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High-Dose Regimen of Interleukin-2 and Interferon-Alpha in Combination with Lymphokine-Activated Killer Cells in Patients with Metastatic Renal Cell Cancer

W. H. J. Kruit, S. H. Goey, *C. H. J. Lamers, *J. W. Gratama, B. Visser, †P. I. M. Schmitz, ‡A. M. M. Eggermont, *R. L. H. Bolhuis, and G. Stoter

*Department of Medical Oncology, *Department of Clinical and Tumor Immunology, †Department of Statistics, ‡Department of Surgery, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, Rotterdam, The Netherlands*

Summary: Seventy-two patients with metastatic renal cell cancer were treated with the combination of high-dose interleukin-2 (IL2), interferon-alpha (IFNα), and lymphokine-activated killer cells (LAK). Seventeen patients were entered in a feasibility part of the study (protocol 1) and 55 in an efficacy part (protocol 2). Protocol 2 differed from protocol 1 in the addition of IFNα to the first 5 days of IL2 infusion. Each patient was planned to receive two induction cycles. IL2, 18 MIU/m^2/day, was administered continuously i.v. on days 1–5, and IFNα, 5 MIU/m^2/day (protocol 2), was administered i.m. on days 1–5, followed by three daily lymphaphereses on days 7–9. On day 12, treatment was resumed with IL2 and IFNα on days 12–15 and LAK reinfusions on days 12–14. In protocol 1, three complete (CR) and one partial (PR) responses were achieved (response rate 24%). The median duration of response and the median survival were 18.1 and 13.9 months, respectively. The 3-year survival was 35%. Of the 51 evaluable patients in protocol 2, 6 achieved a CR and 13 a PR (response rate 37%). The median duration of response was 11.1 months. The median survival was 16.9 months. The 3-year survival was 35%. There were three treatment-related deaths. Other severe toxicities included hypotension, cardiotoxicity, pulmonary edema, renal toxicity, and infectious complications. In the two induction cycles, only 54 and 42% of the planned doses could be administered. We conclude that the use of high-dose regimens of IL2 and IFNα is not warranted, unless we can define more accurately which patients may experience long-term survival as a result of treatment. **Key Words:** Interleukin-2—Interferon-alpha—Metastatic renal carcinoma.

High-dose interleukin-2 (IL2) alone or combined with lymphokine-activated killer (LAK) cells leads to a response in 15–30% of patients with metastatic renal cell cancer (1–11). The first studies of IL2 with the addition of LAK reported relatively high response rates (>30%) and suggested that the combination of IL2 and LAK was superior to IL2 monotherapy (2,4). Interferon-alpha (IFNα) has modest activity against renal cell cancer, with a response rate of ~15% (12–14). In preclinical experiments, a synergistic antitumor effect of IL2 and IFNα has been demonstrated (15–17). In early clinical studies, the combination of IL2 and IFNα has yielded response rates ranging from 22 to 40% (18–21).

The experience with multimodality treatment consisting of IL2, IFNα, and LAK is limited. Only two studies (one only in abstract form) with this combination have been published (22,23). Based on a potential synergism between IL2 and IFNα and a possible additive effect of LAK, as reported in earlier studies, we decided to per-

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Address correspondence and reprint requests to Dr. W. H. J. Kruit at Department of Medical Oncology, Rotterdam Cancer Institute, (Daniel den Hoed Kliniek), Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.

form a phase II study in which we evaluated the toxicity and antitumor efficacy of combination immunotherapy consisting of high-dose IL2 and IFNα with LAK in patients with metastatic renal cell cancer.

PATIENTS AND METHODS

Patient Population

Seventy-two patients with progressive metastatic renal cell cancer were studied. The primary tumor in each patient was removed by nephrectomy. Eligibility criteria included bidimensionally measurable disease, age ≤70 years, performance status Karnofsky index ≥80 [World Health Organization (WHO) grade 0–1], normal organ functions of heart, lung, kidney, bone marrow, and normal serum bilirubin and coagulation tests. Prior immunotherapy or chemotherapy was not allowed. Patients with uncontrolled hypertension, a history of myocardial infarction or arrhythmias, central nervous system metastases, infections, and use of steroid medication were excluded. To exclude significant cardiac dysfunction, every patient had to have normal electrocardiogram at rest and during exercise, normal cardiac multiple uptake gated acquisition scan, and normal echocardiography.

At the start of the study, the planned sample size was 25–40 patients, according to standard rules for the design of a phase II trial. However, once we observed a response rate of approximately 40%, we were prepared to enter more patients because no better treatment was available, and secondly, we wanted to reduce the confidence intervals.

The protocol was reviewed and approved by the institutional review board and the ethical committee. Written informed consent was obtained from each patient.

Treatment

The treatment schedule is displayed in Fig. 1. Seventeen patients were entered into a feasibility part of the study (protocol 1), using Proleukin IL2 (Eurocetus, Amsterdam, The Netherlands). Subsequently, after the treatment scheme proved to be safe, an efficacy study (protocol 2) was carried out, using Teceleukin IL2 (Hoffmann-LaRoche, Basle, Switzerland). In protocol 2, 55 patients were included. Protocol 2 differed from protocol 1 in the addition of IFNα (Roferon, Hoffmann-LaRoche, Basle, Switzerland) to the first 5 days of IL2 infusion in the two induction cycles. Cetus and Roche IL2 prepara-

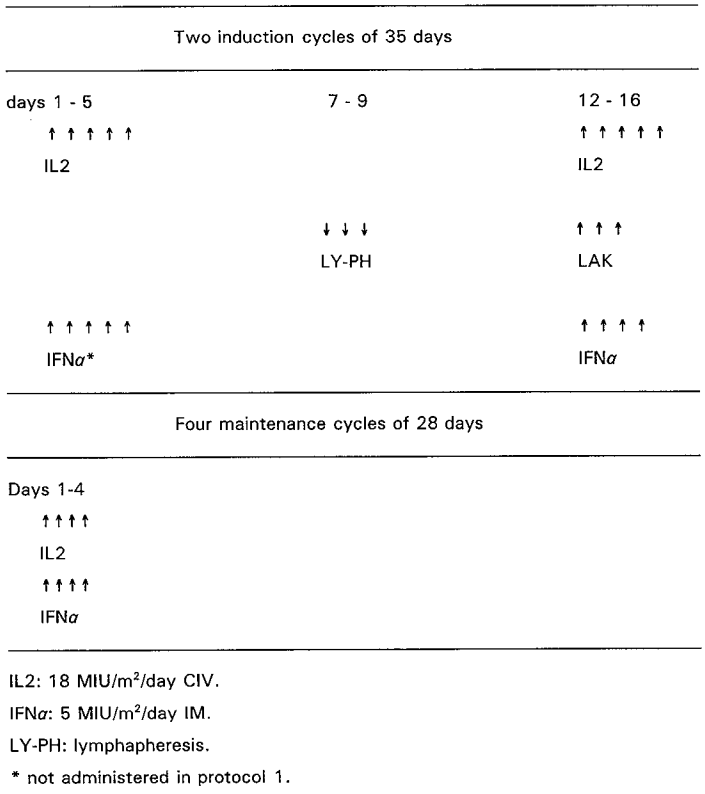

FIG. 1. Induction and maintenance treatment scheme of interleukin-2 with lymphokine-activated killer cells and interferon-α.

tions have different specific activities. To maintain the same dose intensity, we compensated for this difference in activity according to the following rule: 3 million Cetus Units = 6.9 million Roche Units = 18 million International Units (MIU) based on equivalent information from the Biological Response Modifiers Program of the NCI and from the National Institute for Biological Standards and Control, Hertfordshire, United Kingdom. In both protocols, two cycles of adoptive cellular therapy with IL2, IFNα, and LAK were given. Each cycle started with a 120-h priming phase of IL2, 18 MIU/m^2/day, administered as a continuous infusion (c.i.v.) and IFNα, 5 MIU/m^2/day, on days 1–5 (protocol 2) as intramuscular (i.m.) injections. After a rest period of 24 h, three daily runs of lymphapheresis were performed (days 7–9). The autologous lymphocytes obtained were incubated with IL2 for 5 days and reinfused on days 12–14. Infusion of IL2 c.i.v. (108 h) at the same doses as already described was resumed at the start of LAK administration, together with daily i.m. injections of IFNα, 5 MIU/m^2/day (days 12–15). IFNα was administered 3 h before infusion of LAK. IL2 was reconstituted without carrier protein in protocol 1 and with 0.5–0.7% human serum albumin, which was a constituent of the Teceleukin vials in protocol 2 (24).

After a rest period of 3 weeks, this cycle was repeated on day 36. After two induction cycles, each patient was evaluated for response. Patients with stable disease or response were scheduled for maintenance treatment with four monthly cycles of IL2, 18 MIU/m^2/day, and IFNα, 5 MIU/m^2/day, on days 1–4.

Patients were treated and monitored on the clinical research unit during IL2 infusions. Vital signs, daily weight, and fluid balance were carefully monitored. Acetaminophen (Paracetamol), 500 mg every 4–6 h, was used to control fever. Alizapride, loperamide, and codeine were routinely given to suppress nausea, vomiting, and diarrhea, respectively. Prophylactic antibiotics were not used routinely. Because of possible nephrotoxicity, nonsteroidal antiinflammatory drugs such as indomethacin were avoided. Steroids were prohibited. Lymphapheresis and the administration of lymphokines and LAK were performed via tunneled central venous catheters. Intravenous heparin, 15,000 U/day, was given during IL2 treatment episodes to reduce the risk of thromboembolic complications.

Toxicity was graded according to the WHO criteria (25). For toxicities not included in the WHO guidelines, a grading system was used that ranged from mild (grade 1) to life-threatening (grade 4). Initial treatment of hypotension and oliguria consisted of i.v. volume replacement. If volume expansion gave no improvement, low-dose dopamine was added up to doses of 5 μg/kg/min to improve renal perfusion.

The administration of cytokines was interrupted if hypotension WHO grade 3/4 not responding to intravenous fluids or dopamine occurred, if oliguria (urine production <15 ml/h) developed or if the creatinine level rose above 400 μmol/L. Other reasons for interruption were metabolic acidosis, severe arrhythmias or myocardial ischemia, signs or symptoms of lung edema, agitation, or persistent confusion not responding to piperidone, and elevation of serum bilirubin >85 μmol/L.

Treatment was discontinued until the side effects improved to grade 1 toxicity or resolved. Reductions in the dose of IL2 and IFNα by 50% were made in the subsequent cycles if the patient had experienced hypotension not responding to therapy within 8 h, serum bilirubin >85 μmol/L or creatinine >525 μmol/L and WHO grade 3 CNS toxicity.

Treatment was permanently discontinued in case of documented myocardial ischemia, WHO grade 4 CNS toxicity, or serum bilirubin or creatinine levels that failed to return to grade 1 toxicity levels or better.

Response Assessment

Before the start of treatment, all tumor lesions were assessed by routine computed tomography scans of the chest, abdomen, and brain. The two largest perpendicular diameters of each indicator lesion were measured and multiplied. The sum of the products of these diameters was calculated. This procedure was repeated after 8 weeks and every 2 months thereafter. Response criteria were used according to the instructions of the WHO handbook (25). A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks, a partial response (PR) as a reduction in the sum of the products of the two largest perpendicular diameters of all lesions by at least 50% for >4 weeks, without the appearance of any new lesion. Stable disease (SD) denoted <50% tumor reduction and <25% tumor progression. Progressive disease (PD) was defined as the appearance of a new lesion or an increase in size of >25% in any indicator lesion.

The best response observed in a given patient was noted as the overall response. Response duration was calculated from the start of treatment, as were time to progression and survival, using the Kaplan-Meier method.

Activation of Lymphocytes with IL2 In Vitro

Buffy coats harvested by lymphapheresis (Fenwall CS-3000) were placed into culture using a semiclosed

bag system: Travenol-Fenwall PL 732 bags, containing 1,500 ml activation medium with 3×10^6 cells/6,000 IU IL2/ml. The bags were filled with cells and medium using a Travenol-Fenwall model SAV EX 2 Fluid Fill/Weight Unit. The activation medium consisted of 78% RPMI-1640, 20% AIM-V, and 2% autologous human plasma, to which 2 m*M* L-glutamine, 50 μg/ml streptomycin, and 40 μg/ml gentamycin were added to the medium.

Bags were incubated flat at 37°C, 5% CO_2, 95% humidity for 120 h (5 days). Cells were harvested from the bags with a Fenwall Cell Harvester, washed using saline, and resuspended in 5% human serum albumin supplemented with 6,000 IU IL2/ml to a volume of ~500 ml.

Cultures for aerobic and anaerobic microorganisms were obtained immediately after lymphapheresis, 24 h before cell harvest and 1 h before reinfusion of LAK cells into the patient. Samples of LAK were tested for viability and cytotoxicity.

Immunological Studies

In vitro IL2-activated lymphocytes (LAK) were tested for lysis of K562 and Daudi target cells in a 4-h standard ^{51}Cr-release assay. Mononuclear cells isolated from patients on treatment were assayed for (a) cell surface markers detected by monoclonal antibodies in fluorescence assays and (b) cytolysis against natural killer cell (NK)-sensitive (K562) and NK-resistant (Daudi) target cells. The sera from patients were collected at predetermined timepoints before and during treatment for the assay of IFNγ, TNF, IL2, soluble IL2 receptor, IL6, IL8, and C-reactive protein. We have reported a detailed description of these immunological analyses elsewhere (26).

RESULTS

Patient Characteristics

A total of 72 patients were entered in the two parts of the study—17 in protocol 1 and 55 in protocol 2. Their median age was 54 years (range, 30–69 years); 47 (65%) were male and 25 (35%) were female. Patient characteristics per protocol are summarized in Table 1. Ten patients (14%) received palliative radiotherapy before study entry. The median time from initial diagnosis to start of treatment was 6 months. In 25% of the patients (18 of 72), the time that elapsed between the primary diagnosis of renal carcinoma and the development of metastases was >24 months.

TABLE 1. *Patient characteristics*

	Protocol 1	Protocol 2
Age, median (range)	58 (35–68)	54 (30–69)
Male:female	12:5	35:20
Karnofsky, median (range)	100 (90–100)	100 (80–100)
Prior radiotherapy	4 (24%)	6 (11%)
≥2 metastatic organ sites	8 (47%)	33 (60%)

Treatment Characteristics

A total of 33 induction cycles were administered to the patients in protocol 1. One patient developed rapid progressive disease and received only one induction cycle. Therapy was continued with maintenance courses in 10 patients, who received 37 additional cycles. The actual doses of cytokines administered in the two induction cycles, expressed as percentage of the planned dose, were 100 and 94%, respectively. Dose reductions were not necessary. The median number of reinfused LAK cells was 153.8×10^9 (range, 57.6–277.4).

In the second protocol, 18 patients (33%) received only one induction cycle: 3 (5%) died of toxicity, 11 (20%) developed severe adverse events, and 4 patients (7%) were taken off study due to rapid, progressive disease. Five patients (9%) required dose reductions during the first course because of significant toxicities. Six patients (11%) did not receive any LAK infusions. Of the 37 patients (67%) who received a second induction cycle, toxicity necessitated treatment discontinuation in 4 11%). Patients received an average of 54% (range, 23–100%) and 42% (range, 8–100%) of the planned dose of IL2 and IFNα in the two induction courses, respectively. An overview of the administered dose levels of cytokines during the induction cycles in protocol 2 is presented in Table 2. The median number of reinfused LAK cells was 111.2×10^9 (range, 41.3–294.9). The difference in the numbers of activated lymphocytes between both protocols was not statistically significant. Twenty-five patients (45%) in protocol 2 received maintenance therapy for a total of 71 cycles.

TABLE 2. *Percentage of planned dose of interleukin-2 and interferon-α actually given during induction treatment in protocol 2*

	Patients (%)	
Dose	Cycle 1	Cycle 2
>80%	29 (53%)	8 (15%)
60–80%	15 (27%)	7 (13%)
<60%	11 (20%)	22 (40%)
0%	—	18 (33%)

Treatment Results

Of the 68 evaluable patients in the whole study, 23 responded [response rate 34%; 95% confidence interval (CI) 23–46%]. There were 9 complete (CR) and 14 partial (PR) responses. The treatment results per protocol are listed in Table 3. In protocol 1, all 17 patients were evaluable for response and toxicity. The response rate was 24% (95% CI 7–50%), with three CRs and one PR. The median duration of response was 18.1 months (range, 5.5–56.0+). The median survival was 13.9 months (range, 1.9–56.0+). An overview of the characteristics of all responding patients is given in Table 4.

In protocol 2, 51 patients were evaluable for tumor response. Three patients died due to toxicity, and in the fourth patient, posttreatment tumor evaluation could not be carried out. These patients were classified as treatment failures. Six CRs (12%) and 13 PRs (24%) were achieved for an overall response rate of 37% (95% CI 24–52%). The median duration of response was 11.1 months (range, 2.9–31+ months). The median survival was 16.9 months (range, 1.0–48+ months). In both protocols, the 3-year survival was 35%. Responding patients were predominantly patients with lung and lymph node metastases (Table 4).

Toxicity

An overview of the most important grade 3/4 toxicities is presented in Table 5. Toxicity was predominantly observed during the induction cycles. Frequently encountered side effects of any grade were fever, fatigue, malaise, nausea, vomiting, diarrhea, and skin toxicity.

There were important differences in the frequency and intensity of observed toxicities between the two protocols. Treatment was relatively well tolerated in protocol 1 and toxicity did not require dose reductions or permanent treatment discontinuation in any patient. Grade 3/4 hypotension occurred in 9 patients (53%) but only necessitated brief interruption of IL2 administration. Three patients developed supraventricular rhythm disturbances.

TABLE 3. *Treatment results*

	Protocol 1	Protocol 2
Evaluable patients	17	51
Complete response	3 (18%)	6 (12%)
Partial response	1 (6%)	13 (25%)
Overall response	4 (24%)	19 (37%)
Median duration of response	18.1 mos	11.1 mos
Median time to progression	6.0 mos	5.9 mos
Median survival	13.9 mos	16.9 mos
3-yr survival	35%	35%

Only a minority of patients experienced relatively mild neurological symptoms.

In contrast, toxicity was considerable in protocol 2. There were three treatment-related deaths. One patient, a 56-year-old man, died of massive pulmonary embolism during the convalescence period 3 weeks after the first induction cycle was completed. A second patient, a 68-year-old woman, developed intractable hypotension and anuria with severe metabolic acidosis on day 4 of the first episode with IL2 and IFNα. Despite cessation of immunotherapy and termination of its effects by i.v. corticosteroids and maximum efforts in the intensive care unit, she died of multiple organ failure. Blood, urine, and stool microbial cultures were negative. In the third patient, a 61-year-old woman, hypotension and oliguria occurred on day 2 of the second induction cycle, followed by signs of cardiac failure. Echocardiography showed hypokinesis of the left ventricle and low ejection fraction, indicating cardiomyopathy. Despite vasopressor infusion and artificial ventilation, a complete atrioventricular block developed, immediately followed by a dying heart rhythm.

Hypotension grade 3/4 was the most common dose-limiting adverse effect occurring in 42 patients (76%). In 11 patients (20%), treatment was discontinued because of cardiovascular and pulmonary complications: hypotension in 4, reversible cardiomyopathy in 3, rhythm disturbances in 2, and lung edema with respiratory insufficiency in another 2 patients. Transient renal failure grade 3 necessitated dose reductions in 12 patients (22%). Six patients (11%) required dose reduction because of grade 3 neurotoxicity. Sixteen patients (29%) developed infections, mostly catheter related.

Maintenance therapy was given without serious problems in the first protocol. In protocol 2, the toxicity was cumulative with regard to fatigue and renal function disturbances, leading to premature cessation of treatment in 9 of 25 patients.

Immunologic Parameters

We have recently published the results of the immunological monitoring of the patients in this study (26). In short, the most important findings were as follows. During IL2 infusion, peripheral lymphopenia developed, followed by rebound lymphocytosis within 2 days after cessation of treatment and a return to normal during the subsequent 2–3 weeks. The eosinophil counts increased to supranormal levels and eosinophilia persisted during the entire treatment period. Serum concentrations of the secondary cytokines IFNγ and TNFα were increased. The peak levels of serum IL2, IFNγ, and TNFα during

TABLE 4. *Overview of the responding patients*

Sex	Age (yrs)	Sites of disease	Response	Sites of response	Response duration (mos)
Protocol 1					
1 Male	59	Lung/pleural/adrenal	CR	Lung/pleural/adrenal	56+
2 Female	50	Lung	CR	Lung	19
3 Female	58	Lung/lymph node	PR	Lung	6
4 Male	54	Lung	CR	Lung	5
Protocol 2					
1 Female	56	Lung/soft tissue	PR	Lung/soft tissue	14
2 Female	67	Lung/lymph node	PR	Lung	11
3 Male	54	Lung	CR	Lung	17
4 Male	65	Lung/lymph node/bone	PR	Lung/lymph node/bone	15
5 Male	66	Lymph node	CR	Lymph node	15
6 Female	53	Lung	CR	Lung	31+
7 Female	59	Lung	CR	Lung	31+
8 Male	69	Lymph node/lung	PR	Lymph node/lung	9
9 Male	32	Lymph node/bone	PR	Lymph node	29+
10 Male	49	Lymph node	CR	Lymph node	13
11 Female	58	Lung/lymph node	PR	Lung/lymph node	8
12 Female	49	Lung/lymph node	PR	Lung/lymph node	6
13 Male	57	Lung	PR	Lung	7
14 Male	60	Lymph node/adrenal	PR	Lymph node	17+
15 Male	40	Lung	PR	Lung	5
16 Male	55	Visceral	PR	Visceral	14+
17 Male	36	Lung/liver/bone	CR	Lung/liver/bone	8+
18 Female	61	Lung/pleural/lymph node	PR	Lung/pleural	3
19 Male	47	Lung/lymph node/liver	PR	Lung/liver	4

CR, complete response; PR, partial response.

IL2 infusion were two to three times higher in protocol 2 than in protocol 1, which was explained by the better bioavailibility of IL2 after reconstitution with carrier protein in protocol 2 (23). The cell phenotypes of the apheresis products were not significantly different between protocols 1 and 2. Differences between responders and nonresponders treated according to the two protocols were not significant, except for the total number of lymphocytes obtained by apheresis, which was higher in responders than in nonresponders, reaching statistical significance in multivariate analyses ($p = 0.02$).

Clinical Prognostic Factors

The effect of the following baseline clinical parameters on antitumor response and survival was investigated by multivariate analysis: (a) treatment protocol (1 versus 2); (b) performance status (Karnofsky index 80–90 versus 100); (c) time interval between diagnosis of the primary and start of treatment for metastasis ($\leq$24 versus >24 months); (d) number of metastatic sites (1 versus $\geq$2); (e) absence versus presence of metastases in lymph nodes, lung, liver, bone, abdomen, or soft tissues; and (f) weight loss. The only parameter of borderline statistical significance was lymph node metastasis: 15 of 33 patients (45%) with predominant lymph node metastases responded versus 8 of 35 patients (23%) with predominant visceral metastases without lymph nodes ($p = 0.049$). None of these parameters had a significant effect on survival.

DISCUSSION

This triple regimen of high-dose IL2 and LAK in combination with IFNα was developed in our institution in 1988. At that time, treatment with IL2 combined with LAK drew considerable attention. Preclinical animal studies suggested that the addition of LAK cells to IL2 could markedly improve antitumor activity. Several clinical trials using high-dose IL2 and LAK reported relatively high response rates of 30–35% in patients with metastatic renal cell cancer (2,4). A European multicenter study, in which we participated, yielded a response rate of 27% (3). Moreover, animal studies and early clinical studies of the combination of IL2 and IFNα seemed very promising, with response rates of up to 40% (15–21).

Consequently, we investigated whether a triple combination of high-dose IL2 and LAK with IFNα could yield a high rate of long-duration responses in patients

TABLE 5. *Grades 3 and 4 toxicity*

Adverse event	No. of patients (%)			
	Prot. 1	Prot. 2	Prot. 1	Prot. 2
	Grade 3		Grade 4	
Fever	11 (65)	49 (89)	0	0
Fatigue	11 (65)	43 (78)	2 (12)	8 (15)
Anorexia	2 (12)	17 (31)	0	1 (2)
Skin	1 (6)	10 (18)	0	0
Gastrointestinal				
Nausea/vomiting	8 (47)	19 (35)	0	1 (2)
Diarrhea	3 (18)	12 (22)	0	3 (5)
Hepatic				
Bilirubin	0	0	0	0
Alk. phosphatase	2 (12)	8 (15)	0	3 (5)
Transaminases	1 (6)	12 (22)	0	4 (7)
Weight gain	0	6 (11)	0	1 (2)
Hypotension	8 (47)	33 (60)	1 (6)	9 (16)
Cardiac				
Cardiomyopathy	0	3 (5)	0	2 (4)
Arrhythmia	3 (18)	10 (18)	0	2 (4)
Pulmonary	3 (18)	13 (24)	0	2 (4)
Renal failure	0	12 (22)	0	0
Neurologic	0	13 (24)	0	0
Hematologic				
Anemia	0	5 (9)	0	0
Thrombocytopenia	1 (6)	8 (15)	0	2 (4)
Infection	2 (12)	10 (18)	0	2 (4)

with metastatic renal cell cancer. We had intended to use the eventual good results of this phase II study as a basis for a subsequent phase III study, to examine the relative contribution of LAK. Initially, we were concerned about the use of IFNα in the "priming" phase (days 1–5), because IFNα can cause lymphopenia, which would jeopardize the lymphocyte harvest during lymphapheresis. Second, the addition of IFNα might aggravate IL2-related toxicities, particularly hypotension, which would also complicate the lymphapheresis procedure. However, the adverse effects observed in the feasibility part of the study proved to be manageable, whereas the treatment results with a response rate of 24% and a median survival of 18 months were reasonable.

Therefore, we felt encouraged to continue with an efficacy study. After having entered 41 evaluable patients, a preliminary analysis demonstrated a response rate of 39%, a median duration of response of 14 months, and notably, a median survival of 28 months (27). Thus, protocol 2 seemed to be highly effective, although the adverse effects were much more pronounced than in protocol 1. We ascribed this increase in side effects not only to the addition of IFNα into the "priming" days 1–5, but particularly to the observed higher serum levels of IL2, TNFα, and IFNγ after the change from Proleukin to Teceleukin, which can be explained by the better bioavailability of Teceleukin (26,28–30). At the time of the preliminary analysis, we concluded that this combination regimen was the best available therapy for metastatic renal cell cancer. Consequently, the protocol was kept open for the period that was needed for the design and the organization of a phase III comparative study of IL2 and IFNα with or without LAK. The phase II study, reported here as protocol 2, was closed after 55 patients were recruited. The final analysis still showed a response rate of 37%, but a decrease in the duration of response from 14 to 11 months, and more importantly a decrease in the median survival time from 28 to 17 months. A close inspection of prognostic factors to explain this unfavorable development of treatment results revealed that the final 14 patients in the study had a poorer performance status and more extensive disease than the initial 41 patients.

The past few years have witnessed a flood of reports on immunotherapy studies in renal cell cancer. Trials of IL2 monotherapy at intermediate or high dose yielded response rates from 13 to 20% (6,31–36). More recent studies of IL2 and LAK yielded response rates of 9–20% and could not confirm the earlier reported better treatment results compared with treatment with IL2 alone (4,8,37,38). To the present, three randomized trials have been carried out to determine whether the addition of LAK cells offers improved therapeutic benefit (10,39, 40). None showed a higher response rate or longer survival for the LAK arm, and the overall conclusion was that combination therapy of IL2 and LAK was not superior to monotherapy with IL2. More mature data on the efficacy of the combination of IL2 and IFNα also showed lower response rates of 8–12% (38,41,42). In a randomized study, the efficacy of IFNα and high-dose IL2 versus IL2 alone was compared. The study was prematurely closed because the combination was ineffective (11). In a recent final report of the National Cancer Institute Surgery Branch dose-escalating study, the overall response rate of IL2 and IFNα decreased from 38 to 28% (18,43).

The only two other reports on studies of IL2, IFNα, and LAK with similar dose intensity, albeit a different schedule, have yielded response rates of 12 and 24%, with a median survival of 8 months (22,23). The investigators in both studies observed a toxicity profile of the same nature and severity as we did. Of note, we and others who studied intensive regimens of IL2 and IFNα could not administer more than 40–60% of these cytokines due to the severity of side effects (11,23,43,44).

On the basis of our study and in view of other study data, we conclude that these high-dose regimens of IL2 and IFNα with or without LAK are not warranted, unless

we are able to predict those patients who may experience long-term survival as a result of treatment.

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