Pergamon

European Journal of Cancer, Vol. 34, No. 13, pp. 2129–2131, 1998

Printed in Great Britain
0959-8049/98/$—see front matter

PII: S0959-8049(98)00316-5

Short Communication

Treatment of Metastatic Malignant Melanoma with Dacarbazine Plus Fotemustine

A. Seeber,[1,2] M. Binder,[1] A. Steiner,[2] K. Wolff[1] and H. Pehamberger[1]

[1]Department of Dermatology, University of Vienna Medical School, Division of General Dermatology, Waehringer Guertel; [2]Division of Dermatology, Donauspital/SMZ-Ost; and [3]Division of Dermatology, Wilhelminenspital, Vienna, Austria

Despite the poor prognosis of metastatic malignant melanoma, polychemotherapy with dacarbazine and fotemustine has shown promising results in several studies. We report on the clinical efficacy of a new sequential administration regimen with dacarbazine at a dose of 200 mg/m^2 followed 24 h later by fotemustine 100 mg/m^2 every 4 weeks in 63 patients with metastatic melanoma. A complete response was noted in 3 patients (5%), a partial response in 4 patients (6%), stable disease in 33 patients (5%) and progressive disease in 23 patients (37%). The duration of the 3 complete responses was 5, 14+ and 60+ months, for the 4 partial responses, 3, 4, 6 and 13 months. The median duration for stable disease was 4 months. The best response rates were obtained for lung and lymph node metastases. Toxicity was mild and mainly limited to haematological without pulmonary side-effects. Although there was a relatively low objective response rate, this chemotherapy regimen as a palliative treatment, is potentially valuable for patients with progressive stage IV melanoma. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: malignant melanoma, metastatic disease, chemotherapy, dacarbazine
Eur J Cancer, Vol. 34, No. 13, pp. 2129–2131, 1998

INTRODUCTION

THE PROGNOSIS of metastatic malignant melanoma is poor and treatment with chemotherapy is highly unsatisfactory. Dacarbazine (DTIC) is the most effective single agent with a response rate of up to 20%. Hence, various combination chemotherapy regimens have been tested in an attempt to improve the response rate [1]. Of these the polychemotherapy with DTIC and fotemustine has shown promising results, but the sequential scheduling of these drugs has been complicated by lung toxicity [2–4]. We report the clinical response of an adjusted sequential combination treatment with DTIC at a dose of 200 mg/m^2 followed 24 h later by fotemustine 100 mg/m^2 every 4 weeks in 63 unselected patients with metastatic melanoma.

PATIENTS AND METHODS

74 patients with progressive, metastatic malignant melanoma were treated with DTIC at a dose of 200 mg/m^2 followed 24 h later by fotemustine 100 mg/m^2 intravenously. Therapy was repeated every 4 weeks for up to 10 courses or until progression. Response was assessed monthly by clinical examination, complete blood cell count, renal and liver blood chemistry. Chest X-ray, computed tomography scan, bone scan, abdomen ultrasound and sonography of the axillary and inguinal lymph nodes were performed every 2 months for the evaluation of metastasis.

According to the World Health Organisation criteria [5] complete response (CR) was defined as the disappearance of all tumour disease for at least 4 weeks; partial response as the reduction $\geq 50\%$ measured in the most clearly evaluable indicator lesion for at least 4 weeks without appearance of new lesions; stable disease was defined as a reduction of less than 50% in total tumour mass or an increase of less than 25%; and progressive disease as an increase of over 25% in the size of measurable lesions or the appearance of new lesions.

Toxicity was assessed according to common toxicity criteria (CTC) [6].

RESULTS

Out of 74 patients treated, 63 were evaluable for response. 43 were men and 20 women aged from 27 to 82 years (median

Correspondence to H. Pehamberger.
Received 18 Feb. 1998; revised and accepted 6 Aug. 1998.

age 57 years). 29 of the 63 patients were pretreated. 15 patients had received immunotherapy with interferon alpha and 14 patients had prior chemotherapy (4 patients with carmustine, 5 patients with DTIC, 3 patients with cisplatin/carboplatin and 2 patients with cisplatin/tamoxifen). Of these patients, 7 patients had more than one prior therapies, including two patients who had received radiotherapy and one patient who had received isolated limb perfusion with melphalan. Characteristics of the patients are summarised in Table 1.

We observed 3 CRs (5%), and 4 PRs (6%) for an overall response rate of 11%. The duration of the CRs was 5, 14+ and 60+ months, the duration of the PRs was 3, 4, 6, and 13 months. 33 patients (52%) had SD with a median duration of 4 months (range 2–28 months).

The best response was achieved for lung metastases with a 25% response rate and SD in 75%, followed by lymph node metastases with 10% response and 80% SD. 3 out of 29 patients with multiple metastases experienced a PR, two of them had lung and lymph node metastases, the third had metastases on the skin, lymph nodes and the liver. No objective response was seen in liver, bone and brain metastases (Table 2).

Of the 29 patients with prior therapy, 2 patients with multiple metastases had a PR (7%). Of the 34 patients with no prior therapy, 3 had a CR, and 2 a PR, with apparently a better response (15%) than those who had received previous therapy.

The chemotherapy was generally well tolerated (Table 3). Only 9 patients (14%) experienced a grade III–IV thrombocytopenia or leucopenia leading to treatment delay in 5 patients. Nausea was mild and was easily controlled by standard anti-emetic therapy. A significant rise of liver enzymes was seen in only one patient. There was no pulmonary toxicity.

Survival analysis by Kaplan–Meier estimator (Figure 1) revealed a statistically significant longer survival for patients with objective response (log-rank test $P < 0.005$). Difference in, survival between patients with SD and PD was also statistically significant ($P < 0.01$).

Table 1. *Patients' characteristics*

	n (%)
Sex	
Male	43 (68)
Female	20 (32)
Median age (range)	57 (27–82) years
Median No. of courses (range)	4 (1–10) courses
Prior therapy	29 (46)
Immunotherapy	15 (24)
Chemotherapy	14 (22)
Metastases	
Skin	13 (21)
Lymph nodes	28 (44)
Lung	26 (41)
Liver	19 (30)
Brain	17 (27)
Bone	5 (8)
Others	5 (8)
Metastatic sites	
1 site	34 (54)
2 sites	17 (27)
≥ 3 sites	12 (19)

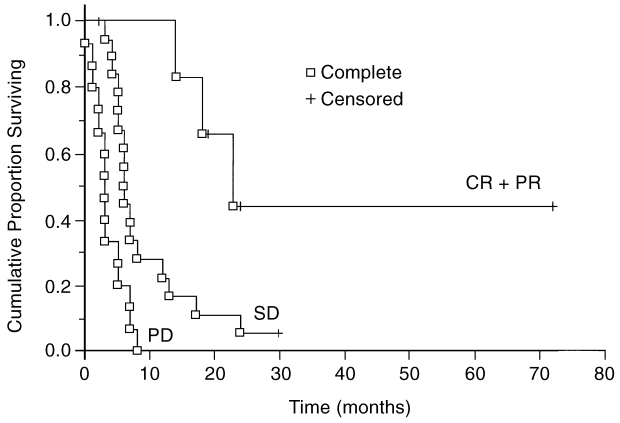

Figure 1. Overall survival according to response to chemotherapy. Kaplan–Meier. CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

DISCUSSION

Following the introduction of fotemustine, a new nitrosurea with special activity on brain metastases, for the treatment of disseminated malignant melanoma [6], the combination of fotemustine with the most effective single agent DTIC has been tested in several studies using two main schedules [2–4, 6]. The alternating combination of fotemustine and DTIC with fotemustine given on days 1 and 8 and DTIC given on days 15–18 or 2–5 yielded objective response rates of 27.2%, 11.7% and 30.8%, respectively, indicating that it could be particularly effective in brain metastases [2, 7, 8]. The sequential administration regimen where DTIC was given 2–4 h before fotemustine intended to achieve a synergistic effect by depletion of the O^6 alkyltransferase (O^6 AT), which acts as a factor in cellular resistance to chemotherapeutic agents [9]. This sequential regimen has been used

Table 2. *Treatment response of sequential dacarbazine and fotemustine*

	Tumour response			
	PD (%)	SD (%)	PR (%)	CR (%)
All ($n = 63$)	23 (37)	33 (52)	4 (6)	3 (5)
Skin ($n = 5$)	3 (60)	1 (20)	1 (20)	0
Lymph node ($n = 10$)	1 (10)	8 (80)	0	1 (10)
Lung ($n = 8$)	0	6 (75)	0	2 (25)
Liver ($n = 4$)	1 (25)	3 (75)	0	0
Brain ($n = 7$)	4 (57)	3 (43)	0	0
Multiple ($n = 29$)	14 (48)	12 (41)	3 (10)	0

PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

Table 3. *Toxicities (%) of sequential dacarbazine and fotemustine*

	CTC Grade				
	0	1	2	3	4
Anaemia	40	12	11	0	0
Leucopenia	32	16	12	3	0
Thrombocytopenia	39	10	7	5	2
Hepatic	60	2	1	0	0
Nausea	43	13	6	1	0

in several studies [3, 4, 10–12] with a good objective response of 33%, 26%, 30%, 27% and 12%, respectively. However, this schedule appears compromised by unexpected lung toxicity in approximately 5% of patients [3, 11]. Lung toxicity is considered to be related to the decrease of the O^6 AT and the glutathione system [11]. It has not been observed with either DTIC or fotemustine as single agent therapy nor in the alternating combination regimen. Depletion of O^6AT occurs with nadir levels at 2–6 h after DTIC administration and its extent is patient, dosage and cycle dependent [9, 10].

To avoid lung toxicity, we used an adjusted sequential regimen. With the intention of decreasing the extent of O^6 AT depletion, we prolonged the interval between the administration of DTIC and fotemustine to 24 h. As it has been shown that increasing doses of DTIC increases the extent of O^6AT depletion [9], leading to greater toxicity without statistical significant higher response or difference in median survival [10], we also reduced the dose of DTIC to 200 mg/m^2 every 4 weeks. We therefore administered DTIC 200 mg/m^2 followed 24 h later by fotemustine 100 mg/m^2 every 4 weeks.

Whilst lung toxicity was not observed in our regimen, the objective response rate of 11% seems low compared with the results reported so far or even with DTIC alone [2–6]. However, our results showed a stabilisation of the disease in more than 50% of the patients with a median duration of 4 months. Although some of these cases may represent only a slowing of tumour progression, 15 out of 33 patients (45%) had stable disease from 6 to 28 months duration, indicating long-term stable disease.

Furthermore our patients were unselected with advanced, progressive stage IV melanoma and a high rate of previous therapy (46%). It has been shown that selected patients for clinical trials with low tumour loads respond better to chemotherapy than unselected patients [13]. Previous therapy may also influence treatment response. Studies reporting high response rates had well selected patients with previous treatment in less than 15% of cases [2, 3, 11, 12]. In contrast, Merimsky and associates reported an objective response in only 11.7% of patients, 55% of whom had had pretreatment [7]. Our response rate, therefore, may better reflect the daily experience of the oncologist searching for palliation in advanced melanoma patients.

The clinical efficacy reported for the sequential use of DTIC and fotemustine on lung metastases and non-visceral metastases was confirmed by our treatment schedule which achieved an objective response in 25% of lung metastases (25% CR) and in 30% of non-visceral metastases (20% PR, 10% CR). There was no objective response in brain metastases confirming the low response of brain metastases to sequential combination treatment. Thus, monotherapy with fotemustine or the alternating combination regimen may be a better choice for patients with brain metastases.

Therapy was well tolerated. Grade 4 thrombocytopenia was seen in only 2 patients and grade 3 nausea in only 1 patient, lower rates than reported for other combination therapy regimens [2, 11]. In contrast to the pulmonary toxicity reported in approximately 5% of patients after the sequential administration of DTIC and fotemustine [3, 11], we observed no lung toxicity in our patients. As side-effects mainly relate to the dosage of DTIC, it is not clear whether the lack of pulmonary side-effects was due to the lower dosage of DTIC or the different scheduling of the two drugs.

Objective remission after chemotherapy has no proven impact on the length of survival [13]. However, survival analysis of our data by Kaplan–Maier estimator suggests that an objective response may be associated with a longer survival, although due to the limited patient number, this result should be treated with caution.

In conclusion, our data demonstrated that the sequential administration of fotemustine 24 h after DTIC has an acceptable clinical efficacy, especially in lung and non-visceral metastases with only minimal haematological side-effects and no lung toxicity. These results were achieved in unselected patients. The regimen described therefore seems to be a valuable palliative treatment in patients with advanced, progressive stage IV melanoma that contributes to increase the quality of life in these incurable patients.

1. Ho RC. Medical management of stage IV malignant melanoma. Medical issues. *Cancer* 1995, **75**(Suppl.), 735–741.
2. Avril MF, Bonneterre J, Cupissol D, *et al.* Fotemustine and dacarbazine for malignant melanoma. *Eur J Cancer* 1992, **28A**, 1807–1811.
3. Amdal S, Gerard B, Bohman T, D'Incalci M. Sequential administration of dacarbazine and fotemustine in patients with disseminated malignant melanoma—an effective combination with unexpected toxicity. *Eur J Cancer* 1992, **28A**, 447–450.
4. Binder M, Winkler A, Dorffner R, Glebowski E, Wolff K, Pehamberger H. Fotemustine plus dacarbazine in advanced stage III malignant melanoma. *Eur J Cancer* 1992, **28A**, 1814–1816.
5. WHO Handbook for Reporting Results of Cancer Treatment. World Health Organisation, Geneva, 1979.
6. Jacquillat C, Khayat D, Banzet P, *et al.* Final report of the French multicenter phase II study of the nitrosurea fotemustine in 153 evaluable patients with disseminated malignant melanoma including patients with cerebral metastases. *Cancer* 1990, **66**, 1873–1878.
7. Merimsky O, Inbar M, Chaitchik S. Fotemustine and DTIC combination in patients with disseminated malignant melanoma. *Am J Clin Oncol* 1992, **15**, 84–86.
8. Oliver V, Aliaga A, Lopez Lpez JJ, *et al.* Long-term complete remissions in patients with disseminated melanoma treated by fotemustine and dacarbazine. *Eur J Cancer* 1993, **29A**, 287.
9. Lee SM, Thatcher N, Dougal M, Margison GP. Dosage and cycle effects of dacarbazine (DTIC) and fotemustine on O6-alkylguanine-DNA alkyltransferase in human peripheral blood mononuclear cells. *Br J Cancer* 1993, **67**, 216–221.
10. Lee SM, Margison GP, Woodcock AA, Thatcher N. Sequential administration of varying doses of dacarbazine and fotemustine in advanced malignant melanoma. *Br J Cancer* 1993, **67**, 1356–1360.
11. Gerard B, Aamdal S, Lee SM, *et al.* Activity and unexpected lung toxicity of the sequential administration of two alkylating agents—dacarbazine and fotemustine—in patients with melanoma. *Eur J Cancer* 1993, **29A**, 711–719.
12. Chang J, Atkinson H, A'Hern R, Lorentzos A, Gore ME. A phase II study of the sequential administration of dacarbazine and fotemustine in the treatment of cerebral metastases from malignant melanoma. *Eur J Cancer* 1994, **30A**, 2093–2095.
13. Kleeberg UR, Engel E, Israels P. Palliative therapy of melanoma with fotemustine. Inverse relationship between tumour load and treatment effectiveness. A multicenter phase II trial of the EORTC—Melanoma Cooperative Group (MCG). *Melanoma Res* 1995, **5**, 195–200.