Recombinant Interferon Alfa-2a With or Without Vinblastine in Metastatic Renal Cell Carcinoma

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Twenty patients with measurable metastatic renal cell carcinoma (RCC) were treated with interferon alfa-2a (Roferon®-A), 36 × 10^6 U intramuscularly 3 times weekly, alone (2 patients) or in combination with vinblastine, 0.10–0.15 mg/kg intravenously every 2 to 3 weeks. Objective responses in the lung, bone, liver, and lymph node metastases were seen in 6 of 18 evaluable patients. Dose reduction of interferon alfa-2a was necessary in 19 of the 20 patients due to intolerable flu-like side effects and fatigue. Bone marrow suppression and increase of γ-GT represented the most often observed objective toxicity. The preliminary results of this combination treatment in RCC are promising and warrant randomized studies exploring the role of vinblastine. The dose of interferon alfa-2a should be reduced by 50% to avoid excessive toxicity and to maximize patient compliance.

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METASTATIC RENAL CELL CARCINOMA (RCC) is a malignancy that is resistant to known cytostatic agents.[1,2] One of the best of the minimally active drugs seems to be vinblastine (VB), for which response rates of 10% to 25% have been reported.[2] It is understandable that new anticancer drugs and immunologically active agents are tested in RCC, since there is some indication that immune mechanisms may be important in such patients.[3] Interferon has shown promising results in preliminary studies.[4–9] A pilot Phase II study was therefore started to evaluate the effectiveness of this drug in metastatic RCC. After treating two patients with interferon alfa-2a (Roferon®-A, F. Hoffmann-La Roche & Co. Ltd.) alone, it was decided to add VB to the treatment, as this cytostatic agent has shown a synergistic or at least additive effect with interferon in *in vitro* studies.[10]

The current analysis was undertaken to evaluate the response rate and toxicity of interferon alfa-2a with and without VB in the treatment of metastatic RCC.

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Patients and Methods

From May 1983 to November 1984, 20 patients with metastatic RCC were included in a Phase II study assessing the therapeutic effect and toxicity of interferon alfa-2a alone or in combination with VB.

All 20 patients had measurable disease, lung metastases being the most frequent indicator lesions. All patients had given their informed consent. Further details for evaluable patients are shown in Table 1.

The following treatment schedule was used: interferon alfa-2a, 36 × 10^6 U intramuscularly (IM), 3 times weekly, and VB 0.10–0.15 mg/kg intravenously (IV), every 2 to 3 weeks. The first two patients received interferon alone. In case of intolerable subjective toxicity, predominantly fatigue and weakness, the interferon dose was reduced stepwise by 25% or temporarily discontinued (for up to 2 weeks or until recovery). VB was given only if the leukocyte count was above 3000/μl and the thrombocyte count was above 100,000/μl. In case of repeated and long-lasting myelosuppression, VB was discontinued permanently. The initial dose of VB (0.1 mg/kg) was increased if no hematologic toxicity was observed after the first three applications.

In patients with no change of disease status, treatment was continued for 6 months, as long as no intolerable toxicity occurred. Interferon/VB was discontinued in any case of progressive disease. Treatment was given mainly on an outpatient basis.

Patients were evaluated for response after at least 4 weeks of treatment. Response and response duration were

evaluated at 4-week intervals according to the World Health Organization (WHO) definitions.[11]

Blood chemistry studies and urinalyses were performed before treatment, biweekly during the first 4 weeks, and monthly thereafter. Clinical examination and neurophysiologic examination, by electromyography and electroneurography (11 patients), were done before treatment and every 4 weeks thereafter. Hematologic toxicity was graded according to WHO recommendations.[11] Serum samples were tested for antibodies to interferon before treatment and every 4 weeks thereafter. Samples were kept in a freezer (−20°C) for up to 3 months before analysis.

Results

Of the 20 patients, 18 were evaluable for response. Treatment was discontinued prematurely in 2 patients due to severe side effects in one and difficulties with follow-up in the other.

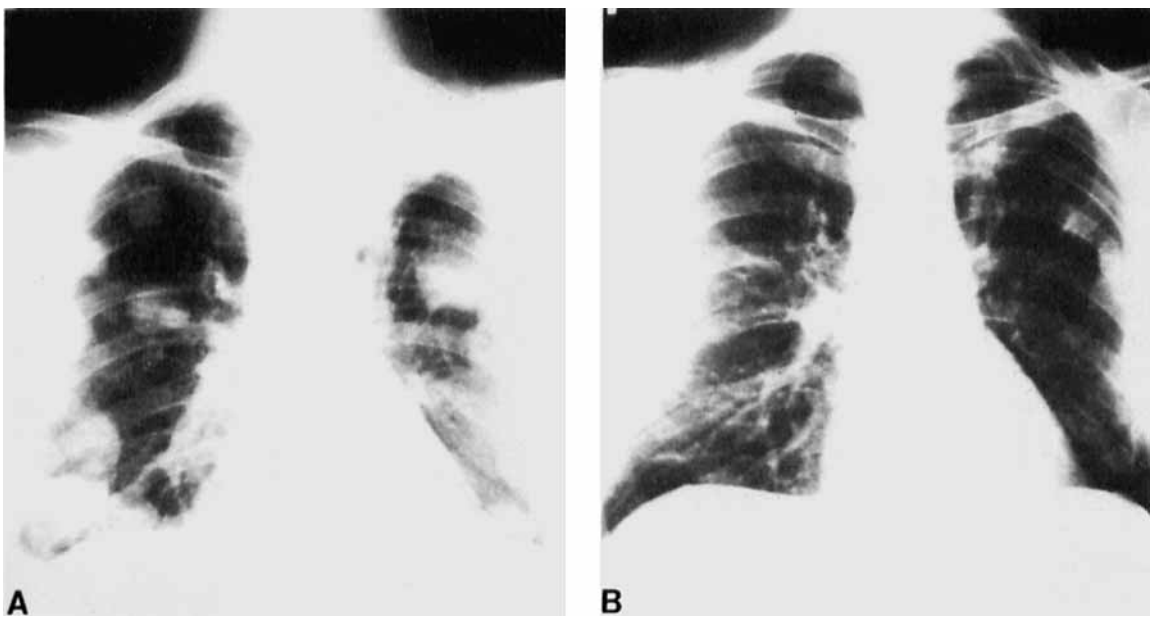
One of the two patients receiving interferon alfa-2a alone achieved complete remission of lung metastases together with an objectively evaluable response (sclerosis) in an osteolytic metastasis of the third left rib (Figs. 1A and 1B and 2A and 2B). The complete remission of lung metastases was observed 9 months after start of treatment and lasted 4 weeks. The lung metastases, along with increasing osteolysis of the third left rib, reappeared after dose reduction and subsequent discontinuation of interferon due to intolerable subjective toxicity. Interferon treatment was restarted 6 months after discontinuation, and a new partial response was obtained.

TABLE 1. Patient Characteristics

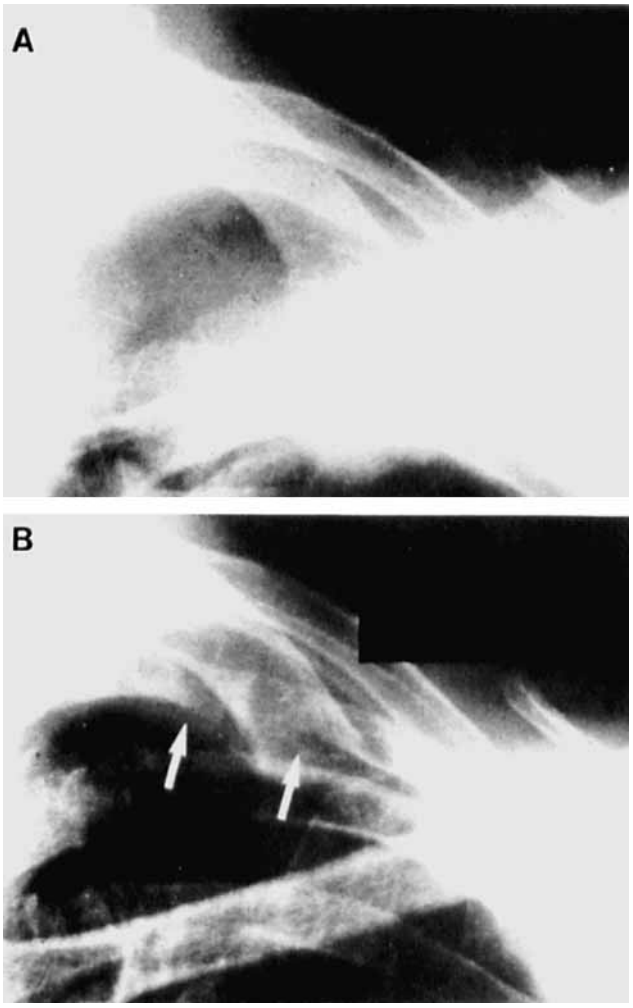
	Responders (6)	Non-responders (12)	Total evaluable (18)
Females/males	1/5	3/9	4/14
Age, mean (range)	53 (43–68)	55 (39–65)	54 (39–68)
Nephrectomy	5	12	17
Diagnosis to trial entry, median (range) in months	5 (1–48)	25 (1–238)	18 (1–238)
Previous chemotherapy	1	3	4
>2 metastatic sites	3	5	8
Indicator lesions			
Lung metastases	3	9	12
Liver metastases	1	—	1
Bone metastases with palpable soft tissue tumor	1	—	1
Soft tissue tumors	—	1	1
Lymph node metastases	1	2	3
Performance status (WHO)			
0	—	3	3
1	5	7	12
2	—	2	2
3	1	—	1

WHO: World Health Organization.

Of the 16 evaluable patients on the interferon alfa-2a/VB combination, 5 achieved partial responses: in lung metastases, 2; retroperitoneal lymph node metastases, 1;



FIGS. 1A AND 1B. (A) Multiple bilateral lung metastases from renal cell carcinoma before start of interferon treatment. (B) Complete response of lung metastases 9 months after start of interferon treatment.



FIGS. 2A AND 2B. Same patient as in Figure 1. Close-up views of upper costae on the left side. (A) Osteolytic defect of the posterior part of the third left rib. (B) Sclerosis and repair of rib lesion (arrows) 9 months after start of interferon treatment.

liver metastases, 1; and bone metastases with surrounding palpable soft tissue tumor, 1 (Figs. 3A and 3B).

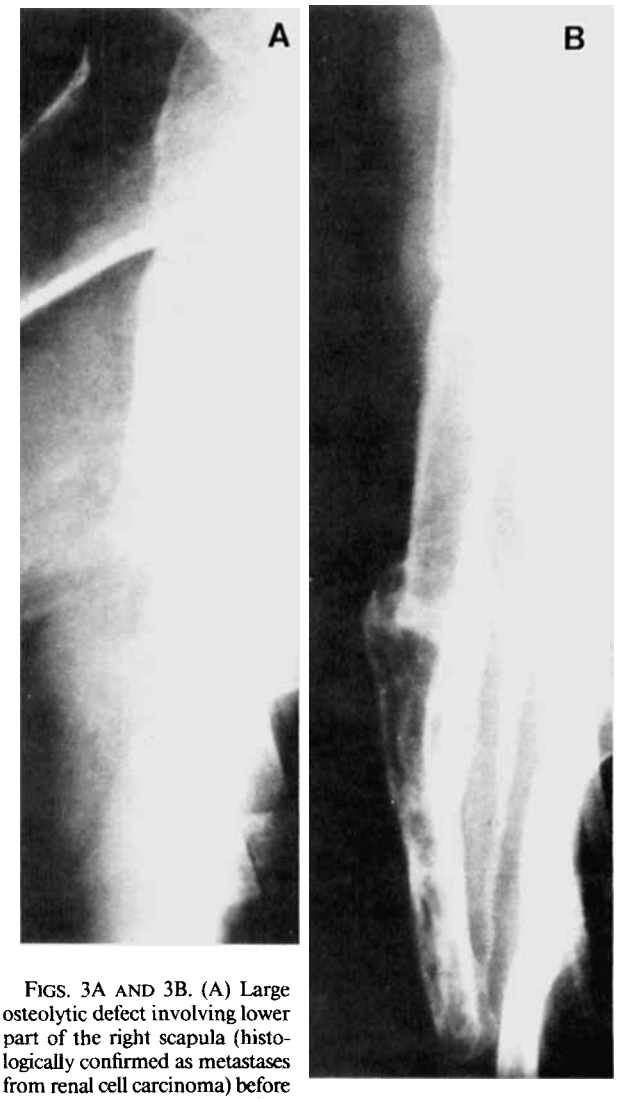
Mixed responses were seen in two additional patients who had metastases in both lungs. In one patient, three metastases showed a reduction in size of more than 50%, but one small lesion slowly increased in size, negating an overall partial response. In the second patient with mixed response, three marker lesions completely disappeared, but again one small lesion slowly enlarged, negating a partial response.

Six patients had no change after a median treatment period of 3.5 months (range, 1–6.5 months). Three patients showed progressive disease. Table 1 compares the distribution of parameters that are generally supposed to be predictive for response in RCC.

On average, 81 days elapsed before a partial response was observed. The mean duration of these partial responses was 222 days (range, 94–353 days).

Toxicity (Table 2)

All patients experienced flu-like symptoms, such as fever or myalgia, and some degree of fatigue or weakness during treatment, especially during the initial period; treatment seemed to be better tolerated after 4 to 8 weeks of therapy. Decreased appetite and weight loss of about 10% were observed often. These constitutional side effects were the main reasons for final discontinuation of interferon in three patients. Gamma-glutamyl transpeptidase (γ-GT) rose above the normal range in 19 patients, but normalized after treatment was discontinued. Reversible elevations in serum glutamic oxaloacetic transaminase (SGOT) and in serum glutamic pyruvic transaminase (SGPT) were observed in 13 patients during treatment. Dry skin and/or dryness of eye, mouth, and throat mucosa occurred in three patients. One patient with large liver metastases developed pancreatitis during treatment; in-



FIGS. 3A AND 3B. (A) Large osteolytic defect involving lower part of the right scapula (histologically confirmed as metastases from renal cell carcinoma) before start of treatment. (B) Sclerosis of the osteolytic lesion 12 months after start of treatment with interferon and vinblastine.

terferon/VB was discontinued, and the pancreatitis was effectively treated by conservative means.

Of the 11 patients evaluable for neurotoxicity, 7 developed a mild, clinical polyneuropathy, 2 with painful paresthesias. The clinical and neurophysiologic findings indicated a VB-induced neuropathy, which may have had an additional component of nutritional neuropathy due to marked weight loss in most of the patients. It was not shown that interferon alone caused polyneuropathy.

Intermittent myalgia, partially exercise-related, and increased muscular fatigue were found in eight patients, with polyphasic muscle potentials on electromyography, suggesting a mild myopathy that did not progress after the first 2 to 3 months. Signs of toxicity of the central nervous system were not observed.

Leukopenia was seen frequently: grade 1–2 in 12 of the 20 patients, but grade 3–4 in only 2 of 20 patients. Thrombocytopenia occurred in 4 of 20 patients (grade 1–2, 3 patients; grade 3–4, 1 patient).

Early discontinuation of VB (before a third injection) was necessary in two patients, due to thrombocytopenia in one and to atopic eczema possibly caused by VB in the other. During long-term treatment, the intervals between VB injections had to be increased repeatedly, to more than 3 weeks, in three patients due to long-lasting leukopenia (leukocyte count $< 3000/\mu l$). In four patients, VB finally was discontinued after 4 to 6 months' combination treatment due to long-lasting leukopenia.

In 19 of the 20 patients, the interferon dose had to be reduced due to constitutional side effects. Intolerable flu-like symptoms and fatigue were the main reasons for its discontinuation in three patients with stable disease. Twelve patients could be treated with the full dose of interferon alfa-2a (36×10^6 U, 3 times weekly) for at least 2 months, but in 6 of these the dose had to be reduced later on. Two other patients received doses between 18 to 36×10^6 U, 3 times weekly for more than 2 months, whereas no maintenance dose could be established in 6 patients.

For responders and nonresponders, the accumulated doses of interferon and VB were similar after 4 weeks. Later, the nonresponders tended to have lower *total* accumulated doses of both drugs, mainly due to a shorter treatment period (Table 3). Antibodies to interferon were not found in any of the patients' serum samples.

TABLE 2. Toxicity

Toxicity	Number of patients (20)
Constitutional symptoms (fever, fatigue, weight loss)	
Mild	7
Moderate	8
Severe	5
Pathologic liver function tests	
Elevated γ-GT	19
Elevated SGOT/SGPT	13
Leukopenia	
Grade 1–2	12
Grade 3–4	2
Thrombocytopenia	
Grade 1–2	3
Grade 3–4	1
Dryness of mucosa/skin (with eczema)	3
Neurologic symptoms	
Grade 1	7
Alopecia	
Grade 1–2	4

γGT: γ-glutamyl transpeptidase; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

Discussion

During recent years, interferons have shown activity in metastatic RCC, whether natural leukocyte, fibroblast, or recombinant interferons were used.[4–9,12] Response rates of 10% to 25% have been observed. The exact therapeutic mode of action of interferon in RCC is unknown, but direct cytostatic activity is likely, in addition to immune mechanisms.[13,14]

On the other hand, during the years 1972 through 1982, 350 patients with metastatic RCC have been treated at The Norwegian Radium Hospital with various cytostatic and hormonal drugs without any objective response. Only three spontaneous remissions were observed.[15] With this background of negative experience in metastatic RCC, it was gratifying to observe objective responses with interferon treatment, with and without VB in 6 of 18 evaluable patients. The same response criteria as previously used and similar methods of examination (clinical, chest x-ray, ultrasound, computed tomography [CT]) were applied; however, radiologic identification and measurement of the same lesion at subsequent examinations were difficult in some cases. To avoid any unjustified overenthusiasm, we preferred to underestimate rather than to overestimate the quality and quantity of responses observed in the indicator metastases.

One may question the clinical relevance of the responses seen in the selected indicator lesions, since these were chosen solely on the basis of their suitability for reproducible measurements.[16] This question is of special interest if the given treatment is, as in the current study, rather toxic. Admittedly, in the current study the mea-

TABLE 3. Accumulated Doses of Interferon and Vinblastine in Patients with Metastatic Renal Cell Carcinoma

	Responders (6)		Nonresponders (12)	
Time	Median	Range	Median	Range
Interferon ($\times 10^6$ U)				
4 weeks	468	216–520	423	216–480
12 weeks	1332	1116–1480	873	216–1332
Total	2790	1791–3908	1134	216–4264
Vinblastine (mg)				
12 weeks	32	0–56	28	0–67
Total	32	0–70	28	0–155

surable disease marker lesions were sometimes much smaller than the patient's nonmeasurable disease elsewhere (bone metastases, retroperitoneal tumor lesions, diffuse liver metastases). This is probably one reason why the observed responses in marker lesions do not always reflect clinical benefit or prolonged survival. Nevertheless, in two patients in the current study, the general condition improved significantly during treatment, together with a marked relief of pain. Furthermore, the primary aim of a Phase II study, as this was, is to evaluate a drug's cytotoxic activity *per se,* independent of its clinical usefulness expressed as survival benefit. In this respect, the current Phase II study clearly indicates that interferon alone or in combination with VB yields a therapeutic effect in metastatic RCC.

Since all previous studies gave disappointing results in the treatment of metastatic RCC, the observed responses during interferon treatment with or without VB were impressive, with 6 of 18 evaluable cases showing objective responses. The above-mentioned difficulties concerning the assessment of response in the selected indicator metastases should not, however, be overlooked; the results should be confirmed in a larger series of patients.

There are several reasons that may help to explain the high number of responses seen in the current study:

1. The relatively high dose of interferon and/or its combination with VB. A dose–response relationship for interferon in metastatic RCC has not yet been established definitively, although some studies make such a correlation probable.[5,17] The current study provides no evidence that responders received larger single doses or larger total accumulated doses of interferon and VB per time unit than nonresponders.

2. VB may have a synergistic or at least an additive effect with interferon.[10] Thus far, no published clinical study using interferon and VB has demonstrated an increased therapeutic effect. One study,[18] using interferon and VB, reported a 13% response rate, the same as with interferon alone. The dose of interferon used, however, was rather low (3×10^6 U per day). The current study is a further attempt to assess this combination, but with high doses of interferon and intermittent VB. The role of VB in this trial remains unclear: in three responders, VB was given for a short time only, or not at all in one patient. Only a randomized study can demonstrate whether VB really adds anything to the treatment of RCC with relatively high doses of interferon.

3. In the current study, most of the patients were in a favorable performance status (WHO grade 0 or 1), while patients whose general condition was bad were ineligible for the trial. This intended selection of presumably good-risk patients may have influenced the overall results significantly.

4. Theoretically, different interferon preparations may have different antitumor effects, thus explaining the varying response rates reported for interferon in RCC from different centers.

The high frequency of intolerable, predominantly subjective, toxicity suggests that lower doses of interferon should be used in future studies to maximize patient compliance. The majority of patients will probably tolerate single doses of about 18×10^6 U 3 times weekly, which is associated with an acceptable level of objective and subjective toxicity.

In conclusion, high doses of interferon alfa-2a, with and without low intermittent doses of VB, are active in metastatic RCC. Very high doses of interferon are associated with unacceptable toxicity. Future studies will be necessary to clarify the role of VB in association with interferon and to establish tolerable as well as effective dose schedules for this combination.

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