

RECOMBINANT HUMAN INTERLEUKIN-2, RECOMBINANT HUMAN INTERFERON ALFA-2a, OR BOTH IN METASTATIC RENAL-CELL CARCINOMA

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ABSTRACT

Background Recombinant human interleukin-2 (aldesleukin) and recombinant human interferon alfa can induce notable tumor regression in a limited number of patients with metastatic renal-cell carcinoma. We conducted a multicenter, randomized trial to determine the effect of each cytokine independently and in combination, and to identify patients who are best suited for this treatment.

Methods Four hundred twenty-five patients with metastatic renal-cell carcinoma were randomly assigned to receive either a continuous intravenous infusion of interleukin-2, subcutaneous injections of interferon alfa-2a, or both. The main outcome measure was the response rate; secondary outcomes were the rates of event-free and overall survival. Predictive factors for response and rapid progression were identified by multivariate analysis.

Results Response rates were 6.5 percent, 7.5 percent, and 18.6 percent ($P < 0.01$) for the groups receiving interleukin-2, interferon alfa-2a, and interleukin-2 plus interferon alfa-2a, respectively. At one year, the event-free survival rates were 15 percent, 12 percent, and 20 percent, respectively ($P = 0.01$). There was no significant difference in overall survival among the three groups. Toxic effects of therapy were more common in patients receiving interleukin-2 than in those receiving interferon alfa-2a. Response to treatment was associated with having metastasis to a single organ and with receiving the combined treatment. The probability of rapid progression of disease was at least 70 percent for patients with at least two metastatic sites, liver metastases, and a period of less than one year between the diagnosis of the primary tumor and the appearance of metastases.

Conclusions Cytokines are active in a few patients with metastatic renal-cell carcinoma. The higher response rate and longer event-free survival obtained with a combination of cytokines must be balanced against the toxicity of such treatment. (N Engl J Med 1998;338:1272-8.)

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METASTATIC renal-cell carcinoma is refractory to chemotherapy, and median survival is usually less than a year.¹⁻⁴ Performance status, number of metastatic sites, time from diagnosis of the primary tumor to the discovery of metastases, and weight loss are important prognostic factors.^{1,5,6} In 1985 and 1987, Rosenberg et al.^{7,8} reported that recombinant human interleukin-2 (aldesleukin) caused dramatic shrinkage of tumors, particularly in patients with metastatic renal-cell carcinoma. These results sparked the development of cytokine treatment in oncology. The pronounced toxic effects described in the initial reports from trials involving a high-dose bolus of interleukin-2 prompted the development of other regimens, such as the continuous infusion of interleukin-2 or subcutaneous injections of interleukin-2 plus interferon alfa.^{9,10}

In 1990 interleukin-2 and interferon alfa were approved for the treatment of metastatic renal-cell carcinoma in most Western European countries. However, the results available at that time were discordant and were based on nonrandomized phase 2 studies.¹¹⁻¹⁶

In this setting, the Groupe Français d'Immunothérapie initiated a randomized trial to determine the effect of interleukin-2 and interferon alfa-2a on metastatic renal-cell carcinoma. Because these cytokines can cause dramatic and durable tumor regression in some patients, the group considered a randomized trial with an untreated control group to be unethical. In this trial patients were treated with recombinant human interleukin-2, recombinant human interferon alfa-2a, or both cytokines.

METHODS

Selection of Patients

Patients between 18 and 65 years of age were eligible if they had histologically confirmed, clearly progressive metastatic renal-

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cell carcinoma that could be measured in two dimensions; an Eastern Cooperative Oncology Group (ECOG) performance status no higher than 1; and normal blood cell counts, normal bilirubin levels, and creatinine levels below 1.7 mg per deciliter (150 μ mol per liter). Patients were excluded if they had brain metastases (confirmed by computed tomography [CT]), cardiac dysfunction (confirmed by electrocardiography and echocardiography), a contraindication to the use of vasopressor agents, active infection, previous treatment with interleukin-2 or interferon alfa, chemotherapy or radiotherapy in the six weeks before enrollment, or current treatment with corticosteroids. Patients with a history of organ transplantation, other cancer, or seizure disorder were excluded. Pregnant or lactating women were also ineligible. The base-line workup consisted of brain, thoracic, abdominal, and pelvic CT and bone scanning. The number of organs with metastases was determined in each patient before randomization, and the organs involved were recorded as lung (including pleura), liver, bone, or other (with details of the site).

Patients who required nephrectomy were invited to enter the trial only after they had undergone the operation. We recommended that patients who had only one metastasis have the metastasis surgically removed. The protocol was approved by the ethics committee of the Centre Léon Bérard in Lyons in compliance with French law. Voluntary, written informed consent was obtained from all patients.

Treatment

Randomization, with stratification according to center, was performed by an interactive computerized procedure at the study data-monitoring center. All data were prospectively monitored on site. Details of ineligible patients were recorded, together with the main reason for exclusion. Eligible patients were randomly assigned to receive either intravenous recombinant human interleukin-2 alone (group 1), subcutaneous recombinant human interferon alfa-2a alone (group 2), or intravenous interleukin-2 combined with subcutaneous interferon alfa-2a (group 3).

In group 1, recombinant human interleukin-2 (Proleukin, Chiron Therapeutics, Paris) was administered as a five-day continuous intravenous infusion at a dose of 18×10^6 IU per square meter of body-surface area per day. This regimen has been widely used in Europe since interleukin-2 received a product license. The treatment schedule consisted of two induction cycles and four maintenance cycles, with a three-week rest period between cycles. Each induction cycle consisted of two five-day courses of interleukin-2 infusion separated by a six-day break. Each maintenance cycle consisted of a five-day infusion followed by three weeks of no therapy.

In group 2, recombinant human interferon alfa-2a (Roferon, Roche, Paris) was given subcutaneously at a dose of 18×10^6 IU per day three times a week for 10 weeks as induction treatment and for 13 additional weeks as maintenance treatment.

In group 3, interleukin-2 was administered exactly as in group 1; in addition, interferon alfa-2a at a dose of 6×10^6 IU per day three times a week subcutaneously was given during the two interleukin-2 induction cycles and during each interleukin-2 maintenance cycle. This regimen had been previously validated by our group in a pilot study (unpublished data).

Patients without disease progression at the time response was evaluated (week 10) received maintenance treatment. In the event of progression of disease, patients in groups 1 and 2 could receive the other cytokine (crossover).

Supportive Care

Patients assigned to receive interleukin-2 had a central venous catheter inserted, and the use of prophylactic antibiotics, usually an intravenous quinolone, was recommended.¹⁷ The patients also received acetaminophen (1 g every four hours) and, if necessary, indomethacin (25 mg every six hours) to reduce febrile reactions; cimetidine or misoprostol to prevent gastrointestinal bleeding;

diphenhydramine for pruritus; and antidiarrheal agents. In addition, antiemetic drugs, anxiolytic agents, and sedatives were administered when required. Colloids were used for the initial treatment of hypotension, followed by vasopressor agents, usually dopamine, if necessary.

Dose Modification and Monitoring of Toxicity

The World Health Organization scoring system was used to classify toxic effects of therapy.¹⁸ Treatment was stopped if hypotension resistant to intravenous vasopressor treatment occurred or if there was any toxic event of grade 3 or higher. Patients with life-threatening or persistent, severe toxic reactions received no further treatment with the trial drugs. In other patients, treatment was resumed at the original doses when the toxic effects improved to grade 1 or less. The doses were reduced, usually halved, if a new episode of toxic effects of grade 3 or more occurred. When unusual or unexpected adverse reactions were reported, a specific warning was sent to all investigators. In addition, all reports of grade 4 toxicity were reviewed by a committee to assess whether the treatment caused the side effect.

Assessment of Response

The World Health Organization criteria¹⁸ were used to determine tumor response. An objective response (more than 50 percent reduction in the sum of the sizes of all lesions) included both partial and complete responses, judged by comparing tumor sizes by CT 10 weeks after the start of treatment with those measured in the 2 weeks before treatment. Tumors were measured at week 25 in patients who had at least stable disease and who had received maintenance treatment. All cases of tumor regression, even those classified as minor responses by the investigators, and doubtful cases were reviewed by an external committee consisting of three radiologists and two physicians who were blinded to the patients' treatment assignments.¹⁹ Rapid progression was defined as progression occurring within the first 10 weeks of treatment (progression was defined as a 25 percent increase in the size of one lesion or the appearance of a new lesion).

Statistical Analysis

The major end point was the rate of response. The secondary end points were event-free survival, defined as survival without disease progression, and overall survival. Survival curves were calculated by the Kaplan-Meier method²⁰ and compared by the log-rank test.²¹

An independent methods review committee evaluated the results of an interim analysis after the enrollment of 31 patients per group to verify the efficacy of each treatment. The predefined criterion for stopping the trial was a response rate of less than 10 percent in one group, together with a difference of at least 15 percent from the treatment group with the closest results to that group. The methods committee recommended continuation of the study as a phase 3 trial to allow the comparison of overall survival between group 1 or 2 (in which the two cytokines could be administered sequentially in a crossover fashion) and group 3 (in which both cytokines were administered at the same time). It was calculated that 138 patients per group were needed for a difference of at least 20 percent in overall survival to be detected, with α set at 5 percent and β at 10 percent.

Univariate analysis and multivariate stepwise logistic-regression analysis were performed with the Logistic procedure of the SAS statistical software package (SAS Institute, Cary, N.C.) to identify prognostic factors for response and rapid progression.

RESULTS

Characteristics of the Patients

From March 1992 to July 1995, 425 patients with metastatic renal-cell carcinoma were enrolled in the

study; 138 were randomly assigned to the interleukin-2 group, 147 to the group receiving interferon alfa-2a, and 140 to the group receiving interleukin-2 plus interferon alfa-2a. During the same period, 722 patients were considered ineligible, because of an ECOG performance status of 2 or higher (25 percent), age below 18 or above 65 years (17 percent), organ dysfunction (13 percent), brain metastases (12 percent), previous treatment (11 percent), refusal by the patient (6 percent), or miscellaneous reasons (16 percent).

There were no statistically significant differences in patient characteristics among the three treatment groups (Table 1). Most patients (77 percent) had a performance-status score of 0, and most (93 percent) had undergone nephrectomy. After review of the data, 7 of the 425 patients were found not to fulfill the eligibility criteria; 11 patients did not receive any cytokine treatment. These patients were included in the intention-to-treat analysis.

Characteristics and Toxic Effects of Treatment

The induction treatment was given to 132, 146, and 136 patients in groups 1, 2, and 3, respectively, and 29, 59, and 47 patients, respectively, received maintenance treatment. The mean percentages of each agent delivered during the induction treatment (including both dose reductions and discontinuations of treatment) were 61 percent (groups 1 and

3) for interleukin-2, and 86 percent and 72 percent (groups 2 and 3, respectively) for interferon alfa-2a. After the failure of their initial treatment, 48 patients initially assigned to interleukin-2 received interferon alfa-2a, and 65 initially assigned to interferon alfa-2a received interleukin-2. No unusual degree of toxicity was observed in these patients.

Table 2 shows the grade 3 or 4 adverse events observed in each treatment group during induction cycles. More adverse events were observed in the groups given interleukin-2 (groups 1 and 3) than in the group given interferon alfa-2a alone (group 2), but there were no significant differences in the number of adverse events between the group given interleukin-2 alone and the group given interleukin-2 plus interferon alfa-2a, except for grade 3 or 4 fever, which was more common with the combined treatment (P=0.02). Fever and hypotension were the most common adverse events in the two groups receiving interleukin-2. All patients recovered and returned to their pretreatment status with respect to these adverse events.

During the treatment periods, or within a month following a treatment course, 22 patients (5.2 percent) died from causes unrelated to renal-cell carcinoma: 13 patients (9.4 percent) in group 1, 1 (0.7 percent) in group 2, and 8 (5.7 percent) in group 3. These patients were significantly more likely to have had low performance-status scores at the start of

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	GROUP 1 (N = 138)	GROUP 2 (N = 147)	GROUP 3 (N = 140)	TOTAL (N = 425)
Sex — no. (%)				
Male	95 (69)	107 (73)	99 (71)	301 (71)
Female	43 (31)	40 (27)	41 (29)	124 (29)
Median age — yr	56	55	56	56
ECOG performance status — no. (%)†				
0	99 (72)	113 (77)	116 (83)	328 (77)
1	35 (25)	30 (20)	21 (15)	86 (20)
2	3 (2)	3 (2)	1 (1)	7 (2)
Unknown	1 (1)	1 (1)	2 (1)	4 (1)
Metastasis-free interval <1 yr — no. (%)‡	87 (63)	109 (74)	95 (68)	291 (68)
Weight loss ≥10% — no. (%)	15 (11)	21 (14)	21 (15)	57 (13)
No. of metastatic sites — no. (%)§				
1	31 (22)	41 (28)	28 (20)	100 (23)
2	50 (36)	37 (25)	45 (32)	132 (31)
≥3	56 (41)	69 (47)	65 (46)	190 (45)
Prior radiotherapy — no. (%)	17 (12)	18 (12)	22 (16)	57 (13)
Prior chemotherapy — no. (%)	1 (1)	4 (3)	1 (1)	6 (1)
Nephrectomy — no. (%)	128 (93)	135 (92)	131 (94)	394 (93)

*There were no statistically significant differences among the treatment groups in any of these characteristics.

†ECOG denotes the Eastern Cooperative Oncology Group.

‡The metastasis-free interval is the time from diagnosis of the primary tumor to the first metastasis.

§Data were missing for one patient in group 1 and two patients in group 3.

TABLE 2. GRADE 3 OR 4 ADVERSE EVENTS OBSERVED DURING INDUCTION TREATMENT.*

ADVERSE EVENT	GROUP 1 (N=138)	GROUP 2 (N=147)	GROUP 3 (N=140)	TOTAL (N=425)	P VALUE
Hypotension resistant to vasopressor agents	94	1	94	189	<0.001
Fever	59	8	79	146	0.001
Performance-status impairment	49	23	53	125	0.001
Nausea or vomiting	47	7	43	97	0.001
Diarrhea	38	1	35	74	<0.001†
Anemia	24	9	22	55	0.009
Pulmonary symptoms	22	5	21	48	0.001
Renal symptoms	21	0	22	43	<0.001†
Neurologic symptoms	17	2	20	39	<0.001†
Increased AST or ALT‡	15	4	16	35	0.005†
Cutaneous signs	14	0	19	33	<0.001†
Cardiac signs	17	1	8	26	<0.001†
Infection	11	1	13	25	<0.001†
Thrombocytopenia	5	0	10	15	0.002†
Increased creatinine	5	0	7	12	0.015†
Weight loss	3	6	2	11	0.375†
Leukopenia	1	1	3	5	0.538†
Hyperbilirubinemia	1	0	3	4	0.127†

*Adverse events are classified according to the World Health Organization system, as described by Miller et al.¹⁸ P values are for the comparison among the three groups. Unless otherwise indicated, P values were calculated by the chi-square test.

†Calculated with Fisher's exact test.

‡AST denotes serum aspartate aminotransferase, and ALT serum alanine aminotransferase.

treatment (P = 0.01), metastasis-free intervals of less than one year from diagnosis (P = 0.01), weight loss of at least 10 percent before treatment (P = 0.004), and doses of interleukin-2 below the median dose received by all the patients given interleukin-2 (P = 0.03).

Response to Treatment

Patients who had received at least five days of treatment with interleukin-2 or four weeks with interferon alfa-2a were assessed to determine whether their disease had responded to treatment. Among the 425 patients randomly assigned to treatment, 44 could not be evaluated for a response by the review committee. Eleven of these patients received no cytokine treatment, the treatment of 10 was interrupted soon after it began because of severe toxic reactions, 13 died before their tumors had been evaluated, 6 had not been evaluated within two

TABLE 3. RATES OF TUMOR RESPONSE AT WEEK 10 AND WEEK 25.

OUTCOME	GROUP 1 (N=138)	GROUP 2 (N=147)	GROUP 3 (N=140)	TOTAL (N=425)
Week 10				
Complete response	2	0	1	3
Partial response	7	11	25	43
Disease stabilization	30	46	31	107
Disease progression	78	87	63	228
Not evaluated	21	3	20	44
Week 25*				
Complete response	1	2	5	8
Partial response	3	7	14	24
Disease stabilization	9	19	3	31
Disease progression	94	114	86	294
Not evaluated	31	5	32	68

*A total of 135 patients received maintenance therapy: 29 in group 1, 59 in group 2, and 47 in group 3.

months after the planned date, and 4 were excluded because of methodologic problems.

In the intention-to-treat analysis, the proportions of patients with a response at week 10 were as follows: 9 of 138 (6.5 percent) in group 1, 11 of 147 (7.5 percent) in group 2, and 26 of 140 (18.6 percent) in group 3 (Table 3). If only the patients who could be evaluated were included in the analysis, the response rates were 7.7 percent, 7.8 percent, and 21.3 percent for groups 1, 2, and 3, respectively.

In both analyses, the response rates were significantly higher (P < 0.01) in the group that received both treatments than in either of the groups that received only one treatment. At week 25, after the completion of maintenance treatment, the response rates were 2.9 percent, 6.1 percent, and 13.6 percent in groups 1, 2, and 3, respectively (Table 3). The response rates remained significantly higher (P = 0.001) in the group receiving the combined treatment. The response rates among the 113 patients who were changed to a different cytokine treatment after their cancer failed to respond to the randomly assigned treatment were in the same ranges as those in the analysis according to the initial treatments (data not shown).

Survival

The median follow-up period for the cohort was 39 months. The event-free survival rates at one year were 15 percent, 12 percent, and 20 percent in groups 1, 2, and 3, respectively (Fig. 1), and were significantly higher in the group receiving the combined cytokine treatment than in the other two groups (P = 0.01). However, the overall survival rates in the three groups were not significantly dif-

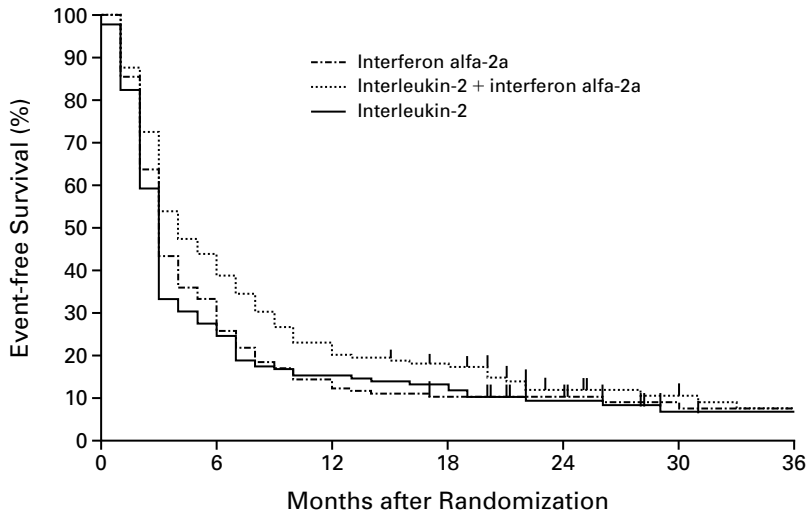


Figure 1. Kaplan–Meier Curves for Event-free Survival among Patients in the Three Treatment Groups. The tick marks represent censored data on patients who were alive without progression of disease. The results shown are from an intention-to-treat analysis. $P=0.01$ for the comparison among the groups.

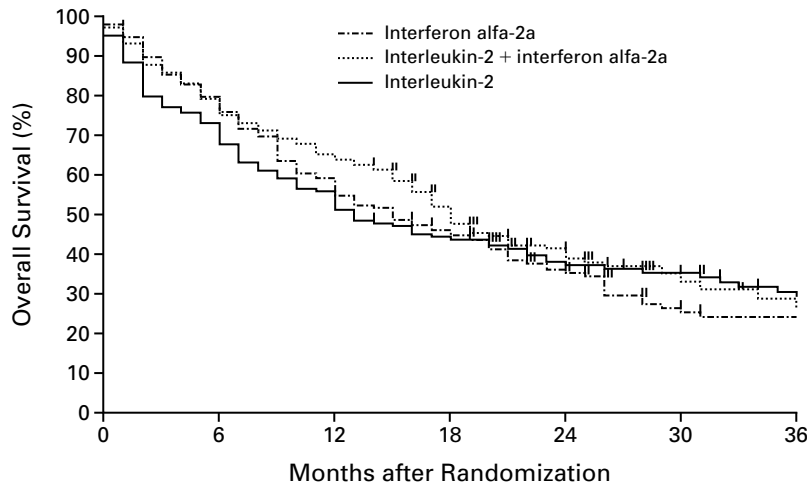


Figure 2. Kaplan–Meier Curves for Overall Survival among Patients in the Three Treatment Groups. The tick marks represent censored data on patients who were alive or lost to follow-up. The results shown are from an intention-to-treat analysis. $P=0.55$ for the comparison among the groups.

ferent from one another ($P=0.55$ by the log-rank test), and the median survival times were 12, 13, and 17 months, respectively (Fig. 2).

Factors Predicting Response

Two statistically independent factors had predictive value for a response to treatment: the number of organs with metastasis (one vs. two or more, $P<0.001$) and the treatment group (1 or 2 vs. 3,

$P<0.001$) (Table 4). Patients with only one metastatic site who received both cytokines had a 37 percent probability of a response, whereas those with multiple metastatic sites had a 23 percent probability of a response.

Factors Predicting Rapid Progression

Multivariate analysis identified five independent predictors of rapid progression (i.e., progression

TABLE 4. MULTIVARIATE ANALYSIS OF FACTORS PREDICTING RESPONSE AND RAPID PROGRESSION.

FACTOR	LOGISTIC RELATIVE RISK (95% CI)*
Factors predicting response†	
Treatment group	3.5 (1.9–6.5)
No. of metastatic sites	3.0 (1.5–5.6)
Factors predicting rapid progression‡	
No. of metastatic sites	2.8 (1.7–4.8)
Metastasis-free interval ≤1 yr	2.5 (2.1–3.9)
Liver involvement	2.1 (1.2–5.0)
Treatment group	1.8 (1.1–2.8)
Mediastinal lymph-node involvement	1.7 (1.0–2.7)

*The odds ratio provided from the logistic model is defined as the exponential value of the β coefficient. CI denotes confidence interval.

†The following factors, which were significantly associated with response according to the univariate analysis, were included in the model: treatment group (1 or 2 vs. 3); number of metastatic sites (1 vs. ≥2); ECOG performance status (0 vs. 1 or 2); bone involvement (yes vs. no); lung involvement (yes vs. no); liver involvement (yes vs. no); and involvement of other sites (yes vs. no).

‡The following factors, which were significantly associated with rapid progression according to the univariate analysis, were included in the model: treatment group (1 or 2 vs. 3); number of metastatic sites (1 vs. ≥2); ECOG performance status (0 vs. 1 or 2); bone involvement (yes vs. no); lung involvement (yes vs. no); liver involvement (yes vs. no); mediastinal lymph-node involvement (yes vs. no); metastasis-free interval ≤1 year (yes vs. no); and weight loss ≥10 percent (yes vs. no).

within 10 weeks): number of metastatic sites (two or more vs. one), treatment group (1 or 2 vs. 3), the time from the diagnosis of primary tumor to metastasis (1 year or less vs. more than 1 year), presence of liver metastases, and presence of mediastinal lymph-node metastases (Table 4).

Patients who had more than one organ with metastasis, metastasis to the liver, and metastasis less than one year after the diagnosis of primary tumor had a probability of rapid progression of at least 70 percent, even if they received both cytokines. This group represented 20 percent of the patients enrolled in the study. In this subpopulation, the response rate with the combination of cytokines was 14 percent, and median survival was six months.

DISCUSSION

There is no standard treatment for metastatic renal-cell carcinoma,^{4,22} but many patients with this condition receive interleukin-2 or interferon alfa outside the setting of a therapeutic trial. These cytokines are the only drugs that have been shown to induce tumor regression in some patients.⁴ There are, however, no data to indicate which patients are most likely to benefit from such treatment and which cytokine regimen is the most active.

Our results confirm that clinically relevant tumor regression occurs in a minority of cytokine-treated patients. Moreover, monotherapy with interferon alfa-2a or interleukin-2 gave very low response rates (7.5 percent and 6.5 percent, respectively, at 10 weeks). The group treated with both cytokines had a response rate of 18.6 percent and significantly longer event-free survival. However, since there was no significant difference in overall survival among the three groups, we cannot conclude that the combined treatment provided a significant advantage.

In our study, the toxicity of the regimens containing interleukin-2 was, as expected, dramatically higher than the toxicity of interferon alfa-2a alone. Indeed, the severity of the toxic reactions to interleukin-2 limits the use of regimens based on this cytokine. In patients who died from non-disease-related causes, we observed a correlation with unfavorable prognostic factors related to the disease. Reducing the toxicity of regimens containing interleukin-2 is therefore a high priority for future studies. Selecting patients with metastatic renal-cell carcinoma who are most likely to respond to cytokine treatment could be one means of achieving this goal. Previous retrospective studies identified performance status, disease-free interval, presence or absence of liver involvement, and number of metastatic sites as predictors of overall survival.^{1,5,6,23}

We found that the factors that predicted a response (metastasis to only one organ and combined treatment) could not be used to select patients effectively. Indeed, patients with several metastatic sites had a 23 percent probability of response with the combined treatment. For this reason, we have identified prognostic factors for rapid progression under treatment, which can be used to select patients with little chance of a response. Patients with more than one metastatic site, liver involvement, and an interval from diagnosis of the primary tumor to the appearance of metastatic disease of less than one year have a 70 percent or higher probability of rapid progression and poor survival (median survival, six months).

In conclusion, significantly higher rates of response and event-free survival were seen with the combined cytokine therapy, but none of the three regimens we tested had any advantage in terms of overall survival. The toxic effects frequently observed with combined therapy emphasize the need for careful selection of patients. It is usually recommended that cytokine treatment be restricted to patients who are ambulatory and have no major organ failure.⁴ Our study identifies a subgroup of patients who have virtually no chance of benefiting from treatment.

Supported by grants from the Association pour la Recherche contre le Cancer.

APPENDIX

In addition to the authors, the following investigators and centers from the Groupe Français d'Immunothérapie (which is part of the Fédération Nationale des Centres de Lutte contre le Cancer) participated in this study: B. Coronel (Hôpital E. Herriot, Lyons); J.-F. Rossi (Centre Hospitalier Universitaire, Montpellier); M. Fabbro (Centre P. Lamarque, Montpellier); J.-P. Bergerat (Centre Hospitalier Universitaire, Strasbourg); A. Caty (Centre O. Lambret, Lille); D. Baume (Institut P. Calmettes, Marseilles); J. Fleury (Centre J. Perrin, Clermont-Ferrand); J.-M. Ferrero, A. Thyss (Centre A. Lacassagne, Nice); R. Delva (Centre P. Papin, Angers); N. Tubiana-Mathieu (Hôpital de la Timone, Marseilles); P. Fargeot (Centre G.F. Leclerc, Dijon); T. Lesimple (Centre E. Marquis, Rennes); T. Dorval (Institut Curie, Paris); M.-B. Orgerie (Hôpital Minjoz, Besançon); T. Conroy (Centre A. Vautrin, Nancy); A. Goupil (Centre R. Huguenin, Saint-Cloud); E. Khenifar (Hôpital Saint-Jacques, Besançon); B. Audhuy (Centre Hospitalier, Colmar); J.-C. Eymard (Institut J. Godinot, Reims); *Tumor Response Evaluation Committee*: L. Ollivier (Institut Curie, Paris); D. Di Stefano-Louineau (Institut P. Calmette, Marseilles); P. Thiesse (Centre L. Bérard, Lyons); *Toxicity Review Committee*: T. Vial (Hôpital E. Herriot, Lyons); G. Nitenberg (Institut G. Roussy, Villejuif); S. Robard (Centre R. Gauducheau, Nantes); *Data Monitoring and Statistical Center*: K. Pignard, M. Drevon, F. Chauvin (Centre L. Bérard, Lyons); N. Rodrigo, J. Maupas (APRET, Lyons); *Methods Review Committee*: H. Sancho-Garnier (Centre Val d'Aurelle, Montpellier); J.-P. Boissel (Hôpital Cardiologique, Lyons) — all in France; M. Buyse (International Institute for Drug Development, Brussels, Belgium).

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