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# A Multicentre Phase II Trial of Vindesine in Malignant Melanoma*

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**Abstract**—*Fifty-three evaluable patients with advanced malignant melanoma have been treated with vindesine* 3 mg/m² *i.v. weekly for a minimum of* 6 weeks. *An objective response rate of* 26% *was attained with* 17% *complete remissions,* 78% *of which were in stage II disease. The treatment was well tolerated, with alopecia the only clinically significant side-effect (*43% *of patients). Vindesine is superior to DTIC and should be considered as the best currently available drug for malignant melanoma.*

## INTRODUCTION

DESACETYL vinblastine amide sulphate (vindesine) is a semi-synthetic vinca alkaloid derivative which has been shown to have activity in a number of solid tumours [1].

Retsas *et al.* [2, 3] first reported promising data on vindesine as a single agent in patients with advanced malignant melanoma and showed an objective response rate of 24%. In view of the promising early data, this multicentre trial was undertaken to assess the efficacy and toxicity of vindesine, given in 6 weekly injections, in the treatment of advanced malignant melanoma.

## MATERIALS AND METHODS

*Patients*

Sixty-three patients with histologically proven advanced malignant melanoma were registered for the study. All had evaluable disease in previously non-irradiated sites. Two patients rapidly deteriorated and were withdrawn prior to receiving any chemotherapy, and 1 patient died of proven pulmonary embolism following two courses of treatment. A further 7 patients received inadequate therapy in the presence of rapidly progressive disease and were not considered evaluable. Fifty-three patients were therefore eligible for assessment, with a mean age of 54.1 yr (range 18–78). There were 23 male and 30 female patients, all with good performance status. On WHO staging criteria, 33 patients were stage III and 20 stage II, the majority of the latter being considered unsuitable for further surgical treatment. Nine patients had previously been irradiated and 15 had received chemotherapy prior to entry into the study. Patients were entered to the protocol between February 1980 and June 1981, there now being a minimum follow-up of 8 months.

*Methods*

All patients were treated on an out-patient basis. Clinical examination and full documentation of all evaluable disease was carried out at each assessment. Full blood count, electrolytes, urea and liver function tests were performed before entry to the protocol and weekly during the treatment period. Patients received vindesine 3 mg/m² intravenously weekly for 6 weeks in a fast-running normal saline infusion. Treatment was delayed for one week in the presence of myelosuppression. Assessment of response was carried out at 6 weeks, again at 12 weeks, and monthly thereafter. Two weeks following completion of the 6-week course of vindesine, 5 patients restarted treatment, receiving 7, 7, 12, 18 and 18 injections respectively. Complete response is defined as the complete resolution of all detectable disease, and partial response as a

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decrease by more than 50% in the size of all measurable lesions in the absence of any new lesion developing over an observation period of not less than 4 weeks.

## RESULTS

The results in 53 evaluable patients are summarized in Table 1. At 6 weeks, 12 patients showed an objective response (22%), 4 of these complete remissions. Late responses were noted in a further 2 patients at 12 weeks. Five patients showing a partial remission at 6 weeks had achieved complete remission at the 12-week assessment. These responses occurred mainly in stage II disease, and in patients with soft tissue disease only. Two of the patients showing late responses had continued on therapy after the 6-week assessment. Details of responding patients are shown in Table 2. Response duration ranges from 4 to 100+ weeks.

*Table 1. Response to vindesine as a single agent in advanced malignant melanoma*

| Assessment | No. of patients | CR | PR | NR | OR,% |
|---|---|---|---|---|---|
| 6 weeks | 53 | 4 | 8 | 41 | 22 |
| 12 weeks | 53 | 9 | 5 | 39 | 26 |

### *Toxicity*

In general, vindesine was well tolerated. All treatment was given on an out-patient basis. Side-effects were common but rarely severe enough to warrant interruption or discontinuation of therapy. Toxicity was graded on WHO criteria [4] and is summarized in Table 3. Alopecia was the commonest side-effect but was fully reversible, despite occasionally being total. Haematological and neurological toxicities were common though rarely severe, but gastrointestinal symptoms were mild and relatively infrequent. Phlebitis was commoner early in the study but the incidence of this was substantially reduced by administration of the drug in a fast-running normal saline infusion. Jaundice, not considered to be drug-related, was noted in one patient who shortly afterwards died of progressive disease, but elevated liver enzymes were also noted transiently in one other patient. Thrombocythaemia, in common with other vinca alkaloids [5], was noted in 13 patients but was not clinically significant.

## DISCUSSION

Malignant melanoma is one of the most insensitive tumours to cytotoxic drugs. Nevertheless, in this study we have found a 26% objective response rate in 53 evaluable patients with 17% complete remissions. The median duration of response had not yet been reached, with 6 patients continuing in complete remission from 6 months to almost 2 yr. These results confirm those of Retsas *et al.* [2, 3] and are superior in terms of response duration. The present study also indicates a more favourable response than that found in other smaller series, including the EORTC Co-operative Melanoma Group, who obtained stabilization of disease in only 3/26 patients [6–9]. A possible explanation for the relatively good response rate in this study is the inclusion of patients with stage II disease.

*Table 2. Details of 14 patients with malignant melanoma showing an objective response to weekly vindesine as a single agent*

| Age | Sex | Stage | Extent of disease | Total dose mg/m² | Duration of response, weeks | Response |
|---|---|---|---|---|---|---|
| 41 | F | 2 | nodes | 18 | 4 | CR |
| 70 | M | 3 | nodes skin liver | 21 | 6 | PR |
| 44 | M | 3 | liver | 18 | 12 | PR |
| 42 | M | 3 | nodes skin | 18 | 16 | CR |
| 60 | F | 3 | mediastinum skin | 54 | 20 | PR |
| 28 | F | 2 | skin | 18 | 24 | PR |
| 52 | F | 2 | nodes | 18 | 24+ | CR |
| 54 | M | 2 | nodes | 18 | 28 | CR |
| 55 | M | 3 | nodes | 36 | 34+ | CR |
| 78 | F | 2 | nodes | 18 | 40+ | CR |
| 48 | F | 2 | nodes | 18 | 40+ | CR |
| 52 | F | 2 | nodes | 54 | 44+ | CR |
| 74 | F | 2 | skin | 18 | 46+ | PR |
| 38 | M | 2 | skin | 18 | 100+ | CR |

*Table 3. Toxicity of vindesine in 53 patients with malignant melanoma*

| | No. of affected patients |
|---|---|
| 1. Haematological | |
| (a) Anaemia | 6 (11%) |
| Grade 1 | 5 |
| Grade 2 | 1 |
| (b) Leucopenia | 16 (30%) |
| Grade 2 | 12 |
| Grade 3 | 4 |
| (c) Thrombocytopenia | 0 |
| Thrombocytosis >400,000 plus >25% increase | 13 (24%) |
| 2. Neurological | 18 (34%) |
| (a) Peripheral | 17 (32%) |
| Grade 1 | 12 |
| Grade 2 | 4 |
| Grade 3 | 1 |
| (b) Constipation | 5 (9%) |
| 3. Alopecia | 23 (43%) |
| Grade 2 | 21 |
| Grade 3 | 2 |
| 4. Gastrointestinal | |
| Nausea/anorexia Grades 1 and 2 | 18 (34%) |
| 5. Miscellaneous | |
| Phlebitis | 9 |
| Lethargy | 9 |
| Jaundice | 1 |
| Elevated liver enzymes (Grade 1) | 1 |

In view of the late responses seen in some of our patients, assessment of response may have been made prematurely in some other series. Traditionally the most widely used agent in the treatment of advanced malignant melanoma has been imidazole carboxamide (DTIC). A pooled overall response rate of 23% has been shown in 1188 patients treated with DTIC [10]. However, significant gastrointestinal toxicity is common, responses are short-lived and likewise mainly found in soft tissue disease [11]. Our results indicate that vindesine is less toxic and probably more efficacious than DTIC for malignant melanoma and should be considered in the development of combination chemotherapeutic regimens for the treatment of advanced disease. In addition, in view of the high patient acceptability it would be a useful drug for evaluation in adjuvant studies.

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