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Interferon Alpha$_{2a}$ and Vindesine in the Treatment of Advanced Malignant Melanoma

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21 patients with advanced malignant melanoma were treated with interferon alpha$_{2a}$ at 9MU daily with vindesine every 21 days. No patient had received previous chemotherapy. The overall response rate was 24% with a median survival time of 33 months in 18 patients. The four complete remissions were maintained for 20, 18, 15 and 11 months, while the single partial remission continues at 18 months after the start of treatment. Side-effects were generally mild or moderate and did not lead to cessation of therapy. This combination provides an active outpatient regimen for advanced melanoma and produces durable remissions.
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INTRODUCTION

THE INCIDENCE of malignant melanoma is rising by about 7% per year in western countries [1]. The majority of patients will develop metastases in sites such as the lymph nodes, liver and brain, but response to conventional anticancer agents is relatively poor, with dacarbazine and vindesine representing the most active agents and more modest responses observed for cisplatin and carmustine. When the drugs are used in combination, overall response rates in the region of 25–30% are seen with few complete remissions and the responses are rarely prolonged beyond a few months [2].

More recently evidence has accumulated for activity of interferon α and β in this disease. The precise mechanism of action has not been determined, but preliminary evidence would suggest that augmentation of natural killer cell is important [3]. These studies were encouraging and gave overall response rates in the range of 6–29% [5–7]. A review of this data suggested that the activity of interferon was optimal when the dose used was 9 MU or greater (data on file, Roche Products). It has also been shown that tolerance and compliance are excellent up to that level [4], and an escalating dose schedule from 3 MU three times per week up to a maximum dose of 9 MU daily was therefore chosen for the present study.

A combination of conventional cytotoxic drugs and the interferons was therefore seen as a logical step forward. For the present study, vindesine was selected in addition in preference to dacarbazine as a result of its superior toxicity profile, although both show modest single agent activity [2].

PATIENTS AND METHODS

21 patients with recurrence of histologically confirmed malignant melanoma were entered into the study. No patient had received prior chemotherapy and patients with a previous history of a separate malignancy or significant cardiac or renal disease were excluded. The patient characteristics are shown in Table 1. The principal sites of disease were lymph nodes and liver, with 2 patients having brain metastases.

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All patients gave written informed consent prior to commencing treatment with vindesine chemotherapy, at a dose of 3 mg/m^2 given intravenously every 21 days for up to 12 months in responding patients. Interferon alpha$_{2a}$ was given concomitantly at a starting dose of 3 MU subcutaneously on alternate days, escalating to 9 MU subcutaneously daily within 2–6 weeks of commencing therapy. Treatment was given on an out-patient basis with subcutaneous injections of interferon self-administered in 5 patients and given by district nursing staff in the remainder. Patients were required to attend the clinic at least every 3 weeks for assessment of serum haematology and biochemistry, and monitoring of any toxicity prior to the next cycle of therapy; tumour measurements were also reassessed at this time.

In responding patients vindesine was discontinued at 12 months, at which time the interferon alpha$_{2a}$ was reduced to 9 MU every 3 weeks. 2 patients were retreated with vindesine and interferon at relapse.

RESULTS

A complete response (CR) to treatment with interferon alpha$_{2a}$ and vindesine was achieved in 4 out of 21 patients, their disease sites being: trachea (1 patient); lymph nodes (2 patients), lung (1 patient). A partial response to therapy was seen in 1 patient with multiple liver metastases, static disease in 2 patients and 12 patients showed evidence of progression, with a further 2

Table 1. Characteristics of 21 patients on study

Mean age	46 yr.	(range 20–68)
WHO performance status (mean)	0.57	(range 0–2)
Males/females	7/14	
Median time from diagnosis to study entry	21	(range 1–192 months)
Sites of disease		
Lymph nodes	14	
Skin	4	
Liver	6	
Brain	2	
Lung	2	
Misc.	6	

Table 2. Analysis of responding patients to interferon alpha$_{2a}$ and vindesine

Response	Sex	Age	Disease sites	Time from diagnosis to entry (months)	Survival (months)	TTR (months)
CR	M	41	Lymph nodes —neck	6	21	11
CR	F	61	Trachea	192	18	15
CR	M	39	Lung and lymph nodes	48	18*	18
CR	F	68	Lymph nodes —neck	11	45*	20
PR	M	24	Liver	31	18*	NR

*Alive with disease.
NR, not relapsed; TTR, time from first response to relapse; CR, complete response; PR, partial response.

patients not evaluable for response due to early death. All 4 complete responders have now relapsed at 20, 18, 15 and 11 months, whilst 1 patient in partial remission continues to have regression of liver metastases at 18 months. The overall response rate seen was 24%. A minor response in liver metastases (normalisation of liver function tests) was seen in 1 further patient considered overall to have progressive disease. On retreatment at the time of relapse of 2 patients initially considered to have a CR, further partial responses were achieved with the same doses of interferon alpha$_{2a}$ and vindesine. One partial response was sustained for 2 months, while the second patient continues to respond at 2 months. A detailed analysis of the responding patients is shown in Table 2.

The survival curve from the start of interferon and vindesine treatment is shown in Fig. 1. Survival from the date of diagnosis to death was a median time of 33 months (range 6–215 m) in 18 patients with 3 patients still alive at 60, 39 and 24 months from the date of diagnosis.

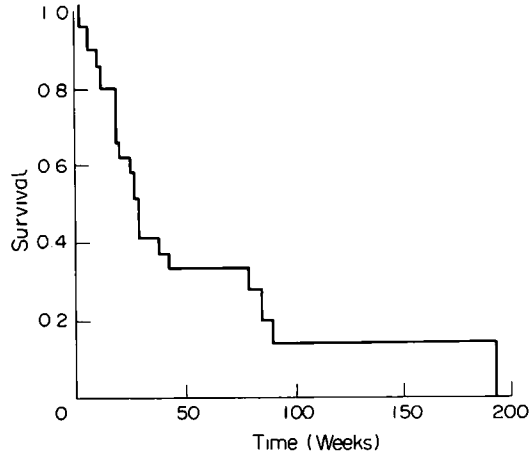

Fig. 1. Survival curve for patients receiving interferon alpha$_{2a}$ and vindesine therapy in the treatment of advanced malignant melanoma.

WHO Grade	0	1	2	3/4
Total WBC	9	7	5	0
Neutrophils	12	4	5	0
Nausea/vomiting	4	13	4	0
Lethargy	7	3	11	0

Fig. 2. Toxicities of interferon alpha$_{2a}$ and vindesine therapy.

The major toxicities experienced by the patients are shown in Fig. 2. These were generally mild or moderate and WHO grade 3 or 4 toxicity was not seen in relation to these side-effects. Grade 1 nausea and vomiting was experienced in 62% of patients during the course of therapy and this was controlled satisfactorily by the administration of oral metoclopramide. However, 19% of patients still suffered grade 2 nausea and vomiting.

Grade 2 lethargy was seen in 52% of patients and was the most debilitating side-effect patients experienced. No patient expressed a wish to discontinue treatment and this effect resolved without dose modification within 3 weeks in all patients.

1 patient developed vitiligo and 1 patient developed an abscess at the subcutaneous injection site requiring antibiotic therapy. Alopecia grade 2 was seen in 81% of patients. Treatment was given on schedule in all except 2 patients in whom bone marrow suppression was seen, but neutropenic fever was not observed.

DISCUSSION

The interferons have previously shown evidence of activity against metastatic melanoma, as have the vinca alkaloids including vindesine [9] but few clinical trials have explored the combined use of these two compounds in advanced metastatic malignant melanoma. Ringborg *et al.* [10] in the study of vindesine in combination with dacarbazine versus single agent dacarbazine in disseminated malignant melanoma, reports an overall reponse rate of 25% in the combined arm with vindesine, against 18% with single agent dacarbazine. A response rate of 45% was achieved by Pectasides *et al.* [11] in 27 patients with advanced metastatic malignant melanoma receiving combination therapy with dacarbazine, vindesine and cisplatin, but in this series the duration of response was found to be short.

In this study of interferon alpha$_{2a}$ and vindesine therapy, the overall response rate of 24% was similar to those reported in previous studies of combinations of interferon and cytotoxic drugs (Table 3). However, the duration of response would appear to be considerably improved, including 1 patient with extensive liver disease in whom prolonged partial remission was maintained. The maximum dose of interferon alpha$_{2a}$ given was 9 MU subcutaneously daily and this was tolerated well with acceptable toxicity. The majority of treatment schedules were uninterrupted and the quality of life in the patients was not seriously affected; patient compliance was excellent.

This phase II study of interferon alpha$_{2a}$ and vindesine chemotherapy suggests that this combination may have a role in the management of patients with advanced malignant melanoma. Further randomised trials are now needed to establish the optimal therapeutic effect of this combination. It is the duration of remission that has been particularly striking compared with single agent phase II studies, and an alternative strategy would be to use the interferon as a form of maintenance therapy.

Table 3. Drugs employed in combination with interferons

Dose of interferon	Other drug	No. of patients entered	Evaluable	Prior treatment	CR	PR	RR%	Ref.
α-2a 3 MU days 1–3 9 MU days 4–70	Dacarbazine 200 mg/m² escalating to 800 mg/m² every 3 weeks	44	43	4	6	7	30	12
α-2a 10 × 10^6 U/m² Monday, Wednesday, Friday	Cimetidine 300 mg orally four times a day	31	31	31	0	2	6.5	8
α-2a 50 × 10^6 U/m² 3 × weekly for 3 months	Cimetidine 300 mg orally four times a day	35	35	10	0	8	23	13
α-2b 20 MU/m² intravenously 5 days/week for 4 weeks +/− 10 MU/m² subcutaneously 3 × weekly	Indomethacin 25 mg orally three times a day	53	47	NS	3	3	13	14
α-2b 9 MU/day intramuscularly for 10 weeks then three times a week	Etretinate 50 or 25 mg/day orally	25	25	0	0	3	12	15
α-2a 3 × 10^6 I.U. escalating to 9 × 10^6 U for 10 weeks 3 × week for 6 months	Vinblastine 0.025 mg/kg weekly	19	17	13	1	1	12	16
α-2a 9 × 10^6 U daily for 10 weeks then Monday, Wednesday, Friday	Dacarbazine 800 mg/m² every 3 weeks	79	75	NS	6	13	25	17
α-2a 3 × 10^6 U D1-3 escalating to 18 × 10^6 intravenously for 10 weeks then 9 × 10^6 intravenously 3 times a week for 6 months	Dacarbazine 400 mg/m² every 3 weeks	15	12	10	1	2	20	18
α-2a 36 × 10^6 U/m² days 3–7	DFMO days 1–7 2.25 g/m²	16	16	5	0	0	0	19
α-2b 10 × 10^6 U/m² days 1–7	Interleukin-2 3 × 10^6 U/m² days 8–13 + days 15–20 every 4 weeks	15	11	0	0	3	20	20
α-2a 12 × 10^6 U/m² days 1–3	Carmustine 150 mg/m² day 3 every 4 weeks	30	30	0	1	1	7	21

DFMO = difluoromethylornithine.

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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