

Twice-daily Dosing of Temozolomide in Combination with Fotemustine for the Treatment of Patients with Refractory Glioblastoma

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Abstract. Alkylating agents, such as temozolomide (TMZ) and fotemustine (FTM) are widely used in recurrent glioblastoma (GBM) regimes. Several strategies have been proposed to prevent resistance to these agents, by combining or sequencing them. We report the results of a pilot study of patients with refractory GBM receiving a regime of twice-daily dosing of temozolomide administered on day 1, (with an initial oral dose of 200 mg/m² and a second oral dose of 75 mg/m² 12 h later), followed by fotemustine in a single i.v. infusion at 75 mg/m² on day 2, repeated every four weeks. Enrolment was stopped at 15 patients due to lack of effectiveness of this schedule for patients with GBM. Toxicity was mild, with no grade 4 side effects reported. Results indicate that our temozolomide -FTM combined schedule is not effective, although well tolerated, in non responsive patients with GBM. Further strategies are required to improve the outcome of these patients.

O⁶ alkylguanine DNA-alkyl transferase (AGAT), involved in DNA damage repair, mediates resistance to alkylating agents, such as temozolomide and fotemustine, widely used in regimes for treatment of recurrent glioblastoma multiforme (GBM). In 1999, Gander *et al.* observed that temozolomide was able to reduce AGAT activity, suggesting that this effect may enhance the antitumor activity of fotemustine (1).

Different strategies have been proposed to prevent the resistance of GBM to alkylating agents, by testing the efficacy and toxicity of either increased temozolomide dose

intensity schedules or combined temozolomide -nitrosoureas regimes. Plowman *et al.* (2) reported a synergic activity of carmustine with temozolomide in GBM, probably due to depletion of AGAT by temozolomide. In 2004, Chang *et al.* (3) assessed the efficacy and safety of the carmustine/temozolomide combination administered before radiotherapy in patients with naive anaplastic astrocytoma. Unfortunately, relevant myelosuppression and a modest response rate were obtained. In 2011, Gaviani *et al.* (4) reported an alternating weekly regimen of temozolomide with a single monthly fotemustine administration. They didn't observe activity while severe toxicity was present in 75% of patients.

Different attempts at enhancing activity of alkylating agents for recurrent GBM led to regimes of twice-daily dosing temozolomide. In 2008, Balmaceda *et al.* (5) proposed an initial oral temozolomide dose of 200 mg/m² followed by nine consecutive doses of 90 mg/m² every 12 h. An enhancement of temozolomide efficacy in GBM, without significant toxicity, was observed.

Moreover, Freidman *et al.* (6) evaluated the efficacy of bevacizumab, alone and in combination with irinotecan, in patients with GBM in first or second relapse. They registered 42.6% and 50.3% six months progression-free survival (PFS-6), respectively; median overall survival (OS) was 9.2 months and 8.7 months, respectively.

The aim of this study was to assess the efficacy and the toxicity profile of a sequential combination of temozolomide and fotemustine in patients with refractory GBM.

Patients and Methods

The study was originally planned for 30 patients. We treated consecutive patients with recurrent GBM after chemoradiation treatment with temozolomide and successive adjuvant temozolomide and second line fotemustine. The study was designed according to the Simon two-stage design (P0=0.10, P1=0.25, a=0.10 and b=0.10). Fifteen patients were enrolled. The characteristics of the studied patients are reported in Table I. Statistical analysis was performed with MedCalc version 11.4.4.0 (MedCalc Software, Broekstraat 52,

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Table I. *Patients' characteristics.*

Gender	
Female	3
Male	12
Age, years	
Median	58.19
Range	40.51-75.96
Karnosky Performance Status	
Median	80
Range	70-100
Surgery	
Undergone	14
Not undergone	1
Extent of resection	
Gross total resection	5
Partial resection or biopsy	9
Cycles of Temozolomide-fotemustine combined therapy standard schedule	
Median	4
Range	2-11

9030 Mariakerke, Belgium). A significance level of 0.05 was set.

Our schedule consisted of a regime of temozolomide twice-daily administered on day 1, (with an initial oral dose of 200 mg/m² and a second oral dose of 75 mg/m², 12 h later), followed by fotemustine in a single endovenous infusion at 75 mg/m² on day 2. Treatment cycles were repeated every 28 days. Patients were withdrawn if they showed progressive disease, unacceptable toxicity, or retracted their consent.

PFS and OS were evaluated from the start of temozolomide-fotemustine regime administration. The response was determined by CT, MRI and clinical examination. The Macdonald criteria (7) were chosen to evaluate the MRI. A greater than 50% decrease in the area of contrast enhancement was classified as a partial response (PR). A complete response (CR) was determined by the disappearance of all target lesions. Stable disease (SD) included patients with no disease progression, but not achieving RP or CR criteria. Finally, an increase of more than 25% in the area of contrast enhancement, the appearance of new lesions and the deterioration of patient's clinical status were defined as disease progression (PD).

Results

Enrolment was stopped at 15 patients due to lack of effectiveness of this schedule for patients with GBM. Among the evaluable patients, 5 patients had SD, with no PR observed. A total of 64 treatment cycles, with our schedule, were administered and the median number of cycles per patient was 4 (% confidence interval, CI=2.99-5.01%). Median OS from the start of chemotherapy was 6.05 months (CI=4.80-7.29 months). PFS-6 was 46.66% (CI=43.20-50.12%). Results are reported in Table II.

Increased transaminases and leucopenia were observed in 40% and 46.66% of these patients, respectively. No grade 4

Table II. *Results.*

Median number of cycles	4.00
Complete Responses	0
Partial Responses	0
Stable Diseases	5
Progressive Diseases	10
Median overall survival (months)	26.96
Median overall survival from chemotherapy (months)	6.05
Median Time to Progression (months)	5.46
6 months-progression free survival (%)	46.66

toxicity was reported. The most common grade 3 toxicity events were lymphopenia and leucopenia (13.33%), with only 6.66% of grade 3 thrombocytopenia. None of the patients had concomitant infections associated with lymphopenia grade 2-3. The most common reason for drug discontinuation was disease progression, which occurred in 66.66% of patients.

Discussion

In this study, although the PFS-6 of patients with GBM treated with our combined schedule was 46.6%, the median OS from the start of chemotherapy was merely 6.05 months. With respect to both bevacizumab, alone or in combination with irinotecan, temozolomide-fotemustine combination shows lower effectiveness, even if toxicity was mild, with no patients withdrawn for relevant side-effects.

In conclusion, our findings indicate that such temozolomide-fotemustine combined schedule is not effective although well tolerated in non responsive patients with GBM. Further strategies are required to improve the outcome of these patients.

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