Suramin in Combination with Weekly Epirubicin for Patients with Advanced Hormone-Refractory Prostate Carcinoma

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BACKGROUND. Suramin and epirubicin are both active agents in the treatment of patients with hormone-refractory advanced prostate carcinoma, with demonstrated antitumor synergism in vitro on human prostate carcinoma cells and different dose-limiting toxicities. The authors conducted this Phase II study to determine the feasibility, toxicity, and antitumor activity of suramin in combination with epirubicin.

METHODS. Only patients with hormone-independent advanced prostate carcinoma who had progressive disease after the last therapeutic maneuver they had undergone, including antiandrogen withdrawal, entered the study. Suramin was administered initially as a 6-day continuous infusion for 10 consecutive weeks and then for 6 days every 28 days for a maximum of 6 months. Doses were determined by a computer-assisted dosing system that used Bayesian pharmacokinetics to maintain suramin plasma concentrations of 200–250 μg/mL. Cortisone acetate 25 mg, administered at 8 a.m. and 8 p.m. daily, was begun 4 weeks after the initiation of suramin therapy. Epirubicin 25 mg/m^2 was given as a weekly intravenous bolus beginning on Day 1 and was continued for a maximum of 6 months.

RESULTS. Twenty-six patients entered the study. Toxicities mainly included World Health Organization Grade 1–2 nausea, fatigue, anorexia, neutropenia, peripheral neuropathy, creatinine elevation, proteinuria, and prolonged prothrombin time, whereas Grade 3 toxicities were uncommon. Among 11 patients with measurable disease, 3 (27%) demonstrated an objective response. Among 24 patients evaluated for prostate specific antigen (PSA) response, 8 (33%; 95% confidence interval 16–55%) had a $\geq$50% decrease in PSA levels, which lasted a median of 32 (range, 8–52) weeks. Median progression free and overall survival were both 8 months.

CONCLUSIONS. The combination of suramin and epirubicin used in the current study is feasible, is associated with moderate toxicities, and has antitumor activity in advanced hormone-refractory prostate carcinoma. However, the results obtained with this combination do not represent major improvements in the treatment of patients with this disease, compared with suramin or epirubicin alone or other available treatments. ***Cancer* 1999;86:470–6.**

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Patients with prostate carcinoma that is no longer responsive to hormonal therapy have very poor survival; the majority die within 12 months. Many cytotoxic agents have been evaluated alone or in combination in the treatment of hormone-resistant patients. Overall results remain unsatisfactory; however, palliative benefits, decreases in prostate specific antigen (PSA) levels, and objective tumor responses have been demonstrated.[1]

Suramin, a polysulfonated naphthylurea previously used to treat patients with trypasonomiasis, onchocerciasis, and acquired immune deficiency syndrome, has received new attention as a potential anticancer agent because of its ability to bind several cellular growth factors and antagonize their growth-promoting effect.[2,3] Suramin has demonstrated significant antiproliferative activity against several human cancer cells in vitro,[4,5] but when tested clinically it has demonstrated definite and reproducible activity, mainly in hormone-refractory prostate carcinoma.[6–11] In this disease, suramin-induced response rates have ranged from 20% to 40% with a PSA decline of >50% in 40–70% of patients. However, these early studies did not control for the confounding effects of flutamide withdrawal or the concomitant use of low dose corticosteroids.[8–12]

Among traditional cytotoxic agents, the antracycline doxorubicin and its less cardiotoxic analogue, epirubicin, are the most active and frequently used agents, with responses observed in up to 30% of patients.[13–16] It is noteworthy that experimental in vitro studies of the testosterone-sensitive human prostate carcinoma cell line LNCaP and testosterone-independent cell line PC-3 have demonstrated significant synergistic antitumor activity between doxorubicin and suramin at clinically achievable concentrations.[17] Furthermore, the combination of doxorubicin and suramin circumvents drug resistance associated with *bcl*-2, which may contribute to the relative drug-resistant phenotype observed in hormone-refractory prostate carcinoma, in Dunning-G rat prostate carcinoma cells.[18]

We therefore conducted the current study to make a preliminary determination of the feasibility, toxicity, and antitumor activity of suramin in combination with the doxorubicin analogue epirubicin. Epirubicin was preferred to doxorubicin because of its more favorable toxicity profile, which can be particularly advantageous for elderly patients.

PATIENTS AND METHODS

Patient Selection

Eligibility criteria for this study included histologically confirmed diagnosis of hormone-independent, advanced prostate carcinoma; progressive disease after the last therapeutic maneuver that patients underwent, including antiandrogen withdrawal for at least 4 weeks; Eastern Cooperative Oncology Group (ECOG) performance status ≤3; life expectancy >3 months; PSA levels ≥10 or measurable disease; leukocyte count ≥3500 mm^3; platelet count ≥100,000 mm^3; normal coagulation parameters; serum creatinine <1.5 mg/dL; serum bilirubin <1.5 mg/dL; transaminases <2.5 times normal values; no hormonal therapy (except luteinizing hormone–releasing hormone [LHRH] analogues, which were continued during the study); and chemotherapy or radiation in the previous 4 weeks or previous treatment with doxorubicin, epirubicin, or suramin. All patients had verified castration levels of testosterone before study entry. Patients with a history of other malignant tumor (except nonmelanoma skin cancer), bleeding disorders, clinically significant cardiac disease, severe neuropathy, active infections, or cerebral metastases were excluded. Approval for the study was obtained from the local Ethics Committee. Patients were informed of the nature of the study and gave their written informed consent.

Treatment

Suramin was purchased from Bayer (Leverkusen, Germany) in 1-g vials and was administered as a 6-day continuous infusion every week through a central venous implantable catheter and an external volumetric pump (Pharmacia CADD-1, Pharmacia Deltec Inc., St. Paul, MN). The initial daily dose of suramin during the first 6 days of therapy was 350 mg/m^2. Thereafter, doses for each weekly infusion of 6 days were determined by a computer-assisted dosing system that used Bayesian pharmacokinetics (MW/Pharm 3.03; Mediware, Groningen, The Netherlands) to maintain suramin plasma concentrations of 200–250 μg/mL.[19] Treatment was continued for 10 consecutive weeks; thereafter, 6 days of suramin therapy were repeated every 4 weeks for a maximum of 6 months from the start of treatment, if no progression or dose-limiting toxicities occurred. All patients on the trial received replacement cortisone acetate 25 mg orally at 8 a.m. and 8 p.m. daily to compensate for suramin-induced adrenal insufficiency. Because in our previous clinical experience with suramin clinical signs of adrenal insufficiency did not develop during the first month of therapy (unpublished data), cortisone acetate was begun 4 weeks after the start of suramin therapy, in the absence of signs of adrenal insufficiency. Furthermore, all patients received weekly vitamin K 10 mg intramuscularly. Cortisone acetate was continued indefinitely, whereas vitamin K was discontinued at the end of suramin therapy.

Epirubicin 25 mg/m^2 was administered as a weekly intravenous bolus from the beginning of suramin therapy for a maximum of 6 months unless intolerable toxicities or disease progression occurred. The weekly schedule of administration of epirubicin was selected to reduce toxicity. Patients received epirubicin as long as the granulocyte count was ≥1000 mm^3 and the platelet count was ≥100,000 mm^3. If granulocyte and/or platelet counts were below 1000

mm^3 and 100,000 mm^3, respectively, treatment was held until counts recovered.

Assessability, Toxicity, and Response Criteria

Pretreatment evaluation included history and physical examination; performance status assessment; complete blood cell count with differential and platelet count; complete blood profile, including prothrombin time (PT) and partial prothromboplastin time (PTT); prostate specific antigen (PSA); urinanalysis; electrocardiogram; chest X-ray or computed tomography (CT) scan; abdominal/pelvic CT scan and/or sonogram; bone scan; and any other appropriate diagnostic procedure to evaluate sites of disease. During treatment, a physical examination, complete blood cell counts, biochemistry, and plasma suramin levels were determined weekly, PSA levels were assessed every 2 weeks, and tests to evaluate the status of disease were repeated every 2 months. After cessation of treatment, patients were monitored at monthly intervals.

Toxicity and responses in patients with measurable or evaluable disease were evaluated according to standard World Health Organization (WHO) criteria.[20] PSA response was defined as a decrease in PSA $\geq$50% of baseline on at least 2 consecutive measurements, lasting for at least 4 weeks, without any evidence of clinical progression.[21,22]

Pharmacokinetics

Plasma samples (0.5 mL) for suramin assay were obtained from heparinized blood drawn from patients at the end of each suramin infusion and analyzed by reversed-phase, ion-pairing high performance liquid chromatography (HPLC) assay.[23] A three-compartment open model with elimination from the central compartment was adopted to describe suramin distribution and elimination.[19] The population parameter estimates for the pharmacokinetic model of suramin were as follows: clearance, 0.29 mL/min/m^2; volume of distribution, 27.6 L/m^2; $t_{1/2}$ g, 1081.9 h; k_{12}, 0.034 h^{-1}; k_{21}, 0.012 h^{-1}; k_{13}, 0.002 h^{-1}; k_{31}, 0.001 h^{-1}. Relative standard error (SE) values for the parameter estimates varied between 11% and 24%. Plasma samples for epirubicin assay (0.5 mL) were separated from heparinized blood samples obtained from patients at the following time points: baseline (predose of epirubicin), 5 and 30 minutes and 1, 2, 3, 4, 6, 9, 12, 18, and 24 hours after the first epirubicin bolus and assayed by a validated reversed-phase HPLC method (Fogli S et al., unpublished data). The performance of the HPLC assays was monitored on each day of analysis; the interassay coefficient of variation was below 10% and the inaccuracy was between −2.5% and 9.4% for suramin, epirubicin, and epirubicinol. Linearity of the calibration curves (r^2>0.995, least-squares method) was obtained in the range of 5–1000 μg/mL for suramin and between 0.5 ng/mL and 10 μg/mL for epirubicin and its metabolite epirubicinol, and the limits of detection were adequate for the measurements of compounds up to the end of the sampling time of the pharmacokinetic study. The plasma levels vs. time curves of suramin, epirubicin, and epirubicinol were modeled using the Kinfit module incorporated into the MW/Pharm computer program (version 3.03, Mediware, Gröningen, The Netherlands).

TABLE 1
Patient Characteristics

Characteristic		No. of patients
No. of patients		26
Age (yrs)		
Median	67	
Range	53–81	
ECOG performance status		
0		12
1		9
2		3
3		2
No. of metastatic sites		
Single		9
Multiple		17
Sites of metastases		
Bone		25
Lymph nodes		11
Liver		5
Lung		5
Others		2
Measurable extraosseous disease		11
PSA (ng/mL)		
Median	139	
Range	15–3560	
Prior treatments		
Prostatectomy		6
Radiotherapy		9
Antiandrogen first-line		26
LHRH agonist		26
Second line hormonotherapy		14
Chemotherapy		3
Pain		
None		3
Requiring therapy		23

ECOG: Eastern Cooperative Oncology Group; LHRH: luteinizing hormone–releasing hormone.

RESULTS

Twenty-six patients with androgen-independent advanced prostate carcinoma were entered into this clinical trial. Patient characteristics are summarized in Table 1. The median ECOG performance status was 1 (range, 0–3), the median age was 67 years (range, 53–81 years), 11 patients had extraskeletal measurable

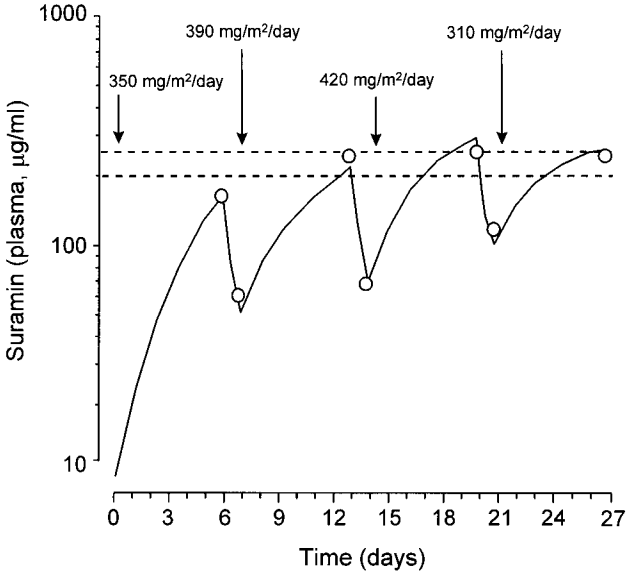

FIGURE 1. A fitted plasma pharmacokinetic profile of suramin, during the first 4 weeks of treatment of a patient with a creatinine clearance of 76.8 mL/min/1.73 m^2, is shown. Points indicate the actual measurement of suramin levels at the end of the 6-day infusion period; suramin doses in mg/m^2/day were calculated by the Bayesian algorithm reported in the text.

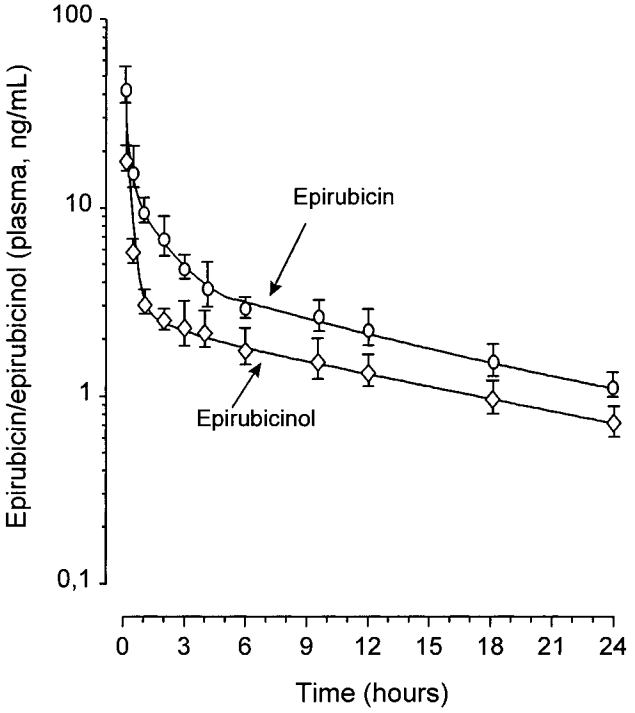

FIGURE 2. A fitted plasma pharmacokinetic profile of epirubicin and epirubicinol, after the first dose of epirubicin 25 mg/m^2, is shown. Points indicate the mean plasma levels of five patients and vertical bars show the standard error of the mean.

disease, 14 patients had received prior second-line hormonal treatment, 9 patients received radiotherapy, and 3 patients received chemotherapy. The use of dose adaptation with Bayesian algorithm allowed the safe delivery of suramin treatment; plasma suramin levels of 200–250 μg/mL were reached after 6–20 days, and concentrations between 100 and 300 μg/mL were maintained during the treatment period with suramin. The plasma pharmacokinetic profile of suramin in a representative patient is reported in Figure 1. Epirubicin and epirubicinol plasma disposition were characterized by a 3-exponent decay (Fig. 2), and the following parameters ($\pm$ SE) were obtained for epirubicin: peak plasma level (C_{max}), 42 $\pm$ 8 ng/mL; area under the curve of plasma concentrations versus time (AUC trapezoidal, 0–24 hours), 81.3 $\pm$ 12.1 ng/mLxh; clearance, 210.9 $\pm$ 34.2 L/h/m^2; volume of distribution at steady state, 3733.5 $\pm$ 482.1 L/m^2; terminal half-life ($t_{1/2}g$), 16.08 $\pm$ 2.4 h. The corresponding pharmacokinetic parameters of epirubicinol were as follows: C_{max}, 18 $\pm$ 2.2 ng/mL; AUC, 42.5 $\pm$ 6.6 ng/mLxh; $t_{1/2}g$, 27.6 $\pm$ 3.9 h.

The median duration of therapy with suramin and epirubicin was 9 weeks (range, 2–29 weeks). All patients were evaluable for toxicity, which included primarily WHO Grade 1–2 nausea, vomiting, fatigue, anorexia, neutropenia, peripheral neuropathy, creatinine elevation, fever, cutaneous rash, and proteinuria (Table 2). WHO Grade 3 toxicities were uncommon and included peripheral neurotoxicity in 1 patient, diarrhea in 1 patient, and neutropenia in 1 patient. Twelve patients developed prolonged prothrombin and/or thromboplastin times but did not need treatment discontinuation. No sepsis, hemorrhage, WHO Grade 4 toxicities, or toxic deaths occurred. Eleven patients with extraskeletal mea-

TABLE 2
Overall Worst Toxicity (26 Evaluable Patients)

	WHO grade (%)			
Adverse event	**1**	**2**	**3**	**4**
Nausea/vomiting	35	19	0	0
Fatigue[a]	23	27	4	0
Anorexia[a]	27	27	4	0
Stomatitis	23	19	0	0
Diarrhea	4	0	4	0
Rash	11	0	0	0
Neutropenia	38	23	4	0
Fever	15	11	0	0
Creatinine elevation	23	4	0	0
Proteinuria	58	0	0	0
Peripheral neurotoxicity	23	0	4	0
Alopecia	23	15	0	0

WHO: World Health Organization.
[a] 1: mild; 2: moderate; 3: severe.

TABLE 3
Responses

	WHO response (11 patients)				PSA response (24 patients)			
	CR	PR	S	P	≥50%	25–50%	S	P
No. of patients	0	3	4	4	8	4	5	7
% of patients	0%	27%	36.5%	36.5%	33%	17%	21%	29%

CR: complete response; PR: partial response; S: stable disease/stable PSA; P: progression of disease/increase in PSA.

surable disease could be evaluated with standard WHO response criteria. Three (27%) of these 11 patients demonstrated an objective response: 1 achieved a complete response in the lung and lymph nodes, the second patient achieved a partial response in the liver and lymph nodes, and the third patient achieved a partial response in the pelvic lymph nodes. All 3 patients had improvement on bone scan and a ≥50% decrease in PSA lasting a median of 28 weeks (range, 20–48 weeks). Twenty-four patients could be evaluated for PSA response (1 patient was not evaluable because treatment was interrupted after only 1 week for creatinine elevation, and 1 patient was lost to follow-up after 3 weeks). Eight of these 24 patients (33%; 95% CI. 16–55%) had a ≥50% decrease in PSA levels for at least 4 weeks, which occurred after a median of 8 weeks from the initiation of therapy and lasted a median of 32 weeks (range, 8–52 weeks); 4 patients (17%) had a decrease in PSA of 25–50%; 5 (21%) had stable PSA for at least 8 weeks; and 7 (29%) had an increase in PSA of ≥25%. In patients who obtained a PSA response ≥50%, an initial decrease in PSA was achieved during the first 4 weeks of treatment, prior to cortisone acetate administration (Table 3). Among the 23 patients with bone pain at baseline, in 15 (65%) significant improvement in pain intensity and/or analgesic consumption was observed.

Progression free and overall survival curves calculated according to the Kaplan– Meier method from the time of treatment initiation are reported in Figure 3. The median time to progression and median survival were 8 months.

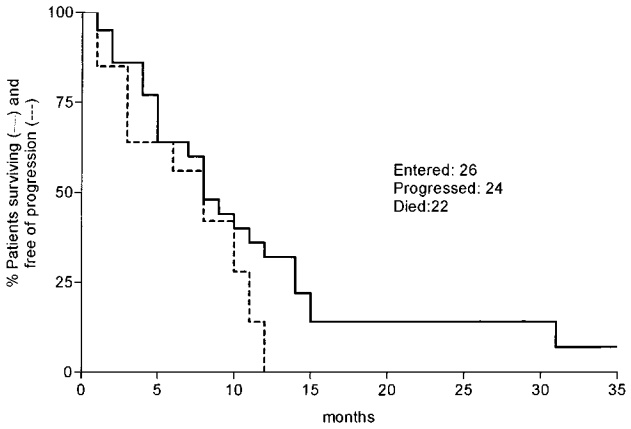

FIGURE 3. Actuarial progression free and overall survival curves are shown.

DISCUSSION

The management of advanced prostate carcinoma progression after initial androgen deprivation is controversial.[1] Suramin is a chemotherapeutic agent that has been used for several decades in the treatment of parasitic disorders. In the 1990s, there was renewed interest in its potential anticancer activity based on initial results in the treatment of androgen-independent prostate carcinoma.[7,8] Several subsequent clinical trials involved patients with androgen-independent prostate carcinoma; the reported response rates from these trials were 17–70%.[7–12] One explanation for the wide variations in response may be the uncontrolled confounding effects of flutamide withdrawal and the use of low dose corticosteroids. More recently, trials in which these factors were prospectively controlled were conducted, and, although suramin still demonstrated antitumor activity, responses were observed in only 14–22% of patients.[24–26]

Doxorubicin and its less cardiotoxic analogue, epirubicin, are among the most active cytotoxic agents in hormone-refractory prostate carcinoma. They have different dose-limiting toxicities from suramin, and doxorubicin has demonstrated synergistic antitumor activity in vitro against human prostate carcinoma cells.[17,18]

On the basis of these considerations, we designed this study to determine the feasibility, toxicity, and activity of a combination of suramin and epirubicin. To prevent the confounding effects of antiandrogen withdrawal, if the antiandrogen had previously been discontinued, patients had to demonstrate evidence of progression at least 4 weeks after its discontinuation. To reduce the possible confounding effect of low dose corticosteroids, cortisone acetate was initiated 4 weeks after suramin-plus-epirubicin therapy was be-

gun. This preceded the first clinical reevaluation, which included PSA measurement. It was therefore possible to determine the steroid-independent response to suramin.

Our study demonstrates that the combination of suramin and epirubicin used herein is feasible, is associated with moderate toxicities, and may have antitumor activity in advanced hormone-refractory prostate carcinoma; however, the extent of this activity appears modest. The relatively high number of patients with extraskeletal disease may reflect the accurate pretreatment staging and/or a relatively advanced stage of our patient population, but it is very unlikely that this significantly affected our findings. The administration of cortisone acetate did not appear to affect tumor response significantly because all patients who had a PSA response $\geq$50% had an initial decrease in PSA during the first 4 weeks, before the administration of the steroid. However, only 33% of patients obtained a $\geq$50% decrease in PSA and 27% obtained an objective WHO response with a median survival of only 8 months. The pharmacodynamic profile of suramin and epirubicin observed in the current study suggested a lack of significant pharmacodynamic interaction between the drugs. Our results are not clearly superior to those achievable with suramin or epirubicin alone. Nevertheless, as outlined before, in studies in which the confounding effects of antiandrogen withdrawal were avoided (as in the current trial), the activity of suramin alone was only 14–22%; therefore, the combination with epirubicin that we used might have a modestly higher activity. If an improvement in antitumor activity exists, this cannot be determined from this study; prospective Phase III randomized studies are necessary. Nevertheless, we do not believe that such a randomized study is worth conducting, because the improvement in antitumor activity (if any) that can be expected from combining suramin with epirubicin is small, the toxicity of this combination (although rarely severe) is not negligible in the majority of the patients, and the therapy with suramin is complex. In fact, although suramin therapy can be simplified if it is administered by intermittent infusion without adaptive control,[27] it still remains quite a complex and toxic therapy. Most importantly, recent clinical studies of the treatment of advanced hormone-refractory prostate carcinoma with estramustine phosphate in combination with other antimicrotubule agents, such as vinorelbine or paclitaxel, have demonstrated more promising antitumor activity, with PSA and WHO responses in up to 50% of treated patients.[28–31]

In conclusion, our study demonstrates the feasibility and activity of a combination of suramin and epirubicin in the treatment of patients with hormone-refractory advanced prostate carcinoma, but it does not suggest major improvements compared with suramin and epirubicin alone. Therefore, the use of this combination regimen outside the setting of a clinical trial is not recommended. A randomized trial comparing this combination with either agent alone does not seem warranted.

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