clinical Status</th>
<th>Treatment</th>
<th>Follow-Up Duration off Chemo. (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>RT, 5140 rads</td>
<td>59</td>
<td>lethargy, anorexia</td>
<td>subtotal</td>
<td>no 115</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>surgery, RT</td>
<td>128</td>
<td>hyperphagia</td>
<td>none</td>
<td>yes 27</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>RT, 5600 rads</td>
<td>109</td>
<td>minimal vision</td>
<td>subtotal</td>
<td>yes 21</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>RT, 4500 rads</td>
<td>70</td>
<td>decreased vision</td>
<td>none</td>
<td>yes 13</td>
</tr>
</tbody>
</table>

* RT = radiotherapy; chemo. = chemotherapy.

Clinical Material and Methods

Since 1977, all children with chiasmatic optic gliomas, either recurring after RT or newly diagnosed when the patient was aged under 6 years, were offered a program utilizing vincristine and actinomycin D. The chemotherapy regimen was not consistent for the first few patients, but became standardized with time. The first patient treated for recurrence (Case 1) received vincristine alone. The first child treated for newly diagnosed optic glioma (Case 5) received 15 μg/kg of actinomycin D intravenously daily for 5 days, followed by vincristine, 1.5 mg/sq m weekly intravenously for 5 weeks. This was followed by a 4-week rest period. Patients received five cycles of chemotherapy. After the first patient, the number of doses of weekly vincristine was extended to eight before the 4-week rest, and since 1979 the length of treatment has been consistent at six cycles over an 18-month period. The dose of actinomycin D was reduced by 50% for children under 12 months old, and the maximum single dose was 500 μg. Actinomycin D was also reduced by 50% for episodes of neutropenia (absolute neutrophil count below 500 cu mm). The maximum single dose of vincristine was 2.0 mg, and the dose of vincristine was converted to 0.05 mg/kg for children under age 12 months. Vincristine was omitted for 1 week and restarted at a 50% dose if painful neuropathy or obstipation occurred.

Four patients with chiasmatic optic glioma recurrence following irradiation have been treated with chemotherapy (Table 1). All had grade I pilocytic astrocytomas involving the chiasm. At recurrence, 11 to 111 months after the initial diagnosis, the children were aged 59 to 128 months. One of the children (Case 1) had neurofibromatosis. Recurrence was documented clinically in all children, and three had computerized tomography (CT) scans with and without enhancement which showed progressive disease. Two of the children, including one patient (Case 1) who was treated prior to the advent of CT scanning, underwent a second subtotal surgical resection documenting tumor recurrence. The tumors were pilocytic astrocytoma, unchanged histologically from the time of initial diagnosis.

Twelve children have been treated primarily with chemotherapy without concomitant RT (Table 2). The children ranged in age from 6 to 60 months at diagnosis; eight of the children were less than 24 months at diagnosis (median 16 months). Two of the 12 patients had neurofibromatosis, although limited to axillary freckling in one child without a relevant family history (Case 9). Chief complaints included visual dysfunction in 10 children, precocious puberty in one child, and behavioral abnormalities in one. All 12 children had CT scans consistent with optic glioma at the time of diagnosis. Eleven of the 12 had biopsies or partial resections. All tissue obtained was diagnosed as pilocytic astrocytoma. One patient with neurofibromatosis (Case 15) was not biopsied because the CT and ophthalmological findings were thought to be diagnostic.

Patients were followed by serial physical, neurological, and ophthalmological examinations. Growth parameters (height and weight) were obtained during and following treatment. Thyroid function, bone age, growth hormone, and somatomedin C levels were obtained for patients with reduced growth velocity. Computerized tomography with and without contrast enhancement was performed before treatment was begun (except for Case 1 who was treated before CT was available); CT was repeated at least after every two cycles of chemotherapy, and at 3- to 6-month intervals following completion of treatment. At the completion of therapy, neuropsychological function was tested in

TABLE 2
Presentation and treatment of newly diagnosed patients with optic glioma*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (mos) at Diagnosis</th>
<th>Presentation</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>visual change</td>
<td>partial resection</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>visual change</td>
<td>biopsy</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>visual change</td>
<td>partial resection</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>precocious puberty</td>
<td>biopsy</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>visual change</td>
<td>partial resection, shunt</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>visual change</td>
<td>partial resection, shunt</td>
</tr>
<tr>
<td>11</td>
<td>36</td>
<td>behavior problem</td>
<td>none</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>visual change</td>
<td>partial resection</td>
</tr>
<tr>
<td>13</td>
<td>30</td>
<td>visual change</td>
<td>biopsy</td>
</tr>
<tr>
<td>14</td>
<td>13</td>
<td>visual change</td>
<td>biopsy</td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td>visual change</td>
<td>none</td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>visual change</td>
<td>partial resection</td>
</tr>
</tbody>
</table>

* Cases 9 and 15 had neurofibromatosis.
four of seven patients with newly diagnosed optic gliomas who successfully completed therapy; individualized testing was performed in three of these, and school group testing in one. Baseline neuropsychological testing has been performed in the three patients still undergoing therapy.

Results

Recurrent Disease

All four children treated for recurrent disease remain free of progressive disease and have been off chemotherapy for 13, 21, 27, and 115 months (Table 1). The longest tumor-free period was in a patient who received vincristine alone. The three patients on whom CT scanning was performed have shown no further recurrence. Two other children treated before 1977 for recurrent optic glioma with a different chemotherapy regimen showed no response and died.

These four children tolerated their chemotherapy well with no significant toxicity except for transient alopecia. One child had recurrent “colds” and fever while receiving chemotherapy but these were unrelated to neutropenia. Neurological evaluation and visual acuity and fields have been stable in all four patients. Two of these children are presently receiving growth hormone replacement therapy; a third child is below the third percentile for height and weight and the somatotropin C levels are below normal. Two of the four have learning disabilities unrelated to visual limitations and are in special education programs.

Newly Diagnosed Chiasmatic Glioma

Of the 12 patients with newly diagnosed chiasmatic optic glioma, seven completed their chemotherapy course, three are still under treatment, and two stopped chemotherapy because of progressive disease during treatment (Table 3). The two patients who developed progressive disease were then treated with RT. All 12 patients are alive a median of 23 months after diagnosis (range 6 to 76 months).

Of the seven patients who completed their course of chemotherapy, five remain free of progressive disease with stable visual and neurological function 60, 40, 16, 12, and 1 month after finishing treatment. Two of these seven children developed progressive disease (documented clinically and on CT scans), 28 and 12 months, respectively, after completion of therapy. These two patients then received RT and are alive with stable disease 72 and 12 months since diagnosis of recurrence (3 and 44 months after RT).

Computerized tomography scans were obtained in all 12 patients prior to and serially during and following chemotherapy (in those who completed treatment). In six patients CT showed shrinkage of the tumor, in one

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Follow-Up Duration Off Treatment</th>
<th>CT Response</th>
<th>Clinical Status &amp; Outcome</th>
<th>Intellectual Status</th>
<th>Endocrine Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4 yrs</td>
<td>improvement</td>
<td>stable vision</td>
<td>normal; IQ: verbal 96, performance 76</td>
<td>normal</td>
</tr>
<tr>
<td>6</td>
<td>4 yrs</td>
<td>initially stable; progressive disease 2 yrs 6 mos posttreatment</td>
<td>initially stable; headaches, oculomotor paresis 2 yrs 6 mos post RT; now stable</td>
<td>normal (no formal testing; regular school)</td>
<td>normal</td>
</tr>
<tr>
<td>7</td>
<td>3 yrs 4 mos</td>
<td>improvement</td>
<td>stable vision</td>
<td>verbal &amp; full-scale IQ 100</td>
<td>precocious puberty (accelerated bone age)</td>
</tr>
<tr>
<td>8</td>
<td>1 yr 2 mos</td>
<td>improvement</td>
<td>stable</td>
<td>normal (not tested; regular school)</td>
<td>normal</td>
</tr>
<tr>
<td>9</td>
<td>1 yr</td>
<td>improvement</td>
<td>stable; no headaches</td>
<td>normal full-scale IQ 119</td>
<td>normal</td>
</tr>
<tr>
<td>10</td>
<td>1 yr</td>
<td>stable 1 yr; then progressive disease</td>
<td>stable 1 yr; then decreased vision; received RT</td>
<td>IQ 85 prior to RT; not tested since</td>
<td>normal</td>
</tr>
<tr>
<td>11</td>
<td>---</td>
<td>initial improvement; then stable</td>
<td>decreased vision 9 mos into treatment; received RT; now stable 9 mos later</td>
<td>not tested</td>
<td>normal</td>
</tr>
<tr>
<td>12</td>
<td>1 mo</td>
<td>stable</td>
<td>improved hemiparesis; stable vision</td>
<td>normal development (no formal testing)</td>
<td>normal</td>
</tr>
<tr>
<td>13</td>
<td>on treatment</td>
<td>partial response (at 3 mos)</td>
<td>stable vision</td>
<td>normal development</td>
<td>normal</td>
</tr>
<tr>
<td>14</td>
<td>on treatment</td>
<td>stable</td>
<td>stable vision</td>
<td>normal development</td>
<td>normal</td>
</tr>
<tr>
<td>15</td>
<td>9 mos</td>
<td>progressive disease, 3 mos</td>
<td>decreased vision; received RT; stable 6 mos later</td>
<td>normal development</td>
<td>normal</td>
</tr>
<tr>
<td>16</td>
<td>on treatment</td>
<td>improvement</td>
<td>blind; improved hemiparesis; developmental delay</td>
<td>delayed development (DQ 50)</td>
<td>normal</td>
</tr>
</tbody>
</table>

* Improvement: smaller tumor, less than 50% tumor reduction; partial response: greater than 50% tumor reduction. CT = computerized tomography; RT = radiation therapy; IQ = intelligence quotient; DQ = development quotient.
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there was greater than 50% reduction in tumor size and in the others less than 50% reduction. No child has shown CT evidence of complete disappearance of the tumor. In one of these six patients CT has shown recurrent disease 12 months posttreatment. Another child with initial tumor shrinkage on CT scans developed progressive loss of visual acuity during treatment and was begun on RT; his visual acuity then stabilized. Computerized tomography has shown the disease to be stable during treatment in five patients: one is presently receiving chemotherapy, two remain stable off treatment, and two developed CT evidence of progressive tumor growth after treatment. In the remaining child CT scanning showed progressive disease 3 months into treatment.

The four patients who developed clinical or radiographic evidence of progression received radiation (5500 rads): three showed tumor shrinkage (less than 50% in all) and one has had no change.

The 12 children treated with chemotherapy for primary therapy have shown few adverse effects. Growth velocity has been normal in all except for the child with precocious puberty who has accelerated growth. Of the six children who completed treatment and have been followed for greater than 1 year, three are above the 90th percentile, two are at the 50th percentile, and one is at the 25th percentile for height. One child presented with some growth failure but by the age of 3 years had achieved the 50th percentile for height and weight.

Five children have finished chemotherapy and are stable. Three have undergone neuropsychological testing and are normal with overall verbal intelligence quotients of 96, 100, and 119, respectively. Four of these patients are of school age and are in regular classrooms. One child (not formally tested) had a history of learning problems prior to diagnosis and is receiving special education.

These 12 children have received a total of 55 cycles of chemotherapy. Over 80% of the planned dose of vincristine was given. Two cycles of actinomycin D caused neutropenia with absolute neutrophil counts below 1000/cu mm. There was no associated infection or fever. One cycle caused thrombocytopenia below 50,000 cu mm, but no clinical bleeding occurred. No child has been hospitalized for treatment of toxicity.

Discussion

The controversies over the natural history and optimal treatment of children with chiasmatic optic glioma stem from very plausible but opposite interpretations of the published experiences. 5–7,9,11,14,16,18,22,23,25,27,31,34–39 Our own data support the concern that optic glioma is potentially an aggressive tumor with a possible fatal outcome. 28 It is also apparent from the literature that some children with this tumor, who have not had definitive treatment, have become long-term survivors. 14,23,29 Unfortunately, we do not know how to select at diagnosis which tumors will act aggressively and which will not. Some studies suggest that patients with neurofibromatosis may have tumors that behave in a more benign fashion, 6,18,21,23,27,31,39 although others have found the opposite. 2 Even if tumors in children with neurofibromatosis do act less aggressively, this behavior is not absolute, and the manifestations of neurofibromatosis may not present until several years after the child’s optic glioma first presents.

A second part of the controversy centers around the efficacy of RT in treating optic gliomas. 10,20,24,34 Virtually all studies are dependent on survival as the endpoint. In series where RT has been used, the survival periods appear to be longer than in series of children with posterior chiasmatic lesions with no definitive therapy. 6,7,25,29,34,37

Response to therapy is difficult to assess. Most patients are young; 75% present in the first decade of life, making evaluation of vision and intellect imprecise. Clinical signs and symptoms of progression may be due to complications of surgery and RT, and not to actual tumor growth.

Few patients with chiasmatic optic glioma have been studied by CT for their response to treatment, since CT is a recent imaging technique and optic glioma studies require many years to find and follow patients. In the few patients with optic gliomas who were followed by CT after receiving RT, varying degrees of response from complete resolution to stable disease have been noted. 5,7,20 Patients with stable disease seem to do as well clinically as those who show tumor regression. 7,20

Investigators have been unable to consistently correlate RT with improvement in visual status. 9,17,31,34,37 Late endocrinopathies and intellectual retardation are frequent and may be caused by these tumors. 5,7,10,26,37 Unfortunately, both intellectual deficits and endocrinopathies have been related to RT to the central nervous system, especially in young children. 1,12,25,32

This preliminary report offers an alternative approach to RT. Our 100% survival data are as good as in any previous study. Our patients have been followed by CT, and objective response to chemotherapy has been demonstrated. In some patients, there has been long-standing disease control. Eight of 12 newly diagnosed patients, all under 5 years of age, have never had to receive RT. Even those who ultimately developed progressive disease following chemotherapy have apparently responded well to RT and may have been spared some of the potentially deleterious effects of RT at a time when their brain was less mature. These preliminary results also suggest that the combination chemotherapy has not had deleterious effects on neuropsychological or neuroendocrinological function, and that such therapy is a reasonable alternative to radiation in young children with chiasmatic optic gliomas.

Acknowledgment

The authors express their appreciation to Margaret Einenkel for help in the preparation of the manuscript.
References


Manuscript received March 8, 1985.
This work was supported in part by Grant CA-14485 awarded by the National Cancer Institute.
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