Chemotherapy as an adjunct in the initial management of cerebellar medulloblastomas

A preliminary report

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Eight consecutive children with biopsy-proven cerebellar medulloblastoma were treated with a combination of whole neuraxis radiation and prolonged chemotherapy using vincristine and cyclophosphamide. There was no evidence of tumor recurrence in the follow-up period, which ranged from 16 months to 7 years and 8 months following diagnosis. Morbidity associated with this regimen has been infrequent and easily reversible.

KEY WORDS

medulloblastoma • pediatric brain tumor • chemotherapy • vincristine • cyclophosphamide

This study reports on eight children with biopsy-proven medulloblastoma, who have completed a course of radiation therapy to the entire neuraxis followed by adjunctive chemotherapy (Table 1).

Clinical Material and Methods

All the patients had midline cerebellar tumors, and all were under the age of 13 years at the time of diagnosis. Six children had surgery and radiation therapy at this institution and two were referred for evaluation during the course of radiation therapy elsewhere. Chemotherapy was begun 4 to 6 weeks after completion of radiation therapy at a time when peripheral blood counts indicated resolution of clinically significant bone marrow depression induced by radiation. After completion of radiation therapy, neurological evaluation and computerized tomography (CT) were carried out to evaluate the amount of residual tumor and the presence or absence of hydrocephalus. In some of the earlier cases, this initial assessment with CT was replaced by technetium brain scan. The patients then received intravenous vincristine sulfate (1.5 mg/sq m) alternating weekly with cyclophosphamide (300 mg/sq m) by mouth (Table 2).

The toxicity of vincristine sulfate and cyclophosphamide therapy is well recognized, and side effects include pancytopenia, hair loss, peripheral neuropathies, and hemorrhagic cystitis. Weekly outpatient assessment and weekly or biweekly blood counts were performed to monitor these side effects. Examination included neurological assessment. The dose of cyclophosphamide was adjusted to maintain total neutrophils above 1500/cu mm. Oral fluid intake was increased when cyclophosphamide was given to decrease the likelihood of bladder irritation. Development of neuritic pain or neuropathy other than alteration in deep-tendon reflexes was considered an indication to decrease the dose of vincristine.

In addition to the routine neurological examinations and blood counts throughout, the children were evaluated at 6-month intervals during the period of chemotherapy, and at yearly intervals following completion of chemotherapy. Evaluation was carried out in the Children’s Research Center at the Yale-New Haven Hospital, and included an electroencephalogram, skull films, CT, and whole-body technetium scan. In the first years of the study, lumbar puncture and radionuclide brain scan were used. Chemotherapy was continued for a period of 2 years.
TABLE 1
Age and follow-up period in eight children with cerebellar medulloblastomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Time From Diagnosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 yrs 5 mos</td>
<td>M</td>
<td>7 yrs 8 mos</td>
</tr>
<tr>
<td>2</td>
<td>11 yrs 5 mos</td>
<td>F</td>
<td>7 yrs 4 mos</td>
</tr>
<tr>
<td>3</td>
<td>7 yrs 4 mos</td>
<td>M</td>
<td>5 yrs 3 mos</td>
</tr>
<tr>
<td>4</td>
<td>6 yrs 4 mos</td>
<td>F</td>
<td>4 yrs 6 mos</td>
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<tr>
<td>5</td>
<td>11 yrs 8 mos</td>
<td>F</td>
<td>4 yrs 3 mos</td>
</tr>
<tr>
<td>6</td>
<td>7 yrs 2 mos</td>
<td>M</td>
<td>3 yrs 11 mos</td>
</tr>
<tr>
<td>7</td>
<td>4 yrs 9 mos</td>
<td>F</td>
<td>2 yrs 10 mos</td>
</tr>
<tr>
<td>8</td>
<td>8 yrs 2 mos</td>
<td>M</td>
<td>1 yr 4 mos</td>
</tr>
</tbody>
</table>

*All patients were evaluated between July and September, 1978, except for one (Case 2) who was evaluated in December 1977.

Results of Treatment
Morbidity has been mild and either easily reversible or not considered significant enough to require therapy. Loss of deep-tendon reflexes was a constant finding in all the children, but was the only significant indication of peripheral neuropathy. Although bone marrow suppression did occur, only brief interruption of therapy was required for reversal and there were no associated clinical symptoms. Dosage of medication may require adjustment to prevent repeated episodes. Failure to gain weight was a frequent parental complaint, but regular school attendance attested to the general well-being of the children. No other significant untoward effects were noted. Although intracranial calcifications have been reported from this institution in 10 of 39 children with leukemia who were treated with radiation therapy, intrathecal methotrexate, and systemic chemotherapy, no evidence of intracranial calcification was noted in these children.

All patients were last evaluated in the summer of 1978, save for one (Case 2), who was last seen in December, 1977; a letter received from her in the summer of 1978 informed us that she was newly married and feeling well. Seven of the eight patients completed a 2-year course of chemotherapy without evidence of recurrent or metastatic disease during follow-up periods ranging from 2 years 10 months to 7 years 8 months following diagnosis (Table 1). The eighth patient is now in his second year of chemotherapy and is also free of disease. Two additional children have been followed for less than 6 months, and are not included in this report. They also are free of disease.

Discussion
Both vincristine sulfate and cyclophosphamide have been reported to produce prolonged remission of the central signs and symptoms of recurrent medulloblastoma. In these reports, chemotherapy was not started until there was clinical evidence of tumor recurrence and only a single chemotherapeutic agent was used. It is well established that a combination of two agents, each with independent toxicity, can produce additional tumor toxicity with minimal increase in morbidity. Combination therapy with vincristine sulfate and cyclophosphamide has been shown to be effective in the control of childhood neuroblastoma, a tumor that histologically closely resembles medulloblastoma. The decision to use adjunctive chemotherapy in the treatment of medulloblastomas was initiated by our results in the treatment of two children referred with clinical evidence of recurrent medulloblastoma. Both had undergone surgery and radiation therapy less than 1 year before examination. Chemotherapy was followed by transient improvement, which was maintained for 10 months in one child and for 6 months in the other.

It appeared from these experiences that chemotherapy with vincristine sulfate and cyclophosphamide had only limited influence in the presence of widespread large tumor masses. However, the cell kill caused by antineoplastic agents follows first-order kinetics; that is, a constant percentage of cells rather than a constant number is killed by a given therapeutic agent. Therefore, it seemed reasonable that chemotherapy used early at a time when the number of residual tumor cells is relatively small, that is, following surgery or radiation therapy, might be considerably more effective. Additionally, it has been suggested that chemotherapeutic agents which are normally excluded from the brain may be permitted to diffuse through the blood-brain barrier following cranial irradiation at a dose of 2000 rads or more.

The vinca alkaloids are cell-cycle-specific agents and block mitosis with metaphase arrest. Most of the biological activity of the drug can be explained by its ability to bind specifically with the protein tubulin, a key component of microtubules. Through disruption of the microtubules of the mitotic apparatus, cell divi-

TABLE 2
Treatment protocol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgery</td>
<td>3 cases</td>
</tr>
<tr>
<td>biopsy</td>
<td></td>
</tr>
<tr>
<td>subtotal excision</td>
<td>5 cases</td>
</tr>
<tr>
<td>radiation therapy</td>
<td>6-7 wks</td>
</tr>
<tr>
<td>posterior fossa</td>
<td>4600-5200 rads</td>
</tr>
<tr>
<td>whole brain</td>
<td>4000-4300 rads</td>
</tr>
<tr>
<td>spinal cord</td>
<td>3000-3750 rads</td>
</tr>
<tr>
<td>chemotherapy</td>
<td>2 yrs</td>
</tr>
<tr>
<td>vincristine (intravenously every 2 wks)</td>
<td>1.2-2 mg/sq m</td>
</tr>
<tr>
<td>cyclophosphamide (by mouth every 2 wks)</td>
<td>200-500 mg</td>
</tr>
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</table>
Adjunctive chemotherapy in cerebellar medulloblastomas

Fig. 1. Follow-up period (cross-hatched bar) and risk period (white bar) in eight cases of cerebellar medulloblastoma.

ion is arrested in metaphase. In the absence of an intact mitotic spindle, chromosomes are dispersed. Apparently the inability to segregate chromosomes correctly leads to cell death.5

Cyclophosphamide is a nitrogen mustard belonging to the class of alkylating agents. In contrast to the vinca alkaloids, the alkylating drugs, although proliferation-dependent, are not cell-cycle-specific and may act on cells at any stage of the cycle. However, the cytotoxic action is usually expressed when the cell enters the S phase of progression and progression is blocked at G1.7

The low toxicity of vincristine sulfate for normal cells is reflected in its use in the presence of impaired marrow function. Peripheral neuropathy is the most common manifestation at usual clinical doses and is the limiting factor. Asymptomatic loss of ankle jerks is the earliest sign of toxicity, and may be followed by numbness, tingling, foot drop, ataxia, and weakness. Vincristine sulfate appears to be remarkably well tolerated by children, and severe neuropathy is uncommon. None of the severe acute central nervous system manifestations reported with nitrogen mustard have been noted with cyclophosphamide. Damage to megakaryocytes and thrombocytopenia is much less common with this drug. Sterile hemorrhagic cystitis is reported in 5% to 10% of cases and is an indication for cessation of therapy. Nausea and vomiting may occur. As noted, the morbidity in our series has been very mild and easily reversible.

Although it is known that tumor kill follows first-order kinetics, less is known about the cell kinetics of the tumor itself. Duration of therapy must of necessity be based on other criteria, which remain empirical. After radiation therapy, the recurrence rate for medulloblastoma in most published series appears to peak in the first 2 years.5 It seemed reasonable that treatment during the first 2 years, when clinical experience indicated tumor growth to be most aggressive, might lead to a higher rate of survival than that reported with surgery and radiation alone, or indeed with shorter periods of adjunctive chemotherapy. Survival rates of 60% to 70% have been reported at 5 years after irradiation,18 although, in general, survival rates of 40% are more usual, with a high percentage of the deaths occurring in the first 2 years.8,13 It may well be, however, that the use of Collins’ “law for embryonal tumors”14 may be more applicable. According to Bloom, et al.,1 in their report on a large series, no child who passed the period of risk, that is, age at the time of diagnosis plus 9 months, died of his disease. Although prolonged survival periods are included in our series, only one child (Case 1) has passed this high-risk period (Fig. 1).
Conclusions

We have neither the length of follow-up period nor the number of patients necessary to propose that prolonged adjunctive chemotherapy represents a significant advance in the treatment of medulloblastoma. Rather, we would like to present this as a preliminary report and suggest that ease of administration, low morbidity, and the promising results obtained with this protocol warrant its consideration in the management of these highly malignant tumors of childhood.

References


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