Our experience with interferon alpha: renal cell carcinoma

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Our 3-year clinical experience using recombinant interferon (rIFN) α-C in patients with metastatic renal cell carcinoma (RCC) is summarized. This type of IFN is a new subspecies of the IFN-α protein family. Its specific activity is 1–2 × 10^9 U/mg protein, the highest among IFN-α species presently available. Pharmacokinetic study indicated good bioavailability of the preparation from the intramuscular injection. A phase II study was performed to assess the response rate related to rIFN-αC at a low dosage. A dose of 3 × 10^6 U daily was administered, followed by 3 × 10^6 U/m^2 every other day to avoid severe toxicity. Among 33 treated patients, a partial remission rate of 9.7% and stable disease rate of 25.8% were achieved. Side effects were usually mild and the treatment was well tolerated by the patients. However, mental deterioration and behavioral changes were observed in five patients with RCC treated by rIFN-αC and were related to neurotoxicity of IFN. The role of vinblastine in addition to IFN in the treatment of RCC was assessed in nine patients who had failed on IFN alone. No response was observed. It appeared that vinblastine had little if any effect in being added to IFN as second-line therapy. We conclude that rIFN-αC has moderate activity in the treatment of RCC. Familiarity with the possible toxicity of this agent will lead to more careful management of patients.

Keywords: Recombinant interferon-αC; renal cell carcinoma; pharmacokinetics; neurotoxicity; behavioral change; dementia; vinblastine.

Introduction

Interferons (IFNs) slow the proliferation of cells by prolonging the phases of the mitotic cycle. Still greater effects occur in cells that are not actively proliferating, but are rather in the G0–G1 resting phase of the mitotic cycle. The anti-proliferative effect is dose dependent and persists only during active treatment.[1] Cytotoxic functions of T cells, natural killer (NK) cells, killer (K) cells, and macrophages have been enhanced in patients treated with IFN. Chronic or continued administration induces suppression of NK cytotoxicity within several days. IFN also has a positive effect on cell differentiation and on the expression of oncogene activity.[1] The antiproliferative effect is achieved by interference with intracellular functions, such as synthesis of proteins and enzymes.[2] IFN activates protein kinases responsible for the phosphorylation of the ribosomal proteins and consequently inhibits protein synthesis.[2]

INF-α was first given to patients with renal cell carcinoma (RCC) by Quesada *et al.* in 1983.[3] Since then, numerous treatment protocols have been used.[4–14] Recombinant IFN-α (rIFN-α) is most frequently administered, in doses of 3–18 million U/m^2, given three to five times weekly. The reported response rates are 5–20%.[15] To achieve a higher response rate but reduced toxicity, new derivatives of IFN-α were produced, one being rIFN-αC, a new subspecies of the IFN-α protein family. Our 3-year clinical experience using rIFN-αC in patients with metastatic RCC is summarized.

rIFN-αC

rIFN-αC (Interpharm Ltd., Ness-Ziona, Israel) is produced by *Escherichia coli* strain JM101. This strain contains TL-αC plasmid derived directly from a genome of one human subject containing the IFN-αC gene. Recombinant IFN-αC, which differs from IFN-αA by 20% of its sequence of amino acids,[14] is characterized by a three- to fivefold higher titer of antiviral units per milligram protein than IFN-αA. Its specific activity is 1–2 × 10^9 U mg protein, the highest among IFN-α species presently available; therefore, less protein must be injected to attain the same biological effect. The rIFN-αC is highly purified and bacteria derived, the final product being free of nucleic acids, endotoxin, or other bacterial contaminants.[16,17]

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Pharmacokinetics of IFN-αC

The pharmacokinetics of rIFN-αC were studied in 11 patients with metastatic RCC.[18] A total of 10 million U was injected intramuscularly, as recommended in the literature, to achieve a higher response rate of metastatic RCC to IFN therapy.[19] The serum level of IFN was evaluated up to 72 hours postadministration. Measurable IFN concentrations appeared in the serum as early as 30 minutes after injection, and peak levels were obtained at 4–6 hours (maximum concentration = 53.2 ± 4.6 U/ml). Relatively high levels persisted for 24 hours and decreased thereafter with an apparent half-life of 3–4 hours. The mean area under the serum concentration curve (AUC) was 1,259 ± 145 U h ml^{-1}, indicating good bioavailability of the preparation from the intramuscular injection. The pharmacokinetic behavior of rIFN-αC is remarkably similar to that of rIFN-αA, as reported in the literature. The data in the present study were derived from cancer patients, some of whose liver and kidney function test results were outside the normal range. However, it has been shown that neither advanced cancer nor chronic renal failure has any influence on the pharmacokinetic behavior of rIFN-αA.[20,21] The same observation was made in our study. The pharmacokinetics of rIFN-αC in patients with mildly impaired renal function showed no significant difference from those with preserved kidney function. It is also reported in the literature that catabolism of rIFN-αA in contrast to IFN-β species is unrelated to liver function.[22]

Clinical use of IFN-αC

We performed a phase II study to assess the response rate related to rIFN-αC at a low dosage in 33 patients with measurable metastatic RCC.[23] The dosage was 3 × 10^6 U daily, followed by 3 × 10^6 U/m^2 every other day to avoid severe toxicity; we achieved a partial remission (PR) rate of 9.7% and stable disease (SD) rate of 25.8%. All patients showed progression of disease (PD) in the 2 months before initiation of therapy.

Different regimes and response rates are reported in the literature. Krown[24] summarized 14 studies of IFN treatment in patients with RCC and found an overall major response rate of 16.6% (range 5–31%). Intermediate doses of IFN were more likely to induce response than very low or very high doses.[4,24] Response rates of 15–26% were achieved by the administration of intermediate dosages (2–20 million U/day) of various types of IFN.[3,5,9] Treatment with high dosages of IFNs (20–36 million U/day or three times per week) yielded response rates of 23–27% for a median duration of 8 months.[7,10]

Data in the literature suggest response occurring more frequently in males with maximal performance status or who had undergone nephrectomy and received minimal systemic therapy, and in whom the disease-free interval (DFI) was long and metastatic disease was confined to the lungs, pleura, or mediastinum.[3,4,6] Umeda and Niijima[11] claimed that in their series of 226 patients there were no statistically significant differences in age, sex, and performance status between responders and nonresponders. Factors predicting poor response were unresected primary lesions and prior treatment of any kind (chemotherapy, hormonotherapy, or palliative radiotherapy).

In our series, we found a tendency toward better response in the following groups of patients. Stabilization was considered as a response in all the cases where progression was the rule before introduction of IFN:

1. Older patients: the mean age of responders was 64.0 years versus 59.0 years for progressors. This age difference was not statistically significant.
2. Patients who had had a previous nephrectomy, with or without adjuvant irradiation, responded better than patients in the other subgroups ($P < 0.05$).
3. Patients treated with nephrectomy, and then by chemotherapy or hormonotherapy, for recurrent or metastatic disease had a lower response rate to rIFN-αC ($P < 0.05$).
4. The response of the bone lesion was surprisingly higher (8.3% PR, 25% SD) compared with that published in the literature.[6,8,14,25]
5. Patients with short DFI, and those with shorter delay between the appearance of the presenting symptoms to IFN administration, appeared to respond better than others. These differences in response were statistically significant ($P < 0.05$). Some authors[3,6,13] reported that a longer interval from diagnosis to treatment may encourage response, whereas others concluded just the opposite.[5]

In our series, median survival was significantly longer for responders than for patients with SD or PD ($P < 0.05$). The survival gain was longer than the median time to progression. This finding raises the question of whether the course of the disease was more indolent in the responders from the start, or whether it was the result of the IFN therapy.

Two patients with RCC arising in a congenital solitary kidney were in a poor medical condition and failed to respond to IFN.[26]

Toxicity of IFN-αC

Side effects were usually mild and the treatment was well tolerated by the patients. This was probably because the IFN we used was highly purified; the low dosage was not the only reason for the low incidence of side effects.[5] There was no correlation between the severity of side effects and the responses, nor between leukopenia and response, as claimed in the literature.[11] Acute side effects (flulike symptoms, fever, chills, etc.) were controlled by paracetamol. No corticosteroids were administered to patients on the protocol, although, as Fossa claimed, combined treatment

of IFN with prednisone does not affect results, but reduces toxicity.[14]

IFN was discontinued in one patient for 7 months because of concomitant acute coronary insufficiency appearing without any previously known ischemic heart disease. No cardiac manifestations occurred on reintroduction of IFN for another 8 months, until the disease progressed, and the treatment was stopped.

Congestive heart failure and lethal pulmonary edema, without any former known heart disease, were noted in a female patient 3 weeks after starting IFN therapy. In this case, the relation between IFN treatment and the cardiac event is, of course, uncertain. Cardiac toxicity has been reported in the literature as sporadic cases of changes in blood pressure, arrhythmias, or myocardial infarction.[27,28]

A 75-year-old man developed a neurologic syndrome of dementia, ataxia, confusional state, and cortical blindness, and died 8 weeks after the appearance of this syndrome. A computed tomography (CT) scan demonstrated no metastases, but did show hypodense areas in the white matter. There were no pathologic findings in blood and cerebrospinal fluid analysis. Autopsy was not permitted. Our impression was that this syndrome was related to IFN toxicity.[23]

IFN related mental deterioration and behavioral changes

Mental deterioration and behavioral changes were observed in 5 patients with RCC treated by rIFN-αC.[29] Mental deterioration in patients with cancer constitutes a diagnostic challenge because it may be due to different etiologies and has a major impact on further treatment planning. Various etiologies underlie the appearance of dementia and behavioral changes in these patients, such as metabolic derangements, paraneoplastic phenomena, metastatic spread to the brain, and iatrogenic causes, including damage after radiation, chemotherapy, and IFN therapy. The appearance of mental and behavioral changes in our patients was attributed to the IFN treatment rather than to the primary disease. These effects occur in about one third of the IFN-treated patients and are severe in only 7%.[30] The adverse reactions to IFN include somnolence and confusion, fatigue, lethargy, psychiatric symptoms, and anorexia, reducing the patient to a catabolic state. The more severe derangements include conceptual disorganization, neurological deficits, and coma.[31–35] These effects are generally reversible.[30,32,36] The mode of action of IFN on the central nervous system (CNS) is not fully understood, and possible mechanisms include competition on membrane receptors with neurotropic hormones such as thyrotropin and endorphinlike opioid effects.[32,37] The incidence of IFN toxicity on CNS is related to the dose and the age of the patients.[5,30] In our study the more severe symptoms occurred in older patients and within a shorter interval after the introduction of IFN treatment. The median age of our patients was 69 years, which is higher than in the other series.[31,36] The association between the patients' age and the onset of these toxic symptoms has not been addressed in the literature. Similarly, there are no data linking site and type of primary malignant process and IFN toxicity. In our series, IFN was the only treatment given close to the onset of dementia. Because metastatic lesions or vascular changes in the brain were not demonstrated by CT, and paraneoplastic CNS effects of RCC were not described, the association between dementia and IFN treatment is most probable. This association is also supported by the fact that the cessation of the treatment resulted in complete reversal of dementia in two patients. That significantly smaller ventricles were found in the more severely demented patients supports the hypothesis of neurotoxicity of IFN rather than structural changes in the brain. The general deterioration of our patients, as reflected by the change in the performance status (from 90% to 100% and 40% to 70% within 1–6 months), the decrease in serum albumin level (27–39% reduction), and the rate of weight loss (≥10 kg/mo) correlated with the severity of dementia. It could be that the general deterioration reflected the overall toxicity of the IFN. Progression of the disease as an explanation of physical deterioration was less likely. The course of the disease in these patients was not fulminant, and the measurable changes in metastases during the period of treatment were small compared with the striking changes in physical parameters. Behavioral and mental changes in patients treated with IFN are warning signs, and treatment should be withdrawn.

Combination of IFN-α and vinblastine

Treatment of patients with metastatic RCC by IFN-α has yielded a response rate of 5–27%, with median duration of response ranging from 3 to 16 months.[38] Early literature data suggested better results by the combination of IFN-α and vinblastine (VBL) rather than for IFN-α alone. The response rate for the combination was 30–40%, and the median duration of response was 3–18 months.[39–43]

In view of the particular antiproliferative action of IFNs, the combination of IFN with cytotoxic drugs would appear to be logical. Synergy between IFN and adriamycin, cyclophosphamide, cisplatinum, vinca alkaloids, and other drugs has already been demonstrated on tumor cell lines.[44,45] The vinca alkaloids possess cytotoxic activity during the S phase by binding to tubulin, the protein that forms the spindle along which the chromosomes migrate during mitosis, and the microtubular apparatus that plays a role in cellular secretion and neurotransmitter transit. Through their high binding affinity to tubulin, the vinca alkaloids inhibit the assembly of microtubules and lead to the dissolution of the mitotic spindle.[46] The mechanism of the possible synergistic action of IFN and VBL is unknown. The binding of IFN-α to the cell membrane by means of a specific receptor could increase the intra-

cellular penetration of certain cytotoxic drugs.[44] Another possible mechanism may be that IFN causes synchronization of the cell cycle in a greater fraction of tumor cells, rendering them more susceptible to the action of VBL.

The combination of IFN and VBL was used in previously untreated patients with metastatic RCC and reported by several authors.

The first trial in 1984 by Figlin *et al.*[47] achieved an 8% objective response rate, which was no better than IFN alone. Better results were reported by Cetto *et al.*,[42] who achieved partial response in 44% of the patients. Fossa *et al.*[41] reported a 33% PR using VBL and 36 million U of IFN-α2a twice a week. Median time to response was 11 weeks, whereas median duration of response was 5 months. Toxicity was generally severe and dose limiting. Lower doses of IFN yielded a lower response rate, but caused less toxicity.[41,43,48] None of these studies demonstrated any advantage for IFN-VBL over IFN alone.

Bergerat *et al.*[40] claimed that the efficacy of the IFN-α and VBL combination was dependent on the type of IFN used, and above all on the doses administered and compliance to the treatment, which has marked side effects.

rIFN-αA and VBL were given in our department to two patients as first-line therapy for metastatic RCC. No response was observed.

A recently published study in which patients were randomized to treatment by IFN alone versus IFN + VBL combination concluded that the role of VBL in this combination is uncertain and that any reported superiority of IFN + VBL as first-line therapy for metastatic disease remains doubtful when compared with IFN alone.[49]

Proceeding on the assumption that VBL may add to the potency of the IFN when given together, we administered this combination to nine patients who had not responded to IFN alone, or had relapsed while on treatment with IFN alone.[50]

In our study, nine patients who either progressed or relapsed on rIFN-α2c treatment entered this series. All the patients had reached the maximal tolerated dose of IFN and had received therapy for more than 2 months before VBL was added. Fossa *et al.*[41] had demonstrated that a minimum of 2 months of IFN-α therapy were needed to achieve a response to IFN. All the patients had clinical and radiological evidence that the disease was still progressing.

The response rate to IFN-VBL combination in our series was 0%. Only two cases of stable disease for short periods were observed. Both of these two patients had factors that favored response to IFN, such as previous nephrectomy and no prior systemic treatment for metastatic disease.[23] All of our patients had sufficient treatment with IFN-α to have had a beneficial effect from this agent alone. It therefore appears to us that VBL has little, if any, effect in being added to IFN as second-line therapy in the treatment of metastatic RCC. The stable disease seen in two patients may have simply resulted from the continuing treatment with IFN and may have been a manifestation of delayed response effect. The primary enthusiasm for this combination seems to be on the decline.

Conclusions

We may conclude that rIFN-αC has moderate activity in the treatment of RCC. Familiarity with the possible toxicity of this agent will lead to more careful management of the patients. Behavioral and mental changes in patients treated with IFN are warning signs, and treatment should be withdrawn. The role of VBL in potentiation of, or synergy with, IFN, either in previously untreated patients with metastatic RCC, or in the second line, is debatable. Further trials are needed to assess its real efficacy.

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