**Procarbazine and High-Dose Tamoxifen as a Second-Line Regimen in Recurrent High-Grade Gliomas: A Phase II Study**

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**Purpose:** A phase II study was conducted in patients with high-grade gliomas that recurred after surgery plus radiotherapy and a first-line nitrosourea-based regimen. Our aim was to investigate the efficacy of procarbazine (PCB) combined with high-dose tamoxifen in relation to tumor control, toxicity, and time to progression (TTP).

**Patients and Methods:** Fifty-three patients were treated with procarbazine in repeated 30-day courses at 100 mg/m^2/d plus tamoxifen 100 mg/d, with a 30-day interval between courses. Thirty-four patients had been pretreated with a first-line nitrosourea-based chemotherapy regimen (group A), and 19 patients had also been pretreated with a second-line chemotherapy regimen consisting of carboplatin and teniposide (group B). Twenty-one of the patients had also been procarbazine pretreated, whereas the remaining 32 patients were not procarbazine pretreated.

**Results:** The response was assessed in 51 patients, 28 of whom had glioblastoma multiforme (GBM) and 23 of whom had anaplastic astrocytoma (AA). There were two complete responses (CR) (4%) and 13 partial responses (PR) (25.5%). The overall response rate (CR + PR) was 29.5% (SE, 6.4; 95% confidence interval [CI], 23 to 35.8). Seventeen patients (32%) had stable disease (SE, 6.2; 95% CI, 21 to 33.6). The median TTP was 13 weeks for patients with GBM and 33 weeks for patients with AA (P = .006). The median survival time (MST) was 27 weeks for patients with GBM and 57 weeks for those with AA (P = .006).

**Conclusion:** Combined PCB and tamoxifen as a second-line regimen gave a reasonably high response rate in patients with heavily pretreated high-grade gliomas. However, although it resulted in an improvement in the patients' quality of life and/or performance status, it was not followed by an increased TTP or MST.

activity are 10 µm for tamoxifen and 8 µm for DMT. Conventional doses of tamoxifen (20 to 40 mg/d) produce tissue concentrations of tamoxifen and DMT ranging from 1 to 2 µm. Couldwell administered 160 to 200 mg of tamoxifen per day, and brain levels of tamoxifen and DMT measured in one patient were 2.6 and 11 µm, respectively.

PATIENTS AND METHODS

Patient Population

Fifty-three patients, from whom informed consent had been obtained, were enrolled from January 1994 through April 1997. All patients had a histologic diagnosis of glioblastoma multiforme (GBM) or anaplastic astrocytoma (AA), according to the World Health Organization classification, and had contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan documentation of a bidimensionally measurable recurrent or progressive tumor, which was defined as an increase in tumor size of more than 25% compared with prior images. All had undergone surgery and radiotherapy, had been treated with at least one chemotherapy regimen that included nitrosourea, were between the ages 18 and 75 years, had a Karnofsky performance status (KPS) score of ≥ 50, had a life expectancy of at least 8 weeks, had an adequate bone marrow reserve (WBC count > 4,000 mm$^3$ and platelet count > 150,000 mm$^3$), had normal baseline liver (serum bilirubin level < 20 mM/L), renal (serum creatinine level < 150 mM/L) and cardiac function, and had no known psychiatric disorders. All had been on a stable dose of corticosteroids for at least 2 weeks. None of the patients had undergone surgery, radiotherapy, or antineoplastic chemotherapy (corticosteroids excluded) for the 6 weeks prior to entering the study, unless there was clear radiographic and clinical evidence of tumor growth during that period and the patient had adequately recovered from prior therapy.

Treatment Plan

Procarbazine (100 mg/m$^2$/d) and tamoxifen (100 mg/d) were administered for 30 successive days with 30-day intervals between cycles. Courses of chemotherapy were repeated every 30 days, provided that hematologic recovery had occurred (neutrophil count ≥ 1,500 mm$^3$ and platelets ≥ 130,000 mm$^3$). Delays in the administration of chemotherapy were allowed for myelosuppression, but no chemotherapy dose modification was permitted. If after a delay of 2 weeks, the improvement in hematologic values required in order to begin a new course had not occurred, the patient was withdrawn from the study. Supportive treatment consisted of glucocorticoids at dosages adjusted according to the patient’s clinical status; the dosage was maintained until the time of neuroimaging evaluation if the patient’s clinical condition so permitted. If the dosage was increased to offset a marked clinical deterioration, this was considered when evaluating response, using the criteria of Macdonald et al. Anticonvulsants were prescribed as required. Antiemetics were administered for nausea or vomiting occurred.

Response Evaluation

All evaluations were performed by a multidisciplinary team consisting of a neuroradiologist, oncologist, neurosurgeon, and radiotherapist according to Macdonald’s criteria. Tumor size was considered the maximum cross-sectional area of the enhancing mass at CT (after iohodinated contrast) or MRI (T1-weighted, after gadolinium) and calculated by multiplying the largest cross-sectional dimension, measured in centimeters, by the largest dimension perpendicular to it.

Complete response (CR) was defined as the disappearance of all enhanced tumor on two consecutive imaging studies taken at least 1 month apart, with the patient off corticosteroids and his or her neurologic status stable or improved. A partial response (PR) was considered a more than 50% reduction in the size of enhancing tumor on two consecutive imaging studies taken at least 1 month apart, with a stable or reduced corticosteroid dose and the patient’s neurologic status stable or improved. Disease was considered to be progressive (PD) if there was a 25% increase in the size of enhancing tumor, if any new tumor was found on CT/MRI scan, or if the patient’s neurologic condition had deteriorated and/or the corticosteroid dose was stable or increased. All other conditions were considered stable disease (SD).

A clinical assessment and a CT scan or MRI of the brain with or without contrast was performed before therapy and after each course; if stable or responsive disease was observed, a further course was given. Otherwise, treatment was stopped. When the baseline brain image was obtained on a CT scan, all subsequent scans to assess response were also CT scans; the same was true for MRI. Patients were considered assessable for response if they received at least one course of treatment.

Responses were calculated by evaluating the greatest imaging response in relation to the course in which it was obtained. In fact, in a phase II study, in which the question is whether chemotherapy has any effect on tumors, the measurement of maximum response (clinical and imaging techniques) may be the most satisfactory approach. Patients were removed from the study because of disease progression, unequivocal allergic reactions to PCB, venous thromboembolism, or delay in hematologic recovery of more than 2 weeks.

Statistical Analysis

Our main objectives were to evaluate overall response, toxicity according to World Health Organization criteria, TTP, and median survival time (MST).

Time to progression was calculated from the beginning of the treatment to tumor progression or to the moment of being withdrawn from the study, and MST was calculated from the beginning of this treatment to death, irrespective of its cause. For this statistical analysis, we considered all 53 patients; TTP and MST were calculated using the Kaplan-Meier method. Differences in survival and progression were tested for statistical significance, using the log-rank test. To determine truly independent variables (ie, prognostic factors), multivariate analysis using the Cox proportional hazards model was performed on variables with a P value of less than .05 at univariate analysis. The following seven variables were considered and evaluated as most likely to be related to TTP and MST: histology (GBM v AA), age (< 55 v ≥ 55 years at diagnosis), KPS score (< 80 v ≥ 80), reoperation for recurrence, pretreatment (group A v group B and PCB-pretreated [PP] group v not-PCB-pretreated [NPP] group, and response obtained with previous treatment.

RESULTS

Patient Characteristics

Fifty-three patients were enrolled onto the trial; the mean age was 51 years (range, 18 to 74 years), and the median KPS score was 80 (range, 60 to 90); group A consisted of 34 patients (64%), and group B comprised the remaining 19 (36%). Twenty-one patients (40%) belonged to group PP and 32 (60%) to group NPP; 32 patients (60%) had responded to
previous therapy and 13 (24%) had undergone second surgery for recurrence; these patients had a tumor that was measurable on a CT or MRI scan performed within 48 hours after surgery (Table 1).

**Responses**

Only 51 patients were assessable for response because two patients, one with GBM and the other with AA, died during the first month of treatment, before any response could be evaluated. One patient died of tetraventricular hemorrhage while receiving a heparin infusion for deep vein thrombosis of the legs; the other died of pulmonary embolism. Both were included in the evaluation of TTP and MST. Among 51 patients evaluated, 42 of whom were on steroids, we observed the following: two CR (4%), and in both cases response to chemotherapy was accompanied by suspension of steroid treatment; 13 PR (25.5%), in eight of which there was a reduction in corticosteroids, which were, on the other hand, stable in the remaining five; and 14 SD (27.5%) (SE, 6.3; 95% confidence interval [CI], 21.2 to 33.7), with a stable corticosteroid dose in 10 SD and a diminished corticosteroid dose in the remaining four. The overall response rate (CR + PR) was 29.5% (SE, 6.4; 95% CI, 23 to 35.8). Among 28 patients with GBM, CR was achieved in one patient (3.5%) after seven courses (a CR was obtained after three courses), PR in eight patients (28.6%) (in two patients after two courses and in six patients after one course), and six patients (21%) had SD (SE, 7.7; 95% CI, 13.7 to 29.2). The overall response rate (CR + PR) was 32.2% (SE, 8.8%; 95% CI, 23.3 to 40.9). In the 23 patients with AA, CR was obtained in one patient (4.3%) after the seventh course (a PR was evident after the second course), PR in five patients (21.7%) (evident in one patient after one course and in four patients after two courses, and SD in eight (34.8%) (SE, 9.9; 95% CI, 24.8 to 44.7). The overall response rate (CR + PR) was 26% (SE, 9.15; 95% CI, 16.9 to 35.2). The percentages for responses and stabilization did not show statistically significant differences depending on histology, age, performance status, previous treatment with PCB, number of previous chemotherapy regimens, reoperation, and response to previous treatment.

**Time to Progression Analysis**

Median TTP, calculated on the basis of all 53 patients registered in the study, was 18 weeks (SE, 5.2; 95% CI, 12.7 to 23.2). The median TTP was 13 weeks for GBM (SE, 6.3; 95% CI, 6.7 to 19.3) and 33 weeks for AA (SE, 9.5; 95% CI, 23.5 to 42.5). The two patients with CR had a TTP of 82 and 114 weeks, the 13 patients with PR had a median TTP of 32 weeks (SE, 12.9; 95% CI, 19 to 44.9), and the 14 patients with SD had a median TTP of 32.4 weeks (SE, 12.5; 95% CI, 19.8 to 44.9). The median TTP of patients who responded to treatment (CR + PR) was 33.4 weeks (SE, 12.1; 95% CI, 21.2 to 45.5).

**Survival Analysis**

The MST, calculated for all 53 patients, was 35 weeks (SE, 6.5; 95% CI, 28.5 to 41.5). The MST was 27 weeks for the patients with GBM (SE, 8.2; 95% CI, 18.8 to 35.2) and 57 weeks for the patients with AA (SE, 10.1; 95% CI, 46.9 to 67). The two patients who achieved CR were still alive after 82 and 126 weeks. The MST was 42 weeks (SE, 13.6; 95% CI, 28.3 to 55.6) for the 13 patients with PR and 54.7 weeks (SE, 13.3; 95% CI, 41.3 to 68) for the 14 patients with SD. The MST of the responders (CR + PR) was 44.3 weeks (SE, 12.8; 95% CI, 31.4 to 57).

**Univariate and Multivariate Analysis**

Univariate analysis, performed for TTP using the log-rank test, showed no statistical significance for KPS (P = .3), age (P = .17), PP versus NPP (P = .48), group A versus group B (P = .2), or reoperation (P = .08), whereas findings were significant for histology (P = .006) and response obtained with previous treatment (P = .01). When multivariate analysis was performed using the Cox proportional hazards model, histology (P = .02) and response to previous treatment (P = .04) were found to be predictive for TTP.

Univariate analysis, performed for MST using the log-rank test, showed no statistical significance for KPS (P = .09), PP versus NPP, (P = .18), group A versus group B (P = .24), reoperation (P = .12), or response to previous treatment (P = .17). Conversely, histology (P = .006) and age (P = .05) were significant. When multivariate analysis was performed using the Cox proportional hazards model, only histology was significant (P = .01) (Table 2).
Toxicity

One-hundred twenty treatment courses were administered, and the number of courses per patient ranged from one to eight. Twenty patients (38%) received only one cycle, 16 patients (30%) received two cycles, eight patients (15%) received three cycles, six patients (11%) received four cycles, one patient (2%) received five cycles, one patient (2%) received seven cycles, and one patient (2%) received eight cycles. The mean number of cycles per patient was 2.2.

The following toxicities were observed at recycling: leukopenia grade 1 in two cycles (1.6%), grade 2 in six cycles (5%), and grade 3 in one cycle (0.8%); thrombocytopenia grade 1 in two cycles (1.6%), grade 2 in one cycle (0.8%), and grade 3 in two cycles (1.6%); and gastrointestinal toxicity grade 3 in three cycles (2.5%) (in one case, treatment had to be discontinued because of this toxicity). Tox icity, evaluated for each patient, was leukopenia grade 2 (five patients) and grade 3 (one patient) and thrombocytopenia grade 2 (one patient) and grade 3 (two patients); patients with leukopenia and thrombocytopenia grade 3 recovered completely after a mean of 10 days, and no patients with these conditions were withdrawn from the study. Four patients had grade 2 nausea and vomiting and two patients had grade 3. Two patients (3.7%) had skin allergy to PCB, which in one occurred during the first cycle (the patient died later of subarachnoid hemorrhage because of heparin infusion before any response could be assessed) and in the other at the second cycle (the disease was stable and treatment was discontinued). Five patients (9.4%) had signs of deep vein thrombosis: this occurred during the first cycle in one patient (this patient died later of tetraventricular hemorrhage and was not assessable), during the second cycle in two patients (they were assessed as SD after one cycle), 20 days after the third cycle in another patient (in PR), and in the last patient 10 days after the end of the second course (in PR). The treatment was discontinued in all five cases. Three patients (5.6%) had fatal pulmonary embolism, which presented during the first course in one patient (the patient was not assessable for response), after the first course in another patient (in PR), and 20 days after the end of the first course in the remaining patient (who had PD). In none of the three cases was it possible to undertake an autopsy investigation; therefore, the diagnosis of pulmonary embolism was made on the basis of clinical symptoms and findings.

**DISCUSSION**

Very few phase II studies have been performed on high-grade gliomas relapsing after first-line chemotherapy including nitrosoureas, and in these series, the response rates ranged from 0 to 37% in GBM and from 16% to 100% in AA.18-24 Only in the study by Levin and Prados23 were there more than 20 patients included for each of the two histologic types; this may, at least in part, explain the response rate variability found among these reports.

Rodriguez et al25 administered single-agent PCB in patients with recurrences after nitrosourea and obtained a response rate of 14% in 37 patients with GBM and of 15% in 46 patients with AA. Newton et al26 also administered PCB and reported response rates of 25% among 35 patients with GBM or AA, without further specifying the response rate in relation to histologic type.

With regard to tamoxifen, Vertosick et al27 administered 40 mg/d to 32 patients and achieved a 21% response rate that consisted predominantly of stabilizations. Couldwell et al28 treated 32 patients, only 34% of whom had been pretreated. The response rate to single-agent tamoxifen (100 mg/m²/d) was 20% in the 20 GBM patients and 33% in the 12 AA patients. However, this series is too small to allow any definite conclusion.

We obtained response rates of 32.2% (CR + PR) in GBM (95% CI, 23.3 to 40.9) and 26% in AA (95% CI, 16.9 to 35.2); all the patients were pretreated with one chemotherapy regimen, and 36% were pretreated with two. Our response rate was good, although it was difficult to demonstrate that it was significantly higher than that obtained with
other chemotherapy regimens or PCB administration alone. The response was not influenced by histology.

Hematologic toxicity was acceptable. The rate of serious thromboembolic complications was high and could have been determined by the type of neoplasia itself,29 the estrogen-like effects of tamoxifen,30,31 or endothelial damage caused by chemotherapy.32 Vertosick et al27 reported a 10% rate for thromboembolic complications during therapy with tamoxifen 40 mg/d, Couldwell et al38 reported a 6% rate with tamoxifen 100 mg/m²/d, and we observed an incidence of 15% (deep vein thrombosis plus pulmonary embolism) with tamoxifen 100 mg/m²/d, but it was associated with chemotherapy. This rate of thromboembolic complications is less than our previous finding35; however, in the present study, a close temporal correlation was found between therapy and the appearance of thromboembolic phenomena.

Like Coyle et al34 we found a 3.7% incidence of maculopapular rashes caused by PCB. However, no cases of allergic pulmonary infiltrates were observed. The TTP and MST in this study are comparable to those reported by other authors for both GBM and AA; the only significant variables in predicting TTP were histology and response to previous treatment. Response to previous treatment was not correlated with response rate and MST, and for TTP, at multivariate analysis, the sensitivity threshold reached (P = .04) is almost the minimum required. These results, which are somewhat contradictory, do not allow us to conclude that response to previous treatment is certainly predictive for TTP obtained with this treatment. Wong et al35 who analyzed 209 patients, found positive correlations between TTP and histology and the number of previous surgical procedures.

The MST obtained in our study seems high compared with other studies and correlates only with histology. Wong et al36 found that histology, the number of previous surgical operations, and KPS were all significantly correlated with MST. In a series of 211 patients with recurrences after nitrosourea, Rajan et al36 reported that histology, age, and KPS were statistically significant factors for survival. It is difficult to identify the factors that were important in achieving our results, because the mechanism underlying the action of tamoxifen is only partially understood. The activity of this drug might depend either on a direct mechanism, by the inhibition of PKC activity and the induction of apoptosis, or it may act indirectly by enhancing the chemosensitivity of resistant cells through affecting the calcium channels. In cells resistant to chemotherapy, these channels are larger and open for a longer period of time,37 and tamoxifen would act by inhibiting the P-glycoprotein mediated drug efflux across the blood-brain barrier.38 The latter mechanism could also explain the good response rate obtained in the procarbazine-pretreated patients (six PR in 20 assessable patients).

The response rate obtained in the present study is good, perhaps higher than rates achieved with other combinations. Unfortunately, however, the response rate does not correlate consistently with TTP or MST.

Recurrent high-grade gliomas are still a difficult problem for the oncologist, and results after treatment for GBM are disappointing. It is therefore questionable whether further chemotherapy should be given to patients with PD following a treatment that includes nitrosourea. Further treatment may be proposed for AA, perhaps after patient groups most likely to benefit from it are identified.

REFERENCES