Results of two sequential phase II studies of interleukin-2 (IL2) in metastatic renal cell carcinoma and melanoma: high-dose continuous intravenous IL2 infusion and subcutaneous IL2 administration in combination with alpha interferon

Resultados de dos estudios fase II secuenciales con interleuquina-2 (IL2) en carcinoma renal metastásico y melanoma: infusión intravenosa contínua de dosis altas de IL2 y administración de IL2 subcutánea en combinación con interferon alfa.

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RESUMEN. se presentan los resultados de dos estudios secuenciales, el primero con dosis altas de interleuquina-2 en infusión intravenosa continua y el segundo con IL2 subcutánea e interferón alfa (IFN alfa), en pacientes con melanoma y carcinoma renal metastásicos en la Clínica Universitaria de Navarra. En el estudio de dosis altas de IL2 en infusión continua se administraron 18 x 10^6 UI/m²/día de IL2 en infusión continua de 5 días por semana durante 2 semanas. Se trataron 22 pacientes y se observaron 3 respuestas objetivas (13,3%). La toxicidad fue severa y frecuente, requiriendo reducción de dosis en todos los casos menos en uno. La tasa de mortalidad fue 9% (2/22). En el ensayo de IL2 subcutánea e interferón, IL2 se administró a dosis de 4,8 x 10^6 UI/m²/día , 5 días a la semana durante 3 semanas consecutivas. La dosis de IL2 se administró cada 8 horas el primer día y cada 12 horas el segundo día a modo de inducción. Interferon alfa se administró por vía subcutánea a dosis de 3 x 10^6 UI/m²/día los días 1, 3 y 5 de cada semana durante el tratamiento de IL2. Entre los 24 pacientes tratados con esta combinación hubo 3 respuestas parciales (12,5%) y la toxicidad fue baja o moderada. Los resultados sugieren que la IL2 sola o en combinación con IFN alfa es poco activa y que la mejoría en la tolerancia podría disminuir su actividad antitumoral.

SUMMARY. The results of two sequential trials, the first one with high dose interleukin 2 (IL2) by continuous intravenous infusion and the second one with subcutaneous IL2 and alpha-interferon (alpha IFN), performed in consecutive patients with metastatic melanoma and renal carcinoma at the Clinica Universitaria de Navarra are presented. In the high-dose continuous IL2 trial, recombinant IL2, 18 x 10^6 IU/m², was administered daily by continuous infusion five days a week for two weeks, and the treatment cycle was repeated after a rest of 2 weeks. Twenty two patients were treated and objective responses were observed in 3 (13.3%). Toxicity was frecuent and severe, and all but one required dose reduction. The mortality rate was 9% (2/22). In the subcutaneous IL2 and alpha IFN trial, subcutaneous IL2, 4.8 x 10^6 IU/m², was administered daily, five days a week, for 3 consecutive weeks. IL2 dose was given every 8 hours on the first day and every 12 hours on the second day, as a loading induction dose. Concomitant alpha-IFN, 3 x 10^6 IU/m² was given subcutaneously once a day on days 1, 3 and 5 weekly each week for the duration of IL2 therapy. Of the 24 patients treated with this combination, 3 partial responses were noticed (12.5%) and the toxicity was mild to moderate. These results suggest that both, IL2 alone or IL2 in combination with alpha-IFN are minimally active and that any improvement in tolerance might impair its antitumor activity.

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Palabras clave

Interleuquina 2-Interferón alfa-Melanoma- carcinoma renal.

Key words

Interleukin 2 - Alpha interferon - Melanoma - Renal carcinoma.

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Introduction

Interleukin 2, IL2, is an immunomodulatory cytokine produced by activated T lymphocytes which exhibits antitumor activity in renal cell carcinoma and malignant melanoma. Response rates in these two immunogenic tumors are modest, in the range of 15-30%, and a small proportion of responses are complete remission. The detection of long lasting tumor regression has been an important aspect of the interest aroused by this new drug (25).

The initial studies of S.A. Rosenberg et al. with high-dose intravenous bolus of IL2 (10,000 to 100,000 IU/kg every 8 hours), given alone or in conjunction with autologous lymphokine activated killer (LAK) cells, often resulted in cumbersome toxicity, requiring admission in the intensive care unit and a high level of expertise was needed in the management of the severe side effects (27). A change in the schedule of IL2 administration, using a daily intravenous continuous infusion, at a lower total IL2 dose (3 to 5 x 10^6 IU/m^2/d), improved the tolerance while preserving the antitumor activity and the patients could be cared of in a conventional hospital setting (33). The major advantage of the continuous IL2 iv infusion was the possibility of early drug stopping at the first signs of critical side effects (hypotension, dyspnea, bronchospasm, pulmonary edema, arrythmia or other) thus allowing for an easier control of toxicity. The final recommended daily dose of IL2 in continuous iv infusion is somewhat lower, between one half and one third, than the dose given by direct bolus iv administration, indicating major pharmacologic differences between both schedules and a relatively more toxic profile, at equivalent doses, for the continuous iv administration.

Another recent therapeutic development has been the combination of IL2 and alpha-interferon (alpha-IFN). Alpha-IFN up-regulates the expression of HLA class I and related tumor-associated antigens on tumor cells enhancing effector cell mechanisms which are sensitive to immunomodulation by IL2. Several animal experiments indicated synergistic effects for the alpha-IFN and IL2 cytokine combination (9, 14,16, 32). In addition alpha-IFN as a single agent has shown antitumor activity in renal cell carcinoma and malignant melanoma (20, 24). The initial studies of alpha-IFN and IL2 combination therapy demonstrated synergism and activity (2, 28). The response rate for IL2-alpha IFN combinations were in the range of 10-35%, similar to IL2 as a single agent, but most of the studies reduced the total dose of IL2, in order to decrease toxicity, thus reflecting a synergistic increase in biological effects (5-8, 15, 17, 19, 21, 23, 30). In addition, different studies of combination therapy using the subcutaneous administration of IL2 and alpha-IFN were developed to improve the schedule and make posible a safe outpatient administration of both drugs (2, 3,13, 22, 26, 31)

Two recent large randomized studies addressed the question of comparing IL2 alone and IL2 in combination with alpha-IFN in renal cell carcinoma and malignant melanoma and demonstrated absence of improvement either in the response rate or in the overall survival (1, 29).

The results of two sequential trials, the first with high dose IL2 by continuous intravenous infusion and the second with subcutaneous IL2 and alpha IFN, performed in consecutive patients at The Clinica Universitaria de Navarra furtherly confirm these observations and the results obtained are presented

Patients and methods

Eligibility. The requirements for entry into the two studies were the same and included histologic documentation of metastatic renal carcinoma or melanoma, presence of measurable disease, Karnofsky index performance status of 60% or greater, expected survival of more than 3 months, peripheral leukocyte counts >3000/mm^3 and platelet count >100,000/mm^3.

Patients were ineligible for these studies if they demonstrated significant renal (creatinine > 1.2 mg/100 ml) or hepatic dysfunction (bilirubin > 1.3 mg/100 ml), and cardiovascular abnormalities (congestive heart failure, uncontrolled clinical hypertension, symptoms of coronary artery disease, history of arrhythmias, or EKG evidence of prior myocardial infarction or arrhythmia). Patients with central nervous system metastases or serious active infection and patients receiving corticoste-

roid treatment were also excluded. IL2 protocol was approved by the Ethics committee and the Spanish Health Department. Informed consent was obtained from the patient prior to therapy.

Treatment schedules

High-dose continuous IL2 trial: Recombinant IL2, (Cetus Corporation, Amsterdam), 18 million IU/m^2, was administered daily by continuous infusion five days a week for 2 consecutive weeks. The treatment cycle was repeated after a rest of 2 weeks (induction phase).

Patients with stable or responding disease continued therapy up to a maximum of 4 additional cycles, repeating each treatment at 4-week intervals (maintenance phase). Treatment was discontinued in case of progressive disease, or because of dose-limiting toxic effects. During IL2 therapy patients were carefully monitored with hourly vital signs, and daily body weight, CBC (differential WBC count and platelet count), total s-bilirubin, s-creatinine and liver function tests (SGOT, alkaline phosphatase, LDH). IL2 infusion was discontinued in the presence of hypotension grade III or IV (defined as a change of > 30 mm in Hg systolic blood pressure and/or requirement of iv fluid therapy and/or pressors for > 8 hrs), significant arrhythmia, suspicion of myocardial ischemia, agitation or persistent confusion, elevation of bilirubin to a level > 5 mg/100 ml, elevation of serum creatinine to a level > 4.5 mg/100 ml, bacterial sepsis, dyspnea at rest, prolongation of the PT > 3 seconds over control, or prolongation of the PTT > 10 seconds over control, and at the discretion of the principal investigator. IL2 was started again when the symptoms and signs of acute toxicity subsided. Hypotension grade III or IV, increase in serum creatinine during the prior cycle > 6 mg/100 ml, rise in serum bilirubin during the prior cycle > 5 mg/100 ml and grade III neurotoxicity (agitation or persistent confusion) in the previous cycle, indicated a subsequent reduction of IL-2 at 50% of the initial dose. Documented myocardial ischemia, grade IV neurotoxicity (coma or seizures), serum creatinine or bilirubin that failed to return to baseline normal levels were contraindications to further therapy with IL-2.

Subcutaneous IL2 and IFN trial: Subcutaneous IL2, 4.8 million IU/m^2 , was administered daily five days a week for 3 consecutive weeks. On the first day of each cycle IL2, at the same dose, was administered every 8 hours, the second day every 12 hours and thereafter every 24 hours until the end of treatment. Treatment cycle was repeated after a rest of 1 week until there was evidence of progressive disease or dose-limiting toxic effects occurred. Toxicity criteria and definitions were similar to the previous IL2 continuous infusion protocol. Concomitant alpha-IFN , 3 million IU/m^2, was given subcutaneously, once a day, on days 1, 3 and 5 of each week for the duration of IL2 therapy.

Assessment of response

Response and toxicity criteria were applied according to the WHO recommendations (35). Survival distributions were estimated by the Kaplan and Meier methods (18).

Results

High-dose continuous IL2 trial (HDIL2): Twenty two patients were treated between July 1989 and March 1990. Seven patients had renal carcinoma and fifteen had malignant melanoma (table 1). There were 16 males and 6 females. Of the seven patients with metastatic renal carcinoma, 5 underwent prior nephrectomy. A total of 40 cycles of HDIL2 were administered (median 2; range 1-4) and all patients completed at least one course of therapy. The median cumulative IL2 dose was 363 x 10^6 IU (range 255-1433 IU).

All patients were evaluable for toxicity and all but one required a dose reduction according to the protocol guidelines. Table 2 summarizes the toxicities associated with continuous IL2 infusion. The most common toxic events were fever, hypotension, nausea and vomiting, asthenia and chills. Cutaneous toxicity with diffuse erythema, pruritus, and occasionally desquamative dermatitis were also seen. Hematologic toxicities were observed in most patients: Eosinophilia ocurred in 32 of 40 cycles, anemia in 19 cycles and thrombocytopenia in 8 cycles. Serum creatinine and bilirubin levels were increased in 30% of the cycles and returned to normal on cessation of treatment, except in two cases. Neurologic abnormalities were infrequent and only one patient presented grade III toxicity. Fluid retention, oliguria and body weight gain were common, and sometimes associated with interstitial edema and respiratory distress. Four patients developed severe toxicity and were removed from study: one patient developed noncardiogenic pulmonary edema after 1 week of therapy in the third cycle and another patient presented duodenal ulcus perforation, and a gastrectomy with Billroth II anastomoses was made. Two pa-

Table I

Patient characteristics

	Renal carcinoma		Melanoma	
	HDIL-2	IL-2 IFN	HDIL-2	IL-2 IFN
Total number of patients	7	13	15	11
Sex				
Male	6	10	10	7
Female	1	3	5	4
Median age	54	61	47	60
Range	27-69	32-70	17-73	19-79
Median Karnofsky	90	80	90	80
Range	70-90	60-90	80-90	60-90
Sites of metastatic disease				
Lung	6	7	7	6
Liver	3	4	4	2
Soft tissue	4	2	4	4
Nodules	1	7	8	4
Bone	4	6	0	1
Adrenal	1	1	0	0
kidney	2	2	0	0
Spleen	1	0	0	2

HDIL-2: High dose of Interleukin-2
IL-2 IFN: Interleukin-2 Interferon.

tients had septic shock and died, one of them with DIC and acute renal failure, which required hemodialysis, and the other with necrotizing cholecystitis. The mortality rate was 9% (2/22).

Objective responses were demonstrated in 3 of 22 patients (13.6%; 95% confidence intervals 2.9% and 34.9%). There were 1 complete response (renal carcinoma) and 2 partial responses (malignant melanoma). Nine patients maintained stable disease (40.9%): 3 renal carcinoma and 6 malignant melanoma, and 10 patients rapidly progressed. The duration of response was 4 months in one of the patients with partial response and 26 months in the patient with complete response. The other patient with partial response died from septic shock during the second cycle. Median survival was 8 months (Fig 1).

Subcutaneous IL2 and IFN trial: Twenty four patients were treated between February 1990 and October 1992. Thirteen had metastatic renal carcinoma and 11 malignant melanoma (table 1). There were 17 males and 7 females. Of the thirteen patients with metastatic renal carcinoma, 10 had previous nephrectomy. A total of 37 cycles of treatment were administered (median:1; range: 1-5) and all patients completed at least one course of therapy.

All patients were evaluable for toxicity. Toxicities associated with the combined administration of subcutaneous alpha-IFN and IL2 were mild to moderate and all patients except two remained fully outpatient during the whole treatment. Fever, malaise, anorexia and astenia were referred by all 24 patients. Erithema, pruritus and desquamative dermatitis were seen in 7 patients. One patient suffered an episode of disorientation and another a transient hypotension. Two patients had the treatment discontinued because of toxicity: One patient had severe renal dysfunction requiring hemodyalisis five days after the second cycle, and another patient had severe elevation of bilirubin and liver enzymes. No treatment related mortality was found. Partial responses were demonstrated in 3 of 24 patients (12.5%; 95% confidence intervals 2.7% and 32.4%): 1 renal carcinoma and 2 malignant melanoma. Four patients maintained stable disease (16.6%: 2 renal carcinoma, 2 malignant melanoma), and 17 patients rapidly progressed. The median duration of response

Table 2

Toxicity of HDIL-2

	Number of cycles	(%)	Grade III - IV	(%)
Hypotension	34	(85)	12	(30)
Fever	38	(95)	13	(45)
Erithema	25	(62.5)	1	(2.5)
Diarrhea	15	(37.5)		
Nausea/vomiting	33	(82.5)	1	(2.5)
Weigth gain	11	(27.5)		
Dyspnea	13	(32.5)	1	(2.5)
Oliguria	22	(55)	4	(10)
Edema	22	(55)	1	(2.5)
Pruritus	21	(52.5)	2	(5)
Chills	25	(62.5)	1	(2.5)
Disorientation	3	(7.5)		
Astenia	30	(75)		
Anorexia	15	(37.5)		
Elevated creatinine	11	(27.5)	4	(10)
Elevated Bilirubin	13	(32.5)	2	(5)
Eosinophilia	32	(80)		
Anemia	19	(47.5)	1	(2.5)
Trombocytopenia	8	(20)	2	(5)
Abdominal pain	4	(10)	2	(5)
Thrombophlebitis	1	(2.5)	1	(2.5)
Gastrointestinal bleeding	2	(5)	2	(5)
Cholecystitis	1	(2.5)	1	(2.5)
Coma	1	(2.5)	1	(2.5)
Pulmonary edema	1	(2.5)	1	(2.5)
Intestinal perforation	2	(5)	2	(5)
Ulcus	2	(5)	1	(2.5)
Sepsis	2	(5)	2	(5)
Exitus	2	(5)	2	(5)

HDIL-2: High dose of Interleukin-2

was 4 months. Median actuarial survival was 7 months (Fig 2).

Discussion

This study confirms the results obtained by other investigators with IL2 and with the combination of IL2 and alpha-IFN. Minimal activity was identified in renal cell carcinoma and malignant melanoma. The response rate was 13.6% for IL2 continuous iv infusion, and 12.5% for IL2 plus alpha-IFN. The results of single institution series with more than 12 patients in renal cell carcinoma indicated similar results with a response rate ranging from 9% to 32% (3, 4, 11, 13, 17, 23, 26, 30, 34). In our series the antitumor effect was disappointingly low, similar for IL2-alpha interferon and for single agent IL2. In part the low response rates found could be attributed to the use of strict response definition criteria, because minor responses and stable disease were relatively high in both series: 40.9% for IL2 and 16.6% for IL2 and alpha- IFN. The results of our series, however appear identical to those obtained in two large randomized trials comparing both modalities of treatment which have been reported recently. In renal cell carcinoma these were IL2 17% and IL2 and alpha-IFN 11%. while in malignant melanoma the responses were 5% and 10% respectively (1, 29).

It is difficult to define what is the role, if any, of alpha-IFN in the combination. It appears that the posible synergism in activity contributed by alpha-IFN is probably lost by the required IL2 dose reduction to make the out-patient treatment regimen more tolerable, because the combination of IL2 and alpha-IFN retains ac-

tivity in spite of an important decrease in IL2 dose.

It is not clear in the literature whether the IL2 dose correlates with the activity, although a dose-effect is suggested in the confirmatory trials that followed Rosenberg et al publication (27). Rosenberg et al trial indicated that IL2 bolus administration was given, according to the program, a median of 29 out of the projected 30 injections in 16 days, and this program achieved a 30% response rate. Dutcher et al, and Clark et al, using the same protocol as reported by Rosenberg et al, presented more ommissions of IL2 injections due to toxicity and had lower response rates. Dutcher et al, giving a median of 22 doses, out of the projected 30 IL2 injections, had 20% responses and Clark et al, giving a median of 15 doses out of the projected 30 IL2 injections, had 10% responses (10, 12).

Phase I trials of IL2 and alpha-IFN indicated a similar building-up in the response rate according to IL2 dose escalation. The study of Rosenberg et al (28) showed an increase in response rate from 17% to 41% by escalating IL2 dose from 3 x10^6 IU/m^2/d to 13.5 x 10^6 IU/m^2/d. In the other hand, Sznol et al, increased IL2 dose in the combination from 3.6 x 10^6 IU/m^2/d to 10.8 x 10^6 IU/m^2/d and obtained as well an increase in response rate from 0% at the lower dose to 25% at the higher dose (30).

These results suggest that there is a compromise between IL2 toxicity and efficacy in most of the programs. The addition of alpha-IFN probably do not change this basic premise and any improvement in tolerance or toxicity might occur at the cost of a decrease in antitumor activity.

The series presented in this report confirm what is already known i.e, marked toxicity associated with partial objective responses of less than 20% for high dose in-patient IL2 therapy and a similar activity with much better tolerance for the out-patient moderate IL2 dose plus alpha-IFN.

The interest of this study is therefore not to add to the current literature but to confirm in a series of a single institution of Spain that a small percentage of patients respond to IL2 based therapy. Better means to indentify the active target population should be investigated in order to define further improvements in this new method of therapy.

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