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Treatment of Advanced Malignant Melanoma with Interferon Alpha and Etretinate

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Abstract—*The combination of recombinant human interferon alpha A* 9 MU *daily intramuscularly and etretinate* 50 mg *daily orally was given to* 25 *patients with progressive advanced, metastatic melanoma. The treatment was well tolerated. Partial responses were seen in three* (12%) *patients lasting from* 2 *to* 8 *months. A further partial response was seen in one of three patients when they were given vindesine and DTIC whilst they continued receiving interferon and etretinate.*

INTERFERON ALPHA has been given to many patients with malignant melanoma with approximately 13% having an objective response [1]. The anti-tumour effect of interferon may act by a direct anti-proliferative effect, by immunomodulation, by altering antigen expression or by inducing differentiation.

Retinoids are more powerful differentiating agents, which have an anti-proliferative effect on several melanoma cell lines in culture [2] but their activity as single agents in patients with melanoma has been disappointing. Stabilization of disease was seen in two of seven patients treated with etretinate [3] and partial responses were seen in two of 18 receiving 13-*cis*-retinoic acid [4]. As interferon and retinoids have different spectra of toxicity and they have been shown *in vitro* to synergistically induce differentiation [5] the combination of drugs was tested.

MATERIALS AND METHODS

Twenty-five patients with advanced metastatic melanoma which had progressed over the previous month and with the characteristics shown in Table 1 were treated. They all gave verbal informed consent. They received intramuscular recombinant human interferon alpha A (Roferon A) at a dose of 9 MU daily until there was intolerance or tumour progression. After 10 weeks daily therapy, injections continued three times a week. Injections were given in the evening with 14 of 25 patients having the interferon given by themselves or by their spouse. They also received oral etretinate 50 mg daily, reducing to 25 mg if poorly tolerated.

Responses were recorded as follows: partial response, greater than 50% decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by two observations not less than 4 weeks apart; stable disease, less than 50% decrease in total tumour size and less than 25% increase in size over a minimum of 4 weeks; mixed response, complete regression of some lesions determined by physical examination but less than 50% decrease in size of some lesions; progression, a 25% or more increase in the size of one or more measurable lesions, or the appearance of new lesions.

RESULTS

Therapy was well tolerated and only discontinued because of tumour progression. Partial responses were seen in three (12%) patients (95% confidence limits 0–25%). They lasted for 8 months in a patient with lung metastases who whilst still responding in the chest developed brain metastases, for 5 months in a patient with multiple skin deposits who relapsed in bone and then brain whilst the skin remained in remission, and for 2 months in a patient with nodal and lung disease. Stable disease of 2–3 month duration was noted in three (12%) patients and mixed responses of 3 and 7+ months duration were noted in two patients. Eight patients showed evidence of progression of disease within 4 weeks of starting therapy.

After failure on interferon + etretinate therapy,

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Table 1. Patient characteristics

Characteristics	No. of patients
Total entered	25
Male	16
Female	9
Median age	53
Previous treatment	
Chemotherapy	0
Radiotherapy	8
Site of disease	
Skin alone	9
Skin and other sites	10
Lung alone	1
Lung and other sites	6
Lymph nodes and other sites	9
Liver	9
Bone	3
Intra abdominal masses	3
< 1 month therapy	6
Interferon dosage reduction	4
Etretinate dosage reduction	16

ECOG performance status	At start	After 1 month treatment
0	11 (44%)	9 (47%)
1	11 (44%)	6 (31%)
2	2	0
3	1	4

five patients were given Vindesine 5 mg and DTIC 400 mg weekly with no responses seen. Three patients were given the same chemotherapy but continued the interferon and etretinate without any unexpected toxicity. One patient had a partial response of skin, nodal and lung disease for 4 months with dramatic improvement in performance status for 12 months.

DISCUSSION

The patients in this study had more advanced disease than in many interferon studies. Nevertheless, the response rate to interferon and etretinate does not appear better than the response rate to interferon alone and a combination cannot therefore be recommended. As the therapy was so well tolerated it would be worth investigating in patients with less advanced disease and the introduction of cytotoxic drugs on disease progression requires further study.

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