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A Combination of Subcutaneous Recombinant Interleukin-2 and Recombinant Interferon-α in the Treatment of Advanced Renal Cell Carcinoma or Melanoma

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In this phase II study, we have evaluated the efficacy and toxicity of low-dose subcutaneous (s.c.) recombinant interleukin-2 (IL-2) and recombinant interferon (IFN)-α in 16 patients with advanced renal cell carcinoma (RCC) and in 4 patients with advanced melanoma. The complete course on this protocol comprised 6 weeks of s.c. IL-2 plus IFN-α followed by a 2-week rest period. The treatment was moderately strenuous for patients, requiring frequent dose reductions; only eight cycles (30%) could be administered to 75–100% of the projected dose. Main side-effects were fever, fatigue, hypotension, liver toxicity, neurotoxicity and skin reactions. Among the evaluable 17 patients, two responses (one partial, one complete) were seen in patients with RCC. This regimen proved to be rather toxic and yielded a modest response rate of 15% in RCC, but initial findings concerning the duration of survival seem promising.
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INTRODUCTION

THE RESULTS of treatment of advanced melanoma and renal cell carcinoma (RCC) have remained far from satisfactory. Chemotherapy alone yields response rates of approximately 20% in melanoma, and 10% in RCC [1, 2]. Interferon (IFN)-α has been used at various doses for RCC and melanoma, with response rates of 15–20% [3–5]. Interleukin 2 (IL-2) entered clinical trials in 1985, when Rosenberg and his coworkers published their observations on treatment with IL-2 combined with lymphokine activated killer (LAK) cells in various cancers [6]. The responses seen were most promising in RCC and melanoma. However, high doses of intravenous IL-2 caused major side-effects in the

original trials [6, 7]. Since then, response rates ranging from 14 to 36% have been reported in above-cited cancers, even with less toxic schedules [8–12].

IL-2 acts as a lymphocytotrophic agent regulating the immune response [13]. IFN-α exhibit antiproliferative and immunomodulatory activity on normal and neoplastic cells [4]. IL-2 seems to be synergistic with IFN-α in experimental models [14].

Based on the moderately favourable results reported by Atzpodien and his coworkers with subcutaneous (s.c.) home therapy with IL-2 and IFN-α [11, 12], we conducted the present study to evaluate the safety, tolerance and efficacy of low-dose s.c. IL-2 and IFN-α in patients with advanced RCC or melanoma.

PATIENTS AND METHODS

Between April 1991 and November 1992, 16 patients with histologically confirmed advanced RCC and 4 patients with advanced melanoma were enrolled for the present study (Table 1). The inclusion criteria were age 18–75 years, measurable disease, adequate myeloid, renal and hepatic functions and Karnofsky index of 80 or higher. Informed consent was obtained for participation in the study.

IL-2 (Proleukin®, provided by Eurocetus, Amsterdam, The Netherlands) was administered on 5 consecutive days for 6 weeks at a dose of 2.4×10^6 U/m^2 s.c. twice daily except for days 1, 2, 22 and 23 when a larger dose (4.8×10^6 U/m^2 two to three times daily) was given as a priming dose. IFN-α-2a (Roferon-A®, Hoffmann-La Roche, Basle, Switzerland) or IFN-α-2b (Intron-A®, Schering-Plough, New Jersey, U.S.A.) was administered at a dose of 6×10^6 U/m^2 s.c. three times weekly (TIW) except for weeks 1 and 4, when the dose was smaller (3×10^6 U/m^2 twice weekly) during the priming phase with IL-2. The duration of a cycle was 6 weeks, and the rest period between cycles was 2 weeks.

Table 1. Patients' characteristics

Variable	RCC *n*	Melanoma *n*
Patients eligible	16	4
Male/female ratio	9/7	1/3
Age range in years (median)	44–69 (58)	21–62 (46)
Karnofsky index		
100	2	0
90	6	3
80	8	1
Disease-free interval		
<1 year	14	2
1–2 years	1	0
>2 years	1	2
Metastatic sites		
Lung only	5	0
Lung + other	7	2
Central lymph nodes	6	1
Bone	2	1
Liver	2	2
Other (e.g. pleura, scar)	7	1
Multiple	8	2
Prior non-surgical therapy		
Chemotherapy	7	1
Hormones	4	0
Interferon	4	0
Radiotherapy	4	0
Several modalities	5	0

After the first cycle, responding patients or patients with stable disease (SD) received one or two additional cycles. Patients off protocol after two or three cycles without evidence of progressive disease received maintenance therapy consisting of 5-day treatment every 4 weeks. The treatment schedule for these 5 days was IL-2 2.4×10^6 U/m^2 s.c. twice daily and IFN-α 6×10^6 U/m^2 s.c. TIW.

Toxicity and response were evaluated according to the WHO criteria [15].

RESULTS

All patients were considered evaluable for toxicity, and 17 patients (13 with RCC and 4 with melanoma) for response. 3 patients were not considered evaluable for response due to an adverse event leading to discontinuation of the first cycle.

One patient with RCC and multiple lung metastases achieved complete response (CR) after having received nearly three cycles. The duration of response was 4+ months. In addition, another patient with RCC and pleural lesion achieved partial response (PR). Of the other patients with RCC, 8 had SD and 3 had progressive disease (PD). The median survival of the assessable patients with RCC was 13+ months (range 6+ to 24+), of the patients with SD 15+ months (range 9 to 24+) and for the patients with PD, it was 8+ months (range 6+ to 9). Of the 4 patients with melanoma, 3 had SD and 1 had PD. The median survival of the patients with melanoma was 7 months.

17 patients received the total of 27 complete cycles. In addition, 9 patients received nine incomplete cycles. 2 patients with RCC received maintenance therapy for 5 months. Dosage was frequently adjusted due to adverse effects.

The dose intensity of IL-2 was as follows: of the 27 complete cycles given, 11 (41%) were with over 90% of the projected cumulative dose cycle, 6 (22%) with 70–90%, 7 (26%) with 50–69% and 3 (11%) with less than 50%. The dose intensity of IFN-α was as follows: six cycles (22%) were with over 90% of the projected cumulative dose, 3 (11%) with 70–90%, 10 (37%) with 50–69% and 8 (30%) with less than 50%. Interruptions were more frequent with IL-2 than with IFN-α.

The toxicity associated with the treatment is shown in Table 2. All patients experienced some form of toxicity, which was mostly reversible and responsive to dose reductions and treatment interruptions. Severe or life-threatening adverse effects were recorded in 14 patients (70%). Fever, chills, fatigue and skin reactions were observed in all patients. Fatigue was cumulative, being most debilitating towards the end of the treatment.

Hypotension was a universal finding. Transient elevations of liver enzymes were observed in 16 patients. Neurological effects, including mental changes, were recorded in 12 patients. Treatment was discontinued due to neurotoxicity in 3 patients.

Anorexia and mild gastrointestinal symptoms were observed in 12 patients. Laboratory evidence of thyroid dysfunction was noted in 9 patients. Mild to moderate haematotoxicity was observed in 8 patients. Reversible eosinophilia and lymphocytosis were common findings. Dyspnoea or cough was reported in 7 patients, but no severe IL-2-induced capillary leak syndrome

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Table 2. Toxicity of IL-2 plus IFN-α treatment

Adverse event	Grade 1–2	Grade 3	Grade 4
Fever and chills	14	6	0
Fatigue	12	8	0
Hypotension	13	6	0
Liver toxicity	14	2	0
Rash	13	0	0
Neurotoxicity	10	4	0
Dizziness	5	3	0
Mood change	3	1	0
Loss of taste	2	0	0
Paresthesia	1	0	0
Collapse	0	1	0
Anorexia	6	4	2
Myalgia/arthralgia	11	0	0
Nausea	10	0	0
Thyroid dysfunction	9	–	–
Anaemia	8	0	0
Dyspnoea/cough	6	1	0
Oedema	4	1	0
Renal dysfunction	4	0	1
Diarrhoea	2	0	0
Cardiac			
Arrhythmia	0	1	0
Angina pectoris	0	1	0
Leucopenia	1	0	0
Candida esophagitis	1	0	0

Findings indicated as number of patients.

was observed. Creatinine elevation was recorded in 5 patients. In 4 patients it was reversible, but there was 1 renal failure which required haemodialysis and, together with rapidly progressing RCC, caused the death of the patient. 2 patients were withdrawn from the study due to cardiotoxicity.

DISCUSSION

In the present trial, combined low-dose s.c. IL-2 and IFN-α was evaluated in patients with advanced RCC or melanoma. Previously, Atzpodien and his coworkers have reported response rates of 29–36% in advanced RCC and 14% in melanoma with a similar regimen [11, 12]. However, we could not confirm the moderately favourable results achieved by them. In our study, among the 17 evaluable patients, 2 responses were seen yielding a response rate of 15% in RCC. 1 patient with RCC and multiple lung metastases achieved CR. This patient was omitted from treatment protocol due to neurotoxicity after nearly three complete cycles. The CR appeared late, 6 months after the initiation of treatment. Another patient with RCC and a pleural lesion achieved PR after having received one cycle, but treatment was then discontinued because of anxiety and fatigue. This response was also rather slow, appearing 6 weeks after the discontinuation of treatment. The median survival for all patients with RCC was 13+ months, for patients with SD 15+ months and with PD 8+ months. No objective responses were seen in patients with melanoma.

The toxicity profile was similar to that reported previously, but in the present study, a high percentage (70%) of grades 3 and/or 4 adverse effects was observed. Thus, the dose intensity remained low: only 41% (IL-2) and 22% (IFN-α) of the 27 complete cycles delivered could be administered at >90% of the intended cumulative dose. This is strikingly different from the dose intensity reported by Atzpodien and his coworkers [12]. In the present study, the main dose-limiting adverse events were hypotension and fatigue. In fact, against our expectations, nearly half of the patients were hospitalised for most of the treatment period.

The combination of radiotherapy and immunotherapy could be an interesting approach since, in the present study, 1 patient with RCC and progressing lung metastasis achieved CR lasting for 10 months after two cycles plus local radiation therapy. In addition, the patient with PR remained stable for 9 months after local radiation therapy for pleural lesion.

It can be concluded that the response rate of the patients with RCC in this trial was somewhat lower than expected. On the other hand, the median survival of 13+ months in the present study compares favourably with other published data. The number of patients with melanoma is too small for conclusions. The toxicity of the present regimen causes major limitations on the use of this combination as outpatient treatment. More tolerable schemes with these agents should be explored.

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