Pergamon

European Journal of Cancer, Vol. 34, No. 5, pp. 754–756, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10089-2

Short Communication

Lack of Efficacy of Recombinant Human Interleukin-6 in Patients with Advanced Renal Cell Cancer: Results of a Phase II Study

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The present phase II study was undertaken to assess antitumoral activity, safety and tolerability of recombinant human interleukin-6 (rh IL-6) in patients with advanced renal cell cancer. Rh IL-6 was administered as a daily subcutaneous injection at a fixed dose of 150 μg/day for a maximum of 42 consecutive days. 12 patients with metastatic renal cell cancer without previous immunotherapy were enrolled and were evaluated for response. No objective clinical responses were observed in the trial. Toxicity was moderate and reversible and mainly comprised fever, influenza-like symptoms, fatigue and moderate hepatotoxicity. Anaemia, leucocytosis, thrombocytosis and induction of an acute phase response were observed in most patients. In conclusion, prolonged subcutaneous administration of rh IL-6 on an outpatient basis is safe and feasible. However, rh IL-6 exhibited no antitumoral activity in patients with metastastic renal cell cancer. Profound regulatory effects on haematopoiesis and inflammatory response of rh IL-6 were observed.

Key words: cancer, therapeutics, kidney neoplasms, immunotherapy, interleukin-6
Eur J Cancer, Vol. 34, No. 5, pp. 754–756, 1998

INTRODUCTION

METASTATIC RENAL cell cancer has a poor prognosis in most patients. Median survival is less than 1 year. However, a minority of patients exhibit a more favourable clinical course with stable disease over prolonged periods and even spontaneous regression of metastatic sites [1, 2]. These observations and the complete resistance towards cytotoxic chemotherapy prompted extensive exploratory efforts of immunotherapy in patients with advanced renal cell cancer. Both interleukin-2 (IL-2) and interferon-alpha (IFN-alpha) show antitumoral activity in some phase II trials [3–5]. In general, only a selected minority of patients appears to benefit from present immunotherapeutic regimens. Therefore, new safe and effective agents for treatment of metastatic renal cell cancer are clearly needed. The present phase II study was undertaken to assess antitumoral activity, safety and tolerability of daily subcutaneous (s.c.) injections of a fixed dose of recombinant human IL-6 (rh IL-6) in patients with medically untreated metastatic renal cell cancer.

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Received 8 Jul. 1997; revised 30 Sep. 1997; accepted 23 Oct. 1997.

PATIENTS AND METHODS

Eligibility criteria for participation in the trial included: diagnosis of histologically verified metastatic renal cell cancer, the presence of bi-dimensionally measurable metastatic lesions, a life expectancy of more than 3 months, age from 18 to 75 years, a WHO performance score of less than or equal to 1 and adequate haematopoietic, renal and liver function. Exclusion criteria were nephrectomy, surgery or radiotherapy of a marker lesion, chemotherapy or administration of any investigational agent within 4 weeks prior to enrolment into the trial, pretreatment with immunotherapy (including interferon,

cytokines and any other type of immune therapy), brain metastases, severe allergic or autoimmune diseases, known HIV infection, active viral hepatitis or Epstein–Barr virus (EBV) infection, immunosuppressive therapy including steroids, presence of a monoclonal gammopathy and pregnant or lactating women. Written informed consent was obtained from all patients.

This was a multi-centre, uncontrolled, non-randomised phase II study. Three centres participated in the trial. Treatment consisted of single daily s.c. injections of 150 μg rh IL-6 for a total of 6 weeks. For the first 2–3 days of treatment all subjects were hospitalised for monitoring of initial tolerability and safety of rh IL-6 treatment. Further treatment was performed on an outpatient basis with fixed weekly examinations in the study centres. After 3 weeks of treatment, an interim tumour staging was performed.

rh IL-6 was provided by Sandoz Inc. (Basle, Switzerland). The protein, originally cloned by Genetics Institute, was expressed in an *Escherichia coli* strain. The specific biological activity of rh IL-6 was 10^8 U/mg protein as measured in the B-13-29 cell line bioassay.

RESULTS

12 patients were enrolled in the trial and were evaluable for response. The median age was 52 years (range 42–68 years); 3 patients were female. WHO performance grade was 0 in 4 patients and 1 in 8 patients. All patients had been treated surgically by nephrectomy or resection of metastases at a median of 9.9 months before enrolment (range 0.9–73.5 months) and 1 patient had undergone additional radiotherapy 25 months before enrolment.

Patients were treated for a median of 40 days (range 20–43 days). Only 5 patients completed the projected treatment period. A total of 7 patients were withdrawn from the study. Reasons for treatment discontinuation were adverse events (3 patients), treatment failure (2 patients), death (1 patient), and withdrawal of consent (1 patient). The median cumulative dose of rh IL-6 received was 6000 μg (range 3000–6450 μg).

All but 1 patient had progressive disease at study entry. No remissions were observed during treatment with rh IL-6 or early follow-up of the patients. At week 3, 4 patients had progressive disease and 6 patients had stable disease; 2 patients were not assessed for response at week 3. At week 6 (end of treatment), 8 patients had progressive disease, 3 patients had stable disease and 1 patient was not assessed. At early follow-up after 1 month, 8 patients had progressive disease, 2 patients had stable disease and 2 patients were not assessed. In 6 patients, new metastatic lesions occurred during treatment or the follow-up period.

Mild to moderate fever, chills, fatigue and influenza-like symptoms were the most common drug-related toxicities observed. They could be managed by paracetamol and ceased upon discontinuation of treatment. In addition, mild to moderate myalgias, moderate increases in cholestatic enzymes, and local erythema at injection sites occurred in some patients. Severe adverse events occurred in 4 patients: WHO grade 2 pain (2), WHO grade 1 hypercalcaemia (1), WHO grade 3 anaemia (1), WHO grade 3 increase in alkaline phosphatase (1). One serious adverse event was reported: a patient died from pneumonia, which appeared while on protocol treatment. Study medication was immediately halted. Post-mortem examination revealed adult respiratory distress syndrome as the cause of death. No definite relationship to the study medication was established. A total of 4 patients required red blood cell transfusions. 2 patients were transfused during the treatment period, 3 patients were transfused during the follow-up period. The effects of rh IL-6 on blood cell subsets are summarised in Figure 1.

Treatment with rh IL-6 resulted in an increase in acute phase proteins fibrinogen and C-reactive protein (CRP) in all

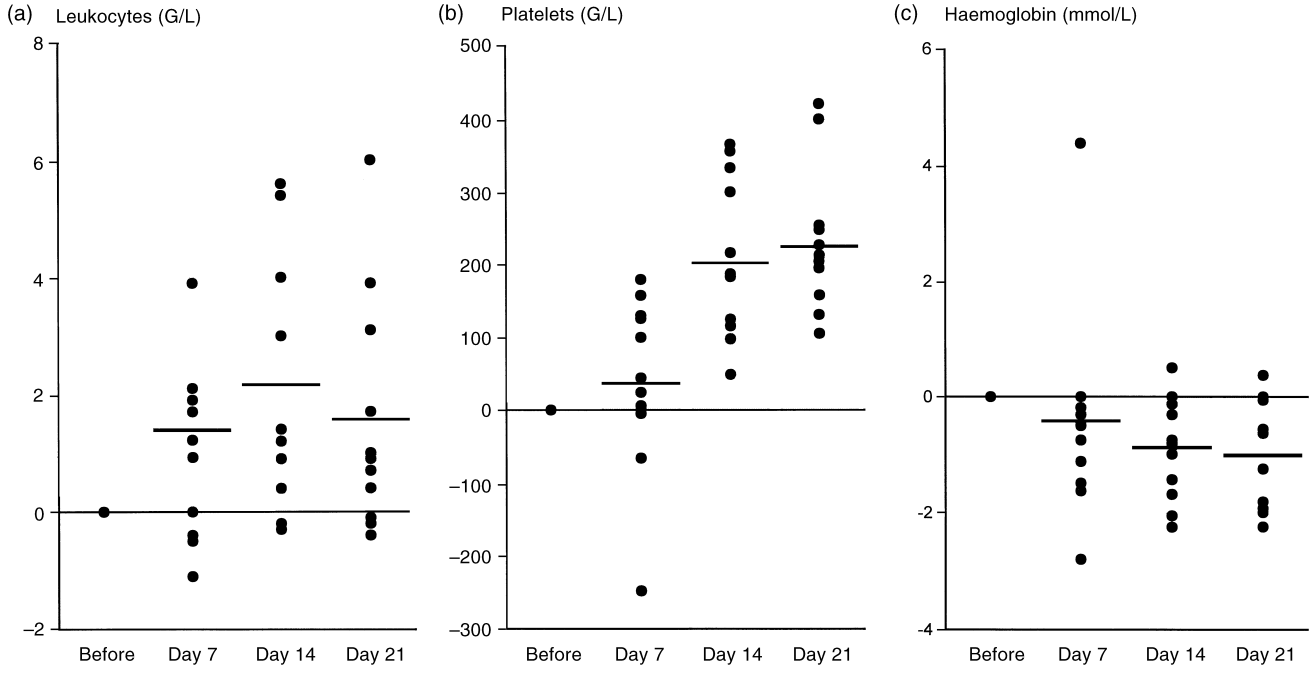

Figure 1. Changes in leucocyte (a), platelet (b) counts and in haemoglobin concentrations (c) in response to treatment with recombinant human interleukin-6 (rh IL-6) in 12 patients with advanced renal cell cancer. Increments are shown in cells × 10^9/l, or mmol/l (c), respectively. The horizontal lines indicate mean values.

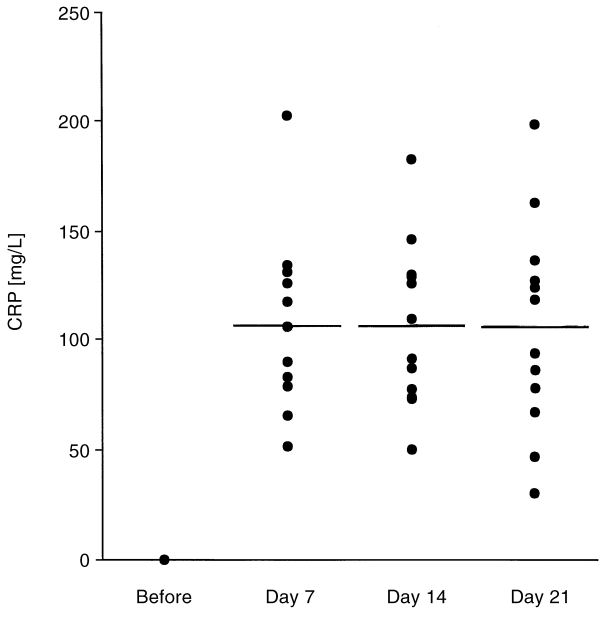

Figure 2. Changes in serum concentrations of C-reactive protein (CRP) in response to treatment with recombinant human interleukin-6 (rh IL-6) in 12 patients with advanced renal cell cancer. CRP concentrations are shown in mg/l. The horizontal lines indicate mean values.

patients. This effect was maintained during the whole treatment period (Figure 2). A more detailed analysis of immunological parameters has been published elsewhere [6]. In addition, profound effects on several hormones were noted, which have been reported elsewhere [7].

DISCUSSION

In this phase II study of a fixed daily dose of rh IL-6, no objective response was observed in 12 immunotherapy-naive patients with advanced and progressive renal cell cancer. This lack of antitumoral activity of rh IL-6 is in concordance with the results of another phase II study in patients with renal cell cancer [8], as well as with clinical effects observed in phase I studies in patients with advanced malignancies [9,10]. Toxicities of the present schedule were within the range of those previously observed in other clinical trials of rh IL-6 [8–11].

An induction of acute-phase proteins was observed in all patients. As described previously [12], an induction of several anti-inflammatory molecules could be detected [6]. No consistent changes in leucocyte subsets, expression pattern of leucocyte surface molecules, immunglobulins, neopterin, beta-2-microglobulin, sCD23, sIL-6R and IL-10 levels were induced by rh IL-6 [6]. These results differ from numerous *in vitro* findings demonstrating a variety of B cell stimulatory effects from IL-6 [13].

In contrast to these negative results on clinical and immunomodulatory effects, a profound increase in the number of circulating platelets was observed in response to rh IL-6 treatment. Platelet counts were not increased before 14 days of exposure and peaked at 3 weeks of treatment. These results are in concordance with other phase I and II trials of rh IL-6 [8–11]. In animal models, IL-6 increases megakaryocyte size and ploidy but not the number of megakaryocytes [14]. Thus, IL-6 acts as a megakaryocyte differentiation factor, rather than as a true thrombopoietin [14]. However, when co-administered with IL-3 [15] or with sIL-6R and gp130 [16], an increase in the number of multilineage haematopoietic colonies by IL-6 has been demonstrated.

In conclusion, rh IL-6 when administered at a fixed daily s.c. dose of 150 μg has no antitumoral activity in patients with metastatic renal cell cancer. Prolonged s.c. administration of rh IL-6 on an outpatient basis is safe and feasible. Only minor evidence of an immunomodulatory effect of rh IL-6 could be detected, whereas rh IL-6 appears to act as a regulator of inflammation and of megakaryocyte differentiation *in vivo*.

1. Motzer RJ, Bander NH, Nanus DM. Renal cell carcinoma. *N Engl J Med* 1996, **335**, 865–875.
2. Vogelzang NJ, Priest ER, Borden L. Spontaneous regression of histologically proved pulmonary metastases from renal cell carcinoma: a case report with 5-year follow-up. *J Urol* 1992, **148**, 1247–1248.
3. Wirth MP. Immunotherapy for metastatic renal cell carcinoma. *Urol Clin North Am* 1993, **20**, 283–295.
4. Vogelzang NJ, Lipton A, Figlin RA. Subcutaneous interleukin-2 plus interferon alfa-2a in metastatic renal cell cancer: an outpatient multicenter trial. *J Clin Oncol* 1993, **11**, 1809–1816.
5. Minasian LM, Motzer RJ, Gluck L, Mazumdai M, Vlamis V, Krown SE. Interferon alfa-2a in advanced renal cell carcinoma: treatment results and survival in 159 patients with long-term follow-up. *J Clin Oncol* 1993, **11**, 1368–1375.
6. Schuler M, Peschel C, Schneller F, *et al.* Immunomodulatory and hematopoietic effects of recombinant human interleukin-6 in patients with advanced renal cell cancer. *J Interferon Cytokine Res* 1996, **16**, 903–910.
7. Späth-Schwalbe E, Schrezenmeier H, Bornstein S, Burger K, Porzsolt F, Born J. Endocrine effects of recombinant interleukin 6 in man. *Neuroendocrinology* 1996, **63**, 237–243.
8. Stouthard JML, Goey H, Vries EGE de, *et al.* Recombinant human interleukin 6 in metastatic renal cell cancer: a phase II trial. *Br J Cancer* 1996, **73**, 789–793.
9. Weber J, Yang JC, Topalian SL, *et al.* Phase I trial of subcutaneous interleukin-6 in patients with advanced malignancies. *J Clin Oncol* 1993, **11**, 499–506.
10. Gameren M van, Willemse PHB, Mulder NH, *et al.* Effects of recombinant human interleukin-6 in cancer patients: a phase I–II study. *Blood* 1994, **84**, 1434–1441.
11. Gordon MS, Nemunaitis J, Hoffman R, *et al.* A phase I trial of recombinant human interleukin-6 in patients with myelodysplastic syndromes and thrombocytopenia. *Blood* 1995, **85**, 3066–3076.
12. Tilg H, Trehu E, Atkins MB, Dinarello CA, Mier JW. Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. *Blood* 1994, **83**, 113–118.
13. Kishimoto T, Akira S, Narazaki M, Taga T. Interleukin-6 family of cytokines and gp130. *Blood* 1995, **86**, 1243–1254.
14. Kimura H, Ishibashi T, Uchida T, Maruyama Y, Friese P, Burstein SA. Interleukin 6 is a differentiation factor for human megakaryocytes *in vitro*. *Eur J Immunol* 1990, **20**, 1927–1931.
15. Ikebuchi K, Wong GG, Clark SC, Ihle JN, Hirai Y, Ogawa M. Interleukin 6 enhancement of interleukin 3-dependent proliferation of multipotential hemopoietic progenitors. *Proc Natl Acad Sci USA* 1987, **84**, 9035–9039.
16. Sui X, Kohichiro K, Tanaka R, *et al.* Gp130 and c-Kit signalings synergize for *ex vivo* expansion of human primitive hemopoietic progenitor cells. *Proc Natl Acad Sci USA* 1995, **92**, 2859–2863.

Acknowledgements—The authors wish to thank the patients and their families for participating in the trial and Mrs U. Gerhards, Clinical Trial Centre, Department of Medicine III, Mainz, for assistance in conducting the trial.