Suramin: Rapid Loading and Weekly Maintenance Regimens for Cancer Patients

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Purpose: Suramin is an anticancer agent with a narrow therapeutic window and a terminal half-life of 45 to 55 days. These characteristics make it necessary to control accurately the serum concentrations of the drug. Therefore, the aim of the present study was to develop a rapid loading regimen, followed by weekly administration of suramin to maintain serum concentrations of between 150 and 300 $\mu\text{g/mL}$ for 8 weeks.

Patients and Methods: Eligible patients were treated with five different loading regimens. Initially, weekly maintenance doses were estimated manually by the treating physician. Subsequently, computer-assisted dosing that used Bayesian pharmacokinetic modeling was used.

Results: Thirty-eight courses of suramin that were administered to 35 patients were studied. The optimal loading regimen consisted of a continuous infusion of 600 mg/m^2 during a 24-hour period, which resulted in a mean serum concentration of 319 $\mu\text{g/mL}$. Potentially toxic concentrations that were observed with shorter

infusions were avoided. Maintenance treatment, which used the weekly administration of suramin during a 6-hour period, seemed to be able to maintain mean suramin serum trough concentrations of 150 $\mu\text{g/mL}$, while preventing mean peak concentrations of more than 300 $\mu\text{g/mL}$. The use of Bayesian pharmacokinetics was superior to manual estimation in tailoring the optimal dose to the therapeutic window.

Conclusions: Continuous infusion is the optimal way of delivering suramin during the loading phase. To maintain trough levels and peak levels within a narrower therapeutic window, suramin will have to be administered more frequently than once a week. Bayesian modeling based on individual serum levels and population pharmacokinetics allows accurate dosing to maintain suramin levels within the therapeutic window.

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SURAMIN (Bayer Nederland BV, Mijdrecht, The Netherlands), a polysulphonated naphthylurea in use for the treatment of trypanosomiasis and onchocerciasis, recently has been shown to inhibit tumor growth. The targets of suramin's antiproliferative activity include the prevention of growth factors from binding to their specific membrane receptors, and the inhibition of enzymes involved with intracellular signaling processes.¹⁻⁷ The increasing attention being paid to growth factors as promoters of cancer cell proliferation and the ability of suramin to interfere with these processes in vitro made the drug an interesting compound to explore as a potentially new anticancer agent.

The serum suramin concentration and the duration of exposure to suramin above a defined concentration that is optimal to produce responses in cancer patients have not been ascertained. In a series of 15 patients with renal cell carcinoma, adrenal cortical cancer, and T-cell leukemia, the responses correlated with the highest achieved suramin concentration, and the four patients who responded all achieved plasma concentrations of greater

than 200 $\mu\text{g/mL}$.⁸ In vitro studies have shown a wide range of suramin concentrations that are required to produce a 50% inhibition of growth (IC₅₀). In one study, IC₅₀ values have been found to vary between 21 and 1,400 $\mu\text{g/mL}$, depending on cell line characteristics and initial cellular density.⁹

The aim of the present study was to establish serum suramin concentrations of 200 $\mu\text{g/mL}$ and to maintain the suramin concentration at that concentration for 8 weeks or more, using a schedule that would minimize hospital stay. The schedule of administration of suramin for the treatment of onchocerciasis, which consisted of weekly administrations of 1 g of suramin for 6 weeks, was inappropriate to obtain these concentrations because suramin concentrations at the end of treatment usually did not exceed 150 $\mu\text{g/mL}$.¹⁰ Therefore, several new loading regimens were studied for their ability to produce suramin serum concentrations of more than 200 $\mu\text{g/mL}$ within a shorter period of time. Additionally, the ability to maintain these concentrations using the weekly administration of suramin on an outpatient basis was studied.

PATIENTS AND METHODS

Patient eligibility criteria included advanced malignancy that was not amenable to therapy, age less than 76 years, serum creatinine less than 125 $\mu\text{mol/L}$, leukocyte count $\geq 3 \times 10^9/\text{L}$, platelet count $\geq 100 \times 10^9/\text{L}$, serum bilirubin $\leq 25 \mu\text{mol/L}$, serum ALT ≤ 1.25 times the upper limit of normal, no disturbances of blood coagulation studies, and no concurrent treatment

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with oral anticoagulant drugs or high-dose acetyl salicylic acid. Toxicity was graded according to World Health Organization (WHO) criteria.¹¹ The protocols used were approved by the ethical committee of the Free University Hospital, and all patients gave written informed consent.

Patients received a test dose of 0.2 g of suramin 1 to 3 days before the first full dose. Treatment consisted of a loading course to establish a target suramin concentration of more than 200 µg/mL followed by an 8-week maintenance regimen that aimed at maintaining serum concentrations of suramin between 200 and 300 µg/mL. Thereafter, patients were evaluated for response. In the case of progressive disease, no further suramin was administered. In patients with stable disease, therapy was scheduled to be continued for another 8 weeks (ie, 16 weeks in total), whereas responding patients were treated until prohibitive toxicity or relapse, whichever came first. Suramin was withheld in the presence of $\geq$ grade 2 (WHO) toxicity, and patients who did not receive scheduled treatment for more than 4 weeks went off study. Hydrocortisone replacement therapy was given routinely from the fifth week on, except in the first 13 patients. These latter patients were followed-up carefully for the development of adrenal cortical insufficiency with repeated corticotropin stimulation tests, and were started on replacement therapy from the time of documentation of adrenal cortical impairment.

The loading (L) regimens used are given in Table 1. Suramin serum concentrations were monitored at least weekly for regimen L₁ and two to three times daily for regimens L₂ to L₅. Maintenance therapy consisted of weekly administration of suramin diluted in 500 mL 0.9% saline administered during a 6-hour period. The actual dosage administered was dependent on serum suramin trough concentrations obtained 1 week previously. Since 1991, computer-assisted dosing that used Bayesian pharmacokinetics was investigated (MW\pharm 3.01; Medi\ware, Groningen, the Netherlands), while the 1-week interval between maintenance cycles was maintained.

Serum concentrations of suramin were determined in serum samples stored at -20°C until assayed with high-performance liquid chromatography. Serum was deproteinized with a mixture of methanol acetonitrile tetrabutylammonium hydrogen sulphate (TBAHS; Merck, Amsterdam, the Netherlands) and sodium phosphate buffer (53 + 5 + 20) at 4°C. Trypan blue (Sigma, St Louis, MO) was used as an internal standard. A sample injection was performed with a WISP 710B autosampler (Millipore Waters, Eiten Leur, The Netherlands). Detection was performed using a variable wavelength detector 238 nm (Millipore Waters, Eiten Leur, the Netherlands). A Nova-Pak 8C18 4µ Radial-Pak column (Millipore Waters, Eiten Leur, the Netherlands) was used with a methanol-acetonitrile mixture, buffered with 0.05 M NaH₂PO₄, and 0.005 M TBAHS (1:1) adjusted to pH 6.5. The detector signal was monitored by a Shimadzu CR-3A integrator (Chrompack,

Table 1. Loading Regimens

Loading Regimen	Dose of Suramin (mg/m ²)	Volume of Sodium Chloride 0.9% (liters)	Duration of Infusion (hours)	Administration Schedule
L ₁	1-1.5 g	1	6	Weekly × 6 weeks
L ₂	350	2	24	Daily × 6-14 days
L ₃	600	0.5-1	6	Daily × 3-8 days
L ₄	600	0.5-1	12	Daily × 4-5 days
L ₅	600	1	24	Daily × 3-5 days

Table 2. Patients Characteristics

Regimen*	L ₁	L ₂	L ₃	L ₄	L ₅
No. of patients	6	4	13	5	10
Male/female	6/0	4/0	12/1	4/1	8/2
Median age, years	69	56	69	52	54
Range	61-74	42-63	42-74	40-75	28-71
Median KPS	80	75	80	70	70
Range	70-90	50-90	60-90	60-80	50-90
Tumor type					
Prostate	6	0	12	2	5
Glioma	0	0	0	3	4
Adrenal gland	0	1	0	0	1
Other	0	3	1	0	0

Abbreviation: KPS, Karnofsky performance status.

*For regimens see Table 1.

Middelburg, the Netherlands). Assessment of suramin concentration in serum or plasma using this method produced similar results.

RESULTS

Thirty-five patients received 38 courses of suramin. Two patients received a second, and one received a third course. Both patients initially responded to suramin, but were withdrawn from the study because of toxicity. They were re-treated with suramin when objective and symptomatic progression occurred, and toxicity had completely resolved. In these two patients, serum concentrations at the start of the second course were 4 and 12 µg/mL, respectively; the therapy-free interval between courses was 203 and 287 days. Patient characteristics according to treatment schedule are listed in Table 2. Table 3 comprises selected pharmacokinetic data that relate to the different loading regimens used.

Regimen L₁, which consisted of weekly administration of 1 to 1.5 g of suramin, produced serum suramin trough

Table 3. Pharmacokinetic Data of Loading Regimens of Suramin

Regimen*	L ₁	L ₂	L ₃	L ₄	L ₅
Dose administered (g)					
Median	7.0	6.6	6.1	5.7	3.7
Range	4.2-8.7	4.0-9.3	4.1-9.3	4.2-6.2	3.2-4.6
Duration (days)					
Median	42	10	5	5	3
Range	21-42	6-14	3-8	4-5	3-5
Serum concentration after loading dose (µg/mL)					
Median	101	197	323	299	312
Range	43-214	160-247	178-450	211-408	244-486
Area under the curve† (g/h/L)					
Median	43	27	28	18	13
Range	23-86	22-44	7-51	15-26	11-35

*For regimens see Table 1.

†Area under the curve at the end of the loading regimen.

concentrations of more than 200 $\mu\text{g/mL}$ only in one patient who received 1.5 g of suramin weekly from the outset. In another patient, this concentration was achieved after 8 weeks of treatment when the weekly dose was increased to 1.5 g. With cumulative dosages of suramin varying between 4.2 to 8.7 g, serum suramin trough concentrations at the end of the sixth week varied between 43 and 214 $\mu\text{g/mL}$ (Table 3; Fig 1). Treatment had to be interrupted in two patients because of grade 3 leukopenia and grade 2 stomatitis (one patient each). A total of three patients had disease progression before they attained the target suramin serum concentration.

Four patients were treated with continuous infusion of suramin at a dose of 350 $\text{mg/m}^2/\text{d}$ (regimen L_2). At the end of treatment, serum concentrations varied between 160 and 247 $\mu\text{g/mL}$ (Fig 1). One patient who attained a serum suramin concentration of 194 $\mu\text{g/mL}$ after 8 days of continuous infusion was discharged from the hospital at his own request. One patient received suramin for 14 days without having attained a suramin concentration of 200 $\mu\text{g/mL}$. In another patient, the

suramin concentration was 201 $\mu\text{g/mL}$ after 14 days of treatment, but this decreased to 150 $\mu\text{g/mL}$ 2 days after the cessation of infusion. It was decided, therefore, to increase the daily dose of suramin to 600 $\text{mg/m}^2/\text{d}$ to attain a serum concentration of suramin between 250 to 300 $\mu\text{g/mL}$ at the end of the loading regimen to maintain the concentration above 200 $\mu\text{g/mL}$ until first scheduled maintenance treatment, ie, about 1 week after the end of the loading phase.

Based on an estimated distribution volume of suramin of 40 L and a target concentration of 200 $\mu\text{g/mL}$, it was calculated that 8 g of suramin had to be delivered to attain its assumed therapeutic concentration. In practice, the administration of a dose of suramin of 600 $\text{mg/m}^2/\text{d}$ for 7 to 8 days during a 6-hour period produced serum trough concentrations of suramin of 266 to 450 $\mu\text{g/mL}$ in four patients who received suramin this way (data not presented); consequently, the duration of the loading phase was shortened to 4 to 5 days (regimen L_3). However, peak concentrations, which were obtained immediately after the 6-hour infusion, occasionally were more than 400 $\mu\text{g/mL}$ (Fig 2). For this reason, the infusion time was lengthened to 12 hours (regimen L_4), but this did not reduce peak suramin concentrations effectively (Fig 2). This observation finally led to the administration of suramin at a dose of 600 $\text{mg/m}^2/\text{d}$ as a continuous infusion (regimen L_5). One patient received the schedule for 5 days; in the other patients, suramin was administered for 3 days. This regimen (L_5) produced suramin serum concentrations of 264 to 381 $\mu\text{g/mL}$ after 3 days, which decreased to 200 $\mu\text{g/mL}$ within 1 week. Figure 2 (L_5) shows the mean serum concentrations of 10 patients who were treated with this schedule and the decrease in serum concentrations of individual patients until the first maintenance treatment.

Two schedules of maintenance treatment administration have been used. In the first 20 patients, suramin was delivered either as a fixed dose of 1 g/wk or 600 $\text{mg/m}^2/\text{wk}$ administered during a 6-hour period, provided that the serum suramin trough concentration in the previous week was either less than 250 $\mu\text{g/mL}$ or 1.5 g when serum suramin trough concentration could not be maintained at approximately 150 $\mu\text{g/mL}$. A total of 15 patients (all had received loading regimen L_1 , L_2 , or L_3) actually started this maintenance schedule. Reasons for withholding scheduled maintenance treatment were poor performance status (one patient), toxicity (three patients), early death (one patient), and nonadherence to the protocol (one patient). However, one of the latter patients who did not receive maintenance treatment

Fig 1. Loading regimens of suramin. (A) L_1 serum suramin concentrations in six patients who received a loading regimen of 1 to 1.5 g of suramin weekly for 4 to 6 weeks. (B) L_2 serum suramin concentrations in four patients in whom suramin was administered as a continuous infusion at a dose of 350 $\text{mg/m}^2/\text{d}$ for 8 to 14 days.

Fig 2. Loading regimens that used the administration of suramin 600 mg/m²/d. L₃, peak and trough concentrations (bars represent mean $\pm$ SD) after administration of suramin 600 mg/m²/d during a 6-hour period. L₄, peak and trough concentrations when suramin 600 mg/m²/d was administered daily during a 12-hour period. L₅, serum concentrations when suramin 600 mg/m²/d was administered as a continuous infusion.

because of grade 3 leukopenia during a first course of suramin, tolerated the second course without toxicity.

The mean ($\pm$ SD) suramin trough concentrations achieved for the initial eight courses using this maintenance regimen (M₁) are presented in Table 4. At times, the maintenance dose seemed to be too high to maintain a stable trough concentration of 200 μ g/mL, and the administration of suramin had to be withheld on one or more occasions. This is reflected in the decreasing mean dose and increasing SD of the dosages administered during the subsequent weeks. Additionally, peak concentrations of more than 350 μ g/mL occurred with these dosages when trough concentrations exceeded 200 μ g/

mL. This observation, combined with the occurrence of four cases of motor neuropathy, was the reason for tailoring the dose of suramin administered each week to a window; the boundaries of which were determined by the maximum concentration considered to be safe (arbitrarily set at 300 μ g/mL) and the serum trough level measured the previous week (regimen M₂). Adherence to the weekly administration of maintenance treatment was continued. A total of 13 patients commenced maintenance treatment according to this schedule (Table 4), including one patient who had been treated previously according to maintenance regimen M₁. Three patients did not start the maintenance phase because of early progression, venous leg thrombosis, and pulmonary embolism as a consequence of disease-related hemiparesis and patient's request (one patient each). With this regimen, lower dosages were administered each week; consequently, mean trough levels were decreased compared with the maintenance regimen M₁. Initially, the suramin dosing, according to this policy, was performed by manual estimation, but later computer-assisted Bayesian pharmacokinetics became available.

Table 4. Suramin Concentrations During Maintenance Treatment

	Weeks							
	1	2	3	4	5	6	7	8
Regimen M ₁ *								
No. of patients on therapy	15	13	13	12	11	9	7	6
Suramin concentration†								
Trough								
Mean	156	169	177	185	187	177	185	194
SD	58	61	69	72	62	68	50	76
Dose (mg/m ²)								
Mean	574	619	561	586	441	414	404	507
SD	147	108	167	223	266	282	279	384
Regimen M ₂ †								
No. of patients on therapy	13	13	11	10	10	9	9	9
Suramin concentration†								
Peak								
Mean	297	273	275	293	321	310	305	319
SD	40	43	36	47	36	29	40	66
Trough								
Mean	186	147	147	147	148	151	155	155
SD	42	36	35	36	29	35	28	18
Dose (mg/m ²)								
Mean	318	314	343	346	365	404	371	371
SD	95	61	74	89	69	130	158	125

*Maintenance regimen using fixed doses of 1 to 1.5 g of suramin (see text).

†Maintenance regimen tailoring doses to prevent suramin serum concentrations > 300 μ g/mL.

‡Suramin concentration in micrograms per milliliters. Top concentrations of regimen M₁ are not presented because these were measured 24 hours after the infusion in the first 13 patients, whereas only later on peak levels were obtained immediately after suramin infusion.

The improved accuracy of the dosing obtained with this technique is shown in Fig 3. In this figure, the deviation of the measured peak concentration from the target level (300 $\mu\text{g/mL}$) in patients who were treated with regimen M_2 has been broken down according to whether the dose of suramin was estimated manually or calculated using pharmacokinetic modeling.

Tailoring the maximum doses administered during maintenance treatment to attain a mean peak value of 300 $\mu\text{g/mL}$ has not been able to prevent completely the occurrence of motor neuropathy. Three of 13 patients who were treated with this tailored regimen developed neuropathy. One of these patients had a recurrence of neuropathy that had been induced by previous exposure to suramin, and a second developed a worsening of a diabetic distal sensorimotor neuropathy. Thus, in only one patient could the development of a motor polyneuropathy be ascribed entirely to the suramin schedule used. The maximum suramin concentration in this latter patient never exceeded 303 $\mu\text{g/mL}$. Other toxicities (patients on regimen M_1/M_2 , respectively) included skin rash (six/five), stomatitis (three/one), edema (nine/zero), nausea/vomiting (eight/six), diarrhea (four/one), visual disturbances (five/three), hallucinations (two/zero), bleeding (two/two), and infection (four/one). Of these patients, one patient with advanced adrenocortical cancer died of intracranial hemorrhage (coagulation studies were normal, no postmortem performed). A second patient, who previously had a myocardial infarction and heart failure, died suddenly shortly after being admitted because of diarrhea and dehydration. A third

patient died before being admitted to the hospital, most probably from urosepsis; a fourth patient died of bronchopneumonia.

DISCUSSION

Suramin has a long plasma terminal half-life (40 to 50 days)¹²; therefore, a loading regimen followed by maintenance treatment once or twice a week seems the most appropriate way of administering the drug. After its intravenous administration, suramin is bound extensively to plasma components. Suramin binding to albumin has been reported to be as high as 99.7%.¹² The drug is not metabolized in the body, and elimination is predominantly by renal excretion.

The mechanism of action by which suramin exerts anticancer activity is unknown. Potential targets are inhibition of enzymes critical for cell growth and differentiation, interaction with intercellular matrix substances, and growth factor receptor blockade.¹³ Suramin is able to inhibit a large number of enzymes, including DNA polymerases,^{14,15} protein kinase C,⁶ and enzymes involved in phosphoinositide metabolism.⁷ Additionally, the drug may interfere with cell adhesion to matrix substances.¹⁶ However, most of the interest in suramin has arisen because of its interaction with growth factor receptors. In this way, suramin may be able to circumvent autocrine or paracrine-stimulated growth of cancer cells.

Because the mechanism of action of suramin is different from cytotoxic drugs, many questions related to its optimal use remain unresolved. It is, for example, uncertain whether the intermittent administration of suramin, which allows for recovery from toxicity, should be preferred to its continuous administration. Theoretically, if suramin's mechanism of action depends on growth factor blockade or enzyme inhibition, a continuous schedule might be associated with improved anticancer activity. Some support for this concept comes from *in vitro* data, which show that tumor cells exposed to suramin for short periods of time resume proliferation after the removal of the drug from the culture medium.¹⁷ Therefore, a maintenance regimen of at least 8 weeks was used in the present study.

Weekly administration of suramin does not produce therapeutic serum concentrations of suramin within a reasonably short period of time. Results reported in the present study using weekly suramin administration agree with those reported previously,¹⁰ although higher concentrations may be obtained when suramin is given for a longer period of time.¹⁸ Such a regimen does not seem appropriate for cancer patients, because three of six patients who received the weekly schedule developed

Fig 3. Deviation from target peak suramin serum concentration (arbitrarily defined at 300 $\mu\text{g/mL}$) in patients who received maintenance according to regimen M_2 (see text) when the dosage of suramin was estimated manually $\square$, based on known top and trough suramin serum concentrations of the previous week, and when calculated using Bayesian pharmacokinetics $\blacksquare$.

progressive disease before they attained the putative optimum suramin concentration of 200 $\mu\text{g/mL}$.

Stein et al⁸ and La Rocca et al¹⁹ described a faster loading regimen that used continuous infusion suramin at a dose of 350 $\text{mg/m}^2/\text{d}$ for 7 days, with dose adaptation after 1 week, if necessary, to achieve serum concentrations of 200 $\mu\text{g/mL}$. In the present study, the same dosage of suramin was given (regimen L_2), but the protocol we used did not allow for dose escalation. This could be the reason why one of four patients who were studied did not reach the target suramin concentration of 200 $\mu\text{g/mL}$ after 14 days of treatment (Fig 1; L_2). Subsequently, we decided to explore loading regimens that used a higher daily dosage. This study shows that regimens that deliver suramin at a dose of 600 $\text{mg/m}^2/\text{d}$ for 3 to 4 days consistently produce suramin serum concentrations of more than 200 $\mu\text{g/mL}$ (Fig 2, L_5).

The unusual pharmacokinetic profile of suramin causes specific problems when the drug is administered at high dosages. Suramin has a narrow therapeutic window, with drug concentrations of less than 150 to 200 $\mu\text{g/mL}$ that possibly might be unable to inhibit tumor growth, whereas steady-state concentrations of $\geq 300 \mu\text{g/mL}$ have been associated with the occurrence of a severe peripheral neuropathy.²⁰ The administration of suramin at a dose of 600 $\text{mg/m}^2/\text{d}$ apparently causes the accumulation of suramin in the vascular compartment. Peak concentrations were considerably higher than suramin concentrations measured 24 hours after the start of the infusion (Fig 2). The clinical importance of these peak suramin concentrations recorded immediately after a 6- and 12-hour infusion period with regard to toxicity of suramin is uncertain. After discontinuation of the infusion, the suramin concentration drops rapidly; therefore, the amount of time that the patient is exposed to these high concentrations is limited. Despite this, some concern still exists about a possible correlation between these high intravascular concentrations of suramin and the risk of neuropathy. This could be so especially because the concentration of free suramin might increase disproportionately at the higher serum concentrations. We observed seven occurrences of motor neuropathy in six patients. Electromyographic confirmation was obtained in all but one. Four cases of motor neuropathy, which were typical of that previously observed to be caused by suramin²⁰ were observed in 15 patients who received maintenance regimen M_1 . Three of 13 patients

on regimen M_2 developed paresis. Of these latter cases, one was a recurrence of a motor neuropathy that previously had been induced by an earlier suramin administration, and a second was an exacerbation of a distal diabetic sensorimotor neuropathy. Thus only one of 13 patients developed a neuropathy that was typical of suramin in the group of patients in whom dosing was controlled by Bayesian modeling. Our clinical impression is that both the severity and the frequency of neuropathy was less with regimen M_2 , but larger numbers of patients will need to be treated with different suramin schedules before these correlations can be made with any degree of statistical security.

Because of the extremely long terminal half-life of suramin, which is more than 45 days, maintenance of suramin trough concentrations through the use of weekly administration of the drug is possible. We did not measure peak concentrations if the infusion times of suramin were less than 6 hours, but it can be anticipated that these peak concentrations would be higher than after the 6-hour infusion used in the current study. Using Bayesian pharmacokinetics it is possible, however, to make estimations of the degree to which dosages will have to be reduced to administer suramin in a shorter period of time. More frequent dosing than once a week will allow the tuning of suramin concentrations to a narrower therapeutic window, whereas the smaller dosages administered each time might improve patients' tolerance to the suramin and counterbalance the burden of the frequent visits to the outpatient clinic.

In conclusion, despite the observation that suramin has definite antitumor activity in a number of tumor types that usually are resistant to conventional chemotherapy, its spectrum of often severe toxicity has introduced questions of whether the antitumor activity is outweighed by this toxicity. It is now apparent that the schedule of administration has not been optimal. High and potentially toxic serum concentrations clearly occur with the currently used schedules of administration. Scheduling strategies such as those reported in this report are necessary to ameliorate this problem. Prospective studies in which suramin concentrations are rigorously maintained within a target therapeutic window, preferably by the use of Bayesian pharmacokinetics, are required. It is only when these studies have been performed that the contribution of suramin to the treatment of cancer patients will be determined.

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