Second-line chemotherapy with fotemustine in temozolomide-pretreated patients with relapsing glioblastoma: a single institution experience

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To evaluate efficacy and safety of fotemustine chemotherapy in temozolomide (TMZ) pretreated adults with recurrent glioblastoma multiforme (GBM). Primary endpoint was progression-free survival at 6 months. Twenty-seven patients (median age: 56 years; median Karnofsky performance status at progression: 80) with relapsed glioblastoma multiforme underwent fotemustine as second-line chemotherapy after failure of homogeneous postoperative treatment consisting of conformal radiotherapy (60 Gy in 30 fractions) with concomitant TMZ (75 mg/m^2 per day), followed by six courses of TMZ (150–200 mg/m^2 for 5 days every 28 days). Patients were assigned to Radiation Therapy Oncology Group recursive partitioning analysis classes for gliomas. After MRI-proven tumor relapse or progression, all patients underwent chemotherapy with fotemustine, given intravenously 100 mg/m^2 every week for 3 consecutive weeks (induction phase) and then every 3 weeks (maintenance phase). Adequate liver, renal, and bone marrow functions were required. Toxicity grading was based on the National Cancer Institute's Common Toxicity Criteria (version 2.0). Response to treatment was assessed on MacDonald criteria. According to an intention-to-treat-analysis, data on all enrolled patients were included in statistical analysis. Eight partial responses (29.6%) and five cases of stable disease (18.5%) were observed. Median time to progression was 5.7 months. Progression-free survival at 6 months was 48.15%. Median survival from the beginning of fotemustine chemotherapy was 9.1 months. Median survival from diagnosis of glioblastoma was 21.2 months. Toxicity was manageable and mainly hematological (grade 3 thrombocytopenia: three cases; grade 4 leukopenia: one case). Fotemustine has shown therapeutic efficacy as single-drug second-line chemotherapy in treatment of TMZ pretreated patients. *Anti-Cancer Drugs* 19:613–620 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Despite advances in neuroimaging and in multimodality treatment, survival of patients with glioblastoma multiforme (GBM) remains poor (median survival of 12–15 months in a recent randomized multicenter phase III trial [1]). Selected patients might achieve a maximum median survival from first diagnosis of 27 months [2]. Survival after relapse is poor, usually in the range of 6–8 months [3].

Second-line treatment may include reoperation, stereotactic radiotherapy (RT), and radioactive implants but chemotherapy is often the only therapeutic opportunity for recurrent gliomas, primarily because of the large dimensions of relapse.

Comparing results with different second-line therapeutic strategies is very difficult because of heterogeneity in first-line treatment, in study design and response assessment.

Furthermore, no data are available concerning second-line chemotherapy in patients at disease progression after failure of the combination of RT plus temozolomide (TMZ), which recently has become the standard of care for patients with newly diagnosed GBM [1].

Few phase II studies reported on second-line chemotherapy in patients previously treated with TMZ either in adjuvant setting [4,5] or at first recurrence [6].

Fotemustine (F) is a nitrosourea compound that has shown a response rate up to 70% [7] in sporadic retrospective series of patients with recurrent malignant gliomas.

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We report our single-center experience focused on fotemustine treatment in 27 patients with recurrent GBM after TMZ failure.

To our knowledge, this is the first study reporting results of a second-line chemotherapy at the first recurrence of disease in a homogenous population of patients treated with concomitant RT plus TMZ followed by sequential TMZ according to the recently published Radiation Therapy Oncology Group (RTOG) trial [1].

Methods

Study design

The current study was a prospective mono-institutional, single arm phase II study in recurrent GBM patients after first-line treatment consisting of RT and adjuvant TMZ chemotherapy. Patients who fulfilled eligibility criteria were enrolled in the protocol at the evidence of recurrence. Primary endpoint was progression-free survival at 6 months (PFS6).

We chose to analyze this survival time as primary endpoint because PFS6 is now commonly used as a measure of efficacy of therapeutic modalities in recurrent high-grade gliomas [8].

Secondary endpoints included overall survival (OS) from initial diagnosis of disease, OS from first progression and toxicity.

Eligibility criteria

Patients with relapsing GBM after failure of first-line treatment with RT plus concomitant and sequential TMZ were included into this study.

Eligible patients needed to have histologically proven GBM at first diagnosis (histological confirmation of tumor recurrence was not required). Patients were required to have radiological unequivocal evidence of tumor recurrence or progression. Patients had to be between 18 and 75 years of age; they had to have a Karnofsky performance status (KPS) ≥ 70 at the moment of starting fotemustine chemotherapy. Patients needed to have a minimum life expectancy of 3 months.

Adequate liver, renal, and bone marrow functions were required and were designed by the following: transaminase level less than four times the upper limit of normal, total bilirubin level less than 1.8 mg/dl, creatinine concentration less than 1.8 mg/dl, absolute granulocyte count greater than 1500/dl or white blood cell count greater than 4000/dl and platelet count greater than 100 000/dl.

Patients had to have completed the last cycle of first-line chemotherapy at least 4 weeks before the beginning of fotemustine treatment. Patients with earlier malignancy (except basal cell carcinoma or cervical carcinoma *in situ*) were excluded. Absence of HIV infection, known psychiatric disorders, or chronic debilitating disease was required.

In addition, patients could not be pregnant or breast-feeding, and adequate contraception was essential. All patients provided written informed consent before inclusion into the study.

Drug schedule

Patients were treated in an outpatient setting with one induction cycle of fotemustine 100 mg/m^2 given intravenously, every week for 3 consecutive weeks, followed by a 5-week rest period.

In the absence of clinical progression or if there was unacceptable toxicity, patients were treated with maintenance cycles of fotemustine 100 mg/m^2, once every 21 days.

Blood count, liver, and renal functions were required every single cycle. Serotonin antagonists were routinely used as prophylaxis against emesis; steroids were permitted for the treatment of peritumoral edema.

Method of evaluation

Toxicity was evaluated according to the National Cancer Institute's Common Toxicity Criteria (version 2.0). After three maintenance cycles, patients underwent MRI scanning to evaluate response according to criteria described by MacDonald *et al.* [9].

Complete response was defined as the complete disappearance of all radiologically measurable disease, with improved or stable neurological status in the absence of corticosteroid therapy. Partial response was a decrease $\geq 50\%$ in tumor size, with an improved or stable neurology on unchanged or decreased dexamethasone requirement. Stable disease was a regression less than 50% or an increase less than 25% of the tumor size, with an improved or stable neurology on unchanged or decreased corticosteroid dose. Progressive disease was a $\geq 25\%$ increase in tumor size or the appearance of new lesions.

In cases of partial or complete response, chemotherapy was continued until progression or severe toxicity or, in any case, until a maximum of 20 cycles. MRI evaluation was performed every three cycles during the maintenance phase of chemotherapy or immediately when disease progression was suspected clinically.

All the MRI scans were evaluated by a multidisciplinary team consisting of a neuroradiologist, a neurosurgeon, a radiotherapist, and a neurooncologist. Response to

therapy was based on objective radiological assessment compared with earlier baseline images according to criteria described by MacDonald *et al.* [9]. The protocol was approved by the Clinical Research Ethics Committee of the University Hospital of Florence.

Statistical analysis

The Kaplan–Meier method was used to estimate OS and progression-free survival (PFS). OS was calculated either from the date of surgery or from the diagnosis of tumor recurrence. OS was measured until the date of death or last follow-up examination. PFS was estimated from the date of radiological evidence of progression until signs of further progression.

Survival curves were compared using the log-rank test. All analysis was performed using STATISTICA, version 6.0, commercially available software package (Statistica for Windows, Statsoft, Tulsa, Oklahoma, USA).

Results

Between March 2004 and October 2006, 27 patients with progressive or recurrent GBM were enrolled in the study, receiving second-line chemotherapy with fotemustine after failure of postoperative treatment with RT plus TMZ. According to an intention-to-treat-analysis, data on all enrolled patients were included in the statistical analysis.

Patient characteristics

Initial presentation

Baseline characteristics of population and postoperative treatment are reported in Table 1 [10].

Median age was 56 years. Symptoms at presentation included endocranial hypertension, seizures or focal neurological deficits. Corticosteroids (dexamethasone) were needed in 20 cases to control neurological symptoms before surgery. Preoperative KPS was recorded.

All patients underwent surgery. Stereotactic biopsy was performed in two cases (7%). Craniotomy was performed in 25 patients (93%). All patients were evaluated with postoperative gadolinium-enhanced MRI that showed residual disease in seven cases (26%).

Postoperative treatment

In the postoperative setting, KPS and Eastern Cooperative Oncology Group performance status were recorded for all patients. Patients were assigned to RTOG recursive partitioning analysis (RPA) classes for gliomas in accordance with methods described by Curran and colleagues (Table 2) [10].

All patients in this study received postoperative concurrent chemo-radiation therapy according to recently published trial performed by Stupp [1]. All patients received fractionated three-dimensional conformal radiotherapy to a total dose of 60 Gy in fractions of 2 Gy per day. Patients were treated with photons (6–10 MV) produced by a linear accelerator. Concomitant

Table 1 Patient characteristics

Characteristics	No. of patients	%
Median age at presentation	56 (range 31–74)	–
Sex		
Male	16	59
Female	11	41
Symptoms at presentation		
One symptom		
Endocranial hypertension	6	22
Seizures	0	0
Focal deficit	6	22
Two symptoms or more	15	56
Median KPS		
At presentation	80 (range 50–100)	–
Postoperative	80 (range 70–100)	–
At relapse	80 (range 70–100)	–
RPA Class [10]		
Class I	0	0
Class II	0	0
Class III	5	19
Class IV	17	62
Class V	5	19
Class VI	0	0
Postoperative ECOG performance status		
0	3	11
1	14	52
2	9	33
3	1	4
Tumor location at presentation		
Frontal	6	22
Parietal	4	15
Temporal	4	15
Frontoparietal	4	15
Temporoparietal	6	22
Temporo-occipital	1	4
Parieto-occipital	2	7
Surgery		
Biopsy	2	7
Partial resection	5	19
Total resection	20	74

ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group.

Table 2 RTOG recursive partitioning analysis classes for gliomas [10]

Class	Definition
I	Age <50, anaplastic astrocytoma and normal mental status
II	Age ≥ 50, KPS 70–100, anaplastic astrocytoma and at least 3 months from time of first symptoms to initiation treatment
III	Age <50, anaplastic astrocytoma and abnormal mental status
	Age <50, glioblastoma multiforme, KPS 90–100
IV	Age <50, glioblastoma multiforme, KPS <90
	Age ≥ 50, KPS 70–100, anaplastic astrocytoma and 3 months or less from time of first symptoms to start of treatment
	Age ≥ 50, glioblastoma multiforme, surgical resection, good neurological function
V	Age ≥ 50, KPS 70–100, glioblastoma multiforme, either surgical resection and neurological function that inhibits the ability to work or biopsy only followed by at least 54.4 Gy of RT
	Age ≥ 50, KPS <70, normal mental status
VI	Age ≥ 50, KPS <70, abnormal mental status
	Age ≥ 50, KPS 70–100, glioblastoma multiforme, biopsy only, receiving less than 54.4 Gy of RT

KPS, Karnofsky performance status; RT, radiotherapy.

chemotherapy consisted of TMZ (75 mg/m^2 per day, 7 days per week from the first day to the last day of RT). Radiochemotherapy started within 45 days after surgery.

It was planned that all patients would receive six cycles of sequential TMZ (150–200 mg/m^2 for 5 days during each 28-day cycle). MRI was used to monitor patients before the beginning of sequential chemotherapy (28 days after the end of radiochemotherapy), after three and six cycles of TMZ or in case of suspected progression.

Surveillance for patients who completed six cycles of sequential TMZ consisted of neurological examination and MRI imaging every 3 months until progression.

First progression

Median PFS calculated from initial surgery to radiological evidence of first progression was 10.4 months (range: 3.9–27.3).

Relapse was classified as 'in field' if more than 80% of radiologically proven recurrent disease was in the radiation target area, 'marginal' if it was 20–80%, and 'distant' if it was less than 20% [11]. In field, marginal, and distant relapses were respectively one, 21, and four cases. In one patient relapse occurred in the contralateral hemisphere.

At recurrence of disease all patients received fotemustine as second-line therapy. No patient underwent either second surgery, further RT, or any other chemotherapy. Median KPS at recurrence was 80 (KPS 70 $n = 4$; KPS 80 $n = 10$; KPS 90 $n = 11$; KPS 100 $n = 2$).

The median number of delivered fotemustine courses was nine (range: 3–20); treatment with fotemustine started within 10 days after radiological diagnosis of recurrence.

At the time of this report, median follow-up from presentation in our institute was 20.3 months (range: 10.6–40.3).

Response to chemotherapy

Radiological response evaluation, on the basis of MacDonald criteria [9], was performed after three maintenance cycles or before if clinical suspicion of progression occurred.

Fourteen (51.8%) patients had evidence of progression; eight (29.6%) partial responses were obtained and five patients (18.5%) showed stable disease.

Third-line therapy

Decisions on further therapeutic interventions were made on individual basis, taking into account patients' KPS, neurological symptoms and motivation for therapy. Four patients with KPS ≥ 70 after failure of fotemustine were treated with further chemotherapy ($n = 2$ altered schedule of TMZ in patients with MGMT promoter methylation; $n = 1$ cisplatin (CDDP) + carmustine (BCNU); $n = 1$ procarbazine + lomustine + vincristine). Not even a single patient underwent second surgery or re-irradiation.

Progression-free survival from the diagnosis of first recurrence

Median PFS was 5.7 months (range: 2.3–27.3). Only one patient had no evidence of progression of disease at the time of analysis. PFS6 was 48.15% ± 0.09; PFS at 1 year was 18.52% ± 0.07 (Fig. 1).

Survival from first recurrence

Median survival from the evidence of first recurrence was 9.1 months (range: 3.3–29.4). At the time of analysis all the patients but five had died owing to disease. Six-month survival was 77.78% ± 0.08, 1-year survival was 42.16% ± 0.09 (Fig. 2).

Survival from the first diagnosis of disease

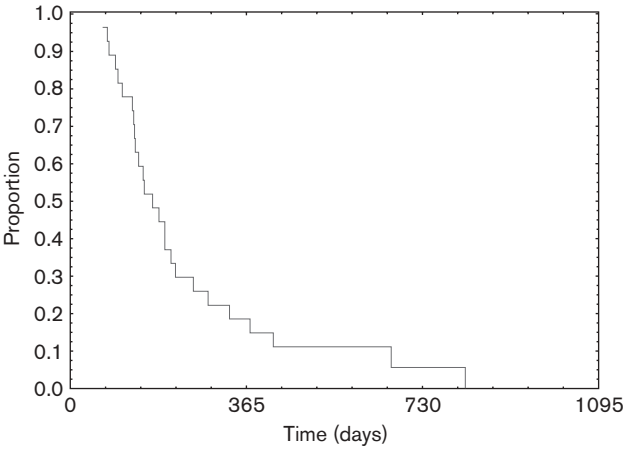
Median survival was 21.2 months (range: 11.1–40.7). At 12 and 24 months from the first diagnosis, respectively, 92.59 (± 0.05) and 45.97% (± 0.09) of patients were alive (Fig. 3).

Subgroups of patients according to prognostic classes and survival

Differences between subgroups of patients classified according to RTOG RPA classes [10] were assessed by the log-rank test.

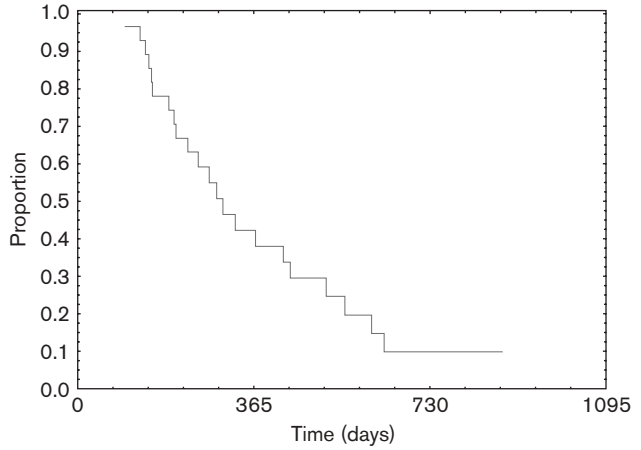
RPA classification was found to have a significant impact on OS from first diagnosis ($P = 0.03$). All RPA class III

Fig. 1



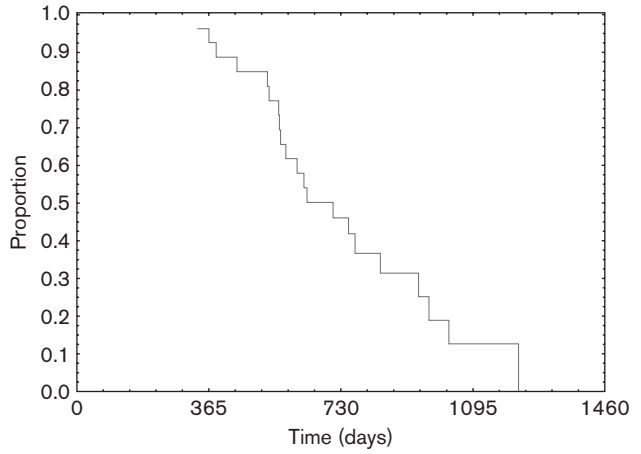
Progression-free survival.

Fig. 2



Overall survival from first recurrence.

Fig. 3



Overall survival from first diagnosis of disease.

($n = 5$) patients were alive at 18 months from the diagnosis; RPA class IV ($n = 17$) and V ($n = 5$) patients had a 18-month survival of 67.1 and 33.3%, respectively. RPA class analysis did not show statistically significant relationship either with PFS after second-line chemotherapy ($P = 0.25$) or with OS after first recurrence ($P = 0.18$).

Toxicity

Toxicity was evaluated according to National Cancer Institute's Common Toxicity Criteria (version 2.0). On the whole fotemustine was quite well tolerated (Table 3).

Toxicity was predominantly hematological. Leukopenia grade 4 was experienced by one patient; he required administration of granulocyte colony stimulating factors and continued chemotherapy at reduced doses. Chemotherapy was interrupted in another patient because of thrombocytopenia grade 3. Two patients required a dose reduction of fotemustine by 25% because of G3 thrombocytopenia. Deep vein thrombosis was observed in two cases. There were no deaths that could be considered clearly treatment-related.

Table 3 Toxicities by grade of severity, according to the National Cancer Institute's Common Toxicity Criteria (version 2.0)

	Grade 1 (No. of patients)	Grade 2 (No. of patients)	Grade 3 (No. of patients)	Grade 4 (No. of patients)
Hematological toxicity				
Thrombocytopenia	11	5	3	0
Leukopenia	8	8	0	1
Anemia	4	1	0	0
Nonhematological toxicity				
Nausea	1	0	0	0
Vomiting	1	0	0	0
Cutaneous rash	1	0	0	0
Deep vein thrombosis	0	2	0	0

Discussion

Fotemustine (diethyl-1-[3-(2-chloroethyl)-3-nitrosoureido] ethylphosphonate) is a liposoluble nitrosourea. It consists structurally of a nitrosourea radical attached to an aminophosphonic acid group, as a carrier, to increase ability of penetration through the blood–brain barrier and through cell membranes.

This drug is actually able to cross the blood–brain barrier. After intravenous administration, fotemustine is largely distributed into the central nervous system as shown by pharmacokinetic analyses. Antineoplastic activity is related to physicochemical properties (high liposolubility, low molecular weight, and low ionization at physiological pH) [12].

A few phase II studies have investigated chemotherapy with fotemustine as single agent [13,14] or in combination with other drugs [15,16] in newly diagnosed high-grade gliomas. Median OS of 10–14.5 months and median PFS of 6.6–9.5 months were reached (Table 4).

Two phase II studies reported on fotemustine as monochemotherapy in recurrent high-grade gliomas [17,18]; patients included in these studies were not previously treated with TMZ.

Frenay *et al.* [17] performed a phase II study using fotemustine as single agent in 38 cases of recurrent gliomas. Ten patients had objective responses (26%), 18 had stable disease (47%).

Table 4 Fotemustine as single agent or in combination with other agents in newly diagnosed high-grade gliomas

Authors	Priou *et al.* [13]	Ozkan *et al.* [14]	Frenay *et al.* [15]	Fazeny-Dorner *et al.* [16]
No. of patients	101	27	33	55
Treatment	Fotemustine	Fotemustine	F + CDDP + VP16	F + D
Median age (years)	51.3	46	57.7	44
Median PS	ECOG PS 1	ECOG PS 1	ECOG PS 2	KPS 90
Median PFS (months)	6.6 (Biopsy or partial surgery); 7.6 (complete surgery); NA for the whole group	8	6.8 (For responding and stable patients); NA for the whole group	9.5
PFS at 6 months	NA	65%	NA	54%
Median OS (months)	11.3	11	10	14.5
Toxicity G3	NA	7%	G 3/4: 36%	G 3/4: 9%
Toxicity G4	NA	None		

CDDP, cisplatin; D, dacarbazine; ECOG PS, Eastern Cooperative Oncology Group Performance Status; F, fotemustine; KPS, Karnofsky Performance Status; NA, not available; OS, overall survival; PFS, progression free survival; VP16, etoposide.

Eleven patients were included in a phase II study reported by Punt *et al.* [18]: one partial response of 13 months duration occurred; seven patients had stable disease for a median duration of 5 months (range: 4–11). Median survival from inclusion in the study was 6 months.

Two phase II studies reported results obtained with fotemustine in association with other chemotherapeutic agents in the treatment of recurrent gliomas [5,19]. One of these [5] included patients who had received previous TMZ-based chemotherapy.

Fazeny-Dörner *et al.* [19] assessed the safety and efficacy of second-line combination of fotemustine and dacarbazine in nitrosourea-pretreated patients ($n = 31$) with recurrent GBM. One patient showed a partial response; 16 cases of stable disease were observed; and three patients had progression after the first cycle of fotemustine + dacarbazine. Median PFS and median survival from beginning of second-line chemotherapy were, respectively, 17 and 45 weeks.

Recently, Silvani *et al.* [5] published a phase II study to evaluate efficacy of a combined treatment with fotemustine and procarbazine (PCB) in relapsing GBM. Thirty-one patients (group I) were treated with fotemustine + PCB as second-line chemotherapy after adjuvant TMZ-based therapy ($n = 29$ cisplatin + TMZ; $n = 2$ TMZ as single agent). Fotemustine + PCB combination was used as third-line chemotherapy in 23 patients (group II) who received CDDP + TMZ as second-line therapy at the first recurrence after having performed adjuvant nitrosourea-based chemotherapy (BCNU + CDDP). For the whole group median PFS from the beginning of fotemustine + PCB therapy was 19.3 weeks, PFS6 was 26.7% and median survival time was 28.7 weeks.

The current study investigated efficacy and toxicity of fotemustine used as single agent in patients with recurrent GBM pretreated with TMZ.

In 2000 Yung *et al.* [20] published results of an inverse sequence treatment modality (nitrosourea in adjuvant setting and TMZ at first recurrence). The PFS6 was 21% and the median PFS was 12.4 weeks; the overall response rate (partial response and stable disease) was 45.6%.

Comparisons between different regimens used in recurrent glioblastoma are difficult because of heterogeneity of first-line treatment and differences in endpoints and response evaluation. Our results in terms of PFS can be favorably compared with the best results reached in the available second-line treatment strategies recently published on glioblastoma patients (median time to progression: 21 weeks [21,22]; PFS6: [23] 39–48% [21]).

For many years, before the evidence-based efficacy of TMZ was shown [1], nitrosoureas-based chemotherapy has been the mainstay of therapy for GBM; consequently the trials on second-line chemotherapy in patients treated with TMZ are few. To our knowledge, this is the first study analyzing a second-line chemotherapy in recurrent glioblastoma where all the patients were homogeneously pretreated with RT and concomitant/adjuvant TMZ, according to the trial performed by the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada [1].

To our knowledge only three phase-II studies reported results of second-line chemotherapy in patients previously treated with TMZ either in adjuvant setting [4,5] or at first recurrence [6] (Table 5); not one of these studies included patients treated with concomitant RT plus TMZ followed by sequential TMZ according to the recently published RTOG trial [1].

Chamberlain *et al.* [4] reported about 40 patients with recurrent GBM treated with cyclophosphamide. Only 19 of these patients received cyclophosphamide at first recurrence after failure of adjuvant TMZ. Interpretation of these data is difficult because the authors did not differentiate results in terms of response or toxicity between patients at first or second progression. For the

Table 5 Phase II chemotherapy trials for relapsing glioblastoma multiforme after temozolomide failure

Authors	Chamberlain *et al.* [4]		Silvani *et al.* [5]		Brandes *et al.* [6]	Current study
No. of patients	19	21	31	23	42	27
Concomitant RT/TMZ	No	No	No	No	No	Yes
Adjuvant chemotherapy	TMZ	Nitrosourea-based chemotherapy	TMZ ($n=2$); TMZ + CDDP ($n=29$)	BCNU + CDDP	No	TMZ
Treatment at first progression	CTX	TMZ	PCB + F	TMZ + CDDP	TMZ ($n=26$); TMZ + CDDP ($n=16$)	F
Treatment at second progression	–	CTX	–	PCB + F	BCNU + CPT-11	–
Median age (years)	51.5		56	50	53.4	56
Median KPS	80		80	80	80	80
Median PFS (weeks)	8.6		19.7	19.3	17	24.5
PFS at 6 months	20%		17.1%	45.8%	30.3%	48.15%
Median OS from recurrence (weeks)	17.2		30.8	26.6	50.3	39.1
Toxicity G3	48 events		G 3/4: eight events		11 events	Three events
Toxicity G4	Three events				One event	One event

TMZ, temozolomide; CDDP, cisplatin; CTX, cyclophosphamide; PCB, procarbazine; F, fotemustine; BCNU, carmustine; CPT-11, irinotecan; KPS, Karnofsky Performance Status; NA, not available; OS, overall survival; PFS, progression free survival; RT, radiotherapy.

whole group of patients, the median time to tumor progression was 2 months, the PFS was 20% at 6 months, and the median survival was 4 months.

More recently, two phase II studies of salvage chemotherapy for relapsing GBM previously treated with TMZ were published.

Silvani *et al.* [5], as discussed above, treated 31 TMZ pretreated patients with second-line combination of procarbazine plus fotemustine. In the adjuvant setting these patients had received TMZ-based chemotherapy ($n = 29$ TMZ + CDDP, $n = 2$ TMZ alone). The median PFS was 19.7 weeks. The PFS6 was 17.1%. The median OS from the beginning of chemotherapy was 30.8 weeks.

Brandes *et al.* [6] treated 42 patients who recurred or progressed after first salvage TMZ-based chemotherapy ($n = 26$ TMZ alone; $n = 16$ TMZ + CDDP). These patients were treated only with exclusive RT in the adjuvant setting.

Chemotherapy at second recurrence consisted of BCNU and irinotecan. The median time to progression was 17 weeks. The PFS6 was 30.3%. The median OS from the time of starting chemotherapy was 11.7 months.

In the present series we recorded similar results in terms of PFS (median PFS: 24.5 weeks, PFS6: 48%) than reported by other series that analyzed TMZ pretreated patients.

Toxicity was moderate and comparable to the previous reported experiences, as well. Our data about OS were somehow surprising probably owing to a small number of patients and excellent results of first-line multimodality treatment. Furthermore, selection bias could be derived from the inclusion of patients maintaining high KPS at recurrence time.

Our protocol was actually written before clear recommendations about exclusion from phase II trials of patients who progressed within first 3 months have been published [24,25]. Among eligibility criteria we did not list a minimum interval time from the end of RT to progression, this feature might be a further potential theoretical shortcoming of the current study considering the risk of inclusion of patients with pseudoprogression leading to an overestimation of results. However, it might be worth stressing that we actually included only one case of early progression (2 months since the end of RT/chemotherapy). Furthermore, this patient had radiological evidence of further progression after three maintenance cycles of fotemustine (3.6 months after diagnosis of recurrence). This single case of potential pseudoprogression should be considered a case of real progression [25].

In our series patients were assigned to RTOG RPA classes [10]. This classification, as is well known, is based upon a combination of the most important prognostic factors: KPS, age, extent of the surgery, radiation therapy dose, and neurological status (Table 2). RPA classification in our series was predictive for OS from diagnosis.

As a small number of patients were included in our series, this analysis essentially confirmed the value of RTOG RPA score system for estimating the prognosis of patients with high-grade gliomas. This is an important issue because stratifying patients according to validated prognostic classes (that are based upon variables easily measured in routine practice) may be strongly helpful for the clinician to propose adequate treatment options.

Considering the encouraging results and moderate toxicity of the present series, even though they relate to a small nonrandomized group of patients, we concluded that fotemustine may represent second-line chemotherapy after TMZ regimen, although, obviously, further prospective studies are needed.

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