Myeloablative chemotherapy for recurrent aggressive oligodendroglioma

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The objective of this study was to ascertain the duration of tumor control and the toxicities of dose-intense myeloablative chemotherapy for patients with recurrent oligodendrogliomas. Patients with previously irradiated oligodendrogliomas, either pure or mixed, that were contrast enhancing, measurable, and behaving aggressively at recurrence were eligible for this study. Only complete responders or major partial responders (75% reduction in tumor size) to induction chemotherapy—either intensive-dose procarbazine, lomustine, and vincristine or cisplatin plus etoposide—could receive high-dose thiotepa (300 mg/m²/day for 3 days) followed by hematopoietic reconstitution using either bone marrow or peripheral blood stem cells. Thirty-eight patients began induction chemotherapy and 20 (10 men, 10 women; median age 46 years; median Karnofsky score 80) received high-dose thiotepa. For the high-dose group, the median event-free, progression-free, and overall survival times from recurrence were 17, 20, and 49 months, respectively. Tumor control in

excess of 2 years was observed in 6 patients (30%). Four patients (20%) are alive and tumor free 27 to 77 months (median, 42 months) from the start of induction therapy; however, fatal treatment-related toxicities also occurred in 4 patients (20%). Three patients died as a result of a progressive encephalopathy which, in 2 instances, was accompanied by a wasting syndrome; 1 patient died as a consequence of an intracerebral (intratumoral) hemorrhage. Fatal toxicities occurred in patients with pretreatment Karnofsky scores of 60 or 70. High-dose thiotepa to consolidate response was a disappointing treatment strategy for patients with recurrent aggressive oligodendroglial neoplasms, although several patients had durable responses. Moreover, as prescribed, high-dose thiotepa had significant toxic effects in previously irradiated patients, especially those with poorer performance status. *Neuro-Oncology* 2, 114-119, 2000 (Posted to *Neuro-Oncology* [serial online], Doc. 99-54, March 22, 2000. URL <neuro-oncology.mc.duke.edu>)

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²Abbreviations used are as follows: I-PCV, intensive-dose PCV; PCV, procarbazine, lomustine, and vincristine.

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Oligodendroglioma is a chemosensitive brain tumor. In striking contrast to other types of malignant glioma, many high-grade oligodendrogliomas respond dramatically and completely to chemotherapy (Cairncross and Macdonald, 1988; Cairncross et al., 1994; Macdonald et al., 1990a). Although no clinical or pathologic feature confidently distinguishes a chemosensitive oligodendroglioma from a resistant one, a specific molecular alteration, allelic loss of chromosome 1p, is a powerful predictor of drug sen-

sitivity and survival in patients with anaplastic oligodendrogliomas (Cairncross et al., 1998). Moreover, symptomatic enlarging low-grade oligodendrogliomas, sometimes called aggressive oligodendrogliomas, and anaplastic mixed oligoastrocytomas, many of which harbor chromosome 1p loss, are also chemosensitive (Maintz et al., 1997; Mason et al., 1996; Glass et al., 1992). Oligodendrogliomas respond to a variety of chemotherapeutic agents, especially drugs that alkylate DNA (Mason et al., 1997), but a combination of procarbazine, lomustine, and vincristine, a regimen known as PCV² (Levin et al., 1980), quickly emerged as the chemotherapy of choice for newly diagnosed and recurrent oligodendrogliomas, and also for mixed gliomas with oligodendroglial features (Kim et al., 1996). Furthermore, salvage chemotherapy regimens may be helpful for some patients. Oligodendrogliomas that have responded to chemotherapy previously and then recur sometimes respond again to PCV,³ to cisplatin plus etoposide (Peterson et al., 1996), or to paclitaxel (Chamberlain and Kormanik, 1997). Although oligodendrogliomas with chromosome 1p loss are chemosensitive, not all responses are long lasting; in fact, previously irradiated, recurrent oligodendrogliomas are seldom cured by such treatment. The median duration of tumor control in patients with recurrent anaplastic or aggressive oligodendrogliomas and oligoastrocytomas ranges from 10 to 24 months (Cairncross and Macdonald, 1988; Cairncross et al., 1994; Glass et al., 1992; Kim et al., 1996; Soffietti et al., 1998; van den Bent et al., 1998), and tumor control in individual patients rarely exceeds 36 months (Cairncross and Macdonald, 1988).

Given the unusual chemosensitivity of oligodendrogliomas, including many complete responses to PCV (Cairncross et al., 1994), and in light of the steep dose-response curve for many cytotoxic drugs, we hypothesized that induction chemotherapy followed by myeloablative doses of thiopeta, an alkylating agent with excellent CNS penetration, might result in long-term control of previously irradiated, recurrent oligodendrogliomas. To test the feasibility of this approach and to rule out extreme results, we designed a multicenter pilot study in which patients with measurable tumors would begin standard dose therapy; major responders to induction therapy ($\geq 75\%$ reduction) would receive high-dose treatment; and all patients would be followed until tumor recurrence or death. This report summarizes our experience with high-dose thiopeta and hematopoietic reconstitution for patients with recurrent, aggressive, pure and mixed oligodendrogliomas.

Methods

Eligibility criteria for this study included age ≥ 18 years; pathologic evidence of an oligodendroglioma with 2 or more of the following anaplastic features: high cellularity, nuclear pleomorphism, mitoses, vascular proliferation, or necrosis (rebiopsy of recurrent disease was not mandatory); prior radiotherapy for either a low-grade or anaplastic lesion; unequivocal tumor progression at least 6 weeks after surgical resection or 2 months after radio-

therapy; measurable contrast-enhancing disease on CT or MRI; and signed, informed consent.

Patients with symptomatic, enlarging, enhancing, previously irradiated nonanaplastic oligodendrogliomas termed aggressive by Macdonald et al. (1990a) also were eligible to participate in this trial. Other eligibility criteria were recurrent anaplastic or aggressive oligoastrocytoma; stable corticosteroid dose for at least 2 weeks prior to baseline imaging; Karnofsky performance score ≥ 60 ; bidimensionally measurable enhancing tumor ($\geq 2 \text{ cm} \times 2 \text{ cm}$); absolute granulocyte count $\geq 1.5 \times 10^9/\text{l}$; platelet count $\geq 150 \times 10^9/\text{l}$; serum creatinine level $\leq 130 \text{ mmol/l}$; and serum transaminase levels ≤ 1.5 times the upper limit of normal. Patients were deemed ineligible if a mixed glioma contained only a minor oligodendroglial element ($\leq 25\%$). Other situations rendering patients ineligible were as follows: known leptomeningeal or systemic metastases; prior treatment with thiopeta; systemic malignancy or serious illness; inability to comply with treatment or follow-up; pregnancy, lactation, or unwillingness to consider effective contraception. Central pathology review was mandatory prior to high-dose therapy, but imaging studies were not reviewed centrally.

I-PCV as used by Cairncross et al. (1994) was the induction regimen for patients who were chemotherapy-naïve or previously had received chemotherapy unrelated to I-PCV. Cisplatin plus etoposide (cisplatin 90 mg/m^2 i.v. on day 1 plus etoposide 150 mg/m^2 i.v. on days 2 and 3, every 4 weeks) was the induction regimen for those who previously had received PCV, I-PCV, or related chemotherapy. Pretreatment clinical, laboratory, and imaging evaluations; all dose calculations, reductions, and delays; and all assessments during induction chemotherapy were performed as described previously (Cairncross et al., 1994). After 2 cycles of the induction regimen, patients were re-imaged, and response was assessed as outlined by Macdonald et al. (1990b). Complete responders (those who had disappearance of all enhancing tumor, were off steroids, and were neurologically stable or improved) received one additional cycle of induction chemotherapy prior to high-dose treatment. Partial responders (those who had 50% or greater decrease in the maximum cross-sectional area of the enhancing tumor, whose steroid dose remained stable or decreased, and who were neurologically stable or improved) and patients with stable disease received 2 additional cycles of I-PCV or cisplatin plus etoposide. Only those who then had achieved a complete or major partial response were eligible for high-dose treatment. In this context, a major partial response was defined as a 75% or greater decrease in the maximum cross-sectional area of the recurrent enhancing tumor.

In addition to a demonstrably chemosensitive oligodendroglioma, the eligibility criteria for the investigational phase of the trial were as follows: adequate bone marrow harvest ($> 2.5 \times 10^8$ nucleated cells per kilogram body weight) or peripheral blood stem-cell collection ($> 2.0 \times 10^6$ CD34⁺ cells per kilogram body weight; harvesting of marrow or peripheral stem cells prior to induction chemotherapy encouraged, but not mandatory); Karnofsky performance score ≥ 60 ; 24-h creatinine clearance within the normal range; normal

coagulation profile; normal electrocardiogram and wall motion studies; carbon monoxide diffusion capacity $\geq 60\%$ of the predicted value; negative hepatitis and human immunodeficiency virus serologies; and secure central venous access.

Thiotepa was given on 3 consecutive days (300 mg/m²/day for 3 days) starting on day -6, with bone marrow or peripheral blood stem cell reinfusion on day 0. The dose of thiotepa was calculated using actual body weight except for very obese patients, in which case the maximum large frame ideal body weight was used (Metropolitan Life Table, 1979 Build Study, Society of Actuaries and Association of Life Insurance Medical Directors of America, 1980). No attempt was made to standardize supportive measures. Instead, investigators were encouraged to follow local institutional guidelines for posttransplant care.

Follow-up clinical, laboratory, and imaging evaluations were to be performed every 3 months for 2 years, then every 6 months for 3 years, then yearly or as dictated by symptoms. For the purposes of statistical analysis and reporting, the following definitions were used: the on-study date was the date that induction chemotherapy began; the date of progression was the date of the first scan documenting a 25% or greater increase in tumor size or any new area of tumor (Macdonald et al., 1990b); and the time to tumor progression (duration of tumor control) was the interval between the on-study date and the date of progression. Event-free survival was considered to be the interval between the on-study date and the date of progression or death due to toxicity. Survival curves were generated to determine median event-free, progression-free, and overall survival times. This study was approved by an Investigational Review Board at each participating institution.

Results

Thirty-eight patients at 6 centers with previously irradiated, recurrent, anaplastic or aggressive oligodendrogliomas and mixed gliomas began I-PCV or cisplatin plus etoposide intending to proceed to high-dose therapy should a complete or major partial response occur during induction therapy. Eighteen patients with recurrent oligodendroglial neoplasms, 10 men and 8 women ranging in age from 18 to 58 years (median, 44 years), did not meet the eligibility criteria for the investigational high-dose phase of this trial. The reasons for ineligibility were as follows: 1 patient had a nonfatal intratumoral hemorrhage during the first cycle of I-PCV; 5 patients progressed during induction therapy; 7 patients had stable disease or only a minor response to induction chemotherapy (less than a 75% decrease in tumor size); 3 patients had major partial responses to induction I-PCV that were only transient (evident after 2 cycles but not after 4 cycles); 1 patient had a durable major response but did not proceed to high-dose therapy because of borderline performance status; and 1 patient had a durable response but declined high-dose thiotepa. Two of these ineligible patients, 1 with stable disease and 1 with a transient major response, received high-dose thiotepa off-

study (see below). This cohort of 18 nontransplanted patients had a median duration of survival of 12 months.

Twenty patients at 5 centers, 10 men and 10 women, ranging in age from 28 to 57 years (median, 46 years) with good Karnofsky performance scores (60 to 90; median, 80) received high-dose thiotepa (Table 1). Sixteen patients had been irradiated previously for a low-grade oligodendroglioma and 4 had radiation for an anaplastic oligodendroglioma. At recurrence, 15 of the 16 patients with low-grade tumors had a second surgical procedure, either a biopsy or a re-resection. The recurrent tumor was classified as an anaplastic oligodendroglioma in 12 instances, an anaplastic oligoastrocytoma in 1 case, and an aggressive low-grade oligodendroglioma in 2 cases. One patient with a symptomatic, enlarging, enhancing, previously irradiated low-grade oligodendroglioma was not rebiopsied at recurrence. The induction chemotherapy regimen was I-PCV in 15 patients and cisplatin plus etoposide in 4. In one patient who did not tolerate I-PCV, the induction chemotherapy regimen began with 2 cycles of I-PCV followed by 2 cycles of cisplatin plus etoposide. Among the 20 patients who met all the eligible criteria and were transplanted, 4 (20%) had a complete response to induction therapy, 3 (15%) to I-PCV, 1 to cisplatin plus etoposide, and 16 (80%) had a major partial response—13 to I-PCV and 3 to cisplatin plus etoposide.

Four patients (20%) died of delayed toxicities related to high-dose thiotepa. Three of the 4 fatal cases developed a severe encephalopathy characterized by apathy, disorientation, and psychomotor retardation. These cognitive and behavioral toxicities were evident soon after high-dose treatment and progressed, and in 2 patients were also associated with profound anorexia and weight loss. Unrelenting cerebral dysfunction and inanition led to death within 6 months. One patient died 3 months after high-dose thiotepa as a result of an intracerebral (intratumoral) hemorrhage that occurred 48 h after stem cell reinfusion. Fatal complications of high-dose therapy occurred in patients with a lower median pretreatment Karnofsky performance score (65 vs 80). Other significant toxicities after high-dose thiotepa included liver dysfunction, transient encephalopathy and persistent thrombocytopenia in patient No. 3, prolonged encephalopathy and anorexia in patient No. 15, prolonged anorexia in patient No. 7, acute pulmonary edema during bone marrow reinfusion in patient No. 8, persistent thrombocytopenia in patient No. 18, and delayed panhypopituitarism in patient No. 2.

For the 20 patients in the high-dose group, the median event-free, progression-free and overall survival times from recurrence were 17, 20, and 49 months, respectively. Seven patients (35%) died from tumor that recurred 10 to 48 months (median, 13 months) from the start of induction chemotherapy, 5 to 41 months (median, 7 months) after high-dose thiotepa. Five patients (25%) are alive with tumor that recurred 13 to 33 months (median, 19 months) from the start of induction therapy, 4 to 27 months (median, 11 months) after high-dose thiotepa. Four patients (20%) are alive and tumor free 27 to 77 months (median, 42 months) from the start of induction therapy, 20 to 70 months (median, 31 months) after high-dose thiotepa. The 2 additional

Table 1. Characteristics of patients receiving high-dose chemotherapy

Case No.	Age ^a /sex	KPS ^a	Prior LGO ^b (yes/no)	Prior RT for LGO/AO ^{b,c}	Diagnosis at induction ^{c,d}	Induction regimen ^e	Response status CR or PR ^f	Duration of control	Current status ^g
1	38F	80	Y	LGO	AO	I-PCV	CR	48	DOD
2	28F	80	N	AO	AO	I-PCV CDDP/VP	PR	77 ^h	A&W
3	49M	90	N	AO	AO	CDDP/VP	CR	12	DOD
4	43M	90	Y	LGO	AgO	I-PCV	PR	33	AWD
5	53F	60	Y	LGO	AgO	I-PCV	PR	15 ⁱ	DOC
6	46M	80	Y	LGO	AO	I-PCV	CR	15	DOD
7	41M	90	Y	LGO	AO	I-PCV	PR	13	DOD
8	30F	80	N	AO	AO	CDDP/VP	PR	11	DOD
9	49M	90	Y	LGO	AO	I-PCV	PR	48 ^h	A&W
10	57F	70	Y	LGO	AO	I-PCV	PR	13 ⁱ	DOC
11	41F	70	Y	LGO	AO	I-PCV	PR	10 ⁱ	DOC
12	45M	80	Y	LGO	AMG	I-PCV	PR	13	AWD
13	46M	60	N	AO	AO	CDDP/VP	PR	9 ⁱ	DOC
14	35M	90	Y	LGO	AO	CDDP/VP	PR	10	DOD
15	48F	60	Y	LGO	AO	I-PCV	PR	35 ^h	A&W
16	34F	90	Y	LGO	AO	I-PCV	PR	19	AWD
17	42F	70	Y	LGO	AgO	I-PCV	PR	22	AWD
18	51M	70	Y	LGO	AO	I-PCV	CR	20	DOD
19	29F	90	Y	LGO	AO	I-PCV	PR	27 ^h	A&W
20	50M	80	Y	LGO	AO	I-PCV	PR	18	AWD

^aAt start of induction chemotherapy. F, female; M, male; KPS, Karnofsky performance status.

^bLGO, low-grade oligodendroglioma.

^cRT, radiotherapy; AO, anaplastic oligodendroglioma.

^dAgO, aggressive oligodendroglioma; AMG, anaplastic mixed glioma.

^eI-PCV, intense-dose procarbazine, lomustine, and vincristine; CDDP/VP, cisplatin plus etoposide.

^fCR, complete response; PR, partial response.

^gDOD, dead of disease; A&W, alive and well; AWD, alive with disease; DOC, dead of complications.

^hStill responding.

ⁱStill responding at death.

patients who received high-dose thiotepe off-study, did poorly: an 18-year-old woman with an atypical oligodendroglioma that did not respond to PCV and radiotherapy initially nor to cisplatin plus etoposide at recurrence died of overwhelming pulmonary infection and hemorrhage 5 weeks after receiving high-dose thiotepe; and a 50-year-old woman with an aggressive oligodendroglioma that responded only transiently to I-PCV died as a result of tumor progression 10 months later.

Discussion

High-dose chemotherapy has proven to be a curative treatment strategy for some types of hematopoietic malignancies. However, intensive chemotherapy as a strategy for cancer cure has often been disappointing when applied to drug-resistant solid tumors. For example, dose intensification of carmustine, a minimally effective chemotherapy for glioblastoma, has sometimes caused serious or fatal pulmonary toxicity while at the same time failing to enhance brain tumor control (Fine and Antman, 1992). Presently, oncologists are examining whether myeloablative chemotherapy will cure (or con-

trol more effectively than standard dose regimens) certain chemosensitive solid tumors such as those of the breast or testis. For drug-sensitive tumors, intensification of a systemic treatment, like chemotherapy, is also logical because many chemosensitive solid cancers are highly metastatic or disseminated at diagnosis. In this context, the Oligodendroglioma Study Group evaluated the utility of dose-intensive chemotherapy for previously irradiated oligodendrogliomas and mixed gliomas, uncommon brain tumors of adults that frequently respond dramatically to PCV chemotherapy but are not cured by such treatment. Some would argue that aggressive local treatment is a more appropriate therapeutic strategy (than is intensive chemotherapy) for cancers that rarely spread, yet some tumors that do not metastasize, like glioma, are generally not amenable to radical surgical resection, nor are they commonly curable with doses of radiation that can be administered safely.

We draw 3 conclusions from this initial study of myeloablative chemotherapy for recurrent aggressive oligodendroglioma. First, thiotepe in a dose of 900 mg/m² given over 3 days causes severe and irreversible toxicity in some patients. Three patients died as a consequence of a chronic encephalopathy, which in 2 instances was

accompanied by profound anorexia and wasting. Borderline pretreatment performance status may have been a risk factor for these fatal toxicities, as all patients with serious reactions had Karnofsky scores of 60 or 70. Previous brain irradiation may also have contributed to severe toxic reactions because, in an ongoing companion study by our group, neither irreversible encephalopathy nor prolonged anorexia has been observed to date in a series of newly diagnosed patients with anaplastic oligodendrogliomas treated with I-PCV chemotherapy and high-dose thiotepa instead of radiation (Cairncross et al., 1997). Second, despite using a dose of thiotepa that had serious toxic effects in 20% of patients, tumor control was not enhanced appreciably for most patients. For the entire high-dose group, the median event-free survival time was 17 months. When deaths due to toxicity were excluded, the median progression-free survival time was only 20 months. Other groups of patients with recurrent anaplastic or aggressive oligodendrogliomas and oligoastrocytomas treated with either standard-dose or moderately dose-escalated PCV have had similar median durations of tumor control (Cairncross and Macdonald, 1988; Cairncross et al., 1994; Glass et al., 1992; Kim et al., 1996; Soffietti et al., 1998; van den Bent et al., 1998). And third, as expected, patients selected to receive high-dose thiotepa lived significantly longer than patients, who for one reason or another, did not advance to the high-dose chemotherapy phase of this study (median survival times, 49 months versus 12 months; $P = .002$, Wilcoxon). These differences in survival reflect selection bias not therapeutic effect. Although high-dose thiotepa may have contributed to exceptionally long tumor control in several patients—perhaps those with oligodendrogliomas harboring specific genetic alterations (Cairncross et al., 1998)—durable control in these cases might still have been achieved with I-PCV alone (Cairncross and Eisenhauer, 1995).

We remain cautiously optimistic that substantially more effective chemotherapies can be developed for oligodendroglial neoplasms, but dose-intensive chemotherapy may not be essential to achieve this goal. Clearly, future high-dose chemotherapeutic strategies for oligodendroglioma will need to be substantially more active and considerably less toxic than thiotepa if they are to have a useful role in the treatment of recurrent neoplasms. In this study, the decision to proceed with the high-dose phase of the trial was based on objective evidence of significant chemosensitivity, that is, substantial shrinkage of a bulky recurrent oligodendroglioma or mixed glioma to PCV or cisplatin plus etoposide. We took this approach so that patients with chemoresistant recurrent tumors could be identified and not subjected to

the risks of high-dose chemotherapy, which we knew to be substantial. This approach, while logical in some respects, undoubtedly had a negative influence on outcome, because we now know from other tumor systems that high-dose chemotherapy is unlikely to be significantly more effective than standard treatment for patients with bulky, recurrent, or previously irradiated cancers.

Given these disappointing results, can there be any justification for intensive chemotherapeutic approaches to the treatment of patients with newly diagnosed aggressive or anaplastic oligodendroglial tumors? Furthermore, is there any intensive chemotherapeutic approach that will substitute for radiotherapy, an effective but sometimes neurotoxic treatment? Although these questions cannot be answered definitively as yet, those who choose to explore the utility of intensive chemotherapeutic strategies for oligodendroglioma must weigh the benefits, toxicities, and cost of this approach against the ease and efficacy of radiotherapy and the increasing safety of radiotherapy as 3-dimensional conformal treatment technologies become commonplace and improve further. If future studies of intensive chemotherapy for newly diagnosed oligodendroglioma are being contemplated, we suggest that a lower dose of thiotepa be considered in order to lessen the risk of neurotoxicity or profound anorexia; that patients with a Karnofsky performance status <80 be excluded from such trials; that other blood-brain barrier penetrating agents be added to moderate-dose thiotepa in an effort to enhance tumor control; and that selection criteria for such studies include minimal tumor burden and allelic loss of chromosome 1p (Cairncross et al., 1998). We also suggest that more extensive molecular analyses accompany such trials so that investigators can better interpret therapeutic successes or failures.

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