hormone treated advanced breast cancer. *Br J Surg* 1986, 73, 752–755.
165. Tubiana M, Koscielny S. The natural history of human breast cancer: implications for patient management. In: Paterson AHG, Lees AW, eds. *Fundamental Problems in Breast Cancer*. Boston, Martinus Nijhoff Publishing, 1987, 333–348.
166. Stoll BA. Components of a prognostic index. In: Stoll BA ed. *Breast Cancer: Treatment and Prognosis*. Oxford, Blackwell Scientific Publications, 1986, 115–131.

Acknowledgement—We thank Ms. Usha Bhadsavle for her help in preparing this manuscript.

Eur J Cancer, Vol. 27, No. 12, pp. 1583–1589, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Recombinant Interleukin-2 in Metastatic Renal Cell Carcinoma—A European Multicentre Phase II Study

H. von der Maase, P. Geertsen, N. Thatcher, C. Jasmin, A. Mercatello, S.D. Fosså, M. Symann, G. Stoter, G. Nagel, L. Israel, R. Oskam, P. Palmer and C.R. Franks

This multinational, multicentre study represents the introduction of recombinant interleukin-2 (rIL-2) in Europe. From December 1987 to June 1989, 57 eligible patients with metastatic renal cell cancer were treated with rIL-2 administered as continuous intravenous infusion. 8 out of 51 evaluable patients responded (16%), 2 complete remission (CR) and 6 partial remission (PR). 10 patients had no change (20%). The response duration for CR was 209 and 394+ days. The median response duration for PR was 371 (range 140–506+) days. Dose-limiting grade 3–4 toxicities were hypotension in 52% of the patients, arrhythmia (4%), dyspnoea (8%), creatinine rise (4%), peripheral neurotoxicity (10%) and central neurotoxicity (10%). Toxicities most often recovered solely on interrupted therapy. 2 patients died due to catheter-related septicaemia and one patient died of rIL-2 induced renal failure. The study confirmed the antitumour efficacy of rIL-2 in renal cell cancer. Toxicities were numerous, but manageable by close observation in a normal oncology ward without routine use of an intensive care unit.
Eur J Cancer, Vol. 27, No. 12, pp. 1583–1589, 1991.

INTRODUCTION

RECOMBINANT INTERLEUKIN-2 (rIL-2) alone or in combination with lymphokine-activated killer (LAK) cells has shown antitumour efficacy in several animal tumour models [1–3]. Since the initial reports from Rosenberg *et al.* [4], a number of clinical trials have confirmed that rIL-2-based immunotherapy can result in durable responses in tumours refractory to conventional therapeutic approaches [5–10]. The contribution of LAK cells to the therapeutic efficacy has still not been clarified. There seems to be no increase in the total number of responding patients although it has been claimed that there may be more complete responses when rIL-2 is combined with LAK cells [11].

Correspondence to H. von der Maase.
H. von der Maase and P. Geertsen are at the Department of Oncology, Herlev University Hospital, Copenhagen, Denmark; N. Thatcher is at the Christie Hospital, Manchester, U.K.; C. Jasmin is at Hopital Paul Brousse, Villejuif; A. Mercatello is at Hopital Edouard Herriot and Centre Léon Bérard, Lyon, France; S.D. Fosså is at the Norwegian Radium Hospital, Oslo, Norway; M. Symann is at the UCL University Hospital St Luc, Brussels, Belgium; G. Stoter is at the Rotterdam Cancer Institute, Rotterdam, The Netherlands; G. Nagel is at the Med. Universitätsklinik, Göttingen, Germany; L. Israel is at the Hopital Avicenne, Bobigny, France; and R. Oskam, P. Palmer and C.R. Franks are at Eurocetus, Amsterdam, The Netherlands.
Revised 6 Aug. 1991; accepted 19 Sep. 1991.

West *et al.* have developed a schedule for continuous rIL-2 infusion obviating the use of an intensive care unit while maintaining antitumour efficacy [10]. Based on this regimen, a European multinational, multicentre, non-randomised phase II trial using rIL-2 alone in metastatic renal cell carcinoma was initiated. The present paper deals with the results from this study representing the introduction of rIL-2 based immunotherapy in Europe. A preliminary report has been presented [8].

PATIENTS AND METHODS

Patients

From December 1987 to June 1989, 61 patients with histologically proven metastatic renal cell carcinoma entered the protocol. The distribution of patients according to the participating institutions is given in Table 1. The protocol entry criteria are summarised in Table 2. All patients had progressive disease, defined as at least 25% increase of the area of any tumour lesion before entering the study. The response status of all patients was reviewed in a blinded fashion by a central review committee consisting of 3 physicians and 2 radiologists. 4 patients were judged to be ineligible and were excluded from all further analysis. The reasons for excluding these 4 patients were as follows: performance status < 80 in 2 cases, lung infection and severe tachycardia in 1 case, and prior chemotherapy in 1 case.

Table 1. Patient contribution by institution

Principal investigator	Institution	City, country	No. of patients
Fosså	Norwegian Radium Hospital	Oslo, Norway	4
Hamblin	Royal Victoria Hospital	Bournemouth, UK	1
Stoter	Rotterdam Cancer Institute	Rotterdam, Holland	3
van Camp	Acad. Ziekenhuis VU Brussel	Brussels, Belgium	1
Janssens	Salvator Ziekenhuis	Hasselt, Belgium	1
Nagel	Med. Universitätsklinik	Göttingen, Germany	3
von der Maase	Herlev University Hospital	Copenhagen, Denmark	14
Philip	Centre Léon Bérard	Lyon, France	5
Rugarli	H.S. Raffaele	Milano, Italy	2
Thatcher	Christie Hospital	Manchester, UK	11
Eremin	University of Aberdeen	Aberdeen, UK	2
Israel	Hopital Avicenne	Bobigny, France	3
Jasmin	Hopital Paul Brousse	Villejuif, France	7
Symann	UCL StLuc Hospital	Brussels, Belgium	4

Table 2. Protocol entry criteria

1. Histologically documented evidence of metastatic renal cell carcinoma.
2. Measurable progressive disease.
3. Ambulatory performance status (ECOG 0–1; Karnofsky ≥ 80%).
4. White blood cells (WBC) ≥ 4000, platelets ≥ 100,000; HCT ≥ 30%.
5. Serum creatinine, bilirubin, prothrombin time and partial thromboplastin time within the institutions normal range.
6. No significant history or current evidence of cardiovascular disease.
7. No evidence of serious active infections requiring antibiotic therapy.
8. No contraindications to the use of pressor agents.
9. No major organ allografts.
10. No brain metastases.
11. No prior chemotherapy or immunotherapy.
12. No patients requiring corticosteroids.
13. No pregnant or lactating women.
14. No prior or current other malignancy (except adequately treated basal cell carcinomas of the skin or *in situ* carcinomas of the cervix).
15. Informed consent.

Table 3. Patients' characteristics

No. of eligible patients	57
Age, median (range)	53 (21–80)
Sex	
Female	19 (33%)
Male	38 (67%)
Karnofsky performance status, median (range)	90 (80–100)
Time from diagnosis to rIL-2, median (range)	5 months (1–175)
Time from metastases to rIL-2, median (range)	1 month (0–14)
Prior therapy	
Nephrectomy	42 (74%)
Embolisation of primary tumour	1 (2%)
Excision of metastatic lesions	8 (14%)
Hormones	9 (16%)
Radiotherapy	6 (11%)
None	11 (19%)
Extent of disease (no. of disease organ sites)	
1	12 (21%)
2	23 (40%)
3	15 (26%)
4	6 (11%)
5	1 (2%)
Sites of disease	
Abdomen	10 (18%)
Bone	12 (21%)
Kidney	24 (42%)
Liver	13 (23%)
Lung	35 (61%)
Lymph nodes	27 (47%)
Pleura	2 (4%)
Skin	1 (2%)
Soft tissue	3 (5%)
Others	4 (7%)

The characteristics of the remaining 57 eligible patients are given in Table 3.

rIL-2 treatment

Recombinant IL-2 (Proleukin) was supplied by Eurocetus B.V., Amsterdam, The Netherlands. The drug was administered intravenously at a dose of 18×10^6 IU/m^2 per day by a 24-h continuous infusion according to the schedule developed by West *et al.* [10].

The total treatment plan consisted of two induction cycles and four maintenance cycles (Fig. 1). Each 15 day induction cycle consisted of a 120 h treatment period followed by a rest period of 6 days, and a further 108 h treatment period. Patients then rested 3 weeks and, in the absence of disease progression, were offered a second induction cycle as described above. 3 weeks following this cycle, patients with stable disease or better

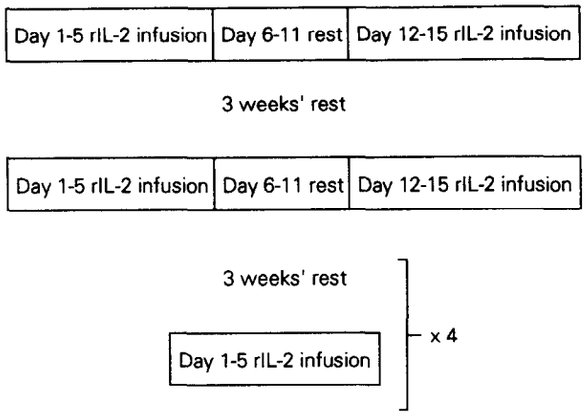

Fig. 1. Treatment plan.

were to receive up to four maintenance cycles, each consisting of a 120 h rIL-2 infusion, repeated every 4 weeks.

Patients were evaluated for response after the two induction cycles and every second month thereafter until progressive disease was observed. Patients off-study, due to progressive disease or unacceptable toxicity, could be offered alternative treatment at the discretion of the investigator.

Dose modifications

Dose escalation above 18×10^6 IU/m^2 per day was not permitted in this study. Dose reductions were made for the control of major toxicities. Infusion of rIL-2 was interrupted in the event of hypotension grade III or IV, significant arrhythmias, suspicion of myocardial ischemia, severe agitation or confusion, elevation of serum creatinine > 400 μmol/l, elevation of the bilirubin > 85 μmol/l, bacterial sepsis, dyspnoea at rest not controlled with low flow binasal oxygen, prolongation of the prothrombin time ≥ 3 s or partial thromboplastin time ≥ 10 s over control, or significant side-effects distinct from the above that warranted interruption of therapy.

In addition, rIL-2 doses were reduced by 50% during the next cycle if the following events had occurred in the previous cycle: hypotension not responding to treatment within 8 h, serum creatinine above 530 μmol/l, serum bilirubin above 85 μmol/l or ≥ grade III neurotoxicity.

All further rIL-2 therapy was stopped if the following events occurred: documented myocardial ischaemia, grade IV neurotoxicity, abnormalities of serum creatinine or bilirubin that failed to return to baseline values, or any other event justifying treatment discontinuation.

Management of toxicity

Paracetamol and/or indomethacin was used prophylactically to avoid fever.

In order to minimise the development of the capillary leak syndrome [12, 13], no supplemental fluids were allowed unless there was documented weight loss resulting from vomiting, diarrhoea or insensible fluid loss.

Patients who experienced grade III hypotension, defined as a decrease in systolic blood pressure of more than 40 mmHg, were treated first by interruption of rIL-2 until the blood pressure returned to within 20 mm Hg baseline (grade I or less). If necessary, infusion of albumin at 12.5 g/h was given. If effective, this was repeated every 4 h as needed. Infusion of dopamine at 5–10 μg/kg/min was used if there was an inadequate response to the initial infusion of colloid and was continued as needed to maintain systolic blood pressure at > 90 mm Hg.

Evaluation of response to treatment

The definitions of the various categories of response were in accordance with the WHO criteria [14]. The duration of complete remission (CR) was calculated from the date CR was first recorded and from day 1 of treatment for partial remission (PR) and no change (NC). Progression-free survival was calculated from day 1 of treatment.

Evaluation of toxicity

The evaluation of haematological, hepatic and renal toxicity was recorded according to the WHO criteria. The grading system for other adverse effects were graded as being mild (grade I), moderate (grade II), severe (grade III) or life-threatening (grade IV).

Statistics

Descriptive statistics were used to tabulate patient characteristics and treatment data. Response duration, progression-free survival and overall survival were determined using the Kaplan–Meier product limit estimator [15]. Survival distributions were compared using the logrank χ^2 test [16].

RESULTS

61 patients entered the protocol. As previously described, 4 patients were excluded from all analysis as they were judged non-eligible for the trial by the review committee. 57 patients were eligible and evaluable for toxicity. However, 6 patients were judged to be non-evaluable for response by the review committee. 5 of these patients were withdrawn early from the trial with no follow-up tumour assessments and 1 patient had insufficient prestudy documentation of disease. In this patient, computed tomography (CT) of the abdomen was not performed prestudy but showed an abdominal mass after the first induction cycle. Thus, an overall response evaluation was not possible although this tumour remained stable during treatment and a PR of lung metastases was obtained. The reasons for early withdrawal were patient request in 2 cases, toxicity in 1 case, and investigator's judgement in 2 cases. 4 of the early withdrawn patients did not receive a full cycle of rIL-2. The remaining patient received a full cycle, but refused all further therapy and examinations despite clear evidence of tumour response. 2 further patients received less than one cycle of rIL-2. These cases were, however, included in the response evaluation as early withdrawal was caused by rapidly progressing disease. Thus, 57 patients were evaluable for toxicity and 51 patients for response. However, response was also based on all eligible patients by conservatively considering patients whose response to treatment we were unable to determine as treatment failures.

The 57 patients received a total of 142 cycles covering 220 infusion periods. The median number of cycles was 2 (range 1–6). The treatment intensity according to the cycle number is given in Table 4. The treatment was interrupted in 89% of the patients. Interruptions occurred 1–5 times per cycle for the majority of patients. The main reason for interruptions was hypotension, being responsible for 84% of the interruptions.

Table 4. Treatment intensity

Cycle no.	1A	1B	2A	2B	3	4	5	6
No. of patients	57	53	39	37	20	12	10	5
Interruptions	63%	62%	72%	65%	60%	75%	80%	20%
Dose								
>90%	64%	44%	44%	38%	35%	50%	60%	60%
50–90%	34%	43%	41%	30%	45%	17%	0	20%
< 50%	2%	13%	15%	32%	20%	33%	40%	20%

Response to treatment

8 of 51 evaluable patients responded to rIL-2 treatment, the overall response rate being 16%. Based on all eligible patients the response rate was 14% (Table 5). 2 patients had a CR and 6 patients a PR. All responding patients had clear evidence of tumour regression after two induction cycles. The CRs were obtained following 64 days and 190 days, respectively. Responding sites included lung, liver, lymph nodes, kidney and abdominal mass. Details about the responding patients are given in Table 6. 10 patients (20%) had NC and 33 patients progressed on therapy.

Several potential prognostic factors were investigated to see whether a particular factor could be predictive for response. However, age, performance status, time between diagnosis and first metastasis, number of disease sites, and presence or absence of the primary tumour were not predictive for an objective tumour response in this cohort of patients. Neither was a rebound lymphocytosis $> 7 \times 10^9$/l, a prognostic factor for response according to West *et al.* [10], or the cumulative rIL-2 dose considering patients receiving at least two induction cycles.

The response duration for the 2 patients with CR was 209 and 394+ days. The median response duration for patients with PR was 371 (range 140–506+) days. The median progression-free survival for the 8 responding patients was 371 (range 140–584+) days, and for the 10 patients with NC 116 (range 64–506+) days. 13 of these 18 patients (4 PRs and 9 NCs) have now progressed. There was no significant difference ($P = 0.47$) in survival between responding patients and patients with NC (Fig. 2a).

The median overall survival was 259 (range 5–841+) days (Fig. 2b). 42 patients have died whereas 15 patients were still alive. 2 patients died free of progression due to endocarditis and development of a second primary tumour, respectively. The latter patient obtained CR 64 days after starting rIL-2 treatment. A gastric adenocarcinoma was diagnosed on day 209 and the patient died due to progression of this tumour without signs of renal cell cancer on day 273.

Table 5. Response to rIL-2 treatment

Response	No. of patients	Percentage of eligible patients ($n = 57$)	Percentage of evaluable patients ($n = 51$)
Complete response (CR)	2	4%	4%
Partial response (PR)	6	11%	12%
No change (NC)	10	18%	20%
Progressive disease (PD)	33	58%	65%
Non-evaluable	6	11%	—

Toxicity

As indicated in Table 7, toxicities were numerous affecting multiple organs. However, the side-effects were usually reversible, manageable, and responsive to treatment interruptions.

Most frequent, but seldom dose-limiting toxicities were fatigue, fever, nausea/vomiting, diarrhoea, pruritus, erythema, rash, and anaemia.

Anaemia was seen in 87% of the patients, requiring blood-transfusions in 36%. Lymphopenia was a predictable finding during rIL-2 infusion, but white blood counts below 4×10^9/l were not observed. Eosinophilia was very common, but the clinical significance remains unclear. Thrombocytopenia was uncommon and grade 4 thrombocytopenia was only found in 1 patient, who at that time had septicaemia.

Biochemical evidence of hepatic toxicity was also very common, with grade 3 elevation of alkaline phosphatase being observed in 16 patients (28%). 11 of these had evidence of metastatic lesions in liver and/or bone prior to start of rIL-2 treatment. The observed changes were reversible in all patients upon treatment discontinuation. Prolongation of prothrombin and partial thromboplastin time was only reported in 2 patients (4%), both of whom were managed with vitamin K.

Creatinine rise was almost universal, but reversible after cessation of treatment. Weight gain was noted in the majority of patients. However, in 62% the weight gain was below 5% and, thus, recorded as grade 0. Clinically significant oedema was reported in 12%.

Hypotension was universal, being responsible for treatment interruptions in 84% of all patients. Most of the patients, however, were clinically asymptomatic. Colloid infusion was frequently given prophylactically and administration of vasopressors was only necessary in 5 patients. Arrythmias and/or tachycardia were observed in 24% and were reported as being dose limiting in 5% of the patients.

Dyspnoea was reported in 19 patients (33%), but only 4 patients had grade III or IV toxicity and treatment interruptions were only necessary in 2 patients (4%). No patients required intubation. 16 of 19 patients with treatment-related dyspnoea had evidence of metastatic pulmonary disease.

Peripheral neurotoxicity was observed in 12% and central neurotoxicity in 32% of the patients, reversible mental changes being the most frequent side effect.

Documented systemic infections were reported in 6 patients (11%).

6 patients were withdrawn from the study due to toxicity. 4 patients because of severe hypotension in combination with arrythmias and/or dyspnoea and/or creatinine rise. 1 patient was withdrawn due to haemorrhagic proctitis, and 1 patient due to somnolence concomitant with rapidly progressing disease. 1 additional patient was taken off study after one cycle because of hypercalcaemia which was also present at study start. Management of this clinical condition was judged by the investigator not compatible with continuation of rIL-2 treatment.

There were 3 treatment-related deaths. 2 patients died of infectious complications, endocarditis (*Staphylococcus epidermidis*) and klebsiellal septicaemia, respectively. 1 patient died from renal failure in combination with rapidly deteriorating disease status.

DISCUSSION

This report presents the initial experience with rIL-2 based immunotherapy in Europe. A total of 14 oncological centres participated in this multinational, multicentre study with a

Table 6. Details of responding patients

First day of treatment	Date			Overall response	Overall response duration	Survival (days)	Disease sites	Response on sites
	Response	Progression	Death					
04.02.88	13.04.88	10.02.89		PR	372	809*	Abdomen	PR
							Kidney	CR
							Lung	PR
							Lymph nodes	CR
29.02.88	31.03.88		18.07.88	PR†	140	140	Lung	PR*
18.07.88	24.01.89			CR	394*	584*	Liver	CR
							Lymph nodes	CR
26.09.88	13.02.89			PR	506*	506*	Kidney	PR
							Liver	PR
10.11.88	10.01.89	Unknown	15.11.89	PR	370	370	Lung	PR
22.11.88	06.12.88	15.12.89		PR	388	435*	Bone	NC
							Lung	CR
06.02.89	10.05.89	25.01.90	16.03.90	PR	353	403	Abdomen	PR
							Liver	PR
							Lymph nodes	NC
							Soft tissue	NC
01.05.89	04.07.89		29.01.90‡	CR	209	273	Abdomen	CR
							Lymph nodes	CR

*Indicates an ongoing response and/or survival.
†Clinical PR, no viable tumour at autopsy (pathological CR). Died of endocarditis.
‡Died due to the development of a second primary tumour.

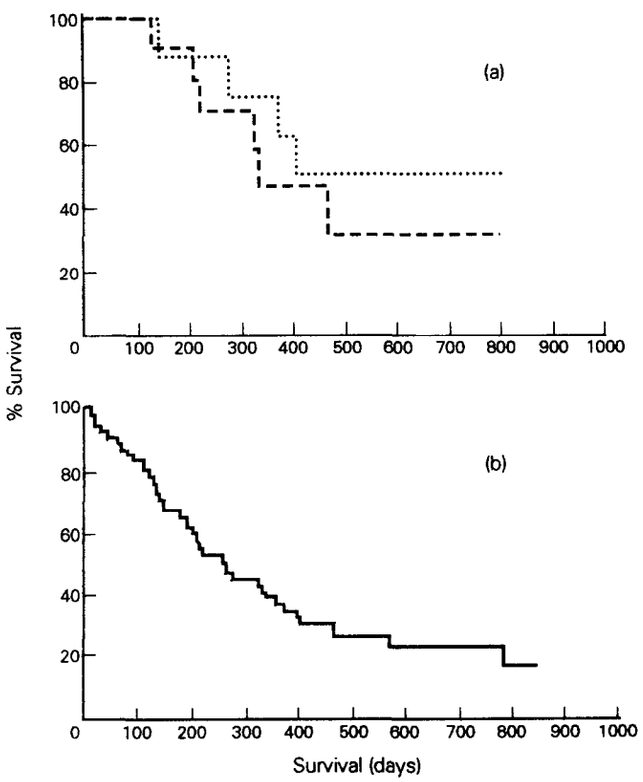

Fig. 2. Overall survival in (a) patients with "no change" (---NC) vs. responding patients (···· CR + PR), $P = 0.47$; and in (b) all patients (—).

Table 7. Toxicity to rIL-2 treatment

Event	Incidence (%)	Grade (%)				
		1	2	3	4	Unknown
Fatigue	100					
Fever	91	15	48	28		
Chills	20	4	4	8		4
Erythema/rash/exfoliation	62	23	30	9		
Pruritus	47	15	21	11		
Nausea/vomiting	72	13	31	19		9
Diarrhoea	45	11	23	9		2
Weight gain	39	33	4		2	
Oedema	12		6	2		4
Anaemia	87	36	37	14		
Thrombocytopaenia	13	9	2	2		
Hyperbilirubinaemia	30	16	14			
AST rise	56	31	19	6		
Alkaline phosphatase rise	75	21	26	28		
Creatinine rise	82	45	33	4		
Hypotension	93	2	28	41	11	11
Arrythmia including tachycardia	24	4	12	4		4
Dyspnoea	33	4	17	4	4	4
Peripheral neurotoxicity	12			10		2
Central neurotoxicity	32	10	6	10		6
Sepsis	11					
Treatment-related death	5					

AST = aspartate aminotransferase.

patient contribution by institution ranging from 1 to 14 patients (Table 1). The acquired experience in handling this complex therapy has, therefore, to be considered as different from institution to institution, which may be one of the reasons for the relatively low treatment intensity (Table 4). This could be of importance since efficacy has been reported to be dependent on treatment intensity [5], although no dose-response correlation was found in the study. On the other hand, the response rate was similar to the 22% (12/54) reported by Rosenberg *et al.* using high-dose bolus rIL-2 alone [9]. The NCI extramural group using high-dose bolus rIL-2 and LAK cells reported a similar response rate of 16% (5/32) [7], whereas Rosenberg *et al.* obtained a response rate of 35% (25/72) using the same rIL-2 and LAK cell combination [9]. In comparison with other treatment possibilities, it should be noted that interferons (IFN) have induced response rates of the same magnitude as in the present and other studies using rIL-2 alone, although IFN seems to induce less CRs [17, 18].

Antitumour responses were seen in 8 of 51 evaluable patients (16%). 2 patients achieved a CR and 6 patients a PR. 1 of the 2 CR patients died due to a second malignancy after 209 days with no signs of recurrence of renal cell cancer. The other patient is still alive without evidence of disease. 2 of 6 patients continue in PR for 140+ and 506+ days, respectively. Patients with NC had a shorter progression-free survival than responding patients. However, no significant difference in survival was observed between stable and responding patients (Fig. 2a). This could indicate that achievement of NC may implicate a survival advantage as opposed to historical controls [19, 20], a possibility also discussed in studies with interferon [18, 21]. Thus, it may be a limitation only to look at the conventional response criterias, i.e. CRs and PRs when the therapeutic effect of biomodulators is evaluated. The possibility that NC may represent a positive treatment result for the patient should be taken into consideration and further investigated in studies using biological response modifying drugs.

Attempts to identify laboratory or clinical parameters predictive for response to rIL-2 treatment have so far failed to give reproducible findings. The magnitude of the rebound lymphocytosis after rIL-2 treatment has been associated with treatment response in one study [10], and the presence of bulky metastatic, especially abdominal, disease or a primary tumour have been associated with a poor response probability in another study [7]. In the present study, neither rebound lymphocytosis nor any demographic characteristic appeared to correlate with response. Comparable characterization of functional and phenotypic changes in peripheral blood lymphocytes or serological assays have not been performed.

The toxicity profile was similar to that reported using rIL-2 bolus regimens [4, 12, 13]. However, taking advantage of the continuous infusion regimen, it was possible to avoid the routine use of an intensive care unit as toxicities most often recovered solely on interrupted therapy. The majority of treatment interruptions were due to hypotension. Our criteria for treatment interruptions were rather conservative, i.e. a decline in systolic pressure of 40 mm Hg or more. Most patients were not clinically shocked, and irreversible kidney or other organ damage was not observed. A higher treatment intensity could have been achieved if other criteria for hypotension related treatment interruptions had been used. Thus, it seems possible, with only little increased risk for the patient, to allow a more pronounced decline in the systolic blood pressure.

4 patients experienced severe dyspnoea, grade III in 2 cases and grade IV in the other 2 cases (Table 7). Interruption of the rIL-2 treatment was only necessary in 2 of these patients (4%). No patients required intubation. This is in contrast to the use of high-dose bolus regimens in which dyspnoea requiring intubation has been reported in approximately 6% of the patients [9, 12, 13]. Furthermore, there was no need for the routine use of an intensive care unit.

There were 3 treatment-related deaths. 2 of these deaths were a result of catheter-related septicaemia. A total of 11% had documented bacterial sepsis in accordance with other reports [6, 9, 22, 23]. The high incidence of bacterial infections seems to be associated with the exposure to rIL-2 [22, 23]. A possible explanation may be an acquired chemotactic defect in neutrophils during the rIL-2 treatment [24]. Thus, prophylactic antibiotic treatment and/or close bacteriological surveillance should be considered as an option. In the third patient, death was due to renal failure during rIL-2 treatment. Although this patient had rapidly progressive disease, we consider rIL-2 to be a significant factor for the death of the patient.

In conclusion, although a multinational, multicentre study is a severe test for a new complex therapy, the study confirmed the antitumour efficacy of rIL-2 administered by continuous intravenous infusion to patients with renal cell carcinoma. Toxicities were numerous, but manageable by close observation in a normal oncology ward, without the routine use of an intensive care unit.

1. Lafreniere R, Rosenberg SA. Successful immunotherapy of murine experimental hepatic metastases with lymphokine-activated killer cells and recombinant interleukin-2. *Cancer Res* 1985, **45**, 3735–3741.
2. Mulé JJ, Shu S, Schwarz SL, Rosenberg SA. Adoptive immunotherapy of established pulmonary metastases with LAK cells and recombinant interleukin-2. *Science* 1984, **225**, 1487–1489.
3. Rosenberg SA, Mulé JJ, Spiess PJ, Reichert CM, Schwarz SL. Regression of established pulmonary metastases and subcutaneous tumor mediated by the systemic administration of high-dose recombinant interleukin 2. *J Exp Med* 1985, **161**, 1169–1188.
4. Rosenberg SA, Lotze MT, Muul LM, *et al.* Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant Interleukin-2 to patients with metastatic cancer. *New Engl J Med* 1985, **313**, 1485–1492.
5. Bradley EC, Louie AC, Paradise CM, *et al.* Antitumor response in patients with metastatic renal cell carcinoma is dependent upon regimen intensity. *Proc Am Soc Clin Oncol* 1989, **8**, 133.
6. Dutcher JP, Creekmore S, Weiss GR, *et al.* A phase II study of Interleukin-2 and lymphokine-activated killer cells in patients with metastatic malignant melanoma. *J Clin Oncol* 1989, **7**, 477–485.
7. Fischer RI, Coltman CA, Doroshow JH, *et al.* Metastatic renal cancer treated with interleukin-2 and lymphokine-activated killer cells. *Ann Intern Med* 1988, **108**, 518–523.
8. Negrier S, Philip T, Stoter G, *et al.* Interleukin-2 with or without LAK cells in metastatic renal cell carcinoma. A report of a European multicentre study. *Eur J Cancer Clin Oncol* 1989, **25** (Suppl. 3), 21–28.
9. Rosenberg SA, Lotze MT, Yang JC, *et al.* Experience with the use of high-dose Interleukin-2 in the treatment of 652 cancer patients. *Ann Surg* 1989, **210**, 474–485.
10. West WH, Tauer KW, Yanelli JR, *et al.* Constant infusion recombinant Interleukin-2 in adoptive immunotherapy of advanced cancer. *New Engl J Med* 1987, **316**, 898–905.
11. Rosenberg SA. Clinical immunotherapy studies in the surgery branch of the U.S. national cancer institute: brief review. *Cancer Treat Rev* 1989, **16**, 115–121.
12. Lee RE, Lotze MT, Skibber JM, *et al.* Cardiorespiratory effects of immunotherapy with Interleukin-2. *J Clin Oncol* 1989, **7**, 7–20.
13. Margolin KA, Rayner AA, Hawkins MJ, *et al.* Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. *J Clin Oncol* 1989, **7**, 486–498.

14. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
16. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
17. Muss HB. Interferon therapy for renal cell carcinoma. *Semin Oncol* 1987, **14** (Suppl. 2), 36–42.
18. Fossâ SD, Stenwig AE, Lien HH. Long-term results in patients with metastatic renal cell carcinoma treated with interferon with or without vinblastine. *World J Urol* (in press).
19. Patel NP, Lavengood RW. Renal cell carcinoma: natural history and results of treatment. *J Urol* 1978, **119**, 722–726.
20. Philip T, Mercatello A, Negrier S, *et al.* Interleukin-2 with and without LAK cells in metastatic renal cell carcinoma: the Lyon first-year experience in 20 patients. *Cancer Treat Rev* 1989, **16** (Suppl. A), 91–104.
21. Silver HKB. Interferon treatment in malignant melanoma. *Interferons in Cancer Treatment.* Medical Education Services, 1986, 81–91.
22. Richards JM, Gilewski TA, Vogelzang NJ. Association of interleukin-2 therapy with staphylococcal bacteremia. *Cancer* 1991, **67**, 1570–1575.
23. Snydman DR, Sullivan B, Gill M, Gould JA, Parkinson DR, Atkins MB. Nosocomial sepsis associated with Interleukin-2. *Ann Intern Med* 1990, **112**, 102–107.
24. Klempner MS, Norin R, Mier JW, Atkins MB. An acquired chemotactic defect in neutrophils from patients receiving Interleukin-2 immunotherapy. *N Engl J Med* 1990, **322**, 959–965.

Eur J Cancer, Vol. 27, No. 12, pp. 1589–1593, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Phase II Study of Weekly 5-Fluorouracil, Cisplatin and Vinblastine in Advanced Non-small Cell Lung Cancer

Peter J. O'Dwyer, Corey J. Langer, Judy Walczak, Michael H. Levy, Kristin Padavic-Shaller, Gary R. Hudes, Sam Litwin and Robert L. Comis

The scheduling of chemotherapeutic agents may be important in optimising their antitumour actions. This has been explored in non-Hodgkin lymphoma, osteogenic sarcoma and bladder cancer with improved results using intensive, weekly dosing schemas. We began a phase II study of cisplatin, 5-fluorouracil and vinblastine in non-small cell lung cancer (NSCLC) on a weekly schedule. 38 patients with advanced or metastatic NSCLC were entered; 32 are evaluable for response. 11 patients were treated with 5-fluorouracil 1.5 g/m^2 and vinblastine 4 mg/m^2 by 24-h continuous infusion, and cisplatin 30 mg/m^2 over 30 min, 6–8 h after the start of the infusion. Because of prohibitive myelotoxicity, the next 27 patients received 5-fluorouracil 1.2 g/m^2 and vinblastine 3 mg/m^2. None had had prior chemotherapy while 6 had had previous radiation therapy. Myelosuppression was the predominant toxic effect. Other side-effects included neuropathy, diarrhoea, mucositis, nausea and vomiting. 32 patients are evaluable for response: there have been 14 partial remissions (44%). Responses have occurred chiefly in lung and lymph nodes. The median survival on this study is 7 months, and responders did not live longer than non-responders. While this regimen is well tolerated by the majority of patients and has a response rate comparable to other active regimens identified in single institution studies, survival does not appear to be enhanced. We conclude that the schedule manipulation described here does not enhance the therapeutic index of these drugs in NSCLC.
Eur J Cancer, Vol. 27, No. 12, pp. 1589–1593, 1991.

INTRODUCTION

THE DEVELOPMENT of chemotherapy regimens for the treatment of advanced non-small lung cancer (NSCLC) has progressed slowly over the past 10 years. Cisplatin, the most active single agent, is incorporated in a variety of combination regimens, the best of which include either a vinca alkaloid or etoposide. Response rates of the order of 40–50% are obtained with cisplatin-containing regimens in single institution studies [1, 2]; such regimens generally yield rates closer to 25 to 30% in larger Cooperative Group trials [3–5]. Despite these modest response rates, a randomised study of cisplatin/vindesine vs. best supportive care has shown a clear survival benefit over untreated controls [6]. Thus there are indications that pursuing further the chemotherapy of NSCLC may provide incremental gains in response and survival.

The issue of drug scheduling is an aspect of the design of chemotherapy regimens which has received little attention in NSCLC. Many chemotherapeutic drugs, including antimetabolites, vincas and epipodophylotoxins demonstrate schedule dependency in preclinical models [7]. In recent years, promising regimens using unconventional schedules have been developed in bladder cancer [8], non-Hodgkin lymphoma [9], and osteo-

Correspondence to P.J. O'Dwyer.
The authors are at the Department of Medical Oncology, Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, Pensylvania 19111, U.S.A.
Revised 16 July 1991; accepted 26 July 1991.