synergy is indicated by the prolonged second responses to α interferon. The duration of response to alpha interferon given after rIL-2 is 3–5 times longer than that expected.

This information provides an anecdotal basis for the continued search for the possibility that rIL-2 in combination with other biological response modifiers may lead to an increased response as compared with single agent treatment. The dosage, schedule of administration and the combination of agents to be used is unknown but is under investigation in many centres.

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Phase I Study Comparing Continuous Infusion of Recombinant Interleukin-2 by Subcutaneous or Intravenous Administration

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22 cancer patients entered a randomised phase Ib trial comparing the effects of low-dose recombinant interleukin-2 (300 μg/m², approximately equivalent to 6.4 × 10⁶ cetus units or 38 × 10⁶ U per day) given continuously by intravenous or subcutaneous infusion. At 48 h after two 5-day courses, median lymphocyte levels (× 10⁹/l) were 6.0 (387% increase) in the subcutaneous arm (n = 9) and 5.9 (369% increase) in the intravenous arm (n = 8). Liver and renal toxicity were similar in the two groups. One minor response lasting 4 months occurred in 12 renal cancer/melanoma patients receiving subcutaneous treatment and one durable complete remission continuing at 30 months and one minor response lasting 10 months occurred in 6 renal cancer/melanoma patients receiving intravenous treatment.
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INTRODUCTION

INTERLEUKIN-2 (IL-2) produces 3–5% complete durable responses in patients with metastatic renal cell cancer and melanoma, and partial remissions in a further 15–20%, in multiple clinical trials [1]. However, though most of this work combined IL-2 with lymphokine-activated killer cells (LAKs), there has been little evidence that LAKs add much to response rate [2, 3], and these early studies used maximum tolerated doses of IL-2 given by intravenous boluses leading to considerable toxicity [2], which necessitated intensive therapy unit support, and some drug-related fatalities. Furthermore, animal studies suggest that efficacy may actually be reduced at high doses [4] and, *in vivo*, subcutaneous dosing leads to longer biological effects than intravenous dosing [5]. More recent studies of IL-2 have focused on less intensive, intermittent schedules with increased duration of treatment [6] though there has not been any direct comparison of the two approaches. Prompted by some evidence that the level of rebound lympho-

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cytosis after IL-2 treatment may be a predictor of tumour response [7, 8], we used this simple test as an index of biological function to monitor a study randomising patients between intravenous and subcutaneous treatment.

PATIENTS AND METHODS

The patients had histologically proven malignancy with bidimensionally measurable metastases at entry without significant cardiac disease or abnormalities on a resting electrocardiogram. Patients were admitted, and haematological and biochemical indices were measured at entry, twice a week during treatment and 2 days after finishing. Daily weight and hourly temperature, blood pressure, pulse and urine output were measured during the infusion.

Dosage and administration

300 $\mu g/m^2$ recombinant IL-2 (Bioleukin), equivalent to 3.75×10^6 cetus units or 22.5×10^6 U per m^2, was given each day by continuous infusion using a battery-operated syringe driver. Half the dose was given over 8 h between 0900 and 1700 and the other half over 16 h between 1700 and 0900 the next day to reduce side-effects overnight and increase our confidence in the adaptability of the regimen for outpatient uses. The lypophilised IL-2 was reconstituted with 1.2 ml sterile water for injection and diluted to 8 ml with sterile water for injection. Fresh solution was made up at 0900 and at 1700 each day.

Dose alteration and discontinuation of treatment

The infusion rate was slowed or temporarily interrupted if side-effects, such as hypotension (80 mmHg systolic), intolerable nausea, fever or malaise, were not controlled by simple measures, such as paracetamol 1 g orally every 4 hours or indomethacin (up to 100 mg orally or rectally every 12 hours) or if the patient developed progressive disease.

RESULTS

Toxicity

Of the 22 patients, 3 in the subcutaneous arm and 2 cases in the intravenous arm went off-treatment after 1 week due to progressive disease (Table 1). The remaining 17 patients completed the two 5-day infusions without major incident, though temporary treatment interruption due to excessive toxicity occurred in 6 patients. There tended to be worse toxicity in the second cycle but there was little difference between that produced in patients receiving subcutaneous or intravenous treatment. Table 2 summarises the renal and hepatic toxicity on the basis of median creatinine, ALT and alkaline phosphatase levels, confirming the similarity between subcutaneous and intravenous routes. Cardiovascular toxicity requiring dose reduction or termination or supplementary intervention was seen in 4 patients, 2 in each arm.

Biological effects of treatment

By day 14, (48 h after discontinuation of treatment) all had evidence of lymphocytosis and eosinophilia. Table 2 summarises absolute lymphocyte and eosinophyl change and shows that levels were similar in both arms.

Outcome

There were insufficient cases to draw conclusions about response rate, nor were the 2 arms balanced with regard to prior treatment. However, 1 patient (No 13) achieved CR of 4×4 cm renal bed recurrence and 3×1 cm lung metastases (Fig. 1),

Table 1. Patients' details

Case	Sex/age	Diagnosis	Sites	Previous treatment	Response
Patients receiving subcutaneous IL-2					
1	M/63	RCC	N	SX, IFN	PD
2	M/38	RCC	P, L, H	Nil	PD
3	M/57	RCC	P, L, B, N	Nil	MR 4 mo
4	F/66	RCC	P, V, N	Nil	PD
5	M/61	RCC	N	SX, Provera	OT (PD)
6	M/67	RCC	R, B, N	SX	PD
7	M/58	RCC	R, V, L, B	SX, IFN, steroids	OT (PD)
8	M/56	MEL	S, H	SX	PD
9	F/33	MEL	S, N	SX	PD
10	M/32	MEL	L, CNS	SX, CTC	OT (PD)
11	F/55	MEL	S, L	SX, IFN	SD 4 mo
12	F/30	MEL	CH, S, C	SX, RT	PD
Patients receiving intravenous IL-2					
13	M/66	RCC	R, L	SX, steroids	CR 30 mo
14	M/50	RCC	L	SX	MR 10 mo
15	M/56	RCC	H, T	SX	SD 4 mo
16	M/46	RCC	P, N, L	Provera	OT (tox)
17	F/47	RCC	L	SX	PD
18	F/34	MEL	L, H	SX, BCG Orally	PD
19	M/61	TCC	L	SX, CTC	PD
20	M/58	PRT	N, B	RT, SX, hormone	PD
21	M/19	SRC	L	CTC	OT (PD)
22	F/47	CX	R	RT, SX	PD

RCC = renal cell cancer, MEL = melanoma, SRC = rhabdomyosarcoma, TCC = transitional cell carcinoma bladder, CX = uterine cervix, PRT = prostate cancer, P = unresected primary, R = local recurrence, S = skin, H = hepatic, N = lymphnode, V = vascular, L = lung, B = bone, T = testis, CH = choroid, C = cardiac, RT = radiotherapy, IFN = alpha interferon, SX = surgery, CTC = cytotoxic chemotherapy, OT = off-treatment, TOX = toxicity, CR = complete remission, PR = partial remission (> 50% reduction in measureable tumour deposits), MR = marginal response (less than 50% reduction in tumour size), SD = stable disease, PD = progressive disease.

which continues at 37 months, and another achieved reduction of extensive lung shadowing (less than PR) for 10 months and is alive at 3 years after 3 further treatments, each associated with symptomatic shrinkage of his lung mass. Finally, 1 patient in the subcutaneous arm had MR of lung and mediastinal deposits, and subsequently underwent nephrectomy for his primary before relapsing after 4 months.

DISCUSSION

Since the initial reports on the use of IL-2, there have been two poles of opinion as to the most appropriate way to use the drug, i.e. high-dose bolus as short-term treatment or prolonged subcutaneous low-dose treatment. Because of the wide publicity they attracted, the original NCI studies [2] were able to be highly selective of the cases entered, and this is well known to influence response rate [9]. Their regimen subjected patients to short-term intense bolus intravenous treatment with IL-2 in combination with LAK cells [10]. When this intensive care unit-based treatment was used in a less selective way, the proportion of responses fell [12] and randomised trials failed to demonstrate a major gain from the addition of LAK cells [2, 3]. However, this regimen has been the most widely tested schedule of IL-2 use and all authors report an incidence of durable complete remission (3–5%). In addition, more than 50% of these CRs

Table 2. Laboratory indices

	Subcutaneous	Intravenous
Creatinine (U/l)		
0*	110	112
4/5	126	160
10/11	171	159
Alanine transaminase (U/l)		
0	20	29
4/5	46	49
10/11	58	81
Alkaline phosphatase (U/l)		
0	112	149
4/5	189	277
10/11	472	402
Lymphocytes × 10^9/l		
0	1.4	1.6
7/8	4.3	4.72
14/15	6.0	5.9
Eosinophils × 10^9/l		
0	0.2	0.2
7/8	0.7	0.6
14/15	6.4	4.1

* Days.

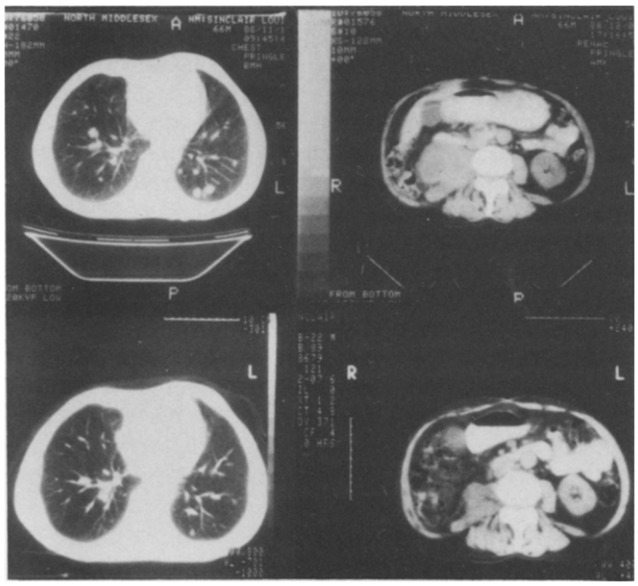

Fig. 1. Computed tomography of chest and renal bed in case 13 before and after treatment with IL-2.

have survived 12 months in complete remission and some patients have now been disease free for more than 4 years.

Lower-dose, more prolonged regimens have considerable advantages in terms of toxicity profile, patient acceptability and the opportunity to transfer treatment to the outpatient clinic or self-administration at home. The success with reducing the toxicity of high-dose interferon-alpha without loss of clinical effect by adopting lower-dose subcutaneous regimen provided the encouragement for this study. Although the number of cases reported in this study are inadequate to address the issue of response, the anecdotal report of single durable CR at 37 months in this study, and reports from other studies of durable responses [11, 12], provides justification for more extensive exploration of low-dose studies, though it will be critical that durable long-term CR is the end point used for assessing the results. From the limited amount of data generated in this study it is clear that the biological effect of IL-2 (as measured by rebound lymphocytosis) in the lower-dose subcutaneous regimen is equivalent to that achieved when the drug is given by intravenous infusion and differs little from that reported from high-dose bolus regimens. The limited data supporting correlation of response with this index [8, 9] provides some confidence that the biological effect could translate into clinical benefit and given its relative simplicity, there is a need for a larger data base.

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