Chemotherapy of recurrent medulloblastoma with combined procarbazine, CCNU, and vincristine

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 Seventeen patients with recurrent medulloblastoma were treated with a combination of three drugs: procarbazine, CCNU, and vincristine (PCV). Tumor recurrence was documented at varying periods following surgery and radiotherapy. Among 16 evaluable patients, ten showed a response to PCV on the basis of subjective neurological improvement and a decrease in tumor size by radiological criteria. Five patients were designated as having stable disease on the basis of no change in neurological status and tumor size. One patient showed uninterrupted progression of disease. The median time to progression for all patients was 45 weeks.

Significant myelotoxicity, exacerbated by prior spinal irradiation, compromised therapy. After an initial response, it was often necessary to reduce the higher doses of CCNU and procarbazine that caused concomitant bone-marrow toxicity; as a consequence of the lowered doses, tumor progression was then frequently observed. The authors conclude that PCV is an effective form of palliative therapy for recurrent medulloblastoma.

KEY WORDS • medulloblastoma • recurrent brain tumor • chemotherapy • combined chemotherapy • procarbazine • CCNU • vincristine

Despite improvements in radiotherapy techniques and survival rates, most patients with medulloblastoma still experience tumor recurrence within 5 years after diagnosis and initial treatment. Although repeat irradiation has been used in the management of symptomatic recurrent tumors, a long-term benefit is observed only infrequently, and the high risk of delayed radionecrosis deters most radiotherapists.

In a study conducted at the University of California, San Francisco (UCSF), three of four patients with recurrent medulloblastoma responded to procarbazine. This investigation was followed by a Phase II study of a combination of three drugs, procarbazine, CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), and vincristine (PCV), which had proved to be as effective as BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) against recurrent cerebral glioma. The early results with medulloblastoma were so favorable that PCV was the standard chemotherapy for this tumor for more than 4 years. The results of our experience with the original PCV schedule, Series 1, and a recent modification of the original schedule, Series 2, are the subject of this report.
TABLE 1
Results of chemotherapy with PCV Series 1 and 2

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<th>Case No.</th>
<th>Age at Diagnosis (yrs)</th>
<th>No. of Courses</th>
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<th>PCV Series 2</th>
<th>Response to Therapy</th>
<th>Time to Progression (wks)</th>
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Clinical Material and Methods

Clinical Material

Seventeen patients with recurrent medulloblastoma were treated with a combination of procarbazine, CCNU, and vincristine (PCV). Of these, 16 were evaluable, and make up this series (Table 1). All patients had undergone suboccipital craniectomy with histological confirmation, and almost all underwent partial or gross total tumor resection. Nine patients required some form of cerebrospinal fluid (CSF) diversionary procedure. All underwent irradiation in the immediate postoperative period, although their therapies were conducted at several different centers using various techniques.

At the time of initial diagnosis these patients ranged in age from 3.5 to 51 years, with a median of 14 years. Ten patients were male, six were female.

Chemotherapy for tumor recurrence was initiated from 10 months to 4.5 years after the completion of postoperative irradiation. Recurrent tumors leading to chemotherapy were in the posterior fossa alone (eight patients), spinal canal (two patients), posterior fossa and spinal canal (one patient), posterior fossa and supratentorial compartment (four patients), all three compartments (one patient), and bony metastases (one patient).

A diagnosis of recurrence was based on: 1) increasing neurological deficit attributable to tumor regrowth only (excluding hydrocephalus, infection, metabolic disorder, or recent irradiation side effects); and 2) confirmatory neuroradiological studies that indicated a new or an enlarged lesion. The histology of the original tumor was reviewed and the diagnosis was confirmed in all cases.

To insure that tumor regression could be attributed to PCV treatment alone, no recurrent case was treated within 2 months of an operation or 3 months of radiotherapy, or within 2 months of previous chemotherapy. Although steroids were used, no improvement was attributed to chemotherapy if the steroid dose was increased concomitantly. Criteria for evaluating response have been reported previously. If the patient's objective neurological examination was improved and the size of the tumor decreased as estimated from scintiphoto or another neuroradiological procedure, then the patient was designated a responder. If the patient showed improvement in one parameter with stability in the other, or stability in both parameters, then he or she was considered to have stable disease.

PCV Therapy

The PCV treatment given in Series 1 consisted of procarbazine, CCNU, and vincristine given in 4-week cycles; full doses were
Chemotherapy of recurrent medulloblastoma

CCNU, 75 mg/sq m, given orally on Day 1; vincristine, 1.4 mg/sq m, given intravenously on Day 1 and repeated on Day 8; and procarbazine, 100 mg/sq m, by mouth daily at bedtime from Day 1 through Day 14. The PCV treatment in Series 2 was given in 6-week cycles; the dose of each drug was the same as for PCV Series 1; however, CCNU was given on Day 1, procarbazine on Days 8 to 21, and vincristine on Days 8 and 29.

A neurological examination, radionuclide scan, and, when it became available, computerized tomographic (CT) scan were all performed at the start of each cycle. The CCNU and procarbazine doses were adjusted appropriately when myelotoxicity was observed. If compromised bone marrow was suspected before chemotherapy was initiated, on the basis of either spinal axis irradiation during the preceding 2 years or previous chemotherapy, then the first course of PCV was given at a reduced dose. Since treatments with reduced dosage were frequently effective, attempts were made to maintain the therapy interval even if dosages had to be reduced. However, when either white blood cell (WBC) or platelet counts failed to recover to levels considered safe for the lowest doses (25%), either treatment was delayed or the patient was treated with vincristine alone. Vincristine dosages were reduced for severe paresthesias or motor weakness.

Results

The valid study group consisted of 16 patients. Ten of these patients (62%) showed a response, five (31%) had stable disease, and one (6%) showed rapid progression. Table 1 summarizes patient response and time to progression.

Figure 1 is a Kaplan-Meier representation showing time to tumor progression for all patients in the valid study group. The data were fitted to an experimental model by the method of least squares. Time to tumor progression was best expressed by the equation: Probability = .94 × EXP (−.0140 × weeks). Standard error of estimate = 0.05, and the correlation coefficient = 0.97. The median time to tumor progression was 45 weeks (49 weeks by the exponential model). In 25% of the patients remission lasted for over 2 years.

Myelosuppression was often the major determinant of the length of remission. Only one patient, a 51-year-old man who had received no spinal irradiation, was able to tolerate three courses of procarbazine and CCNU at full dosage. Although several patients were hospitalized when WBC counts fell below 1000/cu mm, none acquired infection while leucopenic. However, toxicity required reductions in dosage and, in cases of profound myelosuppression, forced discontinuation of treatment altogether, permitting progression of the disease. Since full doses were 75 mg/sq m of CCNU and 100 mg/sq m of procarbazine, at 8 weeks the average tolerated doses were 33 mg/sq m and 44 mg/sq m, respectively. By 45 weeks the average doses were 19 mg/sq m and 25 mg/sq m, respectively.

Discussion

Despite the initial effectiveness of PCV against recurrent medulloblastoma, myelotoxicity compromised treatment. Several patients experienced only a brief response because severe bone-marrow toxicity necessitated reducing procarbazine and CCNU dosages to low levels early in the course of treatment. Paradoxically, in some patients, doses of CCNU and procarbazine as low as 19 mg/sq m and 25 mg/sq m, respectively, controlled the medulloblastoma for months. When the medulloblastoma patients were compared to those previously treated with this regimen for malignant gliomas, we

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found that 8 to 10 weeks after therapy was initiated the latter group tolerated doses of CCNU at 66 mg/sq m and procarbazine at 79 mg/sq m, while the medulloblastoma patients tolerated only 33 mg/sq m and 44 mg/sq m. The severity of myelosuppression with PCV was unrelated to the period of time that had elapsed between spinal irradiation and the initiation of chemotherapy.

Although the concurrent administration of the three drugs was presumed to account for the effectiveness of the PCV combination, as well as for its toxicity, one of us (V.A.L.) investigated the possibility that both effects, the oncolytic activity and myelosuppression, might be independently schedule-dependent. This proved to be the case when, using animal models, we demonstrated two highly significant relationships between a nitrosourea and procarbazine: 1) oncolytic potency of the combined drugs was obtained with a relatively small dose of procarbazine in relation to the dose of nitrosourea; and 2) when procarbazine was administered several days later than the nitrosourea, the combination maintained full oncolytic activity with decidedly reduced myelotoxicity.

Based upon these data, we revised the PCV Series 1 dose regimen to PCV Series 2, which was used in six patients. This revised protocol appears to be effective, with reduced myelotoxicity, and has been employed in the treatment of recurrent medulloblastomas for the past 24 months. The PCV Series 2 regimen is currently being studied in medulloblastoma patients as a postoperative adjuvant to radiotherapy.

Although no cures were obtained in the series reported here, and although the median time to progression was only 45 weeks, the results of this study suggest that the PCV combination has striking short-term effectiveness against recurrent medulloblastoma. It is obvious that other less myelotoxic therapy regimens deserve consideration.

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References


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