Cancer Chemother Pharmacol (2002) 50: 1–5
DOI 10.1007/s00280-002-0458-y

ORIGINAL ARTICLE

**Christopher W. Ryan · Everett E. Vokes
Nicholas J. Vogelzang · Linda Janisch
Ken Kobayashi · Mark J. Ratain**

A phase I study of suramin with once- or twice-monthly dosing in patients with advanced cancer

Received: 25 September 2001 / Accepted: 1 March 2002 / Published online: 9 May 2002

Abstract *Purpose:* The optimal schedule of administration of suramin has not been well defined. The purpose of this study was to determine the maximum tolerated dose and toxicities of suramin when administered using a fixed dosing scheme on a once- or twice-monthly schedule. *Methods:* A total of 40 patients were treated on this phase I dose-escalation study employing a once-monthly (day 1 of each 28-day cycle) and a twice-monthly (days 1 and 8 of each 28-day cycle) schedule. *Results:* The most common dose-limiting events included fatigue, neuropathy, and anorexia. We identified the 1440 mg/m^2 dose level to be the maximal tolerated dose for both schedules, with 83% of patients developing dose-limiting toxicity (DLT) on the twice-monthly schedule, and 67% developing DLT on the monthly schedule. At the 1200 mg/m^2 dose level, only 25% developed DLT on the twice-monthly schedule and 33% developed DLT on the monthly schedule. Trough suramin levels gradually increased with higher dose levels but fell well below the putative toxic concentration of 350 μg/ml. *Conclusion:* Suramin can be safely administered using a monthly schedule without using plasma concentrations to guide dosing.

This work was supported by CA69852-07 and CA14599.

C.W. Ryan (✉) · E.E. Vokes · N.J. Vogelzang · L. Janisch
K. Kobayashi · M.J. Ratain
Department of Medicine,
Section of Hematology/Oncology,
University of Chicago MC2115,
5841S. Maryland Ave., Chicago, IL 60637, USA
E-mail: cryan@medicine.bsd.uchicago.edu
Tel.: +1-773-8341676
Fax: +1-773-7023163

M.J. Ratain
Committee on Clinical Pharmacology,
University of Chicago,
5841S. Maryland Ave., Chicago, IL 60637, USA

N.J. Vogelzang
Cancer Research Center,
University of Chicago,
5841S. Maryland Ave., Chicago, IL 60637, USA

Keywords Suramin · Phase I · Clinical trial · Adaptive control

Introduction

Suramin is a polysulfonated naphthylurea which has been used in the treatment of sleeping sickness since the early 20th century. The mechanism by which suramin exerts its antitumor activity is not well understood. The agent has shown modest activity against prostate cancer and some palliative benefit has been suggested in a randomized clinical trial [5]. Studies have led to the notion that suramin has a low therapeutic index with severe neurologic toxicity at serum concentrations above 350 μg/ml [3] but requires a minimum plasma concentration threshold for in vitro antitumor activity [4]. The drug has an extremely long half-life of 30 to 50 days. The optimal route and schedule of administering suramin have not been completely elucidated, and adaptive control dosing with pharmacokinetic monitoring has often been employed to monitor these factors.

We have previously reported the results of a phase I study using a fixed dosing scheme (based on pharmacokinetic data collected at the University of Maryland) that did not rely on adaptive control [2]. Gradually decreasing doses of suramin were administered to patients on days 1 (loading dose), 2, 8, and 9 of a 28-day cycle. This study demonstrated that suramin can be safely administered with a fixed-dosing regimen that does not result in significantly greater neurotoxicity than that encountered with adaptive control methods. A day-1 dose of 1440 mg/m^2 with a maximum of three cycles was the maximal recommended dose for subsequent clinical trials, and a randomized trial on this schedule was successfully completed by the Cancer and Leukemia Group B [8].

In order to simplify the administration of suramin, we performed a phase I evaluation that condensed the four doses into a day-1 and a day-8 schedule, as well as an evaluation of a once-monthly regimen. As in the

previous study, dosing of suramin was performed without adaptive control.

Materials and methods

Eligibility/monitoring

Patients were required to be at least 18 years of age, have a Karnofsky performance status of 60% or more, a life expectancy of at least 8 weeks, and have histologic or cytologic documentation of a solid tumor or lymphoma that was refractory to standard therapy or for which no standard therapy existed. Required laboratory values included a total WBC count ≥3500/μl, a platelet count ≥100,000/μl, total bilirubin < 1.6 mg/dl, SGOT and SGPT not more than three times the upper limit of normal, and serum creatinine ≤ 1.5 mg/dl. Prothrombin time, activated partial thromboplastin time, and thrombin time could not be above normal limits, and the fibrinogen level could not be below normal limits.

Measurable or evaluable disease were to be documented radiographically or by clinical examination, if present. There were no limitations on prior therapy, but patients must have recovered fully from such treatment, and have received no chemotherapy or radiotherapy within 3 weeks, or nitrosoureas or mitomycin-C within 6 weeks of initiating therapy. Pregnancy was a contraindication to entrance on this protocol. Written, informed consent was obtained from all patients.

Patients were excluded if they had peripheral neuropathy greater than grade 1 (by National Cancer Institute common toxicity criteria), central nervous system disease including brain metastases, prior hemorrhagic or thrombotic cerebrovascular accident, history of bleeding disorder, or muscle disease. Patients were also excluded if they had a significant underlying medical condition that would make administration of suramin hazardous or obscure interpretation of adverse events.

Patients were examined once weekly and the following laboratory tests were obtained: complete blood count, serum chemistries, prothrombin time, partial thromboplastin time, and urinalysis. An electrocardiogram and chest radiograph were obtained at baseline. Electromyogram and nerve conduction studies were performed at baseline and off-study.

At the time of initiation of suramin therapy, all patients were started on dexamethasone 0.5 mg orally twice daily and fludrocortisone 0.1 mg orally once daily. Concurrent therapy with anticoagulants, calcium channel blockers, ketoconazole, or flutamide was not allowed. Aspirin and nonsteroidal antiinflammatory agents and other drugs that could have exacerbated a bleeding disorder were discouraged. Patients with prostate cancer were allowed to continue on simultaneous hormone therapy, with the exception of flutamide. No other concurrent chemotherapy, hormonal therapy, or radiotherapy was allowed.

Dosing regimen and drug administration

The intermittent infusion schedule used in the previously reported study [2] was designed to provide approximately constant peak plasma concentrations over three cycles. That schedule was developed using data and population pharmacokinetic estimates from investigators at the University of Maryland [1], and comprised a day-1 loading dose followed by gradually decreasing doses over subsequent days (days 1, 2, 8, 9) in order to avoid increasing peak concentrations with repetitive dosing. In the two schedules tested in the current study, we combined the four doses into two doses and a single dose, respectively. For schedule 1, suramin was administered on days 1 and 8 of each 28-day cycle (150% of dose level administered on day 1 and 90% administered on day 8). For schedule 2, suramin was administered on day 1 of each 28-day cycle (240% of dose level administered on day 1). The total dose delivered for the second cycle was 68% that for the first cycle (for schedule 1, 90% of dose level administered on day 1 and 72% administered on day 8; for schedule 2, 162% of dose level administered on day 1). All subsequent cycles were administered at 80% of the total dose of the previous cycle. The starting dose level was 800 mg/m^2, with subsequent dose levels of 1000 mg/m^2, 1200 mg/m^2, and 1440 mg/m^2.

Suramin (NSC 34936) was supplied by the Cancer Therapy Evaluation Program of the National Cancer Institute as a powder in 1000-mg vials and was reconstituted with 10 ml sterile water to yield a 10% (100 mg/ml) solution. Each dose was administered in 250 ml normal saline as an intravenous infusion over 1 h.

Plasma sampling and assay methodology

During each cycle, samples were collected for baseline (prior to suramin), trough levels (just prior to dosing and weekly during nontreatment weeks), and peak levels (immediately following dosing). For each sample time, whole blood was collected in 7-ml sodium heparinized tubes, mixed, centrifuged and frozen at –70°C until analysis. Analysis was performed in duplicate using previously described techniques [2] based on the methodology described by Tong et al. [7].

Definition of toxicity/dose escalation

Dose-limiting toxicity (DLT) was defined as any grade 4 toxicity, any grade 3 nonhematologic toxicity, or grade 3 myelosuppression not resolved to grade 1 or less by day 28. Prolongation of prothrombin time to > 17.5 s was considered a DLT. Elevation of liver function tests to grade 3 were dose-limiting only if they had persisted to grade 2 or above on day 28. Anemia, lymphopenia, fever, nausea, vomiting, proteinuria, and alopecia were excluded as dose-limiting criteria. The maximal tolerated dose (MTD) was defined as the dose level which produced a DLT in more than one-third of patients.

A minimum of three patients were evaluated at each nontoxic dose level, and no more than one new patient was treated per week. If DLT occurred in at least one of these patients, a total of 6 to 12 patients were entered at that dose level to exclude DLT in more than one-third of patients. A minimum of three patients were observed for 4 weeks before dose escalation. Escalation to the next higher dose level occurred only if no patient experienced DLT, or if all patients had recovered from toxicity or had only grade 1 nonreversible toxicity. Dose escalation was also permitted if at least four of the first six patients treated had no DLT.

Patients who experienced grade 1 or greater toxicity were not retreated until the toxicity had resolved to grade 1 or less. Patients who experienced DLT were to be retreated at the next lower dose only if they had evidence of tumor response.

Results

Patient characteristics

Of 40 patients enrolled onto this study, 25 were treated on schedule 1, and 15 were treated on schedule 2. Their characteristics are listed in Table 1. The vast majority of patients had prostate cancer and were of good performance status.

Dose escalation

The dose-escalation data are shown in Table 2. Four dose levels were explored within each schedule. Dose level corresponds to that dose administered on day 1 of

Table 1. Patient characteristics

	Schedule1	Schedule 2	Combined
Total patients	25	15	40
Age (years)			
Median	66	69	67
Range	20–79	33–81	20–81
Sex			
Male	21 (84%)	14 (93%)	35 (88%)
Female	4 (16%)	1 (7%)	5 (12%)
Performance status			
90–100	18 (72%)	12 (80%)	30 (75%)
70–80	7 (28%)	3 (20%)	10 (25%)
Disease			
Prostate	19 (76%)	13 (87%)	32 (80%)
Lung	2 (8%)	0	2 (5%)
Other solid tumor	4 (16%)	2 (13%)	6 (15%)

the previously reported study (day 1, 2, 8, 9 schedule) [2]. A total dose comparable to 800 mg/m^2 on the previous study was chosen as the initial dose level as this was the level at which significant toxicity was first experienced in that study. A total of 62 cycles were administered to patients on schedule 1, and 36 cycles on schedule 2. A median of two cycles of therapy were administered to each patient on schedule 1 (range one to six), and a median of three cycles on schedule 2 (range one to three).

Toxicity

Fatigue, anemia, pain, fever, and anorexia were the most common toxicities and were experienced by the majority of patients. Mild proteinuria was detected in most patients.

DLTs are listed in Table 3. The most common DLTs included grade 3 fatigue (five patients), grade 3 neuropathy (four patients), and grade 3 anorexia (three patients). DLTs occurring during the first cycle of suramin administration and thus limiting dose escalation were grade 4 diarrhea (one patient), grade 4 neutropenia (one patient), grade 4 renal failure (one patient), grade 3 neuropathy (one patient), and grade 3 rash (one patient).

Neurotoxicity

Dose-limiting neurotoxicity was observed in four patients. Neurotoxicity occurred on both schedules through a range of dose levels and cumulative doses. These patients developed classic suramin-associated sensorimotor polyneuropathy with corresponding changes noted on electromyogram. No correlation between dose and neurotoxicity was determined in this study.

Renal toxicity

A 71-year-old man with prostate cancer developed acute abdominal pain, nausea and dyspnea several hours after receiving his first dose of suramin (1200 mg/m^2 dose level, schedule 2). Laboratory studies on day 15 revealed a BUN of 99 mg/dl and a creatinine of 8.9 mg/dl, elevated from baseline values of 15 mg/dl and 0.6 mg/dl, respectively. The patient subsequently required hemodialysis. Suramin was deemed as the probable cause of the toxicity.

Unusual toxicities

Colitis: A 60-year-old woman with metastatic breast cancer (1440 mg/m^2 dose level, schedule 1) presented on day 13 with fever, diffuse rash, grade 3 elevation of SGPT, and grade 2 nephritis. She subsequently developed grade 4 watery/bloody diarrhea. Sigmoidoscopy suggested diffuse colitis, although the biopsy revealed a normal colonic mucosa. All toxicities eventually resolved.

Erythema multiforme: Grade 3 skin toxicity was observed in a 71-year-old man with prostate cancer (1000 mg/m^2 dose level, schedule 2). The patient developed low-grade fevers and diffuse itching on day 10, along with swelling of the lips, hemorrhoidal pain and formation of vesicles on the palms and feet. A diagnosis of erythema multiforme was made. The rash resolved over the ensuing 3 weeks.

Hemolytic anemia: A 61-year-old man with prostate cancer (1440 mg/m^2 dose level, schedule 2) developed a diffuse, pruritic rash, fever, and significant myalgias after receiving his first dose of suramin. He developed grade 4 neutropenia and subsequently an autoimmune,

Table 2. Dose escalation

Schedule	Dose level (mg/m^2)	Dose (mg/m^2)		No. of patients	No. of cycles	Patients with DLT	
		On day 1	Over first month			First cycle	Any cycle
1	800	1200	1920	6	20	0	1
	1000	1500	2400	5	11	0	1
	1200	1800	2880	8	18	0	2
	1440	2160	3456	6	13	2	5
2	800	1920	1920	3	7	0	0
	1000	2400	2400	3	6	1	2
	1200	2880	2880	6	15	1	2
	1440	3456	3456	3	8	1	2

Table 3. Cumulative dose-limiting toxicities

Schedule	Dose level	Cumulative dose (mg/m^2)	Age (years)	Toxicity	Grade	Cycle at onset	Outcome
1	800	6287	69	Neuropathy	3	6	Resolved
				Hyponatremia	3	6	Resolved
	1000	6360	67	Hearing loss	3	4	
	1200	6384	60	BUN	3	3	Grade 1
	1200	6384	48	Anorexia	3	3	Resolved
				Weight loss	3	3	Grade 2
				Fatigue	3	3	Resolved
	1440	3456	79	Neuropathy	3	1	
	1440	9389	72	Fatigue	3	3	Grade 2
				Anorexia	3	3	Grade 2
	1440	3456	60	Diarrhea	4	1	Resolved
	1440	4752	69	Dyspnea	4	2	Death
				Atrial flutter	4	2	
	1440	6491	63	Dyspnea	3	2	Resolved
				Fatigue	3	2	Grade 1
				Anorexia	3	3	Grade 1
2	1000	2400	71	Rash	3	1	Resolved
	1000	4020	77	Fatigue	3	2	Grade 2
	1200	2880	71	BUN	3	1	Dialysis
				Creatinine	4	1	Dialysis
	1200	6384	71	Neuropathy	3	3	
	1440	6960	61	Neutropenia	4	1	Resolved
				Coombs' anemia	4	2	Grade 1
				Fatigue	3	3	Grade 1
	1440	5789	81	Neuropathy	3	2	

hemolytic anemia with a grade 4 fall in hemoglobin. The anemia improved with corticosteroid administration.

On-study deaths

Two deaths occurred on study. One was attributable to progressive disease. The other was that of a 69-year-old man with metastatic prostate cancer (1440 mg/m^2 dose level, schedule 1) who developed grade 4 dyspnea, bilateral lower extremity and right upper extremity edema. He was found to be in atrial flutter with hemodynamic compromise. Despite resuscitative attempts, the patient remained persistently hypotensive and hypoxic and died 2 days later. The adverse event was considered possibly related to suramin with multiple pulmonary emboli suggested as an etiology.

Plasma concentrations

Peak suramin levels after the first dose and trough levels prior to the second cycle are summarized in Table 4. As expected, mean peak serum concentrations after the first dose of suramin tended to be higher on schedule 2. No difference in trough levels was observed between the two schedules. While there was a large amount of interpatient variability, all trough values were well below concentrations previously hypothesized to be associated with neurotoxicity (>350 μg/ml). For the four patients who developed dose-limiting neurotoxicity, the mean and standard deviation of peak and trough suramin concentrations obtained during the cycle in which the toxicity developed were 791 ± 337 μg/ml and 158 ± 39 μg/ml, respectively.

Responses

Of the 32 patients, 16 (50%) with prostate cancer had a fall in PSA of 50% or more from the baseline value. Six patients (19%) experienced a fall in PSA of 75% or more. The median duration of PSA response was 10.5 weeks (range 4–12 weeks). Three patients with a PSA response had regression of lymphadenopathy on

Table 4. Peak and trough suramin levels. The values are the means ± SD from duplicate samples assayed for each patient

Dose level	Schedule	Patients	Mean peak cycle 1 (μg/ml)	Mean trough pre-cycle 2 (μg/ml)
800	1	6	545 ± 181	41 ± 22
800	2	3	532 ± 309	27 ± 18
1000	1	5	657 ± 383	78 ± 62
1000	2	3	801 ± 37	71 ± 8
1200	1	8	921 ± 150	91 ± 22
1200	2	6	1100 ± 146	89 ± 26
1440	1	6	933 ± 58	98 ± 22
1440	2	3	1227 ± 354	112 ± 42

CT scan. One patient with prostate cancer had improvement on bone scan. There were no objective responses observed in patients with other solid tumors.

Discussion

We identified the 1440 mg/m^2 dose level to be the MTD for both schedule 1 and schedule 2. At this level, five of six patients (83%) developed DLT on schedule 1, and two of three patients (67%) developed DLT on schedule 2. At the 1200 mg/m^2 dose level, only two of eight patients (25%) developed DLT on schedule 1 and two of six (33%) on schedule 2. We demonstrated that the drug can be safely administered using a once- or twice-monthly schedule without using plasma concentrations to guide dosing. Monthly dosing allows convenient administration that would likely be more acceptable to patients. A phase II trial of monthly suramin in patients with hormone-refractory prostate cancer has subsequently been completed through the University of Chicago Phase II Network; the results are to be published in due course.

Our previous study using a day 1, 2, 8, and 9 fixed dosing schedule of suramin did not lead to an increased incidence of demyelinating neuropathy when compared to adaptively controlled dosing schedules [6]. While four cases of dose-limiting neurotoxicity were observed in the current study, there was no clear relationship between schedule or dose and development of this toxicity.

Plasma suramin levels indicate that high peak levels of suramin were achieved. Higher peak levels were obtained in patients treated on schedule 2. While trough levels showed gradual increases with higher dose levels, trough levels at all doses fell well below the putative toxic concentration of 350 μg/ml. The mean trough concentrations of the four patients who developed dose-limiting neurotoxicity was 158 ± 39 μg/ml, higher than the mean trough concentrations observed after one cycle of dosing, but again less than the putative toxic concentration.

Significant and unusual toxicities were observed in this study, including renal failure, erythema multiforme, colitis, and autoimmune anemia. The relatively high incidence of such complications mirrors the toxicity level noted in other clinical studies of suramin. One on-study death was possibly attributable to suramin toxicity. In September 1998, the Oncology Drugs Advisory Committee of the Food and Drug Administration rejected a New Drug Application for suramin for treatment of hormone-refractory prostate cancer based on an unacceptable safety profile. While further development of this drug is currently not a priority for its sponsor, we have demonstrated that suramin can be safely administered with a convenient dosing regimen.

References

1. Jodrell DI, Reyno LM, Sridhara R, Eisenberger MA, Tkaczuk KH, Zuhowski EG, Sinibaldi VJ, Novak MJ, Egorin MJ (1994) Suramin: development of a population pharmacokinetic model and its use with intermittent short infusions to control plasma drug concentration in patients with prostate cancer. J Clin Oncol 12:166
2. Kobayashi K, Vokes EE, Vogelzang NJ, Janisch L, Soliven B, Ratain MJ (1995) Phase I study of suramin given by intermittent infusion without adaptive control in patients with advanced cancer. J Clin Oncol 13:2196
3. LaRocca RV, Meer J, Gilliatt RW, Stein CA, Cassidy J, Myers CE, Dalakas MC (1990) Suramin-induced polyneuropathy. Neurology 40:954
4. LaRocca RV, Danesi R, Cooper MR, Jamis-Dow CA, Ewing MW, Linehan WM, Myers CE (1991) Effect of suramin on human prostate cancer cells in vitro. J Urol 145:393
5. Small EJ, Meyer M, Marshall ME, Reyno LM, Meyers FJ, Natale RB, Lenehan PF, Chen L, Slichenmyer WJ, Eisenberger M (2000) Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. J Clin Oncol 18:1440
6. Soliven B, Dhand UK, Kobayashi K, Arora R, Martin B, Petersen MV, Janisch L, Vogelzang NJ, Vokes EE, Ratain MJ (1997) Evaluation of neuropathy in patients on suramin treatment. Muscle Nerve 20:83
7. Tong WP, Scher HI, Petrylak D, et al (1990) A rapid HPLC assay for suramin in plasma. J Liquid Chromatogr 13:727
8. Vogelzang NJ, Small EJ, Halabi S, Ansari R, Palchak D, Rago R, Cooper M, Hudson J, Schultz P, Hars V (1998) A phase III trial of 3 different doses of suramin (SUR) in metastatic hormone refractory prostate cancer (HRPC): safety profile of CALGB 9480. Proc Am Soc Clin Oncol 17:A1339