Phase II Trial of Suramin in Patients with Advanced Renal Cell Carcinoma: Treatment Results, Pharmacokinetics, and Tumor Growth Factor Expression


ABSTRACT

Twenty-six patients with advanced renal cell carcinoma were treated with suramin administered by continuous infusion, with dosing determined by a nomogram. One patient achieved a partial response and five patients achieved a minor response or had stable disease for >3 months. Toxicities included an immune-mediated thrombocytopenia in one patient and Staphylococcus sepsis that was not associated with neutropenia in five patients. Pharmacokinetic parameters were determined by the ADAPT II MAP-Bayesian parameter estimation program. Patient data were fit using a two-compartment open model and first-order rate elimination. This showed a wide interpatient variation in time to target level (median, 13.8 days), volume of distribution (median, 15.2 liters/m^3), and t_1/2(a) (median, 20.6 days). The patients who achieved a partial response, minor response, or stable disease had a slower elimination rate of suramin, compared to patients with progressive disease. Tumor specimens were obtained prior to therapy and were analyzed for the production of five different growth factor-specific RNA transcripts. These included transforming growth factor α, acidic fibroblast growth factor, basic fibroblast growth factor, and platelet-derived growth factor types A and B. No difference in the pattern of growth factor expression was seen in tumors of responding and nonresponding patients. Suramin does not have significant antitumor activity in renal cell carcinoma. The wide variability in pharmacokinetics suggests that individual dosing should be used in future trials of suramin for treatment of other malignancies. Pertinent corollary studies of tumor biology and clinical pharmacology should be included whenever possible in clinical trials in patients with renal cell carcinoma.

INTRODUCTION

The investigation of new agents in patients with advanced renal cell carcinoma is warranted by the lack of efficacy shown for the many cytotoxic agents which have been studied (1). Suramin, a polysulfonated naphthylurea, has been investigated as an antiparasitic agent (2), as an antiviral agent in the treatment for the many cytotoxic agents which have been studied (1). Suramin, a polysulfonated naphthylurea, has been investigated as an antiparasitic agent (2), as an antiviral agent in the treatment for the many cytotoxic agents which have been studied (1). Suramin, a polysulfonated naphthylurea, has been investigated as an antiparasitic agent (2), as an antiviral agent in the treatment for the many cytotoxic agents which have been studied (1). Suramin, a polysulfonated naphthylurea, has been investigated as an antiparasitic agent (2), as an antiviral agent in the treatment for the many cytotoxic agents which have been studied (1).

The antineoplastic effects of suramin are postulated to be related to its ability to interfere with the binding of specific growth factors, including PDGF^3 types A and B, fibroblast growth factors, and epidermal growth factor, to their cell surface receptors (10, 17, 18). Accordingly, the rationale for a clinical trial in patients with advanced renal cell carcinoma was the altered expression of growth factors in renal cell carcinoma, suggestive of an autocrine growth effect (19-22), and the selective concentration of the drug in the kidney (23). Therefore, to characterize suramin pharmacokinetics and growth factor expression in renal cell carcinoma patients and to identify prospectively those patients likely to respond to suramin treatment, a phase II trial of suramin was initiated with (a) a pharmacokinetic analysis and (b) an analysis of tumor specimens for expression of TGF-α, acidic fibroblast growth factor, bFGF, PDGF type A, and PDGF type B, using reverse transcriptase polymerase chain reaction.

PATIENTS, MATERIALS, AND METHODS

Between July 1990 and August 1991, 26 patients with advanced renal cell carcinoma were treated with suramin. Eligibility criteria included: bidimensionally measurable disease, WBC count of ≥3000 cells/μl, platelet count of ≥150,000 cells/μl, a normal coagulation profile, Karnofsky performance status of ≥60%, serum creatinine concentration of ≤1.5 mg/dl or creatinine clearance of ≥50 ml/min, serum bilirubin concentration of ≤1.5 mg/dl, no prior cytotoxic chemotherapy, prior treatment with not more than one biological response-modifier regimen, and written informed consent. Patients were excluded for significant cardiac disease (New York Heart Association Class III or IV), a history of a bleeding disorder or cerebrovascular accident, the presence of an active infection, or brain metastases.

Before chemotherapy, each patient was evaluated with a history and physical examination, chest radiography, an automated complete blood count, screening blood chemistry (alkaline phosphatase, lactate dehydrogenase, aspartate transglutaminase, blood urea nitrogen, creatinine, calcium, phosphorus, uric acid, total protein, albumin, and total bilirubin), creatinine clearance measurement, a coagulation profile, and a slit-lamp exam for the anticipated toxicity of vortex keratopathy.

Suramin was obtained from FBA Pharmaceuticals, Mobay Chemical Corporation (New York, NY), through the Division of Cancer Treatment, National Cancer Institute. One-g aliquots were reconstituted with 10 ml of sterile water for injection (USP), to yield a 10% (100 mg/ml) solution. Suramin was diluted further in 500 ml of 5% dextrose in water and was infused over 24 h.

A nomogram devised by the National Cancer Institute was used to individualize dosing based on weekly suramin plasma concentrations (Table 1). The intent of the dosing nomogram was to achieve a serum plasma concentration of 280–300 μg/ml while minimizing the risk of neurotoxicity, which had been correlated with peak plasma concentrations of >300 μg/ml (5, 15). The initial dose was divided into a test dose of 200 mg i.v. over 10 min, followed 20 min later by a continuous infusion of 50 mg/h for 24 h. These doses were titrated upward on the basis of drug-related adverse reactions. Adverse reactions included high levels of protein binding (≥99%) and predominantly renal elimination, with a prolonged terminal elimination half-life of approximately 50 days (3, 16).

Received 5/14/92; accepted 8/7/92.
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1 Supported in part by NIH Grants CM-57732 and CA-05826 and a National Kidney Foundation Young Investigator Award (D. M. N.), R. J. M. and D. M. N. are recipients of an American Cancer Society Cancer Development Award.

2 To whom requests for reprints should be addressed, at Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.
Expression time was quantified using:

\[ t_{\text{response}} = \text{duration of response} \]

The evaluation during treatment included a weekly serum screening profile, complete blood count, and measurement of prothrombin time, partial thromboplastin time, fibrinogen level, and thrombin time. The suramin infusion was withheld if the serum prothrombin time was >17 s (normal, <12 s), the serum aspartate transglutaminase level was >150 mg/dl (normal, <35 mg/dl), the serum creatinine level was >2.5 mg/dl (normal, <1.3 mg/dl), or any symptoms which suggested a suramin-related peripheral neuropathy or any grade 3 or 4 toxicity was present.

An evaluation of indicator lesions was performed monthly. Suramin plasma concentrations were obtained weekly after the infusion was discontinued. Patients without any evidence of progression were considered for subsequent cycles when the serum suramin level was £100 mg/ml. Patients with suramin-related peripheral neuropathy or any grade 3 or 4 toxicity were discontinued. Patients without any evidence of progression were considered for subsequent cycles when the serum suramin level was £100 mg/ml. Patients with suramin-related peripheral neuropathy or any grade 3 or 4 toxicity were discontinued.

All patients were treated with hydrocortisone (25 mg each morning and 15 mg each afternoon, p.o.) at the start of therapy and thereafter. Vitamin K (10 mg s.c.) was administered weekly during suramin infusion. The evaluation during treatment included a weekly serum screening profile, complete blood count, and measurement of prothrombin time, partial thromboplastin time, fibrinogen level, and thrombin time. The suramin infusion was withheld if the serum prothrombin time was >17 s (normal, <12 s), the serum aspartate transglutaminase level was >150 mg/dl (normal, <35 mg/dl), the serum creatinine level was >2.5 mg/dl (normal, <1.3 mg/dl), or any symptoms which suggested a suramin-related peripheral neuropathy or any grade 3 or 4 toxicity was present.

An evaluation of indicator lesions was performed monthly. Suramin plasma concentrations were obtained weekly after the infusion was discontinued. Patients without any evidence of progression were considered for subsequent cycles when the serum suramin level was £100 mg/ml, and dosage was administered according to Table 1.

Standard response and toxicity criteria were applied (25). "Stable disease" had to be maintained for at least 3 months from the day of evaluation following the first cycle of therapy. The duration of response was determined from the date of initiation of therapy.

Pharmacokinetic Analysis. Individual pharmacokinetic parameters were determined during the first cycle of therapy using the ADAPT II MAP-Bayesian parameter estimation program (26). Patient data were fit using a two-compartment open model and first-order rate elimination.

Individual pharmacokinetic determinations included:

\[ V_c = \text{volume of central compartment distribution} \]
\[ V_p = \text{volume of peripheral compartment distribution} \]
\[ V_s = \text{volume of steady-state distribution} (V_c + V_p + V_s) \]
\[ CL_d = \text{distributional clearance} \]
\[ CL_t = \text{total body clearance} \]
\[ t_{1/2\alpha} = \text{distributional half-life} \]
\[ t_{1/2\beta} = \text{terminal half-life} \]
\[ K_e = \text{elimination rate} \]
\[ T_{\text{target}} = \text{time to reach target concentration} \]
\[ TCD = \text{total cumulative dose} \]

Exposure time was quantified using:

\[ \text{Time (days) suramin level} > 100 \mu g/ml \]

Population pharmacokinetic pairs used in the MAP-B Parameter

### Table 1: Nomograms for dose of suramin

<table>
<thead>
<tr>
<th>Suramin level (µg/ml)</th>
<th>Infusion (mg/m²/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cycle</td>
<td></td>
</tr>
<tr>
<td>0–149</td>
<td>425</td>
</tr>
<tr>
<td>150–199</td>
<td>350</td>
</tr>
<tr>
<td>200–240</td>
<td>262</td>
</tr>
<tr>
<td>241–280</td>
<td>200</td>
</tr>
<tr>
<td>&gt;280</td>
<td>Discontinue suramin</td>
</tr>
<tr>
<td>Second and subsequent cycles</td>
<td></td>
</tr>
<tr>
<td>0–149</td>
<td>350</td>
</tr>
<tr>
<td>150–199</td>
<td>280</td>
</tr>
<tr>
<td>200–240</td>
<td>200</td>
</tr>
<tr>
<td>&gt;250</td>
<td>Discontinue suramin</td>
</tr>
</tbody>
</table>

* Patients whose levels remained below 100 µg/ml even at a dose rate of 425 mg/m²/day had their dose rate increased by 25% each 7 days until their blood levels reached 150 µg/ml, and then the nomogram was used.

A 16% assay variance was assigned to all suramin plasma concentration samples. Because the population pharmacokinetic parameters were determined from a small prostate cancer population, a confidence interval of 50% was assigned to the MAP-Bayesian priors.

The Wilcoxon test (28) was used to compare pharmacokinetic parameters and selected clinical characteristics, which included the response to therapy, the base-line renal function, and the pretreatment bidimensional tumor bulk.

**Tumor Analysis.** Biopsy of metastatic tumor was performed on 17 of 25 patients. Tumor was procured by computed tomography-guided needle biopsy (14-gauge Tru-cut needle; Travenol Laboratories) (12 patients) or through surgical excision (5 patients). The specimen was immediately brought to the Department of Pathology, where a representative piece of the tumor was dissected free of non-neoplastic tissue, snap-frozen, and stored at −70°C until the time of RNA extraction. Histological review was performed on a biopsy specimen obtained at the same time.

Preparation of RNA and cDNA from Tumor Specimens. Total RNA was extracted from tissue by the thiocyanate/guanidinium method (29), and cDNA was generated from total RNA as described previously (30).

**Polymerase-catalyzed Chain Reaction.** Amplification was performed as described (31), using a thermostable DNA polymerase (Promega Corp., Madison, WI). Electrophoresis of 10 µl of reaction mixture on a 1% SeaKem agarose (FMC Bioproducts, Rockland, ME) gel containing ethidium bromide was performed to evaluate amplification and size of fragments generated.

**Oligonucleotide Primers.** Oligonucleotide primers were synthesized using a 380A DNA synthesizer (Applied Biosystems, Foster City, CA). Gene sequences used to construct oligonucleotide primers were from published sources. Primer sequences were as described (32).

### RESULTS

**Response and Toxicity.** Patient characteristics and the results of therapy are shown in Table 2. Five patients had been treated previously with interleukin 2 and α2a interferon. One of 26 (4%; 95% confidence interval, 0–19%) evaluable patients achieved a partial response of 8-month duration in a hepatic metastasis and received four cycles of therapy. Two patients achieved minor responses of 5- and 14-month duration and were treated with three and five cycles of suramin, respectively. Three patients who were treated with three cycles of therapy have stable disease at 8+, 12+, and 16+ months.

The observed toxicities associated with suramin are shown in Table 2. Four patients had treatment discontinued because of toxicity. One patient developed fever, hypotension, progressive dyspnea with bilateral pulmonary infiltrates, renal insufficiency (serum creatinine, 3.2 mg/dl), and prolonged prothrombin and partial thromboplastin times with hypofibrinogenemia. Suramin administration to the patient was discontinued (level, 166 µg/ml) and appropriate antibiotics and intensive care unit support were initiated. No infectious etiology was found and the patient recovered fully. The second patient developed profound thrombocytopenia (platelet count, 5000/mm³) after 10 days of therapy. An evaluation including a bone marrow aspiration, coagulation profile, and antiplatelet antibody assay suggested an immune-mediated thrombocytopenia as the etiology. The thrombocytopenia resolved with the discontinuation of suramin and the administration of i.v. γ-globulin therapy. The third patient had treatment terminated because of renal insufficiency.
(serum creatinine, 2.6 mg/dl) and a cellulitis associated with a peripheral i.v. catheter. The fourth patient had therapy discontinued because of sepsis accompanied by hypotension.

Five patients had sepsis that was not associated with neutropenia. The organisms isolated from blood cultures were *Staphylococcus aureus* (two patients), coagulase-negative *Staphylococcus* (two patients), and *Proteus mirabilis* and coagulase-negative *Staphylococcus* in polymicrobial sepsis (one patient). A vortex keratopathy was noted in eight patients and symptoms were ameliorated with artificial tears. There were not treatment-related deaths or grade III/IV neurotoxicity.

**Pharmacokinetic Analysis.** Fig. 1 shows the suramin plasma concentrations for a representative patient who received three cycles of therapy and achieved a minor response. An analysis was performed using the serum plasma concentrations in 25 patients during the first cycle of therapy. The patient who was excluded had progressed after only 7 days of therapy and had not achieved the target serum plasma concentration. The estimated pharmacokinetic parameters of the 25 patients are shown in Table 3. Substantial interpatient variation existed for all pharmacokinetic parameters, including time to achieve target suramin level and rates of terminal elimination ($t_{1/2,\theta}$).

An analysis was performed to determine whether patients who achieved a response (partial or minor) or stable disease (6 patients) had a different pharmacokinetic profile, compared to patients who progressed (19 patients). The patients who achieved stable disease/response had a slower elimination rate, as determined by median $K_{\text{el}}$ ($P = 0.013$) and median $t_{1/2,\theta}$ ($P = 0.05$). An analysis of the relationship of renal function and tumor bulk to selected pharmacokinetic parameters was performed to determine whether these features might influence the volume of distribution or elimination and be predictive of a more favorable treatment outcome. Pharmacokinetic parameters of 13 patients with bidimensionally measurable disease of <50 cm$^2$ (nonbulky) were compared to 12 patients with tumors of >50 cm$^2$ (bulky). This analysis was repeated for tumor bulk of <25 cm$^2$ (10 patients) and >25 cm$^2$ (15 patients). The degree of tumor bulk was not associated with a greater volume of distribution ($V_m$, $V_c$, or $V_d$). Pharmacokinetic parameters were compared for patients with base-line creatinine clearance of >60 (19 patients) versus <60 ml/min (6 patients) and >85 (11 patients) versus <85 ml/min (14 patients). No significant differences were noted in drug elimination ($K_{\text{el}}$, $t_{1/2,\alpha}$, or $t_{1/2,\theta}$) according to base-line renal function.

**Growth Factor Expression.** Six patients had sufficient tumor material for the isolation of high quality RNA. Five of these specimens were obtained from excisional biopsy and one from a core needle biopsy. Other tissue specimens from needle biopsy were not adequate because either the tissue did not contain tumor cells on histological review or the RNA degraded prior to extraction. All six tumor specimens expressed RNA transcripts for ß-actin, indicating the integrity of the cDNAs used and their ability to serve as templates for amplification. Table 4 summarizes the expression of growth factor-specific RNA transcripts for a panel five growth factors. All samples expressed RNA transcripts for TGF-ß, bFGF, and PDGF type A. Five of the six

![Fig. 1. Suramin plasma concentrations (µg/ml) for a representative patient who was treated with three cycles of therapy and achieved a minor response.](image-url)
tumor specimens also expressed acidic fibroblast growth factor and PDGF type B.

Three of the tumors were from patients with a favorable treatment outcome: stable disease (RC-1), minor response (RC-4), or partial response (RC-6). The other three patients who had tumors studied for growth factors (RC-2, RC-3, and RC-5) showed progression. Although the sample size was small, there were no apparent differences in the types of growth factors expressed between patients who achieved a response (partial or minor) or stable disease and patients with a best response of progression.

DISCUSSION

This trial failed to demonstrate an adequate objective response proportion in patients with advanced renal cell carcinoma to support continued study. The observed toxicities of renal insufficiency, coagulopathy, dermatitis, and vortex keratopathy were similar to those previously encountered. The lack of neurotoxicity was most likely a result of using the nomogram, which avoided the excessively high suramin levels previously associated with neurotoxicity. A severe immune-mediated thrombocytopenia was noted in one patient, which resolved when therapy was discontinued. A particularly high incidence of *Staphylococcus* septicemia was noted during the infusion in patients with peripheral access catheters. Suramin has been reported to inhibit β-lactam-induced bacteriolysis of staphylococci and T cell mitogenesis (33, 34).

The investigation of suramin in clinical trials has been hindered by its long elimination half-life and narrow therapeutic window. While the dosage nomogram allows administration of suramin with relatively little neurotoxicity, the time to achieve therapeutic levels was lengthy and the exposure of tumor to therapeutic concentrations relatively brief. The results of *in vitro* studies (35, 36) and a recent phase I trial conducted in patients with advanced prostatic carcinoma (9) suggest that prolonged exposure to suramin may be necessary for optimal efficacy. The pharmacokinetic analysis showed a wide interpatient variability in pharmacokinetic parameters, suggesting that optimal dosing is more complex than previously reported (5). Furthermore, recent studies suggest that the pharmacokinetic parameters of suramin may be disease specific. The population pharmacokinetic parameters in patients with renal cell carcinoma differed from those previously reported both in patients with prostatic carcinoma treated at the Memorial Sloan-Kettering Cancer Center (8) and in patients with acquired immunodeficiency syndrome (8, 16). Variability of suramin pharmacokinetic parameters has resulted in the investigation of individual pharmacokinetic dosing and adaptive feedback control algorithms at our Center (37) and the University of Maryland Cancer Center (9). Adaptive feedback control appears to be a useful tool in maintaining plasma concentrations in a desired range, and studies with new dosing strategies are planned in the treatment of patients with advanced prostatic carcinoma (9, 37).

Patients with renal cell carcinoma who achieved stable disease or a response eliminated suramin with a longer half-life and had a larger volume of distribution than patients with a best response of progression. Tumor bulk has been postulated as an important factor that adversely affects the achievement of high suramin levels (5). However, no direct relationship was found between tumor bulk and the volume of distribution or between renal function and the rate of elimination. Interpatient variability of pharmacokinetic parameters and poor correlation of pharmacokinetic parameters with disease-specific indices may be attributable to the choice of pharmacokinetic model used in our analysis. Recently, a three-compartment first-order rate elimination model has been proposed to provide a better fit of plasma suramin concentration-time data. Use of a three-compartment first-order rate elimination model may result in a longer terminal half-life than our analysis showed. In addition, the total volume of distribution may differ in a three-compartment model and could explain the poor correlation between volume of distribution and tumor bulk.

Renal cancers express RNA for numerous growth factors, including TGF-α, transforming growth factor β, and fibroblast growth factor family members, and it has been suggested that an autocrine or paracrine growth effect is involved in renal tumor growth and metastases (19-22). In order to determine the presence of those growth factors, which could be affected by suramin, and to explore the relationship of tumor growth factor expression to response, biopsies were obtained prior to treatment. RNA transcripts were detected in tumors from both responding and nonresponding patients for numerous growth factors reported to be inhibited by suramin. Because a limited number of specimens were studied and the rate of response to suramin therapy was minimal, no correlation between the expression of a specific growth factor and treatment outcome was identified. However, the expression of bFGF may be an important prognostic factor in renal cell cancer and warrants further study in patients with advanced disease. In a study of primary renal tumors from 61 patients, most of whom had disease apparently confined to the kidney, patients with tumor expression of cytoplasmic bFGF, as determined by immunohistochemistry, had an inferior overall survival when compared to patients.

* Site of biopsy of metastatic renal cancer.
* Polymerase chain reaction product detected by ethidium bromide staining: +, positive; −, negative; w, low levels.
* aFGF, acidic fibroblast growth factor.
* SC LN, supraclavicular lymph node.
* SKRC-44, Sloan Kettering renal cancer cell line 44, derived from a nephrectomy specimen from a patient presenting with metastatic disease.

### Table 4 Expression of growth factor-specific RNA transcripts

<table>
<thead>
<tr>
<th>Sample</th>
<th>Histology</th>
<th>Site</th>
<th>TGF-α</th>
<th>aFGF</th>
<th>bFGF</th>
<th>PDGF type A</th>
<th>PDGF type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC-1</td>
<td>Renal cancer</td>
<td>Mediastinum</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>w</td>
</tr>
<tr>
<td>RC-2</td>
<td>Renal cancer</td>
<td>SC LN</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RC-3</td>
<td>Renal cancer</td>
<td>Skin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RC-4</td>
<td>Renal cancer</td>
<td>SC LN</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RC-5</td>
<td>Renal cancer</td>
<td>Femur</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RC-6</td>
<td>Renal cancer</td>
<td>Liver</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SKRC-44*</td>
<td>Renal cancer</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* M. Egorin, personal communication.
whose tumor cells lacked bFGF expression (38). Moreover, despite the lack of clinical correlations in the present study, we believe that clinical trials in patients with renal cell carcinoma should include appropriate corollary molecular studies to define tumor biology and identify biological markers for response to therapy (39).

In summary, the results of our trial and the trial reported by La Rocca et al. (11) show that suramin does not have significant antitumor activity in renal cell carcinoma. The wide interpatient variability of suramin pharmacokinetic parameters suggests that individual patient dosing should be used in future trials for other malignancies. The continued investigation of new agents in phase II trials is warranted for patients with advanced renal cell carcinoma. Pertinent corollary studies to better understand tumor biology and clinical pharmacology should be included in these trials whenever possible and the role of bFGF expression as a prognostic factor should be studied.

ACKNOWLEDGMENTS

We thank Lisa Gluck for expert technical assistance.

REFERENCES

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