

Low-dose fotemustine for recurrent malignant glioma: a multicenter phase II study

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Abstract Fotemustine at the conventional dose of 100 mg/m² is an active treatment for recurrent malignant gliomas (RMGs). However, it is associated with a relevant incidence of severe myelotoxicity, which is not justified in the palliative setting of this disease. This study was conducted to address whether administration of fotemustine at 60 mg/m² (induction) followed by 75 mg/m² (maintenance) would preserve clinical activity with the advantage of improved tolerance. Forty patients with RMGs pretreated with ≤2 lines of chemotherapy were enrolled. Median age was 57 years (26–80) and median Karnofsky

performance status was 80 (60–100). Thirty-one patients (77.5%) had tissue available for analysis of the O⁶-methylguanine methyltransferase (MGMT) gene promoter which was found to be methylated in 14 cases (45%). Overall, 8 partial responses (20%) and 13 disease stabilizations (32.5%) were observed for a disease-control rate of 52.5%. At 6 months, 21% of patients were free from progression. Grades 3 and 4 platelet and white blood cell toxicity occurred in ≤10% of patients, and no patients discontinued treatment because of toxicity. No significant difference was observed for disease control rate between methylated and unmethylated patients, although a trend toward improved progression-free survival was reported for methylated patients. Low-dose fotemustine has activity comparable with that of the full-dose regimen, therefore it should be preferred for its greater tolerability. The role of MGMT gene promoter methylation status in relation to sensitivity to fotemustine is still unclear and needs further evaluation in future clinical trials.

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Introduction

Malignant gliomas account for approximately 50% of all malignant primary brain tumors in adults [1]. Active treatments include resection of the tumor to the extent that is surgically feasible, radiotherapy, and chemotherapy [2]. Unfortunately, despite optimum treatment, median survival ranges from 12 to 15 months for glioblastoma multiforme (GBM) and from 2 to 5 years for anaplastic gliomas [2]. This dismal prognosis is mainly because of the rapid onset of radio and/or chemo-resistance. Against this background,

administration of salvage chemotherapy is often hampered by factors such as low Karnofsky performance status (KPS) and prior exposure to cytotoxic treatment. For this reason, the tolerance of the drug regimen that is to be administered to patients with recurrent disease is of crucial importance.

Fotemustine is an alkylating drug belonging to the nitrosurea family [3]. Its high lipophilicity enables the drug to cross the blood–brain barrier and penetrate malignant cells [4, 5]. In recurrent malignant gliomas (RMGs), fotemustine has good clinical activity, with a response rate of 15.5–26% [6–8]. The dose of fotemustine to be used in clinical practice was determined in a phase I study by Khayat et al.: 100 mg/m² infusions given weekly for 3 weeks (induction) to be followed, after a rest period of 4–5 weeks (hematological recovery), by triweekly administration (maintenance) [9]. However, in studies of patients with RMGs treated with this schedule, grades 3 and 4 platelet and white blood cell toxicities were common [6, 8], being as high as 55.6% for thrombocytopenia and 50.6% for leukopenia in a recent report [8]. More recently, in a study evaluating fotemustine as second-line treatment for GBM, the induction dose of fotemustine had to be reduced from 100 to 75 mg/m² owing to an unacceptable rate of severe thrombocytopenia [10]. Also, in a retrospective evaluation of 40 patients we found that fotemustine given at 65–75 mg/m² (induction) followed by 75–85 mg/m² (maintenance) is still clinically active for the treatment of RMGs [11]. In addition, we were able to show a disease control rate as high as 66.5% in patients with methylation of the O⁶-methylguanine methyltransferase (MGMT) gene promoter [11].

On this basis, we conducted a multicenter phase II study in order to evaluate prospectively the activity and safety of low-dose fotemustine given at 60 mg/m² (induction) followed by 75 mg/m² (maintenance). Also, we investigated correlation between the MGMT gene promoter methylation status and activity of treatment.

Methods

Study objectives

The primary objectives of the study were to evaluate the activity of low-dose fotemustine in terms of response rate and to assess the tolerance of the low-dose schedule. Secondary objectives were progression-free survival at six months (PFS-6), overall survival (OS), and correlation of treatment activity with MGMT gene promoter methylation status.

Study population

Eligible patients were required to have a histologically proven diagnosis of malignant glioma with radiological evidence of disease progression following ≤ 2 lines of chemotherapy. At least 4 and 8 weeks had to elapse since the last delivery of chemotherapy and radiotherapy, respectively. Presence of evaluable and/or measurable disease was mandatory for study enrollment. In cases of re-surgery, residual disease had to be confirmed radiologically before inclusion in the study. Age between 18 and 80 years, KPS ≥ 60 , and adequate hematological, hepatic, and renal function were among the inclusion criteria. Patients with active infections or other uncontrolled diseases, psychiatric disorders, and/or a previous history of cancer (with the exception of in situ carcinoma of the cervix and adequately treated non-melanoma skin malignancies) were ineligible.

The trial was conducted in full agreement with the Declaration of Helsinki and International Committee on Harmonization guidelines for good clinical practice. All enrolled patients were amenable to compliance with testing and were informed of the investigational nature of the study. The study was approved by the local Ethics Committee and a signed informed consent was obtained from all patients before study entry.

Treatment plan

Fotemustine was administered intravenously over 1 h weekly for three consecutive cycles at 60 mg/m² (induction phase) followed by triweekly cycles at 75 mg/m² (maintenance phase) given after a five-week rest period. Study treatment was continued until disease progression, withdrawal of the patient, or unacceptable toxicity. Ten minutes before each infusion of fotemustine, a 5-HT₃ receptor antagonist was administered for anti-emetic prophylaxis.

Anti-epileptic drugs and glucocorticoids were given during the study period as medically indicated. Glucocorticoids were used at the lowest dose necessary for neurologic stability and any modification of steroidal therapy was taken into account when evaluating response according to the criteria of Macdonald et al. [12].

Response and toxicity assessment

Contrast-enhanced (gadolinium-DTPA 0.2 mmol/kg) MRI of the brain was uniformly adopted for tumor assessment and evaluation of response. Baseline MRI examination was performed within two weeks before the initiation of study treatment. Successive evaluations were carried out after completion of the induction phase, every two cycles during

the maintenance phase, or whenever disease progression was clinically suspected. Response to treatment was assessed according to the Macdonald criteria [12].

Toxicity was assessed before each fotemustine administration by medical history, physical examination, hematology and biochemistry. Adverse events were graded 1 to 4 according to NCI-CTCAEv3 version 3.0 [13]. Fotemustine administration was omitted in case of grade 3–4 thrombocytopenia and/or neutropenia and grade 3–4 non-hematological toxicity except for nausea/vomiting. At recovery, treatment was resumed with a 25% dose reduction.

Analysis of the MGMT gene promoter methylation status

Genomic DNA was isolated from one paraffin section of tissue collected at the time of initial diagnosis (Ex-Wax DNA Extraction Kit S4530, Chemicon), proteinase digestion lasting a maximum of 6 h. DNA was denatured with sodium hydroxide in a volume of 35 μ l and subjected to bisulfite treatment in a volume of 350 μ l (4.4 M sodium bisulfite and 20 mM hydroquinone) for 5 h at 55°C and then purified. Unmethylated cytosine, but not its methylated counterpart, is converted into uracil by the treatment. The methylation-specific PCR was performed in a two-step approach. The results were confirmed in an independent experiment, starting with reisolation of DNA from the tumor. The PCR products were separated on 4% agarose gels.

Statistical analysis

Response rate was adopted in order to evaluate the activity of the study regimen. This phase II trial was planned as a single-stage design as described by A'Hern [14]. A sample size of 40 patients was considered sufficient to give an 80% probability of rejecting a baseline response rate of 10% with a one-sided significance test of 5% if response to treatment was observed in at least eight patients (25%). Descriptive statistics were used to summarize pertinent study information. The objective response rate was reported with its 95% confidence interval. The association between variables was tested by use of the Pearson chi-squared test or Fisher's exact test. PFS and OS were calculated by the Kaplan–Meier product-limit method. PFS was the time elapsing from the start of fotemustine therapy to the date of objective evidence of disease progression or death of the patient in the absence of documented disease progression. OS was estimated from the first day of treatment with fotemustine to the date of death of the patient

from any cause. If a patient had not progressed/died, progression and survival were censored at the time of the last visit. The log-rank test was used to assess differences between subgroups. Significance was defined at the $P < 0.05$ level. SPSS (17.0) statistics software was used for analysis.

Results

From March 2006 to December 2008, 40 patients with RMGs were enrolled at two different Institutions. Patients characteristics are listed in Table 1. Median age was 57 years (range 26–80) and median KPS was 80 (range 60–100). GBM was the most represented histotype (75% of cases). Eighty-five percent of patients had received only one prior line of chemotherapy, namely temozolomide given concurrently and sequentially to radiotherapy; the other patients had been treated with two prior lines, consisting of procarbazine–lomustine–vincristine (PCV) followed at progression by temozolomide.

Table 1 Patients' characteristics

Characteristic	All patients no. = 40
Median age, years (range)	57 (26–80)
Median KPS	80 (60–100)
Gender (male/female)	25/15
Histotype	
Glioblastoma multiforme	30 (75%)
Anaplastic astrocytoma	6 (15%)
Anaplastic oligodendroglioma	4 (10%)
Extent of surgical resection at diagnosis	
Macroscopically radical	12 (30%)
Partial	26 (65%)
Biopsy	2 (5%)
Prior radiotherapy	37 (92.5%)
Second surgery	19 (47.5%)
Prior lines of chemotherapy	
1	34 (85%)
2	6 (15%)
Type of prior treatment	
RT/TMZ-TMZ	34 (85%)
PCV \rightarrow TMZ	6 (15%)
MGMT gene promoter methylation status	
Methylated	14 (35%)
Unmethylated	17 (42.5%)
Unknown	9 (22.5%)

KPS Karnofsky performance status, *no.* number, PCV procarbazine–lomustine–vincristine, RT radiotherapy, TMZ temozolomide

Activity

All patients completed the induction phase of treatment and were, therefore, evaluable for activity. Thirty-four patients (85%) received at least one cycle of fotemustine in the maintenance phase. Overall, the median number of cycles administered was five (range 3–14). Eight patients responded to treatment for a response rate of 20% (Table 2, Fig. 1). Thirteen patients (32.5%) achieved disease stabilization, for a disease control rate (response + stable disease) of 52.5%. Responses were observed in all histotypes (Table 2). In particular, five out of 30 patients with GBM (16.5%) responded to treatment.

Toxicity

Having received at least one cycle of fotemustine, all patients were evaluable for toxicity. Treatment-related adverse events are summarized in Table 3. Severe hematological toxicity consisted of grade 3 thrombocytopenia and leukopenia occurring in 7.5% and 10% of patients, respectively. Also, grades 3 and 4 neutropenia were observed in 5% of patients each. Hematological toxicity was mostly confined to the induction phase (data not shown). In fact, among the 34 patients who received at least one dose of maintenance fotemustine, only one patient (3%) developed a case of severe toxicity, namely grade 3 thrombocytopenia. In all six patients who did not proceed to maintenance fotemustine the reason for treatment discontinuation was disease progression. Severe non-hematological toxicity was uncommon with only one case (2.5%) of grade 3 hypertransaminasemia and nausea/vomiting each (Table 3). The dose of fotemustine was reduced by 25% for four patients. Causes for dose reduction were thrombocytopenia, neutropenia, and hypertransaminasemia. No deaths were reported as being related to the study drug and no patients were permanently removed from the study because of toxicity.

Table 2 Activity of treatment according to histotype

	Histotype			Total pts
	GBM	AA	AOD	
Partial response	5	1	2	8 (20%) (95% CI: 7.6–32.4)
Stable disease	9	4	0	13 (32.5%)
Disease progression	16	1	2	19 (47.5%)
Total pts	30	6	4	40

AA anaplastic astrocytoma, AOD anaplastic oligodendroglioma, GBM glioblastoma multiforme, *pts* patients

Efficacy

At a median follow-up of six months (range 1–36), median PFS was three months (95% CI: 2–4). The number of patients free from progression at 6 and 12 months was 21% and 15%, respectively. Median OS was six months (95% CI: 3–9). At 12 and 24 months from the start of fotemustine therapy, 31.2 and 13.2% of patients, respectively, were alive. PFS at six months was significantly higher among responders than among patients experiencing stable or progressive disease (75% vs. 6.5%, respectively, $P = 0.0002$). All the responding patients free from progression at six months were also alive at one year, compared with patients achieving stable or progressive disease (75% vs. 20%, respectively, $P = 0.0005$).

MGMT promoter methylation status and activity of treatment

MGMT gene promoter methylation status was successfully assessed in tumors from 31 individuals (77.5%). Of the 14 patients with methylated MGMT gene promoter, five (35.5%) responded to treatment, whereas three of 17 unmethylated patients (17.5%) achieved a response ($P = 0.41$). With regard to disease control, this occurred in 10 of the 14 methylated patients (71.5%), whereas 10 of the 17 patients with unmethylated MGMT gene promoter (60%) showed disease control ($P = 0.71$). Figure 2 shows the curves for PFS and OS of patients with methylated versus unmethylated MGMT gene promoter. Methylated patients appeared to experience both a longer PFS and OS, but this did not reach statistical significance (Fig. 2).

Discussion

Fotemustine is a nitrosurea drug with demonstrated activity in RMGs; it is, therefore, among options after failure of first-line chemotherapy. This study was conducted to address whether low-dose fotemustine at 60 mg/m² followed by 75 mg/m² would have clinical activity so that it could improve the risk-to-benefit ratio in the salvage setting of RMGs.

Importantly, the low-dose schedule employed in this study met the primary activity end-point by showing a response rate of 20%. Such activity is in line with the 15.5–26% of responses reported in studies in which fotemustine was administered at 100 mg/m² [6–8]. Moreover, in the subset of GBM patients a response of 16.6% was reported, which again is in line with the 16 and 29.6% of responses observed in two studies evaluating full-dose fotemustine for recurrent GBM [15, 16]. Interestingly, the PFS-6 of 21%, compares similarly with the PFS-6 of 20.9%

Fig. 1 MRI in axial planes of a glioblastoma patient experiencing a long-lasting response to treatment. Baseline T1 sequences after contrast medium infusion (**a, b**) show the presence of the tumor in the right frontal lobe involving the corpus callosum and extending to the left frontal lobe. The FLAIR sequence (**c**) shows an important edematous component. At the end of the induction phase of treatment, the same T1 sequences after contrast medium infusion (**d, e**) demonstrate a reduction of the tumor while the FLAIR sequence (**f**) shows a reduction of the oedema

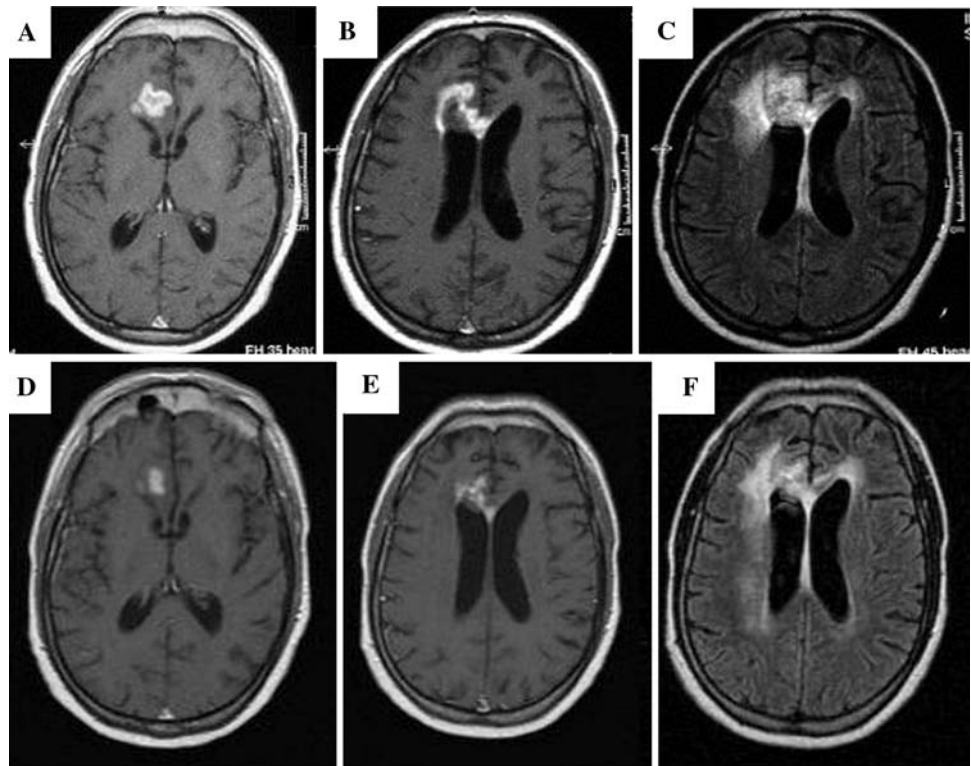


Table 3 Summary of treatment-related adverse events (maximum toxicity per patient reported)

Hematological	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	2 (5%)	8 (20%)	3 (7.5%)	–
Leukopenia	5 (12.5%)	3 (7.5%)	4 (10%)	–
Neutropenia	3 (7.5%)	3 (5%)	2 (5%)	2 (5%)
Anemia	4 (10%)	1 (2.5%)	–	–
Non-hematological				
Hypertransaminasemia	2 (5%)	3 (7.5%)	1 (2.5%)	–
Nausea/vomiting	3 (7.5%)	2 (5%)	1 (2.5%)	–

reported by Brandes et al. [10] in a series of 43 patients with recurrent GBM treated with fotemustine 75 mg/m² (induction) followed by 100 mg/m² (maintenance). Conversely, it compares unfavorably with the values of 48% and 52% reported by Scoccianti et al. [16] and Fabrini et al. [15], respectively. However, it cannot be excluded that these two studies, which were limited to patients with GBM, enrolled a large number of patients with pseudoprogression (treatment-related reaction consisting of an increase in the enhancement and or oedema of the tumoral area), a phenomenon that mimicks tumor progression at MRI in the absence of increased tumor activity. Importantly, pseudoprogression occurs in approximately 30% of patients exposed to concomitant radio-chemotherapy with temozolomide, and correlates with a particularly favorable

prognosis [17, 18]. In this study, in order to minimize this bias, the decision to offer salvage fotemustine was taken only after careful revision of patients imaging, also considering the biology of the tumor in terms of presence of methylation of the MGMT gene promoter, a factor that is more likely to be associated with pseudoprogression [18, 19].

In terms of severe myelotoxicity, tolerability of low-dose fotemustine was excellent, being, in general, safer than in similar studies evaluating a full-dose regimen (Table 4) [6, 8, 10, 15, 16]. Similarly to others, we found that grades 3 and 4 hematological toxicity were mostly confined to the induction phase, whereas its incidence in the maintenance phase was negligible [10]. As a result, it can be argued that fotemustine-related myelotoxicity can be minimized not only by reducing the dose, but also by omitting the induction phase. However, the use of a fotemustine schedule not including the weekly induction phase may result in impaired activity, as suggested by two studies in which a combination regimen of fotemustine plus dacarbazine or procarbazine was used to treat patients with recurrent GBM [20, 21]. These studies, in which a fotemustine schedule of 100 or 110 mg/m² every three weeks was adopted, yielded responses of only 3% and 11.2%, respectively, suggesting that, by omitting the induction phase, the benefits potentially obtainable by addition of a second cytotoxic to fotemustine might be invalidated [20, 21]. In contrast, by maintaining the induction part of treatment, fotemustine is

Fig. 2 Progression-free survival (PFS) (a) and overall survival (OS) (b) curves of patients with methylated versus unmethylated MGMT gene promoter. Methylated patients show a trend toward longer PFS and OS although this does not reach statistical significance

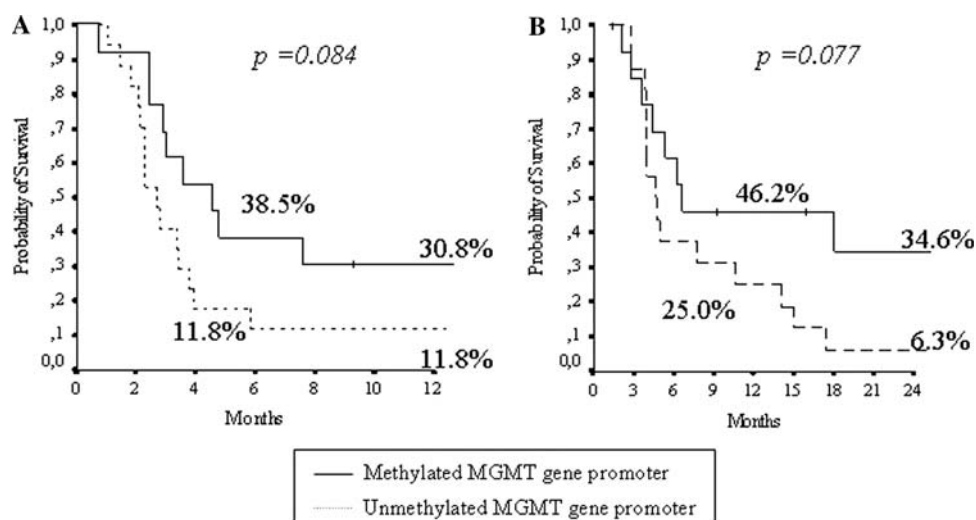


Table 4 Incidence of severe platelet and white blood cell toxicity in trials evaluating single-agent fotemustine for patients with recurrent malignant gliomas

Author (year)	No. of pts	Histotype	Grade 3–4 thrombocytopenia (%)	Grade 3–4 leukopenia (%)	Grade 3–4 neutropenia
Frenay (1991) [6]	38	MGs	23	17	NR
Trevisan (2008) [8]	82	MGs	55.6	50.6	NR
Brandes* (2008) [10]	43	GBM	15	7.5	15%
Fabrini (2008) [15]	50	GBM	8	2	2%
Scoccianti (2008) [16]	27	GBM	11.1	4	NR
This study	40	MGs	7.5	10	10%

GBM glioblastoma multiforme, MGs malignant gliomas, No. number, NR not reported

*Fotemustine given at 75 mg/m² (induction) followed by 100 mg/m² (maintenance); induction phase toxicities reported

still clinically active despite the fact that is being given at a significantly lower dosage as it was in our study.

Against this background, the identification of factors that predispose to sensitivity to fotemustine might be of crucial importance. This is particularly true when we consider that, in this study, response to fotemustine was significantly associated with a longer PFS-6 (75 vs. 6.5%, respectively, $P = 0.0002$) and OS at one year (75 vs. 20%, respectively, $P = 0.0005$). Unfortunately, unlike others [10], we were unable to show a statistically significant correlation between methylation of the MGMT gene promoter as assessed at the time of initial diagnosis and disease control rate. However, it should be taken into account that only 31 out of 40 patients (77.5%) had tumor tissue available for analysis. Also, the correlation between treatment outcome and the status of the MGMT gene promoter was not the primary objective in this trial. Nevertheless, the observation that methylated patients had a trend toward longer PFS and OS is tantalizing (Fig. 2), although it might be related to the fact that methylation of the MGMT gene promoter is associated with a better prognosis irrespective

of treatment [22], rather than to a real prediction of sensitivity to fotemustine.

In conclusion, this study showed that low-dose fotemustine for RMGs has activity comparable with that of the full-dose regimen but significantly less myelotoxicity. For this reason, this schedule is an optimum combination strategy with other anti-tumoral agents, particularly targeted drugs [23]. It is still unclear whether patients with methylation of the MGMT gene promoter obtain a greater benefit from fotemustine chemotherapy compared with unmethylated patients.

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