Pergamon

European Journal of Cancer Vol. 30A, No. 3, pp. 329–333, 1994
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0959-8049/94 $6.00+0.00

0959-8049(93)E0057-W

The Treatment of Metastatic Renal Cell Carcinoma by Continuous Intravenous Infusion of Recombinant Interleukin-2

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Between March 1989 and June 1990, 133 patients were treated with interleukin 2 (rIL-2) for metastatic renal cell carcinoma (RCC) in a multicentre open non-randomised study. The results show an objective response rate of 14% (95% confidence interval 8–21) with 4 patients achieving a complete remission. This is in keeping with the data from previous studies using rIL-2 by continuous infusion. It is of interest that 87% of objective responses occurred in hospitals that entered 5 or more patients.

Key words: interleukin-2, renal cell carcinoma
Eur J Cancer, Vol. 30A, No. 3, pp. 329–333, 1994

INTRODUCTION

METASTATIC RENAL cell carcinoma (RCC) has a very poor prognosis; the median survival is 8 months, and the 1-year survival rate following diagnosis is approximately 40% [1]. Results with chemotherapy are disappointing: single agent response rates are less than 10%, remissions are rarely complete, and the duration of responses is usually less than 3–4 months. [2]. Hormone therapy gives similarly disappointing results with less than 5% of patients responding [3]. Consistently, the highest response rates are reported following interferon-α (rIFNα) treatment: in a review of 13 studies, the cumulative overall response rate was 14% [complete response (CR) = 10, partial response (PR) = 73, n = 573] [4]. However, in a recent small randomised study comparing medroxyprogesterone acetate (MPA) to rIFNα, there was no difference in response rates [rIFNα: CR = 3%, 95% confidence interval (CI) 0–17; PR = 3%, 95% CI 0–17. MPA: CR = 3%, 95% CI 0–17; 0 PR] [5].

Early results using high dose bolus intravenous (i.v.) regimens of interleukin 2 (rIL-2) reported response rates of 20–35%, with the suggestion that the addition of lymphokine-activated killer (LAK) cells was an advantage [6], and these results were initially confirmed by others using a continuous intravenous (i.v.) infusion of rIL-2 with LAK cells [7]. However, the toxicity associated with these schedules was limiting, and large trials could not be performed outside specialist centres. Furthermore, recent studies employing rIL-2 without LAK cells indicated that response rates may be much lower, of the order of 10% [8, 9]. Though these differences appear significant, the contribution that the adoptive transfer of immune competent cells makes to the efficiency of rIL-2 still remains uncertain. A comparative analysis [10] of continuous infusion of rIL-2 and LAK cells, and continuous infusion of rIL-2 without LAK cells, and a recently published randomised trial [11] suggest that the addition of LAK cells does not lead to increased efficacy. Discrepancies between studies are probably the result of patient selection.

Reports from studies using continuous infusion rIL-2 regimens have indicated response rates as high as the earlier more toxic bolus i.v. schedules [12]. However, much of these data are from single specialist centres, and are often subject to patient selection bias. In an effort to obviate this, we have performed a multicentre phase II study of continuous infusion rIL-2 in patients with metastatic RCC with participating centres including district general hospitals.

MATERIALS AND METHODS

Patients

Between March 8 1989 and June 29 1990, patients with metastatic RCC were entered into a multicentre study using continuous infusion rIL-2. Patients were eligible for the study if they had histological evidence of RCC, measurable or evaluable disease, a performance status of 0–1 (ECOG), a life expectancy of > 3 months, aged 18–75 years, white blood cell (WBC) $> 4.0 \times 10^9/l$, platelets $> 120 \times 10^9/l$, haematocrit $> 30\%$ and they had normal renal and liver function. Patients were excluded if they had chemotherapy, radiotherapy or immunotherapy < 4 weeks before commencing rIL-2, a second malignancy, cerebral metastases, significant cardiac disease, autoimmune disease, an organ allograft, a requirement for steroids, active infection, a contraindication to pressor agents, were pregnant or lactating.

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Revised 16 Nov. 1993; accepted 30 Nov. 1993.

All patients meeting the eligibility criteria are included in this report, and their characteristics are shown in Table 1.

133 patients were evaluable for toxicity, and 109 for response. 24 patients were not evaluable for response – the reasons are set out below.

Table 1. Patients' characteristics

	No. of patients (%)
No. of patients analysed	133
No. of patients evaluable for toxicity	133
No. of patients evaluable for response	109
Date of first entry	March 13, 1989
Date of last entry	June 29, 1990
Age (years)	
Median	56
Range	(21–75)
Sex	
Female	36 (27%)
Male	97 (73%)
Baseline performance	
ECOG 0 (KPS 100%)	51 (38%)
ECOG 1 (KPS 80–90%)	82 (62%)
Time from primary diagnosis to study entry (months)	
Median (range)	9.5 (0.3–226)
0–24 months	105 (79%)
> 24 months	28 (21%)
Time from diagnosis to first metastasis (months)	
Median (range)	1 (0–223)
0–24 months	110 (83%)
> 24 months	19 (14%)
Unknown	4 (3%)
Time from metastasis to study entry (months)	
Median (range)	3 (0–71)
0–1 month	43 (32%)
2–3 months	30 (23%)
> 3 months	56 (42%)
Unknown	4 (3%)
Prior therapy combinations	
Surgery (S) alone	55 (41%)
Radiotherapy (R) alone	4 (3%)
Chemotherapy (C) alone	1 (1%)
Hormonal therapy (H) alone	2 (2%)
Immunotherapy (I) alone	1 (1%)
S+I	5 (4%)
S+H	18 (14%)
S+R	10 (8%)
S+C	1 (1%)
Other combinations	21 (16%)
No prior therapy	15 (11%)
Disease sites	
Lung	94 (37%)
Kidney	40 (16%)
Lymph node	40 (16%)
Liver	21 (8%)
Bone	18 (7%)
Pleura	12 (5%)
Adrenal gland	11 (4%)
Soft tissue	8 (3%)
Other	10 (4%)
Extent of disease	
One organ site	55 (41%)
Two organ sites	45 (34%)
Three or more organ sites	33 (25%)

KPS, Karnofsky performance status.

Treatment

All patients were hospitalised and carefully monitored during treatment, though not normally in an intensive care or high dependency unit. rIL-2 (Proleukin, EuroCetus BV, Amsterdam) treatment consisted of two induction cycles and up to four maintenance cycles. In the induction cycles, rIL-2 was administered by continuous infusion at a dose of 18×10^6 U/m^2/day for 5 days (120 h), followed by 2 days rest and a further 5 days treatment. After a treatment-free period of 3 weeks and in the absence of serious complications, a second identical induction cycle was given. Tumour evaluation was performed after the second induction cycle. Responding patients and those with stable disease after the two induction cycles could receive up to four maintenance cycles of rIL-2. Each maintenance cycle consisted of 5 days continuous infusion rIL-2 at 18×10^6 U/m^2/day followed by a 3-week rest period.

Induction therapy was given to 133 patients, 97 of whom received two induction cycles. Maintenance therapy was administered to 52 patients: 39 received two maintenance cycles, 28 received three maintenance cycles and 18 patients received four maintenance cycles.

The rIL-2 infusion was interrupted if WHO grade 3 or greater toxicity occurred. Particular attention was given to hypotension, confusion, dyspnoea, weight gain, urine output and abnormalities of liver and renal function. In addition, the infusion was interrupted if there were significant cardiac arrhythmias, evidence of myocardial ischaemia or other toxicities judged to be severe, and finally, at the patient's request. Following resolution of any toxicities, rIL-2 administration was restarted at 50% of the original dose.

Assessment of toxicity

Patients were seen twice daily during treatment to assess toxicity and vital signs, and prior to each cycle or rIL-2 to assess response. Haematological and biochemical parameters were measured at least three times weekly for objective toxicity assessment. Toxicities were expressed according to the WHO grading system[13]. If the WHO grading system was not available for a particular adverse reaction, events were graded as being mild (grade 1), moderate (grade 2), severe (grade 3) or life threatening (grade 4). All patients were evaluable for toxicity, and were included in the survival analysis.

Assessment of response

Patients were considered eligible for response evaluation if they had completed adequate pre- and post-treatment assessment of their disease status, and had completed at least 5 days of rIL-2.

24 patients were not evaluable for response due to inadequate pre- or poststudy assessment of tumour measurements (12 patients), death within 1 month of starting treatment (7 patients), and 1 patient with lung metastases, for whom the primary *in situ* was converted to a CR by post-IL-2 nephrectomy. A further 4 patients were not evaluable for response because of early withdrawal from the study, i.e. within the first 5 days of rIL-2 treatment. The reasons for early withdrawal were: requirement for steroids because of dyspnoea, pulmonary embolism, renal failure and 1 patient withdrew early at her own request because of toxicity.

Response was defined according to WHO criteria as follows: CR, the disappearance of all known disease as determined by two observations separated by no less than 4 weeks; PR, a > 50% decrease in the product of bidimensionally measured

lesions as determined by two observations separated by no less than 4 weeks and the absence of new lesions; stable disease (SD), a < 50% decrease and a < 25% increase in the product of bidimensionally measured lesions; and progressive disease (PD), a > 25% increase in the size of measurable lesions and/or the appearance of new lesions [13].

RESULTS

Toxicity

Patients remained in hospital throughout the 12-day treatment, and the majority were discharged from hospital within 48 h of receiving the last dose of rIL-2. Only 6 patients (4.5%) required transfer to an intensive care unit.

The most common toxicities (all grades) by course were fever (94%), hypotension (54%), nausea and vomiting (51%), erythema and skin rash (39%), diarrhoea (37%), weight gain (28%), raised creatinine (55%), chills (17%), fatigue/malaise (17%) and infections (5%). Hypotension occurred in more than 50% of patients, with objective grade 4 hypotension occurring in 6 patients (5%). Oliguria and renal failure were recorded in 24% of patients, and 23% had signs or symptoms of pulmonary distress. However, toxicity was generally manageable and rapidly reversible upon cessation of therapy.

The majority of patients (55%) had one or more treatment interruptions during therapy. These interruptions involved stopping the rIL-2 infusion for a short period until resolution of the toxicity, as prescribed by the protocol. However, 26 patients (20%) required subsequent dose reductions, usually for a combination of toxicities. Most treatment modifications were instituted in order to manage known side-effects, e.g. hypotension, oliguria, malaise.

14 patients died within 28 days of stopping treatment: in 10 cases death was disease-related, not treatment-related, but in 4 patients rIL-2 could not be excluded as a contributory factor. The causes of death in 3 of these patients were as follows: pulmonary oedema, pulmonary embolus and uncontrolled hypercalcaemia probably as a result of progressive disease. The fourth patient experienced grade 4 hypotension which did not respond to inotropes or steroids, and after the rIL-2 infusion was discontinued, he deteriorated and died 8 days later. However, there was documented concomitant progressive disease. Thus, the treatment-related mortality in this study was 3% (4/133).

Response

109 patients were evaluable for response (Table 2). The overall objective response rate was 14% (15/109, 95% CI 7.5–20.5%) with 4 CRs and 11 PRs. Responding sites included skin, pleura, lung, lymph node, liver, bone and kidney (Table 3). Eighty per cent (12/15) of responders had been nephrectomised prior to entry into the study whereas only 20% (3/15) of responders still had their primary lesion *in situ* at the start of IL-2 treatment, but this difference was not statistically significant. Overall response rates for nephrectomised and non-nephrectomised patients are 15% (12/79) and 10% (3/30), respectively.

Table 2. Response to rIL-2 (n = 109)

	n	Response rate (%)
Complete response	4	4
Partial response	11	10
Stable disease	45	41
Progressive disease	49	45
Not evaluable	24	—

Table 3. Response to rIL-2 according to site of disease

	No. of sites	No. of responses	% response
Skin	6	5	83
Pleura	12	2	17
Liver	21	3	14
Lymph nodes	40	6	15
Lung	94	15	16
Bone	18	2	11
Kidney	40	2	5
Adrenal gland	11	1	9
Other	10	3	30

The median duration of CR was 10.4 months (range 1.75–14.8+) and of PR was 11.4 months (range 5.5–16.6+). At the time of analysis only 3 CR patients are still alive and in remission at 9.9+, 13.1+ and 16.5+ months. 7 of the patients who achieved a PR are still alive, 4 have no evidence of disease progression at 7.3, 10.9, 11.9 and 16.6 months.

45 patients achieved SD, and for the subgroup of 60 patients with SD or better (CR and PR), median progression-free survival was 9.8 months (range 1.9–22.9+). Progression-free survival and overall survival are shown in Figs 1 and 2, respectively. The median overall survival for all 133 patients was 10.5 months (range 0.2–22.9+).

No responses were seen in patients who received < 50% of the planned dose (i.e. < 5 days, half a cycle), although 1 patient did achieve a PR after just 5 days of treatment. Table 4 shows the time taken to reach a maximum response in terms of the number of cycles delivered.

DISCUSSION

This trial was performed in more than 29 centres, and only 12 centres entered 5 or more patients. It is the largest single study of continuous infusion IL-2, and the first report on the efficiency of rIL-2 in RCC, where treatment was delivered in cancer departments which had no previous experience of it. However,

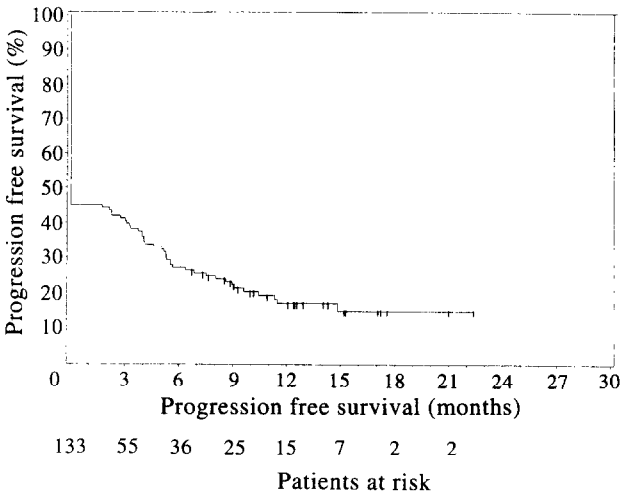

Fig. 1. Progression-free survival. 24/133 patients free from progression.

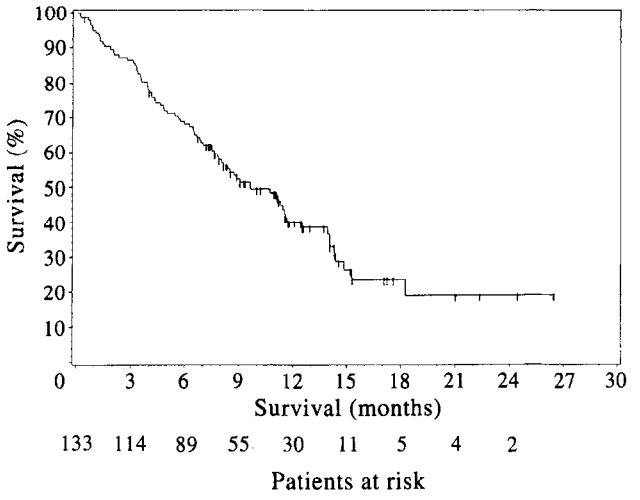

Fig. 2. Overall survival. 81 patients dead, 52 patients alive.

13 of the 15 responses (87%) occurred in centres that entered 5 or more patients, giving in this subgroup of patients a response rate of 17% compared to 6% for the other centres and 14% for the entire patient population. This trend for response to be associated with more experienced centres may reflect a higher treatment intensity due to the better management of side-effects. It also suggests that earlier studies with higher response rates may not reflect the efficacy of this treatment when less experienced and less specialised centres are involved in the administration of rIL-2.

There is a suggestion from our data that previous nephrectomy is a prognostic factor for response to rIL-2. However, this trend did not reach statistical significance, and others have shown that nephrectomy has no influence on the survival of patients treated with rIL-2 [14]. The commonest site of response in this study was skin, after which all other sites demonstrated very similar response rates.

It is well established that the prognosis of patients with RCC is associated with performance status [15], and this relationship has also been shown for patients treated with IL-2 [14]. Our patients were a selected group with performance status 0–1 and, therefore, might be expected to respond better to any active treatment than another group of patients with a poorer performance status. The important question remains whether or not IL-2 is as active as IFN, both in terms of response rates and in terms of survival, if patients with equivalent prognostic factors were compared. The overall response to IFN is 14% [4], but this figure is based on cumulative data and, therefore, a relatively unselected group of patients. It is particularly important that these two treatments are compared in a randomised study, as the toxicity and inconvenience of continuous infusion IL-2 is obviously greater than subcutaneous IFN-α delivered on an outpatient basis.

The toxicities recorded in this study are similar to those reported by others. Patients were generally treated on a normal oncology ward, and there was no evidence of chronic or irreversible toxicity. The number of patients requiring transfer to an intensive care unit was very low (< 5%), and treatment-related mortality was only 3%. Our results clearly confirm the activity and efficacy of the continuous infusion rIL-2 regimen in patients with advanced RCC. The response rate of 14% is in keeping with response rates reported previously in studies using similar regimens and durable remissions were seen.

Table 4. Number of treatment cycles required to reveal maximum response

No. of cycles	Maximum response	No. of patients
1	PR	5
	CR	—
2	PR	4
	CR	3
3	PR	1
	CR	—
4	PR	1
	CR	1

Cycles 1 and 2 were induction cycles consisting of 10 days of IL-2 therapy. Cycles 3 and 4 were maintenance cycles consisting of 5 days of IL-2 therapy, see Materials and Methods, treatment.

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Acknowledgements—Other participating centres in this study were as follows: Prof. C. Rugarli, Milan, Italy; Prof. P. Guillou, London; Dr M.J. Phillips, Taunton; Dr T. Roberts, Newcastle-upon-Tyne; Prof.

A.L. Harris, Oxford; Dr G.J.S. Rustin, London; Mr M. Fordham, Liverpool; Mr C.J. Davies, Rhyl; Dr H. Yosef, Glasgow; Dr P.G. Harper, London; Dr S.G. Vaidya, Romford; Dr M.A. Cornbleet, Edinburgh; Dr V. Svoboda, Portsmouth; Mr P. Whelan/Prof. P. Selby, Leeds; Prof. B. Hancock, Sheffield; Prof. N.M. Bleehan, Cambridge; Dr S. Harland, London; Dr C.G. Rowland, Exeter; Dr M.J. Ostrowski, Birmingham; Dr A.D. Chetiyawardanan, Birmingham; Dr N. Thatcher, Manchester; Prof. T.J. Hamblin, Bournemouth; Prof O. Eremin, Aberdeen; Mr P.S. Veitch, Leicester; Dr J. Towler, Luton; Dr M. Slevin, London; Dr M. Sokal, Nottingham; Prof R.C. Coombes, London; Mr P. Abrams, Bristol, U.K.

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European Journal of Cancer Vol. 30A, No. 3, pp. 333–338, 1994
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0959–8049/94 $6.00+0.00

0959-8049(93)E0074-Z

Survival and Prognostic Factors in Patients with Localised Cutaneous Melanoma Observed Between 1980 and 1991 at the Istituto Dermopatico dell'Immacolata in Rome, Italy

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530 patients with localised cutaneous melanoma consecutively observed between 1980 and 1991 at a hospital for skin diseases in Rome, Italy, were studied. Crude survival proportions were calculated with the method of Kaplan and Meier. Cox proportional hazards regression analysis was used to estimate the effect of prognostic factors on death rates. Females and younger patients had better 5- and 10-year survival rates, while increasing tumour thickness was associated with a decrease in survival time. In the multivariate analysis, an independent association with survival was found for tumour thickness, presence of ulceration, age, sex and cross-sectional profile of neoplasia. Our study confirms that females and young patients with thin melanomas have a better prognosis, while the importance of cross-sectional profile needs further study.

Key words: prognostic factors, cutaneous melanoma, survival analysis
Eur J Cancer, Vol. 30A, No. 3, pp. 333–338, 1994

INTRODUCTION

THE SURVIVAL of patients with cutaneous melanoma has generally improved, due to early detection and treatment; however, death rates from this disease have continued to rise, although less rapidly than the incidence rates [1–3], giving support to the concept of a true increase in incidence.

A number of studies have been conducted to investigate the role of several clinical and histopathological features as prognostic factors. It is particularly important to identify the dominant characteristics to be used to accurately predict the prognosis, and classify patients in different risk groups for disease progression. Most studies have indicated tumour thickness and ulceration as the best predictors of prognosis, while a considerable discrepancy exists in the results regarding the association between survival and other histopathological or clinical variables such as sex, age and anatomical site [4–8].

Although tumour thickness has been reported as the single most important prognostic factor [4–10], the behaviour of the cutaneous melanoma in individual cases is difficult to predict. Hence the need to identify other prognostic factors independent from thickness.

This study was undertaken at the Istituto Dermopatico dell'Immacolata (IDI), a large hospital for skin diseases in Rome, Italy, with the aim of determining the prognostic importance of certain histopathological and clinical variables for patients with localised cutaneous melanoma.

PATIENTS AND METHODS

Patients

Between 1 January 1980 and 31 December 1991, 530 cases of cutaneous melanoma were identified from the records of patients

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Revised 2 Dec. 1993; accepted 9 Dec. 1993.
EJC 30:3-C