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Interleukin-2 in Combination with Interferon-α and 5-Fluorouracil for Metastatic Renal Cell Cancer

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Recent clinical trials for the biological therapy of solid tumours have used recombinant human cytokines in combination with conventional chemotherapy. In patients with progressive metastatic renal cell carcinoma, we established a three-drug combination comprising interferon-α (IFN-α), interleukin-2 (IL-2) and 5-fluorouracil (5-FU), using a regimen which allows outpatient therapy. Treatment consisted of 8 weeks each of IFN-α [6–9 MU/m² once to three times weekly subcutaneously (sc)] combined sequentially with IL-2 (5–20 MU/m² thrice weekly sc for 4 weeks) and 5-FU [750 mg/m² intravenously (iv) weekly for 4 weeks]. Among the first 35 patients treated, there were 4 complete (11.4%) and 13 partial responders (37.1%), with an overall objective response rate of 48.6% (95% confidence interval 32–66%). Regressions occurred in local relapse, in lung, lymph node, bone, pleural, renal and thyroid metastases. Median response duration was calculated at 7+ months. An additional 13 patients (37.1%) were stable throughout therapy and thereafter (median of 6+ months). Response rate of this three-drug combination regimen compared favourably with single agent IFN-α (objective response rate ~16%) and against the sc IFN-α/IL-2 combination (objective response rate ~28%). Systemic toxicity was mild to moderate with no severe 5-FU-related mucositis and no dose-limiting adverse effects of sc IL-2. While the exact mechanisms of the potentially additive or synergistic effects of 5-FU and IFN-α/IL-2 remain to be established in more detail, it appears that the sequential use of IFN-α/IL-2 and IFN-α/5-FU in metastatic renal carcinoma further enhances the therapeutic index of IFN-α/IL-2-based biological therapy. Based on the present data, combined biochemotherapy may be a promising new approach to the therapy of advanced renal cancer.
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INTRODUCTION

METASTATIC RENAL cell carcinoma is a poor prognosis disease, with a 5-year survival below 10%; as yet, no standard therapy has been established [1, 2]. Given the lack of effective single-agent or combination chemotherapy, novel treatment approaches are warranted employing recombinant human cytokines alone or in combination with conventional therapy.

Clinical studies using recombinant interferon-α (IFN-α) at doses of three or more megaunits three to five times per week have produced objective regressions of metastatic renal cell cancer in 5–27% of patients treated, with an overall response rate of approximately 16% [3, 4]. The systemic inpatient use of high dose intravenous (iv) recombinant interleukin-2 (IL-2) in conjunction with lymphokine-activated killer cells has yielded up to 33% responses in advanced renal cell cancer, with dose-limiting toxicity [5–10]. The subcutaneous (sc) administration of low-dose IL-2 [11] has significantly reduced cytokine-related toxicity without abrogating its therapeutic efficacy. Based on preclinical evidence of a synergy between IFN-α and IL-2 [12], both agents have been simultaneously employed in an outpatient treatment regimen with an objective response rate of 36% [13].

Here, we report on a phase II clinical trial combining sc IL-2 and IFN-α with iv 5-fluorouracil (5-FU) in patients with metastatic renal cell cancer; therapeutic response and toxicity of this combination regimen were evaluated in 35 patients with progressive disease. The results of this study are the subject of the present report.

PATIENTS AND METHODS

Patients

35 patients with progressive metastatic renal cell cancer (Table 1) were treated on this protocol. All patients had histologically confirmed tumours, clinically evaluable progressive disease and presented with an ECOG performance status of 0 or 1. In

Table 1. Patients' characteristics

	No. of patients
Evaluable patients	35
Sex	
Male	25
Female	10
Age (years)	
Median	61
Range	38–74
ECOG	
0	26
1	9
≥ 2	0
Pretreatment	
Surgery	34
Chemotherapy	4
Radiotherapy	3
Immunotherapy	2

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97% of patients, tumour nephrectomy was performed prior to systemic therapy.

Treatment plan and patient evaluation

All patients were treated as outpatients. Recombinant human IL-2 (EuroCetus, Amsterdam, The Netherlands) was given sc at 20 MU/m^2 thrice weekly, weeks 1 and 4, and at 5 MU/m^2 thrice weekly, weeks 2 and 3. Recombinant human IFN-α2 was administered subcutaneously at 6 MU/m^2 once weekly, weeks 1 and 4, thrice weekly, weeks 2 and 3, and at 9 MU/m^2 thrice weekly, weeks 5 to 8. 5-FU iv was given as bolus at 750 mg/m^2 once weekly, weeks 5 to 8.

Treatment cycles were repeated every 2 months unless progression of disease occurred. Reevaluation of the patient's tumour status was performed between treatment courses. A complete remission was defined as the disappearance of all signs of disease for a minimum of 4 weeks, a partial remission as a minimum of 50% reduction in the sum of the products of the greatest perpendicular diameters of measurable lesions without an increase in size of any lesion, or the appearance of new lesions, stable disease as less than a partial response in the absence of disease progression for at least 8 weeks, and progression as an increase of at least 25% in the sum of the products of the longest perpendicular diameters of measurable lesions, or the development of new lesions.

Systemic toxicity of this regimen was evaluated at weekly intervals using a grading system adapted from the World Health Organization (WHO).

RESULTS

A total of 35 patients were treated on this study; all patients were evaluable for response and toxicity (Table 1).

Treatment response

4 patients (11.4%) achieved a complete response, and 13 patients (37.1%) had a partial remission (Table 2); the overall response rate of this study was 48.6% (95% confidence interval, 32–66%). Objective tumour regressions occurred in lung (n = 14), lymph nodes (n = 8), bone (n = 2), local relapse (n = 2) and in other tumour sites (n = 4) including pleural, thyroid and renal metastases (Table 2). Objective tumour remissions were always observed during the first treatment cycle. The median response duration was 7+ months, with a range of 2+ to 11+ months. 13 patients (37.1%) presented with stable disease throughout therapy and thereafter (median of 6+ months).

Table 2. Tumour sites and clinical responses

	Response			
Tumour site	CR	PR	SD	PD
Lung	4	10	7	3
Liver	—	—	4	—
Local relapse	—	2	1	1
Lymph nodes	2	6	7	6
Bone	—	2	1	—
Others	—	4*	2	—
Total evaluable	4	13	13	5

* Renal (n = 1), thyroid (n = 1) and pleural metastasis (n = 2). Median response duration was 7+ months (range 2+ to 11+ months). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Toxicity

This outpatient regimen produced no grade IV toxicity and less than one grade III toxic event per treatment week. Grade III anorexia, chills and respiratory distress were observed in 5, 2 and 2% of treatment cycles, and required a 50% dose reduction of IL-2 and IFN-α; grade I or II malaise, fevers and chills were seen in 82, 76 and 60% of treatment cycles, respectively (Table 3). Mild anorexia (grade I/II) occurred in 92% of cycles, and was often associated with nausea and vomiting (87% of treatment cycles), and/or diarrhoea (36% of treatment courses). Mild and transient mucositis was observed during the IL-2/IFN-α and the IFN-α/5-FU phases of therapy; it was limited to 53% of treatment cycles and did not require dose modification. Grade I or II respiratory distress was noted in 37% of cycles, but was never associated with pulmonary fluid retention. Hypotension occurred in 27% of cycles and was usually mild. Alopecia was observed in 17% of treatment cycles. Few patients developed transient paraesthesias (12% of cycles). In all patients, treatment-related systemic toxicity resolved after cessation of treatment. Capillary leak-induced fluid retention and weight gain did not occur upon systemic sc IL-2. None of the patients experienced major 5-FU-related toxicity, and no toxic deaths occurred.

The subcutaneous administration of IL-2 resulted in transient inflammation and local induration at the injection sites, which persisted for up to 2 weeks following treatment.

DISCUSSION

In the present clinical study, we evaluated a three-drug combination of sc IFN-α, IL-2 and iv bolus 5-FU in patients with advanced progressive renal cell cancer. All patients received immunotherapy at home; chemotherapy was administered in the outpatient clinic.

The plethora of biological mechanisms by which IL-2 and IFN-α mediate tumour regression in man have been extensively studied, but are not yet fully understood. It has been hypothesised that IFN-α may augment IL-2-induced killing through activation of cytotoxic lymphocytes, and via enhanced expression of major histocompatability complex class I antigens

Table 3. Systemic toxicity

	Percentage of treatment cycles			
Side-effects	WHO grade I	WHO grade II	WHO grade III	WHO grade IV
Fever	4	72	—	—
Chills	41	19	2	—
Malaise	58	24	—	—
Anorexia	49	43	5	—
Nausea/vomiting	47	40	—	—
Diarrhoea	36	—	—	—
Mucositis	38	15	—	—
Respiratory distress	15	22	2	—
Hypotension	20	7	—	—
Paraesthesias	12	—	—	—
Alopecia	10	7	—	—
Arrhythmias	—	—	—	—

A total of 35 patients were evaluated for toxicity.

on tumour cells [12, 14, 15]. Chemotherapy by itself has been inactive in renal cell cancer; however, various models have been established for combined biochemotherapy, notably for the combination of IFN-α, IL-2 and 5-FU [16, 17].

In this phase II trial, objective tumour regressions have occurred in 48.6% of patients receiving IL-2, IFN-α and 5-FU combination therapy for progressive metastatic renal cell carcinoma. Response rates compared favourably with hormonal therapy (objective response rate below 5%) [18], single-agent chemotherapy (objective response rates below 10% for vinblastine and other cytotoxic agents) [3, 18], single-agent IFN-α (overall objective response rate of 16%) [3, 4, 14], and previous sc IFN-α/IL-2 combination trials conducted at our institution, whereby objective responses were observed in 28–36% of patients with advanced renal cell cancer [13].

The present combination regimen produced sustained remissions for up to 11+ months; among patients with a complete tumour regression, no relapse has been observed.

Systemic toxicity of this three-drug biochemotherapy combination was low, when compared to the intravenous administration of single agent IL-2 [5–10]. With no major 5-FU-related toxicity, this regimen could further reduce side-effects of systemic IL-2 and IFN-α, thus allowing for an outpatient therapy in the palliative setting.

In summary, while the therapeutic efficacy of this outpatient biochemotherapy study was comparable to the most aggressive inpatient regimens in advanced renal cell cancer [4, 5], the present combination regimen appears to further improve the therapeutic index in patients with renal cancer. These results will require confirmation in randomised trials.

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