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Phase II trial of suramin in patients with metastatic renal cell carcinoma

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Summary

This study was conducted to assess the efficacy and toxicity of suramin administered using a fixed dose schedule in patients with advanced renal cell carcinoma. Fourteen eligible patients with advanced renal cell carcinoma were enrolled and treated on a fixed dose schedule of suramin administered over 12 weeks. Suramin was administered by intravenous infusions over 1 hour. None of the 13 evaluable patients demonstrated an objective response. Only 3 patients completed the 12-week therapy course, with the majority developing progressive disease on therapy. The fixed dosage schedule was well tolerated with minimal to moderate toxicity. Suramin in this fixed dose schedule is well tolerated but has no activity in advanced renal cell carcinoma.

Introduction

Metastatic renal cell carcinoma remains a highly lethal disease with five-year survival ranging from 0 to 10% [1]. Therapeutic options are limited with minimal activity of hormonal and chemotherapeutic agents in advanced disease [2]. Biological response modifiers such as interleukin-2 and interferon can induce partial and complete responses in small numbers of patients, however a recent phase III trial demonstrated disappointing response rates of only 7.5 and 6.5% for interferon alfa-2a and interleukin-2, respectively [3].

Suramin is a polysulfonated naphthlyurea which has been used as an antiparasitic agent for 70 years [4]. It has been investigated as an antiviral agent in acquired immunodeficiency syndrome and as an antineoplastic agent in various solid tumors and hematologic neoplasms [5].

Suramin appears to have a narrow therapeutic range, is extensively protein bound, and has a plasma terminal half-life greater than 50 days. As a consequence, when administered by continuous infusion significant dose-limiting toxicities, including coagulopathy and polyradiculopathy, were observed [6]. Eisenberger and colleagues have demonstrated the feasibility of administering suramin in short intermittent bolus injections using adaptive control with feedback to adjust plasma drug concentrations [7]. Subsequent observations showed there was little interpatient variability in pharmacokinetic parameters, which led to a fixed schedule designed to maintain plasma concentrations in the 150–250 μg/ml range [8].

Two previous trials of suramin in metastatic renal cell carcinoma have been performed. La Rocca et al. treated 12 patients with metastatic disease with suramin administered by continuous infusion with serial monitoring of plasma suramin levels. There were no objective responses and toxicity included vortex keratopathy and renal insufficiency [9]. Motzer and colleagues treated 26 patients with advanced renal cell carcinoma with suramin administered as a daily continuous infusion of 350 mg/m^2 to a target serum plasma concentration of 280–300 μg/ml. One patient had a partial response and toxicity included immune-mediated thrombocytopenia and staphylococcus sepsis not associated with neutropenia [10]. Both of these trials enrolled a subset of patients who had received prior immunotherapy or chemotherapy.

Using the recently developed fixed dose schedule of suramin we performed a phase II trial in previously untreated patients with advanced renal cell carcinoma.

Methods

Study design Eligible patients had histologically confirmed renal cell carcinoma and evidence of progressive, bidimensionally measurable metastatic disease. Patients must have been disease-free from prior malignancies for at least 5 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at entry. Patients must not have received prior biological response modifiers or chemotherapy. Prior hormonal therapy was allowed as was radiotherapy if there was documented disease progression within the radiation field (if the only site of measurable disease was within the radiation portal). Patients could not be receiving anticoagulant therapy and patients with brain metastases were excluded. Adequate renal, hepatic, metabolic and bone marrow function was required as manifested by a serum creatinine $\leq$ 1.5 mg/dl, aspartate aminotransferase (AST) $<$ 2.5 times the upper limit of normal, normal prothombin time (PT) and partial thromboplastin time (PTT), serum calcium $\leq$ 10.5 mg/dl and a granulocyte count $\geq$ 1,500/μL and platelet count $\geq$ 100,000/μL. Written informed consent was obtained from all patients.

Therapy Suramin was provided by the Division of Cancer Treatment, National Cancer Institute. One-gram aliquots were reconstituted with 10 ml of sterile water for injection (USP), to yield a 10% (100 mg/ml) solution. Suramin was diluted for infusion in 500 ml of normal saline (USP). The initial dose (day 1) was divided into a test dose of 200 mg administered intravenously (IV) over a 2-hour period. Suramin was administered as a 1-hour IV infusion according to the schedule listed in Table 1. All patients were treated with hydrocortisone 20 mg orally in the morning and afternoon starting with day 1 of therapy. Therapy was held for grade 3 and 4 toxicity (NCI common toxicity criteria) and resumed at the point in the treatment cycle that therapy was held irrespective of the period of treatment delay. Therapy was continued for 12 weeks or until disease progression. Responding patients were eligible for a second 12-week cycle of therapy.

Baseline data Prior to study entry all patients underwent a physical examination, and ECOG performance status and weight were recorded. Pre-therapy determinations were made of hemoglobin level, leukocyte count with differential, platelet count, serum levels of electrolytes, creatinine, calcium, PT and PTT. With the exception of the serum calcium all these studies were repeated on a weekly basis during therapy.

Table 1. Suramin dosing schedule

Week	Treatment day	Dose (mg/m^2)
1	1	1000
	2	400
	3	300
	4	250
	5	200
2	8	275
	11	275
3	15	275
	19	275
4	22	275
5	29	275
6	36	275
7	42	275
8	49	275
9	57	275
10	64	275
11	71	275
12	78	275

Suramin was held for grade 2 or greater neuropathy, creatinine values $>$ 2.9 mg/dl, grade 3 or greater coagulopathy, neutrophil counts $<$ 1500/μL and platelet count $<$ 100,000/μL. In addition therapy was held for unexpected grade 2 or greater toxicity and was discontinued if vortex keratopathy developed. Tumor measurements were repeated at week 14 of study. A complete response (CR) was defined as the complete disappearance of all clinical detectable disease measured by physical examination and/or radiographic studies for a period of at least 4 weeks. Categorization as a partial response (PR) required a $\geq$ 50% decrease in the sum of the products of the 2 longest perpendicular dimensions of all measurable lesions for a period of at least 4 weeks without an increase in the size of any area known to contain malignant disease and without the appearance of any new areas of disease. Progressive disease (PD) was defined as an increase of at least 25% in the size of measurable lesions or the development of any new lesions.

Table 2. Patient characteristics

Characteristic	No. of patients (%)
Age (yrs)	
Median (range)	58 (38–73)
Female	4 (29)
Performance status	
Median (range)	1 (0–1)
Prior nephrectomy	6 (43)
Site of metastases	
Lung	5
Liver	5
Bone	6
Adrenal	3
Nodes/Soft tissue	4
Multiple sites	8

Results

From November 1994 through December 1997, 14 patients were entered into this trial and all were evaluable for toxicity. One patient developed grade 4 hyperglycemia and was removed from study at week 3 without reevaluation of disease status.

Clinical characteristics and treatment Patient characteristics are listed in Table 2. The median age was 58 (range, 38–73 years) and the majority of patients (pts) were male. Eight patients presented with synchronous metastases, 6 having had prior nephrectomy. Eight patients had multiple sites of metastatic disease. Three patients completed the 12-week course of suramin. The median number of doses administered (18 maximum) was 12 (range 7–18). Treatment delays were required in 6 patients secondary to neutropenia (2 pts), thrombocytopenia (1 pt), nausea and vomiting (1 pt), grade 2 AST (1 pt), grade 2 lipase (1 pt), and patient choice (1 pt).

Toxicity There were no treatment-related deaths. Therapy was generally well tolerated. No patient developed neurotoxicity or vortex keratopathy. Eleven patients developed a characteristic, transient grade 1–2 rash. All patients developed grade 1–2 fatigue. Grade 3 and 4 toxicities included diarrhea (G3, 1 pt), anemia (G3, 1 pt), neutropenia (G3, 1 pt; G4, 1 pt), metabolic (hyperglycemia G4, 1 pt), and pulmonary (dyspnea G3, 1 pt).

Response Thirteen patients were evaluable for response. One patient developed grade 4 hyperglycemia during week three of therapy and went off study, without reevaluation of disease status. One patient had stable disease following completion of therapy, and the other 12 patients had disease progression either during therapy (10 pts) or at the completion of protocol therapy (2 pts).

Discussion

Metastatic renal cell carcinoma remains a major dilemma to clinical oncologists. It is a disease whose natural history is typically aggressive and rapidly progressive but alternatively may have a more protracted course. This biological diversity is illustrated by the 6.6% response rate (including 3% complete responders) in the placebo arm of a recently completed phase III trial of gamma interferon in advanced renal cell carcinoma [11].

In the decade of the 1990s the biological response modifiers interleukin-2 (IL-2) and interferon alfa have become the primary therapies used to treat metastatic renal cell carcinoma. The optimal dose and schedules of these agents remains undefined, and the role of combination therapy with or without chemotherapy is uncertain. A recently reported large, phase III trial compared IL-2 administered intravenously at a dose of 18×10^6 IU per square meter, with interferon alfa-2a administered subcutaneously at a dose of 18×10^6 and with a combination of IL-2 and interferon alfa-2a [3]. Overall response rates were 6.5, 7.5 and 18.6%, respectively. Although a higher response rate to the IL-2 and interferon combination was observed there were no differences in overall survival and not surprisingly, the toxicity of the IL-2 plus alfa interferon combination arm was significant.

Suramin has documented activity in hormone-refractory metastatic prostate cancer. A recently completed phase III trial randomized 478 opiate-requiring advanced prostate cancer patients to receive either suramin (treated with the same fixed dosage schedule as used in this phase II trial) with hydrocortisone *versus* hydrocortisone alone. Although there was no improvement in overall survival, patients treated with suramin plus hydrocortisone demonstrated a statistically significant palliative response and delay in disease progression [5].

The mechanism of suramin's antineoplastic activity is unknown. Suramin is known to impact on

numerous growth regulatory systems including the inhibition of viral reverse transcriptase, inhibition of various growth factors including basic fibroblast growth factor, epidermal growth factor, insulin growth factor and many others [10]. The two previous clinical trials of suramin in advanced renal cell carcinoma were designed based on the rationale that renal cell carcinoma demonstrates altered expression of growth factors, making suramin an agent of potential interest [9,10].

This study was designed to assess the efficacy of suramin given on a fixed dose schedule in patients previously untreated for metastatic disease. The fixed dosage schedule utilized in this trial was well tolerated. We observed the characteristic "suramin rash" in the majority of patients, along with mild peripheral edema and progressive fatigue. These findings were consistent with the recently reported phase III trial [5].

Suramin, when administered using this fixed dose schedule, demonstrated essentially no activity in advanced renal cell carcinoma. We believe that further studies of suramin in advanced renal cell carcinoma are not warranted.

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