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Suramin in adrenocortical cancer: limited efficacy and serious toxicity

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Summary

OBJECTIVE No satisfactory treatment for adrenocortical carcinoma (ACC) is available. We investigated the efficacy and toxicity of suramin in the treatment of metastatic ACC since suramin has been recently reported to be active as a single agent therapy for patients with ACC and prostatic carcinoma.

DESIGN We collected data on 9 patients with metastatic ACC treated with suramin in four centres in Germany between 1987 and 1992.

PATIENTS Nine patients (5 women, 4 men; age range 32–67 years) were included. Biochemical evidence of steroid excess was found in 6/9, in three leading to clinical symptoms (hypertension, hyperglycaemia, hirsutism, gynaecomastia).

MEASUREMENTS Tumour responses were assessed by radiological and biochemical evaluation. Other investigations included regular measurements of blood cell counts, coagulation, hepatic and renal function parameters, and serum suramin concentrations.

RESULTS The patients received cumulative doses ranging from 8·2 to 30·2 g suramin over periods of 1–15 months. 3/9 achieved a partial response, 2/9 disease stabilization and 4/9 experienced progressive disease. Tumour responses were transient. Suramin treatment was without direct influence on steroid excess. Serious side-effects included coagulopathy (6/9), thrombocytopenia (6/9), polyneuropathy (2/9) and allergic skin reactions (4/9); the death of two patients was possibly related to suramin therapy. Both toxicity and tumour response were strongly associated with serum level or cumulative dose of suramin.

CONCLUSIONS (1) Suramin is of antineoplastic efficacy in the treatment of metastatic adrenocortical carcinoma. (2) The clinical use of suramin is limited by a narrow therapeutic window with the risk of serious and possibly lethal toxicity at one extreme, and loss of efficacy at the other. Strict monitoring of suramin serum levels is mandatory aiming at levels between 200 and 250 mg/l. Suramin should not be considered as first-line treatment for metastatic adrenocortical carcinoma. (3) To improve treatment options in adrenocortical carcinoma as well as for further investigation on the usefulness of suramin, controlled prospective trials are urgently needed.

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Adrenocortical carcinoma (ACC) is a rare neoplasm with high malignancy. Because of its low incidence, well designed prospective therapeutic trials involving large numbers of patients are lacking. Thus treatment has not been standardized and the prognosis is usually poor. Most patients with metastatic disease are treated with mitotane, an adrenolytic drug, introduced into clinical use by Bergenstal *et al.* (1960). It has never been proved that the use of mitotane in patients with ACC leads to significant prolongation of life and the drug is associated with significant side-effects (Luton *et al.*, 1990). Since trials with cytotoxic chemotherapy or radiotherapy did not improve treatment results and even patients who responded experienced only transient palliative effects (Johnson & Greco, 1986; Percarpio & Knowlton, 1976), other treatment options for adrenocortical cancer are urgently needed.

Suramin, a polysulphonated naphthylurea, has been used successfully in the treatment of African sleeping sickness since 1923. In 1986 its clinical use as an anti-HIV agent revealed remarkable adrenotoxicity leading to adrenocortical insufficiency (Levine *et al.*, 1986; Kaplan *et al.*, 1987). In contrast, we recently found that lower doses of suramin in sleeping sickness improve the adrenocortical function which had been impaired by acute parasitic disease (Reincke *et al.*, 1994). In animal experiments with Cynomolgus monkeys adrenocortical destruction with lymphocytic infiltration was seen after the administration of suramin (Feuillan *et al.*, 1987).

These findings led to the use of suramin in the treatment of ACC. In recent studies, the therapeutic efficacy of suramin as a single agent was shown in patients with ACC (Stein *et al.*, 1989; LaRocca *et al.*, 1990a) and with prostatic

Table 1 Clinical data of patients ($n = 9$) prior to suramin therapy

Patient no.	Sex	Age (years)	Site of disease	Prior therapy	Survival after diagnosis (months)	Survival after onset of metastases (months)
1	m	46	lung, liver	s, rad(a), cyt(a), m	17	11
2	f	32	lung, lc	s	2	2
3	f	57	lc, liver, node	s	6	1
4	m	52	lung, lc	s, ag, m	20	6
5	m	34	lung, liver, lc	s, m, cyt(b), rad(b)	15	15
6	f	53	liver, node, lc	s, ag, m	4	4
7	f	64	node, lc	s, m	16	2
8	f	47	lung	s, ag, m	6	6
9	m	63	bone	s, m	70	2

Site of disease (in order of occurrence): lc, local recurrence.
Prior therapy (in chronological order): s, surgery; m, mitotane; ag, aminoglutethimide, rad, radiotherapy; rad(a), 40 Gy to tumour bed (post-operative); rad(b), 10 Gy for local recurrence; cyt, cytostatic polychemotherapy; cyt(a), cisplatin + etoposide + bleomycin (2 cycles); cyt(b), vindesin + ifosfamide (5) and cisplatin + etoposide (3).

carcinoma (LaRocca *et al.*, 1991; Myers *et al.*, 1992). In this paper we report the results of suramin treatment in nine patients with metastatic ACC treated between 1987 and 1992.

Patients and methods

Patients

Between July 1987 and September 1982 we collected data on 9 patients (5 females, 4 males, mean age 50 years, range 32–67 years) treated with suramin in four hospitals. Patient details are shown in Table 1. All patients suffered from histologically proven metastatic adrenocortical carcinoma. At the start of suramin therapy elevated steroid concentrations were found in six patients, three of whom had clinical signs of steroid excess (Table 2).

In all patients primary treatment consisted in tumour removal by unilateral adrenalectomy; one patient also underwent ipsilateral nephrectomy and post-operative tumour bed irradiation. Treatment after onset of metastases included, in 7 of 9 patients, the use of mitotane with a median daily dose of 6·0 g (range 2·5–8·0 g) and a median duration of therapy of 2 months (range 1–7 months). This led to significant toxicity in all cases (including nausea, vertigo, hallucinations, abnormal liver function tests, allergic skin reactions and leucopenia). Other treatments used were aminoglutethimide ($n = 3$), cytotoxic polychemotherapy ($n = 2$) and local radiotherapy ($n = 1$). Irrespective of treatment, all patients experienced disease progression.

All patients gave written informed consent to suramin therapy after the experimental nature of the treatment had been explained. All former treatment was stopped at least 4 weeks before initiation of suramin therapy except in patient 9 who received additional radiotherapy for bone metastases

Table 2 Endocrine tumour activity at start of suramin therapy ($n = 9$)

Patient no.	Endocrine activity	Pathologically elevated steroids
1	(+)	17α-hydroxyprogesterone
2	–	–
3	+	cortisol
4	(+)	17α-hydroxyprogesterone, dehydroepiandrosterone sulphate, oestradiol
5	+	cortisol, 17α-hydroxyprogesterone, aldosterone, dehydroepiandrosterone sulphate, androstenedione, testosterone, oestradiol, progesterone
6	+	cortisol, aldosterone, androstenedione, testosterone
7	(+)	cortisol
8	–	–
9	–	–

Endocrine activity: +Biochemical and clinical evidence of steroid excess, (+) only biochemical evidence of steroid excess; – no sign of steroid excess.

during the first 4 weeks of his suramin regimen. Two of the nine patients (nos 2 and 3) were treated with suramin after surgery without having received additional therapy for metastases encouraged by very promising initial results in two patients in this series (Allolio *et al.*, 1989a; Baldus *et al.*, 1990) and in the series of the NIH group (Stein, personal communication, 1987; Stein *et al.*, 1989; LaRocca *et al.*, 1990a). Both patients were suffering from rapidly progressing disease.

Before initiation of suramin therapy all patients were in a general state equivalent to a Karnofsky index of at least 50. All patients had normal coagulation parameters, platelet counts above 120×10^9/l and sufficient renal and hepatic function as assessed by a creatinine clearance above 0·7 ml/s and a serum total bilirubin concentration below 25 μmol/l. In patients 4–9 maximum motor conduction velocity measurements in upper and lower limbs showed values within the normal range.

Treatment

Suramin (Germanin, Bayer, FRG) was diluted in 0·9% saline solution and administered intravenously.

On day 0 all patients received a test dose of 200 mg suramin in a bolus injection in order to minimize the risk of anaphylactic reactions. Five patients (nos 1–4, 9) received suramin by bolus injections according to a dose regimen similar to standard therapy in sleeping sickness patients (Hawking, 1978) but achieving a higher cumulative dose during a shorter period. As more data on the toxicity and on target serum concentrations of suramin became available (Stein *et al.*, 1989), the schedule was changed and in patients 5–8 suramin was given by continuous infusion (0·35 g/m^2 body surface/day during 10–16 days) aiming at suramin serum levels around 200 mg/l. After the initial course treatment was interrupted for 14 days in all patients and maintenance doses were then given in weekly to two-weekly intervals depending on serum suramin concentrations.

Baseline and follow-up studies

All patients were evaluated prior to therapy and thereafter at regular intervals (4–8 weeks) by chest X-ray, abdominal sonography, and chest and abdominal computed tomography. Additionally they underwent serial ophthalmological examinations including slit lamp studies. In patients 4–9 monthly measurements of maximum motor conduction velocity in upper and lower limbs were performed. Weekly laboratory studies included blood cell counts, coagulation tests (partial thromboplastin time, prothrombin time (given as Quick value) and thrombin time) as well as renal and hepatic function parameters.

Serum suramin concentration

Serum suramin levels were determined by high-performance liquid chromatography (HPLC) using the method reported by Klecker and Collins (1985) with minor modifications. Measurements were carried out at least twice weekly during the treatment.

Response criteria

A tumour response to suramin was defined as complete (complete response, CR) if there was no sign of measurable disease for at least 6 months. Partial response (PR) was equivalent to a more than 25% decrease, and progressive disease (POD) to a more than 25% increase of the radiologically measurable extent of disease. Stable disease (SD) was defined as $\leqslant$ 25% increase or decrease of measurable disease.

Statistical analysis

Linear and exponential regression analyses were used to determine the correlation between blood or coagulation parameters and suramin serum level or cumulative dose. A correlation was considered statistically significant with a P value less than 0·05.

Results

During treatment periods varying from 1 to 15 months cumulative doses of suramin ranging from 8·2 to 30·2 g were administered (see Table 3).

Efficacy

Three patients achieved a partial response (PR) during suramin therapy. Almost complete disappearance of multiple lung metastases was observed for 5 months in patient 1 and for 7 months in patient 8. In the third patient an extensive vertebral bone lesion (maximum diameter 8 cm) decreased in size by more than 50%. This patient also received local radiotherapy during the first 4 weeks of suramin treatment. There may have been an additive effect but regression of the lesion only became apparent 3 months after cessation of radiation therapy suggesting that the tumour regression was induced largely by continuous suramin therapy. Two of the nine patients showed transient disease stabilization (SD) during suramin treatment and

Table 3 Suramin therapy and tumour response ($n = 9$)

Pat. no.	Tumour response	Suramin therapy: max. serum level (mg/l)	Suramin therapy: serum levels continuously ⩾200 g/ml for ⩾4 weeks	Suramin therapy: cumulative dose (g)	Suramin therapy: duration of therapy (months)	Survival after start of suramin therapy (months)
1	PR(5)	476	+	24·7	7	8
8	PR(7)	361	+	30·2	15	> 36
9	PR(5)	232	+	18·2	8	9
4	SD(3)	283	+	26·1	5	12
6	SD(1)	246	–	11·6	1	2
7	POD	199	–	10·0	1	2
2	POD	169	–	11·5	2	3
5	POD	93	–	12·3	1	1
3	POD	64	–	8·2	1	1

Tumour response: PR, partial response; SD, stable disease; POD, progressive disease (definitions see 'Response criteria'). Duration of response (months) is given in parentheses.

four of nine presented with progressive disease (POD) in spite of suramin therapy. PR or SD was associated with serum suramin levels ⩾200 mg/l whereas in the four patients with POD serum levels ⩾200 mg/l were measured only on single occasions (1/4) or never (3/4) (see Fig. 1). In all three cases with PR tumour regression was observed after a minimum of 4 weeks with serum suramin levels ranging continuously between 180 and 250 mg/l.

In patient 1 (additionally suffering from 21-hydroxylase deficiency) radiologically visible shrinkage of tumour mass was paralleled by a decline in elevated 17α-OH-progesterone levels, returning to elevated levels after relapse. In none of the five other patients with steroid-secreting tumours was an influence of suramin on steroid production detected.

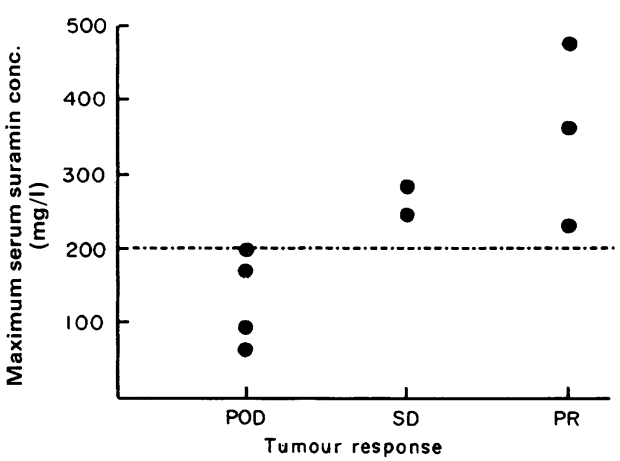

Fig. 1 Maximum serum suramin concentration and tumour response during suramin therapy in nine patients with metastatic ACC. PR, SD, POD: see 'Response criteria'. – · –, Target concentration.

Treatment was terminated in two patients (1 PR, 1 SD) because of major toxicity (see below), in three patients because of relapse after initial tumour response (2 PR, 1 SD) and in four patients because of lack of response to suramin treatment. Relapse occurred in two of the three patients with PR after a period of at least 4 weeks with serum suramin levels continuously below 100 mg/l. In both cases reinduction therapy leading to serum concentrations above 200 mg/l was without effect on tumour progression. Two patients (nos 4 and 8) with initial response to suramin received additional cytotoxic polychemotherapy after they had relapsed. However, no tumour regression was found. The survival after initiation of suramin therapy varied between 1 and more than 36 months (median 9 months); patient 8 is still alive despite progressive disease.

Toxicity (see Table 4)

Renal and hepatic function impairment was only mild and transient: elevation of serum alkaline phosphatase (4/9) and albuminuria (2/9) were reversible during ongoing treatment. Elevation of serum creatinine (177 μmol/l) was seen in the patient with unilateral nephrectomy (patient 1) and was reversible after cessation of treatment.

A coagulopathy with a prolongation of partial thromboplastin time (PTT) and an alteration of prothrombin time

Table 4 Toxicity during suramin therapy ($n = 9$) and association with mode of administration, serum concentration or cumulative dose of suramin

Toxicity	n	Association
Renal function impairment		
albuminuria (> 0·2 g/day)	2	
creatinine elevation (> 133 μmol/l)	1	
Hepatic dysfunction		
alkaline phosphatase elevation (> 200 U/l)	4	
Coagulopathy	6	serum level
Myelotoxicity		
thrombocytopenia (< 120 × 10^9/l)	6	cumulative dose
haemoglobin decrease (> 30 g/l)	2	cumulative dose?
Neurological disorders		
paraesthesia and/or dysgeusia	3	bolus injection
polyneuropathy including	2	
sensorimotor Guillain-Barré-like syndrome	1	serum level
motor polyneuropathy	1	cumulative dose?
Skin reactions		
generalized exanthema	3	bolus injection ($n = 2$)
toxic epidermal necroeysis	1	
Vortex keratopathy	3	cumulative dose?

(given as Quick value) was found in six of nine patients. Its incidence was positively correlated to suramin serum levels (PTT: $r = 0{\cdot}61$, $P < 0{\cdot}01$; Quick: $r = 0{\cdot}75$, $P < 0{\cdot}01$) (see Fig. 2a and b).

Additionally, six patients presented with thrombocytopenia after doses of 8·2–11·6 g suramin while three patients received similar doses without developing thrombocytopenia. However, this side-effect was significantly correlated with the cumulative dose of suramin ($r = 0{\cdot}69$, $P < 0{\cdot}01$; see Fig. 3). The coincidence of coagulopathy and thrombocytopenia did not result in bleeding complications. In two patients who underwent cytotoxic polychemotherapy prior to suramin a haemoglobin decrease was found after doses of 20·6 and 21·7 g, respectively.

Neurological impairment was noted in five patients. Three presented with paraesthesia and/or dysgeusia shortly after bolus injection reversible within minutes to hours. Patient 1 developed a severe Guillain-Barré-like sensorimotor polyneuropathy (PNP) following a period with serum suramin levels between 340 and 470 mg/l. While motor function gradually improved the patient experienced sudden death by acute cardiac failure. Whether autonomic polyneuropathy or progressive disease was involved remains uncertain. In patient 4 a clinically silent motor PNP was detected after a total dose of 19·6 g suramin with serum levels ranging between 120 and 230 mg/l. After cessation of therapy PNP did not improve during a follow-up period of 7 months.

Skin reactions were seen in four patients, two patients showing a generalized rash shortly after bolus injection of suramin reversible within hours. Patient 8 presented with generalized exanthema independent of bolus injection reversible after the administration of steroids and transient interruption of suramin therapy. An additional patient (no. 6) died after 6 weeks of treatment after the sudden development of toxic epidermal necrolysis while suramin

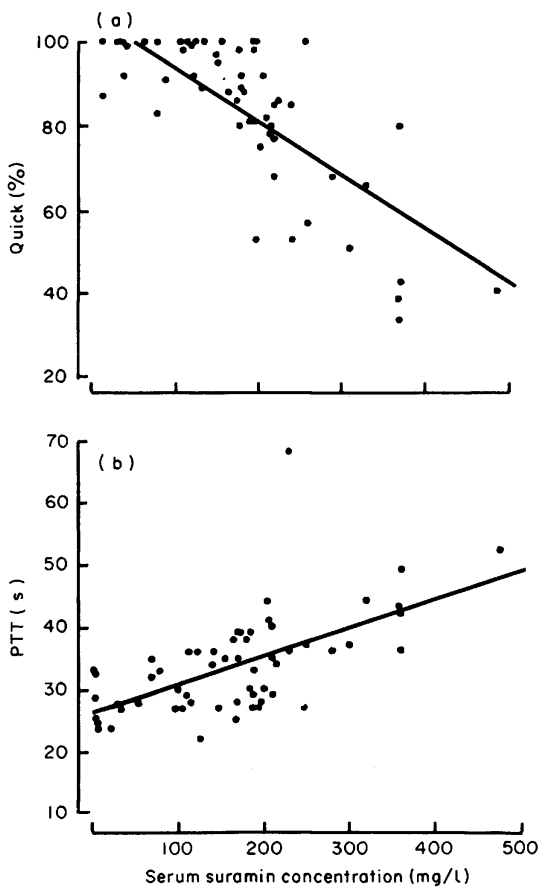

Fig. 2 Correlation between a, Quick value and b, partial thromboplastin time (PTT) respectively, and serum suramin concentration (ssc) ($n = 9$). Quick *vs* ssc: $r = 0{\cdot}75$, $P < 0{\cdot}01$; PTT *vs* ssc: $r = 0{\cdot}61$, $P < 0{\cdot}01$.

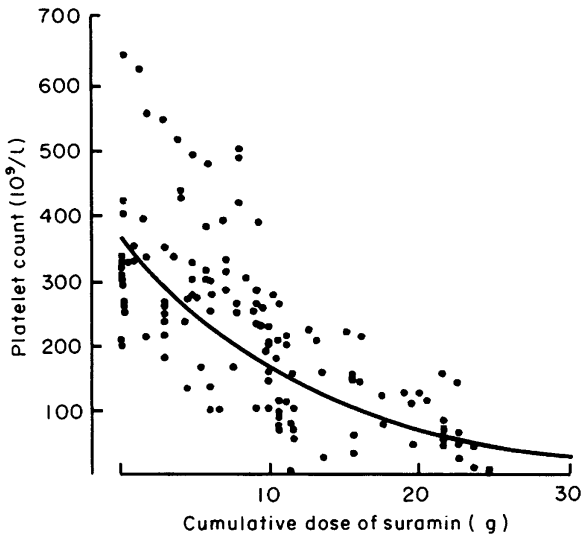

Fig. 3 Correlation between platelet count (pc) and cumulative dose (cd) of suramin ($n = 9$). pc *vs* cd: $r = 0{\cdot}69$, $P < 0{\cdot}01$.

concentrations ranged from 170 to 246 mg/l (May & Allolio, 1991).

Vortex keratopathy was observed as a minor complaint in the three patients with the longest duration of therapy, occurring after a minimum of 8 weeks of treatment. It progressed slowly during ongoing treatment and remained unchanged during follow-up after cessation of suramin.

Discussion

The response rate in our patients is similar to the findings of Stein *et al.* (1989) and LaRocca *et al.* (1990a) in patients with ACC. In our series we observed a dramatic regression of disseminated lung metastases in two patients and a reduction of extensive bone metastases in one patient. The tumour response was related to serum suramin concentrations $\geqslant$200 mg/l (target concentration). In our patients PR occurred only after 4 weeks with serum suramin levels near the target concentration. This is supported by in-vitro results in two adrenocortical carcinoma cell lines NCI-H295 and SW13 showing cytotoxic effects of suramin only at concentrations above 200 mg/l (Allolio *et al.*, 1989b; LaRocca *et al.*, 1990a).

Unfortunately, in accordance with the results of LaRocca *et al.* (1990a) the partial responses were transient. In our patients a relapse was seen 4–6 weeks after suramin levels declined below 100 mg/l. Reinduction therapy with suramin concentrations above 200 mg/l resulted in a high incidence of side-effects without tumour response. This escape phenomenon remains to be explained.

Stein *et al.* (1989) reported that in patients with high tumour bulk it took far higher doses to reach the target serum concentrations and they suggested an accumulation of suramin in tumour tissue. Four of our nine patients suffered from extensive metastases ($\geqslant$3 sites of disease) and target concentrations were achieved in none of these. All experienced progressive disease.

Initially the adrenotoxic properties of suramin (Feuillan *et al.*, 1987) provided the rationale for the use of this drug in adrenal cancer. However, there is increasing evidence that suramin interferes with a variety of regulatory processes involved in malignant cell transformation and growth. Because of its polyanionic molecular structure suramin binds to positively charged proteins and may lead to disturbances of cellular energy balance by inhibition of ATPase (Fortes *et al.*, 1973) or LDL-receptor binding (Schneider *et al.*, 1982). Suramin is known also to influence cell replication by inhibition of RNA- and DNA-polymerases (Basu & Modak, 1985; Jindal *et al.*, 1990).

Furthermore, the suramin molecule shows structural similarities to sulphated glycosaminoglycans (GAGs) which are ubiquitous on cell surfaces and in matrix tissue and take part in cell contact, recognition and growth control (Dietrich & Montes de Oca, 1978). Some GAG-degrading enzymes produced by tumour cells facilitating invasion and metastases are inhibited by suramin (Nakajima *et al.*, 1991). This also leads to GAG accumulation in serum and tissue (Constantopoulos *et al.*, 1980).

The most likely explanation for the anti-tumour activity of suramin may be its interaction with growth factors (GFs) which are able to promote tumour growth by autocrine or paracrine stimulation. Direct binding of the suramin molecule to GFs and/or to their receptors has been described for platelet-derived growth factor (PDGF) (Williams *et al.*, 1984; Hosang, 1985), epidermal growth factor (EGF) (Betsholtz *et al.*, 1986), transforming growth factor beta (TGF-β) (Coffey *et al.*, 1987) as well as for GFs with angiogenic capacity (AFs) (Vaisman *et al.*, 1990; Sato & Rifkin, 1988). An important role for EGF and bFGF and for AFs in promoting malignant growth has been suggested for adrenocortical carcinoma by in-vitro studies (Kamio *et al.*, 1990, 1991; Wellstein *et al.*, 1990; Plouet & Moukadiri, 1990).

In accord with its multitude of possible anti-tumour actions suramin also leads to a variety of side-effects. In our patients alterations of renal and hepatic function parameters were only mild and seemed to be associated with the loading period and/or bolus injection. The incidence of renal

dysfunction noted by Stein *et al.* (1989) was far higher (10/10) than in our patients (2/9); this may be explained by the fact that all patients presented by Stein *et al.* had undergone unilateral nephrectomy (in our patients only 1/9). Other mild side-effects possibly related to transient peaks of suramin concentration after bolus injection were generalized rash (2/9) and paraesthesiae (3/9).

A serious toxicity positively correlated with suramin serum concentration was coagulopathy seen in six of our nine patients. Similar to Horne *et al.* (1988) significant changes of clotting parameters became measurable at suramin serum levels around 250 mg/l. We found an involvement of both intrinsic and extrinsic clotting systems. Horne *et al.* (1988) studied plasma from suramin treated patients and found an accumulation of the GAGs heparan sulphate and dermatan sulphate exhibiting a heparin-like anticoagulant activity. In a recent study Horne *et al.* (1992) found direct inhibitory effects of suramin on procoagulant proteins (factors XII, XI, VIII, X, V) explaining the involvement of the intrinsic clotting system. Such direct effects have already been described by Eisen and Loveday (1973) who also found an anti-thrombin activity of suramin. In contrast to the patients reported by Stein *et al.* (1989) no significant bleeding complications were observed in our patients. A correlation between tumour response and incidence of suramin-induced coagulopathy (Stein *et al.*, 1989) was also not seen in our patients. Another toxicity associated with GAG accumulation was vortex keratopathy. It resulted in minor complaints but may bear the risk of visual function impairment as histological examination of lens epithelia and retinal cells from suramin treated patients revealed significant GAG accumulation (Holland *et al.*, 1988). In our patients keratopathy seemed to be related to the cumulative dose of suramin.

The incidence of myelotoxicity during suramin treatment also seemed to depend on cumulative dose. A specific accumulation of suramin in bone marrow cells has been described repeatedly and may lead to direct interference of the drug with haemopoietic growth factors as is known for heparan sulphate (Buys *et al.*, 1978; Constantopoulos *et al.*, 1980; Roberts *et al.*, 1980; Roberts *et al.*, 1988). This suggests that suramin induced myelotoxicity will be reversible paralleling tissue clearance. Suramin related thrombocytopenia may also be caused by complement activation following the formation of drug–antibody complexes; a case of severe immune mediated thrombocytopenia has been reported recently by Seidman *et al.* (1993).

Another possibly immune mediated toxicity is Guillain-Barré-like polyneuropathic syndrome (GBS) which developed in one of our patients while serum suramin concentrations varied between 300 and 400 mg/l. LaRocca *et al.* (1990b) found a 40% risk of GBS in patients with serum concentrations above 350 mg/l and noted a good response to plasmapheresis. In one additional patient we observed a clinically silent motor polyneuropathy slowly progressing with increasing cumulative dose of suramin, an association that has not been described yet.

An immunosuppressive influence of the drug was proposed by O'Donnell *et al.* (1992) who described two patients who developed keratoacanthoma during suramin therapy. As a possible mechanism for immunosuppression Mills *et al.* (1990) described an inhibitory effect of suramin on the interleukin-2 binding to lymphoid cells possibly leading to altered proliferation and differentiation.

In our series allergic skin reactions were frequent (4/9) and may be serious, as one patient experienced a lethal toxic epidermal necrolysis (May & Allolio, 1991). A history of drug-induced allergic skin reactions was reported by three of the four symptomatic patients and perhaps should be considered an exclusion criterion for suramin treatment. In a recent letter Falkson and Rapoport (1992) suggested the administration of 200 mg hydrocortisone preceding each suramin injection and reported promising reduction of allergic skin reactions. As Wilks *et al.* (1991) demonstrated *in vitro*, combination treatment with steroids and suramin may also support the anti-tumour efficacy by increased inhibition of angiogenesis.

The incidence of serious side-effects (polyneuropathy and coagulopathy) associated with serum suramin concentrations above 300 mg/l and the anti-tumour activity of suramin being found to depend on serum concentrations above 200 mg/l, demonstrate a narrow therapeutic window. This suggests mandatory strict serum level monitoring during suramin therapy.

Suramin treatment is hampered by the unique pharmacokinetic characteristics of the drug: an extremely strong protein binding (99·7%), an extensive lysosomotropic tissue accumulation (>90%), and a lack of metabolism leading to a slow renal clearance and a plasma half-life of 44–54 days (Buys *et al.*, 1978; Collins *et al.*, 1986). Recent studies suggested a computer-assisted Bayesian approach for development of individualized dosing schemes (Scher *et al.*, 1992; Cooper *et al.*, 1992; van Rijswijk *et al.*, 1992).

The use of suramin in combination therapies may lead to a dose reduction and thereby to a reduction of toxicity and/or an enhancement of anti-tumour efficacy. Vierhapper *et al.* (1989) reported on a patient with ACC presenting with partial response during combined treatment with suramin and mitotane. Furthermore, there are in-vitro data suggesting synergistic activities of suramin with cytotoxic drugs like cyclophosphamide (Osswald & Youssef, 1979) and tumour

necrosis factor alpha (Fruehauf *et al.*, 1990). Another possibility for avoiding toxicity may be the use of structural analogues of suramin (Baghdiguian *et al.*, 1990; 1991).

In conclusion, suramin is of limited efficacy in patients with metastatic adrenocortical carcinoma and its use is complicated by a high incidence of serious toxicity. The unique properties of suramin demand further research. At the moment it is not a first-line treatment for metastatic adrenocortical carcinoma. Controlled prospective trials are urgently needed to improve the treatment options for this malignancy.

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