of previous experience and because they had been shown to be active in melanoma. The response rate of 23% is comparable with those achieved by IFN-α and dacarbazine alone and it is concluded that nimustine did not improve the results but only caused more side-effects.

Interferons need further study in combination with chemotherapy and biological response modifiers, for metastatic melanoma and adjuvant therapy of high risk patients in phase III studies. We prepare to investigate the efficacy of a four drug (dacarbazine, vincristine, bleomycin, lomustine)-IFNα_{2b} (DOBC) combination in metastatic melanoma.

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A Phase II Study of Sequential Recombinant Interleukin-2 Followed by Dacarbazine in Metastatic Melanoma

Walter Fiedler, Claude Jasmin, Pieter H.M. De Mulder, Seppo Pyrhönen, Peter A. Palmer, Christopher R. Franks, Ralph Oskam and Dieter K. Hossfeld

16 patients with disseminated malignant melanoma (1 with primary ocular melanoma) entered a multicentre phase II study of recombinant interleukin-2, (rIL-2) given by continuous intravenous infusion on days 1–5 at 18 × 10^6 IU/m^2 per day, followed by dacarbazine 850 mg/m^2 on day 8. After a 2 week rest, a second course was given. In the absence of disease progression, monthly maintenance cycles were given for up to four cycles. 16 patients received one cycle, 14 received two and 6 patients three or more. All 16 patients are evaluable for toxicity and 15 for response. 2 patients responded (13%). 1 patient with lung and pleural metastases achieved partial remission after two cycles and went off treatment after six cycles. 3 months later a complete response was noted lasting 396+ days. A second patient with lung metastases had a partial response lasting 153 days. 3 patients (20%) had stable disease. Mean rebound lymphocytosis (24–48 h after the end of rIL-2 therapy), cell count 4.9 × 10^9/l (2.6–8.8 × 10^9/l) was within the expected limits. Other toxicity was as expected. Thus sequential treatment with rIL-2 and dacarbazine is feasible but synergy did not occur.
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INTRODUCTION

THERE IS no established treatment for metastatic malignant melanoma. Some oncologists regard dacarbazine as the "standard" treatment of this tumour because it has the most consistent activity in this disease [1]. Others feel that claims of a 25% response rate with dacarbazine were too optimistic. Even though some reports with conventional or experimental combinations seem promising, durable complete remissions are rarely induced and few responses are seen in visceral sites.

Recombinant interleukin-2 (rIL-2) administered either as high-dose bolus therapy or as low-dose continuous intravenous infusion can cause tumour regression in patients with disseminated malignant melanoma [2, 3]. Combination trials of rIL-2 and dacarbazine have been initiated to investigate different regimens of sequential administration. Here we report our experience with 5 day continuous rIL-2 infusion followed by bolus dacarbazine.

Table 1. Patients' characteristics

	No. of patients
Primary diagnosis	
Cutaneous melanoma	15
Intraocular melanoma	1
Age (median)	50.5 (38–63)
Sex (female/male)	2/14
Karnofsky performance status (median)	95 (80–100)
Previous therapy:	
No prior therapy	1
Surgery	11
Radiotherapy	2
Surgery plus radiotherapy	2
Disease sites*	
Skin	7
Liver	7
Lung	6
Lymph nodes	4
Bone	3
Others	4

*10 patients had more than one organ site involvement (visceral metastases).

Table 2. Adverse events (all cycles)

	WHO grading (%)				
Adverse events	1	2	3	4	Total
Fever		67	33		100
Nausea/Vomiting	13	50	19		82
Diarrhoea	13	25	6		44
Dyspnoea		6	13		19
Headache	13	13			26
Confusion/dizziness	12				12
Pruritus	19	31			50
Erythema	6	6	6		18
Heart failure				6	6
Hypotension	7	40	47		
Arrhythmia			6		94
Haematological toxicity					6
Haemoglobin	60	7	7		74
Leucocytes	20	13			33
Platelets	27	13	20		60
Bilirubin	20	27	7		54
Aspartate aminotransferase	14	36	21		71
Creatinine	40	13			53
Oedema (incl. face)	6	6			12
Weight gain	20 (5–10%)		13 (>10%)		33

PATIENTS AND METHODS

Patients

16 patients with metastatic, histologically or cytologically proven, malignant melanoma were entered into this study. One of them had primary ocular melanoma. All patients were required to have measurable disease. Median age of the group was 50.5 (range 38–63) and median Karnofsky index 95 (range 80–100). Exclusion criteria included: unresected central nervous system metastasis, major cardiovascular, respiratory or coagulation disorders, active infections, pregnancy or lactation. All patients had serum bilirubin and creatinine levels within the institutional limits. The protocol required a white blood cell count $> 4.0 \times 10^9$/l, platelets $> 100 \times 10^9$/l and haematocrit > 30%. All participants gave informed consent prior to therapy. Further characteristics of patients and sites of metastasis are shown in Table 1.

Treatment regimen

Therapy consisted of a 120 h continuous infusion of rIL-2 (EuroCetus B.V., Amsterdam) at 18×10^6U/m^2/day on days 1–5. Dacarbazine 850 mg/m^2 was administered on day 8 as a short infusion. After a 2 week rest period treatment was recycled. Four additional maintenance courses, separated by 3-week intervals, were planned if the disease did not progress.

Response and toxicity

Response was evaluated after each treatment cycle. Treatment response and response duration were recorded according to WHO criteria [4]. Toxicity was scored following the WHO grading system. Where a WHO grade was not available, a scale of 1–4 was used (mild, moderate, severe, most severe or life-threatening).

RESULTS

Treatment

16 patients received a total of 44 cycles of rIL-2 dacarbazine. All 16 patients were treated with one cycle, 14 patients with two cycles and 6 patients received three or more cycles. At least 90% of scheduled rIL-2 dose was given to all patients during the first cycle, to 13 of 14 patients and 5 of 6 patients during cycles 2 and 3, respectively. Interruption of rIL-2 administration was required on 7 occasions. Reasons included cardiovascular problems in 2 patients, hypotension in 1, oliguria in 1 and others in three instances.

Toxicity

The side-effects of treatment are listed in Table 2. The toxicity profile did not differ significantly from that already known for both IL-2 and dacarbazine. Fever, malaise, hypotension, nausea, vomiting and skin rash were common. Weight gain of more than 10% was noted in 2 patients (13%). Grade 3 haematological toxicity required transfusion of platelets in 1 patient and of packed red cells in 3 patients. 1 patient developed myocardial ischaemia in cycle 4, which responded well to morphine and albumin and which necessitated a 50% rIL-2 dose reduction. After recovery rIL-2 could be resumed at the projected dose. 1 patient died of a cardiac arrest 3 days after completion of the first cycle of rIL-2 dacarbazine. He had a liver metastasis of 20 × 15 cm. Although the patient appeared clinically stable while receiving rIL-2 treatment and did not have major manifestations of rIL-2 induced side effects, his

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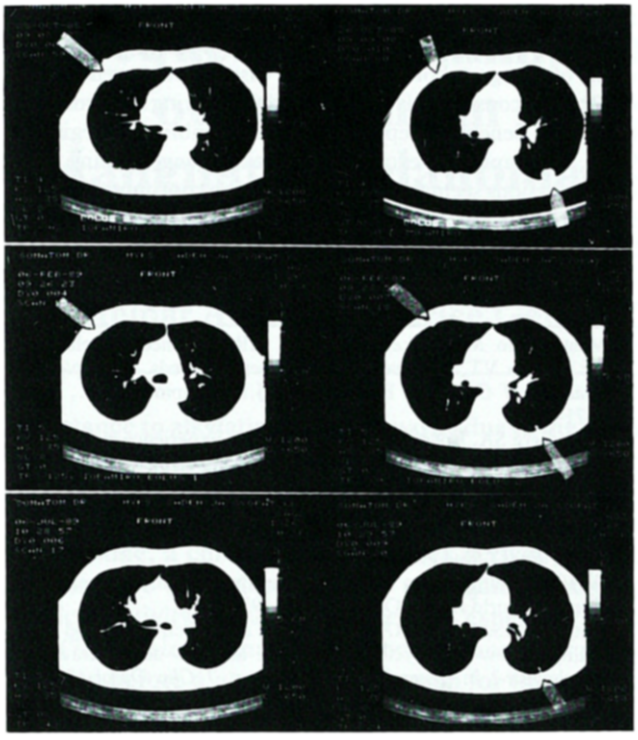

Fig. 1. Computed tomography scans showing tumour manifestations before treatment (upper panel), a partial remission after IL-2/dacarbazine treatment (middle panel) and a complete response 3 months after the end of therapy (lower panel).

condition deteriorated rapidly following completion of the treatment cycle. The patient died a few days later following a period of continued renal and hepatic failure, considered to be disease related by the responsible physician.

Response

15 patients were evaluable for response. 1 patient died 3 days following the first treatment cycle. 2 patients had a remission (13%; 95% confidence limits 0–30%). One of these 2 patients achieved a partial response (PR) after two cycles of rIL-2/dacarbazine treatment and remained in PR until completion of six cycles (Fig. 1). Three months later he was found to be in complete remission (CR) with complete disappearance of metastases in lung and pleura. This patient remains in CR for a duration of 396+ days. The second patient achieved a PR for 153 days in lung metastases. 3 patients had stable disease (20%) lasting 74, 141, and 190 days. Of the whole group, 13 patients have died, median survival was 269 days.

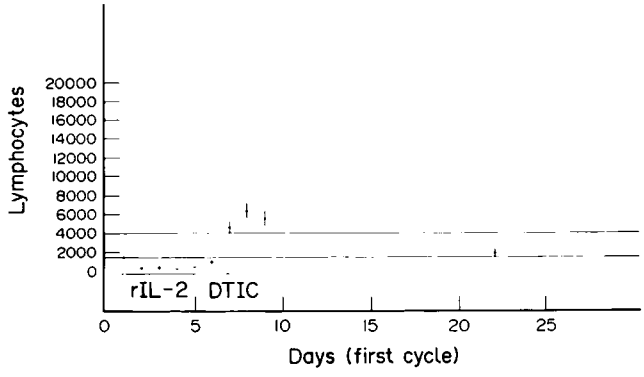

Fig. 2. Means of daily lymphocyte counts per microlitre during the first treatment of cycle. === = Normal range, n = 16, mean (S.E.). DTIC = dacarbazine.

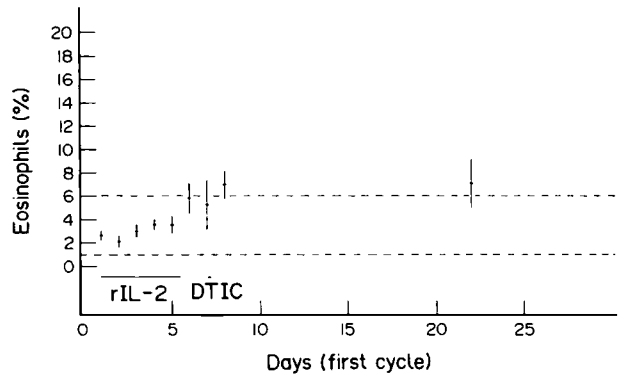

Fig. 3. Mean percentages of daily eosinophil determinations during the first treatment cycle. === = Normal range, n = 16, mean (S.E.). DTIC = dacarbazine.

Mean rebound lymphocytosis (24–48 h after rIL-2 treatment) after the first cycle was 4.5 × 10^9/l (range 3.0–6.9 × 10^9/l, Fig. 2), and was comparable with that obtained after the 2nd cycle (mean 5.2 × 10^9/l; range 3.2–8.3 × 10^9/l). Induction of IL-2 receptors, expressed on mononuclear cells was equally effective in the first and second cycle. Mean percentages for IL-2 receptor positive cells, studied in 3 patients before and after rIL-2 administration, increased from [mean (S.D.)] 2.3 (2%) to 10 (17%) after the first and from 2.6 (2%) to 21 (17%) after the second cycle. Therefore dacarbazine does not seem to have a negative impact on lymphocyte proliferation and activation. Also no inhibition of rIL-2 induced eosinophilia by dacarbazine was detected. Mean eosinophil peak levels were 0.8 × 10^9/l (range 0.1–2.0 × 10^9/l) during the first cycle (Fig. 3), in the 2nd cycle they tended to be more variable (mean: 2.4 × 10^9/l; range 0.1–7.1 × 10^9/l).

DISCUSSION

Recombinant IL-2 has been shown to cause disease regression in patients with malignant melanoma. Responses can be achieved by high dose bolus regimens as described by Rosenberg *et al.* [2] or by low dose continuous infusion regimens as described by West *et al.* [3]. Chemotherapy only leads to short lived responses in malignant melanoma with dacarbazine being the most effective agent, claimed to induce response rates in the 10–25% range [1]. Synergy between rIL-2 and chemotherapeutic agents, usually cyclophosphamide, has been demonstrated in clinical trials as well as in animal models [5, 6]. But this synergy seems to depend at least in part on an immunomodulatory effect of cyclophosphamide [7]. Preliminary results have also been reported about combination therapies of dacarbazine with rIL-2, both given as bolus [8] or low dose continuous infusion regimens [9]. To further evaluate a possible synergistic action between rIL-2 and dacarbazine, a series of combination trials of both agents was initiated in collaborative groups, involving several European centres. We report our experience with a regimen consisting of a 5-day continuous infusion of rIL-2, followed by dacarbazine after 2 days.

16 patients were included in this study. All patients were evaluable for toxicity and 15 for response. The toxicity profile was similar to those already published for rIL-2 and dacarbazine.

Treatment was feasible on general wards. Grade 4 myocardial ischaemia occurred in 1 patient, but was reversible upon treatment termination. One death following hepatic and renal failure 3 days after completion of the first treatment cycle was felt to be disease related.

Rosenberg *et al.*, achieved a response rate of 24% in 42 patients with malignant melanoma treated with high-dose rIL-2 alone [2]. Administration of low-dose rIL-2 in conjunction with low-dose cyclophosphamide resulted in response rates varying from 15% (3 PR of 18 patients treated) to 25% (1 CR, 5 PR in 24 patients) [5, 10]. In two trials using differently spaced rIL-2 dacarbazine regimens 22% (3–41%) (2 CR, 2 PR) of 18 patients and 25% (7–42%) (2 CR, 4 PR) of 24 patients responded [11, 12]. The 13% (0–30%) response rate in our rIL-2/dacarbazine trial seems to lie in the lower range of combination studies using rIL-2 and chemotherapeutic agents. A multivariate analysis adjusting for differences in prognostic factors between the various patient populations treated with these regimens, would further aid in evaluation of efficacy. In addition, this article should incorporate a recent review of a large population of historical controls treated with dacarbazine monotherapy revealing that the true response rate of this agent lies in the order of 10%, when response data were analysed using modern criteria for response assessment.

Although no randomised trial was conducted, the response rate of this combination of rIL-2 followed by dacarbazine was about half as high as the response rate of a combination using the reverse order [11] or of a regimen consisting of two cycles a week apart of rIL-2, followed by dacarbazine after another week [12]. Therefore, it cannot be excluded that dacarbazine, administered 2 days after the end of a rIL-2 continuous infusion, interferes with the IL-2 induced immunological sequelae, this way abrogating the antitumour effect. Although dacarbazine neither appeared to prevent rebound lymphocytosis nor induction of IL-2 receptors nor eosinophilia in the subsequent cycle, it may influence the induction of cytotoxic effector cells and/or secondary cytokine release, if given during the rebound lymphocytosis. In conclusion, treatment with this schedule of rIL-2/dacarbazine is feasible in ordinary oncology wards, but does not seem to be very effective, as only 2 out of 15 evaluable patients responded (13% response rate). This rate seems lower than that reported for either dacarbazine [1] or rIL-2 alone [2, 3]. It should be noted, however, that reported response rates of dacarbazine monotherapy may have been overstated in the past, due to the fact that non-uniform response criteria were applied. In fact, the response to dacarbazine alone in disseminated melanoma does not seem to exceed 10%, based on a Eurocetus review of a large cohort of historical cases. Thus, even though rIL-2 adds considerably to the toxicity during treatment, a therapeutic benefit, as reported for some combination regimens [9, 11, 12], cannot be excluded. Especially longer lasting complete remissions seem to be rare with dacarbazine monotherapy. But, in conclusion, lack of therapeutic synergism between rIL-2 and dacarbazine, given in this regimen, was noted.

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