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Vindesine as a Single Agent in the Treatment of Advanced Malignant Melanoma

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Summary. *The antitumour effect of vindesine (desacetyl vinblastine amide sulfate) in disseminated malignant melanoma has been investigated in our oncology service in a phase-II study.*

Of 25 patients exposed to the drug, 23 were evaluable, and seven of these (30%) were considered objective responders. The observed response of malignant effusions is of particular interest.

Side effects related to vindesine are similar to those of the other vinca alkaloids, although alopecia may be more pronounced with the doses used in this study.

Introduction

Vindesine is a new member of the family of vinca alkaloids, and shows promising antitumour activity [3]. The antineoplastic effect of this compound (99094, Eli Lilly) as a single agent in the treatment of disseminated malignant melanoma was investigated in a study approved by our Ethical Committee.

Methods

Selection of Patients

Twenty-five patients with advanced metastatic disease from malignant melanoma (stage III), who had failed to respond to other treatment or who were considered unsuitable for chemotherapy with DTIC, were included. Before admission to the protocol they were informed of the probable side effects of vindesine. Two patients are not considered evaluable because of incomplete treatment with the drug.

The remaining 23 patients are discussed in this paper in relation to the antitumor effect of vindesine in their disease and to associated side effects (Tables 1 and 2). There are ten males and thirteen females, with a mean age of 51.4 years (range 22 – 73 years). Of nine patients previously treated with chemotherapy, three (Cases 6, 21, and 22) had been exposed to melphalan only, by isolated limb perfusion, while the remaining six had received systemic treatment with various drugs, including both vincristine and vinblastine in each case. Tumour load was assessed in each patient before commencement of vindesine treatment by accurate measurement of two diameters of all cutaneous and subcutaneous metastases, which were recorded on appropriate charts. Lymph nodes were assessed in a similar manner, and visceral metastases were detected and measured by X-ray and scanning investigations.

Dose and Administration of Vindesine

The drug was given in a dose of 3 mg/m^2 as a bolus injection once weekly, for up to six weeks before evaluation of response. This dosage regime was observed in all patients, the exception being Case 4, where the initial dose of 4 mg/m^2 was gradually increased to a maximum bolus injection of 8 mg, which represents the highest single dose given in this series.

Results

Toxicity

The immediate tolerance of vindesine was good, and in most instances the agent was given on an out-patient basis. The side effects are analysed in Table 2 with the exception of one nonevaluable patient, who withdrew from treatment because of severe abdominal pains that he related to the drug, gastrointestinal side effects were generally mild, but did affect 43.5% of patients. Mouth ulcers were seen in one patient only. Fever and shivering following the injection and lasting for 3 – 4 h were reported by three patients. Myelotoxicity was manifest essentially in neutropenia. It was classified as mild when the absolute neutrophil count decreased to not less than 1.5×10^9/litre; moderate when this count was not less than 1×10^9/litre; and severe when the neutrophil count was below 1×10^9/litre. The lowest neutrophil blood count observed was in a partial responder (Case 9) who after four weekly courses of the drug showed a total leucocyte count of 4.4×10^9/litre, with an absolute neutrophil count of only 264/mm^3 (6%). A similar picture was observed during the nadir of marrow suppression in Case 19, the only complete responder in this series (500 neutrophils/mm^3 or 20% of

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Table 1. The antitumour effect of vindesine as a single agent in advanced malignant melanoma

Case no.	Therapy prior to entry in the study							Number of weekly injections before evaluation	Total dose of vindesine (mg)	Result[a]
	Age	Sex	Lymph node block dissection	Immuno-therapy	Radio-therapy	Isolated limb perfusion	Other chemo-therapy			
1. MFL	72	F	*	*	*		*	4	17	F
2. VM	73	F	*	*	*		*	6	33	S
3. AOS	42	M	*	*	*			6	36	MR
4. NC	22	F	*					4	28.5	F
5. RB	41	M	*					6	30	S
6. NG	52	F	*			*		3	17.1	F
7. CJ	69	M						6	34.2	S
8. LF	66	M	*				*	6	36	F
9. HA	62	F						6	30	PR
10. JG	29	F	*	*				6	31.5	F
11. ML	39	M	*		*		*	6	32.4	PR
12. BB	57	M	*	*	*		*	6	37	F
13. PZ	31	M	*	*				4	24.1	F
14. CE	28	M						6	36.5	F
15. HdeS	42	F	*					6	37	MR
16. ME	50	M		*				5	25	S
17. SM	48	F	*		*			3	19	F
18. BBD	58	F			*		*	2	10.5	F
19. DMcL-S	66	F						6	36	CR
20. MW	65	F	*					6	30	PR
21. WH	63	M				*		4	26	F
22. SP	42	F	*			*		6	29.2	PR
23. WA	65	F	*					3	16.5	F

[a] Responses as percentages: CR: 4.3%; PR: 17.4%; MR: 8.7%; S: 17.4%; F: 52.2%

CR: *Complete response* – complete resolution of all detectable disease lasting at least one month

PR: *Partial response* – decrease by more than 50% in size of all measurable lesions lasting at least one month while no new lesions appeared

MR: *Minimal or differential response* – definite objective clinical improvement lasting at least one month, but not qualifying for the above strict criteria

S: *Stasis* – no progression of disease

F: *Failure* – progression of disease

total WBC of 2.5×10^9/litre). Lymphopenia was not observed and this, in immunological terms, may be an advantage of the drug. Anaemia was not a significant problem, although a 3.5 g/dl drop in haemoglobin was seen in Case 14 after six successive weekly injections. Thrombocytopenia was not observed; on the contrary, a rise in the platelet count was seen in the majority of patients. Only one patient, Case 9, showed a decrease in the platelet count after treatment, but this was of no clinical significance.

Neurotoxicity was observed in 47.8% of patients, and was classified as mild when only paraesthesiae were present, moderate when objective neurological signs, such as hypoaesthesia and loss of tendon reflexes, were observed, and severe when clinically troublesome neurological signs were evident. Bilateral foot drop was observed in one patient, Case 9, whose treatment had to be modified despite definite partial response.

In this series, the major toxic effect of the drug was alopecia, which affected 91.3% of the patients. In six cases the alopecia was total.

Evaluation of Responses

Responses are defined and shown in Table 1.

Complete Response (CR) was seen in one patient with severe bone pain and positive scan and an evaluable mass of hard inguinal lymph nodes measuring 10×12 cm, which disappeared completely after six courses of vindesine. She remains asymptomatic on maintenance therapy and in complete remission 22 weeks after the initial response (Case 19).

Partial Responses (PR) were seen in four patients. In one patient, (Case 11) mediastinal lymph nodes compressing the oesophagus disappeared completely after six courses of vindesine, while other subcutaneous and pulmonary metastases also regressed. Two patients (Cases 9 and 20) showed near-complete regression of subcutaneous and cutaneous lesions, while in a fourth (Case 22) a left pleural effusion disappeared and malignant ascites was controlled for over 8 weeks with vindesine chemotherapy alone.

Table 2. Vindesine toxicity

Case no.	Myelo-suppression	Neuro-toxicity	Diarrhoea	Constipation	Alopecia	Mouth ulceration	Abdominal pain	Fever/ shivering
1. MFL	***			*	*			
2. VM	*	*			***			*
3. AOS	*	*	*		***			
4. MC		*		*	***	*		
5. RB	*				**			*
6. NG		*		*	*			
7. CJ	*	*					*	
8. LF	**	**			*			
9. HA	***	***			***			
10. JG	*	*			**			
11. ML	*		*		*			
12. BB	*	*			*			
13. PZ	**				**			
14. CE	*	**			**			
15. HdeS	***		*		***			
16. ME	**	**			**			
17. SM					**			
18. BBD	*							
19. DMcL-S	***		*		***		*	**
20. MW					**			
21. WH	*				*			
22. SP				*	*			
23. WA	*				*			
Incidence as percentage								
Mild (*)	47.8	30.4	17.4	17.4	34.8	4.3	8.7	8.7
Moderate (**)	13.0	13.0			30.4			4.3
Severe (***)	17.4	4.3			26.1			
ALL	78.3	47.8	17.4	17.4	91.3	4.3	8.7[a]	13.0

[a] One non evaluable patient withdrew from treatment because of severe abdominal pains that the related to vindesine

Minimal or Differential Response (MR). Impressive clinical objective and subjective improvement was observed in two patients with visceral metastases. After completion of six courses of vindesine in Case 15, there was complete resolution of ascites with a corresponding improvement of serum alkaline phosphatase values (a fall from 823 IU to 292 IU) (normal 90–330 IU). This patient does not qualify as a partial responder, because during the period of clinical improvement pulmonary metastases showed slow progression.

A second patient, Case 3, had extensive liver deposits and metastases to the small bowel, which caused subacute intestinal obstruction and blood loss. He underwent small-bowel resection and was then treated with vindesine. This produced complete disappearance of one large subcutaneous deposit but less than 50% regression of other measurable disease. He survived 11 months following abdominal surgery, dying of cerebral metastases.

Discussion

Chemotherapy in the management of advanced malignant melanoma is disappointing. The most effective single agent in the treatment of this disease is DTIC, which produces objective responses in 25% of patients [1]. The nitrosoureas also possess some antitumour activity, but do not produce an objective response in more than 18% of patients [4]. Combination of these agents does not improve the response rate [5].

In June 1977 we undertook a study to evaluate the antitumour effect of vindesine in advanced malignant melanoma. Our results indicate that this compound exerts significant antitumour activity in melanoma.

One of the most disputed areas in the evaluation of new anticancer agents is the definition of duration of response. Defined periods of observed response vary with different investigators. Einhorn and Furnas consider a 6-week period necessary for evaluation of response, whereas Costanza et al. consider stabilization over a 2-week interval adequate. We have preferred an observation period of 4 weeks following the sixth weekly injection of vindesine, which we feel is an adequate period for a tumour that is known to be resistant to most chemotherapeutic agents.

The pattern of response in this study is generally similar to that observed with other drugs effective in melanoma. Five of the seven responders were female, and only one of these had received systemic chemotherapy previously. It is encouraging, however, that most responders (5 out of 7) had advanced visceral disease with ascites and pleural effusions, which responded dramatically to this drug, whereas response of visceral disease to DTIC is uncommon [4].

The toxicity of vindesine as administered in this study is acceptable. Myelotoxicity and neuropathy are comparable to those seen with the other two members of the family, but the lymphocyte- and thrombocyte-sparing effect of this drug seems superior. Its use in thrombocytopenic states has already been proposed [6], and the immunological implications of the lymphocyte-sparing effect may be important.

The major toxic effect in this series was alopecia, which was total in 25% of patients, but all responders with significant hair loss were so pleased by their constitutional improvement that they considered alopoecia a small price to pay.

Most responses were seen after the second and third injections of the drug, and it is suggested that a trial of six weekly injections is adequate before change to another drug is considered necessary. It would appear that the optimum dose for response is 3 mg/m^2 as a bolus injection on a weekly basis, and increasing the dose above this level is unlikely to confer significant therapeutic benefit, while toxicity will be increased. There is a narrow margin in the dose responsible for neurotoxicity, and we found the critical level to be above 3 mg/m^2. Until other therapeutic schemes have been explored, we would strongly recommend that vindesine be employed in the management of malignant melanoma on the lines proposed in this paper.

Conclusions

Our results indicate that the antitumour effect of vindesine in advanced malignant melanoma is at least comparable to, and probably superior to, that of DTIC. The median duration of response to vindesine to date is 8 weeks (range 6–27 weeks). With the exception of alopecia, side effects are acceptable and the drug is far better tolerated than DTIC.

If future studies confirm our results, vindesine is likely to become the drug of choice in the treatment of this condition, and an important component of combined chemotherapy in the management of malignant melanoma.

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