

Carboplatin and teniposide as third-line chemotherapy in patients with recurrent oligodendroglioma or oligoastrocytoma: a phase II study

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Background: This study was a phase II study of third-line chemotherapy with carboplatin plus teniposide in patients with recurrent oligodendroglioma.

Patients and methods: Patients with oligodendroglioma progressive or recurrent after surgery, radiotherapy and chemotherapy with PCV (lomustine/procarbazine/vincristine) and temozolomide were treated with 350 mg/m² carboplatin on day 1, and 50 mg/m² teniposide on days 1–3, every 4 weeks.

Results: Response and toxicity were evaluated in all 23 patients enrolled in the study. Two had partial response [8.6%; 95% confidence interval (CI) 1.8% to 28.6%] and 12 stable disease (52.17%; 95% CI 30% to 73%). Median time to progression was 19 weeks (95% CI 11.4–35.0), and 34.8% of the patients (95% CI 20.0% to 61.0%) had progression-free survival at 6 months. Median survival time was 60.7 weeks (95% CI 39.8 to not achieved) and 51% of the patients (95% CI 33.5% to 79.7%) were alive at 12 months. A total of 103 cycles were administered (on average 4.4 per patient; range 1–9). Toxicity was mild and mainly hematological, with grade 4 neutropenia and grade 4 thrombocytopenia in two (8.6%) and three patients (13%), respectively.

Conclusions: Although the response rate of combined carboplatin and teniposide chemotherapy in heavily pretreated oligodendroglial tumors is moderate, the toxicity is manageable, and delay of progression in responders or stable patients may still confer a relevant clinical benefit.

Key words: carboplatin, chemotherapy, oligodendroglioma, salvage therapy, teniposide

Introduction

Oligodendrogliomas are rare tumors, accounting for 3–7% of all primary intracranial brain neoplasms [1]. However, unlike other gliomas, they are reported to be fairly chemosensitive [2]. Standard first-line chemotherapy with PCV (lomustine 110 mg/m² on day 1, procarbazine 60 mg/m² on days 8–21, vincristine 1.4 mg/m² maximum 2 mg total on days 8 and 29) obtained a response rate (RR) of 60–70% with a time to progression (TTP) of 12–18 months for responding patients [3]. At the time of relapse/progression, second-line chemotherapy with temozolomide achieved an RR ranging from 43% to 63%, and a median TTP of 6.7 months [4, 5]. To date there is no standard third-line chemotherapy even if, in view of high chemosensitivity, young age and good performance status of the majority of oligodendroglioma patients, other chemotherapy regimens might be proposed. Carboplatin alone, which is active in about 10% of gliomas [6, 7], acts synergistically with epipodophyllotoxins [8], including teniposide [9, 10]. Combined carboplatin and etoposide has been reported to obtain an objective

RR of 21%, and a median survival of 10 months in patients with recurrent, pretreated high-grade gliomas [11].

A phase II study of carboplatin plus teniposide was thus planned at our institution in order to evaluate tumor control rate and toxicity of this association in oligodendroglioma patients recurring after both nitrosoureas and temozolomide.

Patients and methods

Patients with histologically proven oligodendroglioma or oligoastrocytoma [12] were enrolled in the present phase II study following central review pathology. Inclusion criteria were: age ≥ 18 years, Karnofsky performance score (KPS) ≥ 40 , life expectancy of at least 3 months; adequate bone marrow reserve (white blood cells $\geq 4000/\mu\text{l}$; platelets $\geq 150\ 000/\mu\text{l}$); normal baseline liver (serum bilirubin $>20\ \mu\text{mol/l}$ and transaminases $\leq 2.5\times$ upper normal values), renal (serum creatinine $>150\ \mu\text{mol/l}$), and cardiac function, absence of infectious disease, debilitating chronic diseases, and known psychiatric disorders. All patients had been on a stable dose of corticosteroids for at least 2 weeks, and gave their written consent to the study. None of them had undergone radiotherapy in the 8 weeks before entering the study. All patients had undergone contrast computed tomography (CT) or magnetic resonance imaging (MRI) of the brain showing at least one contrast-enhancing and bi-dimensionally measurable lesion (with at least one diameter $\geq 1\ \text{cm}$), indicative of progressive or recurrent disease after surgery, radiotherapy and both PCV and temozolo-

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mide chemotherapy. The radiological images were obtained within 15 days before chemotherapy and had to display an increase in tumor size of >25% compared with prior images. Patients undergoing surgery for the recurrence before the start of chemotherapy had a repeat MRI or CT scan within 48 h from surgery and only those with measurable disease residuals were considered eligible for this study.

Treatment plan

Carboplatin 350 mg/m² and teniposide 50 mg/m² were administered intravenously on day 1 and on days 1–3, respectively. The treatment was repeated every 4 weeks, for a maximum of 10 cycles. The patients were evaluated weekly for hematological toxicity, and monthly for renal and hepatic toxicity, which was recorded according to World Health Organization criteria [13]. Carboplatin and teniposide were reduced by 75% if hematological toxicity was grade 4 at nadir. Treatment was suspended if bone marrow recovery was unsatisfactory after 1 month, or in the presence of extra-hematological toxicity grade ≥ 3 .

Prophylactic 5-hydroxytryptamine type 3 receptor antagonists were routinely used. Steroids were administered at the lowest dosage required by the patient's neurological status, and any increase due to clinical deterioration was considered in the evaluation of response. All patients received antiepileptic drugs, the plasma concentrations of which were checked several times during treatment in view of possible hepatic metabolism interference induced by chemotherapy [14].

Response evaluation

All response evaluations were carried out by a multidisciplinary team consisting of a neuroradiologist, oncologist, neurosurgeon and radiotherapist. According to Macdonald's criteria [15], tumor size was considered the maximum cross-sectional area of the enhancing mass at CT (post-iodinated contrast) or MRI (T1-weighted, post-gadolinium) and calculated by multiplying the largest cross-sectional dimension (cm) by the largest dimension perpendicular to it.

Complete response (CR) was defined as the disappearance of all tumors with contrast enhancement on two consecutive imaging studies taken at least 1 month apart, with the patient off steroids, and when his/her neurological status was stable or had improved.

Partial response (PR) was considered a $\geq 50\%$ reduction in the size of the enhancing tumor on two consecutive imaging studies taken at least 1 month apart, with a stable or reduced steroid dose, and when the patient's neurological status was stable or had improved.

Disease was considered progressive disease (PD) if there was a 25% increase in the size of the enhancing tumor, any new tumor was found at CT/MRI scan, the patient's neurological condition had deteriorated and/or the steroid dose was stable or had increased. All other conditions were considered stable disease (SD).

A clinical assessment and a CT scan or MRI of the brain with and without contrast were carried out before enrollment and after every two courses of treatment.

Objectives

The main objective was to evaluate the RR (CR plus PR) of carboplatin plus teniposide chemotherapy in recurrent oligodendroglioma. Secondary objectives were: toxicity, TTP (time interval from the start of chemotherapy to progression of disease or exit from the study for any reason), PFS-6 (progression-free survival at 6 months) and MST (median time interval from the start of chemotherapy to death from any cause).

Table 1. Patient characteristics

Median age, years (range)	47.6 (28.0–64.4)
Median Karnofsky performance score (range)	80 (40–90)
Histology at primary surgery (no. of patients)	
Low-grade oligodendroglioma	7 (30.4%)
Low-grade oligoastrocytoma	2 (8.7%)
Anaplastic oligodendroglioma	10 (43.5%)
Anaplastic oligoastrocytoma	4 (17.4%)
Median interval between primary surgery and start of this treatment, months (range)	68.4 (24.0–144.7)
Prior treatments	
PCV followed by temozolomide	19 (83%)
PCV alone	4 (17%)

PCV, lomustine–procarbazine–vincristine.

Statistical methods

The trial was designed as a phase II study, with RR as the main end point. According to Simon's two-stage optimal design [16], our study with its sample size of $n = 72$, had a 5% probability of rejecting (α) the hypothesis of an RR <20% and an 80% probability of accepting ($1-\beta$) the hypothesis of an RR of 35%.

During the first stage, if fewer than five responses are obtained among the initial 22 patients, it would be concluded that the RR is <20%, and the study would be terminated.

Patients who received at least two cycles of treatment were considered assessable for response unless they had definite evidence of progression after the first cycle, otherwise they were considered assessable only for toxicity.

TTP, PFS-6 and MST were calculated with the Kaplan–Meier method; differences in progression and overall survival were evaluated by the log-rank test for statistical significance. To determine truly independent variables, the Cox model of multivariate analysis was applied to variables with $P < 0.05$ on univariate analysis. Age (≥ 50 or < 50 years), KPS (≥ 70 or < 70), presence or absence of an astrocytic component, time between first surgery or the end of radiotherapy and start of carboplatin plus etoposide chemotherapy (≥ 12 months or < 12 months), response to previous PCV and/or previous temozolomide were considered variables connected to TTP and MST.

The Wilcoxon and Mann–Whitney U -tests were used for the analysis of the non-parametric variables within and between groups (i.e. KPS). The McNemar χ^2 test was used to determine the significance of changes when the variables of interest were dichotomous.

Results

Patient characteristics

From January 1994 to December 2002, 23 patients (18 men) were enrolled in the study (Table 1). Median age was 47.6 years (range 28.0–64.6) and median KPS was 80 (range 40–90). The most recent histology before this treatment was low-grade oligodendroglioma (seven patients), low-grade oligoastrocytoma (two patients), anaplastic oligodendroglioma (10 patients) and anaplastic oligoastrocytoma (four patients). All patients presented a progressive or recurrent contrast-enhancing lesion before starting this chemotherapy regimen, but a re-biopsy was not performed

Table 2. Median time to progression and overall median survival according to response and histology

Patients (number)	Time to progression		Median survival	
	Weeks (95% CI)	<i>P</i> value	Weeks (95% CI)	<i>P</i> value
All patients (23)	19.0 (11.4–35.0)	–	60.7 (39.8–NA)	–
Response				
Responsive or stable patients (14)	28.0 (16.4–60.7)	–	98.3 (60.7–NA)	–
Progressive patients (9)	7.0 (4.3–NA)	0.002	23.4 (7.4–NA)	0.0005
Histology				
Pure oligodendroglioma (7)	25.0 (6.0–49.3)	–	98.3 (60.7–NA)	–
Mixed oligoastrocytoma (6)	6.0 (1.7–NA)	0.04	15.4 (1.7–NA)	0.002

CI, confidence interval; NA, not achieved.

because at MRI the appearance of contrast-enhancement in low-grade non-enhancing tumors for which no special treatment (i.e. radiosurgery) has been given is unanimously considered in-direct evidence of anaplasia with an unfavorable prognosis.

All patients had received radiotherapy to limited fields at a dose of 59.4 Gy/33 fractions. The median interval between initial surgery and the start of this chemotherapy was 68.4 months (range 24.0–144.7). Nineteen of 23 patients received PCV at the first recurrence and temozolomide at the second recurrence, while four patients were treated with PCV alone because temozolomide was not available at the time. All 23 patients were evaluable for both response and toxicity and were included in the statistical analysis.

Response to treatment

We observed two PRs [8.6%; 95% confidence interval (CI) 1.8% to 28.6%], and 12 SDs (52.17%; 95% CI 30% to 73%). Both PRs and six SDs were achieved by patients who had low-grade tumors at the latest surgery. Seventy per cent of patients with pure oligodendroglioma and 33.3% of those with mixed oligoastrocytoma remained progression-free during chemotherapy. The change in median KPS value in patients with tumor response or stabilization of disease was significantly different from that observed in patients with disease progression ($P = 0.02$, Mann–Whitney *U*-test): the former group showed a significant improvement in KPS with respect to the baseline (76.4–79.3) ($P = 0.05$, Wilcoxon test), whereas the latter group showed a statistically significant worsening in KPS (75.5–66.7) ($P = 0.04$, Wilcoxon test). A significant correlation ($P < 0.01$, McNemar test) was found between response or stabilization obtained with carboplatin and teniposide and response or stabilization previously obtained with PCV chemotherapy. Multivariate analysis showed that histology was a true independent prognostic factor ($P < 0.01$).

Time to progression

Considering all 23 patients, median TTP was 19 weeks (95% CI 11.4–35.0); PFS-6 was 34.8% (95% CI 20.0% to 61.0%) (Table 2). The patients with response or stabilization had a TTP of 28 weeks (95% CI 16.4–60.7) and PFS-6 of 57% (95% CI 36.3% to 90.0%). Patients with pure oligodendroglioma had a significantly ($P = 0.04$)

longer TTP and PFS-6 (TTP = 25 weeks, 95% CI 6–49.3; PFS-6 = 47%, 95% CI 28.0% to 78.0%) than those with oligoastrocytoma [TTP = 6 weeks, 95% CI 1.7 to not achieved (NA); PFS-6 = 0%].

Survival

Considering all patients, the MST was 60.7 weeks (range 39.8–NA) and 51% of the patients were still alive at 12 months (95% CI 33.5% to 79.7%) (Table 2).

The patients with response or stabilization obtained a significantly ($P = 0.005$) higher MST (98.3 weeks, 95% CI 60.7–NA), with 74.6% (95% CI 53.0% to 100%) of patients alive at 12 months, compared with patients with PD (MST = 23.4 weeks, 95% CI 7.4–NA, of whom none was alive at 12 months). The patients with pure oligodendroglioma had a significantly ($P = 0.002$) longer MST (98.3 weeks, 95% CI 60.7–NA), with 71% (95% CI 50.5% to 100%) of patients alive at 12 months, than those with oligoastrocytoma (MST = 15.4 weeks, 95% CI 1.7–NA; no patients alive at 12 months). The patients with low-grade oligodendroglioma at the most recent surgery had a significantly ($P = 0.04$) longer MST (98.3 weeks, 95% CI 98.3–NA), with 79% (95% CI 56.4% to 100%) of patients alive at 12 months, than those with high-grade tumors (MST = 43.14 weeks, 95% CI 23.4–NA; with 37% (95% CI 17.8% to 76.8%) alive at 12 months). No other variables were found to be significantly correlated with survival.

At multivariate analysis the only true independent predictive variables were histology ($P = 0.003$) and response to this chemotherapy regimen ($P = 0.005$).

Toxicity

All patients were assessable for toxicity. A total of 103 cycles were administered (on average, 4.4 per patient; range 1–9). Treatment-related complications included grade 3 thrombocytopenia in two patients (8.6%) and grade 4 thrombocytopenia in three (13.0%), and grade 3 neutropenia in two (8.6%) and grade 4 neutropenia in two patients (8.6%). Two patients required a 25% reduction in chemotherapy doses due to hematological toxicity; no patients required cytokine therapy for myelosuppression, and there were no treatment-related deaths.

Discussion

Oligodendrogliomas and oligoastrocytomas are rare, chemosensitive tumors. The most active available regimens for first- and second-line therapy are PCV and temozolomide. It is widely debated whether it is more useful to use temozolomide or PCV for first-line therapy because the latter probably has a greater activity, but also a greater toxicity, which is sometimes persistent, and could thus preclude any further chemotherapy. While two lines of chemotherapy are well-established, it remains to be demonstrated whether third-line chemotherapy is beneficial, and, if yes, which could be the regimen of choice. Peterson et al. [17] reported that four of nine patients (44%) with recurrent oligodendroglioma responded to cisplatin and etoposide chemotherapy, mainly as second-line chemotherapy, and three of four patients were previously responsive to PCV. Although their series was small, the authors stated that the regimen could be proposed as first-line therapy instead of PCV in view of the persistent hematological toxicity of the latter.

Friedman et al. [7] reported 88% of disease stabilization (in eight of nine chemo-naïve patients) and suggested that further studies should be undertaken to establish whether carboplatin might replace PCV chemotherapy in view of its better tolerability.

With regard to other salvage therapy regimens employed, Chamberlain and Kormanik [18] studied paclitaxel in 20 oligodendroglioma patients recurrent after radiotherapy and PCV: three patients achieved a PR (15%) and seven an SD (35%) with a median response and SD duration of 10 months (range 5–14).

Carboplatin and teniposide achieved a very modest objective RR in our oligodendroglioma patients, but it is important to bear in mind that this approach was used as a third-line therapy. Nine patients had low-grade tumors without contrast enhancement at the latest surgery, but all of these patients had had disease progression after radiotherapy and two lines of chemotherapy, and had contrast-enhancing, inoperable tumors for which repeat biopsy was not performed because the tumors were known to be malignant. In the setting of palliative chemotherapy, 52% disease stabilization lasting >28 weeks, with 57% of patients without disease progression at 6 months, and with a significant improvement in KPS, are results of appreciable clinical relevance. This regimen should be considered especially for patients with pure oligodendroglioma who have responded to first-line chemotherapy. In fact, the absence of an astrocytic component, and a response to previous chemotherapy, were statistically correlated in multivariate analysis with RR, TTP and survival.

The close correlation between pure oligodendroglial histology, TTP and MST was reported by Kim et al. [19] in their study on PCV as first-line chemotherapy: patients with oligodendroglioma versus oligoastrocytoma grade III achieved a median TTP of 63.4 compared with 13.8 months ($P = 0.03$) and a MST of 76 months compared with 49.8 months ($P = 0.01$).

Smith et al. [20] reported that the chemosensitivity of a subset of oligodendrogliomas was associated with alterations of chromosome arms 1p and 19q. In our population there was a strict correlation between response to PCV and/or temozolomide and disease stabilization with the present regimen, possibly indicating that

some genetic alterations conferring chemosensitivity could maintain their relevance even in advanced disease.

In our study, carboplatin and teniposide chemotherapy did not cause any significant morbidity, with 50% of the patients receiving on average six cycles of treatment. Patients were easily treated in an outpatient setting. The mild toxicity in this heavily pretreated population may possibly be due to an increased teniposide clearance with concomitant anticonvulsant therapy [14, 21]. However, clinical evidence regarding the benefit of dose intensity in oligodendroglioma with respect to tumor response and patients survival is not compelling [22, 23].

In conclusion, the benefit of carboplatin and teniposide when used as a third-line regimen in patients with recurrent oligodendroglioma is marginal in terms of tumor response, but is not negligible in terms of stabilization of disease, which is frequently accompanied by a clinically relevant increase in both KPS and quality of life. Even in these highly pretreated patients, chemosensitivity appears to be a predictable phenomenon, and it is governed by the presence of a pure oligodendroglial histology and responsiveness to previous cytotoxic agents.

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