

## A multi-institutional phase II study on second-line Fotemustine chemotherapy in recurrent glioblastoma

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**Abstract** The present study aims to assess the feasibility and the effectiveness of a second-line Fotemustine chemotherapy in patients with recurrent Glioblastoma after standard primary treatment. Between 2005 and 2007, 50 patients with relapsed malignant glioma (median age = 56.8 years; median KPS = 90) underwent a second-line chemotherapy with Fotemustine. Selected patients were previously treated with a standard 60 Gy Radiotherapy course and Temozolomide Chemotherapy. Patients were stratified into classes according to the prognostic Recursive Partition Analysis. Endpoints of the study were Progression Free Survival at 6 months, duration of Objective Response and Stabilization, Overall Survival and toxicity. At analysis, 36 patients were dead and 14 were alive. Median follow-up from primary diagnosis was 26.6 months. The Efficacy control of the disease was 62%. PFS was 6.1 months; PFS-6 was 52% and median overall survival from primary diagnosis was 24.5 months, with few manageable haematological toxicities. Fotemustine was safe

and effective as second-line chemotherapy in recurrent glioblastoma.

**Keywords** Fotemustine · Glioblastoma · Recurrence · Second-line chemotherapy · Temozolomide

### Introduction

Anaplastic Astrocytoma (AA) and Glioblastoma Multiforme (GBM) represent the most recurrent histotypes among all primitive supra-tentorial brain tumours [1–5]. Clinical management of Malignant Gliomas (MG) is currently an open challenge [6–9] because the median life expectancy is about 12 months.

Re-treatment of MG recurrences is a controversial matter: at the appearance of a recurrence and in presence of specific favourable conditions, a new total or sub-total debulking of the tumour can be proposed. In selected cases, a second surgery can reduce the intra-cranial pressure and can improve the quality of life. Re-intervention alone does not seem, however, to improve the prognosis, as almost all patients die within 6 months from the second surgery [10].

Aggressive local treatments seem to be essential components of the most effective strategies of re-treatment; some studies suggest that chemotherapy is as more effective as the residual tumour volume is reduced, although a successful strategy has not yet emerged. As a consequence, surgery can be proposed, in absence of severe symptoms, only if it is associated to other local or systemic salvage therapies [10–13].

Studies about pharmacological treatment of recurrent MG have given controversial results [14–18].

Fotemustine (FTM) is a third generation chloroethylnitrosourea with a mono-functional/bi-functional antitumor

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activity. The elevated lipophilic properties of FTM contribute to facilitate its passage through the blood–brain barrier assuring the therapeutic concentrations in central nervous system [19]. Different clinical trials, on solid tumours, have demonstrated the marked antitumour activity of FTM, either if employed as single agent, or in association with other anticancer agents or else in combination with other therapeutic modalities [20, 21].

The aim of the present study is to evaluate the tolerance and the effectiveness of FTM in patients affected by supratentorial GBM, already submitted to first line therapy with TMZ and radiotherapy.

## Materials and methods

### Patients

Adult patients with recurrent or progressive, histologically confirmed GBM following surgery, radiotherapy and chemotherapy with TMZ, were enrolled in the study.

Eligible patients were required to have measurable disease with contrast enhancement using MRI or CT scans, with a diagnosis of recurrent or progressive supratentorial GBM performed at the latest 2 weeks before the start of chemotherapy. Main inclusion criteria were: Karnofsky Performance Status  $\geq 70$ , adequate haematological function (absolute neutrophils count  $\geq 1.5 \times 10^9/l$ ; platelet count  $>100 \times 10^9/l$ ; haemoglobin  $>10$  g/dl), normal renal and liver function [serum creatinine level  $<1.25$  times the institution's upper limit of normal (ULN); BUN  $<25$  mg/dl; serum bilirubin  $\leq 1.25$  times ULN; AST and ALT  $\leq 1.25$  times ULN; alkaline phosphatase  $\leq 2$  times ULN].

In all eligible patients, recurrence was diagnosed at least 3 months after radio-chemotherapy completion.

Life expectancy was  $\geq 3$  months. Patients with any prior chemotherapeutic regimen, other than TMZ, were excluded.

All patients provided their fully informed consent to participate in the trial.

### Study design

The current study was conducted in three Italian Oncology Centres, respectively, the Oncology Department of Pisa University Hospital, the Oncology Division of "SS. Annunziata" Taranto Hospital and the Oncology Clinic of Bari University, from 2005 to 2007. It was an open label, prospective, multicenter, non-comparative phase II study. Eligible patients were treated with FTM unless disease progression or unacceptable toxicity was observed.

Tumour response was checked by CT or MRI scans and neurological assessment. The first evaluation was done after the induction phase (7–9 weeks after the first study

drug administration) and successively every 3 months during the study treatment and follow-up observation. Patients with progressive disease (PD) at any point during the study discontinued study treatment under this protocol. Objective evidence of PD was recorded at the time of progression.

### Treatment plan

Patients were treated with a 1 h intravenous infusion of FTM according to the following schedule: Induction phase with FTM  $100$  mg/m<sup>2</sup> on days 1, 8 and 15, followed by a 4–6 week rest period. In non-progressive patients, a maintenance therapy was initiated with one intravenous infusion administration of FTM  $100$  mg/m<sup>2</sup> every 3 weeks until progression or unacceptable toxicity.

### Response evaluation and statistical analysis

The primary efficacy endpoint of the study was the Progression Free Survival at 6 months (PFS-6).

Secondary endpoints were: duration of Objective Response and Stabilization; Overall Survival and toxicity.

All patients receiving the study drug were included in the efficacy and safety analysis.

First disease evolution was assessed by comparing the baseline CT or MRI scans obtained before FTM with the new ones after the induction phase or before if new clinical signs emerged. Response scoring was assigned following R.E.C.I.S.T. criteria [22]. However, as suggested by McDonald et al. [23], the response was scored after a 1 month period of stability, taking into account steroid use and neurologic findings, to minimize the risk of misinterpretations.

The duration of response was measured from the second-line treatment start to the first radiological sign of tumour progression, in the absence of other anticancer treatments.

Complete Response (CR) was defined as the complete disappearance for at least 1 month of all appreciable lesions and the improvement or stability of the neurological status in the absence of corticosteroid therapy. Partial Response (PR) was defined as a decrease of at least 30% in the sum of the largest diameters of all the lesions and an improvement or stability of the neurological status on unchanged or decreased requirement of corticosteroid therapy for at least 1 month. Stable Disease (SD) was defined as a decrease of less than 30% or an increase of less than 20% in the sum of the largest diameters of all the lesions on unchanged or decreased requirement of corticosteroid therapy for at least a 1 month period. Progressive Disease (PD) was the increase of more than 20% in the sum of the largest diameters of all the lesions or the appearance of new lesions.

In case of CR, PR or SD, the time to progression was evaluated until PD, also in case of treatment discontinuation or until the start of new anticancer treatments.

In case of CR, the duration of complete response, defined as the interval between the first assessment of complete response and the objective progression, was considered.

Drug activity was evaluated based upon a one-stage Fleming study design for determination of response rates based on a single treatment group.

Further assessment of the efficacy was based on time to disease progression and time to survival. Median Time To Progression and Median Time To Survival were to be also estimated with their respective 95% Confidence Interval.

Patients were stratified into RPA classes [24] (see Table 1) and Kaplan–Meier event-free survival curves were computed by using the product-limit method [25].

**Expected early toxicity**

The expected toxicity effects during FTM treatment are mainly haematological. Toxicity was evaluated after each FTM cycle completion and it was scored according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI–CTCAE) V3.0–2006 scale.

**Results**

**Patients’ characteristics**

Fifty eligible and evaluable patients were enrolled: 31 males (62%) and 19 females (38%). The median patient population age was 56.8 years (range 30–76 years).

Median follow-up from primary diagnosis resulted to be 26.6 months (range 6.9–86.5 months).

Patients’ characteristics at inclusion are summarised in Table 1. All 50 patients had an hystologically confirmed GBM the majority of them had a good performance status (median score 90). About 24 patients (48%) presented an mono-lobar localization, 11 patients (22%) had an involvement of basal structures and in 15 patients (30%) the GBM involved two or more lobes.

Median time interval between diagnosis and first surgery was 1.3 weeks (range 0–7.7 weeks). Forty-one patients with primary histological diagnosis of GBM received surgery and concomitant radio-chemotherapy ± adjuvant chemotherapy with TMZ [9]. Nine patients with primary diagnosis of AA had received post-operative radiotherapy, followed by a TMZ chemotherapy when biopsy or secondary surgery confirmed an histological evolution to GBM.

**Table 1** Patients’ characteristics

Sex	
19 (38%)	Female
31 (62%)	Male
Age (years)	
56.8	Median
30	Minimum
76	Maximum
Laterality	
28 (56%)	Right
21 (42%)	Left
1 (2%)	Both
Lobe	
8 (16%)	Frontal
8 (16%)	Temporal
6 (12%)	Parietal
2 (4%)	Occipital
11 (22%)	Thalamus - basal ganglia
15 (30%)	Multilobar
Radicality of surgical resection	
22 (44%)	Total resection
25 (50%)	Partial resection
3 (6%)	Biopsy only
Initial grade	
9 (18%)	WHO Grade III Astroцитomas
41 (82%)	Glioblastomas
Karnofski performance status	
90	Median
70	Minimum
100	Maximum
Recursive partition analysis class	
5 (10%)	Class 1
2 (4%)	Class 2
7 (14%)	Class 3
20 (40%)	Class 4
16(32%)	Class 5
0 (0%)	Class 6
Imaging for first disease diagnosis	
33 (66%)	NMR
15 (30%)	CT
2 (4%)	NMR and CT
Time interval from diagnosis to surgery (months)	
0.28	Median
0	Minimum
7.7	Maximum
EBRT dose (Gy)	
59.5	Mean
0.3	Standard Deviation
50	Minimum
60	Maximum

**Table 1** continued

Follow-up time from diagnosis (months)	
20.6	Median
6.9	Minimum
86.4	Maximum

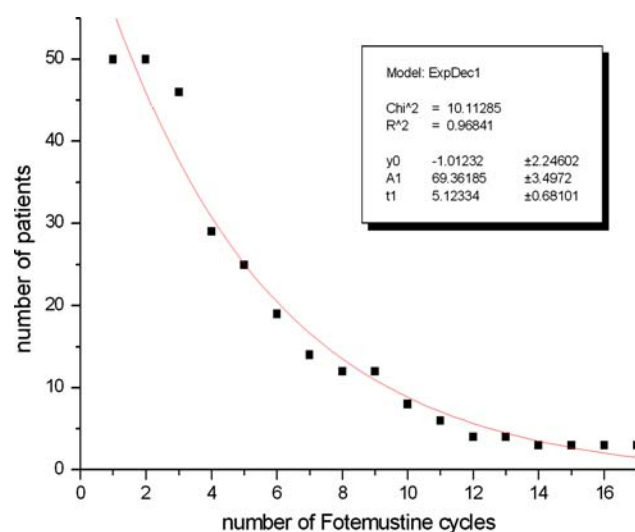
Based on primary conditions, patients were assigned to RTOG Recursive partition analysis classes [25], as shown in Table 1.

Median time interval between surgery and recurrence was 10.6 months (range 3.7–76.9 months); median time interval between diagnosis and FTM induction was 12.5 months (range 6.5–79.4 months).

Before administering FTM a corticosteroid therapy was tailored for each patient, and the same dosage was maintained until disease progression or unacceptable toxicity.

Antiemetic premedication consisted of Dexamethasone 8 mg intravenous and Dolasetron 100 mg intravenous, both administered 15 min before the start of chemotherapy. About 46 patients (92%) received 3 induction 100 mg/m<sup>2</sup> cycles; the remaining 4 patients (8%) received 2 induction 100 mg/m<sup>2</sup> cycles. About 29 patients (58%) entered in the maintenance phase.

An analytical representation of the number of FTM cycles per patient is reported in figure A mono-exponential best fitting function is also reported in Fig. 1 (red curve), together with the fit results. The characteristic constant of the exponential curve was  $5.1 \pm 0.68 \text{ cycles}^{-1}$  (R squared = 0.968).



**Fig. 1** The figure shows the number of cycles of Fotemustine administered per patient (dots). The solid line is the mono-exponential curve best fitting data

## Treatment response

After FTM induction, 1 complete response (CR = 2%), 8 partial responses (PR = 16%), 22 patients with stable disease (SD = 44%) and 19 patients' progressions (PD = 38%), were obtained. The efficacy control of the disease (CR+PR+SD) was 62% (see Table 2 for details).

Five patients with progressive disease and acceptable general conditions discontinued this study and underwent a third line chemotherapy.

## Safety

All 50 patients exposed to FTM were evaluated for safety. The safety data were compared to the safety data registered in the same patients during the TMZ administration; details are reported in Table 3.

Grade 3 thrombocytopenia was documented in 4 patients (8%), grade 4 neutropenia in 1 patient (2%), grade 3 anaemia in 1 patient (2%) and grade 3 lymphopenia in 1 patient (2%), see Table 4

The toxicity incidence rate of FTM has a peak in correspondence of the induction completion and, afterwards, it exhibits a growth with the number of completed cycles (Fig. 2).

None of the patients manifested constitutional or neurological symptoms during FTM treatment. Rises in SGOT and AGPT values (Grade 2) were recorded in 2 patients (4%).

A case of intra-lesion haemorrhage (Grade 2) required suspending the chemotherapy for a two months period; after resolution of CNS bleeding, the patient could restart FTM treatment.

Incidence of toxicity effects during FTM treatment were compared with toxicity events during primary treatment with TMZ. Global incidence of acute toxicity effects was 26% (all grades) during treatment with TMZ and 40% (all grades) during treatment with FTM; this difference was not significant to the level of 0.05 ( $P = 0.30$ ).

## Progression free survival from first recurrence

The median progression free survival (PFS) with FTM was equal to 6.1 months (95% CI 3.5–11.8 months). The median 6 months progression free survival (PFS-6) was equal to 51.5% (95% CI 37–66%). PFS at 1 year was 35.5% (95% CI 21.1–48.3%).

Median PFS were 9.1 months and 5.9 months for patients with primary diagnosis of AA and GBM, respectively. Finally, the PFS-6 with relative 95% CI were, respectively,  $66 \pm 31.4\%$  and  $48.7 \pm 13.5\%$  for these two groups of patients.

**Table 2** Treatment characteristics

Time interval from surgery to recurrence (months)		
10.6		Median
3.7		Minimum
76.9		Maximum
Imaging for recurrence diagnosis		
44 (88%)		MRI
6 (12%)		CT
Patient undergone to second surgery before Fotemustine administration		
22 (44%)		Yes
28 (56%)		No
Time interval from first to second surgery (months)–22 Pts.		
13.4		Median
5.5		Minimum
77.6		Maximum
Number of Fotemustine induction cycles		
2		4 patients
3		46 patients
Disease evolution after Fotemustine induction phase		
19 (38%)		Progression disease
8 (16%)		Partial responding
22 (44%)		Stable disease
1 (2%)		Complete remission

**Table 3** The table compares the number of occurred toxicity events between TMZ and FTM treatments

PTS with Toxicity to TMZ	PTS with Toxicity to FOT	AE and related grade
37	30	None
8	5	Thrombocytopenia G1
0	1	Thrombocytopenia G1 and leucopenia G3
0	1	Thrombocytopenia G1 and leucopenia G1
2	4	Thrombocytopenia G2
0	1	Thrombocytopenia G3
1	0	Thrombocytopenia G2 and anaemia G1
1	1	Thrombocytopenia G2 and leucopenia G2
1	1	Thrombocytopenia G3 and leucopenia G2
0	1	Thrombocytopenia G3 and anaemia G3
1	1	Leucopenia G1
1	0	Leucopenia G2
0	1	Leucopenia G4
0	1	Thrombocytopenia G3 and allergic reaction G2
0	1	CNS haemorrhage
0	2	ALT/AST metabolic laboratory G2

Note that neutropenia and lymphopenia events are merged as leukopenia. One patient with leukopenia G1 had a lymphopenia G2

**Objective response and stabilization**

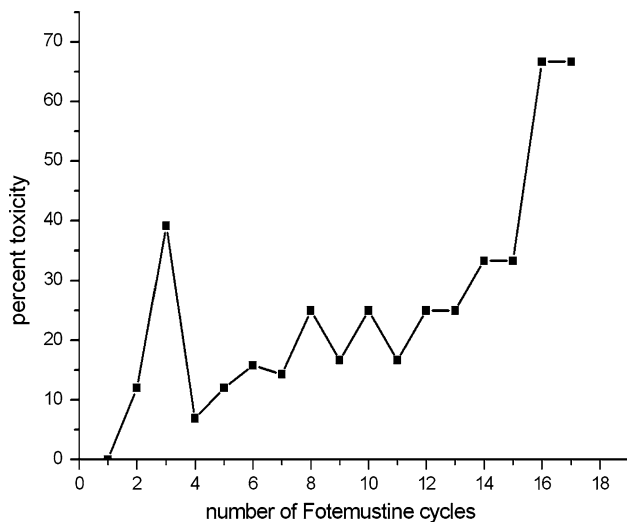
The survival time from the first relapse was defined as the time interval between diagnosis of relapse and death. The median survival time from the first relapse was 8.1 months (range 0.4–32.7).

**Overall survival**

The median overall time to survival was 24.5 months (range 6.9–86.4 months). Survival at 1 year and 2 years from first diagnosis were, respectively, 80.7% (95% CI 76.0–85.4%) and 51.0% (95% CI 36.7–65.3%).

**Table 4** Analysis of all adverse events occurred during Fotemustine conditioning

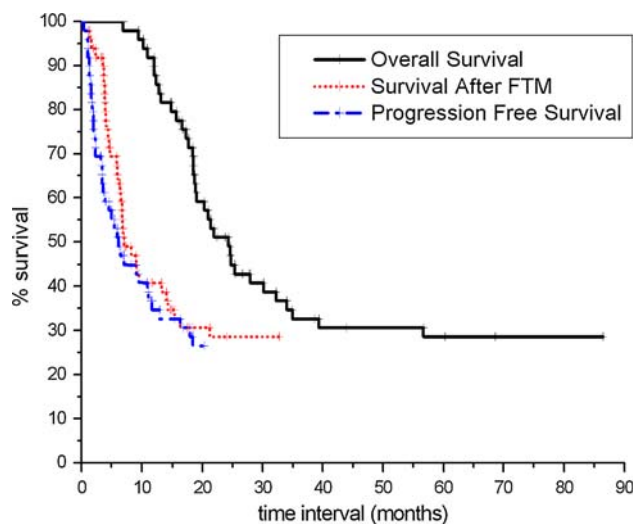
Category	Adverse events	Grade	Toxicity events
Allergy/Immunology	Allergic reaction	G2	1
Blood/Bone marrow	Thrombocytopenia	G1	7
		G2	5
		G3	4
	Lymphopenia	G1	1
		G2	1
		G3	1
Neutrophils	G1	2	
	G4	1	
	G3	1	
Haemorrhage/ Bleeding	Anaemia	G3	1
	CNS haemorrhage	G2	1
Metabolic/Laboratory	ALT/AST	G2	2

**Fig. 2** The figure shows the number of toxicity events as a function of administered cycles of Fotemustine

Data analysis showed an OS, respectively, of 32.3 months for patients with primary diagnosis of AA and 20.3 months for primary diagnosis of GBM. Figure 3 shows Kaplan–Meier curves of the Overall Survival probability after diagnosis, the Survival probability after Fotemustine and the Progression Free Survival after FTM.

The rates of overall survival and survival after the FTM were not dependent on the site of incidence, age, sex and modality of administering primary chemotherapy. The absence of statistical significance in these data may be due to the small number of cases available for the current study.

A surgical total or sub-optimal de-bulking was performed in 22 (44%) patients at recurrence and before

**Fig. 3** The figure shows Kaplan–Meier curves as a function of time in months, respectively, for Overall Survival (solid line), Survival after Fotemustine (dotted line) and Progression Free Survival after Fotemustine (dot-dash line)

Fotemustine administration, to reduce symptoms related to intra-cranial hypertension. Data analysis showed that these patients had a life expectancy equal to not re-operated patients.

Differences among RPA subgroups of patients were assessed by the log-rank test. We found only significant differences on OS from primary diagnosis ( $P = 0.02$ ). In order to reach an acceptable level of statistical accuracy, patients in classes 1 and 2 were merged ( $n = 7$ ); this group had a median OS equal to 13.7 months. Patients in class 3 ( $n = 7$ ) had a median OS equal to 12.6 months. Patients in class 4 ( $n = 20$ ) had a median PFS equal to 10.0 months. Finally, patients in class 5 ( $n = 16$ ) had a median PFS equal to 4.0 months.

A statistically significant correlation did not emerge between RPA class analysis and PFS after recurrence ( $P = 0.3$ ).

## Discussion

Recurrent MG is resistant to most therapeutic approaches. Patients with disease progression after primary radio- and chemotherapy with TMZ should be individually evaluated. Some prognostic factors such as tumour volume and location, performance status, age and response to the first line treatment, should be considered in order to address to the best suited second-line treatment.

A number of phase II studies showed that some drugs can induce an objective response, although the overall survival is substantially unvaried.

Chamberlain et al. [16] reported the use of Cyclophosphamide in 40 recurrent GBM. They reported an efficacy control of 45% and a global grade 3–4 toxicity incidence of 12.5%.

Brandes et al. [17] reported the results of a study using a combination of irinotecan and BCNU. In a series of 42 patients, they found a PFS-6 of 30.3%, a median time to progression of 4.25 months and an efficacy control of 71.4%; severe toxicity occurred in 35.7% of cases.

Promising results have been recently obtained in phase II studies employing an anti-VEGF monoclonal antibody agent (bevacizumab) [26–29]. Although the action mechanism is not yet completely clarified, combination of bevacizumab with irinotecan or other drugs seems to lead to significant advantages in recurrent and primary GBM, albeit with significant toxicity.

Two studies explored the association of FTM with other chemotherapy agents as second-line treatment.

Fazeny-Doerner et al. [30] reported the results obtained with the association of FTM and dacarbazine in 31 patients with recurrent GBM. They found an efficacy control of 55%, a median survival time of 11.25 months, a median time to progression of 4.25 months and major toxicity (grade 3–4) in 23%.

More recently, Silvani et al. [21] employed a procarbazine and FTM combination in 54 patients; the study demonstrated an efficacy control of 64.9%, a median PFS of about 5 months, a PFS-6 of 26.7%. Major toxicity incidence occurred in less than 10% of administered cycles.

Frenay et al. [31] performed a phase II study based on FTM as single agent in 38 patients. They reported an efficacy control of 73%; haematological toxicity (of any grade) was observed in 30% of cases.

FTM alone was also employed by Scoccianti et al. [32] in 27 patients; results showed a PFS-6 of 48.1%, a median time to progression of 5.7 months, an efficacy control of 48.1% and grade 3–4 toxicity in 15% of cases.

The present study aims to establish effectiveness and toxicity of a second-line FTM chemotherapy in pre-treated patients.

The treatment scheme provided an induction phase through three cycles of a 100 mg/m<sup>2</sup> weekly dose; in responding patients, a maintenance therapy was planned, based on the administration of additional cycles every 3 weeks.

Haematological toxicity events occurred in 17 cases (34%); none of the patients presented grade 3–4 non-haematological toxicity. Grade 3–4 toxicity was found in 14% of cases.

Survival analysis showed a PFS-6 of 51.5%, a median survival from the beginning of FTM of 8.1 months, a Progression Free Survival of 6.1 months and a median overall survival from primary diagnosis of 24.5 months.

In the present study, we did not observe any significant difference between respective toxicities of primary and second-line treatments.

As discussed above, our results are comparable to those reported in similar studies based either on second-line FTM, or on other agents.

Therefore, we can conclude that toxicity effects related to a second-line FTM chemotherapy should be mild, delayed, transient and reversible and satisfactory results could be obtained in survival and in terms of quality of life.

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