Second-line chemotherapy with dacarbazine and fotemustine in nitrosourea-pretreated patients with recurrent glioblastoma multiforme

Barbara Fazeny-Dörner[a], Mario Veitl[b], Catharina Wenzel[a], Maria Piribauer[a], Karl Rössler[c], Karin Dieckmann[d], Karl Ungersböck[c] and Christine Marosi[a]

The aim of this study was to assess the efficacy and toxicity of a combination of dacarbazine (D) and fotemustine (F) administered to a homogenous group of patients with recurrent or progressive glioblastoma multiforme (GBM). Thirty-one patients with computed tomography or magnetic resonance imaging scan evidence of recurrent or progressive GBM after first-line chemotherapy with nitrosoureas as well as radiation therapy were given a combination of D (200 mg/m^2) and F (100 mg/m^2). At 30 min after termination of D administration, F was given over 60 min. Treatment was performed in an outpatient setting every 21 days. A total of 140 cycles (range 1–12 cycles; median 4 cycles) was administered. One partial response (3%) lasting for 11 weeks was observed. Sixteen (52%) patients reached stable disease lasting between 7 and 94 weeks. Median survival from start of the D/F combination was 45 (range 10–150) weeks. Median time to progression was 17 (3–101) weeks for all patients. Major toxicity was myelosuppression resulting in exclusion from study in seven (23%) patients [due to thrombocytopenia common toxicity criteria (CTC) grade 2 persisting longer than 3 weeks in three patients, due to thrombocytopenia CTC grade $\geq$ 3 in three and due to leukopenia CTC grade 3 in one patient]. No other toxicity than alopecia occurred. We conclude that the D/F combination is a well-tolerated second-line regimen and can be administered in a complete outpatient setting. D/F shows efficacy even in nitrosourea-pretreated patients and justifies further investigation. *Anti-Cancer Drugs* 14:437–442 © 2003 Lippincott Williams & Wilkins.

Anti-Cancer Drugs. 2003, 14:437–442

Keywords: chemotherapy, dacarbazine, fotemustine, glioblastoma, nitrosourea pretreatment, recurrent gliomas, survival

[a]Clinical Division of Oncology and Ludwig Boltzmann Institute for Clinical Experimental Oncology, Department of Medicine I, [b]Clinical Institute for Medical and Chemical Laboratory Diagnostics, Clinical Chemistry, [c]Department of Neurosurgery and [d]Department for Radiooncology, University of Vienna, Vienna, Austria.

Correspondence to B. Fazeny-Dörner, Department of Medicine I/Oncology, Ludwig Boltzmann Institute for Clinical Experimental Oncology, University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria.
Tel: +43 1 40400 4457; fax: +43 1 2198963;
e-mail: barbara.doerner@chello.at

Received 28 December 2002 **Revised form accepted** 28 March 2003

Introduction

After failure of standard treatment, therapeutic options in recurrent or progressive glioblastoma multiforme (GBM) are limited. The value of second-line chemotherapy is still unclear due to the small number of strictly defined recurrent or progressive GBM included into studies [1,2]. Additionally, it is commonly accepted that no benefit can be expected with a nitrosourea-containing second-line therapy when patients have received a nitrosourea-based first-line pretreatment [3,4].

Median survival with second-line chemotherapy in strictly defined recurrent or progressive GBM is 28 weeks, ranging from 15 to 45 weeks [3,5–14]. In comparison to monotherapies, some multiagent treatment modalities yielded better response rates; however, often at the price of substantial toxicity [3,5–9,14]. Currently, the substance investigated particularly for treatment of GBM is temozolomide, yielding median survivals of 5.4 months in monotherapy and 10.4 months in combination therapy in the second-line therapy setting [5,8].

In our present study, we concentrated on a traditional imidazotetrazine derivate, dacarbazine (D), in combination with fotemustine (F), based on the following rationale. D is a well-tolerated imidazotetrazine derivate (a synthetic analog of the naturally occurring purine precursor *E*-amino-1H-imidazole-4-carboxamide) with proven efficacy in recurrent gliomas [15]. Furthermore, a synergistic effect among the combination of D and F was observed in melanoma cell lines in patients with disseminated malignant melanoma and recurrent GBM [16–18]. F [diethyl 1-(3-(2 chloroethyl)-3-nitrosoureido) ethyl phosphonate] is an alkylating agent characterized by the grafting of a phosphonoalanine group onto the nitrosourea radical with consequent high lipophilia and a high brain permeability coefficient. The improved diffusion through the cell membrane and the blood–brain barrier yields favorable tissue distribution in cerebral

0959-4973 © 2003 Lippincott Williams & Wilkins DOI: 10.1097/01.cad.0000078734.65608.f6

tumor lesions [19]. F yielded a 26% response rate in recurrent malignant gliomas [20] and response rates of 25–28% in patients with cerebral metastases of malignant melanoma [21,22]. A response rate of 27% could be achieved in patients with unresectable GBM by combining F with cisplatin and etoposide [23]. These encouraging results prompted us to investigate the D/F combination in recurrent or progressive GBM in order to assess response, survival and toxicity.

Patients and methods

Eligibility criteria

Patients with recurrent or progressive GBM after failure of first-line treatment consisting of combined radiotherapy and nitrosourea-containing chemotherapy were eligible for inclusion into this pilot study. At initial diagnosis, tumor histology had to be a neuropathologically proven GBM based on the WHO classification [24,25]. Tumor recurrence after initial total gross resection or tumor progression after subtotal resection should have been documented by computed tomography (CT) scan or magnetic resonance imaging (MRI) at the time of study entry. Patients were allowed to have subtotal tumor resection at tumor recurrence. Patients should not have received any other second-line chemotherapy or any application of D and/or F prior to initiation of D/F therapy. Patients had to be ≥ 18 years of age, they had to have a Karnofsky performance score ≥ 60 and a life expectancy of > 8 weeks. Patients were not allowed to be under concurrent cytotoxic chemotherapy due to concurrent malignancy. Other contraindications included any known psychiatric disorder, pregnant or nursing women and uncontrolled infection. Adequate contraception was mandatory. Patients had to be on a stable dose of corticosteroids (or no corticosteroids) for at least 1 week prior to study entry. Patients were required to have adequate liver function (SGOT, SGPT and alkaline phosphatase levels < 2 times institutional normal, and bilirubin levels < 1.5 mg/dl), renal (blood urea nitrogen or creatinine levels < 1.5 times of institutional normal) and bone marrow function (leukocyte count $> 3000/\mu l$ and a platelet count $> 100\,000/\mu l$) before the start of D/F therapy. All patients provided written informed consent before study entry.

Study endpoints

The study endpoints were toxicity and efficacy of the D/F regimen in second-line treatment, defined as response to chemotherapy, survival and time to progression (TTP) from start of D/F therapy.

Therapeutic protocol

Chemotherapy consisted of D in a dosage of 200 mg/m^2 (diluted in 250 ml normal saline) and F 100 mg/m^2 (diluted in 250 ml glucose 5%). Both solutions were protected from light and were given i.v. in an outpatient setting. D was administered over 30 min; to avoid burning sensations during D infusion, 500 ml normal saline were concomitantly administered. At 30 min after termination of D infusion, F was given over 60 min. Cycles were repeated every 3 weeks. Treatment was continued for a maximum of 12 cycles, unless there was progression of disease, unmanageable toxicity, fulfilled off-study criteria or withdrawal of consent.

Modification of the doses or the dose interval of D/F was made for hematologic toxicity based on the platelet and leukocyte count on the day of the planned treatment. D/F treatment was postponed up to a maximum of 3 consecutive weeks in case of thrombocytopenia from National Cancer Institute (NCI) common toxicity criteria (CTC) [26] grade 1 and/or leukopenia NCI-CTC grade 2 with weekly monitoring of blood cell counts; otherwise the doses of D/F were decreased by 25% each. Patients were excluded from further D/F treatment in case of thrombocytopenia NCI-CTC grade 2 lasting longer than 3 weeks, or immediately after thrombocytopenia or leukopenia NCI-CTC grade ≥ 3. After exclusion from study, patients were allowed to be treated individually.

Antiemetics were administered to all patients before and after chemotherapy application according to the institutional standard (ondansetron 8 mg i.v. before and after D and F therapy followed by 8 mg ondansetron orally twice daily for 2 consecutive days). Doses of glucocorticoids (dexamethasone) were adjusted according to the patients' clinical status and were given in the lowest dose necessary for neurologic stability. If the dosage was increased to offset marked clinical deterioration, this was considered when evaluating response, using the criteria of MacDonald *et al.* [27]. Concomitantly ranitidine 300 mg orally was given once daily. Anti-epileptics were administered as medically indicated.

Toxicity evaluation

Toxicity was evaluated according to the NCI-CTC during routine controls in 3-weekly intervals or, if clinically indicated, in weekly intervals [26].

Monitoring of serum chemistry and blood cell counts was performed prior to each cycle of therapy in 3-weekly intervals. In case of hematotoxicity necessitating a delay of chemotherapy application, blood counts were performed in weekly intervals.

Response evaluation

Patients were monitored with either MRI or CT scan after 4, 8 and 12 cycles of therapy in case of clinical and neurological stability, and immediately when disease progression was suspected clinically.

Response evaluation was based on MacDonald's criteria [27]. Complete response (CR) was defined as the disappearance of all measurable disease with improved neurology in the absence of corticoid therapy. Partial response (PR) was a $\geq 50\%$ decrease in tumor size with an improved or stable neurology on stable or decreased dexamethasone dose. Stable disease (SD) was a $< 50\%$ decrease or $< 25\%$ increase of the tumor size with an improved or stable neurology on stable or decreased dexamethasone dose. Progressive disease (PD) was a $> 25\%$ increase in tumor size or the appearance of new lesions. Tumor evaluation was based on the product of the two largest perpendicular diameters of the contrasting lesion.

Off-study criteria

Patients were excluded from further D/F treatment if one of the following was noted: (i) disease progression as defined above, (ii) severe and/or prolonged hematotoxicity as defined above, (iii) deteriorated and unacceptable neurologic status or (iv) withdrawal of consent.

Statistical considerations

All analyses were done by intention to treat.

The reference point for median survival was the date of the first D/F application and the endpoint was survival until death, including deaths from causes not related to the disease. TTP was estimated from the first day of D/F application to the first unfavorable event (e.g. radiographically documented tumor recurrence or progression or death). If a patient died without a scan to document disease status, the TTP was measured until documented clinical worsening or until the date of death. Survival curves and TTP curves were constructed using the Kaplan–Meier's non-parametric method; medians (and their respective 95% confidence intervals) were calculated from the Kaplan–Meier estimates [28,29]. Statistical evaluations were performed with SPSS version 10.0.7 program package. Data were analyzed as of 13 December 2001.

Results

Thirty-one patients (nine females and 22 males) with irradiated and nitrosourea-pretreated recurrent or progressive GBM were treated with D/F regimen between May 1996 and December 2001. All patients were assessable for toxicity and response.

Table 1 lists the characteristics of the 31 patients. Their median age was 50.5 (range: 27–62) years.

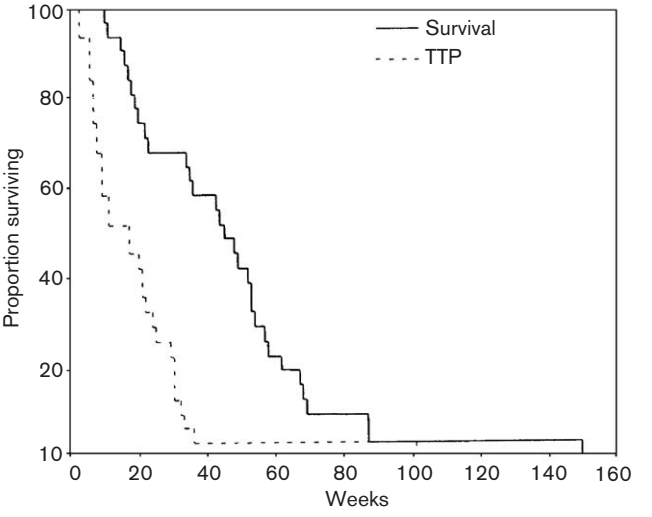
Survival

Median survival from the day of start of D/F was 45 (range 10–150) weeks (Fig. 1). Median survival from the date of initial diagnosis was 83 (range 41–169) weeks.

Table 1 Patients' characteristics at onset of therapy with D and F

Total number of patients	31
Median age (range)	50 (23–65)
Male/female	22/9
Histology of tumor at initial diagnosis and at tumor recurrence	
GBM	31
Treatment after initial diagnosis	
chemotherapy	
lomustine (CCNU) monotherapy	30
combination of lomustine, methotrexate, 5-fluorouracil, cisplatin, etoposide	1
radiotherapy (66 Gy)	31
Surgery at initial diagnosis	
total gross resection	21
subtotal resection	10
Surgery at tumor recurrence	
subtotal resection	6
Corticosteroids at entry	31
Median Karnofsky index at onset	70

Fig. 1



Survival and time to progression in patients with recurrent or progressive GBM after second-line chemotherapy with D/F.

TTP

The median TTP was 17 (range 3–101) weeks (Fig. 1).

Response

One patient (3%) showed a PR lasting for 11 weeks. Sixteen patients (52%) showed SD lasting 7–94 weeks. Three patients (10%) showed early progression after the first cycle of D/F. No CR was been observed. All patients were on dexamethasone at initiation of D/F therapy and dexamethasone could be decreased in five of nine patients with SD. The Karnofsky performance status improved at least 10% in patients with SD and did not improve in any non-responding patient.

Table 2 Synopsis of second-line clinical trials in patients with recurrent/progressive GBM following first-line chemotherapy with nitrosoureas (including trials with more than 16 GBM)

Author	No. patients with GBM out of all patients	Agent and treatment design	Median survival from onset of therapy	Median TTP from onset of therapy	Toxicity of all patients treated	Remarks
Brada *et al.* [5]	138/138	temozolomide 150–200 mg/m^2	5.4 months (23 weeks)	2.1 months (9 weeks)		6-month PFS: 18%
Brandes *et al.* [6]	28/53	procarbazine 100 mg/m^2, q30d, tamoxifen 100 mg/d	27 weeks	13 weeks	5.6% fatal pulmonary emboli	in 15 of 28 patients as third-line therapy
Galanis *et al.* [7]	23/62	mechlorethamine 3–6 mg/m^2 d1 + 8, vincristine 2 mg d1 + 8, procarbazine p.o. 100 mg/m^2 d1–14; q28d	19 weeks	11 weeks	treatment-related death: $n = 2$ (leukopenia WHO 4)	five of 23 patients had no prior chemotherapy
Groves *et al.* [8]	44/44	temozolomide 150–200 mg/m^2 d1–5, marimastat 50 mg d1–28; q56d	45 weeks	17 weeks	11% intolerable joint and tender pain	6-month PFS: 39%; 12-month PFS: 16%
Jeremic *et al.* [9]	30/38	carboplatin 300 mg/m^2 d1–3, etoposide 100 mg/m^2 d1–5, q28d;	43.5 weeks	14 weeks	nausea and emesis: 100%; 16% intractable	
Young *et al.* [10]	225/225	temozolomide 150–200 mg/m^2 d1–5, q28d versus procarbazine 125–150 mg/m^2 d1–28, q56d	6-month survival: 60 versus 44%			
Levin *et al.* [11]	19/88	thioguanine 40 mg/m^2 p.o. q6h $\times$ 12; procarbacine 50 mg/m^2 q6h $\times$ 4; dibromodulcitol 400 mg/m^2 p.o. $\times$ 1 CCNU 110 mg/m^2 p.o.	NE	5.1 months	myelotoxicity WHO 4: $n = 1$	
Poisson *et al.* [12]	24/40	carboplatin 450 mg/m^2 d1; q28d	5 months in patients with SD	4 months		
Prados *et al.* [13]	24/40	paclitaxel 210–240 mg/m^2; q21d	15 weeks	6 weeks	leukopenia NCI-CTC 3 + 4: 7%; thrombocytopenia NCI-CTC 3 + 4: 2%	
Rodriguez *et al.* [14]	37/96	procarbazine130–150 mg/m^2, d1–28; q56d	NE	30 weeks	leukopenia WHO 4: $n = 1$; thrombocytopenia WHO 4: $n = 1$	retrospective study; patients had first, second or third tumor relapse
Sanson *et al.* [3]	26/36	carboplatin 75–100 mg/m^2, d1–3; etoposide 75–100 mg/m^2, d1–3; ifosfamide 750–1500 mg/m^2, d1–3; q28d	29 weeks	12.5 weeks	hematotoxicity WHO 3 + 4: 42%; treatment-related death: $n = 1$	
This paper	31	dacarbazine 200 mg/m^2, d1; fotemustine 100 mg/m^2, d1; q21d	45 weeks	17 weeks	hematotoxicity NCI-CTC 3 + 4: 23%	

NE, not evaluable; PFS, progression-free survival.

Toxicity

Thirty-one patients received a total of 140 (range 1–12; median: 4) cycles of D/F. Major toxicity was thrombocyto- and/or leukopenia resulting in exclusion from further D/F application in seven patients (23%) after 1–7 cycles of D/F. Thrombocytopenia NCI-CTC grade 1 was observed in two patients (in one of them thrombocytopenia lasted longer than 3 weeks, resulting in a 25% dose reduction of D/F; in the other patient, therapy needed to be postponed for 1 week only); three patients experienced thrombocytopenia NCI-CTC grade 2 lasting longer than 3 weeks after 5, 6 and 7 cycles of D/F, respectively, thus leading to exclusion from study protocol.

Thrombocytopenia NCI-CTC grade 3 and 4 was observed in three patients each after 1 and 2 cycles of D/F, resulting in study exclusion. In one patient the substitution of platelets was required. However, no related bleeding complication or hematomas were observed.

Leukopenia of NCI-CTC grade 1 occurred in three patients and of CTC grade 2 in two patients, resulting in treatment delay for 1 week in one patient. Leukopenia of NCI-CTC grade 3 occurred in one patient, resulting in study exclusion. Febrile episodes were not observed and no treatment-related hospitalization or administration of granulocyte colony stimulating factors was necessary. Alopecia was evaluable in 30 patients. The most severe degree observed was NCI-CTC grade 2 ($n = 12$). Under standardized prophylactic antiemetic patients did not suffer from gastrointestinal toxicity. Main complaints of patients concerned side-effects from chronic corticosteroid medication, primarily the cushingoid appearance, myopathy and the vulnerability of the skin.

Discussion

The administration of D/F as second-line chemotherapy in nitrosourea-pretreated patients with strictly defined recurrent or progressive GBM turned out to be feasible in a complete outpatient setting and yielded a median survival of 45 weeks. Our survival and TTP results range in the upper level of those achieved in the available second-line treatment strategies, as summarized in Table 2 [3,5–14].

The efficacy of the D/F combination in nitrosourea-pretreated patients might be explained by two mechanisms: First, a synergistic effect of both substances due to the depletion of the DNA repair system, O^6-alkyltransferase, following D infusion, might contribute to a longer-lasting effect of F and, consequently, a more severe DNA damage. This effect was already described in blood lymphocytes and in the therapy of disseminated malignant melanomas [17,30]. The second explanation for the efficacy of the D and F regimen might be the good tissue distribution of F especially in cerebral tumor lesions attributable to the grafting of an aminophosphonic acid group onto the nitrosourea radical [22]. This proposed mechanism seems to be in accordance with several clinical studies demonstrating efficacy of the different imidazotetrazine derivates (procarbazine, dacarbazine, temozolomide) and fotemustine in monotherapy as well as in combination therapy [10,5,20,23,31].

The toxicity of the D/F combination is similar to the previously reported experience with these compounds [17,19,22,31]. Although strict dose-reduction steps and therapy-exclusion criteria due to hematotoxicity were foreseen in our study, hematotoxicity occurred in 23% of patients and resulted in termination of D/F application. However, we had no indication for an increased hematotoxicity associated with the antiepileptic drug valproate [32]. Apart from alopecia, no other toxicity NCI-CTC grade ≥ 3 was observed, thus making the regimen suitable for completely outward administration. This was enabled by a gapless patients' care provided by a dedicated interdisciplinary neuro-oncologic team. Contrary to Aamdal *et al.* [17], we did not observe any rapidly fatal pulmonary toxicity, which might be due to the lower D dosage used in our study.

Although it is commonly accepted that no benefit could be obtained when using another nitrosourea in second-line therapy in nitrosourea-pretreated malignant gliomas [3,4], our results suggest the efficacy of D to reverse nitrosourea resistance by depletion of the DNA repair system as already supposed by Lee *et al.* [30]. Based on the results of this study, the D/F combination has been successfully incorporated into our own first-line chemotherapy trial with 55 patients suffering from newly diagnosed GBM [31]. Therein, a median survival of 14.5 months was achieved and results are comparable with the recent first-line temozolomide study of Stupp *et al.* [33].

In conclusion, the D/F combination seems to be an efficient chemotherapy regimen in patients with recurrent or progressive GBM even pretreated with nitrosourea.

References

1 Fine HA, Dear KBG, Loeffler JS. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993; **71**:2585–2597.
2 Barda M, Sharpe G. Chemotherapy of high-grade gliomas: beginning of a new era or the end of the old? *Eur J Cancer* 1996; **13**:2193–2194.
3 Sanson M, Ameri A, Monjour A, Sahmoud T, Ronchin P, Poisson M, *et al.* Treatment of recurrent malignant supratentorial gliomas with ifosfamide, carboplatin and etoposide: a phase II study. *Eur J Cancer* 1996; **13**:2229–2235.
4 Levin VA, Wara WM, Davis RL, Vestnys P, Resser KJ, Yatsko K, *et al.* Phase III comparison of BCNU and the combination of procarbazine, CCNU, and vincristine administered after radiotherapy with hydroxyurea for malignant gliomas. *J Neurosurg* 1985; **63**:218–223.
5 Brada M, Hoang-Xuan K, Rampling R, Dietrich PY, Dirix LY, Macdonald D, *et al.* Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. *Annal Oncol* 2001; **12**:259–266.

6 Brandes AA, Ermani M, Turazzi S, Scelzi E, Berti E, Amistà P, *et al.* Procarbazine and high-dose tamoxifen as a second-line regimen in recurrent high-grade gliomas: a phase II study. *J Clin Oncol* 1999; **17**: 645–650.

7 Galanis E, Buckner JC, Burch PA, Schaefer PL, Dinapoli RP, Novotny PJ, *et al.* Phase II trial of nitrogen mustard, vincristine, and procarbazine in patients with recurrent glioma: North Central Cancer Treatment Group Results. *J Clin Oncol* 1998; **9**:2953–2958.

8 Groves MD, Puduvalli VK, Hess KR, Jaeckle KA, Peterson P, Young WK, *et al.* Phase II trial of temozolomide plus the matrix metalloproteinase inhibitor, marimastat, in recurrent and progressive glioblastoma multiforme. *J Clin Oncol* 2002; **20**:1383–1388.

9 Jeremic B, Grujicic D, Jevremovic S, Stanisavljevic B, Milojevic L, Djuric L, *et al.* Carboplatin and etoposide chemotherapy regimen for recurrent malignant glioma: a phase II study. *J Clin Oncol* 1992; **10**:1074–1077.

10 Young WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, *et al.* A phase II study of temozolomide vs. procarbazine in patients with glioblastoma at first relapse. *Br J Cancer* 2000; **83**:588–593.

11 Levin VA, Prados MD. Treatment of recurrent gliomas and metastatic brain tumors with a polydrug protocol designed to combat nitrosourea resistance. *J Clin Oncol* 1992; **10**:766–771.

12 Poisson M, Péréon Y, Chiras J, Delattre JY. Treatment of recurrent malignant supratentorial gliomas with carboplatin (CBDCA). *J Neuro-Oncol* 1991; **10**:139–144.

13 Prados MD, Schold SC, Spence AM, Berger MS, McAllister LD, Mehta MP, *et al.* Phase II study of paclitaxel in patients with recurrent malignant glioma. *J Clin Oncol* 1996; **14**:2316–2321.

14 Rodriguez LA, Prados M, Silver P, Levin VA. Reevaluation of procarbazine for the treatment of recurrent malignant central nervous system tumors. *Cancer* 1989; **64**:2420–2423.

15 Mahaley MS. Neuro-oncology index and review. *J Neuro-Oncol* 1991; **11**:85–148.

16 Fischel JL, Formento P, Etienne MC, Gioanni J, Deloffre P, Bizzari JP, *et al. In vitro* chemosensitivity testing of fotemustine (S 10036), a new antitumor nitrosourea. *Cancer Chemother Pharmacol* 1990; **25**:337–341.

17 Aamdal St, Gerard B, Bohman T, D'Incalci M. Sequential administration of dacarbazine and fotemustine in pts with disseminated malignant melanoma—an effective combination with unexpected toxicity. *Eur J Cancer* 1992; **28**:447–450.

18 Avril MF, Bonneterre J, Dalaunay M. Combination of chemotherapy of dacarbazine and fotemustine in disseminated malignant melanoma. *Cancer Chemother Pharmacol* 1990; **27**:81–84.

19 Khayat D, Lokiec F, Bizzari JP, Weil M, Meeus L, Sellami M, *et al.* Phase I clinical study of the new amino acid-linked nitrosourea S 10036, administered on a weekly schedule. *Cancer Res* 1987; **47**:6782–6785.

20 Frenay M, Giroux B, Khoury S. Phase II study of fotemustine in recurrent supratentorial malignant gliomas. *Eur J Cancer* 1991; **27**:852–856.

21 Jacquillat C, Khayat D, Banzet P. Chemotherapy by fotemustine in cerebral metastases of disseminated malignant melanoma. *Cancer Chemother Pharmacol* 1990; **25**:263–266.

22 Jacquillat C, Khayat D, Banzet P, Weil M, Fumoleau P, Avril MF, *et al.* Final report of the French multicenter phase II study of the nitrosourea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. *Cancer* 1990; **66**:1873–1878.

23 Frenay M, Leburn C, Lonjon M, Bondiau PY, Chatel M. Up-front chemotherapy with fotemustine (F)/cisplatin (CDDP)/etoposide (VP16) regimen in the treatment of 33 non-removable glioblastomas. *Eur J Cancer* 2000; **36**:1026–1031.

24 Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumors. *Brain Pathol* 1993; **3**:255–268.

25 Kleihues P, Sobin LH. World Health Organization classification of tumours. *Cancer* 2000; **88**:2887–2993.

26 National Cancer Institute. *Common Toxicity Criteria*. Bethesda, MD: National Cancer Institute, Division of Cancer Treatment; 1988.

27 MacDonald DR, Cascino TL, Schold Jr SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990; **7**:1277–1280.

28 Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Ass*1958; **53**:457–481.

29 Young KD, Menegazzi JJ, Lewis RJ. Statistical methodology: IX. Survival analysis. *Academic Emergency Med* 1999; **6**:244–249.

30 Lee SM, Thatcher N, Margison GP. O^6-alkylguanine-DNA alkytransferase depletion and regeneration in human peripheral lymphocytes following dacarbazine and fotemustine. *Cancer Res* 1991; **51**:614–623.

31 Fazeny-Dörner B, Veitl M, Wenzel C, Rössler K, Ungersböck K, Dieckmann K, *et al.* Survival with dacarbazine and fotemustine in newly diagnosed glioblastoma multiforme. *Br J Cancer* 2003; **88**:496–501.

32 Bourg V, Lebrun C, Chichmanian RM, Thomas P, Frenay M. Nitrosourea-cisplatin-based chemotherapy associated with valproate: increase of haematologic toxicity. *Annal Oncol* 2001; **12**:217–219.

33 Stupp R, Dietrich PY, Ostermann S, Kraljevic S, Pica A, Maillard I, *et al.* Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol* 2002; **20**:1375–1382.