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A Randomised Trial of Vindesine plus Interferon-α2b Compared With Interferon-α2b or Vindesine Alone in the Treatment of Advanced Malignant Melanoma

D. A. Vorobiof and W. R. Bezwoda

60 patients were entered into a randomised study comparing vindesine (3 mg/m²/week) plus interferon-α2b (6 U/m² 3 times per week) to vindesine alone or to interferon alone for the treatment of metastatic malignant melanoma. Patients receiving the combination therapy arm (schedule A; vindesine plus interferon-α2b) showed a complete and partial response rate of 8/20 (40%) which was significantly higher ($P < 0.05$) than that achieved with either single-agent treatment schedule. In addition, patients receiving the combined treatment schedule had a significantly prolonged survival (median 19 months) when compared to a median of 10 months for interferon alone and 5 months for vindesine alone. The combination was generally well tolerated with only additive toxicity. It is concluded that combination treatment regimens utilising interferons together with chemotherapeutic agents deserve further study in the treatment of metastatic malignant melanoma.

Key words: malignant melanoma, treatment, interferon-α2b, vindesine
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INTRODUCTION

MALIGNANT MELANOMA is one of the most common malignancies in young adults. The first published report of a patient with metastatic malignant melanoma was by Hunter in 1787 [1]. The incidence of melanoma has risen rapidly in white populations during the last 50 years. Well-known risk factors are sun exposure (particularly heavy intermittent, rather than continuous exposure), the number and type of pigmented naevi and a family history of melanoma [2].

It is estimated that 70 000 new cases of malignant melanoma occur each year worldwide. In certain countries, such as Australia, melanoma is one of the five most common cancers.

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The clinical course of malignant melanoma varies widely, from a high cure rate for superficial, localised disease to an invariably fatal condition when metastases have occurred. Patients with advanced malignant melanoma remain a challenge to medical oncologists. While chemotherapy remains the mainstay of treatment for disseminated disease, the introduction of biological response modifiers has added new treatment modalities to the therapeutic armamentarium.

Vindesine, a vinca alkaloid derivative, given either as a single agent or in combination, has been shown to produce a response rate similar to that reported with other cytostatics, such as DTIC and the nitrosoureas in advanced malignant melanoma [3–5]. Interferon (IFN)-α has also been shown to be an effective treatment, with response rates of up to 29% in published reports [6]. The combination of cytostatics and IFNs is a new therapeutic approach in the treatment of advanced malignant melanoma. IFN-α has been combined with DTIC [7–11], vinblastine [12–13], cisplatin [14–16], vindesine [17] and multidrug cytos-

Table 1. Therapy schedules

A	Vindesine + IFN. Vindesine 3 mg/m^3 intravenous (i.v.) weekly for 3 weeks, followed by vindesine 4 mg/m^2 i.v. every 3 weeks plus interferon-α2b 6 U/m^2 subcutaneously, three times per week starting at week 3
B	Interferon-α2b 6 U/m^2 subcutaneously, three times per week
C	Vindesine 3 mg/m^2 i.v. weekly for 3 weeks followed by vindesine 4 mg/m^2 i.v. every 3 weeks

Table 2. Patients' characteristics according to treatment schedule

	A	B	C
Sex			
Male	13	12	12
Female	7	8	8
Performance status			
0	5	6	7
1 and 2	12	12	12
3	3	2	1
Metastatic sites*			
Skin/subcutaneous	2	3	3
Nodes + skin/subcutaneous	10	10	8
Lung and pleura	5	5	5
Liver	5	3	3
Gastro-intestinal	3	2	2
Kidney and adrenal	2	0	2
Treatment schedules			
Mean number of metastatic sites per patient	1.35	1.15	1.15
Mean age ± S.D.	45 ± 13	42 ± 10	41 ± 9

A, vindesine + interferon. B, interferon. C, vindesine. * Total number of metastatic sites = 73.

tatic therapy combinations [18]. In comparison with historical controls and in a few randomised studies published so far, the overall responses were higher for the combined approach when compared with single-agent chemotherapy. There is, however, no comparative data regarding the response to IFN alone as compared to IFN plus chemotherapy.

The aim of this open, phase II, randomised, comparative study was to confirm the therapeutic efficacy of a combined modality approach over single agents.

PATIENTS AND METHODS

The treatment schedule is outlined in Table 1. 60 patients with advanced malignant melanoma were entered into the study between June 1989 and October 1992. Eligibility criteria included histologically documented malignant melanoma, with at least one measurable metastatic disease site, ECOG performance status 1–2, normal peripheral blood haematology, adequate renal and hepatic function (defined as creatinine and bilirubin levels $\leq 1.5 \times$ upper limit of normal), normal cardiac function and informed consent. Patients with central nervous system metastases were excluded. Further patient characteristics are listed in Tables 2 and 3. Randomisation was by the closed envelope random number technique.

Patients were reassessed at week 6 after starting therapy and then at 12-week intervals. Reassessment included all sites of disease found at initial assessment. Patients with gastro-intestinal metastases diagnosed as mucosal lesions and confirmed by endoscopy plus biopsy were followed by endoscopy every 12 weeks. Response definitions were: complete response (CR), complete resolution of all measurable and evaluable disease; partial response (PR) $\geq$ 50% decrease in the sum of the product of measurements in 2 diameters of all measurable disease sites together with resolution of all evaluable disease; stable disease (SD) $<$ 50% decrease in measurable disease without any other progression; and progressive disease (PD), any increase in preexistent disease or appearance of new lesions. Patients who had either stable disease or who were responding continued on the same treatment schedule for as long as response was maintained.

Statistical analysis included χ^2 analysis and survival analysis using Wilcoxon and log rank statistics.

The study was approved by the Committee for Ethics of Human Research of the University of the Witwatersrand, and was carried out in accordance with the principles of the Declaration of Helsinki.

RESULTS

60 patients were entered on the study. 6 patients had a performance status (PS) of 3 at entry, and although not eligible according to the entry criteria, once entered they were included in the analysis. All were evaluable both for response and for toxicity.

Of 20 patients entered to schedule A (vindesine and IFN), 8 responded to treatment with an overall response of 40% (95% confidence limits 19–64%) and a median duration of response of 18 months (confidence interval 12–33 months). 3 patients (15%) had a complete response lasting 20+, 31+ and 38+ months,

Table 3. Randomised trial of vindesine plus IFNα versus vindesine versus IFNα 2b for treatment of metastatic malignant melanoma—results

	CR		PR		SD		PD	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Schedule A (vindesine plus IFN-α)	3/20	(15)	5/20	(25)	1	(5)	11/20	(55)
Schedule B (IFN-α2b)	0/20	(0)	2/20	(10)	0	(0)	18/20	(90)
Schedule C (vindesine)	0/20	(0)	1/20	(5)	2	(10)	17/20	(85)

$\chi^2 = 6.96, P < 0.05$.

respectively (1 patient had soft tissue metastases and the other 2 had lung metastases). 5 patients (25%) had a partial response lasting from 8 to 22 months.

20 patients received schedule B (IFN alone) and 2 patients (10%) (95% confidence limits 1–37%) achieved a partial response of 8 months and 19+ months, respectively. Only 1 (5%) of the 20 patients receiving vindesine alone achieved a partial response for 16 months (Table 3).

The time to best response varied from 3 months, for the sole responding patient receiving vindesine alone, to 12 months for patients receiving either IFNα alone or IFNα plus vindesine. The difference in response rate, documented with the three different schedules, was statistically significant, with a P value of <0.05 (Table 3).

The majority of responses (6/11; 55%) obtained were in patients with soft tissue metastases (skin, cutaneous and lymph node). 4 patients had responses (2 complete and 2 partial) in the size and number of lung metastases, and another patient with an adrenal mass obtained a partial response (Table 4).

3 of 18 patients with PS 0, and 8 out of 36 with PS 1–2 had an objective response to treatment. In 6 patients with PS 3, no responses were documented.

20 patients are still alive, and 40 patients died of progression of disease (in regimen A, 11 are alive and 9 have died; in regimen B, 5 are alive and 15 are dead; and in regimen C 4 are alive and 16 are dead). The median follow-up time was 13 months.

Overall survival by treatment regimen is shown in Figure 1. The survival for patients receiving schedule A was significantly better with a P value <0.05.

All three treatment regimens were fairly well tolerated. 3 patients required modification of the IFNα dose to 50% of the planned dose (1 patient schedule A, 2 patients schedule B) because of nausea, weight loss and flu-like symptoms. Apart from these 3 cases, the symptomatic toxicity due to IFN was of grade 2 or less. Peripheral neuropathy (3 patients grade 2; 3 patients grade 1) was attributed to the vinca alkaloid as it was seen with equal frequency in the two vindesine containing regimens (A and C). Dose intensity was ≥95% of the planned dose for each of the three schedules. 2 patients with prolonged CR (31+ and 38+ months) had therapy discontinued after being in CR for 24 months and have continued under observation in unmaintained CR.

DISCUSSION

The prognosis of disseminated malignant melanoma is generally unfavourable. Untreated patients have a median survival of approximately 6 months with less than 20% surviving for more

Table 4. Treatment of metastatic malignant melanoma. Response by disease site and performance status—results

	Number of patients			
	CR	PR	SD	PD
Cutaneous	0	3	2	3
Cutaneous + node	2	3	3	20
Lung and pleura	2	2	1	10
Other viscera	0	1	2	19
Performance status				
0	1	2	2	13
1 and 2	2	6	1	27
3	0	0	0	6

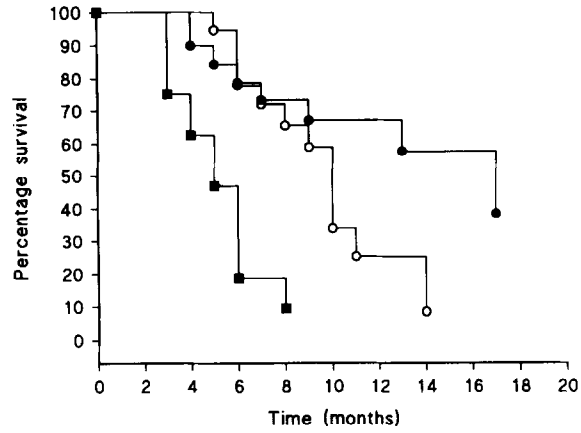

Figure 1. Overall survival of patients with metastatic malignant melanoma. ●—● Regimen A (vindesine + interferon); ○—○ regimen B (interferon); ■—■ regimen C (vindesine). Survival was significantly shorter for patients receiving regimen C (Wilcoxon $P < 0.03$; log rank $P < 0.05$) than for patients receiving either regimen A or regimen B.

than a year [19]. Single-agent chemotherapy yields response rates in the order of 15% [20]. The use of combination chemotherapy has resulted in only a marginal improvement in response rates [20, 21]. Few studies of chemotherapy-treated patients have shown a survival advantage.

Despite initial enthusiasm, treatment with the recombinant IFNs (usually either α2b or α2a) has not resulted in a significantly higher response rate than that obtained with single-agent chemotherapy [20, 22], with the majority of responses occurring in soft tissue and pulmonary metastatic sites. These studies have, however, documented that IFN is an active agent in metastatic malignant melanoma.

While activity has been demonstrated, the mode of action of IFNs in this disease is unclear. Both a direct antiproliferative effect as well as stimulation of the immune response may be part of the mechanism of action [23]. Studies of direct intralesional injection of IFNs [24, 25], which result in a high local regression rate, are consistent with either mechanism of action. The high local concentrations achieved by intralesional injection may exert a direct antiproliferative effect, while IFN stimulation of effector cells may explain the less consistent but none the less adequately documented instances of regression of distal, non-injected lesions. This latter phenomenon is, however, usually confined to cutaneous metastases. It appears likely that different schedules of administration of IFNs or combinations of different types of IFNs will achieve different therapeutic results.

Recent interest has inclined to the combined use of IFN together with cytotoxic drugs. *In vitro* studies have demonstrated synergistic effects of such combinations [25–28]; the basis for which is not yet fully elucidated, although a number of studies suggest a stimulation of apoptotic cell death resulting from the simultaneous use of IFN with a number of chemotherapeutic agents [26–28].

The current clinical study demonstrates a significant *in vivo* synergistic effect of the combination of IFN plus vindesine compared with either treatment alone. While this combination has been previously reported to be effective in a small pilot investigation [17], the current study is the first randomised study assessing the effect of each of these two agents alone and in combination. Not only was the response rate significantly higher,

but a survival advantage was demonstrated for patients receiving the vindesine plus IFN combination.

While the therapeutic effect appeared to be synergistic, toxicity appeared to be only additive, and the combination treatment regimen was tolerable for the majority of patients. It is concluded that the combined use of IFNs and chemotherapy should be explored further to define optimal treatment schedules, dosage regimens and treatment duration.

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