Phase I Trial of Consensus Interferon in Patients with Metastatic Renal Cell Carcinoma: Toxicity and Immunological Effects

Thomas E. Hutson,² Luis Molto, Tarek Mekhall, Paul Elson, James Finke, Charles Tannenbaum, Ernest Borden, Robert Dreicer, Thomas Olencki, and Ronald M. Bukowski

ABSTRACT

Purpose: The purpose of our study was to determine the maximum tolerated dose (MTD), dose-limiting toxicities, and effects on chemokine/cytokine gene expression in peripheral blood mononuclear cells (PBMCs) of consensus IFN (CIFN).

Experimental Design: Cohorts of three to six patients with metastatic renal cell carcinoma (RCC) were treated with escalating doses of CIFN (dose level I, 9.0 µg/m²; dose level II, 15.0 µg/m²; dose level III, 21.0 µg/m²) given s.c. three times weekly in 4-week cycles until progression. The cohort treated at the maximum tolerated dose was expanded to further define toxicity. An additional three patients were treated with i.v. CIFN (15.0 µg/m²) to evaluate route-related differences in gene expression. Cytokine and chemokine gene expression in PBMCs was assessed by reverse transcription-PCR.

Results: A total of 25 patients (18 men and 7 women) were enrolled between January 28, 1999, and November 1, 2000, at dose levels I (n = 4), II (n = 14), and III (n = 7). Dose-limiting toxicity occurred at dose level III (21 µg/m²) and included grade-3 or -4 respiratory distress/failure (n = 3) and hypocalcemia (n = 1) occurring within the first cycle of treatment. Other severe toxicities included grade-3 neutropenia, thrombocytopenia, fatigue, and nausea/vomiting. Studies of cytokine and chemokine gene expression in PBMCs from eight patients revealed induction of IFN-γ, IP-10, and Mig. I.V. administration was associated with a faster induction, but of shorter duration. There were no responses; however, 24 patients had stable disease of variable duration (4–32 weeks) and received a median of three cycles of treatment (range, 1–8 cycles). Overall median survival was 13.5 months, and was 12.7 months in the previously treated patients.

Conclusion: CIFN was safely administered s.c. three times weekly at doses up to 15.0 µg/m². Although there were no responses, the median survival was longer than expected in a previously treated patient population with metastatic RCC.

INTRODUCTION

Metastatic RCC is a tumor that is refractory to standard chemotherapeutic regimens (1, 2). A review of 72 agents evaluated in Phase II trials between 1983 and 1993 involving over 3500 patients resulted in an objective response rate of only 5.6% (2). Because RCC appears to be an immunogenic neoplasm, cytokines such as rHuIL-2 and rHuIFNα have been investigated as therapy. Overall response rates for metastatic RCC patients treated with rHuIL-2 are 15% (3), which are similar to those reported for rHuIFNα (3, 4). A possible increased frequency of complete responses and enhanced response duration with IL-2 have, however, been suggested (4). There have been several trials involving rHuIFNα in patients with metastatic RCC with response rates ranging from 10 to 39% (4, 5). In a randomized trial comparing rHuIFNα with hormonal therapy, response rates were increased and survival was significantly improved for rHuIFNα-treated patients (5). Furthermore, patients with metastatic RCC, who underwent removal of their primary tumor, benefited from the administration of rHuIFNα (6).

CIFN is a synthetic type-I IFN structurally similar to rHuIFNα. The biological activity of CIFN when compared with rHuIFNα-2a in preclinical models has demonstrated greater antiproliferative activity at lower concentrations (7), greater antiviral activity (8), enhanced induction of IL-1α (9), and greater (P < 0.05) ability to induce NK cells (10, 11). Preclinical studies using CIFN have demonstrated antiproliferative activity in several tumor models in which rHuIFNα subtypes exhibited no beneficial effect (12). Whether the improved in vitro antiproliferative activity of CIFN will translate into improved response rates in human malignancies is unknown. A Phase III study using CIFN in patients with hepatitis revealed a toxicity profile that was similar to those reported with other type-I IFNs (13). However, no repetitive-dose Phase I trial has

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been undertaken to establish the MTD. Therefore, we evaluated this agent in patients with metastatic RCC to determine: (a) the MTD of CIFN given s.c. TTW; (b) the toxicity associated with s.c. administration; (c) preliminary observations of antitumor effects in RCC; and (d) the effects on gene (Mig, IP-10, IFNγ) expression.

Mig and IP-10 are IFN-inducible members of the CXC family of chemokines (14–17). These molecules not only have been demonstrated to elicit activated T cells expressing the CXCR3 receptor (18) but also may be involved in mediating antiangiogenic activity (19–21). The ability to induce these proteins during the course of antitumor immunotherapy would, thus, potentially initiate two distinct pathways independently capable of controlling tumor growth and/or causing tumor regression. B7 is an inducibly expressed costimulatory molecule on antigen-presenting cells that, when ligated to CD28 on a cognate T cell, provides the lymphocyte with the requisite second signal necessary for effective activation. The ability to induce B7 with CIFN would thus imply augmented antigen-presenting capacity by the patient’s leukocytes.

PATIENTS AND METHODS

Patients

Patients with histologically proven RCC, with strong clinical evidence or biopsy proof of metastases, were eligible for enrollment. All of the patients were between 18 and 65 years of age; had bidimensionally measurable or evaluable disease; had clinical evidence or biopsy proof of metastases, were eligible for inclusion. In addition, patients were ineligible if they had positive or negative pregnancy tests, known central nervous system metastasis as determined by imaging studies (computed tomography scan or magnetic resonance imaging) within 14 days of the initiation of treatment and at the end of every cycle. Criteria for initiating additional cycles included: responsive or stable disease; ANC ≥1.5 mg/dl; platelets ≥120 × 10^9/liter; bilirubin (total) ≤1.5 m/dl; calcium ≤12 mg/dl; absence of significant effusions or ascites; had no major surgery requiring general anesthesia within the preceding 28 days; and had received ≤2 prior systemic regimens for metastatic RCC.

Exclusion criteria included history or evidence of cardiac arrhythmia or congestive heart failure (New York Heart Association class III or IV); women of childbearing age unless surgically sterile or using effective contraception; pregnant or lactating women; known central nervous system metastasis as determined by imaging studies (i.e., computed tomography scan of the brain) or neurological exam; or history of a seizure disorder. In addition, patients were ineligible if they had positive serological studies for HIV or hepatitis B surface antigen (HBsAg); had a history of another malignancy within the past 3 years excluding basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix; had organ allografts; had a known hypersensitivity reaction to Escherichia coli-derived products; had received chemotherapy, immunotherapy, and/or radiotherapy within the past 28 days; had received prior CIFN; or had received local or systemic antibiotics for infections within the past 28 days.

All of the inclusion and exclusion criteria were assessed within 14 days before the initiation of therapy, with the exception of radiographic studies not required for determination of eligibility or laboratory studies not used to assess organ function. Radiographic studies used to determine eligibility and for initial tumor measurements were performed within 28 days of the initiation of treatment.

Study Drugs

IFN alfacon-1 (CIFN Amgen Inc., Thousand Oaks, CA) was supplied by the manufacturer as a sterile particulate-free solution in single-use vials at a concentration of 0.03 mg/ml. All of the vials were refrigerated at 2–8°C per manufacturer’s recommendation. Before administration, the vials were removed and allowed to warm to room temperature for approximately 30 min before being withdrawn into a plastic syringe and then injected s.c. (or i.v.).

Dose Schedule

Eligible patients were enrolled in cohorts of three to six patients at each dose level (dose level I, 9.0 μg/m^2; dose level II, 15.0 μg/m^2; dose level III, 21.0 μg/m^2) until the MTD was reached. Therapy was administered three times per week in 4-week cycles. No accrual to subsequent dose levels occurred until all of the patients at previous dose levels finished the first 4-week cycle without dose-limiting toxicity. An additional three patients were treated with i.v. CIFN (15.0 μg/m^2) using the same schedule of administration to evaluate route-related differences in gene expression.

Response was assessed every 4 weeks. Patients were evaluated weekly for the first cycle, every 4 weeks correlating with the end of each additional cycle, and at the end of the study. Weekly evaluations consisted of toxicity evaluation, physical examination, and laboratory studies (complete blood count, urinalysis, complete metabolic panel, prothrombin time, partial thromboplastin time, and international normalized ratio). Patients had their vital signs monitored on days of CIFN administration and then as clinically indicated after therapy during the initial 4 weeks. Assessment of tumor response was made by objective two-dimensional measurement of evaluable tumor following WHO criteria via imaging modality (computed tomography scan or magnetic resonance imaging) within 14 days of the initiation of treatment and at the end of every cycle. Criteria for initiating additional cycles included: responsive or stable disease; ANC >1000 cells/μl and platelets >75,000 cells/μl; and resolution of all significant grade-2 or greater toxicity (National Cancer Institute Common Toxicity Criteria, version 2.0). If the ANC or platelet count remained below the specified values for greater than 4 weeks, the patient was withdrawn from the study.

Patient accrual continued until the MTD of CIFN was determined. The MTD was defined as the dose level preceding that producing unacceptable toxicity during cycle one in two or more patients. Although dose escalation proceeded until the MTD was achieved, chronic and late toxicities were carefully observed and graded. Dose-limiting toxicity was defined as the occurrence of any of the following: (a) grade-3 or higher non-hematological toxicity; (b) grade-4 neutropenia for ≥7 days associated with fever or infection; (c) other grade-4 hematolog-
ical toxicity. In the presence of grade-3 toxicity (excluding fever), further treatment was withheld until resolution to no more than a grade-1 toxicity. If the same grade-3 or -4 toxicity occurred with subsequent therapy, the patient was removed from the study. Once the MTD was determined, an additional nine patients were treated at this dose level to further characterize the toxicity.

**Gene Expression Studies**

Eight patients (s.c., n = 5; i.v., n = 3) treated with CIFN were studied during cycle one. The expression of Mig and IP-10 mRNA were evaluated using RT-PCR in PBMCs before and during treatment with CIFN pretreatment on day 1 (at 2, 6, and 24 h) and day 8. In addition, the expression of the CXCR3 receptor, CD80, FasL, FasR and IFNγ were investigated in five patients prestudy and on day 1 (at 2, 6, and 24 h) and day 8. To assess route-related differences, the time to gene expression was compared between patients who received s.c. and i.v. CIFN.

**Isolation of PBMCs and T Cells.** Isolation of PBMCs and T cells was performed as described previously (22). Isolated cells were processed immediately, and RNA was extracted by the guanidine-isothiocyanate/cesium chloride method followed by ethanol precipitation and storage at −70°C until mRNA analysis.

**mRNA Analysis of Gene Expression by RT-PCR/Southern Hybridization.** RT-PCR analysis of GADPH, IP-10, Mig, FasL, FasR, CXCR3, IFNγ, and CD80 mRNA was performed using AMV reverse transcriptase and specific antisense primers (20 µM) at 42°C for 1 h followed by PCR amplification in a Perkin-Elmer/Cetus DNA Thermal Cycler for 35 cycles at 94°C for denaturation, at 60°C for annealing fragments, and at 72°C for DNA synthesis of the RNA fragments. The following sense and antisense primers were used: (a) GADPH: sense, 5'-GAAAGGTGAGGTGAGATGCTC-3', and antisense, 5'-GAAGATGGTGATGGAATTTCC-3'; (b) IP-10: sense, 5'-CCTGGAACCAATTGTTGCTG-3', and antisense, 5'-CATTAACCTCCTCAACAGGAG-3'; (c) Mig: sense, 5'-AGTTGGTGGTCTCTTTGGTGGGTTTCCAAGAGGTTTGAAGGTT-3', and antisense, 5'-CTTCACTACATCTGGTGAATGCTGAGGAGG-3'; (d) FasL: sense, 5'-TGAGGACCAAGGTCTACATGAG-3', and antisense, 5'-GGAAAGATCCAAAGTCTCTCCC-3'; (e) FasR: sense, 5'-ATGCTATATCCCTACTGCTC-3', and antisense, 5'-GCCATAGTGTTTCAAT-3'; (f) CXCR3: sense, 5'-CCTACTGCTATGCCCCACATCTG-3', and antisense, 5'-GCTTCTGGAGCCTTTCTGTTG-3'; (g) CD80 (B7.1): sense, 5'-ACATGAGCTGTGTTGGTGTTGCTC-3', and antisense, 5'-GCTGTGTTCTTCCTCCTTGGCAG-3'; (h) IFNγ: sense, 5'-TGGCTTCTAGCTGCTGTCGAG-3', and antisense, 5'-TCGACCTGGAACCAAGCATCTG-3'. After amplification and electrophoresis, the gels were blotted overnight onto nitrocellulose membranes and, subsequently, were visualized by Southern hybridization with 32P-labeled cDNA encoding the desired single-stranded oligonucleotide (GADPH, IP-10, CD80, FasL, and TRAIL) or double-stranded (Mig) portion of the gene of interest. After overnight hybridization at 42°C, the blots were washed in standard saline-citrate solution and exposed to X-ray film. The probe sequences used were as follows: (a) GADPH: 5'-CAAGGCGTCCCGTCTACGAGTTGACGG-3'; (b) IP-10: 5'-TACTATATCCTATGAGGTTTACACCG-3'; (c) Mig: 5'-GGAAGGGGCTTGGGCAATTTGTTAAGGTTCTTTCAG-3'; (d) FasL: 5'-CTCTCCTGCTAATTGAGTCAATCTGAGC-3'; (e) FasR: 5'-GCCATCTGCTCTAATATTACCC-3'; (f) CXCR3: 5'-TACAAAGGCACTAGAGCAGCGG-3'; (g) CD80 (B7.1): 5'-ATAAGCTTACCTTCAGCCAGGTTGTTCCCG-3'; and (h) IFNγ: 5'-GGCAAGTAACAGCCAGAGAACACGATGACGTCC-3'.

**RESULTS**

**Patient Characteristics.** Twenty-five patients (18 men and 7 women) were treated with s.c. CIFN at dose levels I (n = 4), II (n = 14), and III (n = 7) TTW in 4-week cycles between January 28, 1999, and November 1, 2000. The median age was 59 years (range, 38–76 years) and 19 (76%) had a prior nephrectomy (Table 1). Twenty patients (80%) had received prior systemic therapy (median of one prior treatment; range, one to three treatments) including both biological agents and cytotoxic chemotherapy. Seventeen patients (68%) had been previously treated with IFN. Eleven patients (44%) had an ECOC performance status of zero. The most common histological type of RCC was clear cell (n = 20; 80%).

**Treatment Administered and Toxicity.** Patients received a median of three cycles (range, one to eight cycles) of treatment. Dose-limiting toxicity occurred at dose level III (CIFN 21.0 µg/m²), and the MTD was dose level II (CIFN 15.0 µg/m²). Three of four patients at dose level I experienced mild toxicity (excluding fever, chills, and fatigue). Similarly, all patients at dose levels II and III experienced constitutional symptoms that were generally considered mild to moderate, and in only four patients were these symptoms considered severe.

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics</th>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Patients</td>
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<tr>
<td>Male/Female</td>
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<td>Median age (range), years</td>
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* NOS, not otherwise specified.

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toxicity during cycle 1 which included nausea/vomiting (n = 2), fatigue (n = 1), diarrhea (n = 1), and syncope (n = 1). No grade-4 toxicities occurred at this dose level. Dose-limiting toxicity occurred at dose level III (CIFN 21.0 μg/m²). Three of seven patients developed grade-3 (n = 2) or grade-4 (n = 1) respiratory distress manifesting as dyspnea with minimal hypoxemia. Chest radiographs revealed mild pulmonary edema. One patient developed transient grade-4 hypocalcemia that resolved completely with i.v. and oral calcium replacement along with cessation of therapy. Other grade-3 toxicities at this dose level included fatigue (n = 1), nausea/vomiting (n = 1), neutropenia (n = 1), and thrombocytopenia (n = 1) during cycle one. Both the neutropenia and thrombocytopenia were transient and resolved within one week after therapy was withheld.

During subsequent cycles, toxicity was similar, however, the severity of toxicity increased at dose levels II and III. No patients at dose level I experienced a grade-3 or worse adverse event during subsequent cycles. However, 5 of 14 patients at dose level II and all of the patients at dose level III experienced at least one grade-3 or -4 adverse event. Treatment-related toxicities resulted in treatment delays in five patients (n = 1 at dose level II; n = 4 at dose level III) and dose reductions in one patient (dose level III). Fifty-two % (13 of 25) of patients received three or more cycles of treatment. All of the toxicities resolved on the cessation of therapy, with four patients requiring hospitalization. No treatment-related deaths occurred. The toxicity profile of the three patients treated with i.v. CIFN (15.0 μg/m²) was similar to those patients who received s.c. CIFN.

Preliminary Efficacy. Of the 25 patients entered onto this study, 24 patients had stable disease (duration, 4–32 weeks) and received a median of three cycles of treatment (range, one to eight cycles). There were no responses. Twelve of the 25 patients have died. The overall median survival is 13.5 months (range, 0.5–29.6 months) from the time of enrollment onto this study and the median follow-up for the seven patients still alive is 24.5 months (range, 2 weeks to 29.6 months). Nineteen of the 25 patients developed progressive disease with a median time-to-progression of 5.0 months. The 1-year overall survival rate is 63%, with 24% of patients (n = 5) surviving at 2 years. The median survival for previously treated patients (n = 20) was 12.7 months (range, 0.5–25.5 months). The 1-year and 2-year survival rate for previously treated patients is 58 and 16% (n = 3), respectively.

Gene Expression. After the administration of either s.c. or i.v. CIFN, increased mRNA expression of IP-10 (8 of 8) and Mig (6 of 8) in PBMCs was found in the group of patients studied (Fig. 1). This was accompanied by expression of IFNγ (Fig. 2) in four of five patients. Expression of IFNγ, IP-10, and Mig appeared to peak at 6–24 h after CIFN administration and then decline. Individual patterns of expression showed some variation, with no relationship to dose noted. Route of administration however, may have affected cytokine gene expression. With s.c. CIFN, induction of IFNγ, IP-10, and Mig was up to 5 days. However, in the three patients who received i.v. CIFN, two patients had peak induction of IFNγ in 6 h which then disappeared. Also found was increased expression of FasL mRNA in peripheral blood T-cells in three patients that appeared maximal at 6 h and was sustained through day 5 of therapy (data not shown). Additionally, increased expression of CD80 (B7.1) mRNA was seen in four patients (Fig. 3), who also demonstrated increased expression of IP-10 and Mig mRNA.

In view of the increased expression of Mig and IP-10 mRNA, expression of CXCR3 in peripheral blood T-cells was also evaluated (data not shown). Increased CXCR3 mRNA was detected 24 h after administration of CIFN (3 of 5 patients). This increase correlated with the expression of Mig and IP-10 mRNA in these patients.

DISCUSSION

CIFN (Infergen) is a novel synthetic type-I IFN that has been approved by the Food and Drug Administration for the treatment of hepatitis C infection. Several clinical trials in

Table 2  Cycle one toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
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<th>Dose level I (n′ = 4)</th>
<th>Dose level II (n = 14)</th>
<th>Dose level III (n = 7)</th>
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<td></td>
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<td>1–2</td>
<td>3–4</td>
<td>1–2</td>
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<tr>
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<td>Prolonged PT/PTT</td>
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<td>3</td>
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<tr>
<td>Resp dist/failure</td>
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<td>Dyspnea</td>
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<td>1</td>
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<tr>
<td>Fever/Chills</td>
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* Number of patients; PT, prothrombin time; PTT, partial thromboplastin time; Resp dist, respiratory distress; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate pyruvate transaminase.

† Patients on anticoagulation.
patients with hepatitis C infection have demonstrated efficacy similar to IFN-α-2b, as well as activity in IFN-α-2b-resistant disease (13, 23–25). The MTD from these trials was 15 μg administered s.c. TTW and showed a toxicity profile similar to other type-I IFNs. The dose-limiting toxicities were thrombocytopenia, neutropenia, and depression. The most commonly reported adverse events resulting in dose reductions were fatigue, headache, diarrhea, and depression, occurring in up to 4% of patients during initial therapy. However, the most common laboratory abnormality requiring dose reduction during initial treatment was thrombocytopenia (2–4%); however, during retreatment with 15 μg CIFN, 5% of patients required dose reduction because of neutropenia.

The MTD (15 μg/m²) of s.c.-administered CIFN observed in our Phase I trial is higher than that previously reported in patients with hepatitis C (13, 23–25). Common adverse events observed in this study were constitutional symptoms (fatigue, fevers, and chills), nausea and vomiting, and transient hematological toxicities (anemia, leukopenia, and thrombocytopenia). The adverse events and laboratory profiles observed are also similar to those reported in the literature for other type-1 IFNs.

Fig. 1 Increased expression of Mig (6 of 8) and IP-10 (8 of 8) was detected in RT-PCR-amplified RNA specimens of PBMCs from patients with metastatic RCC after 6 and 24 h of CIFN administration. [L.A.S., A.J.S., 9.0 μg/m² s.c.; R.P., J.A.K., J.P.R., 15.0 μg/m² s.c.; A.V., W.W., J.K., 15.0 μg/m² i.v.]

Although the mechanism of hypocalcemia is unclear, and could represent IFN-induced abnormalities in endocrine calcium homeostasis.

Previous studies have shown that the IFN-γ-inducible chemokines, Mig and IP-10, possess antiangiogenic activity and may function as chemoattractants for effector cells (activated T cells and immature dendritic cells; Ref. 27). In previous reports, we have demonstrated increased expression of IFN-γ, Mig, and IP-10 in PBMCs from RCC patients receiving IL-12 (28, 29). This correlated well with our animal studies, which demonstrated that the ability of IL-12 to mediate regression of RENCA tumors was dependent on the induction of IFN-γ, Mig, and IP-10 in the hosts receiving therapy (30, 31). Indeed, the neutralization of Mig and IP-10 expression by specific antibodies during the course of IL-12 treatment inhibited both T-cell infiltration into the tumor bed and regression of the tumorous lesions (30). The results presented here suggest a similar cytokine and chemokine cascade initiated in patients receiving CIFN therapy. Unfortunately, although murine tumors can be directly assessed for inducible gene expression, most human tumors are inaccessible for analysis. The ability of CIFN to modulate gene expression within the tumor bed, thus, had to be extrapolated from studies performed on peripheral blood leukocytes of treated patients.

In this trial, we extend these observations to patients with advanced RCC receiving s.c. CIFN. CIFN clearly stimulated the expression of IP-10 in the PBMCs of 8 of 8 patients with metastatic RCC, a result not unpredictable based on the molecule’s known inducibility by both type-I and type-II IFNs (16, 17). Interestingly, Mig, a chemokine named for its inducibility by γIFN alone (monokine inducible by γ; Refs. 14, 15), was pulmonary edema on radiographic examination. The development of pulmonary edema with high doses of type-1 IFNs has not been described and is much less common than the capillary leak syndrome seen with IL-2 (3, 26). The mechanism of hypocalcemia is unclear, and could represent IFN-induced abnormalities in endocrine calcium homeostasis.
Because TRAIL and FasL expression has been identified in T cells from RCC patients before, and at various times after, receiving therapy with IFNs, we also evaluated FasL expression in these same patients. There was increased FasL in three of six patients receiving therapy with IFNs, we also evaluated FasL expression in these same patients. There was increased FasL in three of six patients receiving therapy, including three sets of PBMCs that displayed detectable levels of constitutive expres-
sion. Augmented B7 expression by patient PBMCs after CIFN admin-
istration occurs simultaneously. This pattern of expression is clear that CXCR3 and chemokine expression after CIFN administration occur simultaneously. Thus, CIFN may be inducing IP-10 directly, but Mig production by patient PBMCs requires NK-derived IFNγ as a necessary intermediate of type-1 therapy. In this study, we analyzed both s.c. and i.v. administration of CIFN to evaluate route-related effects on IP-10, Mig, and B7. With the use of s.c. CIFN, induction was seen in 5 days. However, in three patients who received i.v. CIFN, two patients had peak induction of IFNγ in 6 h which then disappeared, suggesting a possible route-dependent difference in the immunomodulating ability of CIFN. The results with B7 were more enigmatic. CIFN stimulated B7 accumulation in a total of four patients receiving therapy, including three sets of PBMCs that displayed detectable levels of constitutive expression. Augmented B7 expression by patient PBMCs after CIFN therapy may reflect at least some minimally enhanced antigen-presenting capacity and, hence, tumor immunogenicity within the treated patients.

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