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A Phase II Study of Recombinant Tumor Necrosis Factor in Renal Cell Carcinoma: A Study of the National Cancer Institute of Canada Clinical Trials Group

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Summary: The National Cancer Institute (NCI) Canada Clinical Trials Group conducted a phase II study of recombinant tumor necrosis factor (rTNF) given intravenously daily for 5 days every other week, in measurable metastatic renal cell carcinoma. Two of 26 patients responded with responses lasting >200 days. Toxicity was severe including rigors, fever, headache, fatigue, hypotension, and localized pain. We conclude that rTNF, given as described, has only modest antitumor activity in renal cell carcinoma and produces considerable toxicity. We plan no further studies of rTNF in this disease. **Key Words:** Phase II—Renal—Tumor necrosis factor—Metastatic.

Treatment of metastatic renal cell carcinoma with chemotherapy and progestational agents has been discouraging (1). Only vinblastine sulphate seems minimally effective with an objective response rate of ~20% (1). Early studies of biologic agents have suggested that they may be more promising. Alpha interferon (IFN-alpha) is reported to produce responses in 11–26% of patients (2–5). The demonstration of in vitro synergistic effects on colony formation of IFN-alpha plus IFN-gamma has led to studies showing objective response rates of 28 and 24% (complete response two of 29 and four of 29 patients studied) (6). Rosenberg et al. (7) documented a complete plus partial response rate of 33% in patients using interleukin-2 plus lymphokine-activated killer (LAK) cells. In view of the low objective response rate to IFN in the Canadian Study (11%) and the considerable reported toxicity of interleukin-2 plus LAK cells, it appeared reasonable to study new biologic agents for renal cell carcinoma.

The exact mechanism of action by which tumor necrosis factor (TNF) exerts its antitumor effects is not known. It appears to exert its cytostatic effects during the premitotic phase of the cell cycle (G2) and its cytotoxic effects shortly after mitosis (8). A phase I study of recombinant TNF (rTNF) administered subcutaneously alternating with intravenously, was reported to show unacceptably severe inflammation at the subcutaneous site (9). Hypotension occurred but was corrected by fluid administration. Intramuscular administration caused similar local problems (10). In a phase I trial of intrave-

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nously-administered rTNF given daily for 5 days, the maximum tolerated dose (MTD) was 200 $\mu g/m^2$ with the dose-limiting toxicity being constitutional symptoms and hypotension (11). Low back pain has been reported in several studies in occasional patients (12,13) as well as pain localized to tumor site in a single patient (14). A recommended starting dose for phase II study was 150 $\mu g/m^2$ in order to minimize hypotension. In June of 1988, the NCI Canada Clinical Trials Group undertook a phase II study of intravenous rTNF in metastatic renal cell carcinoma.

MATERIALS AND METHODS

Patients with measurable metastatic renal cell carcinoma who had had no prior chemotherapy, hormonal therapy, or IFN were considered eligible if they met the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, creatinine ≤ 180 micromole (μM)/l, bilirubin ≤ 27 μM/l, calcium ≤ 2.95 μM/l, absence of acute or chronic respiratory problems (unless forced expiratory volume in one second and diffuse capacity of carbon monoxide $\geq 70\%$ predicted and arterial pO_2 ≥ 70 mm Hg with pCO_2 35–45 mm Hg), granulocyte count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, prothrombin time (PT) <14 s, and partial thromboplastin time (PTT) <35 s. The study was reviewed by the institutional review board at each participating center. Informed consent was obtained from all patients. Patients were excluded if actively infected, if they had known cardiac disease of New York Heart Association class II or greater, required medication for arrythmia or cardiac disease, had known vascular or thrombotic disease, known bleeding disorder, known lipoprotein disorder, brain metastases or seizures, or lymphangitic pulmonary metastases. Patients with evaluable but not measurable disease were excluded.

Recombinant TNF was supplied by Genentech through the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD, U.S.A. with an endotoxin content ≤ 1.0 ng of endotoxin per mg of protein. It was given at a starting dose of 150 microgram (μg)/m^2/day intravenously over 30 min daily, for 5 days every other week, after prehydration with 500 ml normal saline given over 60–90 min. Patients were observed for 2 h after the first 5 daily injections. Chills were managed with meperidine and hypotension was treated with saline. Toxicity was graded using the common toxicity criteria. The rTNF dose was reduced by 50% if >20% drop from baseline occurred in the systolic blood pressure. Other toxicity greater than grade 2 was managed with a similar dose reduction. Dose escalation was not permitted.

Patients were followed every 4 weeks to assess tumor size clinically and/or radiographically. Granulocyte and platelet counts as well as chemistries were done on day 5 of the first cycle and days 1 and 15 thereafter. PT and PTT were done on day 1 of each 28 day cycle.

Response criteria were as follows: complete response (CR): disappearance of all clinical evidence of tumor for a minimum of 4 weeks; partial response (PR): $\geq 50\%$ decrease in tumor size (as measured by the sum of the products of tumor diameters) for a minimum of 4 weeks; stable disease (SD): $<50\%$ decrease or $<25\%$ increase in tumor size for at least 8 weeks; progressive disease (PD); at least a 25% increase in the size of measurable lesions; and/or the appearance of any new lesions.

RESULTS AND DISCUSSION

Twenty-six patients from seven cancer centers were entered on study. Of these, four were inevaluable for response due to early interruption of therapy for toxicity for the following reasons: development of symptomatic hypotension with a >40% decrease in systolic blood pressure after initial dose (one patient), grade 4 rigors requiring hospitalization after initial dose (one patient), grade 3 rigors and dyspnea requiring complete bed rest after second dose (one patient), and grade 3 hallucination after fifth dose (one patient).

The median age for all patients was 59 years (range 26–75 years). Most patients had a good performance status of ECOG grade 0 (n = 11) and 1 (n = 11). Four patients were entered with a performance status of ECOG grade 2. Eighteen patients were men and eight were women. Radiotherapy had been administered to four patients. Twelve patients had undergone nephrectomy. The location of disease commonest was lung (n = 19). Other common sites of tumor included kidney (n = 15), soft tissue (n = 8), bone (n = 6), and abdomen (n = 2). One patient had a pleural effusion and two patients had ascites, but all patients had measurable tumor elsewhere.

Ten patients received 10 doses (one cycle), discontinuing therapy due to disease progression. Five patients received 20 doses (two cycles) prior to dis-

TABLE 1. *Phase II study of recombinant tumor necrosis factor in renal cell carcinoma. Most severe toxicity[a] by patient (n = 26)*

	Grade					
	1	2	3	4	5	Total
Arthralgia/myalgia	1	1	2	0	0	4
Chest pain	0	1	0	0	0	1
Constipation	1	0	0	0	0	1
Cardiac dysrhythmias	1	0	1	0	0	2
Fever	1	20	0	0	0	21
Hypertension	2	1	2	0	0	5
Hematuria	0	0	1	0	0	1
Hypotension	8	4	1	1	0	14
Fatigue/lethargy	8	3	2	0	0	13
Localized pain	3	4	2	0	0	9
Reaction to i.v. site	0	1	0	0	0	1
Nausea	8	5	1	0	0	14
Vomiting	6	6	0	0	0	12
Confusion/hallucinations	1	0	1	0	0	2
Headache	7	8	2	0	0	17
Pulmonary	0	0	1	1	0	2
Rigors/chills	5	16	4	1	0	26
None						0

[a] Includes toxicities considered to be "possibly", "probably", or "definitely" related to the drug.

ease progression. Five other patients received six, eight, nine, 15, and 23 doses, respectively, before documented progression. The two responding patients received 70 and 101 doses, respectively.

Hematologic toxicity was minimal with granulocytopenia occurring in two patients (one with grade 1 and one with grade 3). Grade 1 thrombocytopenia occurred in three patients.

Nonhematologic toxicity is shown in Table 1. Rigors, fevers, hypotension, nausea, vomiting, and headache were frequently noted. Minor toxicities occurring in one patient each included grade 1 allergy, diaphoresis, weakness, and numbness, and grade 2 diarrhea and heartburn. Atrial fibrillation, thought to be drug-related, occurred in a patient leading to withdrawal from study. This arrhythmia resolved with digoxin.

Pain occurred in nine patients, most requiring narcotics. Sites of pain included the back most commonly, as well as hips, chest, ribs, and pelvis. In four of the patients, the pain represented an exacerbation of pre-existing pain.

Of 10 patients with a normal alkaline phosphatase at baseline, nine developed increases to 2–5 times normal (grade 1), while one developed an increase between 2.6 and 5 times normal (grade 2). An elevated serum glutamic oxaloacetic transaminase (SGOT) occurred in 10 of 21 patients who were normal at baseline with three of those having a grade 2 elevation. A grade 1 elevation of creatinine occurred in three of 17 patients, all normal at baseline. Of patients entering the study with biochemical abnormalities, there was one patient who developed a grade 3 (5.1–10 times normal) elevation of alkaline phosphatase and one who developed a grade 3 elevation of SGOT. No patient demonstrated hyperbilirubinemia.

Of 22 evaluable patients, there was a response rate of 8%. One patient with one lung lesion and a metastasis in the contralateral kidney after nephrectomy had a CR lasting 204 days (Fig. 1). He relapsed in the left lung at a site previously uninvolved without relapse at the initial sites of disease. Most of his treatment was given at 25% of the initial dose because of the severity of the pain occurring just after the rTNF infusion. A second patient had

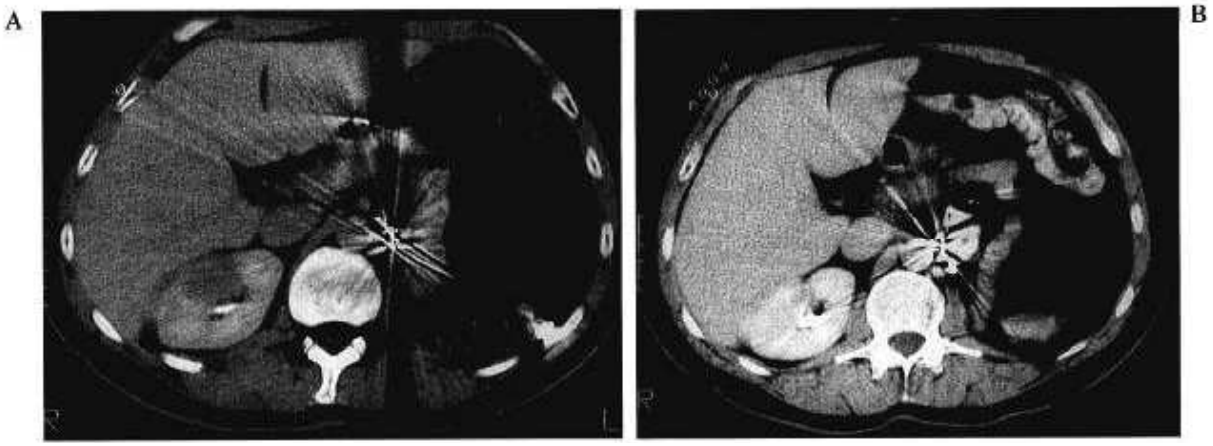

FIG. 1. A: CT abdomen prior to therapy with tumor in the remaining kidney. B: CT after completion of therapy showing complete response in the right kidney.

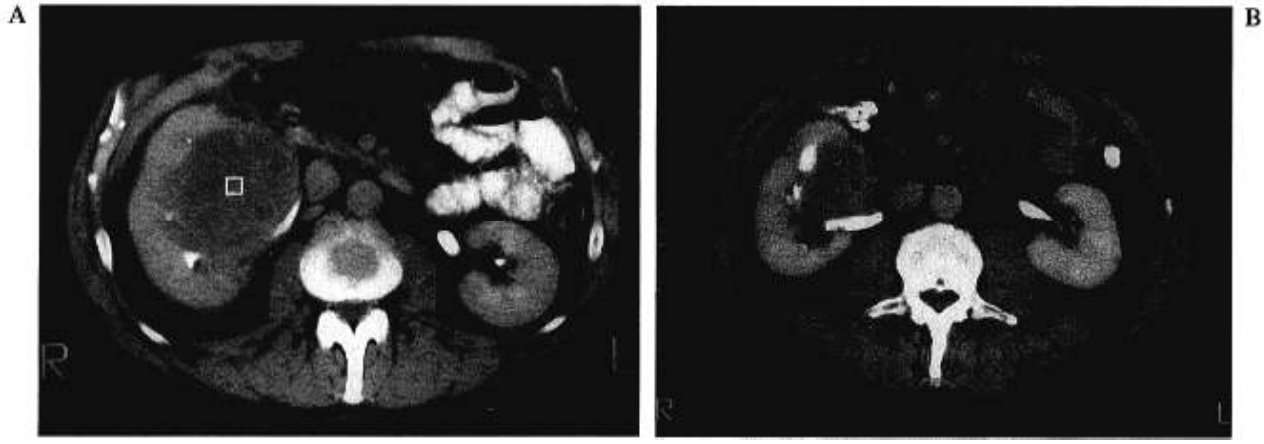

FIG. 2. A: CT abdomen prior to therapy showing a large tumor in the right kidney. B: CT abdomen after rTNF therapy prior to resection.

an objective PR in the primary kidney lesion (Fig. 2) with near complete regression of lung nodules and an "improved" bone scan. His primary tumor was resected and showed extensively necrotic, moderately-to-poorly differentiated renal cell carcinoma with extensive areas of fibrosis and hemosiderin formation at the margins of the tumor. He continues in remission after >2 years.

CONCLUSION

Recombinant TNF caused moderate to severe toxicity, and produced a low response rate. It is noteworthy, however, that both responses occurred in patients with significant renal masses and were quite durable. We conclude that single agent rTNF, given as described in this study, has only limited activity in renal cell carcinoma. We have no plans to study this agent further in this disease.

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