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Phase II Trial of Subcutaneous Interferon Followed by Intravenous Hybrid Bolus/Continuous Infusion Interleukin-2 in the Treatment of Renal Cell Carcinoma: Final Results of Cancer Biotherapy Research Group 95-09

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ABSTRACT

Objective: *We conducted a phase II trial in metastatic renal cell cancer of outpatient subcutaneous (s.c.) interferon-α2b (IFN), followed by an inpatient hybrid schedule of bolus and continuous interleukin-2 (IL-2).* ***Methods:*** *Treatment consisted of monthly IFN 10 MU/m^2 s.c. for 4 consecutive days, followed by 36 MIU/m^2 bolus IL-2, then 72-hour continuous intravenous (i.v.) infusion of 18 MIU/m^2 IL-2 per day. Between May 1997 and June 2000, 25 men and 11 women enrolled, with a median age of 57 years (range, 42–77), including 9 patients over 65. Prior treatment included nephrectomy (31), radiation (8), biotherapy (7), and chemotherapy (4). Sites of disease included 26 lung, 13 lymph node, 9 bone, 8 liver, 4 kidney, and 4 adrenal locations. Patients received an average of 3.1 treatment cycles (range, 1–6).* ***Results:*** *There was 1 complete and 3 partial responses, for a response rate of 11% (3% to 27%; 95% confidence interval [CI]); 40% had stable disease. Median failure-free survival was 2.5 months; median overall survival was 15.0 months. The 1-, 2-, and 5-year survival rates were 53%, 30%, and 12%, respectively. Only 8 patients required a reduction in IL-2 dose. The most frequent grade 3 or 4 toxicities were 11% fatigue, 9% renal insufficiency, and 7% hypotension.* ***Conclusions:*** *Response and survival rates were similar to those seen in other multicenter trials using inpatient high-dose IL-2.*

Key words: renal-cell cancer, interleukin-2, interferon-α

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 2%–3% of all cancer deaths each year. In 2005, it was estimated there would be approximately 36,000 new cases of kidney cancer

diagnosed in the United States and nearly 12,000 deaths.[1] Most patients are diagnosed between the ages of 50 and 70 years. Recent data from Hoag Comprehensive Cancer Center (Newport Beach, CA) for 156 patients diagnosed during 1995–2000 revealed 50% local, 26% regional, and 24% distant at the time of diagnosis. Surgery continues to play a significant role in the management of patients with distant metastases. Patients with solitary metastasis are treated with curative intent, because surgical resection of the involved kidney and the solitary metastasis is associated with a 5-year survival rate of 30%.[2] Randomized trials have confirmed that nephrectomy is associated with improved survival in patients with distant metastases who subsequently are treated with biotherapy.[3,4]

There is no satisfactory systemic treatment for patients with advanced RCC.[5,6] The 5-year survival rate after a diagnosis of distant metastatic disease ranges from 5% to 20%. The 5-year survival rate is less than 5% for patients who have multiple sites of distant metastatic disease at the time of diagnosis. Based on retrospective analyses of outcomes for patients diagnosed with metastatic renal cell cancer, factors associated with a poor prognosis in the setting of metastatic renal cell cancer include poor performance status, elevated serum lactate dehydrogenase, anemia, hypercalcemia, more than one site of distant metastatic disease and no prior nephrectomy.[7–9] For many years, the primary approach to the treatment of metastatic renal cell cancer consisted of hormones and chemotherapy, but prospective trials have consistently shown these to be of limited therapeutic benefit, with objective response rates less than or equal to 5%.[10,11]

For more than a decade, biotherapy consisting of interferon-alpha (IFN-α) and/or interleukin-2 (IL-2) has been considered standard treatment for multifocal metastatic RCC patients who are in good medical condition.[12,13] However, even among medically appropriate patients who receive IL-2-based therapy, only 5%–10% have long-term survival when treated with either high-dose bolus or intermediate-dose, continuous-infusion schedules.[14,15] We previously reported a 9% objective response rate and median survival of 10.5 months for 22 patients (median age, 62 years) with metastatic renal cell cancer who were treated with a hybrid schedule of interleukin-2 (IL-2) that combined high-dose bolus and continuous intravenous schedules of administration administered over 3 days.[16] In this trial, we explored the sequential combination of subcutaneous (s.c.) IFN-α followed by this hybrid schedule of bolus and continuous infusion IL-2.

PATIENTS AND METHODS

Trial Design

Cancer Biotherapy Research Group (CBRG) 95-09 was an open-label, single-arm, phase II trial. The initial study was designed to accrue up to 40 patients within 3 years of initiation. The protocol was reviewed by the institutional review boards of each participating institution. All patients enrolled in this trial gave written, informed consent prior to their participating in the study.

Eligibility

Patients had to have RCC that had been confirmed by histologic examination. They had to be at least 18 years of age at the time of study enrollment. They were to have measurable metastatic disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients could have received prior treatment but with no more than one of the two therapeutic agents. Hematologic parameters for eligibility included a hematocrit $\geq$25%, white blood cell count of at least 3000 cells/μL, platelet count $\geq$100,000/μL, serum creatinine $<$2.0 mg/dL, and a bilirubin $<$2.0 mg/dL. Patients were specifically excluded for prior clotting diathesis, such as phlebitis or pulmonary embolism, prior myocardial infarction, active infection, or pregnancy. Patients with active central nervous system metastases were excluded from participation in the trial. However, patients were eligible if surgery and/or radiation therapy or radiosurgery controlled their brain metastases, and they were not receiving corticosteroids. Therapy was not to commence until at least 4 weeks following whole-brain radiation, or 1 week after stereotactic radiosurgery or gamma knife therapy. Patients with hypertension were ineligible unless blood pressure could be controlled without antihypertensive medication. Other conditions for ineligibility included pregnant or lactating women, concurrent treatment with other anticancer agents, previous organ allograft, family history of malignant hyperthermia, or a history of severe allergic reaction to interferon or interleukin-2.

Treatment Regimen

The biotherapy agents used in this trial were interferon-α2b, (IFN) (IntronA®, Schering; Killingsworth, NJ) and interleukin-2 (IL-2) (Proleukin®, Chiron; Emeryville, CA). Treatment consisted of IFN 10 MU/m^2 s.c. as an outpatient during each evening for 4 consecutive days, followed by hospital admission for a 36 MIU/m^2 bolus of IL-2, then a 72-hour continuous infusion of intravenous (i.v.) IL-2 at a dose of 18 MIU/m^2 per day during the next 3 days. Treatment was repeated every 4 weeks for up to six cycles. The protocol included dose reductions, based on certain severe and life-threatening toxicities. It was recommended that all patients receive an oral histamine-2 blocker as a prophylaxis for gastritis. Whether to use—and choice of—antiemetics, hematopoietic growth factors, and antibiotics, was left to the discretion of treating physicians.

Assessment of Response

Physical examination was used to measure palpable metastatic disease. Radiographic tests for determining eligibility and tumor response included chest X-ray, computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain, and a CT evaluation of the chest and abdomen. Patients were re-evaluated for tumor response every 2 months (at the end of each two treatment cycles) using standard criteria. Complete remission (CR) was defined by the disappearance of all disease for $\geq$4 weeks. A partial response (PR) was defined by at least a 50% reduction in the sum of the products of the cross-sectional diameters of all measurable lesions, without the appearance of new lesions, or increase in the size of any single existing lesion. The 95% confidence interval (CI) for objective tumor response was calculated using the "exact" method. Progressive disease (PD) was defined as an increase in the sum of the products of the cross-sectional diameters of measurable disease. Stable disease (SD) was used to define all conditions between a PR and PD. The response rate was determined based on intent-to-treat analysis for all patients who started treatment and, for evaluable patients, based on having an opportunity to assess response or disease progression.

Determination of Survival

Actuarial progression-free survival (PFS), overall survival (OS), and event-free survival (EFS) were calculated using standard methods. PFS was calculated from the date protocol therapy was started to the date of disease progression; OS was calculated from the first date of treatment to the date of death, regardless of cause; EFS was calculated from the first date of treatment to the date of disease progression or death, whichever was documented first. After completion of treatment, patients were to be evaluated at least every 3 months for a minimum of 2 years to determine the approximate date of disease progression and then at least every 6 months for 3 years or until death.

Evaluation of Toxicity

Before initiation of therapy, a medical history was obtained and patients were examined. Baseline tests included complete blood cell count (CBC), chemistry panel to assess electrolytes and function of the kidney and liver, prothrombin time, partial thromboplastin time, urinalysis, and electrocardiogram. CBC and chemistry panel were repeated weekly during therapy. Toxicity was graded from 0 to 5 for no, minimal, moderate, severe, life-threatening, and lethal toxicity, based on standard criteria. All patients who initiated treatment were considered evaluable for toxicity.

RESULTS

Patient Population

Patient accrual to CBRG 95-09 took place between May 1997 and June 2000, at eight different institutions. There were 36 patients registered for CBRG 95-09, and treatment information was received for 35. The characteristics of the patients who were registered are shown in Table 1. The median age of 57 years is higher than in most series of metastatic renal cell cancer patients who are treated in clinical trials but is the same median age that was observed in CBRG 94-10; a treatment protocol for patients treated with outpatient s.c. IL-2 and IFN in addition to *cis*-retinoic acid and 5-fluorouracil.[17]

Treatment Received

Patients received an average of 3.1 cycles of treatment, with a range from one to six cycles. Thirty-six (36) patients (100%) started the first cycle of therapy, 28 (80%) received at least two cycles, 18 (51%) three cycles, 15 (43%) four cycles, 7 (20%) five cycles, and 4 (11%) six cycles. One

Table 1. Characteristics of Patients with Metastatic Renal Cell Cancer Enrolled in CBRG 95-09

Characteristics	*Sites of metastatic involvement*
36 patients: 25 males, 11 females	Lung: 26
13 ECOG-0, 21 ECOG-1, 1 ECOG-2, 1 ECOG-3	Lymph nodes: 13
Median age: 57 years	Bone: 9
31 had had a nephrectomy	Liver: 8
29 had no prior chemotherapy or biotherapy	Adrenal: 4
8 had prior radiation therapy	Kidney/renal bed: 4
7 had prior biotherapy	
4 had prior chemotherapy	

CBRG, Cancer Biotherapy Research Group. ECOG, Eastern Cooperative Oncology Group.

(1) patient withdrew after the first cycle, despite minimal toxicity and lack of disease progression. Twelve (12) patients discontinued therapy because of progressive disease, 10 after two cycles, one after three cycles, and one after four cycles. Four (4) patients stopped treatment after one cycle because of significant toxicity, 1 for renal insufficiency requiring dialysis, 2 for central nervous system (CNS) toxicity, and 1 because of congestive heart failure. Another patient stopped treatment after two cycles because of a seizure that was caused by brain metastases. One (1) patient with stable disease elected to withdraw after four cycles with worse toxicity of grade 3 fatigue. One (1) patient was withdrawn after four cycles because of hypotension, and 1 after five cycles because of skin rash. A 71-year-old man, who had already experienced progressive disease, was found dead at home a few days after completing a fourth cycle of therapy. The exact, immediate cause of death could not be determined.

Tumor Response and Survival

Thirty-five (35) patients, who were known to have started treatment, were considered evaluable for response; no follow-up information was available on the 36th patient other than that he is known to have survived 2.5 years after starting treatment. Summary data regarding responses, duration of responses, and survival are shown in Table 2. There were 4 patients with objective tumor responses, 1 CR and 3 PR, for a response rate of 11% (3%–27%; 95% CI). The CR was in a 52-year-old woman with lung metastases. She subsequently developed breast

Table 2. Response Rates and Progression-Free Survival and Overall Survival for 35 Patients with Metastatic Renal Cell Carcinoma Who were Enrolled in CBRG 95-09

	Number of responders	*Months without disease progression*	*Months of survival*
Complete response	1	80	80
Partial response	3	18, 7.4, 5.1	24, 22, 12
Stable disease	14	36, 25, 20, 17, 16, 11, 9.1, 5.9, 5.8, 4.8, 3.9, 3.6, 2.9, 2.5	86, 74+, 48, 41, 39, 38, 27, 24, 22, 19, 18 16, 11, 10, 6.3
Progressive disease	16	2.3, 2.1, 2.0, 2.0, 2.0, 1.8, 1.8, 1.7, 1.7, 1.7, 1.7, 1.6, 1.4, 1.3, 1.1, 0.9	76, 21+, 17, 12, 11, 10, 9.8, 9.5, 8.2, 6.4, 4.7, 4.3, 4.3, 4.2, 4.1, 1.6
Inevaluable for response	1	—	31
Total	35	Median = 2.5 months	Median = 15.0 months

CBRG, Cancer Biotherapy Research Group.

cancer and succumbed to that malignancy, but her RCC never recurred. PRs were seen in a 61-year-old woman with lung metastases, a 65-year-old man with lymph node metastases, and a 57-year-old man with lung, lymph node, and adrenal metastases. The response rate among nephrectomized patients was 4/30 (13%) and 0/5 for patients who had not undergone nephrectomy. The response rate among nephrectomized patients who had not received any other therapy prior to treatment in this protocol was 3/17 (18%), compared to 1/18 (6%) for all other patients. Thirty-four (34) patients have died; only 2 were living at the time of this analysis. The median EFS and PFS was 2.5 months; no patients died because of therapy or other causes in the absence of progressive disease. The median OS was 15.0 months. The 1-year survival rate was 53%, 2-year survival rate was 30%, and 5-year survival was 12%.

Toxicity

The toxicities observed were typical of IL-2-based regimens. The frequencies of various grades of toxicities associated with this treatment plan are shown in Table 3. The most frequent toxicities were creatinemia (86%), transaminasemia (77%), nausea/vomiting (71%), chills or rigors (69%), hypotension (65%), fever (65%), fatigue (63%), and skin rash (60%). The highest average toxicity scores were 1.51 for fatigue, 1.49 for fever, 1.46 for hypotension, and 1.46 for chills. The most prevalent grade 3 or 4 toxicities were creatinemia (26%), hypotension 20%, transaminasemia (17%), bilirubinemia (16%), and fever (16%). Only 1 patient died within 2 months of starting therapy. This patient had rapidly progressive disease but also developed renal insufficiency that required dialysis. She died 1.6 months after starting treatment.

Table 3. Number out of 35 Patients with Metastatic Renal Cell Carcinoma Who Experienced Treatment-Related Toxicities During CBRG 95-09 Trial of Sequential Subcutaneous Interferon-Alpha Followed by Inpatient Hybrid Bolus and Continuous-Infusion IL-2

Class	*Grade*	*0*	*1*	*2*	*3*	*4*
Hematologic	Hemoglobin,	34	1	0	0	0
	WBC or ANC	17	8	7	3	0
	platelets	34	1	0	0	0
Renal	Creatinine	5	5	16	5	4
Hepatic	Bilirubin,	28	0	1	0	6
	SGOT,	8	14	7	3	3
	alkaline phosphatase	18	8	5	1	3
Gastrointestinal	Diarrhea,	20	10	4	1	0
	constipation	34	1	0	0	0
	mucositis,	31	2	2	0	0
	nausea/vomiting,	7	7	16	5	0
	anorexia	34	0	1	0	0
Cardiovascular	Hypotension,	12	3	13	6	1
	cardiac	33	0	2	0	1
Neurologic	Headache, CNS	25	2	4	3	1
Pulmonary	Oxygen saturation	23	2	6	4	0
General	Rash,	15	11	7	1	1
	pruritus, fever,	18	3	11	3	0
	infection, fatigue,	12	1	16	5	1
	chills, myalgia	25	6	2	1	1
		11	4	9	10	1
		11	3	16	4	1
		28	5	1	1	0

CBRG, Cancer Biotherapy Research Group; WBC, white blood count; ANC, absolute neutrophil counts; SGOT, serum glutamic oxaloacetic transaminase; CNS, central nervous system.

Grade of toxicity: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening. There were no treatment related deaths.

DISCUSSION

In CBRG 88-14, 6/89 (7%) patients with renal cell cancer responded to the concurrent administration of thrice-weekly interferon given concurrently with 5-day continuous infusion IL-2.[18] In CBRG 92-09, 2/22 (9%) patients responded to a hybrid schedule of high-dose bolus and 3-day continuous infusion IL-2 that had the same dose density, 90 MIU/m^2, as the earlier trial.[16] The 3-day schedule resulted in shorter hospitalizations and appeared to be less toxic. However, this population of patients, which had a median age of 62 years, had a median survival of only 10.5 months. In this trial, we explored sequencing s.c. IFN followed by the hybrid bolus/CIV IL-2. The rationale was that sequential IFN $\rightarrow$ IL-2 therapy might be less toxic than concurrent IFN/IL-2 therapy, and the pretreatment with IFN might increase the expression of certain tumor associated antigens and, perhaps, prime components of the immune system for stimulation by IL-2. This trial produced a response rate of 11%, but 95% confidence intervals from all three trials overlap. Although the median survival of more than 1 year was the best of any CBRG trial in metastatic renal cell cancer, the median progression-free survival of 2.5 months was similar to what had been seen in earlier trials. The toxicity profile was somewhat different in this trial than 92-09, in that fatigue and chills were much more problematic. Toxicity was such that treatment typically had to be given every 4 weeks, whereas in 92-09, IL-2 was delivered every 2 weeks. Thus, during the first 2 months of treatment, the dose-density of IL-2 was higher in CBRG 92-09 than in CBRG 95-09, even though both were inpatient treatments.

Table 4 summarizes all the CBRG trials that have been conducted with IL-2 in renal cell cancer.[16–21] Response rates, PFS, and EFS were also similar, but OS was better in this trial, perhaps because of more favorable prognostic features. Randomized trials have clearly shown that low-dose s.c. outpatient regimens of IL-2 with or without IFN are inferior to the high-dose bolus regimen in terms of response rate and survival of responders, although no survival difference has been seen for the entire group, perhaps because so few patients exhibit an objective response to IL-2.[19,20] The randomized, multicenter trial conducted between 1997 and 2000 by the Cytokine Working Group in patients with metastatic renal cell cancer, had one arm of high-dose bolus IL-2, 600,000 IU i.v. bolus every 8 hours for 14 doses (5 days), then 5 days off, then another 14 doses.[22] They observed a 23% response rate in that arm and a 17-month median survival. In that trial, the median age for patients receiving high-dose bolus IL-2 was 53 years with a range from

Table 4. Summary of Interleukin-2 (IL-2)-Based Trials in Renal Cell Carcinoma Conducted by the Cancer Biotherapy Research Group

Author/Reference	*Regimen*	*Number of patients*	*Response rate*	*Median EFS*	*Median OS*	*1-year survival*
Dillman[19]	IL-2/CTX	14	0%	2.3	8.0	30%
Dillman[19]	IL-2/LAK	31	3%	2.4	8.5	38%
Dillman[19]	IL-2/TNF	14	0%	2.2	7.4	40%
Dillman[19]	Hybrid IL-2 bolus/CIV	22	9%	3.4	10.2	40%
Oldham[18]	IL-2/IFNα	89	7%	2.8	10.5	42%
Oldham[20] Dillman[21]	IL-2/TIL	18	7%	3.0	9.9	48%
Soori[17]	s.c. IL2, IFN, CRA, 5FU	35	5%	2.8	10.9	50%
Dillman[a]	IFNα $\rightarrow$ IL2	35	11%	2.5	15.0	53%

Note: Superscripted numbers beside author names represent corresponding entries in References.

LAK, lymphokine activated killer cell; IFN-a, interferon alpha; TIL, tumor-infiltrating lymphocytes; TNF, tumor necrosis factor α; CTX, cyclophosphamide; CIV, continuous i.v. infusion; CRA, *cis*-retinoic acid; 5-FU, 5 fluorouracil; EFS, event-free survival; OS, overall survival; s.c., subcutaneous.

[a]Refers to this study.

25 to 74 years, and 57% of patients experienced severe or life-threatening hypotension, and 15% grade 3 or 4 CNS toxicity. The median age of patients in the single-institution U.S. National Cancer Institute trial was 48 years, and 36% of patients experienced severe or life-threatening toxicity hypotension, and 10% grade 3 or 4 CNS toxicity.[23] The median survival for patients in that trial was approximately 18 months in both arms.

CONCLUSIONS

It is worth noting that the only randomized trial comparing continuous infusion IL-2 and bolus IL-2 schedules in patients with RCC found no difference in response rates or survival, although all patients were to receive lymphokine-activated killer cells in that trial.[24] As previously discussed, the major limitation for IL-2 utilization is the ability of patients to tolerate such therapy.[25] Clearly, these schedules utilizing continuous-infusion intermediate-dose IL-2—with or without s.c. interferon—are an appropriate option for many patients who are not optimal candidates for high-dose bolus IL-2. Perhaps newer variations of schedule and administration of other agents may enhance efficacy and perhaps even reduce toxicity,[26] but experience has shown that it takes multicenter trials to establish benefit for the general patient population, and randomized trials to determine minor but significant differences in response rates and PFS rates.

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