Fixed Higher Dose Schedule of Suramin plus Hydrocortisone in Patients with Hormone Refractory Prostate Carcinoma

A Multicenter Phase II Study

Emiliano Calvo, M.D.[1]
Javier Cortés, M.D.[1]
Javier Rodríguez, M.D.[1]
Manuel Sureda, M.D.[2]
César Beltrán, M.D.[3]
Joseba Rebollo, M.D.[4]
Rafael Martínez-Monge, M.D.[1]
José María Berián, M.D.[5]
Jokin de Irala, Ph.D.[6]
Antonio Brugarolas, Ph.D.[1]

[1] Department of Oncology, Clínica Universitaria de Navarra, Pamplona, Spain.

[2] Department of Oncology, Hospital General de Catalunya, Barcelona, Spain.

[3] Department of Oncology, Clínica Salvia, Madrid, Spain.

[4] Department of Oncology, Clínica San Miguel, Pamplona, Spain.

[5] Department of Urology, Clínica Universitaria de Navarra, Pamplona, Spain.

[6] Department of Public Health and Epidemiology, University of Navarra, School of Medicine, Pamplona, Spain.

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Dr. Emiliano Calvo's current address: Department of Oncology, Hospital San Jaime, Alicante, Spain.

Address for reprints: Emiliano Calvo, M.D., Department of Oncology, Hospital San Jaime; Ptda. de la Loma, s/n, 03180 Torrevieja, Alicante, Spain; (Fax): (011) 0034 96 692 2706; E-mail: calvo@hsanjaime.com

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BACKGROUND. Using a fixed higher-dose schedule, the efficacy and toxicity of suramin plus hydrocortisone were assessed in patients with metastatic hormone-refractory prostate carcinoma (HRPC).

METHODS. Fifty consecutive patients with HRPC (including those in whom hormonotherapy was withdrawn) and an Eastern Cooperative Oncology Group performance status of 0–2 were recruited. Treatment was comprised of a bolus intravenous infusion of 200 mg of suramin followed by suramin (500 mg/m^2 intravenously [i.v.] over 24 hours) given daily over 5 days as a loading course, followed by suramin (350 mg/m^2 i.v. over 2 hours) administered weekly for 12 weeks. This 12-week course was repeated at 6-month intervals. All patients received concomitant hydrocortisone.

RESULTS. Five hundred fifty weekly doses of therapy were delivered over the course of the entire study. A partial response, based on a $>$ 50% decrease in the prostate specific antigen (PSA) level, was achieved in 27 patients (54%; 95% confidence interval [95% CI], 44.7–65.0%), 16 of whom (32%; 95%CI, 23.9–43.2%) had a $>$ 75% decrease in their PSA levels. The measurable disease objective response rate was 18% (95% CI, 2.3–51.8%). Of the 37 patients with bone pain requiring analgesia, 27 patients (73%; 95% CI, 55.9–86.2%) reduced their medication consumption to a lower level on the World Health Organization analgesic ladder. The median duration of response was 15.5 weeks (range, 6–70 weeks), the median time to disease progression was 13 weeks, and the median overall survival time was 11 months. Treatment generally was well tolerated. Fatigue and severe lymphopenia were the most commonly reported significant toxicities. In addition, there was 1 septic toxic death reported, and 10% of the patients were found to have NCI Grade 3-4 neurotoxicity.

CONCLUSIONS. The results of the current study demonstrated that the fixed-dose suramin regimen administered herein showed high, although short-lived, activity and a good tolerance profile in HRPC patients. ***Cancer* 2001;92:2435–43.**

KEYWORDS: prostate carcinoma, suramin, hormone-refractory, Phase II study, prostate specific antigen (PSA).

Androgen deprivation remains the cornerstone of treatment in patients with metastatic prostate carcinoma.[1] This standard modality of therapy produces very high pain control and objective response rates with median progression-free and overall survival times of 12–18 months and 24–30 months, respectively, times that appear to have remained fairly unchanged over the last 50 years.[2–5] The biologic

selection modulated by hormone therapy favors the proliferation of tumor cell clones no longer sensitive to hormonal therapy and, as a consequence, all patients finally progress to a hormone-refractory state accompanied by progressive painful bone metastases and a decreased quality of life.[6] This provides the rationale for the use of agents with nonhormone-mediated mechanisms of action as a second-line therapy.

During the past few years, several agents have been tested to find new approaches to the treatment of patients with hormone-refractory prostate carcinoma (HRPC). Among these, suramin, a polysulfonated napthylurea with broad-spectrum inhibitory effects on several growth factors and enzymes,[7–11] has shown response rates of up to 40% in patients with measurable disease, and a $>$ 50% decline in prostate specific antigen (PSA) levels in approximately 50% of these patients,[12–16] findings that are better than the disappointing objective response rate of $<$ 10% reported with prior traditional cytotoxic agents.[6,17]

Suramin is believed to have a narrow therapeutic range, is extensively protein bound, and has a plasma terminal half-life of approximately 55 days. As a consequence, when suramin was administered by continuous infusion, significant dose-limiting toxicities (including coagulopathy and polyneuropathy) were observed.[18] Eisenberger et al. demonstrated the feasibility of administering suramin in short intermittent bolus injections using adaptive control with feedback to adjust plasma drug concentrations to minimize cumulative toxicity and assure a suramin blood concentration under the security level ($<$ 300 μg/mL).[15,19] Subsequent characterization of suramin pharmacokinetics demonstrated little interpatient variability and led to intermittent infusions using fixed doses and fixed schedule regimens. These were administered easily in the outpatient setting, while maintaining plasma concentrations in a therapeutic range between 100–300 μg/mL.[20] This significantly simplified, 78-day, fixed suramin dosing schedule that does not require pharmacokinetic monitoring has facilitated the large-scale testing of this agent in patients with prostate carcinoma.[21] Finally, Phase I dose-escalation studies using a fixed dosing schedule demonstrated that declines in PSA levels may be more likely to occur with higher doses of suramin,[22,23] suggesting that patient response to suramin also might be dose-dependent.

Based on the available clinical data, the administration of a fixed higher dose schedule of suramin is attractive and has the potential for improved activity. Therefore a Phase II trial was initiated in patients with metastatic HRCP to define the activity, toxicity, and need for exhaustive blood level monitoring in patients receiving a fixed, higher dose suramin regimen.

MATERIALS AND METHODS

Patient Selection

Eligible patients had histologically or cytologically documented metastatic adenocarcinoma of the prostate that was resistant to maximal androgen blockade (combination of either surgical orchiectomy or a gonadotropin-releasing hormone analogue with an antiandrogen), and all patients had demonstrable subsequent disease progression after antiandrogen withdrawal. All patients were required to have either an increasing PSA level with a pretherapy value of at least 5 ng/mL and/or bidimensionally measurable disease. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and adequate baseline organ function, defined as a leukocyte count $> 3 \times 10^9$/L (absolute granulocyte count $> 1.5 \times 10^9$/L), a platelet count $> 75 \times 10^9$/L, adequate renal (serum creatinine level $<$ 1.6 mg/dL) and hepatic functions (aspartate aminotransferase, alanine aminotransferase, and bilirubin $<$ twice the upper normal limit), and activated partial thromboplastin time (PTT) and prothrombin time (PT) within normal limits. No severe active concurrent medical illnesses, neurosensory abnormalities, bleeding or coagulation disorders, or active major infections precluding suramin therapy or that threatened survival were permitted. Patients with a history of a prior malignancy (other than basal cell carcinoma of the skin) within the last 5 years were not eligible. Written informed consent was obtained from all patients before study entry.

Treatment Plan

Suramin initially was administered as a 30-minute test infusion of 200 mg; if no hypersensitivity reaction occurred, additional 24-hour infusions of 500 mg/m^2 were administered intravenously (i.v.) daily over the following 5 days. Thereafter, a 2-hour infusion of suramin (350 mg/m^2 i.v.) was given weekly on an outpatient basis for 12 weeks or until disease progression. In the absence of significant toxicity or disease growth, suramin therapy was repeated every 6 months. All patients on the current trial received replacement oral hydrocortisone, 20 mg daily, from Day 1 of suramin therapy, to avoid suramin-related adrenal insufficiency.[24,25]

Suramin plasma levels were determined using high-performance liquid chromatography as previously described,[26] and were obtained 30 minutes after the suramin test infusion, every 24 hours during the first week of treatment, and every 4–6 weeks until the

end of therapy. These plasma concentrations, although measured, were not used to determine dosing. Due to structural difficulties in obtaining timely results for all the centers in the current study, it was preplanned to use than for the retrospective evaluation of a possible correlation between toxicity and plasma concentrations of suramin. Suramin was interrupted if a Grade 3 or 4 nonhematological toxicity or a Grade 4 hematologic toxicity (excluding lymphopenia) occurred, and infusion was resumed after recovery, with a subsequent 25% dose reduction until completion of the treatment program.

Patient Evaluation

Pretreatment evaluation included a detailed clinical history and physical examination with special attention to the ECOG performance status and the analgesic requirement status according to the World Health Organization (WHO) three-step analgesic ladder.[27] In addition, all patients underwent a laboratory workup comprised of complete blood cell count with leukocyte differential; platelet count and hemoglobin level; serum levels of electrolytes, creatinine, calcium, PT, and PTT; hepatic panel; and PSA. All studies were repeated every 4 weeks during therapy. Baseline diagnostic imaging studies included a computed tomography (CT) examination of the chest and abdomen and a bone scan. If needed to assess response, because of a pretherapy PSA level < 5 ng/mL or when clinically advisable, the CT and bone scans were repeated every 4 weeks.

The consensus criteria for assessing responses in Phase II trials of cytotoxic agents for the treatment of HRPC were published after the study was activated. In reporting the study results, declines in the PSA levels were tabulated in accordance with the consensus guidelines.[28] A complete response was defined as the disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor for > 4 weeks, during which time no new lesions appeared and a PSA of < 0.2 ng/mL was achieved. Patients with a partial response (PR) met at least 1 of the following response criteria: 1) a reduction of $> 50\%$ of the sum of the products of the perpendicular dimensions of all measurable lesions lasting > 4 weeks, during which time no new lesions appeared and no existing lesions enlarged; and 2) a decrease in PSA levels of $> 50\%$ from the pretreatment levels and no evidence of clinical or radiographic disease progression, sustained for at least 4 weeks. Progressive disease (P) was defined as any of the following: 1) an increase in the product of the perpendicular dimensions of any measured lesion by $> 25\%$ or the appearance of new lesions, regardless of changes in the PSA, on the bone scan, or in the ECOG performance status; and 2) an increase in PSA as follows: in patients whose PSA level had not decreased, P was considered to be a 25% increase over the baseline level and an increase in the absolute PSA value level by at least 5 ng/mL, which was confirmed by a second value. In patients whose PSA had decreased but who had not reached response criteria, P would be considered to have occurred when the PSA increased by 25% over the nadir, provided that the increase was a minimum of 5 ng/dL and was confirmed. In patients whose PSA level had decreased at least 50%, P would be considered to have occurred when the PSA increased 50% above the nadir at a minimum of 5 ng/mL. Stable disease was defined for patients with pretherapy PSA levels < 5 ng/mL as a $< 50\%$ reduction and a $< 25\%$ increase in the sum of the products of two perpendicular dimensions of all measured lesions, and the appearance of no new lesions for > 8 weeks.

The patients who achieved adequate pain relief lasting > 4 weeks, defined as a decrease in the level of the analgesic needs according to the WHO three-step analgesic ladder,[27] were considered to have a pain response.

Statistical Methods

All patients who received at least 4 weeks of therapy or whose disease progressed after the first dose of suramin were assessable for response. Time to P was measured from the date of initial treatment to the date of P (or last follow-up evaluation for patients whose disease had not progressed). Overall survival was measured from the date of the first course of chemotherapy to the date of death or last follow-up examination. Univariate and multivariate actuarial survival were estimated using the Kaplan–Meier method and Cox multiple regression analysis, respectively.[29] Ninety-five percent confidence intervals (95% CI) for response rates were calculated using methods for exact binomial CI estimation.[30] The Mantel–Haenszel method was used to evaluate the difference between a pair of corresponding Kaplan–Meier curves.[31] Qualitative factors were compared using the Pearson chi-square contingency table analysis.

RESULTS

Patient Characteristics

Between January 1995 and October 1999, 50 consecutive patients with metastatic HRPC were entered in the current study. The median age of the patients was 67.5 years (range, 48–84 years), and more than half of the patients (56%) had an ECOG performance status of 2. Forty-four patients (88%) presented with bone metastases, in 28 of whom (56%) it was the only tumor site.

TABLE 1
Patient Characteristics

	No.	%
Patients enrolled	50	100
Age (yrs)		
Median	67.5	
Range	48–84	
Performance status (ECOG)		
1	22	44
2	28	56
Metastatic disease site		
Bone only	28	56
Bone and soft tissue	16	32
Soft tissue only	5	10
Lymph nodes	1	2
No. of involved sites		
1	31	62
2	14	28
≥ 3	5	10
Previous treatment		
Hormonotherapy	50	100
Prostatectomy	5	10
Radiation to prostate	18	36
Prostatectomy and radiation	7	14
Previous chemotherapy	12	24
PSA (ng/mL)		
Median	306.81	
Range	0.20–4200	
Alkaline phosphatase		
Median	343	
Range	243–4415	
Bone pain	37	74
Other medical problems		
Hypertension	5	10
History of cardiac arrhythmia	7	14
Myocardial ischemia	4	8
Peptic ulcer disease	5	10
Diabetes	6	12
Brain vascular disease	3	6

ECOG: Eastern Cooperative Oncology Group; PSA: prostate specific antigen.

All patients had progressed to hormonotherapy and to its discontinuation, and 12 patients (24%) also had been pretreated with chemotherapy. Thirty-seven patients (74%) had disease-related pain at the time of study entry. The patient characteristics are listed in Table 1.

Response Evaluation

Two patients had a pretherapy PSA level < 5 ng/mL and only were evaluated according to radiologic criteria. One patient with early toxicity (a severe skin reaction that warranted treatment interruption after the third week of therapy) was not assessable for response and was considered to be a nonresponder. Twenty-seven patients (54%; 95%CI, 44.7–65.0%) achieved a PR, 16 of whom (32%; 95% CI, 23.9–43.1%) had a > 75% decrease in their PSA level. Of the 22 patients with measurable disease, 11 were followed with CT, 2 of whom (18%) demonstrated a PR.

Twenty-nine of the 37 patients with bone pain that required analgesics experienced enough pain relief to reduce or stop their analgesic consumption (78%; 95% CI, 72–90.8%). Among the 27 patients who achieved an objective PR, 20 were receiving analgesics before the initiation of suramin therapy; 18 of these patients (90%) experienced a significant improvement in their pain relief. Of the 23 patients who did not demonstrate an objective response to suramin, 17 presented with pain symptoms before the administration of suramin; 11 of whom (65%) required fewer analgesics while receiving treatment ($P = 0.10$). The 13 patients with initial bone pain and a > 75% decrease in their PSA level reduced their analgesic intake to a lower step of the WHO analgesic ladder.

Survival

The median progression-free survival was 13 weeks (95% CI, 10.1–15.9 weeks) and the median overall survival time was 11 months (95% CI, 6.9–15.1 months). The median duration of response was 15.5 weeks (range, 6–70 weeks). The actuarial 1-year survival for the entire group was 45.6%. After a median follow-up of 35.5 months (range, 3–73 months), 40 patients had died, 7 patients were alive, and 3 were lost to follow-up at 6 months, 11 months, and 48 months, respectively (Fig. 1). Among the 7 patients alive at the time of analysis, 3 were free of disease after 12 weeks, 29 weeks, and 54 weeks, respectively. Two of these patients achieved a > 75% decrease in their PSA level with suramin therapy. There were no significant differences observed in the response rate ($P = 0.14$), progression-free survival ($P = 0.10$), or overall survival ($P = 0.21$) in patients with bone metastases compared with patients with extraosseous disease locations.

The median time to P and overall survival in the 16 patients with a PSA response with a nadir level < 75% were 43 weeks and 17 months, respectively. This was significantly different from the remainder of the patients (10 weeks and 6 months, respectively) ($P < 0.001$ and $P = 0.03$) (Fig. 2).

Nine responding patients with adequate ECOG performance status and organic function after P were retreated with the same suramin regimen in a compassionate rescue setting. Three of these patients (33%; 95%CI, 7.5–70.1%) achieved new PRs, which lasted 13 weeks, 17 weeks, and 25 weeks, respectively.

Toxicity

A total number of 550 weekly doses of therapy were administered, for a median of 11 courses per patient

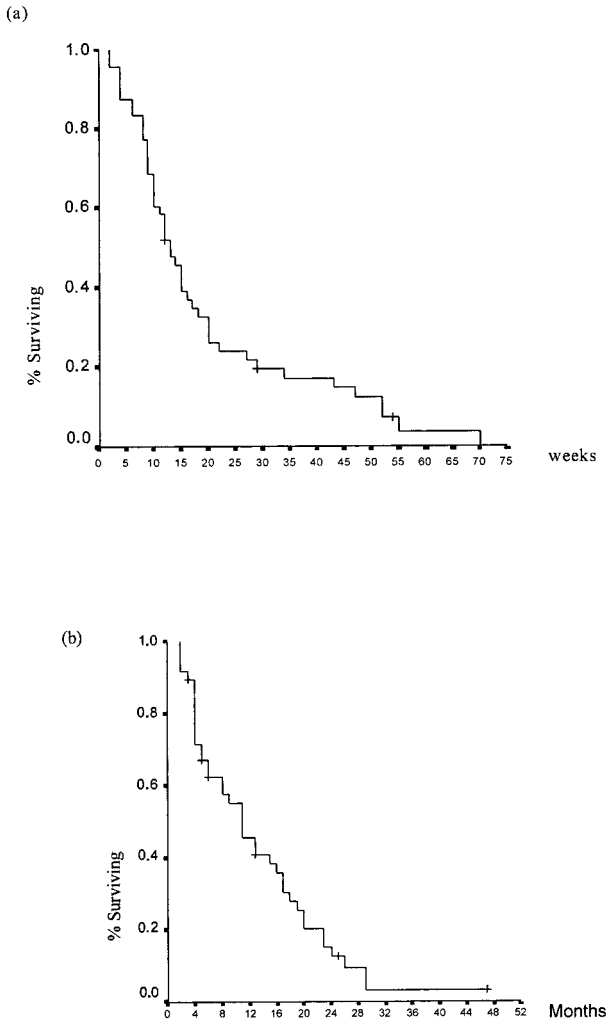

FIGURE 1. (a) Actuarial progression-free survival (weeks) and (b) overall survival (months) curves (Kaplan–Meier analysis).

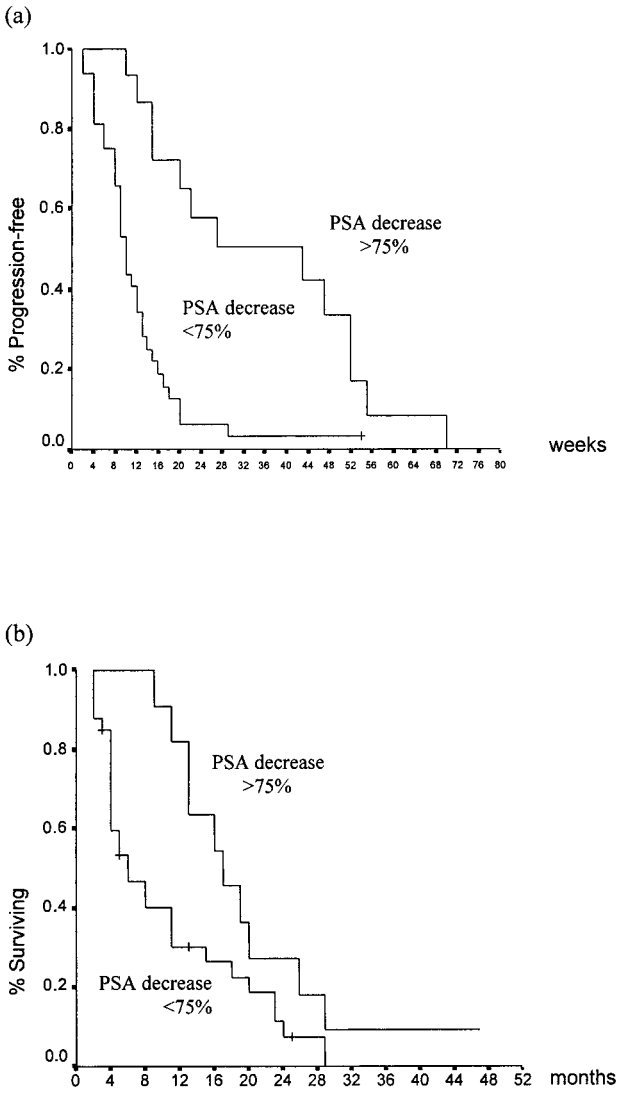

FIGURE 2. (a) Progression-free survival (weeks) and (b) overall survival (months) of patients whose prostate specific antigen (PSA) level decreased by $>$ 75% compared with those patients whose PSA level decreased by $<$ 75%.

(range, 2–30 courses). The median peak plasma concentration for all patients was 227 μg/mL (range, 121–390 μg/mL). A median through plasma suramin concentration was calculated in each patient, and the median for all patients was 146 μg/mL (range, 66–405 μg/mL). Toxicity was evaluated in all patients and all cycles (Table 2). Three patients had median stable suramin concentrations ($>$ 300 μg/mL); one of these patients was found to have Grade 3 hepatic toxicity (median through suramin plasma concentration of 405 μg/mLl). Otherwise, no severe toxicity was observed in patients with a plasma suramin concentration above that level (data not shown).

The most common toxicities were cytopenia and fatigue. Grade 3-4 anemia and lymphopenia were observed in 9 patients (18%) and 28 patients (56%), respectively. Seven of these 28 patients had lymphopenia before entering the study, and the condition worsened during treatment. Grade 3-4 neutropenia occurred in 4 patients (8%) and Grade 3-4 thrombocytopenia was reported in 3 patients (6%). Infection was documented in 15 patients (30%), which was treated uneventfully except for 1 toxic death (the median plasma suramin level in this patient was 170 μg/mL). Severe fatigue (Grade 3-4) was observed in 10 patients (20%). Gastrointestinal toxicity was mild, with Grade 2 emesis and loss of taste occurring in five patients. Grade 2 diarrhea was observed in one patient. Neuromotor and neurosensory toxicities were observed in 9 patients and 10 patients, respectively; these toxicities mainly were Grade 2, with 4 patients (8%) having Grade 3 toxicities and one patient (2%) having a Grade 4 toxicity. A skin rash comprised of

TABLE 2
Toxicity

Toxicity	Grade 1–2 No. (%)	Grade 3–4 No. (%)	Grade 5 No. (%)
Hematologic			
Anemia	15 (30)	9 (18)	0
Lymphopenia	11 (22)	28 (56)	0
Neutropenia	5 (10)	4 (8)	0
Thrombocytopenia	6 (12)	3 (6)	0
Prothrombin time	11 (22)	2 (4)	0
Infection	10 (20)	4 (8)	1 (2)
Gastrointestinal			
Diarrhea	1 (2)	0	0
Nausea/emesis	5 (10)	0	0
Loss of taste	5 (10)	0	0
Neurologic			
Motor	6 (12)	3 (6)	0
Sensory	8 (16)	2 (4)	0
Hearing	0	1 (2)	0
Constipation	2 (4)	1 (2)	0
Mood	7 (14)	0	0
Renal			
Creatinine	4 (8)	2 (4)	0
Hepatic			
Transaminitis	5 (10)	6 (12)	0
Fatigue	17 (34)	10 (20)	0
Skin rash	6 (12)	6 (12)	0
Adrenal	5 (10)	0	0

macular or papular eruptions with pruritus was observed in 12 patients (24%); in 6 of these patients, the rash was generalized. The most serious skin toxicity was a Stevens-Johnson syndrome that developed in one patient, which led us to interrupt suramin therapy. Other toxicities included transaminitis in 11 patients (5 with Grade 2 [10%] and 6 with Grade 3 [12%], respectively), Grade 1-2 renal toxicity in 4 patients and Grade 3 renal toxicity in 2 patients (4%), and adrenal insufficiency in 5 patients (10%) who required increased doses of hydrocortisone.

Suramin was discontinued in 3 patients (6%) because of acute renal failure (2 patients) and skin toxicity (1 patient).

DISCUSSION

Although the number of clinical trials examining the use of suramin in combination with hydrocortisone in patients with HRPC was growing at the time the current study was initiated, to our knowledge only a few studies using fixed schedules had been attempted. The current clinical trial was designed to assess the feasibility, activity, and toxicity of a new regimen of suramin in patients with HRPC, with a fixed higher cumulative dose of the drug (25% increase over the course of 78 days) administered compared with the regimen described by Reyno et al.,[20] in response to previous observations[22,23] suggesting a dose-dependency for suramin efficacy.

The results of the current study demonstrate that, using this fixed dose schedule, suramin can be administered safely in this patient population with limited exposure to prior cytotoxic chemotherapy and that exhaustive monitoring of suramin levels in the blood also might be unnecessary. Moreover, plasma concentrations were not used to determine dosing in the current study.

The effects of suramin on serum PSA levels in the patients treated with the current regimen also were consistent with the results of the lower-dose regimen examined by Reyno et al.[20] The data from the current study show that this combination maintains high antitumor activity in these patients with a poor prognosis. The 54% overall objective response rate appears quite attractive, especially if one takes into account that 44% of the patients had soft tissue disease and that the median PSA and alkaline phosphatase levels were 306 and 343, respectively. The response rate 95% CI (44.7–65.0%) overlaps the results achieved with the fixed lower cumulative dose of suramin that was administered in other studies,[20,21] which is in accordance with observations by Hutson et al.[32] and Bowden et al.,[33] who found no statistically significant association between PSA response levels and suramin concentrations. In any case, we believe the question of whether a dose-response relation exists for a decrease in PSA levels should be addressed in large-scale studies.

Responses in the current study were short-lived (13 weeks, for a median overall survival of 11 months, compared with 10.1 months and 18.8 months, respectively, in the study by Reyno et al.[20]) and might reflect in part a patient population with a poorer prognosis, with a higher percent of patients having extraosseous metastases.[34] However, it is quite in accordance with the survival rates presented in a recently published Phase III study.[21] Similarly, the overall survival time reported in the current study is not significantly different from the reported survival of similar HRPC patients treated with a variety of methods.[35] It certainly is possible that greater antitumor efficacy could be observed in patients with less advanced disease or in those patients treated with a combination with other chemotherapeutic agents,[36] especially given the wide range of noncytotoxic mechanisms of action that are attributed to suramin.

Because the majority of HRPC patients lack measurable disease and because responses in patients with bony disease are difficult to measure, other clinically relevant endpoints, such as pain control and analgesic use, have become more widely used.[37,38]

This finding is of clinical importance because pain due to bone metastases in patients with metastatic prostate carcinoma is one of the leading causes of quality of life impairment. The results of the current study show that the symptoms in the majority of patients with initial metastatic pain improved with the use of suramin. Surprisingly, this finding also was observed in the group of patients who did not achieve an objective response based on decreasing PSA levels, although to a lesser extent. However, these results should be viewed with caution because such patient-derived quality of life endpoints are subject to significant bias introduced by a placebo effect.

Although the correlation between PSA changes and clinically significant endpoints continues to be debated, some authors[39-42] have noted that a post-therapy decline in PSA may be associated with a prolonged survival. In the current series, the decline in PSA levels followed other markers of response that favored suramin, including pain response and time to disease progression. In particular, patients with a PSA decrease $>$ 75% had significantly longer progression-free and overall survival times and a 100% subjective pain response. This finding has been noted previously, and it is especially significant if we consider that approximately 33% of patients fall into this category.[39–42] However, because the current study was not a non-randomized trial, the fact that responders appear to live longer than nonresponders should not be attributed solely to the effect of suramin. In addition, although the independent activity of suramin has been confirmed recently,[21] the concomitant administration of corticosteroids to prevent the incidence of adrenal insufficiency associated with suramin might influence these results.[13,21,37]

This trial also confirmed the findings of prior reports that used a simplified dosing scheme of suramin, demonstrating its feasibility and manageable toxicity.[15,20] In our experience, treatment was administered safely and easily on an outpatient basis at four centers, suggesting that the administration of suramin is possible in different settings, including community hospitals. Moreover, the spectrum and degree of toxicity encountered were not significantly different from those documented in other suramin trials with or without feedback dosing.[12,13,15,19–21,43–45] These mostly were mild to moderate, with only modest clinical significance, with the exception of one toxic septic death. The most clinically significant side effects encountered were a fatigue syndrome, which appeared to be cumulative, and a cutaneous rash that occasionally required increased corticosteroid administration. Severe hepatic, renal, neurologic, respiratory, cardiovascular, or clotting disorders were rare, unlike reports in earlier studies that used different suramin dosing regimens,[16,18] or the recently published Phase II trial with a slightly different fixed schedule conducted by Hussain et al.[46] In this last study, the authors concluded that only 54% of the patients demonstrated an acceptable toxicity profile, a finding that was explained in part to be a result of the different therapy scheme administered, including concomitant androgen deprivation and the repeat administration of the 78-day fixed schedule of suramin.

The current study demonstrated that the administration of combined suramin and hydrocortisone therapy in the schedule and doses described for patients with HRPC is well tolerated and easily administered, but of limited efficacy because it appears to offer mainly moderate and transient palliative benefits. However, a small group of patients responded to retreatment, indicating that disease progression did not represent resistance but most likely an early discontinuation of therapy. Moreover, those patients with a $>$ 75% decrease in their PSA levels most likely could obtain a better outcome with this approach.

Recent studies using chemotherapeutic combinations for the treatment of HRPC appear to indicate that prostate tumors are not as resistant to chemotherapy as is believed traditionally.[6] Thus, combinations using estramustine/paclitaxel[47] and estramustine/docetaxel[48] elicited PSA decreases of $>$ 50% in 65% and 62% of the patients, respectively, with promising response rates reported in patients with measurable soft tissue metastases and median survivals of approximately 1 year. Several Phase-III trials currently are underway to elucidate whether these previous results might translate into improvements in quality of life or survival benefits. More studies are needed to develop suramin combination regimens with chemotherapy, radiotherapy, or hormonotherapy.

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