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A Phase II Study of Metastatic Melanoma Treated With a Combination of Interferon Alfa$_{2b}$, Dacarbazine and Nimustine

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52 patients with metastatic melanoma have been treated with a combination of recombinant interferon-alfa-2b, dacarbazine and nimustine. The objective response rate was 23% with 9 complete responses (CR) and 3 partial responses (PR). The mean duration of the response was 18+ months for CR (6–31+ months) and 7 months for PR patients (4–10 months). The mean survivals were 24+ months (8–38 months) and 7 months (4–12 months), respectively. The mean duration of the response for patients with stable disease was 10+ months (2–48+ months) and the mean survival 17+ months (3–48+ months), while the patients with progressive disease died within 12 months (mean 4 months). The best responding sites were the lymph node, the lung and the subcutaneous metastases. Myelosuppression was the main adverse effect of the therapy. WHO grade 3–4 toxicity was seen in 27 patients leading to delay and reduced dosage of therapy; in 4 patients treatment was discontinued, 8 patients had no side effects. Combination therapy with interferon and dacarbazine and nimustine for metastatic melanoma offers no advantage over interferon and dacarbazine.
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INTRODUCTION

METASTATIC MELANOMA is fatal conventional chemotherapy yielding poor results. Objective responses to dacarbazine can be seen in 15–20% of the patients with a couple of months' duration of the response. Other less active agents include vinca-alkaloids, nitrosoureas, bleomycin and cisplatin. The combinations of these usually increase the toxicity without any obvious effect on the response rate and duration of the response [1].

The efficacy of interferon-alfa on metastatic melanoma is well documented in many clinical studies. The overall response rate is 15–20% irrespective of the type or dose of the interferon [2]. The most commonly used subtypes of the interferons are the recombinant interferon alfa-2a (Roferon A, Hoffman La Roche, Switzerland) and alfa-2b (Intron A, Schering-Plough, USA). The mode of action of interferons (IFN) is not fully known. The antiproliferative effect manifests as a direct non-toxic slowing of all phases of the cell cycle. They modulate the cytotoxic activity of monocytes and killer cells and increase macrophage phagocytic activity. They can also deregulate the C-*myc* gene and reverse the morphology of malignant cells, with loss of tumorigenic potential [3–5]. IFN-α can express an additive or synergistic effect with some cytostatic drugs. Combination of IFN and dacarbazine has produced objective response rates of 25–30% in metastatic melanoma with a significantly long remission and stabilisation of the disease [6–8]. Based on this finding we have treated patients with advanced melanoma since 1987 with a combination of interferon and chemotherapy in a phase II study.

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PATIENTS AND METHODS

Patients

52 patients, aged 25–72 years, with metastatic melanoma were enrolled in this phase II study. All patients had a histologically proven malignant primary tumour and most of the patients had

been biopsied to confirm metastatic spread. All had a measurable disease as determined by ultasonography, computed tomography (CT), X-ray or direct measurement. The metastatic sites were: 12 patients with lung, 10 with liver, 10 with lymph node, 4 with skin and 16 with mixed metastases. Each metastatic site was evaluated separately, but the overall response was determined by the poorest response. Further eligibility criteria were adequate bone marrow reserve, Karnofsky index over 70% and life expectancy of at least 2 months.

The main exclusion criteria were cardiac or renal failure, recent myocardial infarction, or brain metastases. None of the patients had previously received active radio-, chemo- or surgical therapy for the metastases or adjuvant therapy for the primary tumour.

Chemo-immunotherapy

IFN-alfa-2b was administered subcutaneously at a dosage of 3 MU or 5 MU if tolerated three times a week. The dosage of dacarbazine was 250 mg/m^2 × 5 days intravenously, the course was repeated every 3 weeks, and that of nimustine 1 mg/kg intravenously every 42 days. The treatment was continued until progression of the disease; in case of complete remission chemotherapy was discontinued after three courses, but IFN was given as a maintenance treatment.

Evaluation of response

Response was evaluated after every cycle of the treatment using the standard WHO response criteria [9]. A complete remission (CR) required total disappearance of the tumour for at least 1 month; a partial remission (PR) required a decrease of 51–99% (measured as a product of perpendicular diameters); a stable disease (SD) required a decrease of 0–50% in the tumour size (reduction in size of every metastasis, and the overall evaluation was based on the least change). The objective overall response rate included CRs and PRs. Duration of response and overall survival were also recorded. The Karnofsky index (0–100) was used to indicate the quality of life.

Evaluation of adverse effects

Complete blood counts as well as blood chemistry, including liver function tests, creatinine and electrolytes, were determined before and at the end of each cycle. The dosage of drugs was adjusted according to toxicity, graded as using the WHO system [9]. The patients were asked about side-effects after each treatment cycle.

RESULTS

Response to therapy

All 52 patients (27 male and 25 female, mean age 50 years) are evaluable for response and toxicity. The overall response rate was 23% with 9 CRs (17%) and 3 PRs (6%). The mean duration of the response was 16 months (6–31+ months) and 6 months (5–10 months), respectively. The mean survival for CR patients was 22 months (8–38 months) and 7 months (5–12 months) for PR patients. In addition, 16 patients (31%) remained stationary for a mean of time of 16 months (2–34+ months), with a mean survival of 17 months (3–48+ months), while the progressive disease (PD) patients died with a mean survival of 4 months (1–12 months). 16 patients lived over 12 months and 8 patients over 24 months. 8 patients are alive at 7, 14, 19, 23, 24, 48 months with SD and at 29 and 30 months with CR (Table 1).

The best responding tumour sites were the lung (12/18), the lymph nodes (10/19) and the skin (4/6). A response was seen in 10/20 liver metastases.

Table 1. Efficacy of a combined interferon-cytostatic therapy in metastatic melanoma of 52 patients

Response	Patients (%)	Mean duration of response (months)	Mean survival (months)
CR	9 (17)	16 (6–31+)	22 (8–38)
PR	3 (8)	6 (5–10)	7 (5–12)
SD	16 (31)	16 (2–34+)	17 (3–48+)
PD	24 (54)		4 (1–12)

CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease.

Toxicity

Clinically, influenza-like syndrome due to IFN in the beginning of the treatment was seen in 44/52 patients. The dose limiting adverse effect was haematological toxicity. WHO grade 4 myelosuppression was seen in 5, grade 3 in 7 and grade 2 in 12 patients. 6 patients had grade 3–4 vomiting, and 3 had alopecia. 1 patient had transient hepatitis due to dacarbazine. A dose adjustment was performed in 21 patients and the therapy had to be discontinued in 4 patients. On the contrary, 8 patients suffered no side effects (Table 2). During the course of the therapy mild anorexia and lethargy appeared in some patients.

DISCUSSION

In this phase II clinical study we have shown that a combination of IFN and cytostatic chemotherapy produces a tumour response in 23% of patients with metastatic, advanced melanoma. The combination therapy was generally fairly well tolerated. Most of the haematological adverse effects were attributable to chemotherapy and the flu-like syndrome and anorexia to interferon.

The patients or their relatives were taught to inject IFN, and most of them did learn to do so. Chemotherapy was given ambulatorily and patients were hospitalised only for staging purposes and, if necessary, to treat complications, or for terminal care. Phase II IFN-α studies in metastatic melanoma have reported objective response rates varying from 15–20% [2]. In recent studies, IFN-α have been combined with a variety of agents in order to obtain a better response. Combinations with cimetidine, vinblastine, cisplatin or cyclophosphamide have not been successful [2, 6], but dacarbazine has been shown to enhance the efficacy, yielding a response rate up to 38%. The combination of dacarbazine and IFN-α has also been reported to be superior to dacarbazine or IFN-α [6].

To our knowledge, no other studies have been published where multi-drug chemotherapy has been used together with IFN-α. Dacarbazine and nimustine were selected on the basis

Table 2. Toxicity of the IFN-cytostatic therapy

	WHO grade, patients involved (*n*)		
Adverse effect	IV	III	II
Myelotoxicity	5	7	11
Nausea and vomiting	2	4	7
Alopecia	1	2	2
Hepatotoxicity	1		

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.