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A Phase II Study of the Sequential Administration of Dacarbazine and Fotemustine in the Treatment of Cerebral Metastases From Malignant Melanoma

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34 patients with cerebral metastases from malignant melanoma received sequential dacarbazine at 250 mg/m^2 followed 2 h later by fotemustine at 100 mg/m^2; this was repeated on day 8. Maintenance therapy was given every 4 weeks to patients with radiological evidence of response or stable disease until a maximum response was achieved plus two more cycles. A 12% response rate was obtained for cerebral metastases, with 2 complete responses lasting 12 and 36+ months, and 2 partial responses lasting 2.5 and 3.75 months. Toxicity was mainly haematological with grade 3–4 leucopenia and thrombocytopenia in 23.5% of patients. No pulmonary toxicity was seen. This schedule of sequential dacarbazine and fotemustine has low activity against metastatic melanoma, and the response rate for cerebral metastases is not superior to that shown in other studies with single agent fotemustine, but the treatment was well tolerated and can be delivered on an outpatient basis.
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INTRODUCTION

CEREBRAL METASTASES from malignant melanoma are associated with poor prognosis; without treatment the median survival of patients is between 3 and 4 weeks, and in most treatment series, this is prolonged to 2–3 months. Dacarbazine is the most effective drug in metastatic melanoma with response rates of 15–20% [1, 2], while nitrosureas, cisplatin and vindesine have response rates of approximately 15%. Combination chemotherapy occasionally produces higher response rates but the duration of response is not prolonged over single agents [3, 4]. The effectiveness of chemotherapy is site dependent, with only cerebral or hepatic metastases responding in approximately 8% of cases [5].

Fotemustine is a chloronitrosurea and its chemical formula includes a bioiostere of alanine which facilitates cellular penetration and passage across the blood brain barrier. It is reported to have particular activity against cerebral metastases with response rates of approximately 28% [6]. Adducts formed at the O^6 guanine position are cytotoxic, and this is the initial site of fotemustine attachment. The normal guanine structure is

restored by the DNA repair enzyme, O^6 alkylguanine alkyltransferase. This repair enzyme may be depleted by repeated challenges of drugs, such as dacarbazine, that form O^6 guanine adducts, and this confers a theoretical synergism between the two compounds. The present phase II study evaluates the efficiency of sequential dacarbazine and fotemustine in cerebral metastases from malignant melanoma.

METHODS AND MATERIALS

34 patients with cerebral metastases from malignant melanoma were entered into the study. Patients were eligible if they had histologically proven metastatic melanoma, white cell count $\geq 4.0 \times 10^9$/l, haemoglobin ≥ 11 g/l, platelet count $\geq 100 \times 10^9$/l and no major disturbances in renal or hepatic biochemistry. The study group consisted of consecutive patients presenting between June 1990 and December 1993 who fulfilled these criteria, and their characteristics are summarised in Table 1. The presence of cerebral metastases was confirmed by computerised axial tomography. 5 patients had received prior chemotherapy and immunotherapy, 1 patient prior adjuvant immunotherapy and 1 patient prior radiotherapy to a non-visceral site. 20 patients had cerebral metastases only, while 12 patients had extracranial visceral metastases and 6 patients had non-visceral sites of disease in addition to cerebral metastases.

The treatment regimen consisted of an induction cycle of dacarbazine at 250 mg/m^2 in 250 ml normal saline given over 1 h, followed 2 h later by fotemustine 100 mg/m^2 in 250 ml of 5% dextrose over 1 h. This cycle was repeated on day 8. Maintenance therapy was given to patients who, 3–4 weeks later, had radiological evidence of stable disease or response and was administered every 28 days until maximum response was achieved plus two more cycles.

Tumour response was defined according to World Health Organisation criteria [7], and response assessment was made by computerised axial tomography every two maintenance cycles. A complete response was defined as the disappearance of all tumour disease for at least 4 weeks; partial response as the reduction in the sum of the products of the largest perpendicular diameter of each lesion by at least 50% for at least 4 weeks; stable disease was defined as a decrease of less than 50% in total tumour size or an increase of less than 25%.

Toxicity was assessed according to common toxicity criteria (CTC).

Table 1. Patient characteristics

Male/female	22/12 patients
Median age (range)	45.5 years (23–66)
ECOG Performance Status (0–3)	0 11 patients 1 11 patients 2 10 patients 3 2 patients
Prior chemotherapy or biochemotherapy	4 patients
Prior radiotherapy	1 patient

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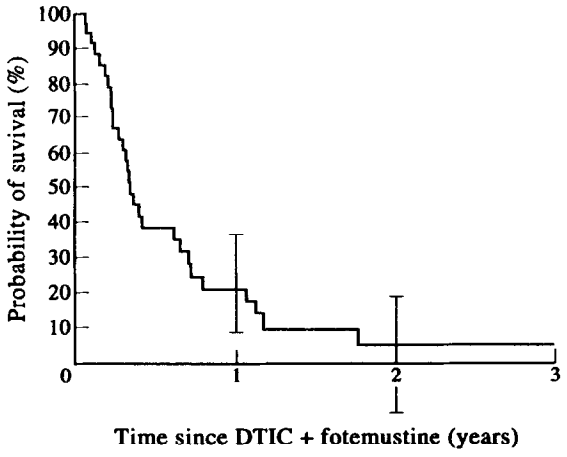

Figure 1. Overall survival in 34 patients with cerebral metastases treated with sequential dacarbazine and fotemustine.

RESULTS

21 patients received the induction cycle alone. The number of patients who received maintenance cycles were as follows: one cycle, 2 patients; two cycles, 5 patients; three cycles, 5 patients; five cycles, 1 patient. The overall response rate for cerebral metastases was 12% (4/34 patients, 95% CI: 1–21%). There were 2 complete responses and 2 partial responses. The complete responders had no other visceral sites of disease, had received no prior chemotherapy or biochemotherapy and were of ECOG performance status 0. The duration of these complete responses was 12 and 36+ months, and the duration of the partial responses was 2.5 and 3.75 months. 9 patients had stable disease while on treatment, 3 patients remain alive at 5+, 16+ and 36+ months from the time of initial diagnosis, only 1 of whom remains progression-free at 3 years. The median survival was 4.5 months (Figure 1). 12 patients had metastatic disease at visceral sites other than the brain, of which there were 2 partial responses (lung, liver) and 3 patients with stable disease (lung, liver, peritoneum). 6 patients had metastatic disease in non-visceral sites, of which there was 1 complete response, 2 partial responses and 1 patient with stable disease.

The treatment was well tolerated and delivered on an outpatient basis in all cases. There were no treatment delays to day 8 of the induction cycle, and only 2 patients had treatment delays during maintenance therapy. The major toxicities are shown in Table 2. Grade 3–4 leucopenia and thrombocytopenia occurred in 8 patients (23.5%) and 2 patients died secondary to haemorrhages into cerebral metastases during induction chemotherapy. This was associated with grade 4 thrombocytopenia in both cases, but both patients were left in the denominator for the

Table 2. Toxicities of sequential dacarbazine and fotemustine

	CTC Grade			
	0	1–2	3	4
Anaemia	25	8	1	0
Leucopenia	23	3	4	4
Thrombocytopenia	22	4	4	4
Hepatic	27	4	2	1
Nausea and vomiting	24	10	0	0

Table 3. Response rates of fotemustine alone in cerebral metastases

Source	Response/ number of patients	Response rate
Jacquillat *et al.* [6]	9/36	28%
Calabressi *et al.* [12]	1/7	14.3%
Schallreuter *et al.* [13]	3/5	60%
Overall	13/48	27%

analysis of response. Transient reversible elevation of liver enzymes, alanine and aspartate transferase were seen in 5 patients, of which only 2 had ≥ grade 2 toxicity. 10 patients experienced ≥ grade 2 nausea and vomiting which was controlled on standard antiemetics (metoclopramide and dexamethasone). No alopecia, neurological or renal toxicities were seen, and there were no infection episodes.

DISCUSSION

There are three published phase II studies with sequential administration of dacarbazine and fotemustine in the management of metastatic melanoma. Binder [8] administered cycles of dacarbazine at a dose of 200 mg/m^2 followed by fotemustine 100 mg/m^2 every 4 weeks. Lee and colleagues [9] and Gerard and colleagues [10] performed dose escalation studies with dacarbazine increasing from 400 mg/m^2 to 1000 mg/m^2, followed by fotemustine 100 mg/m^2 4 h later, every 4 weeks. This present study involves an induction cycle on days 1 and 8 of dacarbazine at 250 mg/m^2 and fotemustine 100 mg/m^2 2 h later, and maintenance cycles every 4 weeks if there is evidence of response or stable disease.

The activity of single agent fotemustine in cerebral metastatic melanoma is approximately 28% (Table 3). Our data suggests that sequential dacarbazine and fotemustine is associated with activity against metastatic melanoma, but the response rate for cerebral metastases is not superior to that obtained for fotemustine alone. This finding is supported by other studies: Avril and associates [11] compared fotemustine monotherapy to non-sequential dacarbazine and fotemustine, and obtained a similar response rate of approximately 26% for cerebral metastases in both treatment arms. The response rate obtained by our schedule of sequential dacarbazine and fotemustine was 12%. Sequential dacarbazine and fotemustine may improve responses at other visceral sites, with reported response rates of approximately 30% [9]. However, our study does not address the issue of extracranial visceral and non-visceral disease as only 12 patients had extracranial visceral sites and 6 patients had non-visceral sites of disease. Addition of dacarbazine to fotemustine is reported to increase toxicity compared with single agent fotemustine, in particular, nausea and vomiting [11], myelosuppression with increasing doses of dacarbazine [9, 10] and hepatic dysfunction occur more frequently. Fatal pulmonary toxicity was described in 6/107 patients by Gerard [10]. Pulmonary toxicity is thought to be closely related to the scheduling of these two drugs. Our treatment schedule reports 4/34 (12%) grade 4 leucopenia and thrombocytopenia, mild nausea and vomiting, and no clinical evidence of pulmonary toxicity. The response and toxicity data in our study suggest that the sequencing of dacarbazine followed 2 h later by fotemustine does not result in a depletion of the repair enzyme O^6 alkylguanine transferase, since the response rate is much lower than the 27–30% reported when the drugs are scheduled with fotemustine being delivered 4 h after dacarbazine [9, 10]. In these circumstances, toxicity, particularly pneumonitis, becomes apparent, further suggesting that the depletion of O^6 alkylguanine transferase is dependent on specific scheduling.

In conclusion, this study confirms that responses are seen with dacarbazine and fotemustine in patients with metastatic melanoma. However, this combination does not appear to improve response rates in cerebral metastases compared with single agent fotemustine.

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