J Cancer Res Clin Oncol (1993) 119:745–755

Journal of Cancer Research and Clinical Oncology

Renal, metabolic, and hemodynamic side-effects of interleukin-2 and/or interferon α: evidence of a risk/benefit advantage of subcutaneous therapy

Axel Schomburg, Hartmut Kirchner, Jens Atzpodien

Department of Hematology and Oncology, MHH University Medical Center, W-3000 Hannover, Germany

Received: 10 July 1992/Accepted: 24 March 1993

Abstract. Systemic immunotherapy with recombinant interleukin-2 (rIL-2) via intravenous (i.v.) and subcutaneous (s.c.) administration produces objective responses in a proportion of advanced cancer patients. While most of the previous investigations chose the i.v. route for cytokine application, there is an increasing number of trials employing s.c. rIL-2 therapy. The comparison of reported response rates for i.v. versus s.c. therapy reveals no significant differences between these modalities. In an effort to describe systemic toxicities of s.c. cytokine therapy with regard to renal, metabolic, and hemodynamic abnormalities and to compare these effects to toxicities reported upon i.v. therapy, we retrospectively evaluated 148 treatment cycles of s.c. immunotherapy given to 107 outpatients. Our study cohorts consisted of 15 patients who received s.c. rIL-2 at doses of $(4.8–14.4)\times10^6$ IU m^{-2} day^{-1} 5 days/week for a total of 8 weeks, 20 patients who received rIFNα2b at $(3.0–6.0)\times10^6$ m^{-2} day^{-1} thrice weekly for a total of 6 weeks, and 72 patients who were given s.c. rILFNα2b at 6.0×10^6 U/m^2, three times per week, plus s.c. rIL-2 at $(14.4–18.0)\times10^6$ IU/m^2 on days 1 and 2, followed by 4.8×10^6 IU m^{-2} day^{-1} 5 days/week for 6 consecutive weeks. These treatment regimens were well tolerated in the outpatient setting; no toxic death occurred, and none of the patients developed life-threatening toxicity due to a capillary leak syndrome. Upon s.c. combination therapy, dyspnea at rest occurred in 6% of patients and grade III and IV hypotension occurred in 7% and 4%, respectively; plasma protein was significantly decreased (mean nadir ± standard deviation, 67±5 g/l). In addition, s.c. therapy led to a significant increase in serum creatinine (mean peak ± standard deviation, 115.1±21.4 μmol/l) and urea nitrogen (mean peak ± standard deviation, 6.5±2.5 mmol/l); electrolyte disturbances and direct nephrotoxicity never caused major clinical symptoms. This was in marked contrast to a multitude of dose-limiting and life-threatening adverse reactions reported upon i.v. rIL-2 therapy. We conclude that palliative low to intermediate-dose s.c. rIL-2/rIFNα combination therapy, in contrast to i.v. treatment, can be administered in the ambulatory setting with good practicability and excellent safety. This outpatient regimen is as effective against metastatic renal cell cancer as the most aggressive i.v. rIL-2 protocol reported.

Key words: Renal – Metabolic – Hemodynamic toxicity – Immunotherapy – Interleukin-2 – Interferon α

Introduction

Contemporary immunotherapy exploits the therapeutic potential of recombinant human cytokines. Among these, recombinant interferon α (rIFNα) and recombinant interleukin-2 (rIL-2) are most widely used. Based on the chemotherapy model, initially, the concept of a linear dose/response curve prompted trials with high-dose rIL-2 via i.v. administration (Rosenberg et al. 1987; West et al. 1987). However, there is growing evidence from in vitro experiments (Grimm et al. 1985; Roussel et al. 1990) and clinical trials (Edwards et al. 1984; Shau et al. 1988; Schoof et al. 1988; Hersh et al. 1989; Parkinson et al. 1990) for a non-linear dose/response curve, whereby biological and therapeutic activity is attained at cytokine doses far below the maximum tolerated dose in man. In addition, there is evidence that high doses of biological response modifiers given alone (Kleinerman et al. 1986; Hartmann et al. 1986; Talmadge et al. 1987; Muss 1987; Krown 1987; Richards et al. 1988) or combined (Budd et al. 1989; Farace et al. 1990; Kawamura et al. 1985) might actually suppress the desired effect of immunostimulation.

At high doses, rIL-2 invariably induced a wide spectrum of serious adverse effects. These covered severe "influenza-like symptoms" such as fever, chills, nausea, vomiting, diarrhea, arthralgias, anorexia, and malaise. Toxicities also could mimic critical illness through a capillary leak syndrome and its consequences, including hypotensive dysregulations sim-

Abbreviations: rIFNα, recombinant interferon α; rIL-2, recombinant interleukin-2; LAK, lymphokine-activated killer cells; TIL, tumor-infiltrating lymphocytes; TNF, tumor necrosis factor

Correspondence to: J. Atzpodien, Abt. Hämatologie u. Onkologie (6860), Medizinische Hochschule Hannover, W-3000 Hannover, Germany

ilar to septic shock, tissue injury analogous to graft-versus-host disease, and a vast range of multi-organ dysfunctions. The latter, upon high-dose rIL-2 therapy, included a multitude of renal, metabolic, cardiovascular, respiratory, gastrointestinal, hepatic, hematopoietic, infectious, dermatological, and neuropsychiatric toxicities, which eventually were life-threatening. The sequelae of increased endothelial permeability, referred to as vascular leak syndrome, have been extensively documented in clinical trials using i.v. rIL-2, wherein patients required standard oncology or intensive care.

In an effort to reduce morbidity and mortality from systemic rIL-2 therapy significantly, we devised treatment strategies dissociating the therapeutic benefit of cytokine administration from treatment-related adverse effects. Treatment regimens using rIL-2 via s.c. injection at dose levels approximately 10–30 times lower than in previous regimens have demonstrated significant therapeutic efficacy while drastically reducing treatment-induced toxicity (Atzpodien et al. 1990; Sznol et al. 1991).

In the present study, we evaluated 107 patients receiving out-patient s.c. immunotherapy. The majority of patients were treated with rIL-2/rIFN-α2b combination therapy. To assess the toxicity of each cytokine in depth, we also analyzed patients receiving rIL-2 or rIFN-α2b single-agent therapy. We monitored hemodynamic, renal, and metabolic adverse effects following 148 treatment cycles. Treatment-related toxicity was assessed in comparison to pretreatment status and off-therapy levels, and also to reported toxicity assessments provided by other investigators following i.v. rIL-2 therapy.

These clinical analyses serve as the focus of the present report.

Patients and methods

Patients. Patients' characteristics are indicated in Table 1. A total of 107 patients were treated, of which 34 were women and 73 were men. Patients presented with renal cell carcinoma (n=91), malignant melanoma (n=7), mesothelioma (n=3), Hodgkin's disease (n=2), fibrosarcoma (n=2), colorectal carcinoma (n=1), and lung cancer (n=1); 99 patients had advanced-stage metastatic cancer. Eight renal cell carcinoma patients were treated in the surgical adjuvant setting after surgery for metastatic disease. In all patients, standard therapy had failed or no standard therapy was available.

Prior therapy included chemotherapy in 16 patients (vinblastine in 5, mafosfamide in 5, dacarbazine in 4, methotrexate in 4, 5-fluorouracil in 3, and cyclophosphamide in 1 patient), limited-field irradiation in 25 patients, immunotherapy in 19 patients (rIFNα in 8, rIFNγ in 3, TNFα in 2, and various tumor vaccines in 6 patients), hormone therapy in 10 patients (tamoxifen in 7, corticosteroids in 2, and medroxyprogesterone in 1 patient). The sites of disease included lung (73% of patients), bone (22%), liver (15%), pleura (11%), soft tissue (10%), skin (7%), lymph nodes (5%), pancreas (2%), and local relapse (19%).

Patient eligibility requirements included a minimum performance score of 2, as defined by ECOG criteria, an expected survival of at least 3 months, no evidence of brain metastases, and adequate bone marrow, cardiac, renal, and hepatic functions. In no patient treated had systemic anticancer therapy been administered for at least 4 weeks prior to entry into the study. Patients requiring continued therapy with corticosteroids were ineligible. There was no patient with additional renal disease besides renal cell carcinoma; all patients except 1 in the rIL-2 cohort, 3 in the rIFNα cohort, and 15 patients in the combined-therapy group were uninephric due to previous nephrectomy for renal cell carcinoma. Written informed consent was obtained from all patients prior to the initiation of therapy.

Study design. Three different immunotherapeutic regimens were used in this study. Clinical trials employing rIL-2, rIFNα, and the combination of both cytokines were initiated and performed sequentially. All treatment was given in an outpatient setting; the s.c. injections were self-administered. A total of 148 treatment courses given to 107 patients were evaluated retrospectively for drug-induced toxicity.

Fifteen patients received s.c. pulsed rIL-2 (Eurocetus, Amsterdam, The Netherlands). This therapy consisted of rIL-2 at a single dose of 4.8×10^6 IU/m^2 given three times daily on days 1, 15, 29, and 43 and twice daily on days 2, 16, 30, and 44, followed by 4.8×10^6 IU/m^2 on days 3–5, 8–12, 17–19, and 22–26.

Twenty patients were treated with s.c. rIFNα2b (Schering-Plough, Munich, Germany). Patients received 3.0×10^6 units/m^2 IFNα on days 1, 3, and 5, followed by 6.0×10^6 units/m^2, given three times weekly for 5 more weeks.

Seventy-two patients received a combination of low-dose s.c. rIL-2 and s.c. rIFNα2b. Patients were given rIL-2 at $(14.4–18.0)\times10^6$ IU/m^2 on days 1 and 2, followed by 4.8×10^6 IU/m^2 daily, 5 days/week, for 6 consecutive weeks; rIFNα2b was administered at 3.0×10^6 units/m^2, twice during week 1, and at a dose of 6.0×10^6 units/m^2 each, three times a week for 5 more weeks.

Supportive care routinely included 1 g acetaminophen orally every 8 h, metoclopramide orally every 8 h, 1 g metamizole if necessary, and antiemetics and antidiarrheals via the oral route as required. Grade III toxicity resulted in a 50% dose reduction for the following week; patients with grade IV toxicity had treatment withheld until toxicity resolved or therapy was terminated. Treatment cycles were repeated as long as there were no signs of progression of disease and it was thought to be in the patients' best interest.

Clinical, hematological and laboratory studies. Patients were seen prior to and at weekly intervals following the initiation of therapy. Toxicity evaluations were attentively recorded, and assessed according to the WHO adapted grading system. Toxicity was defined as the maximum grade of observed adverse effects during therapy or up to 2 weeks thereafter. Peripheral venous blood samples were drawn and examined for the reported parameters at the aforementioned times. Pretreatment baseline and peak (or nadir) values were individually recorded. Recovery values in these patients were obtained 2 weeks after the last cytokine injection. Laboratory values reported by other investigators were converted to SI units wherever necessary.

Statistics. Homogeneity of the study groups was assessed by the χ^2 test with continuity correction. Statistical analysis of the mean ± SD changes in all hemodynamic, hematological, and laboratory parameters was performed using a paired-sample Student's t-test, comparing the differences between baseline, recovery and therapy values, and a Wilcoxon's matched-pairs signed-ranks test to investigate the pair-to-pair variability of the patients' data. All P values less than 0.05 were considered statistically significant.

Results and review

Therapeutic efficacy

Table 2 presents a survey of immunotherapy trials employing rIL-2 and/or rIFNα in a total of 343 evaluable patients with metastatic renal cell carcinoma. Response rates ranged from 0% in a phase II trial performed by Pichert et al. (1991) to 50% reported by West et al. (1987). The 95% confidence limits for response rates among all ten studies ranged from 0% to 88%. Given the size of patient cohorts with renal carcinoma in these studies (n=6–83), there was no significant difference in therapeutic activity between treatment regimens employing rIL-2 via intravenous bolus or continuous infusion and regimens using rIL-2/rIFNα via subcutaneous injection.

Table 1. Patient background[a]

Parameter		Treatment modality		
		rIL-2	rIFNα	rIL-2/rIFNα
Treatment courses		21	34	93
Patients		15	20	72
Male		10	12	51
Female		5	8	21
Age (years)				
Median		54.0	61.0	55.0
Range		32–72	41–74	30–69
≤30		–	–	1
31–40		2	–	6
41–50		3	3	13
51–60		8	6	34
61–70		1	9	18
≥71		1	2	–
Performance status (ECOG)	0	8	14	55
	1	5	4	11
	2	2	2	6
Disease				
Renal cell carcinoma		12	20	59
Malignant melanoma		3	–	4
Mesothelioma		–	–	3
Hodgkin's disease		–	–	2
Others		–	–	4
Site of disease				
Lung		10	17	51
Liver		4	4	8
Bone		1	7	16
Skin		–	1	8
Local relapse		1	4	15
Abdominal lymph nodes		1	6	11
Mediastinal lymph nodes		2	2	18
Peripheral lymph nodes		2	1	7
Others		2	4	19
Number of organ sites involved				
0		–	–	8
1		7	9	19
2		4	8	20
3		3	2	14
>3		1	1	11
Prior therapy				
Chemotherapy		4	2	10
Radiation therapy		1	4	20
Immunotherapy		3	1	15
Hormone therapy		2	3	5
Primary surgery		15	18	67
Relapse surgery		2	3	21
Any 2 or more		8	8	34
Any 3 or more		–	2	11
None		–	–	2

[a] A total of 107 patients were studied (34 female and 73 male). One group of patients received s.c. interleukin-2 (rIL-2), a second group received s.c. interferon α (rIFNα), and a combination of both was administered to the third group. ECOG, Eastern Cooperative Oncology Group

Administered dosages

As shown in Table 1, patients in our study were sequentially assigned to three different treatment groups. Immunotherapy schedules and dosages were used as outlined in *Patients and methods.*

In patients receiving s.c. rIL-2 as a single drug, 95.5% (range, 83.0%–100.0%) of the projected dose of rIL-2 was administered. In patients receiving s.c. rIFNα only, 96.8% (range, 77.6%–100.0%) was administered. Patients treated with rIL-2/rIFNα s.c. combination therapy received a mean 83.2% (range, 50.0%–100.0%) and 97.8% (range, 75.0%–100.0%) of the projected doses of rIL-2 and rIFNα respectively (data not shown).

Toxicity

Toxic death. No toxic deaths occurred in our study cohort. In contrast, toxic deaths were reported in most clinical investi-

Table 2. Response rates in metastatic renal cell carcinoma patients receiving rIL-2- or rIFN-α-based immunotherapy [a]

Treatment	*n*	Responders (PR/CR) (%)	95% confidence interval	Reference
rIFN-α s.c. rIFN-α2b s.c. 3–6 MU $m^{-2}day^{-1}$ thrice weekly	20	15	3–38	
rIL-2 s.c. rIL-2 s.c. 4.8–14.4 MIU $m^{-2}day^{-1}$	12	0	0–27	
rIL-2 s.c./rIFNα s.c.				
rIL-2 s.c. 14.4–18.0 MIU m^{-2} and 3.6–4.8 MIU $m^{-2}day^{-1}$ rIFNα2b s.c. 6.0 MU m^{-2}	50	28	16–42	Atzpodien et al. 1990
rIL-2 s.c. 1.5 M Roche U $m^{-2}day^{-1}$ rIFNα2a s.c. 1.5 MU $m^{-2}day^{-1}$	23	22	8–44	Sznol et al. 1991
rIL-2 i.v./rIFNα				
rIL-2 i.v./bolus 6.0–27.0 MIU m^{-2} q 8 h rIFNα i.v./bolus 3.0–6.0 MU m^{-2} q 8 h	35	31	17–49	Rosenberg et al. 1989 b
rIL-2 const. i.v. inf. 6.0–12.0 MIU m^{-2} rIFNα2a i.m. 3.0–12.0 MU m^{-2}	15	40	16–68	Hirsch et al. 1990
rIL-2 const. i.v. inf. 18.0 MIU m^{-2} day^{-1} rIFNα2a s.c. 6 MU m^{-2}	6	0	0–46	Pichert et al. 1991
rIL-2 i.v. bolus ± LAK cells				
rIL-2 0.6 MIU/kg q 8 h + LAK cells	36	33	19–51	Rosenberg et al. 1987
rIL-2 0.6 MIU/kg q 8 h + LAK cells	32	16	5–33	Fisher et al. 1988
rIL-2 constant i.v. infusion ± LAK cells				
rIL-2 6.0–42.0 MIU m^{-2} day^{-1} + LAK cells	6	50	12–88	West et al. 1987
rIL-2 18.0 MIU m^{-2} day^{-1} ± LAK cells	83	24	18–22	Negrier et al. 1989
rIL-2 18.0–27.0 MIU m^{-2} day^{-1} + LAK cells	25	16	5–36	Davis et al. 1990

[a] *n*, number of patients; LAK, lymphokine-activated killer cells; MIU, 10^6 international units

Table 3. Effects of immunotherapy with interleukin-2 and/or interferon α on blood pressure levels

Treatment	*n*	Patients experiencing hypotension (%)			
		I[a]	II	III	IV
rIL-2 s.c.	15	40	7	–	–
rIFNα s.c.	20	10	–	–	–
rIL-2 s.c./rIFNα s.c.	72	14	14	7	4
rIL-2 i.v. bolus ± LAK/TIL[b]					
Clark et al. (1990)	30	NR[c]	NR	81	NR
Dutcher et al. (1989)	36	NR	NR	67	NR
Fisher et al. (1988)	35	NR	NR	74	NR
Lee et al. (1989)	317	NR	NR	65	3.3
Margolin et al. (1989)	93	NR	NR	74	NR
Parkinson et al. (1990)	47	NR	NR	72	NR
Rosenberg et al. (1989 a)	214	NR	NR	74.4	NR
Stahel et al. (1989)	26	46	15	30	7.7
rIL-2 constant i.v. infusion ± LAK					
Clark et al. (1990)	22	NR	NR	59	NR
Dutcher et al. (1991)	36	NR	NR	45	NR
Negrier et al. (1989)	42/53	8/4	32/38	47/50	5/0
Shiloni et al. (1989)	20	10	30	50	10

[a] WHO grade of hypotension
[b] TIL, tumor-infiltrating lymphocytes
[c] NR, not reported

gations using i.v. rIL-2. The frequency of toxicity-related deaths in most trials was below 5% of patients treated (West et al. 1987; Rosenberg et al. 1988 a), yet infrequently, death rates of 5%–10% upon constant infusion protocols with or without lymphokine-activated killer (LAK) cell administration (Albertini et al. 1990) or even of more than 10% upon constant and bolus i.v. therapy (Mann et al. 1990; Dutcher et al. 1991) were reported.

Capillary leak. In the present study, systemic rIL-2 therapy caused no serious adverse effects due to an increase in vascular permeability.

In contrast, upon i.v. rIL-2 therapy, a severe and eventually life-threatening increase in vascular permeability could result in a multitude of adverse symptoms. This capillary leak syndrome included pulmonary toxicity due to interstitial edema of the lungs, increased body weight due to fluid reten-

Table 4. Mean serum creatinine levels following immunotherapy with interleukin-2 and/or interferon α

Treatment	*n*	Baseline (μmol/l)	Peak (μmol/l)	Recovery (μmol/l)
rIL-2 s.c.	15	98.3±13.4 (80–124)	116±20.1* (80–145)	98.3±17.1 (71–124)
rIFNα s.c.	20	103.1±34.8 (62–186)	107.1±27.3 (71–177)	96.1±28.9 (62–168)
rIL-2 s.c./rIFNα s.c.	72	101.8±23.4 (53–159)	115.1±21.4* (71–177)	97.8±23.6 (53–195)
rIL-2 i.v. bolus ± LAK cells				
Belldegrun et al. (1989)	52[b]	NR	300.6±26.5	NR
Belldegrun et al. (1987)	99	93.7±2.6	304.1±16.8	NR
Chien et al. (1990)	11	44.2[a]	238.7[a]	NR
Huang et al. (1990)	21	99.9±0.6	199.8*	109.6
Lotze et al. (1986)	5	N.R.	141.4	NR
Ognibene et al. (1988)	5	88.4±2.6	178.6±24.8*	NR
Saxon et al. (1991)	54	NR	274.0±168.0	NR
Textor et al. (1987)	12	99.9±4.4	236.9±26.5*	NR
Webb et al. (1988)	17	88.4	229.8*	106.1
rIL-2 constant i.v. infusion ± LAK cells				
Cochat et al. (1991)	15	55±4	133±22*	61±8
Lotze et al. (1986)	6	NR	114.9	NR
rIL-2 i.v. bolus/const. i.v. infusion + LAK cells				
Shalmi et al. (1990)	10	88.4±8.9	168.0±26.5	NR

[a] Chien et al. reported mean baseline values of 0.5 mg/dl and mean peaks of 2.7 mg/dl
[b] Renal carcinoma patients only
* $P<0.05$

tion, profound decreases in systemic blood pressure levels accompanied by a substantial acceleration in heart rate, hypoproteinemia due to augmented endothelial permeability, and renal insufficiency with increased serum levels of creatinine, nitrogen, and uric acid.

Pulmonary toxicity. In our patients, no pulmonary fluid retention developed as assessed by routine chest X-ray during and after therapy. Dyspnea at rest occurred in 9% and 6% of patients treated with s.c. rIL-2 or s.c. rIFNα, respectively; it was noted in 6% of those treatment with s.c. rIL-2/rIFNα combination therapy (data not shown).

In contrast, dyspnea at rest was reported upon i.v. rIL-2 therapy in up to 20%–36% of patients (Davis et al. 1990; Rosenberg et al. 1988 a; Dutcher et al. 1989, 1991; Saxon et al. 1991; Margolin et al. 1989; Parkinson et al. 1990). Severe respiratory distress necessitating thoracocentesis for pleural effusion occurred in 2%–4% of patients upon i.v. rIL-2 bolus administration (Rosenberg et al. 1987, 1988 a, 1989 a). Intubation was required in fewer than 10% of patients in most i.v. trials, and occasionally in more than 10% upon rIL-2 i.v. bolus therapy with (Rosenberg et al. 1987; Stahel et al. 1989) and without (Rosenberg et al. 1988 a) LAK cell infusions.

Weight changes. No significant weight gain occurred in the 107 patients reported in this investigation. Rather, weight loss due to anorexia was noted in most patients. Thus, 11.1% of patients treated with rIFNα lost between 5% and 10% of their baseline weight, while 33% and 7% of the patients treated with rIL-2/rIFNα lost 5%–10% and 10%–15% of body weight, respectively (data not shown).

In contrast, in the vast majority of patients receiving i.v. rIL-2 body weight increased significantly. In most investigations, a gain of more than 5% of baseline weight was noted in approximately half of all patients. Increases of more than 10% occurred in more than 30% of patients receiving i.v. bolus therapy (Rosenberg et al. 1987; Fisher et al. 1988; Margolin et al. 1989; Dutcher et al. 1989; Clark et al. 1990; Lee et al. 1989) with LAK cell infusion or upon constant i.v. rIL-2 administration (Clark et al. 1990). Increases in body weight of more than 20% were reported upon i.v. bolus therapy with and without adoptive cell administration (Rosenberg et al. 1988 a, 1989 a).

Changes in systemic blood pressure and heart rate. In this trial, mean values of blood pressure nadirs were 120 : 77 mm Hg (16 : 10.3 kPa) upon s.c. rIL-2 therapy (range, 100 : 70–150 : 90 mm Hg; 13.3 : 9.3–20 : 12 kPa) 119 : 78 mm Hg (16 : 10.4 kPa) upon s.c. rIFNα therapy (range, 100 : 70–150 : 90 mm Hg; 13.3 : 9.3–20 : 12 kPa), and 114 : 72 mm Hg (15 : 9.6 kPa) upon combination therapy (range, 80 : 50–145 : 90 mm Hg; 10.7 : 6.7–19.3 : 12 kPa). The mean decreases in systolic blood pressure compared to pretreatment levels were 15 mm Hg (2 kPa), 12 mm Hg (1.6 kPa), and 22 mm Hg (3 kPa), respectively (data not shown). In patients treated with s.c. rIFNα only, hypotension did not surpass grade I (Table 3). Grade II hypotension was seen in 7% of patients receiving s.c. rIL-2, only (Table 3). Grade III and IV hypotension occurred in 7% and 4% of the patients treated with combined s.c. rIL-2/rIFNα (Table 3). Heart rates surpassing 100 beats/min were rarely recorded upon s.c. rIL-2 therapy. Tachycardia was mild and never caused major clinical symptoms (data not shown).

In contrast, decreases of mean arterial pressure of 17.0 mm Hg (2.3 kPa) to 26.8 mm Hg (3.6 kPa) have been reported upon rIL-2 i.v. bolus therapy (Gaynor et al. 1988; Webb et al. 1988; Ognibene et al. 1988; Chien et al. 1990), and of 16 mm Hg (2.1 kPa) to 19 mm Hg (2.5 kPa) upon constant i.v. infusion (Cochat et al. 1991; Christiansen et al. 1988). Grade III hypotension was observed in the majority of

Table 5. Peak serum creatinine levels following immunotherapy with interleukin-2 and/or interferon α

Treatment	*n*	Patients (%) with peak creatine levels:		
		>177 μmol/l	>531 μmol/l	>885 μmol/l
rIL-2 s.c.	15	6.7	0	0
rIFNα s.c.	20	0	0	0
rIL-2 s.c./rIFNα s.c.	72	2.8	0	0
rIL-2 i.v. bolus ± LAK/TIL				
Clark et al. (1990)	30	92.0	4.0[a]	NR
Rosenberg et al. (1987)	157	93.0	15.3	2.5
Rosenberg et al. (1988 a)	221	82.1	14.3	2.4
Rosenberg et al. (1988 b)	20	50.0	10.0	0
rIL-2 constant i.v. infusion ± LAK				
Clark et al. (1990)	22	71.0	10.0[a]	NR
Davis et al. (1990)	43	30.0	NR	NR
Sondel et al. (1988)	11	0	0	0
West et al. (1987)	40	30.0[b]	NR	NR
rIL-2 i.v. + IFNα				
Rosenberg et al. (1989 b)	26	78.6	7.2	2.4
Rosenberg et al. (1989 b)	30	59.0	9.8	0
Rosenberg et al. (1989 a)	128	64.7	7.1	0.5

[a] Percentage of patients with peak creatinine levels above 4.0 mg/dl
[b] Percentage of patients with peak creatinine levels above 3.0 mg/dl

patients treated with rIL-2 via i.v. bolus, and in approximately half of the patients receiving rIL-2 via constant i.v. infusion (Table 3). Grade IV hypotension in these trials occurred in up to 10% of patients treated. Furthermore, Textor et al. (1987), Ognibene et al. (1988), and Gaynor et al. (1988) reported a significant increase of 54.4 beats/min to 87.0 beats/min in heart rate, with mean peaks of 113±3, 138.4±6.9, and 110 beats/min upon i.v. rIL-2 therapy.

Changes in plasma protein levels. In our patients, total protein levels significantly decreased from pretreatment baseline levels of 70.9±2.8 g/l (range, 61–85 g/l) to mean nadirs of 68±6 (61–82) g/l upon s.c. rIL-2, to 66±3 (67–71) g/l upon s.c. rIFNα, and to 67±5 (59–80) g/l upon s.c. rIL-2/rIFNα combination therapy ($P<0.01$ when compared to baseline values). We observed mean albumin nadirs of 35.7±3.6 g/l and 38.8±3.9 g/l upon s.c. rIL-2 therapy with and without rIFNα, respectively (pretreatment values, 43.5±3.2 g/l and 42.4±4.5 g/l; $P<0.05$ only in the single-agent rIFNα cohort). Recovery values after termination of therapy were not significantly different from pretreatment levels (data not shown).

In contrast, Lotze et al. (1986) reported mean total protein nadirs of 55–63 g/l (range, 51–67 g/l) upon i.v. bolus rIL-2 therapy, and Cochat et al. (1991) observed marked hypoproteinemia with mean nadirs of 58±2 g/l in 15 children treated i.v. with constant-infusion rIL-2 ($P<0.01$ when compared to baseline levels of 70±1 g/l). Mean albumin nadirs of 30 g/l were described by Fisher et al. (1989) in a total of 261 patients, and by Webb et al. (1988) upon i.v. bolus rIL-2, while Kozeny et al. (1988) and Textor et al. (1987) reported mean nadirs of 26.7±0.8 g/l and 22±1 g/l, respectively (data not shown).

Hypercreatininemia. In our patient cohort, serum creatinine levels prior to therapy ranged from 53 μmol/l to 186 μmol/l (mean, 100±11 μmol/l), as indicated in Table 4. Uninephric patients ($n=88$) had significantly higher pretreatment creatinine levels (111.3±22.8 μmol/l) when compared to binephric patients (79.0±8.7 μmol/l; $P<0.001$). Upon s.c. immunotherapy, there was a trend toward increased creatinine levels when compared to baseline values in all treatment groups, as shown in Table 4. This difference failed to reach statistical significance in patients treated with s.c. rIFNα only ($P=0.11$). As shown in Table 4, serum creatinine increases in patients treated with s.c. rIL-2 with or without rIFNα proved to be statistically significant ($P<0.001$). Upon s.c. combination therapy, increases in serum creatinine levels were significantly more prominent in uninephric (peak mean 130.4±52.4 μmol/l) than in binephric (mean peak 92.1±16.7 μmol/l) patients ($P<0.05$). Among the patients treated with s.c. rIL-2 only 6.7% had creatinine increases above 177 μmol/l (2.0 mg/dl; Table 5); in those receiving s.c. rIL-2/rIFNα combination therapy, creatinine values greater than 177 μmol/l were observed in 2.8% of patients (Table 5).

In contrast, serum creatinine upon i.v. rIL-2 therapy frequently reached mean peak values two to three times the levels observed in s.c. therapy (Table 4). Upon i.v. rIL-2 bolus administration, more than 10.0% of patients regularly experienced creatinine increases above 6.0 mg/dl, and increases above 10 mg/dl were reported for up to 4.6% of patients (Table 5). Upon constant i.v. infusion, moderate increases of serum creatinine occurred (Tables 4 and 5).

Azotemia. In the 107 patients studied in this investigation, blood urea nitrogen levels prior to therapy ranged from 2.1 mmol/l to 11.9 mmol/l (mean, 6.0±1.1 mmol/l). There was not significant difference between binephric ($n=19$; mean 5.7±1.9 mmol/l) and uninephric ($n=88$; mean 6.0±1.6 mmol/l) patients ($P=0.85$, χ^2). Pretreatment blood urea nitrogen values correlated to the interval between nephrectomy and the onset of therapy ($r=0.065$). Upon s.c. rIL-2/rIFNα combination therapy, there was no significant increase in urea nitrogen levels (mean peak value 6.5 mmol/l versus pretreatment value). S.c. single-agent

Table 6. Effects of immunotherapy with interleukin-2 and/or interferon α on blood urea nitrogen levels

Treatment	*n*	Baseline (mmol/l)	Peak (mmol/l)	Recovery (mmol/l)
rIL-2 s.c.	15	5.8±2.3 (3.5–11.6)	7.8±2.0 (5.3–11.6)	6.7±2.4 (3.2–10.9)
rIFNα s.c.	20	6.6±2.1 (2.5–10.9)	6.1±2.8 (1.9–10.2)	6.1±1.7 (2.8–8.8)
rIL-2 s.c./rIFNα s.c.	72	5.8±1.7 (2.1–11.9)	6.5±2.5 (2.1–13.7)	5.9±1.7 (2.5–9.8)
rIL-2 i.v. bolus ± LAK cells				
Belldegrun et al. (1987)	99	4.8±0.2 (1.4–14.3)	20.0±1.1 (4.6–53.9)	NR
Chien et al. (1990)	11	NR	21.4	NR
Huang et al. (1990)	21	5.35±3.6	12.9	4.3
Kozeny et al. (1988)	8	4.3±0.5	8.3±0.99	NR
Margolin et al. (1989)	93	5.4	14.3	5.4
Textor et al. (1987)	12	5.0±0.4	7.1±0.7	3.6
rIL-2 constant i.v. infusion ± LAK cells				
Christiansen et al. (1988)	1	5.0	11.8	NR
Sondel et al. (1988)	11	NR	NR	NR
Sosman et al. (1988)	6	NR	NR	NR[b]
rIL-2 i.v. bolus and constant infusion				
Shalmi et al. (1990)	10	6.4±0.6	8.6±1.6	NR

[a] Sondel et al. reported peak values of 20–30 mg/dl (7.1–10.7 mmol/l) in 55% of patients

[b] Sosman et al. reported peak values above 40 mg/dl (14.3 mmol/l) in 33% of patients

Table 7. Effects of immunotherapy with interleukin-2 and/or interferon α on serum uric acid levels

Treatment	*n*	Baseline (μmol/l)	Nadir (μmol/l)	Peak (μmol/l)	Recovery (μmol/l)
rIL-2 s.c.	15	332± 88 (198–515)	290± 80 (173–445)	410±102 (250–571)	383± 84 (249–545)
rIFNα s.c.	20	350± 87 (228–574)	340± 97 (228–574)	390±100 (228–581)	358± 82 (245–526)
rIL-2 s.c./rIFNα s.c.	72	373±100 (163–606)	342± 82 (133–480)	402±131 (165–6969	367±103 (164–498)
rIL-2 i.v. bolus ± LAK cells					
Belldegrun et al. (1987)	27	303.5	NR	541.5	NR
Chien et al. (1990)	11	261.8	NR	666.4	NR
Webb et al. (1988)	17	303.5	NR	583.1	321.3

* $P<0.05$

therapy with rIL-2 or rIFNα failed to yield significant changes (Table 6).

This was in marked contrast to results obtained in i.v. rIL-2 therapy where blood urea nitrogen peaks frequently surpassed 10 mmol/l, as shown in Table 6.

Hyperuricemia. In our patients, uric acid levels significantly increased in those patients receiving single-agent s.c. rIFNα (mean peak 390 μmol/l; $P=0.013$ when compared to the mean baseline value of 350 μmol/l), or s.c. rIL-2 (mean peak 410 μmol//l; $P<0.01$ when compared to mean baseline levels of 332 μmol/l). Upon s.c. rIL-2 therapy, the mean nadir values also proved to be significantly different from pretreatment levels ($P=0.044$), as shown in Table 7. In patients receiving s.c. rIL-2/rIFNα combination therapy (Table 7), there was a statistically significant decrease, while no major treatment-related increase in uric acid occurred ($P=0.09$, when compared to pretreatment levels).

In contrast, serum uric acid levels increased upon i.v. rIL-2 via bolus infusion, as shown in Table 7. These changes were highly significant [$P<0.0001$ as reported by Webb et al. (1988) and $P<0.001$ according to Belldegrun et al. (1987) respectively].

Changes in serum electrolyte levels. In the patients studied in our trials, alterations in serum electrolyte levels never caused major clinical symptoms. Subcutaneous immunotherapy resulted in transient, albeit significant hypokalemia, hyponatremia, hyperchloridemia, hypomagnesemia, hypophosphatemia, and hypocalcemia. Mean potassium na-dirs reached 4.1±0.5 mmol/l (range, 3.3–4.8 mmol/l) upon s.c. rIL-2 therapy, 4.4±0.2 mmol/l (range, 4.0–4.8 mmol/l) upon s.c. rIFNα therapy and 4.3±0.4 mmol/l (range, 3.6–5.3 mmol/l) upon s.c. rIL-2/rIFN-α combination therapy. Combined s.c. rIL-2/rIFNα therapy resulted in mean sodium and phosphate nadirs of 139.1±3.4 mmol/l (range, 131–147 mmol/l) and 0.94±0.22 mmol/l (range, 0.52–1.26 mmol/l), respectively. All changes resolved within 2 weeks after completion of therapy (data not shown).

Upon i.v. rIL-2 therapy via bolus infusion, Textor et al. (1987) reported potassium mean baseline levels of

4.2±0.1 mmol/l and treatment-induced mean nadirs of 4.1±0.1 mmol/l. Cochat et al. (1991) observed mean potassium nadirs of 3.0±0.1 mmol/l (baseline, 4.0±0.1 mmol/l) upon constant i.v. infusion. Kozeny et al. (1988) described occasional potassium peaks of 5.8 mmol/l upon i.v. bolus therapy. Mean nadirs of serum sodium levels upon i.v. rIL-2 bolus infusion reached 137.0±1.0 mmol/l (1987) and 133.8±3.2 mmol/l (1988); Chien et al. (1990) reported the occurrence of hyponatremia in 73% of 11 patients. Upon rIL-2 therapy via constant i.v. infusion, Cochat et al. (1991) reported mean sodium nadirs of 130.0±1.0 mmol/l, while West et al. (1987) found 5% of patients developed a hyponatremia of less than 125 mmol/l. Mean phosphate nadirs upon i.v. rIL-2 bolus therapy were reported at 0.76 mmol/l by Kozeny et al. (1988), at 0.77 mmol/l by Textor et al. (1987), and at 0.61 mmol/l by Webb et al. (1988), while Cochat et al. (1991) described a mean phosphate nadir upon i.v. rIL-2 via constant infusion of 0.72±0.06 mmol/l (data not shown).

Changes in urine volume. Upon out-patient s.c. immunotherapy, oliguria is a parameter with little validity; anuria did not occur in the patients reported in this study (data not shown).

In contrast, upon i.v. rIL-2 administration, oliguria occurred with a frequency of 20%–50% (Sosman et al. 1988; Boldt et al. 1988), of 50%–75% (Clark et al. 1990; Sosman et al. 1988), or even of more than 75% (West et al. 1987; Saxon et al. 1991; Clark et al. 1990; Chien et al. 1990; Bar et al. 1990). Anuria upon i.v. rIL-2 therapy was occasionally observed in more than 30% of patients (Fisher et al. 1988; Margolin et al. 1989; Parkinson et al. 1990; Dutcher et al. 1989).

Changes in urinalyses. In our patients, mild proteinuria (1+) was observed in 12.8% of weekly urinalyses after single-agent s.c. IFNα therapy, it never occurred in patients receiving s.c. rIL-2 therapy, and was seen in 14.1% of analyses following s.c. combination therapy (data not shown). Proteinuria exceeding 1+ (3 g/l) did not occur. Microhematuria (below 10 erythrocytes/low-power field) was found in 4.2% of urinalyses following rIFNα, in 11.2% following rIL-2, and in 19.7% following rIL-2/rIFNα combination therapy. Hematuria of 10–20 erythrocytes/low-power field only occurred upon combination therapy in 2.8% of analyses; hematuria of 20 or more erythrocytes/field did not occur (data not shown). We observed urinary casts in 9.7% of weekly urinalyses upon single-agent rIFNα therapy, in 4.0% following single-agent rIL-2 therapy, and in 2.8% following combination therapy; the number of casts never exceeded four elements per low-power field (data not shown).

With i.v. rIL-2 therapy, reported urinalyses occasionally showed mild to moderate proteinuria, which occurred in 34% (Hirsch et al. 1990) and 80% (Shalmi et al. 1990), and was reported not to exceed 1 g/l in most patients (Rosenberg et al. 1987). Hematuria was described in 11% of patients on i.v. rIL-2/rIFNα therapy (Hirsch et al. 1990), and gross hematuria in 0.54%–0.6% of patients (Rosenberg et al. 1988 a, 1989 a). Urine sediment abnormalities following i.v. rIL-2 therapy included various amounts of cellular casts (Textor et al. 1987; Shalmi et al. 1990), hyaline and fine granular casts in 76.5%, and pigmented, broad, coarse-granular casts in 23.5% (Webb et al. 1988), tubular epithelial cells or broad coarsely granular casts in some patients (Belldegrun et al. 1987).

Discussion

Systemic rIL-2 therapy at various dose levels has resulted in similar response rates irrespective of the mode of administration. However, the severity of rIL-2-induced adverse effects was significantly different when i.v. versus s.c. and high-dose versus low-to intermediate-dose therapy was compared.

In the present investigation, we have described systemic toxicity of s.c. rIL-2 therapy in comparison to that reported with i.v. rIL-2 therapy. Previously, a multitude of i.v. rIL-2 studies had been monitored for hemodynamic, renal, and metabolic adverse reactions by numerous investigators. Despite discrepancies with regard to supportive drugs, dose modifications, the definition of adverse effects and abnormalities of laboratory parameters, reported toxicity was similar in most studies.

Upon i.v. rIL-2 therapy, toxic deaths occasionally occurred in more than 5% of patients (Albertini et al. 1990; Mann et al. 1990; Dutcher et al. 1991), and a number of serious side-effects were observed, notably respiratory distress requiring intubation in more than 10% of patients (Rosenberg et al. 1987, 1988 a; Stahel et al. 1989), sepsis in more than 20% (Albertini et al. 1990; Dutcher et al. 1991; Stahel et al. 1989; Clark et al. 1990), and renal dysfunctions leading to prolonged anuria in more than 30% of patients (Fisher et al. 1988; Margolin et al. 1989; Parkinson et al. 1990; Dutcher et al. 1989). Also, rare phenomena such as myocardial infarction (Lee et al. 1989; Nora et al. 1989) and colonic ischemia (Rosenberg et al. 1989 b; Sparano et al. 1991) were reported. These adverse reactions were life-threatening and dose-limiting.

Following i.v. rIL-2 therapy, the increase in vascular capacitance, decrease in peripheral vascular resistance, and augmented permeability of the endothelium for macromolecules regularly caused hemodynamic changes consistent with a high-output and low-resistance state similar to the early phase of septic shock. These abnormalities and the additional i.v. administration of eventually huge volumes of liquids were accompanied by fluid retention leading to weight gain, an increase in cardiac index, tachycardia, hypoalbuminemia, and oliguria. Multi-organ dysfunctions on the basis of this capillary leak syndrome were not directly related to rIL-2, but rather caused by rIL-2-stimulated endogenous lymphocytes and their release of secondary cytokines. Thus, animals revealed higher tolerance to therapy with rIL-2 when they were immunoincompetent following prior exposure to cyclophosphamide or irradiation (Rosenstein 1986).

Impairment of renal function is a phenomenon well described following i.v. rIL-2 therapy. Since most patients with metastatic renal cell carcinoma are uninephric at the onset of systemic therapy, nephrotoxicity of therapeutically applied cytokines deserves particular attention. In addition, increased creatinine levels have been reported following tumor nephrectomy (Stahel et al. 1989; Textor et al. 1987; Belldegrun et al. 1989), rendering patients with a solitary kidney more vulnerable to nephrotoxicity.

The exact etiology of rIL-2-induced nephrotoxicity is still uncertain. It is additionally obscured by the influence of supportive drugs, such as nonsteroidal anti-inflammatory drugs and vasopressors (Christiansen et al. 1988). The majority of investigators suggested that reduced renal function is due to a

renal hypoperfusion syndrome. The latter is believed to be secondary to hypotensive dysregulation in response to augmented capillary permeability. The lack of profound urinary sediment abnormalities and the rapid normalization after rIL-2 therapy support a merely hemodynamic etiology of impaired renal function. This is backed by the observation that prolonged rIL-2 therapy does not cause chronic renal insufficiency. It has also been reported that rIL-2 directly reduces renal prostaglandin synthesis, which may further add to renal hypoperfusion (Christiansen et al. 1988).

Christiansen et al. (1988) conjectured that hypotension alone could not explain the renal dysfunction observed. Kozeny et al. (1988) did not find any evidence for renal tubular dysfunction; Shalmi et al. (1990) hypothesized that nephrotoxicity resulted from an intrinsic intrarenal dysfunction without signs of acute tubular necrosis up-on rIL-2 therapy. Textor et al. (1987) found evidence for tubular injury by measuring the tubular enzyme *N*-acetylglucosaminidase, and Cochat et al. (1991) observed proteinuria in most patients consistent with rIL-2-induced nephrotic syndrome; this side-effect was also noticed by Hirsh et al. (1990) in 34% of 26 patients and by Hisanaga et al. (1990) in one patient studied. Whitehead et al. (1990) hypothesized that rIL-2-induced nephrotoxicity was due to immune complex formation with deposition in the kidney or to direct renal toxicity of rIL-2 besides the known hypoperfusion contributing to prerenal azotemia.

Disturbances in electrolyte levels following i.v. rIL-2 regimens are well described. While only a few patients developed life-threatening electrolyte or acid/base abnormalities (Michie et al. 1988), these changes might have contributed to a multitude of organ dysfunctions including myocardial complications (Lee et al. 1989; Nora et al. 1989; Glauser et al. 1988). Hypoproteinemia could aggravate electrolyte imbalances. Hypophosphatemia was believed to result from increased utilization of phosphate by rapidly proliferating lymphatic cells (Webb et al. 1988; Cochat et al. 1991). Other investigators suggested that hypophosphatemia is caused by acid/base disturbances like respiratory alkalosis, as demonstrated by Textor et al. (1987), but Cochat et al. (1991) reported no alkemia in arterial blood gases upon rIL-2 therapy.

As shown in this investigation, systemic toxicity upon s.c. rIL-2 therapy was always manageable, transient und reversible. Treatment was given in an outpatient setting. No toxic death occurred. No sepsis, episodes of respiratory insufficiency, anuria, or severe cardiovascular disturbances were observed. Furthermore, in contrast to i.v. therapy, there were no profound decreases in plasma protein levels and no serious increases in serum creatinine, blood urea nitrogen, and uric acid levels. In addition, no symptomatic alterations in serum electrolyte levels occurred.

Given the lack of clinical symptoms indicative of capillary leak. S.c. low-dose rIL-2 therapy appeared to operate below a threshold dose beyond which profound increases in endothelial permeability occur. The absence of leakage-related toxicity, however, was not associated with a reduction in therapeutic efficacy. Rather, in our studies effective doses of rIL-2 could be defined at levels more than five times lower than the capillary leak threshold.

On the other hand, s.c. therapy achieved dosages critical for the induction of non-specific "influenza-like" toxicity such as fever, chills, malaise. The latter may reflect some of the therapeutic mechanisms caused by the humoral and cellular response to systemic rIL-2. While therapeutic benefit of rIL-2-based immunomodulation and life-threatening capillary leakage are not necessarily linked, it appears that clinical efficacy and nonspecific toxicity of low-dose rIL-2 are in part due to common biological mechanisms that remain to be characterized in more detail.

In summary, s.c. rIL-2/rIFNα therapy, as described in this study, abrogates the toxic increase in endothelial permeability and most of its sequelae, generally referred to as capillary leak syndrome. Given the clinical safety, good practicability, and tolerance of low to intermediate-dose s.c. rIL-2 in the palliative setting, further clinical and laboratory studies are warranted to substantiate the dose/toxicity correlation and improved risk/benefit ratio of this novel mode of therapeutic immunomodulation.

References

Albertini MR, Sosman JA, Hank JA, Sondel PM et al. (1990) The influence of autologous LAK cell infusions on the toxicity and antitumor effect of repetitive cycles of interleukin-2. Cancer, 66:2457–2464

Atzpodien J, Körfer A, Franks CR, Kirchner H et al. (1990) Home therapy with rIL-2 and IFN-a2b in advanced human malignancies. Lancet, 335:1509–1512

Atzpodien J, Körfer A, Schomburg A, Kirchner H et al. (1993) Outpatient treatment of metastatic renal cell cancer patients: IL-2 in combination with IFN-α. Ann Oncol (in press)

Bar MH, Sznol M, Atkins M, Doroshow JH et al. (1990) Metastatic malignant melanoma treated with combined bolus and continuous infusion interleukin-2 and LAK cells. J Clin Oncol 8:1138–1147

Belldegrun A, Webb DE, Austin HA, Rosenberg SA et al. (1987) Effects of interleukin-2 on renal function in patients receiving immunotherapy for advanced cancer. Ann Int Med 106:817–822

Belldegrun A, Webb DE, Austin HA, Rosenberg SA et al. (1989) Renal toxicity of interleukin-2 administration in patients with metastatic renal cell cancer: effect of pre-therapy nephrectomy. J Urolo 141:499–503

Boldt DH, Mills BJ, Gemlo BT, Ellis TM et al. (1988) Laboratory correlates of adoptive immunotherapy with recombinant interleukin-2 and lymphokine-activated cells in humans. Cancer Res 48: 4409–4416

Budd GT, Osgood B, Bama B, Bukowski RM et al. (1989) Phase I clinical trial of interleukin-2 and alpha-interferon; toxicity and immunologic effects. Cancer Res 49:6432–6436

Chien CH, Hsieh KH et al. (1990) Interleukin-2 immunotherapy in children. Pediatrics 86:937–943

Christiansen NP, Skubitz KM, Nath K, Kennedy BJ et al. (1988) Nephrotoxicity of continuous intravenous infusion of recombinant interleukin-2. Am J Med 84:1072–1075

Clark JW, Smith JW, Steis RG, Longo DL et al. (1990) Interleukin-2 and LAK cell therapy; analysis of a bolus interleukin-2 and a continuous infusion interleukin-2 regimen. Cancer Res 50:7343–7350

Cochat P, Floret D, Bouffet E, David L et al. (1991) Renal effects of continuous infusion of recombinant interleukin-2 in children. Pediatr Nephrol 5:33–37

Davis SD, Berkmen YM, Wang JC et al. (1990) Interleukin-2 therapy for advanced renal cell carcinoma: radiographic evaluation of response and complications. Radiology 177:127–131

Dutcher JP, Creekmore S, Weiss GR, Atkins M et al. (1989) A phase II study of interleukin-2 and LAK cells in patients with metastatic malignant melanoma. J Clin Oncol 7:477–485

Dutcher JP, Gaynor ER, Boldt DH, Atkins M et al. (1991) A phase II study of high-dose continuous infusion interleukin-2 with lymphokine activated killer cells in patients with metastatic melanoma. J Clin Oncol 9:641–648

Edwards BD, Hawkins MJ, Borden ED et al. (1984) Comparative in vivo and in vitro activation of human natural killer cells by two recombinant alfa-interferons differing in antiviral activity. Cancer Res 44:3135–3139

Farace F, Mathiot C, Brandely M, Fridman WH et al. (1990) Phase I trial with recombinant interleukin-2 (rIL-2) immune activation by rIL-2 alone or following pretreatment with recombinant interferon-gamma. Clin Exp Immunol 82:194–199

Fisher RI, Coltman CA, Doroshow JH, Paietta EI et al. (1988) Metastatic renal cancer treated with interleukin-2 and LAK cells. Ann Int Med 108:518–523

Fisher B, Keenan AM, Garra BS, Lotze MT et al. (1989) Interleukin-2 induces profound reversible cholestasis; a detailed analysis in treated cancer patients J Clin Oncol 7:1852–1862

Gaynor ER, Vitek L, Sticklin L, Fisher RI et al. (1988) The hemodynamic effects of treatment with interleukin-2 and LAK cells. Ann Int Med 109:953–958

Glauser FL, DeBlois G, Bechard D, Fairman RP et al. (1988) Review: cardiopulmonary toxicity of adoptive immunotherapy. Am J Med Sci 296:406–412

Grimm EA, Wilson DJ et al. (1985) The human lymphokine-activated killer system. V. Purified recombinant interleukin-2 activates cytotoxic lymphocytes which lyse both natural killer-resistant autologous and allogeneic tumors. Cell Immun 94:568–578

Hartmann D, Adams JC, Meeker AK et al. (1986) Dissociation of therapeutic and toxic effects of polyinosinic-polycytidylic acid admixed with poly-L-lysine and solubilized with carboxymethyl cellulose in tumor-bearing mice. Cancer Res 47:1331–1338

Hersh EM, Murray JL, Hong WK, Arnett FC et al. (1989) Phase I study of cancer therapy with recombinant interleukin-2 administered by intravenous bolus injection. Biotherapy 1:215–226

Hirsh M, Lipton A, Harvey H, Levitt D et al. (1990) Phase I study of interleukin-2 and interferon alpha-2a as outpatient therapy for patients with advanced malignancy. J Clin Oncol 8:1657–1663

Hisanaga S, Kawagoe H, Yamamoto Y, Kurokawa M et al. (1990) Nephrotic syndrome associated with recombinant interleukin-2. Nephron 54:277–278

Huang CM, Elin RJ, Ruddel M, Rosenberg SA et al. (1990) Changes in laboratory results for cancer patients treated with interleukin-2. Clin Chem, 36:431–434

Kawamura H, Rosenberg SA, Berzofsky JA et al. (1986) Immunization with antigen and interleukin-2 in vivo overcomes Ir gene low responsiveness. J Exp Med 162:381–386

Kleineman ES, Kurzrock R, Wyatt D, Fidler IJ et al. (1986) Activation or suppression of the tumoricidal properties of monocytes from cancer patients following treatment with human recombinant gamma-interferon. Cancer Res 46:5401–5405

Kozeny GA, Nicolas JD, Creekmore S, Fisher RI et al. (1988) Effects of interleukin-2 immunotherapy on renal function. J Clin Oncol 6:1170–1176

Krown SE (1987) Interferon treatment of renal cell carcinoma. Current status and future prospects. Cancer 59:647

Lee RE, Lotze MT, Skibber JM, Rosenberg SA et al. (1989) Cardiorespiratory effects of immunotherapy with interleukin-2. J Clin Oncol 7:7–20

Lotze MT, Matory YL, Rayner AA, Rosenberg SAI et al. (1986) Clinical effects and toxicity of interleukin-2 in patients with cancer. Cancer 58:2764–2772

Mann H, Ward JH, Samlowski WE et al. (1990) Vascular leak syndrome associated with interleukin-2: chest radiographic manifestations. Radiology 176:191–194

Margolin KA, Rayner AA, Hawkins MJ, Boldt DH et al. (1989) Interleukin-2 and lymphokine-activated killer cell therapy for solid tumors: analysis of toxicity and management guidelines. J Clin Oncol 7:486–498

Michie HR, Eberlein TJ, Spriggs DR, Wilmore DW et al. (1988) Interleukin-2 initiates metabolic responses associated with critical illness in humans. Ann Surg 208:493–501

Muss HB (1987) Interferon therapy for renal cell carcinoma. Semin Oncol [Suppl 2] 14:36

Negrier S, Philip T, Stoter G, Franks CR et al. (1989) Interleukin-2 with or without LAK cells in metastatic renal cell carcinoma: a report of a european multicentre study. Eur J Cancer Clin Oncol 25 [Suppl 3]: S21–S28

Nora R§, Abrams JS, Tait NS, Silverman HJ et al. (1989) Myocardial toxic effects during recombinant interleukin-2 therapy. JNCI 81:59–63

Ognibene FP, Rosenberg SA, Lotze MT, Parrillo JE et al. (1988) Interleukin-2 administration causes reversible hemodynamic changes and left ventricular dysfunction similar to those seen in septic shock. Chest 94:750–754

Parkinson DR, Abrams JS, Wiemik PH, Hawkins MJ et al. (1990) Interleukin-2 therapy in patients with metastatic malignant melanoma: a phase II study. J Clin Oncol 8:1650–1656

Pichert G, Lost LM, Fierz W, Stahel RA et al. (1991) Clinical and immune modulatory effects of alternative weekly interleukin-2 and interferon alfa-2a in patients with advanced renal cell carcinoma and melanoma. Br J Cancer 63:287–292

Richards JM, Barker E, Latta J, Vogelzang NJ et al. (1988) Phase I study of weekly 24-hour infusions of recombinant human interleukin-2. JNCI 80:1325–1328

Rosenberg SA, Lotze MT, Muul LM, White DE et al. (1987) A progress report on the treatment of 157 patients with advanced cancer using LAK cells and interleukin-2 or high-dose interleukin-2 alone. NEJ 316:889–897

Rosenberg SA, Lotze MT, Mulé JJ et al. (1988 a) New approaches to the immunotherapy of cancer using interleukin-2. Ann Int Med 108:853–864

Rosenberg SA, Packard BD, Aebersold PM, White DE et al. (1988 b) Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. N Engl J Med 319:1676–1680

Rosenberg SA, Lotze MT, Yang JC, White DE et al. (1989 a) Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. Ann Surg 210:474–485

Rosenberg SA, Lotze MT, Yang JC, White DE et al. (1989 b) Combination therapy with interleukin-2 and alpha-interferon for the treatment of patients with advanced cancer. J Clin Oncol 7:1863–1874

Rosenstein M, Ettinghausen SE, Rosenberg SA et al. (1986) Extravasation of intravascular fluid mediated by the systemic administration of recombinant interleukin-2. J Immunol 137:1735–1742

Roussel E, Gerrard JM, Greenberg AH et al. (1990) Long-term cultures of human peripheral blood lymphocytes with recombinant human interleukin-2 generate a population of virtually pure $CD3^+CD16^-$ CD56 large granular lymphocyte LAK cells. Clin Exp Immunol 82:416–421

Saxon RR, Klein JS, Bar MH, Blanc P et al. (1991) Pathogenesis of pulmonary edema during interleukin-2 therapy: correlation of chest radiographic and clinical findings in 54 patients. AJR Am J Roentgenol 156:281–285

Schoof DD, Gramolini BA, Davidson DL, Eberlein TJ et al. (1988) Adoptive immunotherapy of human cancer using low-dose recombinant interleukin-2 and lymphokine-activated killer cells. Cancer Res 48:5007–5010

Shalmi CL, Dutcher JP, Feinfeld DA, Wiemik PH et al. (1990) Acute renal dysfunction during interleukin-2 treatment; suggestion of an intrinsic renal lesion. J Clin Oncol 8:1839–1846

Shau H, Kim A et al. (1988) Suppression of LAK Induction by neutrophils. J Immunol 141:4395–4402

Shiloni E, Pouillart P, Jannssens J, Franks CR et al. (1989) Sequential dacarbazine chemotherapy followed by recombinant interleukin-2 in metastatic melanoma. A pilot multicentre phase I–II study. Eur J Cancer Clin Oncol 25 [Suppl 3] S45–S49

Sondel PM, Kohler PC, Hank JA, Storer B et al. (1988) Clinical and immunological effects of recombinant interleukin-2 given by repititive weekly cycles to patients with cancer. Cancer Res 48:2561–2567

Sosman JA, Kohler PC, Hank JA, Sondel PM et al. (1988) Repetitive weekly cycles of interleukin-2. II. Clinical and immunologic effects of dose, schedule, and addition of indomethacin. JNCI 80:1451–1461

Sparano JA, Dutcher JP, Kaleya R, Brandt LJ et al. (1991) Colonic ischemia complicating immunotherapy with interleukin-2 and interferon-alpha. Cancer 68:1538–1544

Stahel RA, Sculier JP, Jost LM Klastersky J et al. (1989) Tolerance and effectiveness of recombinant interleukin-2 (r-met Hu IL-2[ala-125]) and LAK cells in patients with metastatic solid tumors. Eur J Cancer Clin Oncol, 25:965–672

Sznol M, Janik JE, Sharfman WH, Longo DL et al. (1991) A phase Ia/Ib study of subcutaneously (SQ) administered interleukin-2 (IL-2) in combination with interferon-alfa 2a (IFN). Proc Am Soc Clin Oncol 10:700

Talmadge JE, Tribble JE, Pennington RW et al. (1987) Immunomodulatory and immunotherapeutic properties of recombinant gamma-interferon and recombinant tumor necrosis factor in mice. Cancer Res 47:2563–2570

Textor SC, Margolin K, Blayney D, Doroshow J et al. (1987) Renal, volume, and hormonal changes during therapeutic administration of recombinant interleukin-2 in man. Am J Med 83:1055–1061

Webb DE, Austin HA, Belldegrun A, Rosenberg SA, et al. (1988) Metabolic and renal effects of interleukin-2 immunotherapy for metastatic cancer. Clin Nephrol 30:141–145

West WH, Tauer KW, Yannelli JR, Oldham RK, et al. (1987) Constant-infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. N Engl J Med 316:898–905

Whitehead RP, Ward D, Hemingway L, Konrad M, et al. (1990) Subcutaneous recombinant interleukin-2 in a dose escalating regimen in patients with metastatic renal cell adenocarcinoma. Cancer Res 50:6708–6715