The treatment of oligodendrogliomas and mixed oligodendroglioma-astrocytomas with PCV chemotherapy

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Abstract

Malignant oligodendrogliomas have been shown to be responsive to chemotherapy. The authors administered systemic chemotherapy to seven patients with oligodendroglioma or anaplastic oligodendroglioma, and to 14 with mixed oligodendroglioma-astrocytoma. Fourteen patients underwent chemotherapy before and seven after irradiation. The PCV (procarbazine, methyl-l-(2-chloroethyl)-l-nitrosourea (CCNU), and vincristine) chemotherapy was administered every 6 weeks (42-day cycles) for two to five cycles as follows: CCNU, 110 mg/sq m on Day 1; procarbazine, 60 mg/sq m/day on Days 8 to 21; and vincristine, 1.4 mg/sq m/day on Days 8 and 29. Complete or partial (> 50% reduction in tumor mass) responses at 20 to 100+ weeks after treatment were noted in 11 (79%) of the 14 patients treated before irradiation, including two with anaplastic oligodendroglioma and nine with mixed tumors. Complete responses were seen in two patients, one with anaplastic oligodendroglioma and one with a mixed tumor. Partial responses were seen in three of seven patients treated after radiotherapy. Stabilization of tumor growth followed PCV chemotherapy in four patients (two treated before and two after radiotherapy). Tumor growth progressed in two patients during therapy despite an initial response and in two patients despite therapy. The authors conclude that mixed oligodendrogliomas as well as anaplastic oligodendrogliomas are responsive to PCV chemotherapy.

Key Words • oligodendroglioma • mixed glioma • procarbazine • CCNU • vincristine

Previous studies have underscored the fact that over 50% of patients undergoing surgical treatment for oligodendroglioma failed to survive longer than 5 years postoperatively.13,14,16,19 While the prognosis is better for patients with pure oligodendroglioma in whom surgical excision has been performed,14,16 the survival rate for those with malignant oligodendroglioma13,16,19 or mixed oligodendroglial tumors7,20 was similar to that for equivalent grades of other astrocytomas. Presented with these data, many investigators argue for irradiation of oligodendrogial tumors. However, evidence suggests that postoperative irradiation of oligodendrogliomas does not improve median survival time.

Recent reports suggest that anaplastic oligodendroglioma is highly sensitive to chemotherapy.3,15 Cairncross, et al.,4 reported that patients in whom anaplastic oligodendroglioma recurred after irradiation responded to chemotherapy regimens, most notably PCV (procarbazine, methyl-l-(2-chloroethyl)-l-nitrosourea (CCNU), and vincristine) chemotherapy. In a subsequent study, similar responses were noted in patients with anaplastic oligodendroglioma treated prior to radiotherapy; patients with mixed oligodendroglioma-astrocytomas ("oligaoastrocytomas") and low-grade oligodendrogliomas were not included in the treatment study. We report our experience in administering PCV chemotherapy to 21 patients harboring oligodendrogial tumors of varying types.

Clinical Material and Methods

Patient Inclusion Criteria

A prospective study was performed between 1989 and 1991, with the following patient inclusion criteria: 1) oligodendroglioma or oligoastrocytoma was pathologically verified; 2) measurable disease was exhibited on pretreatment contrast-enhanced computerized tomography (CT) or magnetic resonance (MR) brain imaging; and 3) Karnofsky Performance Scale (KPS) score was 60 or greater. Patient age and prior therapy with irradiation or drugs were not exclusion criteria; however, a patient was excluded if the white blood cell count was below 3000/cu mm, the platelet count was...
below 100,000/cu mm, or the hemoglobin concentration was below 10 gm/dl.

**Histopathology of Tumors**

The histopathology of all tumors was examined by a neuropathologist (D.N.L.). In selected cases, immunohistochemical preparations for glial fibrillary acidic protein were also studied. The approximate percentage of the oligodendroglioma component was measured in each tumor: essentially "pure" oligodendrogliomas were defined as "100%" and oligoastrocytomas as "25%," "50%," "75%," or "90%;" these were subject to sampling error. The oligodendroglial portions were designated as either "oligodendroglioma" or "anaplastic oligodendroglioma" if they showed increased cellularity, frequent mitotic figures, cellular pleomorphism, marked endothelial proliferation, and/or necrosis. The astrocytic components were graded according to the Daumas-Duport grading system. This system was designed for the classification of supratentorial astrocytomas in adults and has not been evaluated in mixed gliomas; however, it provides a simple and reproducible means of grading the astrocytic component.

**Chemotherapy Administration**

Chemotherapy was administered in 42-day cycles as follows: lomustine (CCNU), 110 mg/sq m orally on Day 1; procarbazine, 60 mg/sq m/day orally on Days 8 to 21; and vincristine, 1.4 mg/sq m intravenously (to a maximum of 2 mg) on Days 8 and 29.

**Laboratory Measurements**

White blood cell and platelet counts and hemoglobin concentration were determined weekly, while serum alkaline phosphatase, lactate dehydrogenase, serum glutamic-oxaloacetic transaminase, and serum glutamic-pyruvic transaminase levels were measured every 6 weeks. Pulmonary function testing was performed in patients who developed pulmonary symptoms.

**Toxicity Levels**

Hematological toxicity levels were graded at their nadir as follows: Grade 1: white blood cell count 3.0 to 3.9/cu mm, platelet count 75,000 to 120,000/cu mm, and hemoglobin concentration 10.0 to 11.9 gm/dl; Grade 2: white blood cell count 2.0 to 2.9/cu mm, platelet count 50,000 to 74,900/cu mm, and hemoglobin concentration 8.0 to 9.9 gm/dl; Grade 3: white blood cell count 1.0 to 1.9/cu mm, platelet count 25,000 to 49,000/cu mm, and hemoglobin concentration 6.5 to 7.9 gm/dl; and Grade 4: white blood cell count less than 1.0/cu mm, platelet count less than 25,000/cu mm, and hemoglobin concentration below 6.5 gm/dl.

The four grades of hepatic function abnormalities were defined as follows: Grade 1: less than 2.5 times normal; Grade 2: 2.6 to 5 times normal; Grade 3: 5.1 to 20 times normal; and Grade 4: greater than 20 times normal. For patients at a Grade 1 toxicity level, the dosages of CCNU and procarbazine were reduced by 25%. For those at a toxicity level of Grade 2 or greater, all chemotherapy was withheld until toxicity was resolved and then re-initiated at a dosage with 25% reduction of procarbazine and CCNU.

**Assessment of Response**

Assessment of response followed evaluation of CT scans or MR images obtained after the completion of each cycle of chemotherapy. For nonenhancing tumors, the initial tumor area was measured using the perpendicular cross-sectional diameters at the level of the largest tumor extent. If enhancement accounted for less than 20% of the nonenhanced area of a tumor, subsequent assessments were based on the largest area of the nonenhancing mass. Measurement of tumor area did not include areas of cystic change, edema, or calcification. For tumors with enhancement on CT and MR imaging, the cross-sectional area of the largest enhancing mass was calculated using the same approach. Tumor volumes were not calculated, but the number of scan slices and the width of each slice were noted. A complete response was defined as the total disappearance of all enhancing or nonenhancing tumor or edema abnormalities demonstrated on CT or MR imaging, excluding calcifications or periventricular or white matter abnormalities not in continuity with the known tumor mass as demonstrated on T1-weighted MR images. A partial response was defined as a greater than 50% diminution in tumor area. Stable disease was defined as a 0% to 50% reduction in tumor area in the setting of a stable neurological examination, stable KPS score, and a stable or reduced corticosteroid dosage. Progressive disease was defined as an increase in tumor area or radiographic evidence of stable disease in the setting of clinical deterioration or increase in corticosteroid dosage. Duration of response was measured from the date of initiation of the first chemotherapy cycle until either disease progression or the latest evaluation.

**Results**

Twenty-one patients (13 men and eight women), aged 22 to 65 years, were treated for oligodendroglioma (two patients), anaplastic oligodendroglioma (five patients), or oligoastrocytoma (14 patients) (Table 1). Of the oligoastrocytomas, a low-grade appearance of both components was found in one patient, a low-grade oligodendrogial and a grade III astrocytic component in two, an anaplastic oligodendrogial and a grade II astrocytic component in three, and malignant oligodendrogial and astrocytic (grade III or IV) components in eight. Chemotherapy was administered before irradiation in 14 patients and at recurrence in seven. One patient in the latter group received one cycle of melphalan, which was discontinued due to Grade 4 myelosuppression, prior to PCV chemotherapy.

**Oligodendroglioma**

Two patients with oligodendroglioma were treated...
TREATMENT OF GLIOMAS WITH PCV CHEMOTHERAPY

TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>Oligodendroglial Component (%)</th>
<th>Grade of Oligodendroglial Component</th>
<th>Astrocytoma Component Grade</th>
<th>Type of Operation†</th>
<th>PCV Before R?</th>
<th>No. of PCV Cycles</th>
<th>Type of Response§</th>
<th>Response Duration (wks)</th>
<th>Death (wks after treatment)</th>
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*PCV = procarbazine, methyl-(2-chloroethyl)-1-nitrosourea (CCNU), and vincristine; RT = radiation therapy; Y = yes; N = no.
†Oligo = low-grade oligodendroglial components; anap = anaplastic oligodendroglial component.
‡R = total or partial resection of brain tumor; B = stereotactic or open brain biopsy.
§CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; SD → PD or PR → PD = initial response, then progression.
|| = Continued response through last follow up.
*Autopsy 8 months after initiation of PCV chemotherapy revealed a component (10%) of grade 4 astrocytoma.
††Lost to follow-up review.
‡‡Radiation therapy not yet started.

with PCV chemotherapy, one before and one after irradiation. There was no evidence of radiographic or clinical change after three cycles of PCV chemotherapy administration prior to radiation therapy in one patient (Case 1) with a nonenhancing mass and a KPS score of 100. Her disease remains stable at 83+ weeks. Case 2, previously treated with irradiation and one cycle of melphalan chemotherapy, experienced disease progression after two cycles of PCV chemotherapy despite initial radiographically demonstrated stability of a right frontoparietal tumor. Six months later, rapid growth of the frontal portion of this tumor was noted on a cranial MR image. Postmortem examination 8 months following the initiation of PCV chemotherapy revealed that the frontal portion was an astrocytoma grade IV, comprising about 10% of the entire tumor.

Anaplastic Oligodendrogliaoma

Five patients with anaplastic oligodendrogliaoma received PCV chemotherapy. A complete response was noted in one patient (Case 4) treated with four cycles of PCV chemotherapy prior to radiotherapy. The patient remains free of disease at 40+ weeks, as demonstrated radiographically. A partial response was noted in one patient (Case 5) who received three cycles of PCV chemotherapy before irradiation and remains at the same response level at 100+ weeks. Another patient (Case 3) was treated with two cycles of PCV chemotherapy before urticaria necessitated discontinuation of procarbazine administration. She received two additional cycles of chemotherapy, with hydroxyurea substituted for procarbazine, and remained at a stable disease level for 52 weeks before tumor recurrence, at which time radiotherapy was initiated. Two patients were treated for recurrent disease following radiotherapy. One patient (Case 7) continues to exhibit a response after more than 54 weeks. The other patient (Case 6), who exhibited a partial response after two cycles of PCV chemotherapy, developed a recurrence after the fourth cycle.

Oligoastrocytoma

Of the 14 patients with oligoastrocytoma who were treated with PCV chemotherapy, one (Case 17) exhibited a complete response lasting more than 28 weeks; initiation of irradiation has not yet been necessary.

J. Neurosurg. / Volume 76 / May, 1992

743
Partial responses were noted in 10 patients, eight of whom were treated before radiotherapy. Two of the eight patients (Cases 10 and 20) continued to respond at 78 and 26 weeks, respectively, before being lost to follow-up study. Five patients (Cases 11, 12, 19, 16, and 9) remain without tumor recurrence at 50+, 45+, 30+, 26+, and 16+ weeks, respectively. In addition, an 18-fluorodeoxy-D-glucose positron emission tomography scan of one patient (Case 16) revealed partial resolution of a previously hypermetabolic mass lesion. One patient (Case 8) has sustained a response for 54+ weeks, despite evidence of the enlargement of an intratumoral cyst without a change in the noncystic portion. Two patients (Cases 13 and 15) treated following radiotherapy, continue to respond at 24+ and 60+ weeks, respectively.

Stable disease was noted in two patients, both treated following radiotherapy. One patient (Case 14) was lost to follow-up study at 39 weeks and the other (Case 18) developed disease progression at 39 weeks (at the completion of his fifth cycle) and died at 45 weeks. Progressive disease was seen in one patient (Case 21), who was lost to follow-up study at 12 weeks.

Toxicity Levels

A total of 75 cycles of PCV chemotherapy were administered to the 21 patients (median three cycles, range two to five cycles). Side effects included nausea and/or vomiting (60 cycles) and paresthesias in the distal extremities (five patients). The incidence of nausea and vomiting decreased with the intravenous administration of Odansatron (Zofran) therapy prior to the administration of CCNU.

Hematological toxicity levels included leukopenia in 27 cycles (11 Grade 1, 14 Grade 2, and two Grade 3) and thrombocytopenia in 18 cycles (seven Grade 1, eight Grade 2, two Grade 3, and one Grade 4). A Grade 2 elevation in liver enzymes (one cycle in Case 7) resolved after a 3-week delay of chemotherapy administration and did not recur after a 25% reduction in the next dose of CCNU and procarbazine.

Two patients developed urticaria; in one (Case 3), therapy was continued after substituting hydroxyurea for procarbazine, while the other (Case 15) responded to the discontinuation of chemotherapy.

Discussion

Role of Chemotherapy

The PCV chemotherapy regimen is of benefit in the treatment of malignant oligodendrogliomas and oligoastrocytomas. Our experience suggests a role for PCV chemotherapy administration prior to irradiation in a diverse group of anaplastic oligodendrogliomas and mixed oligoastrocytomas. In this study, 11 (79%) of 14 patients undergoing pre-irradiation chemotherapy demonstrated a greater than 50% reduction in tumor size, while responses were noted in four of seven patients treated following radiotherapy. Only two patients treated following irradiation had progression of disease while undergoing chemotherapy. Responses occurred in patients with anaplastic oligodendrogliomas as well as those with oligoastrocytomas; responses in the latter group occurred regardless of the extent of histological mix or degree of malignancy. No response was seen in either patient with “pure” oligodendrogliomas.

Confounding Variables

Factors that could account for the radiographic responses included corticosteroid use4 and, in patients receiving PCV chemotherapy after irradiation, effects of radiation. Corticosteroids have been shown to alter the radiographic appearance of recurrent malignant brain tumors.4 However, none of our patients required an escalation in corticosteroid dosage during therapy. In addition, PCV chemotherapy treatment was not initiated until more than 3 months had elapsed after completion of radiotherapy, in the setting of recurrent disease. Because most patients had a normal neurological examination with a KPS score of 100, improvements in clinical status could not be monitored in all.

Several authors have documented the efficacy of PCV chemotherapy of irradiated astrocytoma10,12 and malignant oligodendroglioma.3 These articles did not identify a response prior to radiotherapy or a response that mandates therapy of either homogeneous or mixed oligodendroglioma. Only the report of Macdonald, et al.15 documented a pre-irradiation response in three patients with pure anaplastic oligodendrogliomas.

Common Progenitor Cell

Experimental and pathological observations have suggested that the oligodendroglial and astrocytic cell populations in mixed gliomas may be derived from a common stem cell.6,7 In nitrosourea-induced glioma models, mixed oligodendroglial and astrocytic tumors are the most commonly induced gliomas.17 In addition, immunohistochemical studies of human oligodendrogliomas and mixed gliomas have postulated that both types of cells and tumors are derived from A2B5+ progenitor cells.9 Finally, pathological examination of mixed glial tumors often demonstrates cells that are transitional between oligodendroglias and astrocytes, both at the light microscopic2 and electron microscopic14 levels. These data point to a possible histogenetic similarity between oligodendrogliomas and oligoastrocytomas, suggesting that mixed tumors may be related to “pure” oligodendroglial tumors. In contrast, pure astrocytomas may be derived from a separate lineage, conveying different chemotherapeutic susceptibility characteristics. This may therefore provide a rationale for a unified therapeutic approach to these seemingly diverse tumors.

Conclusions

The response of anaplastic oligodendroglioma to chemotherapy led us to study this approach in patients with tumors containing a component of oligodendroglioma. Our results suggest a unique chemotherapeutic
Treatment of gliomas with PCV chemotherapy

sensitivity for many tumors with an oligodendrogial component. This approach decreases total tumor burden, and it is hoped that it will improve the efficacy of radiotherapy. As recurrence invariably occurred in a previously reported group of patients with anaplastic oligodendroglioma who underwent chemotherapy following irradiation,* we do not believe that chemotherapy will allow us to avoid radiation therapy altogether.

We conclude that PCV chemotherapy administered before irradiation may be of benefit as initial therapy following surgery in patients with malignant mixed gliomas or anaplastic oligodendrogliomas. Further clinical studies must be performed to assess the efficacy of PCV chemotherapy as initial treatment for pure and mixed oligodendrogial tumors.

References


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