Eur J Cancer, Vol. 28A, No. 11, pp. 1814–1816, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Fotemustine plus Dacarbazine in Advanced Stage III Malignant Melanoma

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19 patients with advanced malignant melanoma were treated with fotemustine and dacarbazine. Data recorded and available for evaluation in all patients included clinical and histopathological parameters of the primary melanoma, blood chemistry, blood cell count, chest X-ray, ultrasound and bone scan for initial staging of the site of metastases and follow-up during treatment. Dosage was fotemustine 100 mg/m² and dacarbazine 200 mg/m² intravenously twice monthly on days 1 and 8, repeated for a maximum of six courses. There were two complete and three partial responses in 5/19 patients (26%), and 8 patients (42%) had stable disease. 6 (32%) patients had no response. Median length of complete and partial responses was 3.9 months, and that of stable disease 4.2 months. The main side-effects were thrombocytopenia in 10 patients (53%) and nausea in 6 (32%); the nausea was easily suppressed by ondasetron. Thus, fotemustine–dacarbazine may be new treatment in advanced melanoma.
Eur J Cancer, Vol. 28A, No. 11, pp. 1814–1816, 1992.

INTRODUCTION

ADVANCED MALIGNANT melanoma exhibits one of the poorest prognoses among all human malignant neoplasms [1] and curative treatment in patients with disseminated disease is extremely rare [2]. Among the most active drugs investigated, dacarbazine (DTIC) has been reported to achieve response rates of 15–25%, with a median response duration of 2–4 months [3, 4]. Numerous studies have been performed to improve these response rates by combining dacarbazine with chemotherapeutic agents of different groups, thus exhibiting different effects on the cell cycle of malignant cells; thus, response rates of up to 50% have been reported [5], no combination regimen containing one or more of these agents has been demonstrated to be superior to the single agent dacarbazine in randomised trials [1, 4, 6]. Nevertheless, dacarbazine in combination with numerous nitrosourea derivatives has shown the most promising results [6]. We hereby report the results of a study using the nitrosourea derivative fotemustine in combination with dacarbazine.

PATIENTS AND METHODS

The study involved 19 patients with advanced malignant melanoma. Inclusion criteria were as follows: histologically confirmed malignant melanoma of primary and/or metastatic lesions, 20–75 years of age, absence of concurrent malignancies and a Karnofsky's performance status of $\geq$ 70%. Patients with inadequate bone marrow function (leucocytes $\leq$ 5000/μl, platelets $\leq$ 100 000/μl) prior to treatment were excluded. For pretreatment evaluation a detailed medical history, physical and neurological examination, complete blood cell count, renal and liver blood chemistry, electrocardiography, chest X-ray, computed tomography (CT) scan, bone scan, abdomen ultrasound and sonography of the axillary and inguinal lymph nodes were performed. Individually, biopsy of metastases was done.

When therapy was started all patients presented with progressively growing disease and none of the patients had received any chemo- and/or immunotherapy within a period of 3 months prior to treatment with dacarbazine–fotemustine. However, 2 patients had previously received dacarbazine mono-chemotherapy and 2 patients had received interferon alfa prior to treatment with dacarbazine–fotemustine, respectively.

The treatment comprised dacarbazine (Dome) 200 mg/m² and fotemustine (Muphoran, Servier) 100 mg/m² after an interval of 2 h intravenously twice monthly on days 1 and 8. Treatment was repeated for a maximum of six courses. Dosage of both drugs was adjusted according to World Health Organization (WHO) rating scale for acute and subacute toxic side-effects [7]. Informed consent was obtained in all patients.

According to protocol design all patients were investigated monthly for evaluation of tumour development, including CT scan, sonography and bone scan if appropriate. Complete pretreatment re-evaluation as listed above was repeated every 2 months. Tumour response was documented through clinical re-evaluation of all initial sites and was classified according to WHO criteria [7].

Complete response (CR) was defined as the total disappearance of all known disease for at least 4 weeks. Partial response (PR) was defined as a $\geq$ 50% decrease measured in the most clearly evaluable indicator lesion for a minimum of 4 weeks without appearance of new lesions. Duration of CR and PR was measured from the time of evidence of response to the date of progression. Stable disease (SD) was defined as a decrease in total tumour volume up to 50% for a minimum of 4 weeks. At least a 25% or more increase in the size of measurable lesions or the appearance of new lesions was considered as progressive disease (PD).

Statistics

Data of patients were stored and analysed using an IBM mainframe computer with the aid of SAS statistical package [8]

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Revised 27 Mar. 1992; accepted 31 Mar. 1992.

Table 1. Characteristics of patients with metastatic melanoma treatment with dacarbazine–fotemustine

	No. of patients 19	
Sex		
Male	13	(68%)
Female	6	(32%)
Median age (yrs)	69	
Min	36	
Max	79	
Sites of metastases		
Lung	13	(68%)
Brain	4	(21%)
Bone	2	(11%)
Distant lymph nodes	9	(47%)
Liver	5	(26%)
Spleen	1	(5%)
Intestines	1	(5%)
Cutaneous/subcutaneous	6	(32%)
No. of metastatic sites		
1	6	(32%)
2	8	(42%)
> = 3	5	(26%)

All per cent values are rounded to the nearest integer.

using univariate statistical methods [9]. All per cent values are rounded to the nearest integer.

RESULTS

Clinical efficacy

The main characteristics of the 19 patients are listed in Table 1. There were 13 men and 6 women, with a median age of 69 years (range 36–79). The median Karnowsky's performance status was 85% (range 70–90) at study entry.

Pulmonary metastases were diagnosed in 13 patients (68%), distant metastatic lymph nodes in 9 (47%) and visceral metastases in 6 patients (32%) (see Table 1); 3 patients (16%) presented with brain metastases and 2 patients (11%) with bone metastases. Distant cutaneous/subcutaneous metastases were seen in 6 patients (32%). As shown in Table 1, 6 patients (32%) presented initially with one site of distant metastases, 8 patients (42%) with two sites and 5 patients (26%) with ≥ three sites of metastatic disease.

A mean number of 4.8 cycles (range 3–6) of fotemustine–dacarbazine were administered. In patients who achieved an objective response, regression of metastases occurred within a mean period of 1.5 months.

Objective responses (CR+PR) were obtained in 5 patients (26%), whereas in 8 patients (42%) SD was observed. However, in 6 patients (32%) no response could be achieved (Table 2).

Table 2. Responses to fotemustine–dacarbazine

Response	CR	PR	SD	PD	Total
No. of patients (%)	2 (11)	3 (16)	8 (42)	6 (32)	19

Table 3. Duration of responses treatment with fotemustine–dacarbazine

Month	CR+PR	SD
2	—	2
3	1	3
4	1	2
>=5	3	1
Median	3.9	4.2

Pulmonary lesions as well as visceral disease showed the highest response rate (21%). No responses were seen in patients with brain metastases.

3 of the 5 patients achieving objective response (CR+PR) had metastatic involvement of only one site. The median duration of PRs was 3.9 months (Table 3). In 1 patient with a metastatic involvement at three sites (lung, visceral disease and distant lymph node involvement) a CR could be obtained and the patient now has been free of disease for a period of 6 months. In 8 (42%) out of 19 patients a SD was obtained. The median duration of SD was 4.2 months (Table 3).

Toxicity

Toxicity was mainly of haematological nature and was characterised by delayed thrombocytopenia and leukopenia. Temporary withdrawal of fotemustine–dacarbazine therapy was necessary in 10 patients (53%) for transient thrombocytopenia ranging from WHO grade 2 to grade 4 toxicity (Table 4). WHO grade 2 leucocytopenia was observed in 5 patients (26%) and in 4 patients (21%) WHO grade 1 anaemia was observed.

Treatment-related thrombocytopenia appeared usually after the first two courses of treatment. In 1 patient treatment-related thrombocytopenia was the cause for haemorrhages. The maximum duration of withdrawal of fotemustine–dacarbazine in patients with thrombocytopenia was 5 weeks. In none of the patients was substitution of thrombocytes necessary.

In contrast to the haematological alterations mentioned above, elevation in liver function enzymes was also observed but was transient and always reversible. The most pronounced elevation was observed in lactate dehydrogenase (LDH) and alkaline phosphatase (AP) in 4 patients (21%). Serum alanine aminotransferase (ALAT) and serum aspartate aminotransferase (ASAT) did not change significantly during treatment. In none of the patients was WHO grade 4 liver function toxicity reached. Renal function tests remained unchanged by fotemustine–dacarbazine therapy. Gastro-intestinal toxicity was mild to moderate in 5 patients (26%) and was easily managed by administration of standard antiemetic therapy (Ondasetron, Zofran, Glaxo) [10]. None of the patients developed pulmonary side-effects (i.e. pulmonary fibrosis) during the course of therapy.

Table 4. Haematological toxicity treatment with fotemustine–dacarbazine

WHO grade	0	1	2	3	4	Total
Leucocytes	14	—	5	—	—	19
Haemoglobin	15	4	—	—	—	19
Thrombocytes	9	—	2	5	3	19

DISCUSSION

At present, chemotherapy in metastatic malignant melanoma remains disappointing with the permanent need for new treatment modalities.

Among the panel of cytotoxic agents used in the treatment of metastatic melanoma, dacarbazine applied as a single agent has revealed the highest response rates [3, 4, 11–14]. However, dacarbazine has shown response rates of only 15–25% [6, 11, 15]. It has been demonstrated that the combination of dacarbazine and fotemustine after an interval of 2–3 h exhibits higher response rates than the application of single agents [16]. This effect may be due to the methylation of the O^6 alkyltransferase by saturating the enzyme with dacarbazine prior to fotemustine administration [16, 17]. In our study the application of the nitrosourea derivative fotemustine and dacarbazine in a 3-week interval scheme resulted in an overall response rate (CR+PR) of 26%, and in 42% of the patients SD was achieved. In 2 patients a CR was observed and was still present after a period of 5 months. Stabilisation or decrease of metastatic volume up to 40% was particularly observed in patients with multiple site involvement. Out of the non-responding 6 patients, 4 (21%) presented initially with widespread brain metastases. This finding is in contrast to various reports [18–22] describing the efficacy of nitrosourea derivatives in brain metastases. Similarly, bone metastases in 2 patients (11%) also did not respond to fotemustine–dacarbazine therapy.

Toxicity was generally mild to moderate and severe with regard to thrombocytopenia in the patients treated with fotemustine and dacarbazine combination chemotherapy. The main side-effect was myelosuppression, especially transient thrombocytopenia [16, 17]. With regard to disturbance of liver function the most pronounced elevation was observed in LDH and AP in 4 patients (21%); ALAT and ASAT did not change significantly during treatment. In a cumulative of 96 cycles of fotemustine–dacarbazine no life-threatening side-effects and particularly no pulmonary side-effects were observed. This is in contrast to other studies reporting on the occurrence of pulmonary toxicity after the sequential application of dacarbazine–fotemustine [16, 23].

We fully recognise the limitation of statistical analysis of small sample sizes. (66% confidence interval of 5 out of 19 objective responses: 16.2–36.4%.) However, our study shows that the combination chemotherapy with fotemustine–dacarbazine is active against disseminated disease of malignant melanoma with an overall response rate of 26%; in 42% of the patients stabilisation of disease was observed. Further studies of fotemustine–dacarbazine combination chemotherapy in patients with advanced malignant melanoma are therefore warranted.

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