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Original Paper

Suramin-induced Neutropenia

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This paper presents a retrospective review of 6 cases of severe neutropenia attributed to suramin, the response to granulocyte-colony stimulating factor (G-CSF) and the possible mechanism. Plasma suramin concentrations, G-CSF, platelet-derived growth factor-AB (PDGF-AB) and fibroblast growth factor basic (FGF basic) levels were measured and correlated with neutropenic course. The time course of neutropenia was unpredictable and occurred both during and following discontinuation of suramin. Neutropenia rapidly resolved with G-CSF. Neither the measured growth factor levels nor plasma suramin concentrations correlated with neutropenia. We conclude that neutropenia secondary to suramin is unpredictable and responds to G-CSF administration permitting further suramin therapy. The mechanism remains unknown. Published by Elsevier Science Ltd

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INTRODUCTION

SURAMIN IS a polysulphonated naphthylurea which, since 1988, has been evaluated in clinical trials for metastatic prostate cancer [1]. Suramin's antitumour activity has been primarily attributed to its inhibition of several polypeptide growth factors. These include platelet-derived growth factor, fibroblast growth factor, transforming growth factors alpha and beta, vascular endothelial cell growth factor, platelet-derived endothelial cell growth factor, epidermal growth factor, insulin-like growth factors 1 and 2, interleukin-2, keratinocyte-growth factor, scatter factor and transferrin [2–4]. Clinical trials have documented a myriad of toxicities, which have included neutropenia, occurring in 26–43% of patients [1, 2, 5]. Severe grade III–IV neutropenia (grade III: absolute neutrophil count (ANC) = 500–999; grade IV: ANC < 500) has occurred in 2–15% of these patients. However, the mechanism for and optimal management of suramin-induced neutropenia has not been thoroughly investigated. This report describes 6 men with metastatic prostate cancer who developed severe neutropenia associated with suramin therapy, their response to granulocyte-colony stimulating factor (G-CSF) and an analysis of several growth factors during their clinical course.

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PATIENTS AND METHODS

The 6 patients who received suramin were enrolled in one of two clinical trials within the Clinical Pharmacology Branch (CPB) at the National Cancer Institute. 3 patients were treated in the CPB trial 262. This study is a phase II clinical trial investigating leuprolide, flutamide and suramin in previously untreated patients with metastatic prostate cancer. All of the patients received flutamide 250 mg orally three times a day beginning on day 1 and continued until disease progression. Depot leuprolide at a dose of 7.5 mg intramuscularly (i.m.) was started on day 5 and repeated every 4 weeks indefinitely. Suramin was initially administered on days 1–5 as a short intravenous (i.v.) infusion (1 h) at a fixed dose (day 1 = 16.1 mg/kg; day 2 = 11.4 mg/kg; day 3 = 9.3 mg/kg; day 4 = 8.2 mg/kg and day 5 = 7.5 mg/kg). Thereafter, suramin was given at variable doses utilising an adaptive control with feedback algorithm to maintain plasma suramin concentrations between 175–300 μg/ml for a total duration of 8 weeks [6]. Due to suramin's known adrenal toxicity, replace-

ment doses of hydrocortisone were given at a dose of 30 mg per day.

The other 3 patients had progressive metastatic prostate cancer following combined androgen blockade. These 3 men were enrolled in the CPB trial 304. 2 of the men had progressed following discontinuation of flutamide. The third man had flutamide discontinued at study entry. They were treated with suramin and replacement doses of hydrocortisone in a similar manner as patients in trial CPB 262. Additionally, these patients received aminoglutethimide 250 mg orally four times daily. Those patients who had not undergone bilateral orchiectomy were continued on leuprolide.

All patients in this report developed grade III–IV neutropenia, based on the established criteria of the Cancer Therapy Evaluation Program of the National Cancer Institute [7]. This neutropenia was felt to result from suramin and was treated with G-CSF. The cases are otherwise dissimilar and are therefore reported separately. A summation table is provided (Table 1).

Immunoassays (Quantikine™, R&D Systems) for human G-CSF, human platelet-derived growth factor-AB (PDGF-AB) and human fibroblast growth factor basic (FGF basic) were performed using plasma specimens that had been collected throughout the patient's clinical course and stored at −30°C. These samples were obtained at times required to measure plasma suramin concentrations during the patient's therapy.

Plasma suramin concentrations were determined by a method described by Supko and Malspeis [8]. Pharmacokinetic parameters were derived from a three-compartment open-linear model using Bayesian estimation (Abbottbase Pharmacokinetic System software program, Abbott Laboratories, Abbott Park, Illinois, U.S.A.; Version 1.0 for DOS).

Patients

Case 1 was a 68-year-old caucasian male with stage D1 prostate cancer. He was treated on CPB 262 beginning 20 December 1993. During therapy, he developed fluid overload that was medically manageable with an otherwise uncomplicated course. He completed suramin therapy on 11 February 1994 with estimated pharmacokinetic parameters in the normal range (terminal $T_{1/2} = 53.1$ days). Throughout his course, he had suramin concentrations within the desired range (175–300 μg/ml) with only three transient peak concentrations above 300 μg/ml (322, 324 and 332 μg/ml) during the second week of therapy. His prostate specific antigen (PSA) level had declined from 19.1 to 4.4 ng/ml during this period. Follow-up complete blood count was remarkable at an absolute neutrophil count (ANC) of 625 on 24 February 1994. On 3 March 1994 he presented with a fever and an ANC of 0. His suramin plasma concentration at that time was 132 μg/ml. He was treated with gentamicin and ceftazadine, as well as G-CSF 5 μg/kg subcutaneously (s.c.) daily for 4 days. A bone marrow biopsy showed no myeloid maturation beyond the promyelocyte and early myelocyte stage, without an increase in myeloblasts consistent with a left shift in granulocyte maturation. Following G-CSF administration, the patient defervesced. His ANC increased to 7000 by the fifth day of hospitalisation and he was subsequently discharged. He represented on 22 April 1994 febrile and with a white blood count (WBC) of 1500 and ANC of 75. His suramin plasma concentration was 68.86 μg/ml. He was treated with the same antibiotic regimen and G-CSF for 5 days. Once again the patient had an increase in ANC to 8023. He has had no further problems.

Case 2 was a 44-year-old black male who presented with metastatic prostate cancer to bone and soft tissue. He began treatment on CPB 262 on 13 December 1994. His bone pain rapidly improved and his PSA plummeted from 296 to 2.8 ng/ml by 5 January 1995. The following day his WBC was 4200 and his ANC was 840. His suramin plasma concentration was 186 μg/ml at that time. He was treated with G-CSF at a dose of 5 μg/kg s.c. on 6 January 1995 and given one additional dose of suramin on 9 January at which time the WBC was 7100 and the ANC 3621. Three days later his WBC again declined to 3100 with an ANC of 124. His suramin plasma concentration was only 167 μg/ml at that time. Furthermore, his pharmacokinetic parameters were within the population normal range (i.e. terminal $T_{1/2} = 64$ days). G-CSF was again administered at a dose of 5 μg/kg daily for 4 days resulting in an increase in his WBC to 18300

Table 1. *Patient details*

Patient	Age	Race	Base WBC/ANC	Nadir WBC/ANC	Days G-CSF*	Dose of suramin to nadir/total	Suramin Cp at nadir (μg/ml)	Recurrence
1	68	C	6300/4284	2000/0	D 74–77	11683/11683	132	Yes
				1500/75	D 124–128		69	
2	44	B	6900/3174	4200/840	D 25	8417/9017	186	Yes
				3100/124	D 31–34		167	Yes
3	59	C	4100/2747	900/0	D 29–32	9411/10536	185	Yes
				2200/1474	D 37–38		195	
4	65	C	5300/3604	1400/434	D 37–45	7721/10796	175	No
5	66	C	3600/2880	1000/510	D 31–37,39,41,43	7804/11054	137	Yes
				1500/ND	D 67–71		ND	
6	60	C	3900/1248	3100/837	D 22,25,29,32,39,46,53	5619/12469	141	No

WBC, white blood count; ANC, absolute neutrophil count; G-CSF, granulocyte-colony stimulating factor; C, caucasian; B, black; Cp, plasma concentration; ND, no data.

*Designates day (D) in cycle since beginning suramin.

(ANC = 12627). He was afebrile throughout his course and received no other medications. However, due to his significant neutropenia, no further suramin was administered.

Case 3 was a 59-year-old caucasian male who underwent radical prostatectomy in January 1993 followed by pelvic radiation for pathological stage C disease. He subsequently developed metastatic disease to bone and began treatment on CPB 262 on 2 August 1993. His concomitant non-protocol medications included amitriptyline and hydromorphone. His WBC at the time of starting therapy was 4100 with an ANC of 2747. He tolerated treatment well, but developed neutropenia (WBC 800, ANC 0) and fever on 30 August 1993. His suramin plasma concentration was 185 μg/ml on that day. He was treated with G-CSF 5 μg/kg daily for 4 days. His suramin therapy was held at the onset of neutropenia. The patient's WBC rose to 7800 (ANC 6300) on 3 September 1993 and his suramin was resumed on that day. On 7 September 1993, his WBC had again declined to 2200 with an ANC of 1474 (suramin concentration = 195 μg/ml). Rather than forgoing his last scheduled dose of suramin, he was treated with concomitant G-CSF and suramin. His WBC rose to 7900 on 8 September 1993 and he was given one additional dose of G-CSF. Thereafter, the patient received no further G-CSF or suramin and had no recurrence of neutropenia.

Case 4 was a 65-year-old caucasian male diagnosed with stage D1 prostate cancer in 1989 and treated at that time with pelvic radiation. He progressed in 1992 and was treated with orchiectomy and flutamide. He again progressed and was enrolled in the CPB 304 trial on 14 February 1994. His flutamide was simultaneously discontinued. Concomitant non-study medications included prochlorperazine, omeprazole, lovastatin, allopurinol, propranolol hydrochloride, hydrochlorothiazide and potassium chloride. His pretreatment WBC was 5300 (ANC 3604) which declined to 1400 (ANC 434) on 22 March 1994 (36 days into therapy). His suramin plasma concentration was 174.8 μg/ml on that day. G-CSF was begun at 5 mcg/kg s.c. daily. Suramin therapy was held at that time. Two days later he presented with neutropenic fever and was treated with broad spectrum i.v. antibiotics. His WBC increased to 27500 over the next 9 days. G-CSF was discontinued at that time and his suramin therapy was resumed at full dose. The patient received seven more doses of suramin over 2 weeks to complete his scheduled 8 weeks of treatment without further complications.

Case 5 was a 66-year-old caucasian male diagnosed with metastatic prostate cancer to bone in January 1992. He was treated with orchiectomy, flutamide and palliative radiation to his right shoulder. He progressed in September 1993 and flutamide was discontinued. On further progression, he was enrolled in the CPB 304 trial on 10 January 1994. His concomitant medications included morphine, pindolol, guanfacine hydrochloride, codeine and dexamethasone. The patient's pretreatment WBC was 3600 with an ANC of 2880. On 9 February 1994 his WBC declined to 1000 with an ANC of 510 (suramin concentration = 137.1 μg/ml). Suramin therapy was held and G-CSF initiated at a dose of 5 μg/kg s.c. daily. On 14 February 1994, his WBC was 4800 (ANC 4032) and suramin was reinstituted without dose modification. His G-CSF was decreased to an every other day regimen for four additional doses. Suramin therapy was completed on 28 February 1994 as planned at which time his WBC was 6100 (ANC 5307). His suramin plasma concentrations were maintained within the targeted range and the pharmacokinetic profile fitted the model well (terminal $T_{1/2}$ = 26 days). The patient's WBC subsequently fell to 1500, 17 days after his last dose of suramin. He was once again given G-CSF at a dose of 5 μg/kg s.c. for 5 additional days. The WBC rose to 17000 and G-CSF was discontinued. Thereafter, no further myelosuppression was documented.

Case 6 was a 60-year-old caucasian male diagnosed with localised prostate cancer in September 1986. He underwent radical prostatectomy followed by pelvic radiation, leuprolide and flutamide for pathological stage D1 disease. In 1990, his disease progressed to bone and he received palliative radiation to the right femur. He again progressed and flutamide was discontinued in September 1993. On further progression, he began treatment in the CPB 304 trial (3 January 1994). His baseline WBC was 3900 (ANC 1248) at that time. His WBC declined to 3100 (ANC 837) on 12 January and further suramin therapy was held over the next 9 days. His plasma suramin concentration was 141.2 μg/ml at time of nadir. A bone marrow biopsy showed prostate cancer cells and normal haematopoiesis. The WBC increased to 4400 (ANC 2244) on 24 January with no other intervention. G-CSF was begun at 5 μg/kg s.c. biweekly on that day and on 26 January, suramin was restarted. The patient's ANC remained normal and the G-CSF dose was decreased to once a week on 3 February. The patient was able to receive all scheduled doses of suramin thereafter, without dose reduction, and completed suramin therapy on 25 February 1994. No subsequent neutrophil complications were noted.

RESULTS

For the 6 men with significant neutropenia treated with G-CSF, the mean (±S.D.) and median baseline and nadir WBC and ANCs are presented in Table 2. There was a 68% reduction in the WBC. There was a 94% reduction in ANC. The mean days to nadir WBC count was 39 days. The mean time to nadir ANC was 22 days. These results are compared to those from 170 men treated on CPB 262 and 304 who did not require G-CSF support (Table 2). Their mean number of days to nadir WBC and ANC were 71 and 66 days, respectively. Their mean reduction in WBC and ANC were 33 and 34%, respectively.

Human G-CSF, PDGF-AB and FGF basic plasma concentrations showed no consistent pattern of change with respect to suramin therapy or fluctuations in WBC or ANC for the 5 patients in whom these levels were measured (Figure 1).

There were also no differences in pharmacokinetic parameters between the 6 patients with neutropenia and other patients in the CPB 304 and CPB 262 studies, who did not develop neutropenia (Table 3).

DISCUSSION

Neutropenia is a well-described toxicity commonly associated with cytotoxic chemotherapy. The time to nadir WBC and recovery from bone marrow suppression vary depending on whether the chemotherapeutic agents' effect stem cells is cycle-active or phase-specific. However, these times are relatively predictable, usually varying by only a few days for a given individual agent, assuming dose and route of administration are constant and there is no significant damage to the primary organ of metabolism or elimination. In most chemotherapy regimens, treatment is given at specific, fixed intervals based on anticipated recovery from myelosuppression. Most cytotoxic chemotherapy agents are almost com-

Table 2. Leucopenia and neutropenia: mean ± S.D. (median)

	Base	Nadir	% Decline
White blood count			
6 cases	5050 ± 1425 (4500)	1633 ± 929 (1500)	68
170 controls	6546 ± 2358 (6000)	4367 ± 1928 (4400)	33
Absolute neutrophil count			
6 cases	2966 ± 1015 (2957)	183 ± 241 (66)	94
170 controls	4628 ± 2215 (4059)	3038 ± 1269 (2913)	34

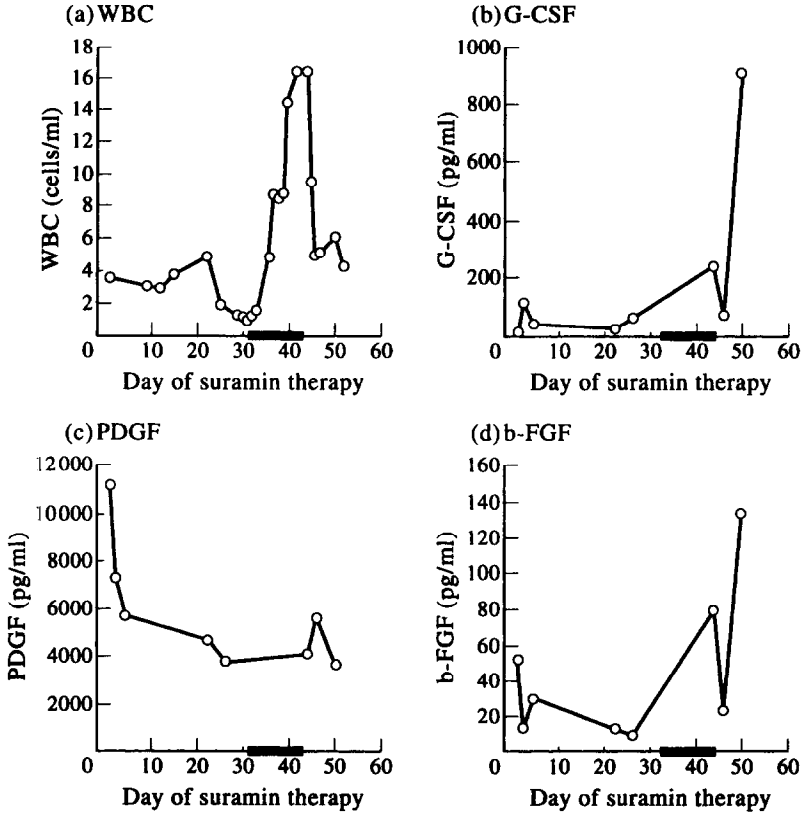

Figure 1. Growth factor plasma concentrations in a representative case (case 5) with respect to suramin therapy and white blood count. WBC, white blood count; G-CSF, granulocyte-colony stimulating factor; PDGF, platelet-derived growth factor; b-FGF, basic-fibroblast growth factor. The black bar denotes days 31–43 of suramin therapy when G-CSF was administered.

pletely cleared by the liver and/or kidneys within 24–48 h. In the absence of drug re-exposure, myelosuppression does not recur once it has resolved [9]. However, suramin is not a classic cytotoxic chemotherapy. The primary postulated mechanism of antitumour activity is through inhibition of growth factors not direct cell killing.

Neutropenia associated with suramin has several unique features as illustrated by these case reports. The time to nadir is highly variable compared to a more predictable occurrence with standard cytotoxic chemotherapy. This may reflect a mechanism of action that is different than simply stem cell toxicity. One hypothesis is that inhibition of growth factors leads to an arrest in granulocyte maturation. Bone marrow findings in case 1 support this hypothesis.

Cytokines known to regulate the growth and differentiation of neutrophils include interleukin (IL)-1, IL-3, IL-6, granulocyte/macrophage-CSF (GM-CSF), G-CSF and mast-cell growth factor/stem-cell factor [10]. Of these, only G-CSF is known to be inhibited by suramin. G-CSF plasma concentrations were not decreased in our patients during or prior to the onset of neutropenia. Neither b-FGF nor PDGF, two other growth factors which are known to be inhibited by suramin, were consistently affected prior to or concomitant with the development of neutropenia. One alternative mechanism for suramin-induced neutropenia may be interference with binding of G-CSF or GM-CSF to neutrophil receptors. Doukas and associates recently demonstrated that suramin strongly inhibits nucleotide interaction with the nucleotide-binding site of GM-CSF and GM-CSF bioactivity [11]. Other potential mechanisms include reduction of growth factor production from stromal cells, which could be affected without detectable variations in the plasma of the patients, or inhibition of other potentially important cytokines, such as tumour necrosis factor or gamma-interferon.

Table 3. Pharmacokinetic parameter estimates

	Cooper *et al.*[6]	Non-neutropenic patients CPB 262, CPB 304	Six patients developing grade III–IV neutropenia	
CL	0.33 ± 0.11	0.334 ± 0.13	0.334 ± 0.117	ml/h/kg
Vc	0.052 ± 0.01	0.061 ± 0.01	0.055 ± 0.008	l/kg
K12	0.16 ± 0.048	0.159 ± 0.02	0.155 ± 0.005	h^{-1}
K21	0.12 ± 0.026	0.120 ± 0.01	0.115 ± 0.009	h^{-1}
K13	0.034 ± 0.008	0.027 ± 0.01	0.029 ± 0.009	h^{-1}
K31	0.0054 ± 0.002	0.0058 ± 0.002	0.006 ± 0.002	h^{-1}
K10	–	0.005 ± 0.002	0.006 ± 0.003	h^{-1}
alpha	–	0.0181 ± 0.004	0.018 ± 0.003	h^{-1}
beta	–	0.0007 ± 0.0003	0.001 ± 0.001	h^{-1}
gamma	–	0.299 ± 0.012	0.292 ± 0.004	h^{-1}
Vss	32.7 ± 12.43	30.8 ± 8.04	31.3 ± 11.6	l
$T_{1/2}$	1205 ± 482	1142 ± 504.5	1205 ± 706.4	h

CL, total body clearance; Vc, central compartment volume of distribution; K12, K21, K13, K31, intercompartment rate constants; alpha, beta and gamma, rate constants characterising the three separate phases of plasma drug decay; Vss, volume of distribution at steady-state; $T_{1/2}$, half-life.

In reviewing these cases, possible variables predictive of neutropenia were discerned. However, evaluation is limited due to the small number of cases. Nonetheless, the mean baseline WBC is lower in the case reports compared to the patients who did not develop severe neutropenia. Additionally, 3 of 6 patients had received prior pelvic radiation which potentially compromised haematopoietic reserves. One additional patient had received prior shoulder irradiation. However, for the patients who did not develop severe neutropenia, 47 of 170 had received prior pelvic radiation. 13 additional patients were radiated to sites of metastatic disease and 3 further patients received strontium-89. Hence, prior radiation was not significantly more common in the patients who developed severe neutropenia ($P = 0.20$ for any prior radiation and $P = 0.35$ for prior pelvic radiation using Fisher's exact test). Total suramin doses and suramin plasma concentrations were not different in these two groups. Plasma suramin concentrations obtained proximal to the time of nadir ANC were within the targeted concentration (132, 68, 186, 185, 195, 174.8, 137 and 141 μg/ml). These pharmacokinetic parameters estimated for these 6 patients do not differ from those previously reported by our group in a separate cohort of patients [6] or from those treated on CPB studies 304 and 262 that did not develop neutropenia (see Table 3). Patients in the trial by Cooper and associates [6] were treated with suramin therapy during the course of a phase I/II clinical trial of the drug at the NCI. Plasma suramin concentrations were targeted at 175, 215 and 275 μg/ml using a continuous infusion schedule with adaptive control with feedback dosing—the incidence of severe neutropenia was 2%.

Neutropenia occurred both during therapy, as well as days to weeks after the last dose of suramin. Unlike most chemotherapy agents that are cleared within days, suramin is 99.7% protein bound with a terminal half-life of 48 days (range 44–54 days) [12]. Hence, biologically-effective concentrations of suramin may persist for weeks to months following the last administration of suramin. This might also explain recurrence of neutropenic episodes weeks later following temporary reversal with the administration of G-CSF.

G-CSF appears to effectively reverse suramin-induced neutropenia and allow continuation of treatment. Therapy can be effective when given intermittently or prophylactically in a patient who has recovered from neutropenia (case 6). Patients should be monitored for delayed neutropenia that can be marked and associated with a febrile illness (cases 1 and 5). Initiation of G-CSF in a non-febrile patient may also allow uninterrupted treatment with suramin (cases 2 and 4). Patients who develop neutropenia may be retreated with full doses of suramin without recurrence of myelosuppression (cases 4 and 6). Response to treatment was not compromised by the development of neutropenia. All 6 patients had a declining PSA at time of onset of neutropenia (median 70%; range: 50–99%). The 3 patients treated on CPB trial 262 (cases 1–3) all achieved a partial response. The 3 patients treated on CPB trial 304 (cases 4–6) all had stable disease as their best response. The overall complete and partial response rates for CPB trials 262 and 304 were 69 and 3%, respectively.

In summary, neutropenia secondary to suramin occurs at unpredictable times relative to the therapeutic course. It reverses rapidly with G-CSF. It may subsequently recur and can again resolve with G-CSF administration. Treatment with suramin can be safely continued without interruption in patients effectively managed with cytokine therapy.

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