Medulloblastoma in children

Survival and treatment

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The authors review treatment and results in 45 cases of medulloblastoma arising in childhood. The surgical mortality rate observed was 11%. Of those completing postoperative cerebrospinal irradiation at this institution, 53% have survived for 3 years, 41% for 5 years, and 22% for 10 years. The extent of surgical resection of the cerebellar tumor had no significant bearing on the prognosis. Those cases remaining free of recurrent disease had received significantly higher doses of postoperative irradiation, approaching 5000 rads to the whole brain or posterior fossa and 4000 rads to the spinal axis. Repeat irradiation and chemotherapy (vincristine, the nitrosoureas, and methotrexate) provided good palliation in most cases and significantly extended the survival time. However, 28 of 29 patients who developed locally recurrent or metastatic disease have died. Vincristine was considered the chemotherapeutic drug of choice and in 14 cases its use was associated with remissions lasting 2 to 18 months. The combination of chemotherapy and repeat irradiation was followed by remissions of longer duration compared to retreatment by irradiation alone when the disease recurred within 2 years. The inherent value of ventricular shunting procedures and steroid therapy for recurrent intracranial disease could not be ascertained. The findings in this study suggest that the primary treatment of medulloblastoma should be extended to include chemotherapy and optimum radiation therapy, since once recurrent disease develops retreatment is essentially palliative and a fatal outcome is virtually certain.

KEY WORDS • medulloblastomas • chemotherapy • radiation therapy • childhood tumors

MEDULLOBLASTOMA was once generally regarded as a rapidly and uniformly fatal brain tumor in children. Sporadic examples of long-term survival after operation and radiation therapy were often attributed to atypical behavior of this disease in older patients, or to misdiagnosis. More recently it has been increasingly recognized that a significant proportion of cases successfully completing cerebrospinal axis irradiation survive for years without evidence of recurrent disease. Survivals up to 50% at 3 years, 40% at 5 years, and 30% 10 years after the diagnosis was established have been documented in some series. This experience has fostered the belief, particularly among radiotherapists, that some children with medulloblastoma can hope for a cure after postoperative cerebrospinal axis radiation. It is also apparent, however, that since

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this disease can recur many years later, the long-term survivors may continue indefinitely at risk of relapse. This review analyzes the influence of treatment on the prognosis for indefinite survival and the present results of repeat irradiation with and without various forms of chemotherapy for metastatic and recurrent medulloblastoma.

Clinical Material and Methods

Summary of Patients

From 1953 through 1973, 45 children with medulloblastomas were treated at this institution, and were followed through 1975. Thirty-seven of these patients underwent primary treatment at this medical center. Eight additional patients who had surgery and radiation therapy elsewhere were subsequently treated here for recurrent disease. Of the 45 cases, 38 were observed since 1960 and were known to the first author during life. Follow-up studies were complete in all cases, to death or for periods of 2 to 13 years after the diagnostic operation in the survivors. The diagnosis of medulloblastoma was confirmed histologically in all patients. In patients who died, the pertinent clinical information indicated that death was due to recurrent disease.

At the time of diagnosis the 37 patients treated primarily at this institution ranged in age from 1 to 16 years with mean and median ages of 8 years. Thirteen of them were 5 years of age or younger; 11 were between 5 and 10 years of age; and 13 patients were 10 to 16 years of age. Of these, 18 were male and 19 were female. The eight recurrent cases in this series ranged in age from 5 to 16 years at the time the tumor was diagnosed with mean and median ages of 9 years. Seven of this group were boys and one was a girl.

Treatment of Primary Tumor

The extent of tumor removal after wide suboccipital craniectomy varied among these 45 patients from a diagnostic biopsy to radical or grossly total excision of the neoplasm. We did not feel it was feasible to attempt any form of operative staging retrospectively from the patients' clinical records. Ventricular shunting was done preoperatively in one case and in the early postoperative period in five. Three others had Torkildsen shunts placed during the surgical operation. Forty of the patients completed a primary course of external beam radiotherapy to the entire central nervous system (CNS) except for the rostral cerebrum in five cases. In most cases cobalt teletherapy was employed. The dose in rads was somewhat variable among these patients but over three fourths received 4000 rads or more to the whole brain including the posterior fossa, plus 3000 to 4000 rads to the spinal axis. In the more recent cases, typically, 4000 rads were delivered to the CNS with an additional increment of 1000 rads to the posterior fossa, in five fractions a week, over 4 to 6 weeks.

Treatment of Recurrent Tumor

Diagnosis and localization of recurrent disease were determined from examination of the patients or review of the clinical records, and in most of the retreated cases confirmed by cerebrospinal fluid cytology, myelography, serial radioisotopic brain scanning, cerebral angiography, ventriculography, or biopsy. In terminal cases with uncontrolled, probably disseminated disease, recurrences were categorized at the more manifest intracranial or intraspinal site. Spinal metastases were reirradiated at doses of 2000 to 4000 rads. Intracranial disease was retreated in the range of 2000 to 5000 rads to the whole brain or posterior fossa depending on the extent, dose, and date of previous irradiation to the CNS.

Vincristine chemotherapy was generally given at doses of 1 to 2 mg/sq m by weekly intravenous injections. The duration of vincristine chemotherapy varied from several weeks to several months on a continuous basis and over longer intervals on an interrupted schedule. Methotrexate and the nitrosoureas were the other chemotherapeutic agents used on more than one occasion. Methotrexate was administered into the lumbar thecal sac or the lateral ventricle at doses of 9 to 12 mg/sq m, repeated as feasible up to four times over several weeks. We gave bis-chloroethyl-nitrosourea (BCNU) intravenously in doses of 60 to 100 mg/sq m on two successive days, and methyl-1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (MeCCNU) was administered as a single oral dose of 130 to 220 mg/sq m; both drugs were repeated bimonthly if possible.

The individual variations found necessary in chemotherapeutic management were largely attributable to the fragile condition of
The results in 32 children who completed primary surgical and radiation treatment for medulloblastoma at this institution are shown as a survival curve (Fig. 1). The slope of the curve in this group has a roughly biphasic configuration. The initial mortality is precipitous over the first 2 or 3 years, by the end of which time the cumulative total reaches 47%. Subsequently there is a continuous late mortality among the survivors of 5% to 10% per year to 13 years after diagnosis. The proportion of patients surviving at 5 years is 41%, and it declines to 22% 10 years after the initial surgery and radiotherapy.

Twelve patients are living at this time, and the nine patients who have been followed for periods of 3 to 13 years have remained free of their disease over an average postoperative interval of 7.5 years. Four of the nine long-term survivors have lived longer postoperatively than the sum of their age in years at diagnosis plus 9 months. Six of the children with long survival are perfectly normal. One has a nonincapacitating cerebellar ataxia. Two have required special education for mild mental deficiency; one of these has also had some retardation of growth. These two patients were under 2 years of age when diagnosed and received radiation doses of 4000 to 4500 rads to the brain. Two other patients have been followed for more than 2 years with no sign of recurrent disease, and one patient remains well more than 2 years postoperatively after prior successful treatment of a spinal metastasis.

Results

Primary Treatment and Survival

Four of the patients operated on for medulloblastoma at this institution died within 2 weeks, giving a surgical mortality rate of 11%. One other child died of his disease during the fifth postoperative week while receiving radiation therapy, giving a patient mortality rate at this center of 14%. The operative mortality was confined to the youngest cases in our experience. The four deaths in children ranging in age from 1 to 4 years constituted a 31% operative mortality for medulloblastoma in the 13 patients 5 years of age or younger. In contrast, only one of 24 children beyond 5 years of age failed to survive surgery and radiation therapy for this disease (4%). Radical or subtotal resection of the tumor or simple biopsy had no significant association with the surgical mortality.

Recurrent Disease

Analysis of Possible Factors Influencing Prognosis. Of 40 patients completing a course of cerebrospinal radiation therapy after surgical diagnosis, 29 developed recurrence of their disease during the follow-up period and 28 of these have died. The effect of the type of primary treatment (surgery and radiation therapy) in these 40 cases was analyzed, and results were arbitrarily divided into those with short- or long-term survival and early or late recurrent disease (Table 1). No singular differences in sex, incidence, or age at diagnosis were found among the surviving children compared to those who developed recurrences early or late. The extent of surgical resection had no significant relationship to the prognosis observed in these 40 cases.
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TABLE 1
Survival and recurrence in 40 patients with medulloblastoma who completed radiation treatment

<table>
<thead>
<tr>
<th>Result*</th>
<th>No. of Patients</th>
<th>Ratio Male:Female</th>
<th>Age at Diagnosis (Yrs)</th>
<th>Type of Operation</th>
<th>Average Radiation Dose in Rads</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average</td>
<td>Range</td>
<td>Biopsy</td>
</tr>
<tr>
<td>survival &gt; 3</td>
<td>9</td>
<td>4:5</td>
<td>8</td>
<td>2-16</td>
<td>3</td>
</tr>
<tr>
<td>survival &lt; 3</td>
<td>2</td>
<td>1:1</td>
<td>13</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>recurrence &lt; 2 (early)</td>
<td>22</td>
<td>13:9</td>
<td>8</td>
<td>1-16</td>
<td>9</td>
</tr>
<tr>
<td>recurrence &gt; 2 (late)</td>
<td>7</td>
<td>4:3</td>
<td>9</td>
<td>6-11</td>
<td>1</td>
</tr>
</tbody>
</table>

*Survival without recurrent disease; years from operation and diagnosis.

The 11 children who have remained free of disease had received more craniospinal radiation as a group than had those who developed recurrences during the follow-up period. The correlation of the higher radiation doses to the brain and spinal axis with survival and freedom from recurrent disease proved highly significant (p < 0.001).

Twenty-two patients had early recurrence of medulloblastoma during the first 2 postoperative years, and to date 21 have died within 3 years of diagnosis. The length of remission after diagnosis ranged from 4 to 20 months with a mean and median duration for the group of 10 months. Early recurrences were more frequently intracranial in location, observed in 14 of 22 patients at an average of 12 months postoperatively. Spinal recurrences in eight children occurred significantly earlier, with a mean of less than 7 months from operation and diagnosis (p = 0.01). The site of recurrence in these cases could not be correlated to the type of surgical resection or to differences in radiation dose. Half of the cases with early recurrence had 4000 rads or less radiation to the brain. The eight children with spinal recurrences had received an average of 3600 rads to the spinal axis, not significantly different than the doses received by surviving patients.

Seven patients first relapsed more than 2 years postoperatively and survived more than 3 years after diagnosis of their disease. The length of remission in these late recurrent cases ranged from 2.4 to 8.2 years, averaging 4.7 years (median 4.3 years). Late recurrence of medulloblastoma initially occurred in the posterior fossa in six cases and was probably local in the other. Radiation treatment was not the main determining factor in the extended survival in this group since the cerebrospinal doses were not significantly different from the CNS irradiation received by the patient who developed early recurrences. The type of surgical resection was also not significantly different in the groups with early and late recurrence. The longest survivor who ultimately died of her disease 10.5 years after diagnosis had a primary remission of 8.2 years after operation and cerebrospinal irradiation of 3600 rads.

Analysis of Treatment. Fourteen of the 22 children who manifested early recurrence (within 2 years postoperatively) of medulloblastoma (six intracranial and eight intraspinal) were treated with additional irradiation and/or chemotherapy; the other eight did not receive either form of therapy when signs of recurrent intracranial disease developed. Recurrences were diagnosed an average of 9 months postoperatively in the retreated group and after 12 months in the untreated. This difference was not significant. The average survival after intracranial and/or spinal recurrences were first diagnosed in the former group was 10 months compared to less than 2 months in the eight patients who did not receive further irradiation or chemotherapy (p < 0.001). Average survival from operation and diagnosis was 19 months in the retreated group. Those with intracranial recurrences generally lived longer on the average (22 months) than those developing spinal metastases (17 months), with one notable living exception (Case 11, Table 2). The eight patients with untreated recurrences lived an average of 14 months after the tumor was first diagnosed. The differences in overall
TABLE 2

Results of radiation therapy and/or chemotherapy in 14 children with early recurrence of medulloblastoma*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Treatment</th>
<th>Remission (mos)</th>
<th>Site of Defined 2nd Recurrence</th>
<th>Retreatment</th>
<th>Remission (mos)</th>
<th>Additional Therapy, Ineffective</th>
</tr>
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<tbody>
<tr>
<td>initial recurrence intracranial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>rad</td>
<td>8</td>
<td>CR</td>
<td>S</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>rad, S, V + MeCCNU</td>
<td>14</td>
<td>SP</td>
<td>rad</td>
<td>2</td>
<td>MTX</td>
</tr>
<tr>
<td>3</td>
<td>rad</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>4</td>
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<td>4</td>
<td>CR</td>
<td>rad</td>
<td>5</td>
<td>S, V</td>
</tr>
<tr>
<td>5</td>
<td>V + BCNU</td>
<td>3</td>
<td>CR</td>
<td>AraC</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>rad, S, V + MTX</td>
<td>4</td>
<td>SP</td>
<td>rad</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>initial recurrence intraspinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>rad</td>
<td>4</td>
<td>CR</td>
<td>S, V</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>rad, V</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>MTX</td>
<td>5?</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>rad, V</td>
<td>3</td>
<td>SP</td>
<td>rad, MTX</td>
<td>2</td>
<td>S, BCNU</td>
</tr>
<tr>
<td>11</td>
<td>rad, V + BCNU</td>
<td>23+</td>
<td>—</td>
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<tr>
<td>12</td>
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<td>CR</td>
<td>S, V</td>
<td>18</td>
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<tr>
<td>13</td>
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<td>5</td>
<td>CR</td>
<td>V, MeCCNU</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>rad</td>
<td>2</td>
<td>SP</td>
<td>rad</td>
<td>0</td>
<td>—</td>
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</tbody>
</table>

*Rad = radiation therapy; S = ventriculoatrial or peritoneal shunt; V = vincristine chemotherapy; MTX = intrathecal methotrexate; AraC = intrathecal cytarabine; CR = intracranial recurrence; SP = intraspinal recurrence.

Postoperative survival between the retreated and untreated groups with recurrent disease nearly reach levels of statistical significance (0.05 < p < 0.10), and become significant when those cases with treated intracranial recurrences are compared with the untreated cases (0.025 < p < 0.05).

The results of treatment in 14 children with early postoperative manifestations of recurrent medulloblastoma are itemized in Table 2 according to the principal site of the initial recurrence. The 12 patients receiving a second course of radiation therapy all benefited, with periods of remission lasting from 2 to over 23 months. With radiation therapy alone seven children were improved for an average of more than 4 months. In five cases chemotherapy combined with radiation therapy significantly lengthened the average interval of well-being to over 10 months (p < 0.05). One patient (Case 9), who developed paraplegia 8 months after diagnosis with normal myelography and malignant cerebrospinal fluid cytology did not improve neurologically after intrathecal methotrexate therapy, but did live 5 months longer. Another (Case 5), who had a normal ventriculogram but was acutely ill from malignant meningitis, had a brief but complete symptomatic remission in response to chemotherapy. A second tumor recurrence at the same or different sites was subsequently defined in 10 children who were again retreated. Improvement after further radiation therapy and/or chemotherapy was observed in six cases lasting 2 to 18 months. Case 12 was exceptional in that symptoms of intracranial recurrence developed 9 months postoperatively and 4 months after radiation therapy for myelographically verified lumbar deposits. This patient was begun on vincristine, subsequently shunted, and remained well on drug therapy for 18 months. When three of the patients had subsequent relapses and repeat manifestations of progressive intracranial disease, they were treated by shunting and/or chemotherapy without any worthwhile results, although life may have been prolonged a few weeks.

Results of treatment in six children with recurrence of medulloblastoma intracranially more than 2 years postoperatively and who lived 3 years or longer after this diagnosis was established are indicated in Table 3. One (Case 2) continued in a vegetative state after tumor biopsy and radiation therapy, and died in a nursing home over 6 years later. The youngest patient was a girl aged 6 years when
TABLE 3
Results of radiation therapy and/or chemotherapy in six of seven children with late intracranial recurrence of medulloblastoma*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Duration of Primary Remission (yrs)</th>
<th>Treatment</th>
<th>Remission (mos)</th>
<th>Site of Defined 2nd Recurrence</th>
<th>Treatment</th>
<th>Remission (mos)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>8.2</td>
<td>reop, rad</td>
<td>21</td>
<td>CR</td>
<td>V</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>6.7</td>
<td>none</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>6.0</td>
<td>reop, rad</td>
<td>54</td>
<td>SP</td>
<td>rad</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>4.3</td>
<td>V</td>
<td>12</td>
<td>CR</td>
<td>rad</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>S, V</td>
<td>10</td>
<td>CR</td>
<td>none</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>rad</td>
<td>9</td>
<td>CR</td>
<td>S, V</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>2.4</td>
<td>S, V</td>
<td>6?</td>
<td>CR</td>
<td>none</td>
<td>—</td>
</tr>
</tbody>
</table>

*V = vincristine chemotherapy; reop = reoperation and subtotal resection of recurrent cerebellar tumor; S = ventriculoatrial or peritoneal shunt; rad = radiation therapy; CR = intracranial recurrence; SP = intraspinal recurrence.

the tumor was first partially removed (Case 1). This was the only instance in this series where the time of recurrence after primary treatment of cerebellar medulloblastoma (8.2 years) exceeded the patient's chronological age at diagnosis plus 9 months. Four children were better and remained stable for a year or longer after recurrences were first diagnosed and treated. Good therapeutic responses were observed after reoperation plus a second course of radiation therapy (two cases), further irradiation alone (two cases), and vincristine chemotherapy with or without shunting (four cases). In five patients, retreatment for the first intracranial recurrence was clearly restorative. In the patients in Cases 1 and 3, who relapsed 8 and 6 years after the diagnosis was established, retreatment provided an additional 2 and 6 years, respectively, of essentially normal living. In Case 7 any improvement noted was marginal and did not alter this handicapped child's functional level. Three of four children treated for recurrence a second time had useful remissions of 5 to 18 months. Subsequent therapeutic attempts in these patients ultimately failed.

It proved difficult in our experience to ascertain the individual efficacies of steroid therapy and shunting in the management of either early or late recurrent medulloblastomas. The patients who were given steroids in the terminal phase of the disease had clearly no beneficial results. In less severely ill children who responded to retreatment by a combination of shunting, radiation therapy and/or chemotherapy, steroids when administered were generally withdrawn after a few days or weeks. Shunting for recurrent intracranial medulloblastoma when combined with chemotherapy and/or radiation therapy was followed by improvement and lengthened survival in seven patients. Shunting was performed on two children as the only therapy for local recurrence of cerebellar medulloblastoma, and was not found helpful. Insertion of shunts with or without further irradiation and/or chemotherapy was of no benefit to six other patients in the terminal weeks of their disease.

Discussion

The extent of tumor resection at the diagnostic surgery for cerebellar medulloblastoma had no significant bearing on the prognosis in our experience. The operative mortality of 11% compares favorably with an average surgical death rate of 24% among 18 selected reports to 1965.14 Our surgical mortality was clearly age-dependent, and the higher risks of operation for medulloblastoma in the youngest children probably deserve more recognition. Review of our data indicates that intraoperative management should be determined by the findings in each case after a wide decompressive suboccipital exposure. Biopsy should always be done for histological verification, of course, and may be all that is advisable in some cases, especially where tumor is widespread, adherent, and highly vascular. In other patients, essentially all of a soft localized neoplasm can be
safely removed from the cerebellar vermis or fourth ventricle.

The prognosis in the patients who completed postoperative irradiation at this institution approximated or exceeded the experience reported in several series.\textsuperscript{3,11,14,23} Children who have remained free of recurrent disease had been treated with significantly higher average doses of radiation to the brain and spinal axis, approaching 5000 rads and 4000 rads, respectively. The correlation of higher spinal irradiation and survival seemed a carry-over effect, reflecting the tendency of our radiotherapists to increase the dose to the spine when higher levels of radiation were administered to the brain. Spinal metastases generally were the earliest manifestations of recurrent medulloblastoma, and this development appeared independent of the levels of previous radiation to the spinal axis in our patients. Recurrence of medulloblastoma after conventional treatment, accordingly, seems related most closely to the postoperative radiation dose to the posterior fossa and/or brain. Intracranial doses of 5000 rads are at the upper limit generally recommended for treatment of medulloblastoma.\textsuperscript{5,4} Even lower doses have been considered potentially harmful to the developing brain of children under the age of 3 years.\textsuperscript{5} This view gains support by our findings of mild mental deficiency in both of our long-term survivors who were irradiated before 2 years of age. No late radiological effects attributable to spinal axis doses up to 4000 rads were documented in our experience.

Radiation therapy was found generally effective for palliative management of intracranial recurrences and spinal metastases, with control of disease progression for several months or longer. None of our reirradiated cases have survived save one, and this patient is not considered cured. The advisability of reoperation for late intracranial recurrences to reduce the tumor burden remains questionable, in our view, since reirradiation alone has occasionally been followed by prolonged or indefinite survival.\textsuperscript{3,14,24} Our results do indicate that the addition of vincristine chemotherapy enhanced the palliation observed after reirradiation of locally recurrent and metastatic spinal medulloblastoma, possibly by suppression of occult disease not encompassed by the radiotherapy ports. The most prolonged secondary remissions after early recurrence of the disease were observed in two patients who also received one of the nitrosoureas. Since these drugs presently appear most efficacious in the chemotherapy of malignant gliomas,\textsuperscript{10} the combined use of BCNU or 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) with vincristine appears most promising at the present time.

In general, the value of chemotherapy in the treatment of medulloblastoma has not been ascertained to any great extent. Although vincristine, for example, has been recommended for symptomatic treatment of recurrent medulloblastoma for more than a decade,\textsuperscript{13} in a recent review only five cases treated with this drug were cited, with three responding to it.\textsuperscript{10} In our experience, seven patients had useful clinical remissions after vincristine chemotherapy alone or with shunting. Vincristine used with other chemotherapeutic drugs and/or radiation therapy proved of palliative value in seven additional patients. Intrathecal and intraventricular methotrexate has been recommended for recurrent medulloblastoma after hopeful results in 12 cases.\textsuperscript{16,17} Subsequently, however, enthusiasm for methotrexate waned because of the relatively brief duration of any remission and the association of intraventricular methotrexate with a fatal necrotizing encephalopathy.\textsuperscript{21} The use of this drug for recurrent or metastatic medulloblastoma in our experience was severely limited by the hematological toxicity it produced in children with previous spinal irradiation. In a total of 19 collected cases (number responding/total) the following newer chemotherapeutic agents have also been reported effective against recurrent medulloblastoma: the nitrosoureas BCNU (3/9)\textsuperscript{6,19,25} and CCNU (2/5),\textsuperscript{6,18,20,26} procarbazine (3/4);\textsuperscript{12} and 4'-demethyl-epipodophyllotoxin-β-D-thenylidene-glucoside (PTG) (1/1).\textsuperscript{22} To our knowledge no information has been published to indicate that steroids have any specific or overall benefit in patients with recurrent medulloblastoma.

From the foregoing observations it seems that there is justification presently for the consideration of chemotherapy as part of the primary treatment of medulloblastoma. This approach has already been tried in small numbers of patients. Single intravenous injections of triethylene melamine in addition to cobalt-60 irradiation have been reported in seven patients with medulloblastoma who remained free of known recurrent disease for
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2 to 8 years. Two children in our series received vertebral arterial infusions of triethylene melamine postoperatively during their course of radiation therapy; recurrent disease developed in one within 10 months and in the second after 6 years.16

Intermittent adjuvant chemotherapy with vincristine, combined in some instances with intrathecal methotrexate with or without CCNU following radical surgery and irradiation of the whole cerebellar axis has been reported in a preliminary fashion in 14 children with medulloblastoma;2 the prognosis for survival up to 30 months postoperatively in the patients receiving some form of chemotherapy appeared better than in an otherwise comparable group who had received radiation therapy alone.2

From observations on the efficacy of various chemotherapeutic agents in the therapy of recurrent medulloblastoma, vincristine presently appears to be the drug of choice for consideration as part of the primary treatment of this disease, in conjunction with radiation therapy. In accordance with the prevailing practice of using multiple chemotherapeutic drugs acting by different mechanisms for therapy of malignant disease, one of the nitrosoureas might be given empirically with vincristine. This chemotherapeutic approach has recently been designed for a prospective randomized study of medulloblastoma by the Children's Cancer Study Group A of the U. S. National Cancer Institute, using vincristine, CCNU, and prednisone in addition to conventional surgery and radiation therapy. Our experience would not favor the use of intrathecal methotrexate routinely, and presently there are insufficient data on other drugs showing activity against malignant gliomas. The addition of some form of chemotherapy as the third modality for primary treatment of this disease seems eminently reasonable in our view, since the maximum prognosis for survival with postoperative irradiation alone appears relatively fixed at present, and up to half of the children with medulloblastomas may be expected to die in the first 2 or 3 postoperative years.

References

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