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Feasibility and pharmacokinetics of intraperitoneal suramin in advanced malignancy

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Abstract *Purpose*: Bioactive lipids have been causally linked to intraabdominal malignancies such as ovarian cancer. In advanced tumors confined to the peritoneal cavity, inhibition of lipid growth factors present in ascites might induce tumor remissions. The systemic toxicity of the growth factor inhibitor suramin has so far hampered its use in standard oncologic practice, but this could be alleviated by intraperitoneal administration. In this study the feasibility, toxicity and pharmacokinetics of intraperitoneal suramin administration are described. *Methods*: Patients with histologically verified cancer confined to the abdominal cavity, for which no effective therapy was available, were treated with intraperitoneal suramin through a Tenckhoff catheter. Patients with ascites were treated with low-volume continuous i.p. infusions of 500 mg/24 h, and patients without ascites were treated with intermittent large-volume i.p. infusions of 1000 mg three times a week. Regular pharmacokinetic sampling of plasma and ascites fluid was carried out. Patients were treated for 6 weeks or until development of progressive disease or until plasma suramin levels exceeded 250 mg/l. *Results*: Nine patients were treated in ten periods, three with intermittent i.p. suramin, and seven with continuous i.p. suramin, for a median of 28.5 days (16–42 days), with a median suramin dose of 12 g (range 9–21 g). Treatment was discontinued because of high systemic suramin levels in three patients (all in the intermittent schedule), progressive disease (five patients) or completion of planned treatment (one patient). Toxicity was mild, without any of the systemic side effects commonly associated with suramin. Intraperitoneal suramin levels were consistently higher than plasma levels in all patients, but this effect was most marked in the continuous infusion schedule. *Conclusions*: Intraperitoneal suramin infusion in patients with advanced peritoneal cancers is feasible and well-tolerated. Continuous low volume i.p. infusion in patients with ascites confers the largest pharmacokinetic advantage.

Key words Ascites · Lysophosphatidic acid · Mesothelioma · Ovarian cancer · Suramin

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Introduction

In some cancers, tumor remains confined to the abdominal cavity even in the presence of advanced disease. Typical examples of such tumors are ovarian cancer and peritoneal mesothelioma. In most patients this growth pattern is associated with peritoneal effusions or ascites. Growth factors present in these fluid collections may play a central role in this particular pattern of spread. We and others [1] have postulated that the growth factor in ovarian cancer responsible for the disease characteristics is a bioactive lipid such as lysophosphatidic acid (LPA). The growth factor-like and mitogenic properties of LPA have been well documented, and they occur in the absence of serum or of synergizing peptide growth factors [2, 3, 4, 5]. Xu et al. have shown LPA to be elevated in the plasma of ovarian and other gynecological cancer patients [6]. We have recently demonstrated the presence of LPA-like bioactivity in ascites and other malignant effusions of patients with a variety of cancers [7].

A potential application of these findings in cancer therapy is that LPA or LPA-like activity could become a novel target for therapy. Suramin, in addition to being a nonspecific inhibitor of well-known peptide growth factors (such as EGF, PDGF, IGF-I and IGF-II, bFGF, VEGF, and TGF-β), is the only inhibitor of LPA so far recognized [8]. It is a polysulfonated naphthylurea that was originally developed as an antiparasitic agent at the beginning of the 20th century. In recent years it has also been evaluated for its antiproliferative properties in the treatment of cancer patients. Its mechanism of antitumor action is thought to lie mainly in competitive inhibition of growth factor receptor binding [9]. Substantial dose-dependent systemic toxicity has prevented its routine use so far [9], although moderate response rates have been observed in hormone-refractory prostate cancer [10, 11, 12], follicular lymphomas [13] and ovarian cancer [14].

In general, intraperitoneal (i.p.) chemotherapy is thought to achieve high regional chemotherapy concentrations without the accompanying systemic exposure and resultant toxicity [15]. Especially in small-volume disease such as peritoneal carcinosis, the pharmacokinetic advantage of i.p. chemotherapy over systemic administration is believed to be considerable [16]. To our knowledge, i.p. suramin administration has never been reported, but we hypothesized that i.p. inhibition of LPA-like activity with suramin might be feasible in patients with peritoneal disease, as suggested previously by Stein [9]. In this report we describe the development and pharmacokinetics of a continuous i.p. suramin regimen for patients with peritoneal cancers.

Methods

Objectives

In this single-institution non-randomized feasibility study, the aim was to establish the feasibility and toxicity of an i.p. administration schedule for suramin. The goal, more specifically, was to reach prolonged i.p. levels of suramin of at least 500 mg/l, with plasma levels below the concentration of 250 mg/l that is associated with systemic toxicity. The treatment protocol was approved by the Institutional Review Board and Medical Ethics Committee. Patients were enrolled from January 1995 until October 1998.

Patients

Eligible patients had histologically verified cancer confined to the abdominal cavity, including peritoneal carcinosis of any primary malignancy, for which no effective standard therapy was available. Life expectancy had to exceed 3 months, with age between 18 and 70 years, and ECOG-ZUBROD performance status 0 to 2. Adequate organ function requirements included a creatinine clearance of at least 60 ml/min, bilirubin under 25 μmol/l, white blood cell count over 3.0×10^9/l, platelets over 100×10^9/l and no serious unrelated conditions expected to interfere with treatment or follow-up. Written informed consent was obtained from all patients.

Treatment plan

All patients received an i.p. catheter of the Tenckhoff type under laparoscopic guidance [17]. Intraperitoneal chemotherapy started six or more days after implantation of the catheter, after adequate distribution of a 2-l volume of dialysis fluid containing 25% Hypaque had been documented by computed tomographic scanning of the abdomen. A test dose of 100 mg suramin was administered intravenously (i.v.) to exclude rare idiosyncratic reactions.

In patients who did not have significant ascites, 1 g of suramin dissolved in 2 l of peritoneal dialysis fluid was instilled i.p. over 30 min, and left in place until the next administration. This was repeated three times in the first week of treatment ('intermittent schedule'). After this week, maintenance treatment was administered 3 times a week, in doses of 1 g until plasma suramin levels exceeded 200 mg/l, after which the maintenance dose was decreased to 750 mg of suramin. When plasma suramin exceeded 250 mg/l, treatment was withheld for 1 week.

In patients with rapidly accumulating ascites, the regimen was one of continuous ambulant infusion of low volume (10 ml over 24 h) suramin 500 mg per day ('continuous schedule'). Treatment continued for 6 weeks, or until plasma suramin levels exceeded 250 mg/l.

Ascites was drained as the need arose in the continuous administration regimen, but at least once weekly, while the abdominal cavity was drained before each suramin instillation in the patients without ascites.

Apart from dose modifications based on plasma and i.p. suramin levels, treatment was withheld in cases of grade II leukopenia, grade II thrombopenia, grade III emesis, grade III diarrhea, grade II neuropathy, any nephropathy and any unanticipated significant toxicity. After resolution of symptoms, a 25% dose reduction was applied.

All patients were scheduled to receive treatment for 6 weeks, unless plasma suramin levels or clinical condition prevented this. In cases of remission or stable disease and patient preference, a second treatment period of 6 weeks was allowed.

Clinical assessments

During treatment patients were seen at least weekly by both a physician and a research nurse. Apart from pharmacokinetic sampling and peritoneal fluid cultures, complete blood counts and serum chemistry were performed weekly. After the treatment period, evaluation was performed including tumor markers, cytology of peritoneal washing and CT scans. Possible responses were documented when measurable or evaluable disease was present.

Pharmacokinetic analysis

Pharmacokinetic sampling of both plasma and peritoneal fluid took place before the first treatment, and 5 min, 30 min, and 1, 2, 4, 12, 24 and 48 h after the first instillation of suramin. After this, plasma and peritoneal fluid samples were taken before every instillation in the intermittent treatment group, and once or twice weekly in the continuous administration group, depending on the frequency of visits to the hospital. After flushing the i.p. catheter with 50 ml of normal saline, peritoneal fluid samples were taken, with a second or third sample after as much fluid as possible had been drained, to check that suramin distribution was adequate. Suramin levels in plasma and peritoneal fluid were determined by a previously described HPLC method [18].

Results

Patient and treatment characteristics (Tables 1 and 2)

Nine patients were treated with i.p. suramin in ten episodes, for a median treatment duration of 28.5 days (range 16–42 days). Three patients were treated with the intermittent schedule, and seven patients (including the

Table 1 Patient characteristics

Patient no.	Sex	Age (years)	Diagnosis	Presence of ascites	No. of previous chemotherapeutic regimens
1	M	44	Peritoneal mesothelioma	Yes	–
2	F	50	Ovarian cancer	No	2
3	M	47	Peritoneal mesothelioma	No	–
4	M	39	Cholangiocarcinoma	Yes	1
5	F	51	Ovarian cancer	Yes	5
6	M	63	Peritoneal mesothelioma	Yes	–
7	F	66	Peritoneal mesothelioma	Yes	–
8	M	49	Ovarian cancer	Yes	2
9	M	49	Peritoneal mesothelioma	Yes	–

first patient who was treated twice) were treated with the continuous schedule. The patient characteristics are summarized in Table 1. The total suramin dose ranged from 9 to 21 g, with a median of 12 g, but due to frequent and variable paracenteses, variable amounts of ascites containing suramin were withdrawn from the patients, especially in the continuous infusion group. Treatment was discontinued because of plasma suramin levels exceeding 250 mg/l (three patients), progressive disease (five patients), or because the planned 6-week treatment period was completed (one patient).

Toxicity

Intraperitoneal suramin treatment was generally well tolerated. One patient developed a skin rash, which was controlled with oral clemastine. Fatigue occurred in all patients, but no bone marrow suppression, neurotoxicity, nephrotoxicity or adrenal insufficiency were encountered. One patient was admitted for progressive disease and dyspnea, thought to be due to pulmonary embolism. On the day of admission suramin was stopped and i.v. heparin was started, but the patient died suddenly within 24 h. Although permission for autopsy was not granted, the clinical picture was suggestive of pulmonary embolism.

Pharmacokinetic data

Intermittent i.p. suramin in patients without ascites (Table 2, Fig. 1a)

In all three patients receiving intermittent suramin, systemic concentrations rose after peak peritoneal fluid concentrations had been achieved. Peritoneal fluid trough suramin levels were mostly under 200 mg/l and plasma concentrations rose to peritoneal fluid levels in all three patients. As can be seen in Table 2 (patients 1a, 2 and 3), peritoneal fluid suramin levels rarely rose above the predefined target level of 500 mg/l, even

Table 2 Treatment characteristics

Patient no.	Schedule	Days on suramin	Days of plasma suramin 250 mg/l	Days of peritoneal suramin 250 mg/l	Days of peritoneal suramin 500 mg/l	Reasons for discontinuation	Total suramin dose[a] (g)
1a	Intermittent	14	0	3	0	High plasma suramin[b]	6
1b	Continuous	22	8	20	2	High plasma suramin	11
2	Intermittent	28	6	23	0	High plasma suramin	9.8
3	Intermittent	37	15	22	0	High plasma suramin	16.3
4	Continuous	26	0	2	0	Progressive disease	12
5	Continuous	16	0	16	16	Progressive disease	13
6	Continuous	42	0	42	34	End of study period	21
7	Continuous	38	0	37	31	Progressive disease	19
8	Continuous	28	0	28	28	Progressive disease	14
9	Continuous	18	0	18	9	Progressive disease	9

[a] Suramin removed as a consequence of ascites evacuation not considered
[b] After 14 days patient 1 went to have continuous i.p. suramin, which led to high plasma suramin levels after 29 days (data not shown)

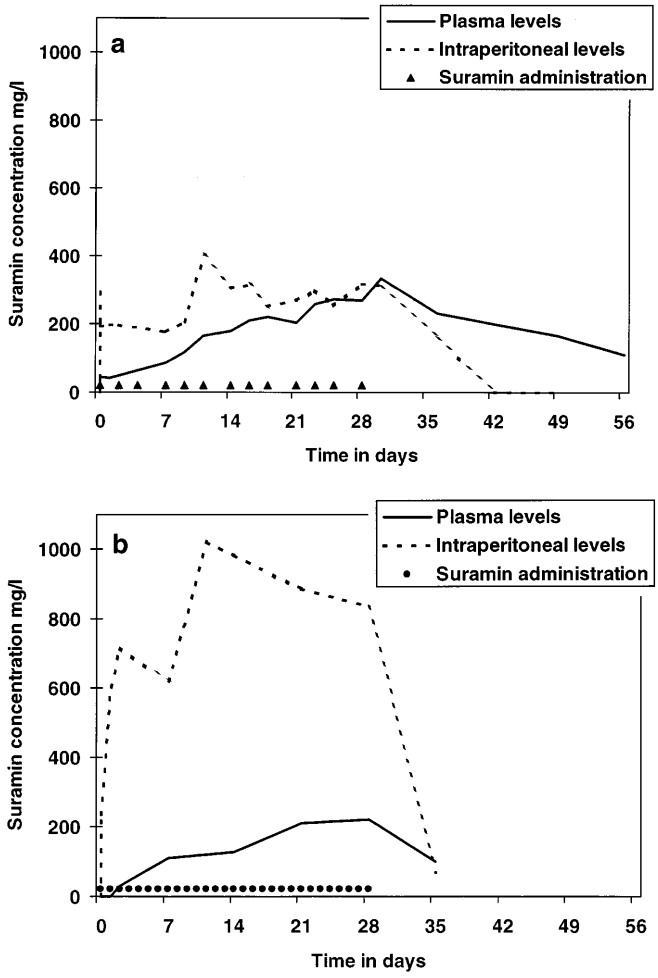

Fig. 1a,b Typical time-concentration curves. **a** Patient 2 treated with intermittent i.p. suramin for 28 days (total suramin dose 9.8 g). **b** Patient 8 treated with continuous i.p. suramin for 28 days (total suramin dose 14 g)

though peritoneal levels were generally higher than systemic ones. A typical time/concentration curve during intermittent treatment is shown in Fig. 1a.

Continuous i.p suramin in patients with ascites (Table 2, Fig. 1b)

In all treatment periods with continuous suramin administration, peritoneal fluid suramin levels were consistently higher than plasma levels (Table 2, patients 1b, 4–9). Peritoneal fluid levels were above the predefined target level of 500 mg/l during most of the treatment period (median 81% of treatment days), and above 250 mg/l for most of the treatment period (median 100% of treatment days). In only one patient did the plasma suramin concentration reach 250 mg/l. A typical example of the time/suramin concentration curve during continuous suramin administration is given in Fig. 1b. The amount of ascitic fluid that was drained to alleviate symptoms, was 1–4 l per week in all but one patient. In patient 4 ascites production was so massive that 10–15 l of fluid were drained weekly. In this patient, peritoneal fluid suramin levels were only slightly higher than plasma concentrations. The pharmacokinetic advantage of i.p. administration thus seems most evident in patients with moderate amounts of ascites.

Efficacy

Measurable disease was present in one of nine patients (patient 4), who progressed during therapy. The case of a patient (patient 1) with peritoneal mesothelioma whose ascites and all other symptoms disappeared after suramin treatment, although peritoneal washing cytology remained tumor-positive, has been previously reported as a case report [19]. Unfortunately, the disease progressed 3 years after the end of treatment. In another mesothelioma patient (patient 6) ascites production all but disappeared, but pleural effusions developed during treatment, eventually leading to death. In one ovarian cancer patient (patient 2), CA-125 stabilization was noted and in another ovarian cancer patient (patient 8) CA-125 decreased by 50%, but in neither case was this associated with decreased ascites production or other signs of a clinical response.

Discussion

The objective of this study was to develop a regimen in which peritoneal fluid levels of suramin of at least 500 mg/l, an arbitrarily selected concentration well above that required for inhibition of a large number of growth factors, could be achieved for a prolonged time. Both continuous i.p. infusion regimens (in patients with ascites production) and intermittent i.p. regimens of suramin administration were employed in a total of nine patients. In six of ten treatment courses (in nine patients), this was achieved for a median of 20 days (range 3–27 days). Suramin administration had to be discontinued in four courses (in three patients) because of plasma suramin levels reaching 250 mg/l, a level commonly associated with systemic toxicity.

Systemic suramin toxicities such as fatigue and malaise, neuropathy [20, 21], mineralocorticoid insufficiency [22] and corneal deposits [23] are dose-dependent, but more unpredictable reactions such as a wide spectrum of cutaneous eruptions [24], occasional neutropenia [25], thrombocytopenia [26] and renal failure [27] have also been described. Suramin toxicity is most marked at plasma suramin levels over 350 mg/l, but may occur at concentrations as low as 200 mg/l [11]. Efficacy decreases with lower suramin levels, i.e. under 200 mg/l [9]. Apart from fatigue, none of these 'classical' suramin-associated side effects was seen in our patients.

So far, marked interpatient variability in suramin pharmacokinetics has generally frustrated the development of a safe, simple and repeatable dosing

schedule. Therefore, the most common approach has been to use some type of adaptive control, although fixed dosing schedules have been described [28, 29, 30, 31]. In combination with the relatively modest benefits at the plasma concentrations that are feasible with i.v. administration [10, 12], suramin has not acquired an accepted role in standard treatment for any malignancy.

The intermittent administration design was based on standard protocols of i.p. chemotherapy in peritoneal dialysis fluid [16], with the suramin dose as applied in suramin-loading schedules with i.v. suramin administration [10, 12]. Only when we treated the first patient with ascites did the plasma levels appear to rise quickly without achieving high peritoneal fluid levels. An additional disadvantage of that schedule was the discomfort associated with the infusion of 2 l of fluid on top of the ascites present. It was therefore decided to try and use the ascites as the solvent for a continuous low-volume suramin infusion in order to achieve higher and more constant peritoneal concentrations (with less discomfort). In this continuous i.p. infusion regimen, peritoneal fluid suramin concentrations were consistently higher than 250 mg/l, and plasma suramin levels rose above predefined levels (defined as levels >250 mg/l) in only one of seven patients in this group, as opposed to all three patients in the intermittent administration group. The pharmacokinetic advantage of the i.p. approach was thus high in those patients with ascites, compared to the patients without ascites where continuous small-volume infusion would not have guaranteed adequate i.p. distribution of suramin. Even though the pharmacokinetic profile in this intermittent large-volume infusion group was not as favorable, a small advantage could be documented.

The lack of high plasma suramin levels in the continuous infusion group was probably the result of the frequent draining of ascites (containing suramin), leading to a decreased systemic exposure to suramin without a reduction in peritoneal concentrations. The total administered suramin dose is therefore not a useful parameter in this group of patients. In addition, the amount of ascites is difficult to measure and the volume changes over time in these patients. It is impossible to calculate the bioavailability of suramin after i.p. administration, since accurate estimation of the administered dose is required for the comparison of exposure after i.p. and i.v. administration.

The most favorable situation was documented in patients with moderate amounts of ascites, where peritoneal fluid concentrations were above the target of 500 mg/l for most of the study period. Massive ascites production, however, as was seen in one of our patients, with associated draining of 5–10 l per week, kept systemic suramin levels low, but did not lead to sustained high peritoneal levels.

In the first two patients, considerable differences between the first sample, taken after flushing with saline, and later samples, taken after draining the peritoneal fluid, existed in 30% of samples, with a twofold difference in a few instances. Since generally the lowest levels were determined after fluid had been evacuated, we conclude that contamination of the Tenckhoff catheter with suramin-containing saline due to inadequate flushing was responsible for this problem. In a previous study of the chemical stability of suramin, we did not find any indication that suramin adheres to, or interacts with, infusion devices [32]. We therefore optimized the protocol for flushing of the Tenckhoff catheter, with increased adherence to the sampling and flushing guidelines. For consistency, we decided to use the last sample values in all situations. In later patients we did not find significant differences between consecutive samples, and we postulate that this was the result of increased awareness of the problem, and stricter instruction of the research nurses handling the procedure. Because adequate drug distribution was documented in all patients before the start of treatment, we do not think that these differences arose from unequal distribution of suramin within the abdominal cavity.

We believe that our findings are encouraging, but we cannot be certain that this optimism is justified, as considerable uncertainty exists about the following questions. First, it is unknown for how long LPA and other growth factors need to be inhibited before significant growth inhibition occurs. We chose 6 weeks of prolonged i.p. suramin exposure as a target, but found that 28 days was more feasible: plasma suramin levels tended to rise and patient fatigue generally increased after a month. It might be preferable to try and treat patients for a number of 4-week courses instead of one extended course. In the one patient treated twice (patient 1, one 29-day and one 22-day period) no significant toxicity was observed, and a clinical response resulted.

Second, the optimal concentration for growth factor inhibition by suramin is unclear. Although in vitro data suggest an IC_{50} of 100 mg/l and an IC_{85} of 1000 mg/l for suramin inhibition of LPA-induced DNA synthesis [8], there are no in vivo data to support this, especially since it is not feasible to reach suramin concentrations over 300 mg/l systemically. We chose 500 mg/l as an attainable target concentration that would block a substantial part (at least 60%) of LPA-induced synthesis, with a minimal risk of unexpectedly high systemic toxicity. When in the first patients plasma levels were seen to rise within a few weeks, we decided not to escalate the dose further. Suramin is highly bound to plasma proteins ($>99.7\%$), with very low total body clearance (0.41 ml/min) and a terminal half-life of 40 to 50 days [33]. Interpatient variability in elimination from plasma is mainly due to the different rate of drug movement from the central to the peripheral compartment, rather than the rate of total body clearance that shows little variation between individuals [28].

The pharmacokinetic measurements in the intermittent infusion schedule suggest rapid clearance of suramin from the peritoneal cavity with redistribution immediately after administration. In the continuous regimen, a similar phenomenon was seen when the drug was stopped. Peritoneal fluid levels fell below plasma

levels within a few days. This may have been a consequence of the extensive plasma protein binding of suramin, compared to the low-protein ascites environment. If this is the case, free suramin levels may be much higher than indicated by overall suramin levels in ascites compared to plasma. Therefore, much lower target peritoneal fluid suramin concentrations might be appropriate. To investigate this, an ultrafiltrable suramin assay is necessary, and a functional test for the ability of suramin-containing ascites fluid to inhibit growth factor activity would be helpful.

In order to investigate antitumor efficacy and further evaluate toxicity, we propose a phase II dose of 500 mg over 24 h in a continuous low-volume infusion for 4 weeks in patients with peritoneally disseminated cancers with moderate amounts of ascites. Once-weekly plasma and ascites suramin levels should be measured to confirm the data of the present study.

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