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Granulocyte-Macrophage Colony-Stimulating Factor and Interferon-Alpha 2B in Patients with Advanced Renal Cell Carcinoma

Key Words
Granulocyte-macrophage colony-stimulating factor
Interferon-α2B
Renal cell carcinoma

Abstract

Objective: Biological response modifiers such as interferon-α2B (IFN-α2B) have well-known clinical activities against renal cell carcinoma (RCC). Recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) has antitumorigenic effects both in vitro and in vivo. Therefore, a phase-I/II trial of IFN-α2B and GM-CSF was performed in patients with metastatic RCC. **Methods:** 21 patients in groups of 3 patients received GM-CSF at 7 different dose levels (15–300 μg) subcutaneously in combination with IFN-α2B at a fixed dose of 10×10^6 IU s.c. three times weekly for 12 weeks. **Results:** Two complete remissions have been observed, both with lung metastases only. With increasing dose levels of GM-CSF a slight tendency to more toxicity was detectable. Due to grade-3 toxicities 5 patients (24%) dropped out of the treatment schedule. Increases in WBC, neutrophils, lymphocytes, and monocytes were noted but were not related to the dose levels of GM-CSF. **Conclusions:** Results demonstrate that simultaneous administration of GM-CSF and IFN-α2B is tolerated up to doses of 120–150 μg GM-CSF three times weekly. But there is no additional antitumorigenic effect of GM-CSF because the overall response rate of the combined administration of GM-CSF/IFN-α2B is similar to IFN-α2B alone and there is no obvious dose relationship between increasing doses of GM-CSF and the responses.

Introduction

There is no satisfying therapy for patients with metastatic renal cell carcinoma (RCC). Since deKernion et al. [1] in 1983 reported on objective responses of 16% using a partially purified interferon-α (IFN-α) preparation, numerous subsequent phase-II trials with recombinant IFN-α have yielded reproducible response rates varying between 14 and 26% [2, 3].

The granulocyte-macrophage colony-stimulating factor (GM-CSF) is generally indicated for bone marrow failure secondary to administration of chemotherapeutic drugs or radiationtherapy, bone marrow transplantation, and a variety of congenital or iatrogenic neutropenias [4]. Furthermore, there are preclinical data on the tumoricidal effects of GM-CSF. GM-CSF is a potent inducer of tumor necrosis factor-α, interleukin-6 (IL-6), and other cytokines, as well as an activator of antitumor macrophages

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	Number of patients
Eligible patients	21
Males	14 (67%)
Females	7 (33%)
Age, years	
Median (range)	65 (39–75)
Body weight, kg	
Median (range)	80.5 (54–97)
Karnofsky index, %	
70	4 (19%)
80	6 (29%)
90	9 (43%)
100	2 (9%)
Nephrectomy	16 (76%)
Sites of metastatic disease	
Lung only	10 (48%)
Lung and other	5 (23%)
Only other	6 (28%)

[5]. GM-CSF showed tumoricidal activity by stimulating antibody-dependent cytolysis of tumor cells by mature human neutrophils and eosinophils [6].

The aim of this phase-I/II trial was to ascertain the efficacy and toxicity of different doses of GM-CSF in combination with a unique dose of IFN-α2B in patients with metastatic RCC.

Material and Methods

From November 1995 to August 1996, 21 patients with advanced RCC were recruited into this phase-I/II trial. The eligibility requirements included evidence of progressive disease with measurable metastases, life expectancy of at least 3 months with a performance status above 70% on the Karnofsky index, and adequate renal, hepatic and bone marrow function. The ineligibility criteria were patients with serious active infection, hepatic and brain metastases, and patients who had previous treatment with IFN, GM-CSF or other lymphokines as well as previous radiation therapy, chemotherapy or immunotherapy within the last 5 years. The patients characteristics are outlined in table 1.

Patients received a unique dose level of IFN-α2B of 10×10^6 IU and 7 different dose levels of GM-CSF (15, 30, 60, 90, 120, 150 and 300 μg), three times weekly for 12 weeks. The first group of 3 patients began with the lowest dose level of GM-CSF, escalation to the next dose level occurred only if, after 3 weeks of therapy, a minimum of 2 patients had leukocytes lower than 20,000/μl and no serious side effects. All patients self-administered the medication subcutaneously in the evening, on an outpatient basis. IFN-α2B (IntronA®) and GM-CSF (Leucomax®) was supplied by Essex Pharma GmbH/Schering Plough (Munich, Germany). The dose of IFN-α2B had to be reduced experienced grade-3 toxicity (WHO) attributable to IFN-α2B or GM-CSF, respectively. If toxicity persisted after changing the dosage, the patient was withdrawn from the study.

Patients were monitored three times in the first week of therapy, weekly for the next 3 weeks and every 4 weeks thereafter with physical examination, complete blood cell count, and serum chemistry determination. Response evaluation (UICC criteria) was performed after every 3 months.

Survival was calculated using the Kaplan-Meier estimate [7].

Results

21 consecutive patients with histologically confirmed progressive metastatic RCC entered this phase I/II trial. All patients had not received prior therapy.

Tumor Response

We were unable to evaluate the response in 6 of the 21 patients, as their treatment was discontinued due to grade-3 side effects (WHO), and 1 patient died of tumor progress within 8 weeks. The remaining 15 patients received treatment over 12 weeks as a complete treatment cycle. Two of them had a complete remission (CR) (lasting for 52+ and 66+ weeks), but there were no partial remissions (PRs). 9 patients (60%) had stable disease (SD; median 43, range 16–66 weeks), and in 4 (27%) patients the tumor showed initial progression. The overall objective response rate was 13% (90% confidence interval 2–36%). The two objective responses occurred in patients with lung metastases only. Concerning the dose levels of GM-CSF the 2 CRs were seen with 90 and 150 μg GM-CSF. Patients with SD were evaluated at each dose level besides 300 μg. After a median follow-up of 38 (8–68) weeks the median survival time from the start of therapy amounted to 61 weeks. Death occurred in 11 patients after 8–61 (median 32) weeks. The median time to progression was determined to 19 weeks.

Toxicity

Toxicity associated with the combined administration of IFN-α2B and GM-CSF is shown in table 2. 18 of 21 patients (86%) experienced a flu-like syndrome with fever, chills, and fatigue. In 7 patients (34%) the symptoms nausea, vomiting, and weight loss occurred. Neurotoxicity characterized by somnolence and disorientation was experienced by 1 patient (5%), but 8 patients (38%) developed paresthesias of the hands and feet. Two patients (10%) suffered from dyspnea, in 1 case as grade-3 toxicity. This patient chose to withdraw from further participation

8 weeks. One patient (5%) developed cardiovascular complications resulting in discontinuation of treatment. The maximum severity of adverse events reached grade-3 toxicity (WHO), and was reported for 7 patients (33%). As to be expected in treatment with IFN-α2B, 6 of 9 (66%) grade-3 toxicities (WHO) consisted of nausea/vomiting, neurologic and flu-like symptoms. 13 patients or 62% suffered from grade-2 toxicity (WHO) and 1 patient (5%) from grade-1 toxicity. Clinical side effects were consistently controlled with the use of antipyretics, antiemetics, and administration of the trial drugs in the evening when possible. However, due to grade-3 side effects (WHO), 5 patients dropped out of the treatment schedule (1 patient with 30 μg, 1 with 120 μg, 1 with 150 μg, and 2 with 300 μg GM-CSF, respectively). With increasing dose-levels of GM-CSF a slight tendency to more toxicity was found. At dose levels of 120 μg GM-CSF and higher, 5 of 9 patients suffered grade-3 toxicity compared to 2 of 12 patients in the first 4 groups. At the final dose level of 300 μg GM-CSF, grade-3 toxicity occurred in 2 patients after a short time of treatment. One patient suffered an angina attack immediately after the first drug application and the second patient dropped out on day 15 of treatment. Therefore, the maximum tolerable dose of GM-CSF is estimated to be below 300 μg three times weekly.

Leukocyte elevation above 15 × 10^9/l, attributable to increasing GM-CSF doses, was reported in 4 patients (19%) only: in 2 patients at a dose level of 150 μg leukocytes elevated up to 25 × 10^9/l, and in 2 patients at doses of 60 and 90 μg GM-CSF. There was no obvious dose relationship between increasing doses of GM-CSF and the leukocyte counts. Low hemoglobin values due to WHO toxicity grade 2 requiring transfusions occurred in only 3 patients (14%). No platelet values below 100,000/μl were reported. Concerning chemistry values of renal and liver function there were no significant differences detectable between baseline and controls during treatment.

(n = 21)

Side effect	WHO grade			Total
	I	II	III	
Fever, chills, fatigue	4	10	4	18 (86%)
Nausea/vomiting	2	4	1	7 (34%)
Weight loss	2	4	1	7 (34%)
Dyspnea	1	0	1	2 (10%)
Cardiac ischemia	0	0	1	1 (5%)
Neurologic				
Somnolence	0	0	1	1 (5%)
Parethesias	5	3	0	8 (38%)
Local	2	1	0	3 (14%)

Discussion

GM-CSF and other cytokines are widely used to reduce the period of neutropenia following chemotherapy to reduce infectious complications and allow the treatment to be given at full dose [8]. Concerning side effects of GM-CSF, Steward et al. [9] reported on pyrexia at doses above 1 μg kg^{-1} in all patients. These were clinically insignificant and resolved within 1–2 h. At doses of 10 μg kg^{-1} day^{-1} the total leukocyte count elevated to more than 250–400% of the starting values. The count fell to pretreatment levels within 72 h of discontinuing therapy. Serious toxicity occurred at a dose level of 60 μg kg^{-1} with an acute onset of left-sided chest pain in 3 patients due to pericarditis [9]. Compared to the present study the maximal dose of 300 μg GM-CSF three times weekly is nearly half the dose of 10 μg kg^{-1} day^{-1} and the therapy discontinued for 48 h. At these low dose levels, a leukocyte elevation up to 25 × 10^{-9}/l was detected in only 4 patients and the leukocyte counts increased maximally up to 100% above the starting values. The present data showed no obvious dose relationship between increasing doses of GM-CSF and the leukocyte counts. One patient developed an acute anginal attack at the first GM-CSF administration (300 μg). The symptoms resolved after discontinuation of GM-CSF. At dose levels above 90 μg GM-CSF, a modest increase in side effects was apparent. 5 of 9 patients suffered grade-3 toxicity compared to 2 of 12 patients in the first 4 groups. At the final dose level 2 of 3 patients experienced unacceptable toxicity after only a short time of treatment, thus clearly indicating that the maximum tolerable dose had been surpassed when applying 300 μg of GM-CSF.

Initial reserves about the possibility of growth-promoting activity of GM-CSF on renal tumor cells in vitro at physiological concentrations [10] were later dissipated [11]. Other studies have ruled out an antitumor effect of GM-CSF, because it induces macrophage tumoricidal activity in vitro [12] and is capable of stimulating antibody-dependent cytolysis of tumor cells by mature human neutrophils and eosinophils [6]. Hill et al. [5] demonstrated in a murine tumor model that GM-CSF (120 μg/kg) administered subcutaneously for 7 days was associ-

cytotoxicity of macrophages was enhanced by GM-CSF treatment with a parallel increase in TNF-α and IL-6 production of macrophages [5].

The use of biologic response modifiers such as IFN-α as anti-tumor treatment has been explored throughout the last decade [1, 2]. Horoszewicz and Murphy [3] in 1989 reviewed 16 separate trials that examined IFN-α in metastatic RCC in a total of 573 patients and reported about a combined response rate of 14% (83 of 573 patients). The best response rates were gained with intermediate doses of IFN-α (3–10 $\times$ 10^6 U/day) [3]. IFN's mechanism of antitumor activity is not completely understood. However, Kosmidis et al. [13] have shown that the administration of IFN-α in RCC patients results in the augmentation of T-cell responses and cytokine production in vitro. Because of the in vitro and in vivo evidence of synergism between different biologic response modifiers [2], we used GM-CSF as an inducer of biological response modifiers in combination with the well-known IFN-α2B in patients with advanced RCC. The overall objective response rate in the present study was 13% (2 CRs), which is comparable to the combined response rate of 14% found by Horoszewicz and Murphy [3]. Kosmidis et al. [13] using an equivalent IFN-α dose schedule of 15 $\times$ 10^6 IU/week reported about 15% objective responses (4 PR of 26 patients). The median survival time of 61 weeks or 14 months in our study supports information from a previous study of cytokine treatment in metastatic RCC performed at our institute. In this randomized trial of IFN-γ versus IFN-α and IL-2, the median survival time of 60 patients amounted to 13 months [14]. Comparable to the above-mentioned IFN-α studies both CRs in the present study occurred in patients with lung metastases only. In regard to the dose levels of GM-CSF the 2 CRs were seen with 90 and 150 μg GM-CSF. The 9 patients with SD were evaluated at each dose level beside the highest dose level suggesting no clear dose-response relationship to increasing GM-CSF doses. Because of the missing dose relationship between increasing doses of GM-CSF and the evaluated remissions, it is obvious that GM-CSF did not contribute to treatment outcome in this combination.

The toxicity of IFN-α is dose-related and reversible. Daily doses of 1–9 $\times$ 10^6 U/day are tolerated well by most patients [2, 15]. In the present trial, 86% of the patients experienced a flu-like syndrome with fever, chills, and fatigue and 34% of the patients developed nausea, vomiting, and weight loss. Three of 5 patients which were withdrawn from study due to grade-3 toxicity suffered from flu-like syndrome, nausea, vomiting, and weight loss. In a patients with metastatic RCC received recombinant IFN-α2B by either the subcutaneous or intravenous route. Approximately 60% of patients receiving intravenous therapy had grade-3 toxicity, while only 30% of patients on subcutaneous therapy had such difficulties. The subcutaneous dosage was 2 $\times$ 10^6 IU/m^2 three times weekly escalating to dosages of 10 $\times$ 10^6 IU/m^2. In all patients, a flu-like syndrome occurred and in 33% nausea and vomiting. Somnolence was noted in 5% of the patients, comparable to the present study, and cardiovascular toxicity experienced as symptomatic tachycardia was limited to 1 patient on intravenous therapy [15]. Therefore, the toxic profile of the present study is predominantly formed by the IFN-α.

In conclusion, our results demonstrate that simultaneous administration of GM-CSF and IFN-α2B is well tolerated up to doses of 120–150 μg GM-CSF three times weekly. But there is no additional antitumorigenic effect of GM-CSF because the overall response rate of the combined administration of GM-CSF/IFN-α2B is similar to IFN-α2B alone.

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