Treatment of medulloblastoma with procarbazine, hydroxyurea, and reduced radiation doses to whole brain and spine


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Forty-seven patients with medulloblastoma were treated postoperatively with procarbazine, followed by craniospinal radiation therapy in combination with hydroxyurea. The radiation dose to the posterior fossa was 55 Gy; the spinal cord received 25 Gy and the whole brain 25 to 35 Gy (mean 33 Gy).

Seventeen tumors recurred. Only one initial recurrence was in the spinal subarachnoid space; 10 (59%) were in the posterior fossa, and four (24%) were supratentorial. The estimated 5-year disease-free survival probability was 55%; the 5-year overall survival rate was 66%. Myelotoxicity occurred in 38% of patients, but in only one case was it severe enough to warrant reducing the total dose of radiation. It was concluded that good-risk medulloblastoma patients may be treated with radiation dosages as low as 25 Gy to the spinal axis and to the whole brain without increasing the risk of recurrence outside the posterior fossa. Chemotherapy with procarbazine followed by radiation therapy and hydroxyurea during radiation therapy was well tolerated and may play a role in reducing radiation dosages outside the posterior fossa.

Key Words • medulloblastoma • procarbazine • hydroxyurea • radiation therapy • brain neoplasm

Approximately 18% of intracranial tumors in children are medulloblastomas. Because of the tendency of these tumors to disseminate along the cerebrospinal fluid (CSF) pathways and to recur even after gross total surgical resection, medulloblastomas are normally treated by postoperative irradiation of the entire craniospinal axis. The 5-year survival rate for patients treated in this manner has ranged from 50% to 70%, depending on the extent of disease at the time of initial treatment.\(^1^3\) Craniospinal irradiation in children has undesirable side effects, such as diminished growth of the spine and soft tissue, acute and chronic myelosuppression, decreased endocrine function, and delayed injury to the central nervous system (CNS).\(^4^5\)

Chemotherapy has proved effective for treating recurrent medulloblastomas following irradiation,\(^5^6^7^8^9\) but when used as an adjuvant to craniospinal radiation therapy, it has shown only minimal benefit over craniospinal irradiation alone.\(^1^1^6\) One reason suggested for this observation is that myelotoxicity following craniospinal irradiation substantially limits the amount of adjuvant chemotherapy and may thereby lessen its potential effectiveness.

In an attempt to avoid the detrimental effects of craniospinal irradiation and to minimize the myelotoxic effect of chemotherapy in patients with medulloblastoma, a treatment regimen was devised, consisting of administering procarbazine before and hydroxyurea during radiation therapy in conjunction with reduced radiation doses to the spinal axis and whole brain (25 Gy each). The purpose of this study was to determine the effect of such treatment on the incidence of local and distant recurrence and on the 5-year survival rate in these patients. In addition, long-term follow-up results will determine if this therapy reduces the detrimental side effects of craniospinal irradiation.

Clinical Material and Methods

Study Entry Criteria

All patients with the initial diagnosis of medulloblastoma seen by the Neuro-Oncology Service between
January 15, 1979, and August 29, 1986, were candidates for this study. All patients had undergone initial surgical debulking either at the University of California, San Francisco, or at a referring hospital. The biopsy material from all patients was reviewed by one of us (R.L.D.), except in three cases in which the diagnosis was based on the interpretation of the pathologist from the referring institution.

For staging purposes, the following studies were performed on every patient: magnetic resonance (MR) imaging or contrast-enhanced computerized tomography (CT) to assess the extent of tumor resection; total spinal axis myelography with a water-soluble contrast agent; and CSF cytology within 2 weeks after the primary tumor operation. A “good-risk patient” was defined as one in whom more than 75% of the tumor was resected surgically (confirmed on CT and/or MR imaging), who had a negative myelogram and CSF cytology, in whom no evidence of CNS or extraneural metastasis was found, and who was over 2 years of age. (These characteristics correspond to the stage of M0, T1–T3, according to the criteria of Chang, et al.) Those who did not meet these criteria were considered “poor-risk patients.”

At the beginning of the study, all patients with medulloblastoma were considered eligible, regardless of risk criteria. After July 1, 1984, only good-risk patients were entered because of the concern that poor-risk patients should be treated more aggressively with a six-drug chemotherapy (BTRC 8422) protocol before and after radiation therapy.

Chemotherapy

All patients received a single daily oral dose of procarbazine, 100 mg/sq m, for 14 consecutive days starting 2 to 4 weeks after the initial surgical tumor debulking. Hydroxyurea was given orally at a dose of 250 mg/sq m every 6 hours on Mondays, Wednesdays, and Fridays during radiation therapy. The only other medication received was dexamethasone when necessary. Dexamethasone was tapered as quickly as was possible following surgery. Ventriculoperitoneal shunts, without tumor filters, were placed only when hydrocephalus failed to resolve postoperatively. Complete blood and platelet counts were obtained every 2 weeks before, during, and for 2 weeks after treatment; when patients exhibited myelosuppression, these counts were obtained weekly.

Radiation Therapy

Radiation therapy was initiated within 24 to 48 hours following the last dose of procarbazine. Initially, the planned radiation dose schedule was: 55 Gy to the posterior fossa at 180 cGy/day; 35 Gy to the whole brain at 180 cGy/day; and 25 Gy to the spinal cord at 160 cGy/day. Lesions demonstrated by myelography were focally irradiated with an additional 15 Gy. Later in the study, the whole-brain radiation dosage was reduced to 25 Gy for good-risk patients. All patients were treated with a linear accelerator at energy levels greater than 8 MeV; the minimum dose rate at tumor depth was 50 rads/min. All radiation treatment plans were simulated and doses were specified at the central midplane axis in the skull and at a depth of 4 cm to the spinal field. The brain and posterior fossa were irradiated with parallel lateral opposed fields, 20 × 20 and 8 × 8 cm, respectively. The spinal axis was treated by a single direct posterior field 5 cm wide.

Evaluation of Response

At the completion of radiation therapy and every 2 to 3 months thereafter for the following year, all patients underwent contrast-enhanced CT or MR imaging and a lumbar puncture for CSF cytology and analysis of protein, glucose, and polyamine levels. During the 2nd year postirradiation, a contrast-enhanced CT scan or MR image was obtained at 3- and 4-month intervals. Beginning with the 3rd year, patients were evaluated at 6-month intervals if they were disease-free. Tumor recurrence in the CNS was documented by MR imaging or contrast-enhanced CT or by positive CSF cytology; extraneural metastasis was documented by radionuclide bone scans and plain radiographs. At the time of recurrence, the extent of tumor involvement was determined by restaging CT and/or MR imaging and myelography. It was possible to perform myelography in 10 patients; seven patients could not undergo myelography because of the risk of tonsillar herniation.
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Results

Patient Characteristics

Fifty patients were entered in this study between 1980 and 1986. One patient was excluded from the analysis because he received only procarbazine, hydroxyurea, and focal irradiation to the posterior fossa; whole-brain and spinal cord irradiation was withheld because of his young age (10 months). Two patients were lost to follow-up evaluation.

Of the 47 remaining patients, 37 were considered “good-risk” and 10 were considered “poor-risk,” based on the previously defined criteria. The medium age was 10 years; 68% of the patients were under 15 years old. The median follow-up period was 137 weeks.

Toxicity

Myelotoxicity occurred in 18 patients (38%) (Table 1) and was the only significant side effect. In all patients except one, myelosuppression occurred after the 1st week of spinal irradiation. There was no significant morbidity or mortality related to myelosuppression. Hydroxyurea was decreased or discontinued during irradiation in all 15 patients with toxicity Level 3 or 4. In three of four patients in whom radiation therapy was withheld for more than 1 week because of myelosuppression, the treatment was restarted within 3 weeks and completed to the full planned dosage. In one patient with persistent myelosuppression, radiation therapy was stopped after 720 cGy was delivered to the spinal cord; this patient developed a recurrent tumor in the subfrontal region and frontal lobe which subsequently disseminated along the spinal axis.

Response of Treatment

Seventeen patients (36%) developed recurrence or progression of their tumors (Table 2). Ten of these patients (27%) were in the good-risk group and seven (70%) in the poor-risk group. Ten of the tumors (59%) initially recurred in the posterior fossa. One patient had simultaneous recurrence in the spinal axis and the frontal lobe, and two patients developed a recurrence in the spinal axis after initial recurrences in the posterior fossa and frontal lobe.

The 5-year disease-free survival rate, estimated from Kaplan-Meier survival curves, was 63% in the good-risk patients and 25% in the poor-risk patients (Fig. 1 left). The estimated time to tumor progression for poor-risk patients was 75 weeks. The estimated overall 5-year survival rate was 68% for the good-risk and 50% for the poor-risk patients (Fig. 1 right). Thus, the 5-year disease-free survival rate is a better measure of therapeutic effectiveness than the overall 5-year survival rate. All patients were offered chemotherapy at the time of tumor progression or recurrence.

Discussion

The rationale for the treatment tested in this study is that prior and concurrent chemotherapy in conjunction with craniospinal irradiation may permit a reduction of the spinal and cranial irradiation dosage, ultimately reducing cerebral and spinal toxicity. Procarbazine alone and in combination with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) has shown activity against medulloblastoma; the response rates have ranged from 40% to 50%. Hydroxyurea has not been tested as a radiosensitizer in patients with medulloblastomas, but it has improved the response rate to radiation therapy administered to patients with glioblastoma multiforme. Whether this effect is due to cell-cycle-specific cytotoxicity or to enhancement of radiation-induced cell injury is unknown. Since medulloblastomas have higher labeling indices than glioblastomas,
the assumption was made that the administration of hydroxyurea during radiation therapy might be beneficial. Based on these assumptions, the patients in this study received procarbazine before and hydroxyurea during radiation therapy, and the radiation doses to the whole brain and spinal axis were reduced while maintaining conventional dosage to the primary tumor site (posterior fossa).

This study showed that reducing the dosage of spinal radiation was not associated with a higher recurrence rate along the spinal axis: 59% of the recurrences were in the posterior fossa and only one patient had an initial recurrence of a solitary lesion in the spinal axis. Two patients developed spinal axis involvement after the initial posterior fossa recurrence; in both cases, the spinal metastases were the result of progressive dissemination of their disease. Metastases outside the CNS occurred in two patients (11%). These findings are consistent with the previous observation that medulloblastomas tend to recur locally rather than to metastasize, and further substantiate the proposal that decreasing the radiation dosage to the whole brain and spinal cord did not increase the chances of failure outside the primary posterior fossa tumor site.

It is also likely that the radiation dose to the whole brain can be reduced without increasing the risk of cerebral metastasis. At the beginning of this study, the whole brain was irradiated with 35 Gy; this dose was reduced to 25 Gy as it became evident that the reduction of spinal radiation had not increased the frequency of recurrence along the spinal axis. Recurrences in areas of the brain other than the posterior fossa occurred in three of 13 patients who received less than 27 Gy of whole-brain radiation and in two of 34 patients who received 32 Gy to the whole brain; however, two of three patients who received these reduced cerebral radiation dosages were in the poor-risk group, whereas both patients who received more than 32 Gy were in the good-risk group. Thus, no conclusions can be drawn concerning the relationship between the reduction of whole-brain irradiation and cerebral tumor recurrence pattern.

The overall 5-year disease-free survival rate in our patients (55%) was similar to that reported by the Children’s Cancer Study Group (50%) in patients treated with surgery and standard-dose craniospinal radiation therapy. Our overall 5-year survival rate (66%) is also comparable to that in other series of patients treated with surgery and standard-dose craniospinal radiation therapy. However, the good-risk patients in our study had higher 5-year disease-free (63% vs. 25%) and overall survival rates (68% vs. 55%) than the poor-risk patients. These results are also in agreement with previous reports. Although chemotherapy given before irradiation and the use of a radioprotector during radiation therapy did not dramatically improve the 5-year disease-free and overall survival rates, as compared to previous reports, this approach permitted the use of smaller doses of radiation to the spinal axis and probably to the whole brain, without an increase in spinal metastases or tumor recurrence outside the posterior fossa. Investigators undertaking new clinical trials in patients with medulloblastomas should consider decreasing the dose of radiation to the whole brain and spinal axis in good-risk patients and testing more aggressive forms of therapy directed to the posterior fossa, which still remains the primary site of failure despite radiation dosages of 50 to 55 Gy. To improve survival rates in poor-risk patients, a minimum of standard-dose craniospinal irradiation should be given, intensified radiation therapy to the posterior fossa should be considered, and more effective chemotherapy regimens need to be developed.

Acknowledgments

The authors thank Irene Asturias and Mary Ellen Kuhlmann for manuscript preparation.

References

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Manuscript received April 30, 1987.
Accepted in final form September 8, 1987.
This work was supported in part by National Institutes of Health Grant CA-13525.
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