Pergamon

European Journal of Cancer Vol. 33, No. 8, pp. 1326–1329, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00120-2

Short Communication

Fotemustine and Dacarbazine Plus Recombinant Interferon Alpha2a in the Treatment of Advanced Melanoma

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Forty-three consecutive patients with advanced melanoma not previously treated with cytotoxic drugs (22 of them had already received adjuvant recombinant interferon alpha2a (rIFNα2a)) were given a combination of intravenous (i.v.) fotemustine (FM), 100 mg/m^2 on day 1, and dacarbazine (DTIC), 250 mg/m^2 i.v. on days 2–5, every 3 weeks. rIFNα2a was administered at the dosage of 3 MIU subcutaneously 3 times a week until progression. Four complete and 13 partial responses were registered, for an overall response rate of 40% (95% CI, 25–56%). Activity of this regimen was similar in patients with mainly visceral (10/22, 45%) or soft tissue (6/13, 46%) involvement. The median duration of responses was 24 weeks. Median survival time was 40 weeks, with a 13% 2 year survival rate. Neutropenia and thrombocytopenia affected 67% and 51% of patients, but were of WHO grade 4 in only 2% and 5% of them, respectively. Side-effects attributable to rIFNα2a were mild and manageable. In conclusion, the combination of FM + DTIC and rIFNα2a seemed well tolerated and relatively active in patients with advanced melanoma. However, the role of rIFNα2a in affecting the long-term outcome of patients is still questionable. © **1997 Published by Elsevier Science Ltd.**

Key words: melanoma, fotemustine, dacarbazine, rIFNα2a

Eur J Cancer, Vol. 33, No. 8, pp. 1326–1329, 1997

INTRODUCTION

DACARBAZINE (DTIC) is considered an active drug for the treatment of advanced malignant melanoma producing a response rate of approximately 20%. The addition of one or more cytotoxic agents to DTIC increases the response rate in several phase II studies [1], but no randomised trials have demonstrated a significant improvement of survival after combination chemotherapy as compared to DTIC alone. The combination of DTIC plus recombinant interferon alpha 2a (rIFNα2a) has been used in phase II studies [2, 3]. Although subsequent randomised trials failed to demonstrate a survival advantage for patients treated with DTIC + rIFNα2a over DTIC alone, some authors have noted a significant prolongation of response duration and/or of time free of progression with the addition of rIFNα2a to DTIC [4, 5].

Fotemustine (FM) is a chloronitrosourea that has been demonstrated to possess activity in patients with advanced malignant melanoma. In a large multicentre trial conducted in France, a major response was reported in 24% of patients (mostly pretreated) [6]. Interestingly, activity was also observed in patients with central nervous system (CNS) metastases. A subsequent multicentre European trial confirmed an overall response of 21% [7].

Some authors obtained interesting results combining DTIC and FM in the same regimen, but the optimal doses and schedule of both drugs are undefined [8–10]. A possible relationship between response rate and dosage of DTIC combined with FM has been suggested [8], but an increased and sometimes fatal pulmonary toxicity has also been reported when DTIC was given with FM on the same day [8, 11]. Therefore, we planned a phase II study to test the combination of FM and DTIC given sequentially in 5

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Received 12 Nov. 1996; revised 17 Feb. 1997; accepted 24 Feb. 1997.

days, attempting to increase the dose intensity of both drugs by recycling the treatment every 3 weeks. Furthermore, in order to prolong the duration of responses and/or delay the progression of the disease, we administered low doses of rIFNα2a throughout the whole treatment. We report herein the activity and toxicity of this regimen.

PATIENTS AND METHODS

Selection of patients

From April 1994 to October 1995, all eligible patients affected by advanced, histologically proven melanoma were entered into this trial. Inclusion criteria were: age between 18 and 75 years, ECOG performance status ≤2, presence of measurable disease not amenable to surgery, no previous cytotoxic treatment, adequate bone marrow reserve, and normal hepatic and renal functions. Presence of CNS metastases did not represent an exclusion criterion. Patients gave their informed consent to participate in this study, which was approved by the Ethical Committee for Biological Research of the National Tumour Institute of Naples.

Work-up procedures

At entry, a complete medical history was obtained, and a physical examination (including assessment of performance status) was performed. Routine biochemical and haematological laboratory tests were carried out. The extent of the disease was evaluated by chest X-ray, liver ultrasonography and bone scintigraphy in all patients. A computed tomography (CT) scan of brain, lung, or abdomen was performed when indicated.

Treatment

Fotemustine, 100 mg/m^2, was diluted in 250 ml of 5% dextrose and infused (protected from light) over 1 h on day 1. Dacarbazine, 250 mg/m^2, was diluted in 500 ml of normal saline and administered on days 2–5. Anti-HT_3 receptors plus a loading dose of steroid were used to prevent emesis. Cycles were repeated every 3 weeks in the presence of a neutrophil count $\geq 2.0 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l. Otherwise, a 1–2 week delay was allowed to obtain bone marrow recovery. During the interval between cycles, rIFNα2a 3×10^6 IU was self-administered subcutaneously, preferably in the evening, three times a week. Paracetamol, 500 mg orally, was prescribed to prevent or attenuate any 'flu-like syndrome. A discontinuation of rIFNα2a administration was planned only in the presence of intolerable side-effects, or > grade 2 neutropenia or thrombocytopenia. Local irradiation (2 cGy/day × 5 days/week) for a total dose of 40 Gy was performed concurrently with chemotherapy in patients with CNS metastases. Patients achieving a complete response stopped their treatment after a minimum of eight cycles. These patients received a maintenance treatment with rIFNα2a alone. Patients showing partial response or unmodified disease continued to be treated until tumour progression.

Assessment of activity and toxicity

Every two courses, all initially documented lesions were reassessed to evaluate response to therapy according to WHO criteria. Duration of response was calculated from the day it was first assessed (CR) or from the starting day of therapy (PR) to appearance of progressive disease or last follow-up. Time to progression and survival were calculated from the first day of treatment to progression, death or last follow-up. Progression-free and survival curves were generated with the method of Kaplan and Meier [12] according to an *intention-to-treat analysis*, and compared by the Gehan test [13]. Toxicity was assessed by physical examination, blood cell count and biochemistry performed at each cycle of therapy. It was scored according to the WHO classification, and the worst toxicity for each patient was registered.

Statistical considerations and sample size

The response rate was the main end-point of this phase II study. According to the Simon two-stage optimal design, defining at 20% the minimum activity rate (p_0) of interest for this experimental regimen, and choosing a 40% alternative hypothesis of activity rate (p_1), with an alpha error = 0.05 and a beta error = 0.20, at least four major responses should have been registered among the first 13 patients in order to continue enrolment, and the trial could be considered positive if 13 or more responses were reported among a final series of 43 patients.

RESULTS

Activity

The characteristics of the 43 consecutive patients enrolled in the study are listed in Table 1. A total of 207 courses were administered, with a median number of 5 courses/patient (range, 1–10). Three CRs were achieved in patients with multiple soft tissue and visceral involvement, while a further CR was registered in a patient with a single mucosal localisation. 13 patients showed a PR with this treatment. All the responses were registered after two (13 cases) or four (4 cases) cycles of therapy. The other patients were classified as SD or PD. However, 3 patients died before the first planned assessment of response, and 1 patient received only one course before being taken out of the study because of persistent myelotoxicity. The overall activity rate was 44% (14/39) according to a *standard* analysis and 40% (95% CI, 25–56%) according to an *intention-to-treat* analy-

Table 1. Patients' characteristics

Characteristics	
Total entered	43
Eligible	43
Males/females	18/25
Age (in years)	
median	52
range	24–75
Performance status (ECOG)	
0	20
1	19
2	4
Previously treated with rIFNα2a	22
Main metastatic site	
viscera	22
soft tissue	13
CNS	6
bone	2
Number of metastatic sites	
1	20
2	9
3	14

Table 2. Worst acute toxicity reported by patients (n = 43)

Toxicity	WHO Grade 1–2	3	4	Total (%)
Neutropenia	26	2	1	67
Thrombocytopenia	11	9	2	51
Anaemia	6	1	–	16
Nausea and vomiting	14	–	–	33
Stomatitis	8	1	–	21
Diarrhoea	4	–	–	9
Hepatic	2	–	–	5
Fever	9	–	–	21
Headache	2	1	–	7
Asthenia/myalgia	2	–	–	5

sis. Fifty per cent (10/20) of asymptomatic patients achieved a response, compared to 32% (6/19) with PS 1 or 25% (1/4) with PS 2, but this difference did not reach a statistically significant level. The dominant metastatic site also affected the probability of response rate. Only 1/6 patients with CNS metastases, and no patient with bone localisation, achieved a major response, while patients with visceral extension of disease had a similar response rate (10/22, 45%) to patients with only soft tissue involvement (6/13, 46%). No significant difference in response was observed according to visceral site of metastasis (response rate was 33% for pulmonary and 43% for hepatic metastases). Multiple metastatic sites did not significantly impair the response rate (8/23, 35%) in comparison to a single site (9/20, 45%). Furthermore, previous administration of rIFNα2a in the adjuvant setting did not identify a poorer response rate. Indeed, 8 responses (2 CRs) were obtained among the 22 pretreated patients.

Toxicity

Acute side-effects are summarised in Table 2. No toxic deaths were reported, since the 3 early deaths (after one cycle) were caused by a rapid worsening of the clinical condition due to the disease. The most common toxicities were neutropenia and thrombocytopenia. However, they were usually moderate, being of WHO grade 4 only in 1 (2%) and 2 (5%) patients, respectively. As mentioned above, 1 patient was withdrawn from treatment after the first cycle because of persistent thrombocytopenia. As a consequence of moderate haematological toxicity, courses were given with few delays or dose reductions, and the average dose intensity was 27 (range 8–33) mg/m^2/week for FM, and 276 (range 130–342) mg/m^2/week for DTIC. rIFNα2a was temporarily discontinued in 19 (44%) patients, mainly because of intercurrent neutropenia between chemotherapy administrations, but it was promptly resumed after neutrophil recovery. No patient had a definite interruption of rIFNα2a administration due to its particular side-effects.

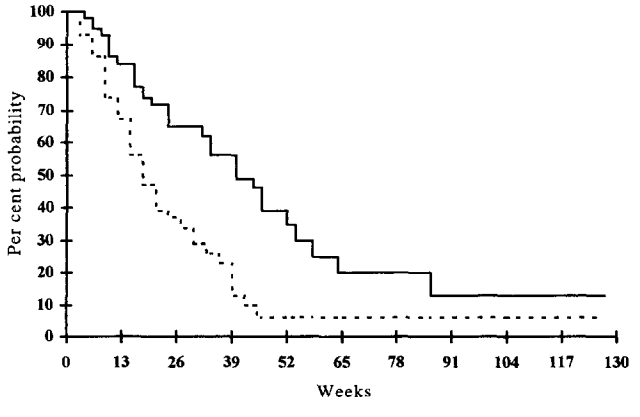

Figure 1. Survival (solid line) and progression-free survival (dotted line) of the whole population.

Follow-up analysis

As of September 1996, 2 of the 4 CR patients were still without evidence of recurrence after 74 and 127 weeks. 2 other CR patients relapsed after 18 and 24 weeks, respectively. The partial responses lasted from 6 to 39 weeks. The median duration of all responses was 24 weeks. After a median potential follow-up of 89 weeks, 38 patients progressed, of whom 32 eventually died of their disease. 11 patients are still alive from 26 to 127 weeks after the start of therapy. The survival and treatment failure curves for the whole series are shown in Figure 1. Median survival time was 40 weeks. Median survival time was more than twice as long for responders (53 weeks) than for patients considered induction failures (23 weeks) ($P < 0.005$). No relevant difference in progression-free survival was observed between patients that had already received rIFNα2a as adjuvant treatment (14 weeks) and those who had not been pretreated (18.5 weeks).

DISCUSSION

The first phase II study of the combination of DTIC and FM was conducted in France [15], and evaluated the sequential administration of FM 100 mg/m^2 on days 1 and 8, and DTIC 250 mg/m^2 on days 15–18. This induction therapy was followed, after a rest period of 5 weeks, by maintenance treatment in responding patients with FM 100 mg/m^2 on day 1 and DTIC 250 mg/m^2 on days 2–5 every 3–4 weeks. The final analysis of this study reported an overall response rate of 27%. However, apart from patients with non-visceral metastases (objective remission rate 38%), patients with CNS localisations seemed to benefit more than patients with visceral sites of disease. Indeed, the response rate was 26% in the former and only 18% in the latter. These results were similar to those previously reported with FM alone [6, 7]. However, the authors stressed the reduced haematological toxicity of this regimen in comparison with the weekly × 3 administration of FM alone. Therefore, it could be concluded that the sequential administration 1 week apart of the two drugs may obtain at best an additive cytotoxic effect on neoplastic cells. *In vitro* studies have suggested that FM and DTIC, sharing the same target for their biochemical activity (alkylation of the O^6 of the guanine molecule), may exert a synergistic effect when given together. Indeed, the pre-exposure of cells to DTIC causes a progressive depletion of the enzyme, O^6-alkylguanine-DNA alkyltransferase, which is responsible for the subsequent increased sensitivity of cells to the alkylation of FM [14]. Interestingly, a phase II study, in which DTIC was administered at increasing dosage (400, 500, 800 mg/m^2) 4 h before FM (100 mg/m^2) every 4 weeks, showed that the response rate was linearly related to DTIC dosage, being 24%, 30% and 40%, respectively. Among patients receiving the highest dosage of DTIC, 5/13 (38%) patients with visceral metastases showed a partial response [8].

In our trial, FM was followed by DTIC over a few consecutive days, recycling the treatment every 3 weeks, to exploit the synergism and to increase the dose intensity of both drugs. The actual average dose intensities of FM and DTIC given to our patients was quite close to the planned doses, and substantially higher (at least for DTIC) than those achieved in the schedule used by Avril and associates [9], and even higher than that obtained in the 1-day every 4 weeks regimen [8]. These findings could explain the higher response rate in our trial, confirming that the two drugs, when given in close sequence, may exert a more than additive effect on neoplastic cells. It is noteworthy that no significant differences of activity of our regimen were observed between patients with visceral and soft-tissue localisations, nor among patients with one or more sites of disease. However, the limited efficacy of this regimen in patients with CNS metastases could reflect the clinical variability of such patients. Indeed, the probability of response is related to the site and size of cerebral metastases. Moreover, the low response rate obtained with the combination of DTIC plus FM, as compared to that previously reported with FM alone given for 3 consecutive weeks [6, 7], suggests that the dose intensity of this latter drug during the induction treatment plays a relevant role in achieving an objective response to brain metastases.

The inclusion of rIFNα2a in the management of our patients did not negatively affect the dose intensity nor worsen the acute side-effects of the cytotoxic treatment. The low intermittent dosage of rIFNα2a used and the concomitant administration of paracetamol prevented 'flu-like symptoms in most patients and rendered them acceptable in the others. Moreover, the occurrence and severity of these symptoms usually decreased during repetitive administration of rIFNα2a. As a consequence, the majority of patients received the planned dose of rIFNα2a, and this treatment did not seem to impair their quality of life. However, the effect of rIFNα2a treatment on response duration or time to progression is difficult to evaluate considering the non-randomised design of our study. Taking as reference a large multicentre Italian trial, aimed at evaluating the addition of low or high doses of rIFNα2a to DTIC in comparison to DTIC alone in advanced melanoma [4], we would stress that the median duration of responses for patients receiving low-dose rIFNα2a in that trial (5.5 months) was similar to ours (24 weeks). Furthermore, as in that series, 2 of our 4 patients achieving a CR showed a long-lasting freedom from recurrence whilst on rIFNα2a maintenance only. Also, the time to treatment failure was quite similar (4.4 months and 17 weeks, respectively) in the two studies. However, a recent large randomised trial failed to show any difference in time to treatment failure or survival of patients with advanced melanoma with the addition of rIFNα2a to DTIC [15].

In conclusion, this phase II trial demonstrated that the administration of FM and DTIC in strict sequence represents a very active regimen for patients with advanced melanoma, exploiting the synergistic effect of the two drugs without causing severe acute side-effects. The role of rIFNα2a in affecting the long-term outcome of patients with advanced melanoma treated with combination chemotherapy remains questionable and deserves further randomised studies.

1. Mastrangelo MJ, Rosemberg SA, Baker AR, Katz HR. Cutaneous melanoma. In De Vita VT, Hellman S, Rosemberg SA eds. *Cancer Principles & Practice of Oncology*. Philadelphia, Lippincott, 1982, 1124–1170.
2. Bajetta E, Negretti E, Giannotti B, *et al.* Phase II study of interferon alpha-2a and dacarbazine in advanced melanoma. *Am J Clin Oncol* 1990, **13**, 405–409.
3. Kirkwood JM, Ernstoff MS, Giuliano A. Interferon alpha-2a and dacarbazine in melanoma. *J Natl Cancer Inst* 1990, **82**, 1062–1063.
4. Bajetta E, Di Leo A, Zampino MG, *et al.* Multicenter randomized trial of dacarbazine alone or in combination with two different doses and schedules of interferon alpha2a in the treatment of advanced melanoma. *J Clin Oncol* 1994, **12**, 806–811.
5. Falkson CI, Falkson G, Falkson HC. Improved results with the addition of interferon alpha2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. *J Clin Oncol* 1991, **9**, 1403–1408.
6. Jacquillat C, Khayat D, Banzet P, *et al.* Final report of the French multicentre 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.
7. Kleeberg UR, Engel E, Israel P, *et al.* Phase II trial of Fotemustine (FM) in patients with metastatic melanoma (EORTC-MCG 18881). *Oncologie* 1991, **14**, 81–83.
8. 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.
9. Avril MF, Bonneterre J, Cupissol D, *et al.* Fotemustine plus dacarbazine for malignant melanoma. *Eur J Cancer* 1992, **28A**, 1807–1811.
10. Aamdal S, Calabresi F, Moreschi M, *et al.* Phase II trials with alkylating agents dacarbazine and fotemustine in the treatment of advanced malignant melanoma (AMM): from antagonism to synergy. *J Cancer Res Clin Oncol* 1990, **116**(Suppl, 1), 469.
11. Aamdal 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, **28**, 447–450.
12. Kaplan E, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–461.
13. Gehan EA. A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. *Biometrica* 1965, **52**, 202–233.
14. Lee SM, Thatcher N, Dougal M, Margison GP. Dosage and cycle effects of dacarbazine (DTIC) and fotemustine on O^6-alkylguanine-DNA alkyltransferase in human peripheral blood mononuclear cells. *Br J Cancer* 1993, **67**, 216–221.
15. Falkson CI, Ibrahim J, Kirkwood J, *et al.* A randomized phase II trial of dacarbazine (DTIC) versus DTIC + interferon alfa-2b (IFN) versus DTIC + tamoxifen (TMX) versus DTIC + IFN + TMX in metastatic malignant melanoma: an ECOG trial. *Proceedings of ASCO Meeting*, Philadelphia, 1996, 435.

Acknowledgement—The fotemustine utilised in this study was kindly furnished by the Institute de Recherches Internationales Servier, Rome, Italy.