Response to vincristine of recurrent brain tumors in children

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Seventeen children with clinical evidence of a recurrent brain tumor were treated with vincristine 1.5 mg/sq m weekly for 12 weeks with doses on alternate weeks thereafter. Eight of the 16 patients who received four or more doses of vincristine showed significant objective responses; these included patients with high- and low-grade astrocytomas and patients with medulloblastoma. Six of the eight who responded remained asymptomatic for more than 2 years. The toxicity encountered was minimal except for seizures possibly related to vincristine in three children, who were able to resume treatment. Vincristine therapy results in long-term regression in a wide variety of pediatric brain tumors and causes little or no toxicity.

KEY WORDS • brain tumor • chemotherapy • vincristine

Since the advent of cancer chemotherapy, numerous agents have been tried in the treatment of intracranial neoplasms with initially disappointing results. More recently, individual cases and reports of small series have cited patient responses to methotrexate, procarbazine, vincristine (VCR), as well as the nitrosoureas, used alone or in combination. The chemotherapy trials have been recently reviewed. Based on the responses to VCR reported by several investigators, the Oncology and Neurosurgery Divisions of the Children's Hospital of Philadelphia elected to conduct a Phase 2 trial of this agent for children with recurrent brain tumors.

Clinical Material and Methods

All patients with recurrent primary brain tumors were eligible for the study, regardless of histology, after it was determined that they would no longer benefit from further surgery or radiation therapy. The chemotherapy regimen called for intravenous VCR, 1.5 mg/sq m weekly (2 mg maximum single dose) for 12 weeks, then every other week for 2 years. Recurrence of the tumor or progressive disease terminated the study. Recurrence was defined by clinical evidence of progression with recurrent symptoms or signs. Surgical, radiological, or histological confirmation of recurrence was not mandatory. Each child was evaluated by physical examination and complete blood studies before initiation of treatment and then at least once monthly. Other studies were done on an individual basis depending on the type and location of the lesion and its pattern of recurrence or spread. The protocol did not limit the use of steroids at the time of recurrence; however, steroid dosage was tapered off as rapidly as possible.
Between January, 1970, and June, 1973, 17 children under 16 years of age were included in the study and received chemotherapy for periods ranging from 2 weeks to 24 months. An adequate trial of 4 weeks was achieved in 16 patients.

**Summary of Cases**

All 17 children entered into the study are included in the evaluation. Table 1 lists their diagnoses, other defining data, date of entry into the study, duration of VCR treatment, and their response to it. All diagnoses were histologically proved by biopsy or autopsy except in Case 2; during exploration of the posterior fossa in this patient a biopsy was considered unwarranted, and an autopsy was not obtained. All patients had previously received at least one course of radiation therapy. One patient (Case 15) died shortly after receiving the second dose of weekly VCR and cannot be evaluated for response. The other 16 received at least 4 weeks of treatment.

Significant responses, defined as stabilization or improvement of neurological status, were obtained in eight of the 16 patients who received an adequate trial, with durations lasting from 2 months to more than 4 years (Table 2). The response of 2 months in one patient (Case 11) was short since the parents withdrew their child while improvement continued. The median duration of response was over 29 months. Significant responses were obtained for all types of tumors, low-grade as well as high-grade gliomas and medulloblastoma.

**Illustrative Cases**

Details of the courses of the following two patients illustrate the type of response seen.

**Case 8.** This 2½-year-old boy developed a left hemiplegia in July, 1970. A carotid arteriogram showed a right frontoparietal mass which proved to be a Grade III cystic astrocytoma. The mass was subtotally resected, followed by radiation therapy with 4650 rads in 8 weeks. There was partial improvement of the left hemiplegia, and a repeat arteriogram in January, 1971, was normal. Some months later the patient complained of drowsiness and increasing left-sided
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### TABLE 2

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Evidence of Recurrence or Progression</th>
<th>Evidence of Response</th>
<th>Length of Time to Response</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>pontine glioma</td>
<td>progressive ataxia; unable to withdraw steroids</td>
<td>stabilization of neurological signs; able to remove steroids</td>
<td>8 weeks</td>
<td>alive without disease</td>
</tr>
<tr>
<td>5</td>
<td>pontine glioma</td>
<td>new involvement of 7th, 9th, and 10th nerves</td>
<td>markedly improved 7th, 9th, and 10th nerves</td>
<td>6 weeks</td>
<td>physically retarded, mentally bright alive with normal vision rt eye</td>
</tr>
<tr>
<td>6</td>
<td>optic glioma</td>
<td>rt eye: 20/200; lt eye: no light perception; biopsy of recurrence</td>
<td>rt eye: 20/40; lt eye: no light perception</td>
<td>4 months</td>
<td>alive without disease</td>
</tr>
<tr>
<td>8</td>
<td>astrocytoma III</td>
<td>arteriogram 1/71, no evidence of tumor; arteriogram 11/71, recurrence; progressive It weakness</td>
<td>improvement of lt hemiparesis</td>
<td>4 weeks</td>
<td>physically normal, mentally slow</td>
</tr>
<tr>
<td>10</td>
<td>medulloblastoma</td>
<td>increased intracranial pressure; unable to sit up</td>
<td>all signs resolved except for mild ataxia; attended regular school</td>
<td>2 weeks</td>
<td>died of disease after 17 month response</td>
</tr>
<tr>
<td>11</td>
<td>medulloblastoma</td>
<td>increased intracranial pressure; unable to sit alone</td>
<td>able to sit alone and walk with support</td>
<td>3 weeks</td>
<td>parents stopped therapy, died of disease</td>
</tr>
<tr>
<td>13</td>
<td>medulloblastoma</td>
<td>mild ataxia; spinal fluid cytology showed malignant cells</td>
<td>no evidence of progression of signs</td>
<td>unevaleuable</td>
<td>alive without disease</td>
</tr>
<tr>
<td>17</td>
<td>malignant glioma, cord metastases</td>
<td>spinal fluid cytology; unable to walk due to back pain</td>
<td>back pain decreased; able to walk</td>
<td>4 weeks</td>
<td>alive with partial paraplegia</td>
</tr>
</tbody>
</table>

weakness, and a further study in November, 1971, showed recurrent tumor. Treatment with VCR was instituted and continued for 2 years; an improvement was seen within 4 weeks. In July, 1975, a 4 × 4 cm mass, which proved to be a foreign body granuloma, developed in the area of the craniotomy flap. A moderate spastic left hemiparesis remains and the patient attends a school for the handicapped.

**Case 10.** This patient had a medulloblastoma which had been treated initially with radiotherapy. It recurred 2 years later and was subjected to a second course of radiotherapy. A shorter period of control was obtained at this time. At the time VCR therapy was started, the patient had severe signs of cerebellar dysfunction and increased intracranial pressure. Within 14 days after chemotherapy administration was begun, he was able to sit alone and eat without assistance; shortly thereafter he was back at school with only minimal ataxia and no signs of increased intracranial pressure. He remained in a stable state for almost 17 months while receiving VCR but then developed signs of recurrence and died shortly thereafter of progressive disease.

Four patients (Cases 2, 3, 4, and 7) were receiving steroids at the time VCR therapy was begun, and three of these (Cases 2, 3, and 7) showed no response to VCR. The fourth (Case 4), however, who had been steroid-dependent prior to initiation of VCR, had all steroids tapered off without any exacerbation of signs or symptoms following 8 weekly doses of VCR.

**Toxicity**

The degree of toxicity encountered was mild. In all patients except one, constipation was readily controlled with stool softeners during the initial period of weekly VCR. Only one patient required repeated doses of milk of magnesia and occasional enemas. Three patients had seizures while on VCR, but ad-
ditional VCR was tolerated without further seizures. Two patients had mild jaw pain relieved by analgesics (acetaminophen), and neither required reduction of drug doses. One patient had generalized muscle aches following the fifth weekly dose of VCR. The sixth dose was omitted, and then the patient was restarted at 75% of the calculated dose for one dose only. All further doses were at full strength.

Hematological toxicity also was minimal. No patient's platelet count fell below 150,000/cu mm nor did any white blood count fall below 3000/cu mm. In two patients the hemoglobin levels dropped below 9 gm% during the initial 12 weeks of VCR; these children were given blood transfusions. In three other patients the hemoglobin levels fell to between 9 and 10 gm%, but rose spontaneously without the necessity of reducing the dose of VCR. The five patients who received VCR for 2 years had a median hemoglobin level of 12.3 gm% at the end of the 2-year period. No unusual or opportunistic infections were noted.

Discussion

The existence of a blood-brain barrier is one reason given for failure of chemotherapy in intracranial neoplasms, and much attention has been directed to the creation of lipid-soluble agents. Actually, much of an intracranial tumor has an effective blood supply, and the problem of a blood-brain barrier occurs only at the tumor-brain interface where the diffusion of intravascular molecules into the tumor is limited by the lipid content of the brain.5,17,31,38 Vincristine is known to cause peripheral neurotoxicity,20,21,29,30,32 but does not usually have an adverse effect on the central nervous system, in spite of its partial lipid solubility.5 Vincristine apparently acts on the spindle mechanism of dividing cells, and the relatively low mitotic activity of brain tumors probably accounts for the slow response in several reported patients.5,37 Because of the relatively slow rate of response, it is difficult to determine what is an adequate trial. Three of our patients received only four or five doses, and in retrospect, these trials may have been inadequate. A minimum of eight doses of weekly VCR should be given unless there are rapidly progressive signs after the fourth dose.

The present results are consistent with previously reported case studies, except for our six long-term survivors who do not appear now to have active disease. After the initial response, the improvement of these patients was usually rapid and soon thereafter reached a long-lasting plateau. The degree of clinical recovery may be dependent upon the amount of permanent damage that existed at the time therapy was initiated.

In five patients with pontine gliomas and clinical signs of progressive disease, two had significant responses lasting longer than 2 years. Lassman and Arjona's study15 of 27 children with pontine glioma showed no remission lasting longer than 18 months when treated with high voltage irradiation. Also, once a child had relapsed after radiotherapy, second courses of radiotherapy caused no significant responses.10,19,36

Optic gliomas are very low-grade tumors with variable natural history.11 In an uncontrolled study with small numbers, it is difficult to determine the exact role of VCR in the dramatic response seen in one child (Case 6). The relentless progressive destruction of her optic nerve was reversed concurrently with beginning VCR treatment, and good vision returned over a period of several months. This response is much like that reported by Lassman, et al.16

The response of three out of four children with medulloblastoma is better than that reported previously.4 Because of its rapid growth rate and relatively high mitotic index, medulloblastoma would be the brain tumor most likely to respond to the action of VCR, which is dependent at least in part on cell division.9 In Case 11, the patient responded to a level where she still had marked physical limitations; this may suggest that her residual brain damage was so great that regression of the tumor could not produce significant improvement in her symptoms and signs. In Case 13, spinal fluid cytology was positive for tumor cells at the first signs of increasing ataxia and personality change. This patient's response is of long duration with virtually no physical deficit.

The results of surgery and radiation therapy in high-grade astrocytomas have been disappointing.34,38 Radiation therapy increases the length of survival, but usually for no longer than 2 years. The response of our patient (Case 8), was truly remarkable. He
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had both clinical and radiographic evidence of recurrence, and was treated only with VCR.

The overall toxicity noted was mild. Only two children had to have any dose reductions and both were able to return rapidly to the prescribed levels of VCR. The occurrence of a seizure following a dose of VCR has been observed before. Seizures in three children within a few days of VCR therapy must be considered a manifestation of toxicity although seizures could be a result of coexisting brain pathology. All three patients were placed on maintenance phenobarbital therapy and no further seizures occurred in spite of continued VCR treatment. The frequency of seizures apparently related to VCR in our patients with primary intracranial disease is considerably higher than the approximate 1% seen in children treated with VCR for other malignancies. The pre-existence of intracranial pathology may well make these children more susceptible to this side effect.

The amount of peripheral neuropathy, if any, caused by VCR was apparently submerged within the significant neurological abnormality caused by the primary disease. The children who finished the 12 weekly doses and went on to prolonged alternate-week therapy were able to tolerate the medication with no significant long-term side effects. Total alopecia was noted in all children while receiving the 12 weekly doses. During the alternate-week therapy, a scalp tourniquet allowed most children to have normal regrowth of hair.

Conclusions

The responses of our eight patients and those reported by other investigators strongly support the value of VCR in the treatment of a wide range of brain tumors. The toxicity encountered in these children was minimal except for seizures which were not recurrent or dose-limiting. The response rates by histological type cannot be calculated from such a small sample, but these results probably equal those of any other single agent. Indeed, three multi-agent trials reported do not have response rates greater than those seen here despite the superiority of multi-agent therapy in other childhood malignancies. At this time, controlled Phase 3 trials need to be initiated. Treatment should be started early before severe neurological impairment becomes permanent.

References


This study was supported by USPHS Grants CA 14489 and CA 11796 from the National Cancer Institute.