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Phase II Study of Fotemustine in Recurrent Supratentorial Malignant Gliomas

M. Frenay, B. Giroux, S. Khoury, J.M. Derlon and M. Namer

38 adults with recurrent supratentorial malignant gliomas, including glioblastoma multiforme (21), anaplastic astrocytomas (9), probably transformed low-grade astrocytomas (6), pinealoblastoma (1) and non-metastatic tumour of unknown histology (1), were treated with fotemustine 100 mg/m² intravenously every week for 3 consecutive weeks followed by a 5-week rest period. Maintenance treatment consisted of one infusion every 3 weeks. Patients were divided into three groups according to treatment effect. 10 objective responses (26%) with a median time without progression of 32.7 weeks, 18 stabilisations (47%) and 10 failures (26%) were observed. Pathological findings of the initial primary tumour and neurological functional status were unequally distributed in these groups. Haematological and liver toxicities were mild, delayed, transient and reversible. Thrombocytopenia and leukopenia were more frequent (30%) in patients treated with prior chemotherapy. Fotemustine is a well tolerated active drug in recurrent malignant gliomas with an original and short treatment schedule.
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INTRODUCTION

LIPOPHILIC NITROSOUREAS are the most important group of antineoplastic drugs in chemotherapy of malignant gliomas [1].

The standard drug is carmustine with a transient efficacy as monochemotherapy in recurrent gliomas and as adjuvant treatment combined with radiotherapy and surgery [2, 3]. Polychemotherapy with drugs crossing the blood–brain barrier does not increase efficacy compared to carmustine alone [4, 5]. Fotemustine, a new chloroethyl nitrosourea compound, is characterised by a high lipophilicity (log P = 1.25) and a chemical structure including a phosphonoalanine carrier group grafted onto the nitrosourea radical to achieve both a better penetration through the cell membrane and a better antitumoral activity [6]. In *in vivo* models fotemustine compared favourably with carmustine on intrathecal L1210 leukaemia grafted into mice and in xenografts of human glioma [7, 8]. A clinical phase I study with weekly administration for 3 consecutive weeks showed delayed, cumulative and dose-related thrombocytopenia, leukopenia and mild nausea and vomiting. The recommended dose for further phase II studies was 100 mg/m² [9]. Thus, a phase II study was initiated in recurrent malignant gliomas to assess the tolerance and antitumoral activity of fotemustine using this original fractionated schedule.

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MATERIALS AND METHODS

From October 1985 to October 1988, 38 patients with recurrent supratentorial primary brain tumour were treated by fotemustine in a multicentre study (Table 1). All patients had computed tomography (CT) findings of progressive disease in relation to earlier examination and 32 had significant neurological impairment. No biopsy was performed at recurrence.

According to the WHO classification [10], histological examination of initial tumours showed glioblastoma multiforme in 21 (55%), anaplastic astrocytoma in 9 (24%) and pinealoblastoma in 1 (3%). In 6 patients (16%) with primary low grade astrocytomas,

Table 1. Patients' characteristics

Median age (years) (range)	49 (18–65)
Sex ratio (M:F)	2.2 (26:12)
Neurological status (Order's scale)	
Type 1	9
Grade 2	23
Grade 3	6
Grade 4	0
Histopathological diagnosis (%)	
Glioblastoma multiforme	21 (55.3)
Anaplastic astrocytoma	9 (23.7)
Probable degenerated low-grade astrocytoma	6 (15.8)
Pinealoblastoma	1 (2.6)
No histology	1 (2.6)
Location* (%)	
Right/left	17/19
Median	2
Frontal	18 (28.0)
Parietal	19 (29.7)
Temporal	17 (26.6)
Occipital	9 (14.1)
Thalamus	1 (1.6)
Symptoms at inclusion* (%)	
Focal neurological deficit	22 (58)
Headaches	10 (26.3)
Personality changes	15 (39.5)
Epilepsy	6 (16)
No symptoms	7 (18.4)
Prior treatment (%)	
Macroscopically complete resection	19 (50)
Partial resection	8 (21.1)
Biopsy	11 (28.9)
Radiotherapy	38 (100)
Chemotherapy	10 (26.3)
Delay without progression (months)	
Glioblastoma multiforme	11.5
Anaplastic astrocytoma	42
Others	57.3
Associated treatment (%)	
Anti-oedema	74
Anticonvulsant	76

*Total >38 as several locations or symptoms were observed per patient.

malignancy was supposed by CT findings (contrast enhancement of lesion with central low attenuation area). One 18-year-old patient with a recurrence 10 years after the initial tumour had no histology, but the primary brain location and the absence of an argument for metastatic lesion justified the inclusion.

Median age was 49 years (range 18–65) and sex ratio 2.2:1 (26 M: 12 F). Median Karnofsky performance status was 70% (50–100%). Neurological functional status was assessed by Order's scale [11, 12] with 9 patients noted grade 1, 23 grade 2 and 6 grade 3. No patient was grade 4.

Prior treatment of the primary tumour included surgical resection in 27 cases (extensive in 19 and partial in 8) and biopsy in 11 cases, followed by conventional radiotherapy in all patients (55–60 Gy with 30 fractions over 6 weeks) and combined chemotherapy in 10 cases. Chemotherapy was performed with nitrosoureas (carmustine, lomustine) alone in 1 case or combined with other cytostatics (cisplatin, 5-fluorouracil [5-FU]) in 7 cases. 2 other patients received either cisplatin or a combination of cisplatin and 5-FU. Delay between prior treatment and inclusion in this trial was on average 11.5 months for glioblastoma, 42 months for anaplastic astrocytomas and 57.3 months for other histologies.

Concomitant treatment included anticonvulsant therapy in 29 cases with phenobarbitone, and anti-oedema therapy in 28 cases with steroids. Haematological, renal and liver parameters were normal at inclusion. No major disease other than brain tumour was present.

Fotemustine was given intravenously at the dose of 100 mg/m^2 infused over 1 h in 250 ml 5% dextrose protected from light. The treatment plan consisted of one administration weekly, for 3 consecutive weeks, followed by a 5-week rest period. Fotemustine was then given every 3 weeks until emergence of toxic effects or progressive disease. A reduction in dose of up to 50% or 75% of the initial dose was then provided for according to blood cell toxicity.

Toxicity was assessed before each administration and during the rest period, by clinical and biological examinations e.g. complete blood count and platelets, blood urea nitrogen, creatinine, transaminases, alkaline phosphatase and bilirubin. Toxicities were graded according to WHO criteria.

Antitumoral activity was evaluated by comparing contrast enhancement size on CT scan 8 weeks after the first administration, with a quantification of the tumour size based on the product of the two largest diameters of the lesion. A reduction of more than 50% of the target lesion associated with improvement of neurological symptoms and discontinuation of anti-oedema therapy were required for diagnosis of objective response (group 1). Stabilisation (group 2) was defined by a reduction of less than 50% with no change in clinical status or steroid dose and failure (group 3) by a progression of the tumour lesion with deterioration in the clinical status. Survival curves were analysed by the Kaplan–Meier method [13].

RESULTS

Antitumoral activity

All patients received induction treatment with the full dose. 13 received maintenance treatment with doses ranging from 100 to 1300 mg/m^2 (1–13 courses). Three groups of patients were defined according to antitumoral activity parameters (Table 2).

Group 1 was represented by 10 patients with objective partial response (26%, 95% CI 12–40%). Three responses were observed in glioblastoma multiforme (3/21) (Fig. 1), 3 in anaplastic astrocytomas (3/9), 3 in transformed low grade astrocytomas and 1 response in the unknown histology type. The median age was 51 years, associated with a relatively good neurological status (9 patients with type 1 or 2, and only 1 patient with type 3). Median duration of response was 32.7 weeks. 1 patient was still alive 1 year after his inclusion. Median overall survival from inclusion was 40 weeks. Among the 10 objective responses, 3 were obtained in patients with prior chemotherapy including nitrosourea.

Group 2 consisted of 18 patients (47%) with 11 glioblastomas, 5 anaplastic astrocytomas and 2 low grade astrocytomas. Median age was 47 years with a good functional status for all patients (18 patients with type 1 or 2). Median duration of stabilisation was 21 weeks, 4 patients were still alive 1 year after inclusion and there were 2 long-term survivors (95–104 weeks). Median overall survival was 42.5 weeks.

Group 3 consisted of 10 patients (26%) who failed to respond with a median survival time of 15.2 weeks. In this group, median age was 51 years and half of the patients had a poor prognosis according to neurological status (5 patients with type 3). Anti-oedema therapy was unchanged or increased in all patients.

Table 2. Antitumoral activity

	Group			
	1	2	3	Total
Response	Objective	Stabilisation	Progression	
Patients	10	18	10	38
Response rate (%)	26.3*	47.4	26.3	
Median age (years)	51	47	51	49
Sex ratio (M:F)	1.5 (6:4)	3.5 (14:4)	1.5 (6:4)	2.2 (26:12)
Neurological status (grade 3/grade 1 + 2)	1/9	0/18	5/5	6/32
Histologies (%)				
Glioblastoma multiforme	3/21 (14.3)	11/21 (52.4)	7/21 (33.3)	—
Anaplastic astrocytoma	3/9 (33.3)	5/9 (55.6)	1/9 (11.8)	—
Others	4/8 (50)	2/8 (25)	2/8 (25)	—
Percent of glioblastoma	30%	61%	70%	55.3%
Median duration of response (weeks)	32.7	21	—	—
Median duration of overall survival (weeks)				
$P < 0.001$†	40	42.5	15.2	30

*95% CI: 12.3–40.3%
†Kaplan–Meier method and logrank test.

Toxicity

Haematological parameters were assessed in 35 patients (92%) and liver or renal function tests in all patients. Toxicities encountered are summarised in Table 3.

The most common side-effect was a delayed reversible and cumulative haematological toxicity. Thrombocytopenia and leukopenia greater than grade 0 were observed in 52.6 and 63% of cases, respectively, with 23 and 17.2%, respectively, of grade III–IV (8 and 6/35). Anaemia was observed in 28.6% of cases (10/35) with 2 of grade III. Haematological toxicity in terms of thrombocytopenia and leukopenia occurred at median day 31 and 38 with the nadir at day 34 and 48 respectively and recovery at day 49 and 56. 1 patient out of 13 treated according to the maintenance schedule stopped therapy after four courses due to haematological toxicity (cumulative dose: 700 mg/m^2).

Prior chemotherapy was associated with more frequent grade III–IV thrombocytopenia and leukopenia, observed in 30% and 30% of pretreated vs. 20% and 12% of non-pretreated patients, respectively. Liver toxicity occurred in 31.6% (12/38) with an increase in ALT alone in 8 cases or in association with other hepatic parameters in 4 cases. ALT enzyme values reached grade III in 2 cases. These biological abnormalities were without clinical significance. Delay in occurrence of biological abnormalities varied from day 6 to day 43 after the first infusion of fotemustine.

Nausea and vomiting appeared a few hours after infusion in 18% (22/124 infusions) and were usually mild. No other toxicity was noted.

DISCUSSION

Fotemustine was administered according to an original sequential treatment plan, compared with other nitrosoureas which are given every 5 or 6 weeks [5]. The induction treatment with a total dose of 300 mg/m^2 over 3 weeks had the advantage of delivering a greater quantity of cytotoxic drug over a short period of time and also permitted a rapid assessment of antitumoral activity. This treatment improved and stabilised 74% of patients (28/38) with an objective response rate of 26% (10/38). The activity of fotemustine based on the response rate is probably similar to that observed with other drugs.

However, the initial response rates published in recurrent gliomas with standard nitrosoureas (carmustine, lomustine) are difficult to compare and interpret since the evaluation criteria did not include CT [14, 15]. More recently, an EORTC phase II clinical trial with a hydrophilic nitrosourea (elmustine) reported an objective response rate of 20% on CT clinical

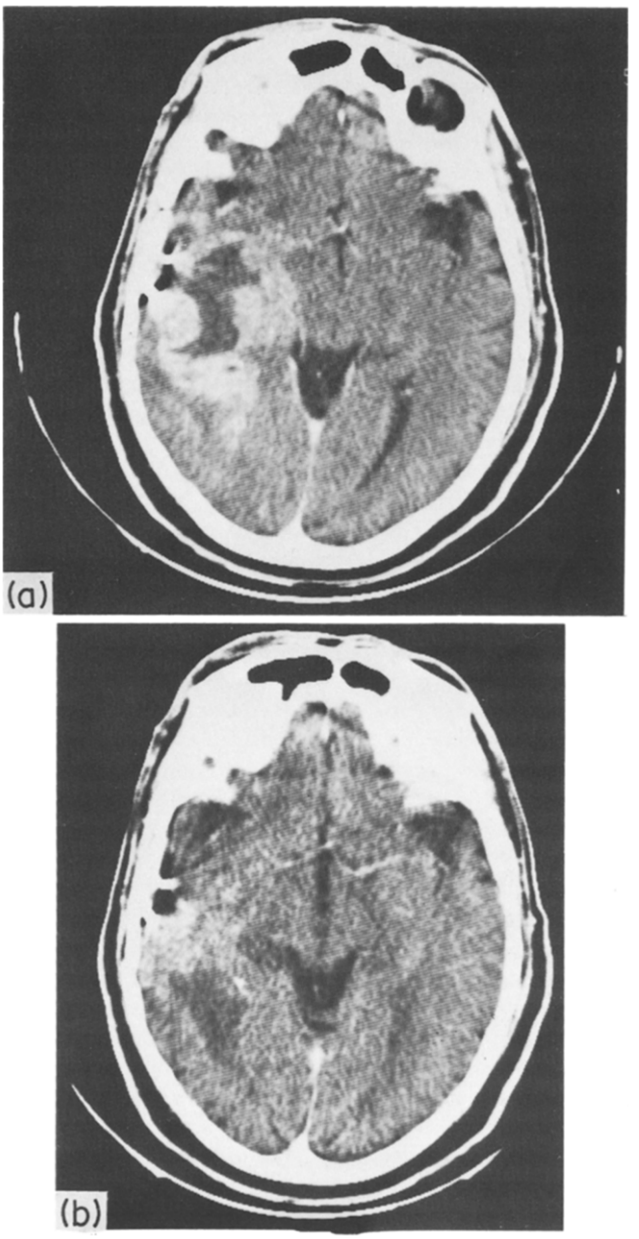

Fig. 1. (a) Recurrence of right temporoparietal glioblastoma with prior surgery and radiotherapy (disease-free survival: 14 months) and (b) same patient with partial response after 3 infusions of fotemustine (CT 5 months after beginning of treatment and without steroids). This patient was not treated with maintenance schedule for personal reasons.

Table 3. Toxicity (WHO classification)

	Grade					Median day (range)			Prior chemotherapy*		
	0	1	2	3	4	Start	Nadir	Recovery	None $n = 28$	Prior $n = 10$	Total $n = 38$
Haematological ($n = 35$)											
Haemaglobin	25 (71.4%)	4	4	2	0	42 (15–53)	—	—	4%	10%	5.7%
Leukopenia	13 (37%)	7	9	3	3	38 (17–60)	48 (36–50)	56 (44–66)	12%	30%	17.2%
Thrombocytopenia	15 (43%)	4	8	5	3	31 (17–51)	34 (20–50)	49 (27–84)	20%	30%	23%
Liver ($n = 38$)											
ALT	26 (68.4%)	6	4	2	0	18 (5–45)					
AST	35 (92%)	0	3	0	0	18 (6–28)					
Alkaline phosphatase	36 (95%)	1	1	0	0	(5–40)					
Bilirubin	36 (95%)	2	0	0	0	(23–40)					
Nausea/vomiting (%) ($n = 124$ courses)	102 (82.3%)	7 (5.7)	12 (9.7)	3 (8.4)	0 —						

*Haematological toxicity grade 3–4.

evaluation and discontinuation of anti-oedema therapy [11, 16, 17].

It should be noted that in the objective response group, 3 of the 8 patients were previously treated by nitrosoureas (carmustine or lomustine). The interval between prior chemotherapy and fotemustine was short for 2 of them, respectively 3 and 4 months, leading to the possible non-crossresistance between the two nitrosoureas for these 2 patients. Patients' characteristics in these three groups showed non-comparability for two major prognostic factors, i.e. neurological status and histological diagnosis. The first group comprised a majority of anaplastic astrocytoma and transformed low grade astrocytomas (70%) associated with a good neurological presentation (90% grade 1–2). The second group had a majority of glioblastoma (60%) but with a good neurological status (100% grade 1–2). Group 3, on the other hand, included a high rate of glioblastoma (70%) with a poor neurological status (50% grade 3). Thus response rate to treatment seemed to be related to neurological impairment and histological diagnosis. Age has also been considered as a prognostic factor [18] but no difference was observed in median age between the three groups.

Overall survival curves show two populations (Fig. 2). The first was represented by groups 1 and 2 which have comparable median survival (40 and 42.5 weeks), and the second by group 3 (progressive disease) with shorter median survival (15.2 weeks). Since this is an uncontrolled study, the statistical analysis with $P < 0.001$ has no real value. These results lead to two hypotheses. Firstly, it is possible that the difference was related to a naturally slow development of disease in the former two groups compared to the latter, which is supported by the heterogeneity of prognostic factors in these groups. The second hypothesis concerns the value attributed to stabilisation of the lesions which could be regarded as a relatively good result, showing a break in the evolution process of the tumour.

Toxicities related to treatment with fotemustine were mild and similar to those observed with other nitrosoureas [15]. Myelosuppression was more frequent when prior chemotherapy had been performed. Nevertheless, in certain patients, the risk of severe myelosuppresion was unpredictable and required monitoring of haematological parameters 5 or 6 weeks after the first infusion, especially in patients previously treated with nitrosourea chemotherapy.

In the management of this disease where there is a poor prognosis, it has been suggested that chemotherapy (e.g. carmustine) might be more effective in recurrent disease than at the time of presentation of the original neoplasm [2]. Taking

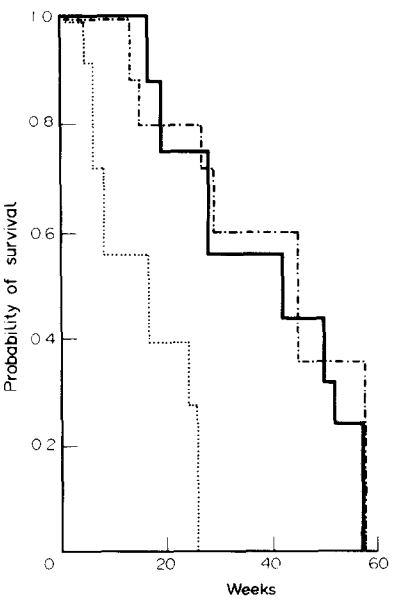

Fig. 2. Overall survival curves: group 1 = objective response (———), group 2 = stabilisation (– – – –) and group 3 = failure to respond (· · · · · · · · · · · ·). Kaplan-Meier method and logrank test.

this into consideration, it would appear that fotemustine, with a short and original treatment plan and an encouraging rate of objective response and stabilisation (74%) of lesions, may be proposed as safe chemotherapy in the outpatient management of recurrent malignant brain tumour.

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Phase I Trial of Recombinant Human Tumour Necrosis Factor α in Patients with Advanced Malignancy

Heinold Gamm, Albrecht Lindemann, Roland Mertelsmann and Friedhelm Herrmann

A phase I clinical trial was conducted with recombinant human tumour necrosis factor alpha (rhTNF-α) in 62 patients with advanced malignancy refractory to previous standard therapy. rhTNF-α was given as a 30 min infusion twice a day at 6 h intervals. A total of 10 different dose levels was escalated in cohorts of 6 patients ranging from 2.5 to 200 μg/m² twice a day for 5 days every second week for a total of 8 weeks followed by a 4-week observation period. Major side-effects of TNF-α therapy, seen in almost all patients studied, were fever and chills. As dose-limiting side-effects hypotension and liver toxicity were recorded in 4 of 5 patients treated with 200 μg/m² twice a day. Pharmacokinetic studies revealed a TNF-α serum half-life of 13 to 25 min, a dose-dependent decrease in TNF clearance, and a dose-dependent increase in the area under the time/concentration curve. No anti-TNF-α antibodies could be detected, except in 1 patient. Tumour response to TNF treatment was poor. Only in 3 of 57 evaluable patients was partial tumour regression observed.
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INTRODUCTION

TUMOUR NECROSIS FACTOR (TNF) was first identified by Carswell and coworkers [1] in 1975 as an antitumour activity found in the serum of BCG or *Clostridium parvum* primed animals upon treatment with endotoxin. In the first preclinical studies partly purified TNF caused not only a haemorrhagic tumour necrosis in the transplantable Meth A sarcoma model of mice, but also had *in vitro* antitumour activity against a broad spectrum of human tumour cell lines including human leukaemia lines [2–5], but not against diploid fibroblasts.

Tumour necrosis factor comes in two forms: TNF-α—a product of a variety of different cells including T-cells, B-