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ORIGINAL ARTICLE

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A phase I/II study of continuous infusion suramin in patients with hormone-refractory prostate cancer: toxicity and response

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Abstract *Introduction*: Suramin is a synthetic polysulfonated naphthylurea which has been used for the treatment of African trypanosomiasis and onchocerciasis, but since the mid-1980s has received attention as a possible antiretroviral and antineoplastic agent. *Objective*: This clinical trial of suramin was undertaken as a phase I/II study in patients with hormone-refractory prostate cancer, with the hypothesis that the intensity of therapy with suramin could be increased significantly if measures were undertaken to maintain the plasma concentrations of the drug under 300 μg/ml. *Methods*: We report the clinical results of this trial, wherein patients were treated at three different targeted plasma suramin concentrations (275, 215 and 175 μg/ml) for varying periods of time (2, 4 or 8 weeks), with delivery of the drug by continuous intravenous infusion. *Results*: The major toxicity observed in this trial was neurologic, consisting of a motor and sensory peripheral neuropathy that resulted in both paresis and paralysis of the limbs. Nearly all of this severe (CTEP grade III, IV) neurologic toxicity was observed in the patients treated at a plasma suramin concentration of 275 μg/ml for 4 or more weeks. A single patient treated at 215 μg/ml for 8 weeks developed moderate (CTEP grade III) proximal lower extremity weakness, and no patient treated at 175 μg/ml developed this toxicity. The second most common toxicity observed was infection of the central venous catheter. The overall response rate for all of the evaluable patients was 17% (13 of 75 patients). In addition, prostate-specific antigen (PSA)-defined responses were observed in six patients receiving therapy at 175 μg/ml, but these responses were confounded by cessation of therapy with flutamide during suramin treatment. *Conclusions*: In summary, although plasma suramin concentrations were maintained below 300 μg/ml, neurologic toxicity nonetheless occurred with high frequency in patients treated at 275 μg/ml for 4 or more weeks. Therapy at 215 and 175 μg/ml was in general well tolerated, but central venous catheter-related infection, as well as the inconvenience and expense of continuous infusional therapy, make this method of drug delivery impractical. Only moderate antitumor activity was observed during this trial, but it is possible that both continuation of flutamide and flutamide withdrawal during suramin therapy confounded the assessment of suramin's activity in hormone-refractory prostate cancer.

Key words Suramin · Prostate cancer · Toxicity · Pharmacokinetics · Adaptive control with feedback · Concentration controlled trial · Flutamide · Flutamide withdrawal

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Introduction

Investigation of the potential antitumor activity of suramin began following observation of tumor regression in occasional patients treated with the drug during its evaluation as a treatment for AIDS [2, 3, 18]. Preliminary evidence of activity was first observed in adrenocortical carcinoma [13], and then in hormone-refractory prostate cancer [6, 14, 19] and follicular lymphomas [17]. While a myriad of mechanisms have

been offered as explanations for its antitumor activity (e.g. peptide growth factor antagonism, inhibition of glycosaminoglycan metabolism), an exact understanding has not been fully elucidated (Cooper et al., in preparation; 10, 19, 20, 23). Regardless of its mechanism of action, prolonged exposure of patients to the drug has been argued as necessary for suramin to exert an antitumor effect. In tissue culture, suppression of human prostate cancer cell survival requires that the cells be exposed to relatively high concentrations (200 to 300 μg/ml) of the drug for 96 to 144 hours [15].

Another hypothesis that prevailed at the time of the development of this clinical trial was that neurologic toxicity secondary to suramin was a function of its plasma concentration. In particular, plasma concentrations ≥ 350 μg/ml were thought to be strongly associated with the onset of an acute Guillain-Barré-like syndrome, with limb paresis or paralysis and less-pronounced sensory deficits, occasionally accompanied by bulbar and autonomic dysfunction. On the other hand, there appeared to be no association between the total cumulative dose of the drug and this toxicity. Therefore, it was reasoned that the drug's efficacy could be substantially increased by delivering it as a prolonged continuous intravenous infusion, maintaining plasma concentrations within the preclinically relevant range, but below those concentrations associated with neurologic toxicity [12].

This study compared both the toxicity and response data for patients treated at three targeted plasma suramin concentrations (275, 215 and 175 μg/ml) utilizing a continuous infusion regimen. Since initial studies suggested suramin has a narrow therapeutic window, the aim of the first part of this trial was to determine the maximum tolerated duration of continuous infusion suramin therapy, when targeting a plasma concentration of 275 μg/ml (2, 4 and 8 weeks of treatment). This plasma concentration (275 μg/ml) was chosen after a previous trial at the National Cancer Institute had shown that suramin could be administered at a targeted concentration of 300 μg/ml with limited toxicity, but the frequency of neurotoxicity was increased when plasma suramin concentrations increased above 350 μg/ml [12]. In an attempt to lower toxicity without compromising the efficacy seen in the previous study, suramin was administered in this trial by continuous intravenous infusion utilizing adaptive control with feedback, to maintain predetermined suramin plasma concentrations.

Methods

Patient eligibility

Patients were eligible for this study if they had progressive hormone-refractory prostate cancer. All patients were required to have progressive disease after their last therapeutic maneuver and treatment must have been completed as least 1 month prior to enrolling in this protocol. Each patient met the following eligibility criteria: (1) age greater than 18 years, (2) a histologic diagnosis of adenocarcinoma of the prostate confirmed by the National Cancer Institute's Laboratory of Pathology within the Clinical Center of the National Institutes of Health, (3) progression of disease demonstrated by a rising prostate-specific antigen (PSA) despite total androgen blockade, (4) life expectancy greater than 3 months, (5) Karnofsky performance status 80% or better, and (6) ability to make necessary trips from home to the National Cancer Institute for treatment and follow-up. All patients signed written informed consent prior to enrolling in this study and the protocol was reviewed and approved by the Institutional Review Board of the National Cancer Institute. The conduct of this trial was monitored by the Cancer Treatment Evaluation Program (CTEP) and no other forms of antitumor therapy were allowed during the study period (including radiation therapy).

Patients were excluded if they had a hemoglobin concentration less than 9 g/dl, a white blood cell count less than $3.0 \times 10^3/\mu l$, a platelet count less than $150 \times 10^3/\mu l$, any history of a bleeding diathesis or coagulation disorder and/or conditions requiring anticoagulation. Patients were also excluded if there was clinical or radiologic evidence of cerebral metastases, or past history or clinical evidence of stroke. Patients with a creatinine clearance of less than 60 ml/min were not enrolled in this study. Abnormalities of liver function tests that could not be attributed to metastatic disease (e.g. elevated alkaline phosphatase reflecting metastatic bone disease) and replacement of 50% or more of the liver parenchyma with metastatic disease were also exclusion criteria. Any patient having received chemotherapy, radiotherapy, or treatment with biologic response modifiers could not be placed on this trial until a minimum of 28 days had elapsed, and the patient had met the above criteria for progressive disease.

Pretherapy evaluation

All baseline studies documenting the extent of the patient's disease were completed within 2 weeks of the initiation of therapy with suramin. Radiographic and nuclear medicine studies obtained prior to the administration of suramin included CT scans of the chest, abdomen, and pelvis, bone scan and chest X-radiograph. Those radiologic examinations that were positive were repeated 1 month after completion of suramin therapy and every 3 months thereafter.

PSA was measured by the Hybritech (San Diego, Calif.) method with an upper limit of normal of 4.0 ng/ml. PSA was determined every week while patients were receiving suramin and monthly thereafter.

Response evaluation

A complete response required disappearance of any pretreatment tumor masses, complete normalization of the bone scan, and normalization of the PSA for at least 28 days. A partial response was defined as a decline in the PSA concentration by 50% or more on two consecutive occasions with at least 14 days separating the two measurements. Tumor mass regression was scored as a partial response if there was a 50% or more reduction in the sum of the products of the perpendicular diameters of all measurable lesions lasting for at least 28 days.

Progressive disease was defined as any of the following criteria: an increase in the sum of the products of the perpendicular diameters of all measurable lesions of more than 25%, and/or the appearance of new lesions; the development of one or more new lesions on bone scan; the need for radiation therapy; if any one of three consecutively rising PSA values was 50% or more than the baseline for those who never responded to therapy; or if any one of three consecutively

rising PSA values was 50% or more than the nadir for those who had some response to therapy. Regardless of the percentage change in serial PSA determinations, patients with a baseline or nadir PSA less than 20 ng/ml were not declared to have progressed until the PSA had increased by an absolute value of 10 ng/ml or more; this requirement was developed in order to avoid making erroneous conclusions from minor fluctuations in the PSA at these low concentrations.

Toxicity assessment

Toxicity was determined by the established criteria of the National Cancer Institute's CTEP [25].

Suramin administration

Suramin (Mobay Pharmaceutical Company) was supplied in 10-ml vials containing 1 g suramin sodium (USP) as a sterile freeze-dried powder. Vials were reconstituted in 10 ml sterile water. Initial intravenous doses of suramin were further diluted in 150 ml 0.9% NaCl (NS) and infused over 1 h. When the drug was to be delivered by continuous intravenous infusion, it was diluted to a final volume of 90 ml and placed into a Pharmacia-Deltec portable infusion pump. The drug in the pump's reservoir was replaced every 24 h or 48 h. Because of the prolonged nature of this continuous infusion therapy, all patients were required to have central venous catheters.

Treatment program

Suramin was administered by an initial intermittent intravenous infusion followed by a continuous intravenous infusion. Continuous infusion therapy was aimed at the achievement and subsequent maintenance of a specified plasma concentration for a specified period of time. In order to achieve and maintain the specified plasma suramin concentration, an adaptive control with feedback strategy was employed [4, 22].

On day 1 of therapy, suramin was given as a single intravenous infusion, 15 mg/kg over 1 h. No further dosing with suramin was given until day 5. In the interim, serial blood samples were obtained for the determination of plasma suramin concentrations by high performance liquid chromatography [24]. From the single intermittent dose of suramin and the ensuing plasma suramin concentrations, an initial estimate of each patient's pharmacokinetics was made, using a three–compartment open linear model. Estimation of individual pharmacokinetics was performed in the context of a population pharmacokinetic model, i.e. a Bayesian approach. These estimations were performed using the Abbottbase Pharmacokinetic Systems program (Abbott Laboratories, Abbott Park, Ill; version 1.0 for DOS). On day 5, patients began a continuous intravenous infusion of suramin, the rate of which was calculated to achieve the specified plasma suramin concentration by day 10. Thereafter, the infusion rate was adjusted to maintain this concentration for a predetermined period of time (2, 4 or 8 weeks). Plasma suramin concentrations were determined at least twice weekly during therapy, and individual pharmacokinetics were re-estimated once weekly. Dosing recommendations were provided for the subsequent 7 days in an attempt to maintain the targeted plasma suramin concentrations (275, 215 and 175 μg/ml).

In the first phase of the study, the rate of the continuous suramin infusion was calculated to maintain a constant plasma suramin concentration of 275 μg/ml. Successive cohorts of patients were assigned to have that concentration maintained for 2, 4 or 8 weeks. After determining that maintenance of a plasma suramin concentration of 275 μg/ml for 4 or more weeks produced unacceptably severe and frequent neurologic toxicity, it was decided to treat a second cohort of patients at a concentration of 215 μg/ml for 8 weeks. While this latter therapy did prove less toxic, a single patient in the 215 μg/ml cohort did develop moderate lower extremity proximal muscular weakness (CTEP grade III), prompting the treatment of a third and final cohort of patients at 175 μg/ml for 8 weeks. Details of the pharmacokinetic model used in this trial have been reported previously [4].

Concomitant hormonal therapy

Those patients not having undergone orchiectomy continued to receive medical castration with leuprolide (Depot Lupron, TAP Pharmaceuticals, Deerfield, Ill.; 7.5 mg intramuscularly every 4 weeks). In order for patients to be eligible for this trial they were required to have failed therapy with flutamide; however, they continued to receive flutamide throughout their suramin treatment. Seven patients treated at the 175 μg/ml concentration, discontinued flutamide while receiving suramin and were not eligible for response evaluation, but they were evaluated for toxicity (see Results). In addition, because of the known adrenocortical toxicity of suramin, all patients received replacement doses of hydrocortisone (20 mg orally every morning, 10 mg orally every evening), and continued such replacement therapy indefinitely.

Results

Patient population

The patient pretreatment characteristics of the population are listed in Table 1. All patients had demonstrated evidence of disease progression in the face of total androgen blockade (medical or surgical castration plus flutamide) before initiating therapy with suramin. One-third of the patients had been treated with a second-line hormonal manipulation before enrolling in this protocol, and more than 50% had previously received radiotherapy as primary treatment for localized disease or for palliation. The vast majority of patients (90.5%)

Table 1 Patient demographics

Pretreatment characteristics	
Total number of patients	86
Number Evaluable	
Toxicity	85
Response	75
Mean Age (years) ± SD	64.4 ± 7.6
Range	47–80
Bone only metastasis (%)	76 (90.5)
Measurable soft tissue disease (%)	8 (9.5)
Previous Treatment	
Total androgen blockade	
LHRH antagonist (%)	44 (52.4)
Orchiectomy (%)	40 (47.6)
2nd hormonal treatment (%)	29 (34.5)
Radiation therapy (%)	58 (69.0)
Chemotherapy (%)	23 (27.4)
Biologic response modifier (%)	3 (3.6)
Baseline PSA (μg/ml)	
Mean	546.1
Range	8.6–4040.1

had disease limited to bone. Of the 86 patients entered on this study, 85 were evaluable for toxicity. One patient could not be evaluated for toxicity or response because his medical record was damaged while being copied to microfiche. Patients were excluded from response evaluation if they did not complete the initial infusion regimen designed to achieve the targeted suramin plasma concentration on days 1–10 ($n = 3$) or had their flutamide discontinued while receiving suramin ($n = 7$).

Suramin delivery

Suramin was administered for 2, 4 or 8 weeks. The initial patients were given a maintenance infusion for 2 weeks. Subsequent patients were treated on 4- and 8-week maintenance infusion schedules. In addition, some patients in the 2- and 4-week groups ($n = 3$ and $n = 1$, respectively) received up to three cycles of therapy.

Table 2 shows the number of patients treated by the various dosing schemas used in this trial. The administration of suramin by continuous infusion at a targeted plasma concentration of 275 μg/ml was relatively well tolerated when given over a 2-week (duration I) or 4-week period (duration II). Suramin was administered for 2 weeks to eight patients. Three of those patients received more than one cycle (one patient received three cycles, two patients received two cycles). The number of days of therapy delivered per patient per cycle was 12.1 ± 3.5 days (mean ± SD). Eight patients received suramin targeted to a plasma concentration of 275 μg/ml for 4 weeks. One patient received two cycles of therapy. The 4-week infusion group received 24.7 ± 6.3 days of therapy per cycle (mean ± SD).

Patients treated on duration III (8-week infusion) and at a targeted concentration of 275 μg/ml were less likely to complete a full course of therapy than those patients in Duration I and II cohorts. Only 4 of 22 evaluable patients completed a full 8-week course when treated at this dose level (275 μg/ml). The duration of continuous infusion suramin given in this cohort was 30.7 ± 19.4 (mean ± SD) days. This inability to deliver an 8-week course of therapy led to the lowering of the targeted plasma suramin concentration to 215 μg/ml in the next cohort of patients.

The success in delivering suramin by continuous infusion at a targeted concentration of 215 μg/ml is shown in Table 2. In this group, 26 patients were treated, and 18 (69.2%) received at least 95% of the planned infusion. The average number (± SD) of days of treatment that each patient received was 48.6 ± 15.0 days.

In an effort to further reduce toxicity during an 8-week infusion the target concentration was reduced to 175 μg/ml. A group of 22 patients were treated at a targeted plasma concentration of 175 μg/ml for 8 weeks and all patients (100%) completed at least 95.0% of the planned infusion. The average duration of therapy (± SD) delivered was 50.3 ± 10.5 days.

Toxicity

Toxicity was substantial on this trial, especially at duration III with a target plasma concentration of 275 μg/ml (see Table 3). Neurotoxicity was the most commonly seen major toxicity (CTEP grade III–IV). Paresthesias and motor nerve neuropathy occurred most frequently in these patients. In a number of patients, these side effects resolved over a period of months. One patient developed a severe cervical radiculopathy after 4 weeks of continuous infusion suramin at a targeted dose of 275 μg/ml. Despite cessation of suramin, the patient's neurologic symptoms progressed

Table 2 Summary of patients treated at each suramin dose level

Duration level	Target concentration of suramin (μg/ml)	Number of patients treated	Number of cycles started[a]	Number of patients completing cycle[b]	Average number of days of of therapy (% of cycle)[c]
I (2 weeks)	275	8	12	8	12.1 ± 3.5 (86.3%)
II (4 weeks)	275	8	9	4	24.7 ± 6.3 (88.1%)
III (8 weeks)	275	22[d]	22	4	30.7 ± 19.4 (54.8%)
III (8 weeks)	215	26	26	18	48.6 ± 15.0 (86.8%)
III (8 weeks)	175	22	22	22	50.3 ± 10.5 (89.9%)

[a] Total number of cycles administered
[b] Number of patients receiving > 95% of planned infusion
[c] Average number of days of therapy delivered per patient cycle; mean ± SD
[d] One pt not evaluable for toxicity or response

Table 3 CTEP grade III–IV toxicity by target plasma concentration and duration of infusion

Duration level	*N*	Neuro-motor	Neuro-constipation	Infections	Cardiac	Renal	Hemato-logic	Fever	Hepatic	Coagulation	Other
I (2 weeks)	8	–	–	–	–	–	1	–	–	–	–
II (4 weeks)	8	1	–	–	–	–	–	–	–	–	–
III (8 weeks)	21	6	1	2	–	–	1	–	3	1	–
III (8 weeks)	26	1	1	–	2	1	1	–	–	–	1
III (8 weeks)	22	–	–	–	1	–	2	2	–	–	–

Table 4 Toxicity of continuous infusion suramin

Duration level	Target concentration (μg/ml)	*N*	CTEP grade I and II	CTEP grade III and IV	Death
I (2 weeks)	275	8	8 (100%)	1 (12.5%)	0
II (4 weeks)	275	7	7 (87.5%)	1 (12.5%)	1
III (8 weeks)	275	21	21 (100%)	14 (66.7%)	1
III (8 weeks)	215	26	26 (100%)	7 (26.9%)	0
III (8 weeks)	175	22	22 (100%)	5 (22.7%)	0

to a Guillain-Barré-type syndrome with marked upper extremity weakness. Nerve conduction studies demonstrated a sensorimotor polyneuropathy affecting motor neurons more than sensory neurons. The patient died of sepsis approximately 2 weeks after the onset of his symptoms.

One additional death was associated with suramin and occurred in a patient in the duration III cohort targeted to a suramin concentration of 275 μg/ml. This patient developed bilateral subdural hematomas on day 41 of his cycle. He went on to develop acute renal failure, and DIC before dying.

Toxicities according to duration and plasma concentration are shown in Table 4. Duration I and II patients uniformly experienced CTEP grade I–II toxicity usually consisting of fatigue, rash and mild paresthesias. One patient in the duration I group experienced CTEP grade IV thrombocytopenia. The single patient who experienced CTEP grade IV toxicity in the duration II group developed the Guillain-Barré-type syndrome described above.

Toxicity was prohibitive in patients targeted to receive 8 weeks of suramin at 275 μg/ml. In this group, 14 (66.7%) developed CTEP grade III or IV toxicity. Seven patients in this group developed CTEP grade III or IV neurologic toxicity. There was one case of *Staph. aureus* endocarditis. Hematologic toxicity occurred in one patient, and three patients in this group developed CTEP grade III or IV hepatic toxicity. A further breakdown of CTEP grade III–IV toxicity for all groups is shown in Table 5.

The incidence of CTEP grade III or IV toxicity in duration III patients targeted to 215 and 175 μg/ml was 26.9% and 22.7%, respectively. A higher percentage of patients treated at 175 μg/ml were able to complete a 56-day course of therapy, compared to patients targeted to a plasma concentration of 275 μg/ml. CTEP grade IV toxicity was not encountered in the 175 μg/ml group. CTEP grade IV neurotoxicity was also absent in the group of patients targeted to receive a plasma suramin concentration of 215 μg/ml for 8 weeks; however, one patient developed CTEP grade III neurotoxicity in this treatment group.

Table 5 CTEP grade III and IV toxicity profile for all patients treated with continuous infusion suramin (total valuable patients, $n = 85$)

Toxicity	Number of patients (%)
Neurological	10 (11.7%)*
Neuromotor	8
Neuroconstipation	2
Infectious	2 (2.4%)
Endocarditis	1
Pneumonia	1
Cardiac	3 (3.5%)
Congestive heart failure	1
Atrial fibrillation	2
Renal	1 (1.2%)
Acute renal failure	1
Hematologic	5 (5.9%)
Anemia	2
Thrombocytopenia	1
WBC/neutropenia	2
Fever	2 (2.4%)
Hepatic	3 (3.5%)
Bilirubin	1
ALT/AST	2
Coagulation	1 (1.2%)
Other	1 (1.2%)
Total	28 (32.9%)

Infectious complications were common in this trial, the most common manifestation being bacteremia secondary to central line infection. No patient required vasopressor support care for bacteremia secondary to central line infections and the vast majority received intravenous antibiotics as outpatients while continuing to receive suramin therapy.

CTEP grade III and IV neuromotor toxicity occurred in 8 of 85 patients (9.4%) receiving suramin in this trial (all CTEP grade IV toxicities occurred in patients in the 275 μg/ml target group). This toxicity was most commonly manifest as symmetric paresthesias followed by lower extremity weakness. Two additional patients developed severe ileus on suramin, which resolved upon cessation of suramin treatment.

Response

Response rates are shown in Table 6. The majority of patients had disease limited to bone and could only be evaluated by bone scan and changes in PSA. Improvement in pain was not used as a criterion by which to judge response, both because of its subjective nature and because many patients enrolled in this trial had their pain management optimized at the same time that suramin therapy was initiated.

The overall response rate (complete plus partial responses) for all of the evaluable patients entered on this study was 17.3% (13 of 75 patients). In addition, 14 patients (18.6%) had sustained declines in their PSA of less than 50% from baseline. Patients treated in duration I and II both had response rates of 12.5% (2 of 16 patients). Duration III patients treated at a targeted dose of 275, 215 and 175 μg/ml had response rates of 21.1%, 12.0% and 26.7%, respectively.

An additional six patients in the duration III group ($n = 7$) targeted to a suramin concentration of 175 μg/ml had responses, but were excluded from the response data because they had flutamide withdrawn while they were receiving suramin. Two of the seven patients in the nonevaluable group had response durations of ≥ 52 weeks. Three of nine patients with soft tissue disease had objective tumor regression while on study; however, none of these responses could be attributed to suramin alone. Two of the three patients underwent flutamide withdrawal while on study.

Table 6 Overall response data (PSA)

Duration level	*n*	Number with > 50% decline	Overall response (%)
I (275 μg/ml)	8	1	12.5
II (275 μg/ml)	8	1	12.5
III (275 μg/ml)	19	4	21.1
III (215 μg/ml)	25	3	12.0
III (175 μg/ml)	15	4	26.7
Total	75	13	17.3

Duration I suramin at a concentration of 275 μg/ml for 2 weeks; duration II suramin at a concentration of 275 μg/ml for 4 weeks; duration III suramin at a concentration of 275 μg/ml for 8 weeks, at 215 μg/ml for 8 weeks, or at 175 μg/ml for 8 weeks; none of the patients had a complete response

Discussion

The above results demonstrate that suramin has moderate activity in hormone-refractory prostate cancer when given by continuous infusion for 8 weeks at targeted plasma concentrations of 175, 215 and 275 μg/ml. A targeted plasma concentration of 175 μg/ml was relatively well tolerated by patients. However, neurologic toxicity was the most common CTEP grade III and IV toxicity encountered in this trial. It occurred most frequently in the patients targeted to a plasma concentration of 275 μg/ml and CTEP grade IV was absent in the 215 and 175 μg/ml target groups. Neurotoxicity constituted 35.7% of all CTEP grade III and IV toxicity. Further analysis of neurotoxicity in these patients suggests that exposure to suramin plasma concentrations greater than 200 μg/ml for more than 50 days is associated with an increased risk for neurotoxicity [1].

Central venous catheter infections were another significant source of morbidity in this trial, a finding that is not surprising, given that continuous infusion suramin is associated with an increased rate of infection when compared to intermittent infusional therapy [19]. While none of the infections was severe or life threatening, they did necessitate intravenous antibiotics, most commonly vancomycin.

Overall, the toxicity profile seen in this study resembled that of previous suramin studies, although the degree of toxicity was lessened, especially in the cohorts receiving lower targeted concentrations of suramin. [1] In addition to the toxicities mentioned above, fatigue, rash, and mild paresthesias were encountered in a significant number of patients, although these toxicities were mild (CTEP grade I and II). Our results suggest that when suramin is given by continuous infusion at a targeted plasma concentration of 175 μg/ml, the toxicity profile is equivalent to intermittent suramin infusional therapy in terms of hematologic and neurologic toxicity [6–8]. Infections, however, especially from central venous catheters, are greatly increased in patients who receive this drug by continuous infusion.

The lower toxicity rate encountered with the lowest targeted plasma concentration of suramin did not appear to adversely effect the response rate. The overall response rate for evaluable patients treated at the 175 μg/ml target concentration was 26.7%. Seven additional patients in this group underwent flutamide withdrawal while they were receiving suramin and six of those patients had what would be considered a partial response. These patients were not included in the response data. Flutamide withdrawal has been shown to have therapeutic efficacy in some patients (approximately 33%) with progressive disease while receiving flutamide, and either medical or surgical castration [9, 21]. Six of the seven patients (85.7%) who underwent flutamide withdrawal in the presence of suramin

responded with a decline in their PSA by 50% or more. Two of these patients had responses lasting 365 and 379 days, respectively.

While the withdrawal of flutamide appears to have influenced the response of some of the patients in this trial, responses were still seen in patients who continued receiving flutamide, even after documented progressive disease. The overall response rate of the trial (evaluable patients), in the absence of flutamide withdrawal was 17.3%. In the group of patients receiving 56 days of suramin targeted to 175 μg/ml, exclusion of the flutamide-withdrawal patients yielded a response rate of 26.7% (4 responses in 15 patients). In addition, responses were seen in patients treated at all targeted suramin concentrations. The overall response rate seen in this trial is markedly lower than that reported by Eisenberger et al. [6–8]. The major differences between these two trials is that all patients in the University of Maryland trial underwent flutamide withdrawal an average of 24 days prior to starting suramin and received suramin by intermittent infusion rather than by continuous infusion. The therapeutic manipulation of flutamide withdrawal may have played an unknown role in their reported response rate; however, a reanalysis of this maneuver has not supported a decreased response rate of suramin.

The overall response rate in our trial is also lower than that seen in the first published trial of suramin in prostate cancer carried out at the National Cancer Institute [16, 19]. The response rate in the previous trial for patients with disease limited to bone only was 38%. The lower overall response rate seen in this trial may be due to the number of patients who did not receive the optimal duration of therapy due to toxicity or that all patients evaluated for response continued flutamide while receiving suramin. If one subscribes to the mutated androgen receptor theory (mutation in codon 877) to account for the withdrawal phenomenon, then flutamide should act as an agonist in a subset of patients. We have recently completed a separate trial aimed at evaluating the activity of suramin in patients in whom the flutamide withdrawal and hydrocortisone variables were removed. All patients were required to have progressive disease following the addition of hydrocortisone and flutamide discontinuation. In that study, we found that 7 of 37 evaluable patients (19%; 95% confidence intervals 8.0% and 35.2%) had a $\geq$ 50% decline in PSA associated with suramin [5].

The reason for a lack of correlation between increasing suramin concentration and increased response rate is not immediately clear. The inability of patients to complete a full 8-week course when targeted to a plasma concentration of 275 μg/ml could have played a role. It is possible that in order for suramin to be active, it must reach a certain threshold concentration above which there is no further antitumor effect. Given the different effects mediated by the growth factors suramin is capable of binding, direct dose response interaction may be too simplistic a mechanism for explaining suramin's antitumor activity. At present, clinical trials utilize a fixed-dose intermittent schedule of suramin [11]. That regimen is significantly less intense than the 175, 215 or 275 μg/ml continuous intravenous infusion regimens (8-week durations) reported here. However, the fixed-dose intermittent schedule will most likely not produce a substantial degree of neurologic complications.

In summary, suramin is an agent that has moderate activity in hormone-refractory prostate cancer. When suramin is given as a continuous infusion the response rate was not improved over that of intermittent dosing and was not enhanced by increasing the plasma concentration. The delivery of suramin by continuous infusion poses practical problems and the use of central venous catheters in this setting is complicated by a high rate of infection. Further studies are needed to define both the optimal dosing regimen and the most effective sequencing combinations for this agent.

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