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Brief Communications**PCV chemotherapy for recurrent glioblastoma****F. Schmidt, MD, J. Fischer, U. Herrlinger, MD, K. Dietz, MD, J. Dichgans, MD and M. Weller, MD**

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ABSTRACT

The authors administered procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, lomustine), and vincristine (PCV) to 86 patients with recurrent glioblastoma. There were three partial responses, but no complete responses. Median progression-free survival was 17.1 weeks and progression-free survival at 6 months was 38.4%. World Health Organization grade III/IV hematologic toxicity was common (25.6%), but nonhematologic toxicity was mild.

With surgery and radiotherapy, there is a 2-year survival of 9% for glioblastoma (GB). Adjuvant nitrosourea-based chemotherapy enhances 2-year survival by 4%.¹ Chemotherapy for recurrent GB results in a progression-free survival of 9 weeks and a 6-month survival rate of 15%.² Temozolomide given at recurrence induces a progression-free survival of 11 weeks and a 6-month progression-free survival rate of 21%.³

METHODS.

We reviewed records of 86 patients with recurrent or progressive GB treated with procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, lomustine), and vincristine (PCV) between 1994 and 2003 (table 1). All patients had received radiotherapy. PCV was administered at 8-week intervals: CCNU 110 mg/m² PO day 1, procarbazine 60 mg/m² PO days 8 to 21, vincristine 1.4 mg/m² (maximal dose 2 mg) IV days 8 and 29. Charts were evaluated for neuroimaging, prior therapy, Karnofsky performance score (KPS) before PCV (95 patients), toxicity, and dose of steroids (98 patients). Response was assessed according to MacDonald criteria. Progression-free and overall survival rates were calculated from the first dose of CCNU until progression and death and analyzed by the Kaplan-Meier method. A Wilcoxon or log-rank test was performed to assess an effect of therapy-dependent and -independent variables on survival. Some patients were previously reported: 15 in NOA-01,⁴ five in European Organization for Research and Treatment of Cancer 26981,⁵ five were treated with gemcitabine⁶, and eight with gemcitabine and treosulfan.⁷

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Table 1 Patient characteristics**RESULTS.**

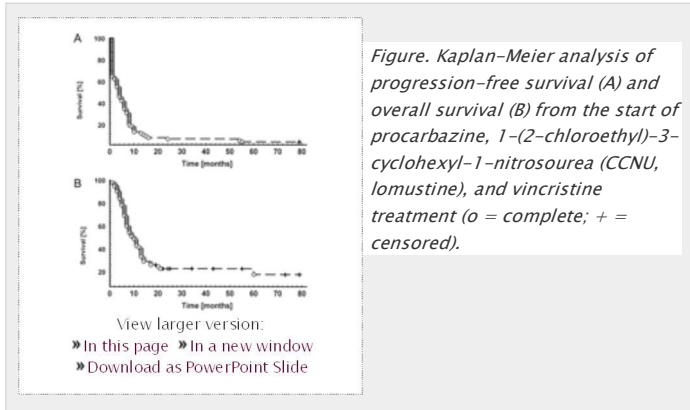
Eighty-three patients were treated at first relapse or progression. Sixty-six patients were confirmed dead. The median number of cycles was two (range one to five). Twenty-eight patients received only one cycle, 20 completed four or more cycles, 37 were on steroids when starting PCV (median dexamethasone dose 7 mg/day, range 2 to 20 mg/day). Adverse events were documented in 72 patients. Their frequency (table 2) is commonly underestimated in retrospective series. All patients had a lung function test before PCV and again during therapy when any complaint with breathing was made. There was no instance of lung fibrosis. During PCV, one patient developed neutropenic fever, two required cytokine support, and six required transfusions at least once. Two patients developed leukoencephalopathic changes that were considered radiochemotherapy-related without clinical symptoms. PCV was delayed or the dose of one or more drugs reduced because of myelosuppression in 28 patients. PCV was stopped in eight patients with stable tumor because of adverse events: seven for hematologic toxicity and one for progressive leukoencephalopathy.

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Table 2 Adverse events

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MRI or CT was performed at 2- to 3-month intervals. There was a partial response in three patients (3.5%), but no complete response. Stable disease was documented in 45 patients (52.3%). Only 18 patients (20.9%) showed progressive tumor growth during the first 8 weeks of therapy. The median time to progression was 17.1 weeks (figure). Progression-free survival at 6 months was 38.4%. The median survival from the start of PCV was 34.3 weeks. The median survival for progression-free patients at 6 months was 57.9 weeks compared with 25.7 weeks for patients who progressed in the first 6 months. The survival rates were 73.3% at 6 months, 31.4% at 1 year, and 9.3% at 2 years after the start of PCV. There was no apparent association of the effects of PCV when given at recurrence and the type of chemotherapy that had been administered previously. Patients preexposed to nimustine (ACNU)⁴ did not differ in terms of median progression-free or overall survival from patients who were nitrosourea naïve at relapse. Similarly, chemotherapy-naïve patients did not experience a longer progression-free or overall survival than patients who were not.



Some patients considered to have progressive disease early after the completion of radiotherapy exhibit transient increases in apparent tumor volumes, a pattern referred to as pseudoprogression.⁸ To exclude that the apparent benefit derived from PCV was confounded by a large population of such pseudoprogressive patients, we compared patients diagnosed with progressive disease within 3 months after radiotherapy (n = 26) with patients progressing later than 3 months after radiotherapy (n = 60). Progression-free survival at 6 months was 23.1% for patients progressing early and 41.7% for patients progressing late. Median survival from PCV was 30 weeks for patients progressing early and 42.9 weeks for patients progressing late. Accordingly, pseudoprogression is unlikely to be a major confounding factor in this series.

Age (older than 50 or 50 or younger) was not a prognostic factor. The impact of initial KPS (>80% or ≤80%) on median progression-free survival ($p = 0.75$) or overall survival ($p = 0.08$) also did not reach significance. There were too few patients with KPS <70 for a meaningful statistical analysis. The progression-free survival was 4.3 weeks for 38 patients on steroids and 25.7 weeks for 46 patients not on steroids when starting PCV ($p < 0.0001$, log-rank test). Patients with resection prior to PCV had a better outcome with a median progression-free survival of 25.7 weeks compared with 12.9 weeks for those without resection ($p = 0.04$, Wilcoxon test). Of 27 patients (31.4%) surviving 1 year from the start of PCV, 12 (44.4%) had had a resection prior to PCV.

The prognostic impact of being steroid free and having had a resection was interrelated and cannot be separated because only seven of 29 patients (24.1%) treated surgically were on steroids, whereas 31 of 55 patients (56.4%) started on chemotherapy without a prior resection were on steroids. Further, the median KPS was 90 in steroid-free patients and 80 in steroid-treated patients.

DISCUSSION.

We confirm the findings of a Dutch series of patients with recurrent GB⁹ who experienced an objective response rate of 11% (5% here), a median progression-free survival of 13 weeks (17.1 weeks in the current study), and a median overall survival of 33 weeks (34.3 weeks in the current study). None of their patients, but 29 of our patients (28.7%) had previously been treated with nitrosoureas. The results also compare well with the results with temozolomide in a multicenter setting³ (progression free at 6 months: 21% in the Dutch study, 38.4% in our study; overall response rate: 5.4% in the Dutch study, 5.0% in our study) and with 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU)¹⁰ (progression free at 6 months: 17.5%; overall response rate: 15%). Yet, dose-intensified treatment schedules of temozolomide for recurrent GB may produce similar or better progression-free survival rates at 6 months.

Our series represents patients with favorable prognostic factors in terms of age, KPS,

frequency of reoperations, and steroid dependence (see [table 1](#)). Moreover, the lack of a standard assessment may have resulted in an overestimation of the benefit derived from PCV. Patients who were not on steroids and who had a resection prior to PCV had a better outcome. The prognostic impact of being steroid free and of having had surgery was interrelated because steroid dependency was more common in the nonsurgical group. World Health Organization grade III/IV hematologic toxicity was common (26%). A dose reduction or delay of chemotherapy was necessary in 30% of the patients. The treatment was stopped because of toxicity in 13%, but overall nonhematologic toxicity was mild. Compared with BCNU,¹⁰ hematologic toxicity was probably similar or somewhat worse in our study, but nonhematologic toxicity, in particular pulmonary toxicity, was less prominent. With temozolomide becoming the first-line treatment,⁵ it will be important to determine whether PCV compares favorably with nitrosourea treatment alone in terms of efficacy and safety in patients with progression or recurrence after radiotherapy and temozolomide. Responsiveness to PCV and outcome of the 12 patients pretreated with temozolomide included here were identical to those in the population as a whole.

FOOTNOTES

Disclosure: The authors report no conflicts of interest.

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