LIGODENDROGLIOMAS and oligodendroglia–astrocytomas (oligoastrocytomas) are thought to be uncommon, comprising 5% of primary brain neoplasms.\(^{17,20}\) Low-grade homogeneous oligodendroglial tumors are slow growing and often are diagnosed years after the onset of symptoms. Less certain is the natural history of the Grade III or Grade IV tumor that contains varying mixtures of oligodendroglial and astrocytic cells. These two cell types may emerge from a bipotential precursor.\(^{3,19}\) Recent molecular evidence suggests that oligodendroglomas and oligoastrocytomas share common genetic alterations that are distinct from the changes that characterize astrocytomas.\(^{12,15}\) Alternatively, the two cell types may derive from transitional cells with characteristics that lie intermediate between those of mature oligodendroglial and astrocytic cells.\(^{10}\) For example, certain murine glioma cell lines may differentiate toward either the oligodendroglial or astrocytic phenotype, depending on environmental growth signals.\(^{9}\) In either case, the cells comprising the oligoastrocytoma population may share common features of morphology and sensitivity to chemotherapy.

Unlike other brain tumors (except brain lymphomas) anaplastic oligodendroglialomas have been shown to be responsive to procarbazine, lomustine (CCNU), and vincristine (PCV) chemotherapy.\(^{5,8,16}\) We have suggested that tumors that contain various proportions of oligodendrogial and astrocytic cell populations are likely to respond to this regimen as well and have reported the initial response of a small group of patients.\(^{9}\) Similariy, Kyritsis and coworkers\(^ {13}\) report cases of drug-induced remissions of oligoastrocytomas as do Cairncross, et al.\(^ {4}\) Our present study was designed to identify the benefits of PCV therapy in patients with Grade III and Grade IV oligoastrocytomas.

Clinical Material and Methods

We provided PCV chemotherapy to 32 consecutive patients between January 1989 and June 1995. All patients were above the age of 18 years and had pathologically confirmed glioma with oligodendroglia component. Included were patients with varying proportions of oligodendroglial and astrocytic cells. All 32 patients were af-
Procarbazine, CCNU, and vincristine therapy for oligoastrocytoma

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conflicted by a Grade III or Grade IV tumor and all had measurable residual tumor on computerized tomography (CT) or magnetic resonance (MR) imaging after operation and prior to chemotherapy.

Pathological Criteria

All pathological material was evaluated by a neuropathologist (D.N.L.) who was blinded to each patient’s treatment and response. In each case, the tumor was classified as an oligodendroglial tumor (> 99% oligodendroglioma) or an oligoastrocytoma (1%–99% oligodendroglioma). In accordance with World Health Organization (WHO) criteria,11 we took a simple, descriptive approach by diagnosing all tumors with both an oligodendroglial and astrocytic component (whether intermixed or separate) as oligoastrocytomas. Regions with “microgemistocytes” in otherwise oligodendrogial lesions did not result in a diagnosis of oligoastrocytoma. We estimated the percentage of the oligodendroglial component as 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, or more than 99% (oligodendroglioma). We recognize that some neuropathologists would classify as astrocytoma those lesions with less than a 25% oligodendroglial component and that they would identify as oligodendroglioma those masses with more than a 75% oligodendroglial component. The astrocytoma component was classified according to WHO criteria.11 In general, the astrocytoma component was judged as Grade III if mitoses were present and as Grade IV if necrosis or prominent endothelial proliferation was evident. The oligodendroglial component was graded separately according to WHO criteria. This was judged to be anaplastic oligodendroglioma if there was high cellularity, frequent mitoses, nuclear pleomorphism, prominent endothelial proliferation, and/or necrosis. For the purpose of analyses in which patients were grouped according to grade, the astrocytic grade was used for the 25 patients whose tumors had a 1% to 99% oligodendroglioma component, whereas the oligodendrogial grade was used for the seven patients who had anaplastic oligodendroglioma.

Data Collection and Statistical Analyses

All medical records were reviewed by members of our team (H.P. and L.K.) and entered into a database (available on request). Common toxicities were defined. Responses to therapy were evaluated by identification of changes within enhancing mass lesions. The “best response” was defined as the greatest area of reduction in the enhancing tumor, seen on neuroimaging, that persisted through two cycles of PCV therapy. A complete response was defined as the total disappearance of a previously enhancing tumor without the need for an increase in corticosteroid dose. A partial response was defined as a greater than 50% reduction in cross-sectional tumor area and stable disease as a 0% to 50% reduction. Progressive disease was defined as a greater than 25% increase in tumor cross-sectional area. We defined time to progression as the interval between the first provision of PCV, lasting for at least 3 months (two cycles), and either the first evidence of progression or the date of last evaluation if progression had not occurred. We identified the duration of survival as the period of time from the start of PCV administration until death or the most recent evaluation. For time to progression and duration of survival we evaluated the impact of prior radiotherapy, the histological grade, and the percentage of tumor cells identified as oligodendroglioma using log-rank tests. Failure of therapy was defined as a radiographically determined recurrence (on CT or MR imaging) or interim growth of T2-weighted enhancement or T2-weighted abnormality (if T2-weighted enhancement had disappeared). Patients were identified as alive with responsive disease, alive with progressive disease, or dead of disease based on clinical status and imaging evaluations. In cases in which clinical data had aged more than 3 months, the caregiver or patient was contacted for survival and status information.

Chemotherapy Administration

The PCV chemotherapy was administered in cycles lasting 6 weeks. Patients were included in the study if their white blood cell counts were in excess of 3000 and their platelet counts above 150,000, and if there were no discerned hepatic, renal, or infectious contraindications.9 Lomustine was administered orally at 110 mg/m2 on Day 1, followed by 1.5 mg vincristine intravenously on Day 8 and Day 22. Between Days 8 and 22, we administered 60 mg/m2 procarbazine, usually in conjunction with anti-emetic medications. A booklet (available on request) was prepared to provide patient education. Evaluations consisted of a hemogram and liver function studies obtained on Days 1, 8, and 22, and MR imaging at the start of cycles 1, 3, and 5.

The mean and median number of treatment cycles was four. The maximum duration of treatment was eight cycles (one patient) and the minimum was two cycles (two patients). The median duration of follow-up review for all 32 patients was 19.3 months with a range from 2.8 to 75.5 months. The mean follow-up time was 24.2 months with a standard deviation of 19.9 months.

Radiation Therapy

Radiation therapy, given prior to or following PCV, was provided at doses ranging from 55.8 Gy to 70.2 Gy in 1.8-Gy daily fractions. The dose administered depended on the grade of the astrocytic component of the tumor. Grade III tumors received doses from 55.8 to 63 Gy depending on the location and extent of the residual mass after surgery. Grade IV tumors received at least 59.4 Gy and at most 70.2 Gy if the tumor location afforded a highly focal approach to irradiation. In all cases, postsurgical, prechemotherapy MR imaging volumes were used to delineate irradiation volumes. An area 2 cm in width surrounding the T2-weighted MR imaging volumes was irradiated to 45.0 Gy. Boost volumes included a 1.5-cm edge surrounding the T2-weighted gadolinium-enhancing mass. Grade IV tumors treated to 70.2 Gy were provided a second boost volume, above 59.4 Gy. This volume was defined by a 1.1-cm edge surrounding the T2-weighted gadolinium-enhancing mass (prior to chemotherapy). The two patients who were treated as a consequence of tumor progression during PCV therapy received irradiation of the largest tumor volume as determined from postsurgical or postchemotherapy MR imaging studies.

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Population Description

The 32 patients treated (Fig. 1) had varying mixtures of cell populations and were evaluated for toxicity (data available on 29 patients only), response, and response duration throughout a cumulative total of more than 124 cycles of PCV chemotherapy. The number of cycles was unknown for one patient; three patients are currently undergoing PCV chemotherapy and, therefore, we could not determine their total number of cycles. Nine of the patients were women and 23 were men. Their median age was 39.8 years at the time of diagnosis, which was defined as their age at the date of first biopsy or resection showing tumor. The oldest patient diagnosed was 64.6 years old, whereas the youngest was 24.9 years old. Their mean age was 40.7 years with a standard deviation of 11.4 years.

Three of the 32 patients received salvage regimens of PCV chemotherapy after failure of their response to initial PCV treatment. These three treatment courses were not included in the results of this study. This study focuses on 32 treatment courses administered to 32 patients.

Results

Chemotherapy Toxicity

Throughout more than 124 cycles of chemotherapy, instances of toxicity have been few. Nine patients suffered from Grade 3 or 4 hematological toxicity. There were no reports of hepatic toxicity or renal toxicity. One patient developed interstitial lung changes that likely were related to receiving CCNU. Three patients experienced skin rash of Grade 4 severity and three patients suffered from Grade 3 or 4 emesis in spite of concurrent administration of antiemetic medication with the PCV. Ten patients experienced a total of 23 dosage delays due to toxicity. Four patients experienced dose reductions (usually no more than 25%) for CCNU, five for procarbazine, and one for vincristine. Four patients stopped PCV treatment due to toxicity (three for skin reactions to procarbazine and one for Grade 4 marrow suppression) but all had at least partially responded by the time of their last cycle.

Response Rates

Table 1 summarizes the response rates as well as the progression and survival analyses of the treated population. Twenty-nine (91%) of the 32 patients treated with PCV responded to therapy. These included 10 patients with a complete response and 19 with a partial response. Of the 19 patients with a partial response, three have not completed their PCV treatment regimen. One patient was identified as having stable disease and two progressed during treatment. The 32 patients had a median time to progression of 14.5 months. The median time to progression for the 91% responses was 21 months, and the median survival time was 24 months.
progression of 15.4 months following commencement of PCV administration.

Five patients who achieved complete response and seven patients who achieved partial response continued to exhibit their responses as of their most recent follow-up evaluation. Two of the patients with partial response are currently undergoing PCV therapy. These patients have not progressed as of a median of more than 10 months since commencing therapy. The longest duration of freedom from progression in this group of current responders is greater than 65 months, whereas the minimum is 3 plus months with a mean of more than 21 months (standard deviation of ± 21 months).

**Time to Progression**

Twenty-six patients had Grade III or anaplastic tumors (astrocytic or oligodendroglial grade) and six patients had Grade IV tumors (astrocytic grade). The 26 patients with a Grade III/anaplastic tumor type (seven patients with complete response, 17 with partial response, one with stable disease, and one with progressive disease) had a median time to progression of 23.2 months, whereas the six with a Grade IV tumor type (three patients with complete response, two with partial response, and one with progressive disease) had a median time to progression of 12.4 months (p = 0.0916) (Table 1, Fig. 2).

The percentage of oligodendroglial component was known for 29 patients. The seven patients with 1% to 49% oligodendroglia (two with complete response, four with partial response, and one with stable disease) had a median time to progression of 12 months; the 15 patients with more than 99% oligodendroglia (two with complete response and five with partial response) had a median time to progression of 63.4 months (p = 0.0479) (Table 1 and Fig. 2 upper).

Alternatively, the 26 patients who harbored Grade III/anaplastic tumors can be divided into two groups: one with more than a 99% oligodendroglioma component (anaplastic oligodendroglioma—graded on oligodendrogial features alone) and the other with less than a 99% oligodendroglial component (Grade III oligoastrocytoma—graded on astrocytic features). Seven patients had anaplastic oligodendrogliomas (two patients with complete response and five with partial response) and 19 had Grade III oligoastrocytoma (five patients with complete response, 12 with partial response, one with stable disease, and one with progressive disease). Six patients had Grade IV oligoastrocytoma (three with complete response, two with partial response, and one with progressive disease). The median times to progression in these three groups were 63.4 months, 13.8 months, and 12.4 months, respectively (p = 0.0479) (Fig. 2 lower).

Age, gender, the number of treatment cycles administered, and the order of radiotherapy did not prove to be statistically significant determinants of time to progression according to the log-rank test.
Duration of Survival

The median duration of survival for all patients treated was 61.4 months. The 16 patients treated with three or fewer cycles had a median survival time of 61.4 months, whereas those receiving four or more cycles had a median of 49.8 months. The 26 patients with Grade III tumors had a median survival time of 61.4 months and the six patients with Grade IV tumors had a median survival time of 16.0 months ($p = 0.0121$). The seven patients with anaplastic oligodendrogliomas had a median survival time of more than 76 months; the 19 patients with Grade III oligoastrocytomas had 49.8 months; and the six with Grade IV oligoastrocytomas, 16 months ($p = 0.0154$) (Fig. 3 upper). The seven patients with 1% to 49% oligodendroglioma had a median survival duration of more than 43 months; 15 patients with 50% to 99% oligodendroglioma had 49.8 months; and seven patients with greater than 99% oligodendroglioma had greater than 76 months (Fig. 3 lower). With respect to gender, the 23 men had a median survival duration of 49.8 months, whereas the women had more than 56 months ($p = 0.0449$). Age, number of cycles of chemotherapy, and the order of radiotherapy were not significant predictors of mortality according to the log-rank test.

Discussion

The decision to use a course of PCV to treat a broad spectrum of Grade III and Grade IV oligoastrocytomas varying from anaplastic oligodendrogliomas (containing a homogeneous population of these cells) to Grade III or Grade IV tumors containing varying proportions of both oligodendrogial and astrocytic cells, was based on the presumption that the oligodendroglial lineage conveyed a unique sensitivity to this therapy. Of the 32 patients treated, 89% of the oligoastrocytomas and all of the Grade III oligodendrogliomas displayed at least a partial response to therapy. This response was durable at 5 years for one-half of the latter group and for 10% of the former. Although our population is small, the response rates for all patients with any contribution of oligodendroglioma (1%–99%) was 91%. The trend to improved time to progression and survival duration with increasing oligodendroglioma component raises testable hypotheses regarding mechanisms of cell-cycle sensitivity and resistance of cells from common bipotential origins.

Several aspects of this response are noteworthy. The therapy used in this study caused no significant morbidity through an average of four cycles for the entire population. One-fourth of the patients were able to sustain five cycles of treatment. Patients were easily treated in an outpatient setting and often at a distance from the hospital. Although CCNU-induced nausea was common, it was transient and quickly responded to antiemetic medications. Rarely, procarbazine-induced gastrointestinal difficulties occurred. Similar response rates were seen in PCV recipients both prior to and following radiation therapy (94.7% and 91.7%, respectively). The significance of the extended time to progression for the latter group (25.5 vs. 15.4 months) did not prove statistically significant. However, in favor of preirradiation PCV therapy are uncertainties regarding the benefits of irradiation of oligoastrocytomas. Three series have identified benefit accruing from irradiation of tumor in patients with oligoastrocytomas. More recent reviews have identified minimal benefit. Notably, within the oligoastrocytoma group (1%–99% oligodendroglioma component), the percentage of oligodendroglioma component did not significantly affect either response rate or time to progression. The group with 1% to 49% oligodendroglioma component had a median time to progression of 12 months and a response rate of 85.7%, whereas those with a 50% to 99% oligodendroglioma component had a median time to progression of 23.2 months and a response rate of 93.3%. Although not directly comparable, response rates similar to these were achieved using nitrosourea-based regimens designed by Duffau and colleagues, who treated 20 patients with oligoastrocytomas; Soffietti, et al., who provided therapy to two patients with oligoastrocytomas; and Kyritsis.
and coworkers. Nonnitrosourea-based regimens have also been used to treat these tumors. Soffietti, et al., unsuccessfully provided carboplatin therapy to patients in whom PCV therapy had failed. Stewart and colleagues treated one patient with fluorouracil with partial benefit. The high response rates were reflected in prolongation of survival, which suggests a benefit of PCV therapy. Patients with Grade III oligoastrocytomas experienced a 49.8-month survival time with chemotherapy before or after radiation therapy. Even the 16-month survival period of patients with Grade IV oligoastrocytomas suggests the benefit of this therapy. As given, PCV chemotherapy has not been optimized. The lack of hematological toxicity argues that the maximum safe level of PCV has not been reached and that the use of “intensified PCV” is supportable. Dose-intensification strategies that use pretherapy marrow storage or posttherapy granulocyte colony-stimulating factor could further enhance efficacy and safety.

We are aware of the possibility that others may systematically exclude from therapy all but the most obvious oligodendroglioma-containing tumors. Alternatively, large studies, such as those conducted by the Brain Tumor Collaborative Group (BTCG) or its successors, may have systematically provided nitrosourea-based therapy to tumors that actually had a lineage consisting of both oligodendroglioma and astrocytoma. The extended survival of 15% to 20% of BTCG patients may reflect the sensitivity of tumors to varying proportions of both oligodendroglioma and astrocytic cells. A retrospective analysis of these survivors, currently underway, may result in changes within the ongoing Canadian-American protocol using PCV to treat “anaplastic oligodendrogliomas.”

Lacking in our study are the specific markers that might permit more objective identification and quantification of oligodendroglial cells within oligoastrocytoma tumors. Our data are supported by further study, a major need will exist for easily usable markers of oligodendroglioma and oligodendroglial-derived cells. Biologically, oligoastrocytomas may be similar to oligodendrogliomas. Burger, et al., and Herpers and Budka have demonstrated transitional cells that have features of both oligodendrogliomas and oligoastrocytomas. In addition, recent in vitro studies have shown that the phenotype of neoplastic glia may assume features of oligodendrogial or astrocytic cells in response to specific growth factors. Molecular similarities unite both oligodendroglioma and oligoastrocytoma tumors. These neuropathological, cell biological, and molecular genetic data indicate biological similarities between oligoastrocytomas and oligodendrogliomas. The demonstration that Grade III and Grade IV oligoastrocytomas are also sensitive to PCV chemotherapy extends these biological similarities to the arena of clinical cancer chemotherapy.

References


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