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Short Communication

A Phase II Study of Continuous Infusional 5-Fluorouracil (5-FU) and Subcutaneous Interleukin-2 (IL-2) in Metastatic Renal Cancer

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In this study, the safety with efficacy of infusional 5-fluorouracil (5-FU) (200 mg/m^2/day) combined with subcutaneous interleukin-2 (IL-2) (9–27 × 10^{6}IU/day) was investigated in patients with metastatic and renal cancer. In the 24 patients evaluated, the overall response rate was 17% (1 CR, 3 PR). The major toxicity was the vascular leak syndrome (VLS) which required inotrope support in 18% of treatment cycles. Other common systemic toxicities were vomiting, oedema and malaise (grades 1 and 2). There was no enhanced or novel toxicity from the combination of drugs. Based on this study, it will be feasible to use infusional chemotherapy with other cytokine combinations. © **1997 Elsevier Science Ltd.**

Key words: cancer, therapeutics, immunotherapy, chemotherapy, interleukin-2

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INTRODUCTION

THE CYTOKINES interferon-alpha (IFN-α) and interleukin-2 (IL-2) used individually produce responses in 10–15% of patients with metastatic renal cancer [1, 2]. In selected patients, the combination of IFN-α and IL-2 produced a response rate of 35% [3], whilst the addition of the antimetabolite 5-fluorouracil (5-FU) to IFN-α and IL-2 gave a higher response rate in a separate study [4]. In breast cancer and some gastrointestinal malignancies, continuous infusional 5-FU produces higher response rates than bolus administration [5, 6]. We report here the results of a study examining continuous infusional 5-FU combined with IL-2 in patients with metastatic renal cancer.

PATIENTS AND METHODS

25 patients with histiologically confirmed progressive metastatic renal cancer were treated at the Royal Marsden Hospital, London. Eligibility criteria included: performance status of 0–2 (ECOG), age >18 years, WBC>3500/mm^3, platelets >125 000/mm^3, haemoglobin>10 g/dl, glomerular filtration rate of >60 ml/min, bilirubin <1.7 mg/dl, and albumin >30 g/l. Exclusion criteria: cerebral metastases, cardiac failure, second malignancies or chemotherapy, radiotherapy or immunotherapy within the previous 4 weeks. Nephrectomy was not an entry requirement. Written informed consent was obtained from all patients.

The 4 week treatment cycle included continuous infusional 5-FU 200 mg/m^2/day) via a Hickman line. In week 1, IL-2 was administered subcutaneously at 9 × 10^6 IU three times daily on days 1 and 2, and at 9 × 10^6 IU twice a day on days 3–6. During weeks 2 and 3, patients received IL-2 9 × 10^6 IU once daily Monday to Friday. In week 4, the patients continued 5-FU alone and were assessed for response. Treatment toxicity was assessed weekly employing a modified World Health Organisation grading system [7]. 5-FU related myelosuppression of ≥grade 2 lead to treatment interruption until recovery of WBC ≥3 × 10^9/l. Recovery within 7 days lead to resumption of treatment at full dose, within 7–14 days a 25% dose reduction, beyond 14 days to a 50% dose reduction. Patients with 5-FU-related palmar– plantar erythema received pyridoxine 50 mg three times daily throughout treatment, those with ≥grade 3 toxicity had treatment discontinued until resolution and resumed with a 25% dose reduction. Patients with ≤grade 2 diarrhoea receive loperamide, >grade 2 resulted in treatment interruption, and resumption with a 25% dose reduction, IL-2 toxicity of ≥grade 2 lead to a 50% dose reduction in week 1 of the subsequent cycle. Tumour re-

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Table 1. Patients' characteristics

	No. of patients
Patients entered	25
Sex	
Male	15
Female	10
Age (years)	
Median	59
Range	40–68
ECOG	
0	14
1	8
2	3
Pretreatment	
Surgery	18
Radiotherapy	9
Hormonal	7
Immunotherapy	5
Chemotherapy	1
Disease sites	
Lung	16
Renal/renal bed	13
Lymph nodes	9
Bone	8
Hepatic	7
Other	6

sponses were assessed using the standard UICC criteria [8]. Patients with a complete response (CR), partial response (PR) or stable disease (SD) after cycle 1 received a second cycle and a third cycle if they demonstrated a CR or PR compared to the precycle 2 assessment.

RESULTS

The patient characteristics are shown in Table 1. 24 patients completed the first cycle and were eligible for response evaluation. One patient was withdrawn within the first week of cycle 1, due to the development of cerebral metastases. 4 patients responded (1 CR, 3 PRs) to give an overall response rate of 17%, 6 patients had stable disease. The CR patient had bone and lymph node disease and reached CR after two cycles. 3 patients had PRs; these occurred in pulmonary metastases in 2 patients and in pulmonary and hepatic metastases in 1 patient. 3 of the 4 responding patients demonstrated a partial response by the end of cycle 1, the fourth patient following cycle 2. The 4 responding patients have continued follow-up for 14–21 months. The CR patient remained disease-free for 20 months then relapsed with subcutaneous disease. One PR patient has been observed for 20 months without evidence of progression, the other 2 progressed after 7 months and 10 months at pre-existing site of disease.

The mean diagnosis to treatment interval for the responding patients was 53.5 months and 14.6 months for the non-responders.

The treatment-related toxicities are recorded in Table 2. The most serious was the vascular leak syndrome (VLS); 6 patients (18% of treatment cycles) required inotrope support for hypotension and oliguria during the high-dose IL-2 treatment, but no patients required cytokine discontinuation. The most frequent toxicity was nausea and vomiting which occurred in 64% of treatment cycles; other frequent toxicities included erythema (39% of cycles), malaise (35%) and anaemia (31%). There was no 5-FU toxicity that required dose modification and no evidence of enhanced or novel toxicity resulting from this combination of treatments. There were four episodes of Hickman line related sepsis which resolved with antibiotics. The one treatment withdrawal occurred after cycle 1 due to persistent grade 2 oedema.

DISCUSSION

For patients with metastatic renal cancer, recent work suggests that the addition of 5-FU to the combination of IFN-α and IL-2 can result in an enhanced response rate [4]. In a number of tumour types, infusional 5-FU, as opposed to bolus administration, increases response and survival rates [5, 6]. Prior to appraisal with combination cytokine therapy, we examined the effects of infusional 5-FU with IL-2 monotherapy. The major treatment limiting toxicity in this study was VLS which required inotropes in 18% of treatment cycles. This side-effect is closely associated with the use of high-dose IL-2 and this frequency is comparable to others using similar doses [9]. The other major toxicities recorded in this trial, nausea and vomiting, malaise, cutaneous erythema and flu-like symptoms, were not dose-limiting and only 1 patient withdrew from the study due to toxicity.

The objective response rate was 17% (1 CR, 3 PR) which is similar to IL-2 or IFN-α monotherapy, but lower than generally recorded for combination cytokine therapies. Whilst IFN-α and the combination of IFN-α and IL-2 appear to be potentiated by 5-FU, the data from this study suggests that this may not be the case with IL-2 alone, although the small number of patients and the wide variation in patient characteristics in different trials makes accurate interstudy comparisons difficult. In IL-2 monotherapy,

Table 2. Toxicity (percentage of treatment cycles)

	Grade 1	Grade 2	Grade 3	Grade 4
Vascular leak	15	29	18	
Malaise	27	4	4	
Anaemia	2	29		
Erythema	21	18		
Infection	2	16		
Nausea/vomiting	53	11		
Fever	9	9		
Chills	13	4		
Flu-like	7	2		
Neutropenia	4	2		
Diarrhoea	13			

the disease to treatment interval is an important prognostic factor [7], and the interval of 53.5 months for the responders versus 14.6 months for the non-responders in this study suggests that it is also important in chemo-immunotherapy.

In this study, we have shown that infusional chemotherapy can be combined with subcutaneous IL-2 administration to produce a regimen that has predictable and manageable toxicity and efficacy comparable to other cytokine treatments. Following this study, we plan to investigate the use of infusional 5-FU with combination cytokine therapies, with the aim of producing enhanced response rates and survival.

1. Fossa S, Jones M, Johnson P, *et al.* Interferon-alpha and survival in renal cell cancer. *Br J Urol* 1995, **76**, 286–290.
2. Jones M, Philip T, Palmer P, *et al.* The impact of interleukin-2 on survival in renal cancer: a multivariate analysis. *Cancer Biother* 1993, **8**, 275–288.
3. Atzpodien J, Korfer A, Franks CR, Poliwoda H, Kirchner H. Home therapy with recombinant interleukin-2 and interferon-gamma2b in advanced human malignancies. *Lancet* 1990, **335**, 1509–1510.
4. Atzpodien J, Kirchner H, Lopez-Hanninen E, Deckert M, Fenner M, Poliwoda H. Interleukin-2 in combination with interferon alpha and 5-fluorouracil for metastatic renal cell cancer. *Eur J Cancer* 1993, **29A**(Supp. 5), S6–S8.
5. Lokich JJ, Ahlgren JD, Gullo JJ, Phillips JA, Fryer JG. A prospective randomised comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a mid-Atlantic Oncology Program study. *J Clin Oncol* 1989, **7**, 425–432.
6. Findlay M, Cunningham D, Norman A, *et al.* A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). *Ann Oncol* 1994, **5**, 609–616.
7. WHO. *Handbook for Reporting Results of Cancer Treatment.* WHO offset publication no. 48, Geneva, World Health Organisation, 1979.
8. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
9. Lotze MT, Chan AE, Seipp CA, Simpson C, Vetto JT, Rosenberg SA. High dose recombinant interleukin-2 in the treatment of patients with disseminated cancer: responses, treatment-related morbidity and histological findings. *JAMA* 1986, **256**, 3117–3124.