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Phase II Study of Recombinant α-Interferon in Malignant Melanoma

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Ninety-seven evaluable patients with measurable, advanced, malignant melanoma were treated with recombinant α interferon in a cooperative phase II efficacy trial, whose primary objective was to estimate the response rate. Interferon (rIFN α-2a, Roferon-A) was injected subcutaneously daily for 70 days. Dose was escalated in four steps from three million units to 36 million units over ten days. Eight patients responded objectively and six patients (6%) had a complete response. The median duration of complete response was 11 months. Patients achieving complete response had only cutaneous, nodal, or pulmonary disease; some had extensive prior therapy; some could tolerate no more than three million units per day. Few patients could tolerate the target dose of 36 million units daily for 70 days. Limiting toxicity was primarily fatigue. Interferon in tolerable doses is effective in a small subset of patients with melanoma. Comparison of published trials of dacarbazine and recombinant α interferon indicates the two drugs have similar activity.

Key Words: Malignant melanoma—Interferon—Recombinant α interferon—Phase II clinical trial.

Malignant melanoma affects over 27,000 patients each year in the United States, and the incidence appears to be rising (1). Nearly one-third of patients develop advanced disease, and advanced disease is rapidly fatal in the great majority of patients. The only standard therapy, dacarbazine, produces responses of limited duration and has limited impact on quality of life in no more than one-fourth or one-fifth of patients (2). This drug would not meet current standards of the Food Drug Administration for efficacy, which standards now include a demonstration of impact on survival and quality of life.

The interferons are a family of at least eighteen distinct proteins divided into three classes according to biological and physicochemical properties. The α interferons consist of at least 16 subtypes having amino acid sequence homology of approximately 75%. They are produced by leukocytes after viral stimulation and inhibit viral replication. This property is used to define potency (3–5). α Interferon binds to a unique cell surface receptor after which it is internalized and degraded (6,7). The receptors number about 5,000 per cell and are of high affinity with dissociation constant of 10^{-10} to 10^{-11} M (8). Several α interferons have been genetically engineered for large-scale production by recombinant DNA technology and have been used widely in clinical trials.

In addition to its antiviral properties, interferon has antiproliferative and immunomodulatory properties which are of potential importance in inhibiting tumor growth (5). Many freshly explanted human tumors are inhibited to some extent by α interferon when tested in the human tumor stem cell assay (9–11).

Typically, concentrations of interferon in the range of 80 to 800 U/ml are employed and inhibition in the range of 50–70 percent is taken as significant. Mela-

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nomas are often sensitive in the range of 50 percent inhibition and a few are inhibited as much as 70–90 percent by these concentrations of interferon (9,11). However, there has been no convincing correlation of in vitro sensitivity at these levels with clinical tumor response to treatment with interferon.

Interest in interferon as a clinical anticancer agent has often centered about its immunoregulatory properties. Of possible relevance to antitumor immunity, interferon has been reported to increase natural killer activity (12–20), to increase the expression of Class I and II human leukocyte antigens (HLA) and tumor antigens (21–23) including melanoma antigens (23), and to enhance macrophage activation and macrophage-mediated tumoricidal activity (24–26).

α Interferon is highly active in the control of hairy cell leukemia (27–29). Responses have also been reported previously in a number of other malignancies including malignant melanoma (30–36). This report concerns a Phase II multicenter trial conducted to evaluate the clinical safety and to establish the efficacy of rIFN α-2a in patients with advanced disseminated malignant melanoma.

MATERIALS AND METHODS

Patients with histologically documented malignant melanoma and measurable metastatic or advanced disease were eligible for enrollment in this study. Patients with disease in ominous sites such as brain, with poor performance status, with intercurrent medical problems, and with very limited life expectancy were excluded from participation. Prior therapy except interferon was permitted. Patients were enrolled at each of the five study centers independently but concurrently.

The treatment plan included an induction phase for the subcutaneous injection of rIFN α-2a: 3 million units daily for three days, followed by 9 million units daily for three days, followed by 18 million units daily for three days. Patients then received 36 million units daily for 61 days. Patients without progressive disease at the end of 70 days were eligible for maintenance therapy consisting of interferon at the previously tolerated dose, but given three times weekly. Maintenance therapy required the absence of progressive disease, the absence of unacceptable toxicity, and the acceptance of the patient and the patient's physician.

Complete response was defined as the disappearance of all clinical evidence of disease without the appearance of any new evidence of disease. Partial response was defined as a 50% decrease in the sum of the products of perpendicular diameters of index lesions in all organs containing measurable disease with the appearance of no new lesions and with no evidence of progression at any site.

RESULTS

Patient characteristics are given in Table 1. One-hundred-twelve patients were entered into the study. Fifteen patients were excluded from evaluation. Reasons for exclusion included concomitant therapy in three instances, presence of brain metastases at entry in two instances, prior malignancy in one instance, failure to return for follow-up in two instances, and major protocol violations in the remaining seven. The great majority of patients had had prior therapy in addition to surgery and about one-third had prior chemotherapy. The patients' performance status was excellent: one-third were asymptomatic and most of the remainder were ambulatory and minimally symptomatic. Accrual of evaluable patients by study center was M. D. Anderson, 27; Georgetown (Neefe), 24; University of California, 20; University of Arizona, 15; and New England Deaconess, 11. The patients from M. D. Anderson have been reported previously (37).

Eight patients had objective responses and six of these were complete responses for a complete response rate of 6%. Complete response was seen in patients

TABLE 1. *Characteristics of evaluable patients*

N	97
Sex	
Male	62
Female	35
Age	
Median	49
Range	18–82
Site of Disease	
Cutaneous/Nodal	56
Liver	26
Lung	51
Other Visceral	19
Prior Therapy	
Surgery	97
Chemotherapy	31
Radiotherapy	20
Immunotherapy	19
Hormonal	2
Performance Status (ECOG)	
0	67
1	26
2	2
Days Receiving Treatment	
Median	53
Range	2–434
Best Response	
Complete Response	6
Partial Response	2
Response, less than partial	12
Stable	35
Progressive Disease	42

with cutaneous and nodal disease or lung disease. Complete responses were not seen in other sites. The partial responses were seen in a patient with liver disease and a patient with liver and lung disease. Three of the responders had prior chemotherapy. The median time to the first objective sign of response was 0.9 months (range, 0.9–1.0 months) for the two partial responders and 1.9 months (range, 0.7–3.9 months) for the six complete responders. The median time to complete response was 2.0 months (range, 0.7–3.9 months). The median duration of response was 7.9 months from the start of therapy for those two patients with partial response and 10.8 months (range, 2.3–45 months) for the patients with complete response. A single patient remained in complete remission, continuously disease-free for 45 months, until a relapse in the central nervous system. This individual had bulky cutaneous disease at his right elbow and bulky right axillary adenopathy. In addition, he had innumerable tumor nodules clearly evident on chest x-ray film and computed tomography of the chest. This patient had shown rapid disease progression through four prior regimens of chemotherapy, radiotherapy, and immunotherapy. He received three doses of 3 million units, three doses of 9 million units, and then treatment was suspended because of moderate fatigue. Therapy was resumed at 3 million units per day. The patient achieved a complete response and after a total treatment duration of eighteen months, therapy was discontinued because of patient preference in the absence of evidence for any benefit of continued therapy.

Two additional patients had objective evidence of response considered by the investigator to be the equivalent of partial response but scored as mixed/minor response, and not included in the reported response rate. One had a soft tissue mass decreasing in size by a third and a lung mass, evaluable but not measurable, which disappeared. The second had three lesions which disappeared, one which decreased by more than half, and a small lesion which more than doubled in size.

The toxicities were substantial but manageable. Side effects resulting in dose attenuation or drug discontinuation are shown in Table 2. Fatigue was the most common side effect and this was moderate or severe in well over half the patients. In many cases the fatigue was dramatic: the performance status of 69 patients declined such that they were in bed > 50% of the time; sixteen patients were totally confined to bed and unable to tend to normal self-care activities. Anorexia or nausea and vomiting were also very common among patients discontinuing interferon because of intolerance of side effects. Changes in mental status, possibly or probably related to interferon administration, occurred in 21 patients. These changes included confusion, drowsiness, and forgetfulness. Disorders of mood and affect, including anxiety, depression, agitation, and sleep disturbances, occurred in five patients. Neurological disorders including diplopia, altered gait, paresthesias, slurred speech, visual disturbances, or tremor, occurred in eight patients. Weight loss was a common problem among patients discontinuing interferon; 18 patients had weight loss > 5% of total body weight and 10 patients had loss > 10%. Forty-six patients discontinued therapy partially or entirely because of significant side effects. Eight patients had life-threatening toxicities. These were scored by the primary physician as severe and this was defined as disabling toxicity requiring hospitalization. In all eight cases, interferon was discontinued. Four of these patients had changes in mental status approaching obtundation or coma. Four other patients had gastrointestinal disturbances including emesis or diarrhea, resulting in dehydration or hypotension. Twelve patients died within 30 days of the last dose of interferon. In none of these cases did the patient's physician consider that administration of interferon was likely to have contributed to the patient's death given the setting of advanced and progressive disease. Coincident occurrence in time prevents an absolute judgement that administration of interferon did not contribute in some proportion to any of those patients' deaths. No unexpected or unexplained deaths occurred.

TABLE 2. *Common Side Effects*

Symptom	Mild or moderate	Severe
Anorexia, Nausea, Vomiting	23 (%)	12 (%)
Alteration in Mood or Affect	3	2
Change in Mental Status	19	3
Neurologic Symptoms	8	0
Fatigue	61	16
Fever and Diaphoresis	4	4
Headache	3	0
Myalgia	6	5
Rash	3	0
Weight Loss	11	10

Seventy-seven patients remained on study for at least 30 days. Of these only 32 were receiving the target dose of 36 million units at 30 days. By day 72, only 34 patients remained on study and of these only four remained at the target dose. Only one individual was able to receive the target maintenance dose of 36 million units for a duration of 12 months; this individual was a man weighing nearly 300 pounds.

It may be concluded that patients on this study received the largest doses of interferon that could be administered on a daily schedule of subcutaneous administration. The value of the dose escalation scheme over the initial ten days of therapy cannot be deter-

mined without a comparison arm. Most of the patients discontinuing therapy because of adverse experiences did so within the first 21 days of therapy. From this one may conclude that the gradual escalation of dose is not of itself sufficient to permit the administration of the target dose of 36 million units daily.

DISCUSSION

We have observed a response rate of 8% in 97 patients with malignant melanoma treated with α interferon. Most patients who responded had disappearance of clinically evident disease and the complete response rate was 6%. Kirkwood and Ernstoff have reported a similar complete response rate of 8% in a review of melanoma patients treated with recombinant α interferon (38). We believe that there is a small but reproducible remission rate which may be induced in malignant melanoma with recombinant α interferon.

Our patients were treated with daily subcutaneous injections for 70 days with a target daily dose of 36 million units. Very few patients were able to tolerate a full 70 day course of recombinant α interferon at this dose. Therefore, we may conclude that our patients received a maximal achievable dose according to this scheme of administration. It is important to note that some of the responders in this trial and some responders in other trials have been treated with doses of interferon which are much smaller (30). Edwards et al. (19) have reported a dose optimum of about 3 million units for achieving induction of natural killer activity. It is possible that higher response rates could be achieved with smaller doses of interferon than used in this trial.

Dacarbazine is often taken to be standard therapy for metastatic malignant melanoma. Comis reported a response rate of 24% among 851 patients treated with dacarbazine (39). In five cooperative studies reviewed by Comis, the response rates were 16–31%, but the complete response rate was 5% (38 of 730 patients). Carbone et al. (40) reviewed 275 patients treated by the Eastern Cooperative Oncology Group and found 13 complete responses among 275 patients (5%). Median survival of the complete responders was 183 weeks. Bellet et al. reported four of 36 patients treated with dacarbazine as complete responders with response durations of 33+, 33+, 18+, and 12 months (41). Similar complete response rates have been reported by others (42,43). If one will accept that a meaningful impact of therapy upon quality of life and survival is not often associated with partial response but may be associated with complete response, then it appears that dacarbazine and α interferon, with similar complete response rates probably have comparable activity. Some of those patients in our study who responded to α interferon had previously failed to respond to dacarbazine. Thus, it appears that the sets of responders for the two agents are not identical.

The small but real level of activity observed in patients with melanoma treated with recombinant α interferon should encourage efforts to identify subsets of patients who may have increased likelihood of response. Moreover, there is a pressing need to identify the mechanism of action in responding patients, since this knowledge might suggest strategies which could be used to enhance the response rate. ℭ

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