Antitumor Activity of Suramin in Hormone-Refractory Prostate Cancer Controlling for Hydrocortisone Treatment and Flutamide Withdrawal as Potentially Confounding Variables

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Background. A prospective Phase II clinical trial was conducted to assess the clinical activity of a pharmacokinetically guided suramin regimen in patients who had documented progression of metastatic prostate cancer after hydrocortisone plus antecedent or simultaneous withdrawal of flutamide.

Methods. Fifty-four patients whose disease had progressed after castration and flutamide administration were enrolled on this trial. The study was divided into two parts. Initially, 52 patients received hydrocortisone (30 mg/day) and for those patients receiving flutamide, at study entry (34 patients) flutamide was simultaneously discontinued. Forty-three patients whose disease progressed on hydrocortisone received suramin for 6–8 weeks. Six patients who progressed on hydrocortisone became ineligible for suramin due to clinical deterioration, four patients are still responding to hydrocortisone at more than 1 year, and one patient elected to postpone initiation of suramin. Suramin was given as intermittent infusions at fixed doses on days 1–5 and thereafter dosing was guided by adaptive control with feedback to maintain plasma suramin concentrations between 300–175 μg/ml. Antitumor activity was assessed by prostate specific antigen (PSA) decline and soft-tissue disease response.

Results. Ten patients (19%; 95% CI, 9.6%–32.5%) responded to hydrocortisone therapy with either a 50% or greater PSA decline for at least 4 weeks (9 patients) and/ or a partial response of measurable soft-tissue disease (2 patients). Five of these patients (10%) demonstrated a 80% or greater PSA decline. All responders to hydrocortisone had simultaneous flutamide withdrawal, and had been receiving flutamide as part of initial combined androgen blockade. Seven of 37 evaluable patients (19%; 95% CI, 8.0%–35.2%) responded to suramin with a 50% or greater decline in PSA for 4 weeks or longer. One patient (3%) had a 80% or greater decline in PSA. There were no soft-tissue disease responses to suramin. The median time to progression was 1.9 months for hydrocortisone and 2.6 months for suramin therapy. The median survival for all patients was 14.6 months.

Conclusion. Suramin has antitumor activity in metastatic prostate carcinoma independent of the therapeutic effect of hydrocortisone administration or flutamide withdrawal. The role of prior flutamide withdrawal and hydrocortisone replacement should be taken into account in future studies of suramin.
Key words: prostatic neoplasms, suramin, hydrocortisone, flutamide, prostate specific antigen.

Suramin is a polysulfonated naphthylurea that has been used in the treatment of parasitic disorders since the 1920s. Though suramin has long been known to disrupt a variety of cellular enzyme systems, renewed interest in this compound was stimulated when suramin was noted to block the activity of viral reverse transcriptases and to block the interaction between a variety of peptide growth factors and their membrane-bound receptors. Based on the premise that tumor cell proliferation was regulated in part by autocrine and paracrine peptides and that suramin was capable of disrupting these key regulatory interactions, the antitumor activity of suramin was explored in a variety of experimental systems.

Prostate cancer was of particular interest to those interested in the clinical development of suramin. Suramin was reported to block the activity of basic fibroblast growth factor and other heparan-binding growth factors implicated in prostate cancer growth, and in vitro studies indicated that suramin was capable of inhibiting prostate cancer growth at clinically achievable concentrations. In addition, suramin was noted to produce adrenal cortical degeneration, an observation of clinical importance in patients with prostate cancer, because lowering adrenal androgen levels might also slow the proliferation of prostate cancer cells.

Stimulated by these considerations, researchers evaluated suramin in clinical trials for activity against metastatic hormone-refractory prostate cancer, a disease notoriously resistant to conventional cancer therapies. Considerable interest was aroused when initial reports from the National Cancer Institute (NCI) indicated that suramin, when coadministered with hydrocortisone (to alleviate suramin-induced adrenal insufficiency), showed significant evidence of antitumor activity in this disease, albeit with notable toxicity.

Since the initial reports of suramin activity in metastatic hormone-refractory prostate cancer, numerous studies have been conducted with suramin in this patient population. A number of these have emphasized methods to improve the therapeutic index of the compound by repeated determination of circulating suramin concentrations and sophisticated methods of pharmacokinetic modeling. The magnitude of the antitumor effect observed in these studies varied, and the possibility that confounding variables may have contributed to the previously reported activity of suramin in hormone-refractory prostate cancer arose after considering the activity of glucocorticoids in this disease. The second potential variable to emerge was the apparent activity of flutamide withdrawal as a positive therapeutic maneuver.

Because suramin has been coadministered with hydrocortisone in all of the previously reported peer-reviewed studies, there are no definitive reports of suramin's activity in patients for whom this variable has been adequately controlled. In addition, because the activity of flutamide withdrawal was first published in 1993, there have been no studies of suramin where this potential confounding variable has been removed prospectively.

Based on our own clinical trial of flutamide withdrawal combined with aminoglutethimide, which accrued patients from January to September 1992, as well as personal communication with investigators at Memorial Sloan-Kettering Cancer Center, New York, regarding their subsequently published data on clinical responses to withdrawal of flutamide, we initiated a clinical trial designed to prospectively control for variables of hydrocortisone administration and flutamide withdrawal. Our goal was to assess the independent activity of a pharmacokinetically guided intermittent method of suramin administration in patients with clearly documented progressive metastatic hormone-refractory prostate cancer. To accomplish this goal, we first treated patients with progressive prostate cancer with hydrocortisone plus flutamide withdrawal, if still receiving flutamide at study entry. Suramin therapy was initiated only after disease progression was documented after these initial therapeutic maneuvers.

Patients and Methods

All patients had advanced prostate cancer that was refractory to hormonal therapy (i.e., failed castration and flutamide). Karnofsky performance status greater than or equal to 80%, a life expectancy greater than 3 months, hepatic transaminases less than 1.5 times the upper limit of normal, a normal bilirubin, hemoglobin greater than 8.5 g/dl, a creatinine clearance greater than 60 ml/minute, a normal urinalysis, an absolute neutrophil count greater than 1500/mm³, and platelet count greater than 120,000/mm³. All patients were required to have documented progression of disease after their last therapeutic maneuver with a verified rising prostate specific antigen (PSA) and/or new metastatic lesions on bone scan or new metastatic soft-tissue disease. All patients must have completely recovered from the toxicity of any previous therapy. Exclusion criteria included recent clinically significant bleeding, history of hemorrhagic stroke, clinical evidence of intracranial...
suramin were fixed (day 1 = 7.5 mg/kg, day 2 = 9.3 mg/kg, day 3 = 9.3 mg/kg, day 4 = 8.2 mg/kg, and day 5 = 7.5 mg/kg). After the initial five fixed daily doses of suramin, drug administration was individualized for each patient so as to maintain the plasma suramin concentration between 175 and 300 μg/ml for the remainder of the treatment period. This control of drug concentration was effected by using a previously described pharmacokinetic model. Patients were not treated for more than 8 weeks, and no repeat cycles were given. If a patient experienced disease progression or if the PSA normalized during suramin therapy, then treatment was stopped after 6 weeks of therapy.

Therapeutic efficacy was assessed by serial measurements of PSA levels and soft-tissue tumor masses. For measurable soft-tissue disease, a complete response was defined as the complete disappearance of all radiographic evidence of disease for a duration of at least 1 month. A partial response required that the sum of the product of the largest perpendicular diameters of all measured lesions decrease by 50% or more for at least 1 month. A PSA response required a decrease of 80% or greater from baseline on three consecutive occasions at least 2 weeks apart and for a duration of 4 or more weeks. Response rates were also determined based on a greater than or equal to 50% decline in PSA for the same duration, based on published multivariate analysis in which this end point was associated with improved survival. Progression was defined as an increase in the sum of the products of the perpendicular dimensions of all measurable lesions of greater than 25% and/or appearance of new lesions. The development of two or more lesions on bone scan was scored as progressive disease, as was the need for radiation therapy. Criteria for progression by PSA measurement were the average of three consecutive PSA measurements demonstrating a greater than or equal to 50% increase in PSA from baseline for nonresponders or above the nadir value measured for responders. Patients with a PSA level below 40 ng/ml were required to have the PSA increase by greater than 20 ng/ml for progression. Prostate specific antigen response duration was measured from the time of PSA decline of greater than or equal to 50% to the time of PSA increase from nadir PSA value by greater than or equal to 50%.

Toxicity was determined according to the established criteria of the NCI's Cancer Therapy Evaluation Program. The probability of survival or time to progression was calculated using the Kaplan–Meier method. The difference between concomitant and antecedent discontinuation of flutamide therapy relative to starting hydrocortisone was compared using the Mantel–Haenszel technique. Survival duration was calculated for all 52 patients treated with hydrocortisone on study, from the date hydrocortisone began until date of death or last follow-up. Time to progression for hydrocortisone was calculated from the date hydrocortisone was started until the date of progression on hydrocortisone (or last follow-up for the four patients who had not progressed). Survival duration for suramin was calculated from the date suramin was begun until death or last follow-up and was based on 43 patients who received suramin treatment. Time to progression for patients receiving suramin was defined from start of suramin until progression or last follow-up on suramin. Of the 43 patients who received suramin treatment, 4 were not included in this time-to-progression analysis because they...
received radiation at a point that rendered them unevaluable. Time to start of suramin was calculated from the time of study entry until the time suramin administration began. Of 52 patients receiving hydrocortisone on study, 41 received suramin. Four patients who were still responding to hydrocortisone therapy had observations censored at time of last follow-up, as did one patient who had not yet begun suramin. The remaining six, who developed complications preventing progression to suramin, had their observation time censored at date of progression from hydrocortisone. Changes in circulating adrenal androgens during hydrocortisone and suramin therapies and differences in on-study PSA for concomitant and antecedent flutamide withdrawal were assessed using the Wilcoxon signed rank test. All P values are two-sided.

Results

Patients

Between December 1992 and May 1993, 54 patients with metastatic prostate cancer were entered on this prospective trial. Their pretreatment characteristics are listed in Table 1. Their median age was 66 years (range, 46–79 years). All patients had progressed after prior medical or surgical castration. All patients had previously received and failed flutamide treatment. Thirty-four patients (63%) stopped flutamide at study entry, and 20 patients (37%) had ceased flutamide earlier a median of 5 months (range, 1–27 months) before the study. For the 20 patients with antecedent flutamide withdrawal, therapy was discontinued due to progressive disease in 18 patients and due to toxicity in 2 patients. Discontinuation of flutamide for this group of patients occurred before referral to the NCI, and there was no systematic evaluation for response to this maneuver. The median on-study PSA values were 74.4 ng/ml (range, 3.5–4327 ng/ml) and 267.5 ng/ml (range, 17.9–778.1 ng/ml) for the concomitant and antecedent flutamide withdrawal patients, respectively (P = 0.038). Thirty-six patients (67%) had metastatic disease to bone only, and 18 patients (33%) had additional measurable soft-tissue disease.

Response Data

Patient data and response rates for this trial are schematically illustrated in Figure 1. Fifty-four patients were registered for the study. Fifty-two patients were treated with hydrocortisone plus concomitant or antecedent flutamide withdrawal, and all were assessable for response and toxicity. Forty-three patients received suramin therapy. Eleven patients who received hydrocortisone were not treated with suramin. These included three patients with rapidly progressive disease, two patients with the interim development of brain metastases, one patient with extensive liver metastases and liver dysfunction, one patient who had not yet started suramin due to personal preference, and four patients who were still responding to hydrocortisone. Of 43 patients treated with suramin, 37 patients were evaluable for response. Four patients were not evaluable for response, having received radiation therapy within 4

![Figure 1](image-url)

*Continued Response, Part 1, N=4; 13+, 14+, 14+, 16+MO

Figure 1. Schema, entry of patients and response (>50% PSA decline) to hydrocortisone and suramin therapies. N: number; D/C: discontinue; RR: response rate; NE: not evaluable; MO: months.
weeks before initiating suramin therapy. Two other patients who had their hydrocortisone initiated before referral to the NCI and who were immediately treated with suramin also were excluded from evaluation because this key maneuver was undertaken outside the realm of this study. All 43 patients treated with suramin were assessable for toxicity.

Ten (19%; 95% confidence interval [CI], 9.6%–32.5%) of 52 patients treated with hydrocortisone with or without flutamide withdrawal responded. Nine of these 10 patients had a greater than or equal to 50% decrease in PSA, and 5 of these patients had a greater than or equal to 80% decline in PSA, both for at least 4 weeks. Two of these 10 patients achieved a partial response in measurable soft-tissue disease, one of whom had a low baseline PSA of 3.5 ng/ml. One of the responding patients had improvement in bone scan as well as a greater than or equal to 50% PSA decline.

Of the 18 patients with measurable soft-tissue disease, 2 patients (11%) achieved partial responses in soft-tissue disease. The responding sites were retroperitoneal lymph nodes and a pelvic wall mass, both of which were bidimensionally measurable on abdominal-pelvic computed tomography scan. For the 34 patients with bone-only disease, 5 patients (15%) demonstrated a greater than or equal to 50% decline in PSA. One of these patients had an improved bone scan.

Ten of the 34 patients (29%; 95% CI, 15.1%–47.5%) treated with concomitant flutamide withdrawal and addition of hydrocortisone responded. For the 34 patients with concomitant flutamide withdrawal, 17 patients (50%) had received flutamide as a component of initial combined androgen blockade (medical or surgical castration combined with flutamide). Seventeen patients (50%) had received flutamide as secondary hormonal treatment, having failed initial hormonal therapy. All responding patients to hydrocortisone had received flutamide as part of initial combination androgen blockade. No patient in whom flutamide had been started and stopped before study entry (antecedent flutamide withdrawal) and who received hydrocortisone alone showed a significant PSA decline or soft-tissue response. Thus, all responders to hydrocortisone were those who had simultaneous flutamide withdrawal and hydrocortisone administration.

Forty-three patients were treated with suramin. Forty-one patients had progressed on hydrocortisone while on study, and two patients were treated directly with suramin due to prestudy therapy with hydrocortisone. Of these 43 patients, 37 were evaluable for response. Four patients were unevaluable due to receiving radiation therapy within 4 weeks before treatment with suramin. The two patients who received hydrocortisone before study entry were also excluded from response analysis. Seven of the 37 patients (19%; 95% CI, 8.0%–35.2%) had a greater than or equal to 50% decline in PSA. Only one of the 37 patients (3%) had a greater than or equal to 80% decline in PSA. When we compared measurable soft-tissue disease to bone-only disease, 6 of 25 patients (24%) with bone-only disease showed a PSA decline greater than or equal to 50%. None of these patients demonstrated an improved bone scan. One of 12 patients (8%) with soft-tissue disease showed a PSA decline of greater than or equal to 50%. No patient showed significant size reduction in bidimensionally measurable tumor.

**Time to Progression and Survival**

The median time to progression for patients treated with hydrocortisone was 1.9 months, with 17.3% (95% CI, 9.4%–29.7%) and 7.7% (95% CI, 3.0%–18.2%) of patients estimated to have not experienced progression of disease at 6 and 12 months, respectively. The median time to progression for patients having concomitant flutamide withdrawal was 1.8 months, versus 2.1 months for patients who had had antecedent flutamide withdrawal. Of patients with concomitant flutamide withdrawal, 23.5% (95% CI, 12.4%–40.0%) and 11.8% (95% CI, 4.7%–26.3%) are estimated to have not had progression of disease at 6 and 12 months, respectively. Of patients with antecedent flutamide therapy and withdrawal before inception of hydrocortisone, 5.6% (95% CI, 1.0%–25.8%) are estimated to be progression free at 6 months, with all patients estimated to have progressed by 12 months (Fig. 2). There was a trend toward a significant differences in time to progression for patients who received hydrocortisone with or without...
concomitant flutamide withdrawal ($P = 0.095$). The median time to initiation of suramin therapy was 3.3 months, with 29.2% (95% CI, 18.1%–43.5%) and 15.7% (95% CI, 7.9%–28.9%) estimated to have not begun suramin at 6 and 12 months, respectively.

The median time to progression for patients receiving suramin therapy is 2.6 months. At 6 months, 12.8% (95% CI, 5.6%–26.7%) of patients are estimated to have not progressed. There was no significant difference in time to progression on suramin between patients who had initial flutamide withdrawal and those who did not. The median time to progression of disease for patients whose PSA declined by greater than or equal to 50% for at least 4 weeks on suramin was 3.9 months.

The median survival of the 52 patients (excluding 2 patients treated directly with suramin) is 14.6 months. We estimated that 88.9% (95% CI, 77.0%–94.6%) and 65.4% (95% CI, 51.8%–76.8%) of patients are alive at 6 and 12 months, respectively. The median survival for patients with and without concomitant flutamide withdrawal was 14.7 months compared with 11.3 months, respectively. This difference is not statistically different ($P = 0.39$). The median survival from the start of suramin was 11.2 months, with 76.2% (95% CI, 61.4%–86.5%) and 46.9% (95% CI, 30.6%–63.9%) of patients estimated to be alive at 6 and 12 months, respectively, after starting suramin (Fig. 3). There was no difference in survival between patients who underwent concomitant flutamide withdrawal and those who did not during initial treatment with hydrocortisone once they began suramin ($P = 0.52$).

**Hormone Studies**

Of 52 patients treated with hydrocortisone therapy, 31 had testosterone levels measured, and all were below 25 ng/ml. Of 43 patients treated with suramin, 17 had testosterone levels determined and in 16 cases were below 25 ng/ml. In the remaining patient, the testosterone level was 45 ng/ml. The intent of the hydrocortisone therapy was to decrease circulating androgens of adrenal origin by corticotropin suppression, either in the setting of concomitant flutamide withdrawal or after flutamide had been withdrawn previously. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) were assessed as surrogate markers of adrenal androgen output. Of 52 patients treated with hydrocortisone, 13 had measurements of DHEA and DHEA-S before initiation and at time of disease progression. Eleven of these patients showed a decrease in DHEA (Fig. 4A) (mean decrease, 46 ng/dl; standard deviation = 83), and 11 also had decreased DHEA-S (Fig. 4B) (mean decrease, 0.3 µg/ml; standard deviation = 0.3). The likelihood that the differences observed were significantly different from zero was assessed by the Wilcoxon signed rank test: $P_2 = 0.08$ for DHEA and $P_2 = 0.0039$ for DHEA-S. Thus, it is likely that suppression of adrenal androgens was achieved with hydrocortisone for most patients in whom this maneuver was introduced. Interestingly, the serum levels of DHEA and DHEA-S in many cases increased in patients who went on to receive suramin. Of 43 patients who commenced treatment with suramin, 20 had determinations of DHEA and DHEA-S that bracketed this therapy. Thirteen patients demonstrated an increase in serum levels of DHEA and DHEA-S. The serum level of DHEA (●, ○) and DHEAS (●, □) was assessed before and after hydrocortisone alone (Panels A and B) and suramin (Panels C and D).
Table 2. Frequency (% of Patients) of Toxicity Episodes With Suramin (43 Patients)

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<th>Toxicity</th>
<th>Grade I-II</th>
<th>Grade III-IV</th>
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<td>Infectious</td>
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DHEA and 10 an increase in serum DHEA-S (Fig. 4C, D) (average increase in DHEA = 44 ng/dl, standard deviation = 91; average increase in DHEA-S = 0.06, standard deviation = 0.5). The likelihood that each of these changes on suramin was not equal to zero was $P_2 = 0.03$ for DHEA but only $P_2 = 0.90$ for DHEA-S by Wilcoxon's signed rank test. There was no discernible correlation between DHEA or DHEA-S levels or their change observed in relation to whether a patient received concomitant or sequential flutamide withdrawal or to the clinical response of the patient to either part of the protocol.

**Toxicity**

Clinical and laboratory toxicities (Table 2) were graded using the NCI Cancer Therapy Evaluation Program Common Toxicity Criteria. Clinically significant toxicity occurred only during treatment with suramin. Common Grade I–II clinical toxicities were fatigue, followed in decreasing order of frequency by skin rash, fever, peripheral edema, infection, nausea, and weight loss. Severe (Grade III–IV) clinical toxicities were limited to one patient with acute renal failure on the eighth day of suramin in association with pneumonia, one patient with gram-negative sepsis associated with atrial fibrillation, and one patient with hepatic failure in the setting of pneumonia and a urinary tract infection. In contrast to previous reports, sensorimotor neuropathy was mild (Grade I) and uncommon.

Hyperglycemia, anemia, renal insufficiency, hypoproteinemia, and impaired coagulation (prolonged prothrombin time or partial thromboplastin time) were the most common Grade I–II laboratory abnormalities documented. However, baseline laboratory abnormalities were common in this patient population, including anemia in 63% of patients and hyperglycemia in 35% of patients at study entry. Severe (Grade III–IV) hematologic toxicity included lymphocytopenia, thrombocytopenia, anemia, and prolonged prothrombin time or partial thromboplastin time. Severe neutropenia was seen in only one patient.

**Discussion**

The current report describes the activity of suramin in a clinical trial in which the variables of flutamide withdrawal and hydrocortisone therapy have been prospectively controlled as potentially confounding variables. In addition, by virtue of trial design, the activity of low dose hydrocortisone with or without flutamide withdrawal has also been prospectively evaluated.

Responses to the therapies administered in the current trial have been analyzed in two distinct categories (measurable disease and PSA). Twelve patients who received suramin had evidence of measurable soft-tissue disease. None achieved a greater than 50% reduction in the cross-sectional diameter of their measurable tumor. Thus, by conventional criteria of measurable disease, suramin fails to demonstrate significant activity when administered under these circumstances. Responses to suramin were also assessed using PSA criteria. When using a 50% decline in PSA lasting for 4 or more weeks, the response rate to suramin was 19%. This PSA response is considerably less than that reported in previous NCI trials\(^{16,17,39}\) and in the frequently cited trial from the University of Maryland.\(^{23}\) However, none of these trials prospectively controlled for flutamide withdrawal or hydrocortisone administration. In contrast, investigators at Memorial Sloan-Kettering reported a similar low response to suramin when patients had progressed after discontinuation of flutamide and subsequently hydrocortisone before receiving suramin.\(^{40}\) In this preliminary report,\(^{40}\) only 1 of 10 patients (10%) had a greater than 50% decline in PSA, which persisted...
for more than 2 months. This latter trial involved a much shorter dosing schedule (2 weeks), which may contribute to a lower response rate.

Although flutamide withdrawal and hydrocortisone administration are important variables, other variables may be responsible for the low response rate to suramin observed in the current trial. One important factor may be the method of suramin administration. We note, however, that the method of suramin administration (pharmacokinetically guided with peak and trough suramin levels maintained between 300 and 175 μg/ml) is essentially the same as that previously reported to have considerable activity in this disease. It is also possible that the combination of suramin and hydrocortisone have synergistic qualities when they are simultaneously administered in patients who have previously received neither of these therapies. Because both of these agents are capable of suppressing adrenal steroid secretion, it is possible that the simultaneous introduction of suramin and hydrocortisone represents a particularly effective (though toxic) form of medical adrenalectomy. However, our data showed the opposite effect, with DHEA and DHEA-S levels increasing after initiation of suramin. Finally, patients receiving suramin in the current trial may be in a poorer prognostic group compared with those in other trials, because they have failed the additional therapeutic maneuver of hydrocortisone withdrawal. Additional randomized and appropriately controlled trials are necessary to clarify this issue. One important prospective, randomized clinical trial that compares hydrocortisone plus placebo with hydrocortisone plus suramin has recently been initiated.

In addition to evaluating suramin, this trial also prospectively evaluated the activity of low dose hydrocortisone in the setting of concomitant or prior flutamide withdrawal. When using measurable disease as a response criteria, no patient receiving hydrocortisone without simultaneous flutamide withdrawal had responses in measurable disease. For those receiving the simultaneous combination of hydrocortisone and flutamide withdrawal, 11% (2 of 18) responded by these criteria. When using PSA response criteria (≥50% decline for 4 or more weeks), no patient receiving hydrocortisone after prior flutamide withdrawal responded, compared with 26% (9 of 34) of patients receiving hydrocortisone and undergoing simultaneous flutamide withdrawal. To the contrary, investigators at Memorial Sloan-Kettering have demonstrated the independent activity of hydrocortisone. Four of 20 patients (20%) who had progression off of flutamide demonstrated a greater than or equal to 50% PSA decline and symptomatic improvement with hydrocortisone using a slightly higher dose of 40 mg/day.40

It is also of interest to note that there is a trend toward a longer time to progression for those patients receiving hydrocortisone plus concomitant flutamide withdrawal compared with hydrocortisone and antecedent flutamide withdrawal (see Fig. 2). Caution is warranted in direct comparison of these data due to the nonrandomized nature of this study. Furthermore, patients with antecedent flutamide withdrawal may have comprised an overall worse prognosis group as evidenced by their significantly higher median on-study PSA level.

All patients who had a response to hydrocortisone administration and discontinuation of flutamide had received flutamide as a component of initial combined androgen blockade. It is possible that the hormonal milieu in which flutamide withdrawal occurs may be a critical component of the magnitude of response to this maneuver, with optimal response requiring suppression of both testicular and adrenal androgens. Further studies of this phenomenon will be most interesting to correlate with the presence of androgen receptor mutations,41 because flutamide functions as an androgen receptor antagonist. These data are consistent with our previous hypothesis that flutamide withdrawal is maximally active in the presence of adrenocortical suppression in castrated patients. We also note that other investigators have obtained data in support of this concept.42

Measurement of the adrenal androgens DHEA and DHEA-S suggest that hydrocortisone likely caused decreases in these circulating adrenal androgens in most patients. We did not observe any correlation between the level of DHEA or DHEA-S and clinical response to hydrocortisone plus flutamide withdrawal. In contrast to our data, Herrada et al.42 observed that there was a trend to early progression after flutamide withdrawal in patients with elevated DHEA levels. The numbers of responding patients in our study were low, however, and this issue should be evaluated in larger prospective trials using flutamide withdrawal.

Also of interest was our observation that a number of patients who received suramin in the setting of continued hydrocortisone demonstrated an increase in serum DHEA and DHEA-S during this treatment. This finding could reflect adrenal injury, altered binding to serum proteins in the presence of suramin, or altered metabolism of the hormones. Suramin has been demonstrated to inhibit human adrenal steroidogenic enzyme activities in a dose-dependent fashion.43 There was no clear relation of this finding to disease response. Nonetheless, these findings again highlight the need to assess adrenal androgen response to the introduction of
novel therapies in this disease and may be important to consider in future suramin trials.

In summary, suramin has independent antitumor activity in hormone-refractory prostate cancer when the potentially confounding variables of withdrawal of flutamide and hydrocortisone administration are prospectively controlled. The absence of activity of hydrocortisone treatment alone (in patients with prior flutamide withdrawal) suggests that the addition of hydrocortisone contributes minimally to the reported activity of hydrocortisone plus suramin in previously reported trials.16,17,23 The activity of suramin is less and of briefer duration in this trial compared with these previous reports, but our patients may have had more advanced disease or heavier pretreatment or there may have been an additive or synergistic activity with the withdrawal of flutamide.

References


