Phase II Study of Suramin plus Aminoglutethimide in Two Cohorts of Patients with Androgen-independent Prostate Cancer: Simultaneous Antiandrogen Withdrawal and Prior Antiandrogen Withdrawal

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ABSTRACT

Management of prostate cancer progression after failure of initial hormonal therapy is controversial. Recently, the activity of the simple discontinuation of antiandrogen therapy has been established by several groups, as well as the enhanced activity when combined with adrenal suppression (i.e., aminoglutethimide and hydrocortisone). Furthermore, suramin has generated considerable interest following the reports of response rates ranging from 17 to 70%. More recently, suramin response rates of 18 and 22% have been reported when the potential confounding variables of flutamide withdrawal and hydrocortisone were prospectively controlled. On the basis of the activity of combining aminoglutethimide with flutamide withdrawal, we designed a protocol in which suramin was combined with aminoglutethimide in two cohorts of patients (those with simultaneous antiandrogen withdrawal compared to those who had previously discontinued antiandrogen therapy).

Eighty-one evaluable patients were enrolled in this study between June 1992 and November 1994. Patients were a priori divided into two cohorts, those receiving prior antiandrogen withdrawal (n = 56) and those receiving simultaneous antiandrogen withdrawal (n = 25) at the time the patients were enrolled into the trial. For the group that discontinued antiandrogen prior to enrolling in therapy, the partial response rate (>50% decline in PSA for >4 weeks) was 14.2%, whereas the partial response was 44% for those patients who discontinued their antiandrogen at the time of starting suramin and aminoglutethimide. The median time to progression was 3.9 months in patients failing prior antiandrogen withdrawal and 5.5 months in those patients having concomitant antiandrogen withdrawal (P = 0.36 for the overall difference). The progression-free survival estimate at 1 year for patients having prior antiandrogen withdrawal was 19.8% [95% confidence interval (CI), 11–32.9%]. For those patients who experienced antiandrogen withdrawal simultaneous with the treatment, the progression-free survival estimates at 1 and 2 years were 27.1 (95% CI, 13.2–47.6%) and 4.5% (95% CI, 0.8–21.6%). The median survival time for those patients having prior antiandrogen withdrawal was 14.2 months, whereas the median survival was 21.9 months for those having concomitant antiandrogen withdrawal (P = 0.029 for the overall difference).

In conclusion, the partial response rate of 44% for those who had concomitant flutamide withdrawal with adrenal suppression was consistent with that of other reports using a similar maneuver. Although this study was not randomized and thus we should not over-interpret the results, flutamide withdrawal plus adrenal suppression appears to have greater activity than flutamide withdrawal alone. Furthermore, these data suggest that suramin adds little to the response rate observed for other adrenal suppressive agents in the presence of antiandrogen withdrawal. This interpretation is in agreement with those studies controlling for adrenal suppression and flutamide withdrawal prior to suramin administration, which noted modest activity of short duration. Given that antiandrogen withdrawal is now accepted as an active maneuver for a subset of patients progressing after maximum androgen blockade, we propose that future trials attempting to maximize response rates incorporate this maneuver whenever possible into prospectively designed regimens.

INTRODUCTION

Metastatic prostate adenocarcinoma is now the leading cause of visceral malignancy in the United States and the second leading cause of cancer-related deaths in men (1). It has been estimated that 15.4% of men will be diagnosed with prostate cancer at some point in their life (1). Moreover, the number of
new cases of prostate cancer has shown a steady rise over the past 20 years. With the aging of the population and no effective preventive strategies, prostate cancer will continue to represent a major public health issue in the decades ahead.

Total androgen deprivation is considered by many to be the optimal endocrine maneuver recommended for patients with metastatic prostate cancer (2, 3). This can be accomplished by orchietomy or LHRH analogues, plus antiandrogen therapy (i.e., flutamide and bicalutamide). Unfortunately, nearly all patients will eventually relapse, and at that time, therapeutic alternatives are limited (4). Management of prostate cancer progression after initial hormonal therapy is controversial (4, 5). The exact mechanism of action of suramin is not understood. It is known to inhibit the action of a variety of heparin-inhibitory glycosaminoglycans, inhibit angiogenesis, and induce adrenal insufficiency. In addition to adrenocortical necrosis, a number of toxicities have been attributed to suramin (e.g., anaphylactoid reactions, neutropenia, renal failure, thrombocytopenia, infection, coagulopathies, rash, vortex keratopathy, and hepatitis; Refs. 12-30). The primary dose-limiting complications (demyelinating neuropathy and proximal muscle weakness without demyelinating neuropathy; Ref. 31) can be minimized by maintaining total dose administered to less than 157 mg/kg over 6 weeks or using a pharmacologically guided regimen to limit plasma concentrations greater than 200 μg/ml to less than 50 days within a 6-week period (32).

Several groups have demonstrated that adrenal-suppressive agents, such as ketoconazole or aminoglutethimide, have activity against androgen-independent prostate cancer (33, 34). Although these agents are typically administered with corticosteroids, nonrandomized trials have suggested antitumor activity beyond that seen with low-dose glucocorticoids alone (21, 22, 33, 34). Aminoglutethimide is known to inhibit a variety of cytochrome P-450 dependent enzymes and aromatase (35). In particular, it inhibits pregnenolone synthesis, the precursor for adrenal steroids. Thus, aminoglutethimide induces a medical adrenalectomy by suppression of steroidogenesis. The side effects associated with this agent are relatively mild and are usually limited to rashes, somnolence, adrenal dysfunction, hypothyroidism, and occasional nausea and vomiting (36, 37).

We have previously reported our experience with aminoglutethimide and simultaneous flutamide withdrawal in patients with androgen-independent prostate cancer (38). That trial was initiated in March 1992 following the dramatic response associated with that maneuver that was observed in one patient (38). All of the patients enrolled in that trial had previously failed combined androgen blockade, suramin, and hydrocortisone (38). In that report, we noted a 48% response rate when using a response criteria of PSA decline >80% for 4 or more weeks (38). Furthermore, responses were not limited to PSA declines: clinical parameters such as anemia and pain also improved in a number of patients (38).

Since the initial demonstration that combination chemotherapy can be administered safely and effectively, oncologists have attempted to create combinations of therapy that have different mechanisms of action and nonoverlapping toxicities. Because the activity of aminoglutethimide, suramin, and antiandrogen withdrawal had each been previously demonstrated in independent trials and because the toxicities of these agents do not significantly overlap, we next sought to administer these therapies in combination in an attempt to produce maximal response rates with a minimum of toxicity. Because not all patients were receiving an antiandrogen at the time that the patients were referred to the NIH, we designed our protocol prospectively to include two groups of patients, i.e., those receiving SAW and those receiving PAW. The results of these patient cohorts are presented herein.

PATIENTS AND METHODS

Patient Eligibility. Patients were eligible for this study if they had progressive androgen-independent prostate cancer. All patients included had progressive disease after their last therapeutic maneuver. Treatment other than LHRH analogues and flutamide (or bicalutamide) must have been completed at least 1 month prior to enrolling in this protocol. If flutamide (or bicalutamide) had previously been discontinued, at least 1 month must have elapsed and the patient must have demonstrated evidence of progressive disease. Each patient met the following eligibility criteria: (a) histological diagnosis of adenocarcinoma of the prostate confirmed by the NCI Laboratory of Pathology; (b) progression of disease demonstrated by a rising PSA despite complete androgen blockade; (c) life expectancy greater than 3 months; (d) Karnofsky performance status of 80% or better; and (e) ability to make necessary trips from home to the NCI for treatment and follow-up. All patients signed written informed consent prior to enrolling in this study, and the protocol was reviewed and approved by the Institutional Review Board of the NCI. The conduct of this trial was monitored by the Cancer Treatment Evaluation Program of the NCI. No other forms of antitumor therapy were allowed during the study period (including radiation therapy).

*The abbreviations used are: LHRH, luteinizing hormone-releasing hormone; CI, confidence interval; PSA, prostate-specific antigen; NCI, National Cancer Institute; PAW, prior antiandrogen withdrawal; SAW, simultaneous antiandrogen withdrawal.
Patients were excluded for hemoglobin concentrations <9 g/dl, absolute neutrophil count <1500/mm³, platelet count <120×10⁹/mm³, history of a bleeding diathesis or coagulation disorder, and/or conditions requiring anticoagulation. Patients were also excluded if there was clinical or radiological evidence of cerebral metastases, past history or clinical evidence of stroke, abnormal urinalysis, or an externally draining urinary catheter. Patients with a creatinine clearance of less than 60 ml/min were not eligible for enrollment into this study. Abnormalities of liver function tests (ALT < 1.5 × normal) excluded patients from this trial, as did replacement of 50% or more of the liver parenchyma with metastatic disease. Any patient who had received chemotherapy, radiotherapy, or treatment with biological response modifiers could not be placed on this trial until a minimum of 28 days had elapsed and the patient met the criteria for progressive disease (see below).

Pretherapy Evaluation. All baseline studies documenting the extent of the patient's disease were completed within 2 weeks of the initiation of therapy with suramin. Radiographic and nuclear medicine studies were obtained prior to the administration of suramin and included computed tomography scans of the chest, abdomen, and pelvis, bone scan, and chest X-ray. Radiological findings compatible with metastatic deposits were repeated 1 month after completion of suramin therapy and then every 3 months thereafter.

PSA was measured by the Hybritech Tandem-R (San Diego, CA) assay. PSA was determined weekly while patients were receiving suramin and then monthly thereafter.

Response Evaluation. A complete response required disappearance of any pretreatment tumor masses, complete normalization of the bone scan, and normalization of the PSA for a duration of at least 28 days. A partial response was defined as a decline in the PSA concentration by 50% or greater on two consecutive occasions, with at least 14 days separating the two measurements. That response was required to be maintained for at least 28 days. Tumor mass regression was scored as a partial response if there was a 50% or greater reduction in the sum of the products of the two longest perpendicular diameters of all measurable lesions lasting for at least 28 days (39, 40).

Progressive disease was defined by any of the following criteria: an increase in the sum of the products of the two longest perpendicular diameters of all measurable lesions of greater than 25% and/or the appearance of new lesions; the development of one or more new lesions on bone scan; the need for radiation therapy; one of three consecutively rising PSA values 50% or greater than the baseline for those who never responded to therapy; or any one of three consecutively rising PSA values 50% or greater than the nadir for those who had some PSA decline in response to therapy. Patients with a baseline or nadir PSA less than 20 ng/ml were not declared to have progressed until the PSA had increased by an absolute value of 10 ng/ml or more; this requirement was developed to avoid making erroneous conclusions from minor fluctuations in PSA at low concentrations. Treatment failure was defined as any situation (e.g., toxicity) that resulted in discontinuation of therapy and clinical benefit.

Toxicity Assessment. Toxicity was determined by the established criteria of the NCI Cancer Treatment Evaluation Program (41).

Antiandrogen Withdrawal. As noted above, all patients demonstrated disease progression despite having received medical or surgical castration and an antiandrogen. In all patients except one, the antiandrogen was flutamide. If flutamide had been discontinued prior to referral to the NIH, then the patient was required to demonstrate progression of disease postflutamide withdrawal. If flutamide had not been discontinued prior to enrolling in the study, then it was stopped on day 1. Thus, this trial contained two cohorts of patients, those treated with prior discontinuation of flutamide and those treated with simultaneous flutamide withdrawal. These individuals were not randomized.

Suramin Administration. Suramin (Mobay Pharmaceutical Company) was supplied in 10-ml vials containing 1 g of suramin sodium, USP, as a sterile freeze-dried powder. Vials were reconstituted in 10 ml of sterile water. Initial i.v. doses of suramin were further diluted in 150 ml of 0.9% NaCl and infused over 1 h.

Suramin was administered by intermittent i.v. infusion using an adaptive control with feedback strategy to maintain peak concentrations of 300 µg/ml and trough concentrations of
40 Suramin plus Aminoglutethimide

Table 2  Response data

<table>
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<th>Simultaneous antiandrogen withdrawal</th>
<th>Prior antiandrogen withdrawal</th>
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<td>56</td>
</tr>
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<td>Complete response</td>
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<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>11 (44%)</td>
<td>8 (14.2%)</td>
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<tr>
<td>Median time to progression</td>
<td>5.5 months</td>
<td>3.9 months</td>
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<tr>
<td>Median survival time</td>
<td>21.9 months</td>
<td>14.2 months</td>
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<tr>
<td>Survival at 1 yr</td>
<td>76% (CI, 56.6–88.5)</td>
<td>53.6% (CI, 40.7–66.0)</td>
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<td>Survival at 2 yr</td>
<td>43.6% (CI, 26.3–62.7)</td>
<td>26.2% (CI, 16.3–39.2)</td>
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</table>

175 μg/ml for 8 weeks (42–44). During the initial 5 days of therapy, we administered fixed doses (day 1, 16.1; day 2, 11.4; day 3, 9.3; day 4, 8.2; and day 5, 7.5 mg/kg) based on ideal body weight. Serial blood samples were obtained for the determination of plasma suramin concentrations. From the first 5 doses and the ensuing plasma suramin concentrations, an initial estimate of each patient’s pharmacokinetic parameters were made, using a three compartment open linear model. Estimation of individual pharmacokinetics was performed in the context of a population pharmacokinetic model, i.e., a Bayesian approach (43). These estimations were performed using the Abbottbase Pharmacokinetic Systems program (Abbott Laboratories, Abbott Park, IL; version 1.0 for DOS). On day 5, patients began to receive individualized therapy to maintain the suramin plasma concentrations between the targeted 300 and 175 μg/ml concentrations.

Concomitant Hormonal Therapy. Those patients who had not undergone bilateral orchiectomy continued to receive medical castration with leuprolide (Depot Lupron, TAP Pharmaceuticals, Deerfield, IL; 7.5 mg i.m. every 4 weeks). All patients received physiologic doses of hydrocortisone (20 mg p.o. every morning and 10 mg p.o. every evening) starting on day 1 of protocol therapy to prevent complications associated with suramin- and/or aminoglutethimide-induced adrenal insufficiency. Low-dose hydrocortisone was continued for the duration of the patient’s life.

Aminoglutethimide was prescribed at a dose of 250 mg p.o. four times a day starting on day 1. If grade III toxicity was encountered, which was attributable to aminoglutethimide, the drug was discontinued and reinstated following resolution of the complication at a dose of 250 mg twice a day.

Statistical Analysis. All survival and progression-free survival durations were calculated from the on-study date until date of progression, death, or last follow-up as appropriate. The Kaplan-Meier method was used to calculate the probability of survival or progression-free survival as a function of time. The Mantel-Haenszel method was used to determine the statistical significance of each pair of Kaplan-Meier curves. The Wilcoxon rank-sum test was used to determine the significance of the difference in Gleason scores, time from diagnosis, and PSA between the two groups (PAW and concurrent antiandrogen withdrawal). All Ps were two-sided.

RESULTS

Demographics. Eighty-two patients were enrolled in this study between June 1992 and November 1994 (see Table 1 for patient demographics). The median age was 63 years (range, 40–80 years). All of the patients had Karnofsky performance status of greater than or equal to 80%. Fifty-six patients had flutamide (or bicalutamide in the case of one individual) discontinued prior to enrolling in this study and had shown progression of disease following that discontinuation; 25 had flutamide withdrawal at the time that suramin, hydrocortisone, and aminoglutethimide were initiated. One patient never had antiandrogen therapy. He had rapidly progressing disease after receiving leuprolide plus combination chemotherapy; thus, this patient was not eligible for response evaluation, but he was included in adverse event reporting.

Nine of the patients had both measurable soft tissue disease and bone metastases; 71 had only bone metastases. One patient had soft-tissue disease only. Forty-one patients had surgical castration, and 40 received a LHRH agonist. As noted above, all but 1 patient had failed antiandrogen treatment in addition to medical or surgical castration; 24 patients had failed additional hormonal maneuvers (i.e., megestrol acetate, ketoconazole, or estradiol). Fourteen patients had failed chemotherapy. Twenty-two patients had received prior radiation to the prostate/pelvis, 24 had received radiation to a metastatic bone site, and 3 had received strontium. There was a median of 33.3 months and mean of 42.2 months from the time of diagnosis to enrollment in this study for all patients. For those patients who underwent antiandrogen withdrawal (PAW), there was a mean of 43.2 months (median, 32.8) from the time of diagnosis to enrollment in the study, which was similar to the mean of 39.8 months (median, 31.9) for those who had SAW. The median PSA value at the time of starting the study for patients with PAW was 174.4 ng/ml (range, 17–3434 ng/ml). For those patients who underwent antiandrogen withdrawal at the time of treatment, the median PSA value at diagnosis was 174 ng/ml (range, 6.2–12,613 ng/ml; P = 0.38, Wilcoxon rank-sum test). Forty-four patients were initially diagnosed with stage D2 prostate cancer (29 with PAW and 15 with SAW), 18 with stage D1 (13 with PAW and 5 with SAW), 10 with stage C (6 with PAW and 4 with SAW), and 9 with stage B (8 with PAW and 1 with SAW) prostate cancer. There were no significant differences detected between the two treatment groups.
Response and Survival Results. As noted above, the patients were a priori divided into two cohorts, those who received PAW and those who received SAW. Among all patients, the response rate was 23.5% (19 of 81 patients had a partial response; 95% CI, 14.8–34.2%; see Table 2). There were no complete responses. For the group that discontinued antiandrogen prior to enrolling in therapy, the response rate was 14.2% (8 of 56 patients had a partial response; 95% CI, 6.4–26.2%). For those individuals who discontinued their antiandrogen on the same day as starting the protocol, the response rate was 44% (11 of 25 patients had a partial response; 95% CI, 24.4–65.1%).

Essentially all of the partial responses noted were a consequence of PSA declines of >50% lasting for greater than 4 weeks. Ten patients had evaluable soft tissue disease. Among those patients with soft-tissue disease, two showed a reduction in measurable disease. One of those individuals had PAW, and the other had SAW.

The median time to progressive disease was 4.4 months for all patients. The median time to progression was 3.9 months in patients who had their antiandrogen withdrawn prior to starting and 5.5 months in those patients who had concomitant antiandrogen withdrawal. The difference between these groups was not significant (P = 0.36) using the Mantel-Haenszel test (see Fig. 1). The progression-free survival estimate at 1 year for patients who had PAW was 19.8% (95% CI, 11–32.9%). For those patients who experienced SAW, the progression-free survival estimates at 1 and 2 years were 27.1% (95% CI, 13.2–47.6%) and 4.5% (95% CI, 0.8–21.6%).

Presently, 22 of the evaluable patients are alive: 13 (23% of the 56 patients) of them had PAW and 9 (36% of the 25 patients) had SAW. The median survival time for all patients was 15.3 months. For those patient groups having prior versus concomitant antiandrogen withdrawal, the median survival times were 14.2 and 21.9 months, respectively (P = 0.029, Mantel-Haenszel test; Fig. 2).

Toxicities. The toxicities associated with aminoglutethimide and suramin are listed in Table 3. There were a total 38 episodes of grade III or IV complications in 29 patients. Grade IV thrombocytopenia occurred in four patients (5%), and there were four episodes of grade III arrhythmias. All of the arrhythmias were atrial fibrillation and were treated with digoxin. All of the arrhythmias occurred toward the end of the 8-week suramin treatment. There was one episode of grade IV rash, which developed 41 days after the completion of the suramin treatment. There was one episode of grade IV rash, which developed 41 days after the completion of the suramin treatment; however, the patient was still receiving aminoglutethimide. This rash consisted of diffuse erythematous papules over the thorax, dorsum, brachium, and facies and was associated with exfoliation. Following discontinuation of therapy and a short course of steroids, the complication was resolved. One patient developed grade IV infection without the isolation of an organism. One patient had grade IV renal dysfunction, which required dialysis. The onset of acute renal failure occurred on day 9 of suramin dosing; however, the patient was not rechallenged. Although one patient developed grade III neurosensory changes, none of the patients presented with evidence of significant neuromotor changes with this regimen. There were no fatal toxicities, and all toxicities were reversible.

DISCUSSION

Hormonal manipulation in patients with stage D prostate carcinoma is, unfortunately, noncurative in nature. Patients undergoing initial hormonal therapy for stage D2 prostate cancer will typically progress 12–18 months after initiating therapy (45), depending on extent of disease and the criteria for progression. After initial hormonal therapies have failed, the cancer is often
referred to as androgen independent. Patient survival in trials of androgen-independent prostate cancer is typically reported in the range of 5.7–18.8 months (see Table 4; Refs. 46–53).

Patients with androgen-independent metastatic prostate cancer have a relatively limited set of options, and none of these options have been shown to prolong survival in a prospective randomized setting. Options for androgen-independent prostate cancer currently include discontinuation of antiandrogens, adrenal suppression, and/or experimental therapies such as suramin, aminoglutethimide, suramin, androgen-independent prostate cancer (21, 38, 54, 56). Additional reports have covered trials combining concomitant flutamide withdrawal and adrenal suppression (21, 22, 38, 54–56, 65). Additional reports have covered trials combining chemotherapy with adrenal suppressive agents (ketoconazole plus doxorubicin or prednisone plus mitoxantrone; Refs. 46, 49, and 53). In this report, we present the first trial combining adrenal suppression plus suramin in two cohorts of patients (those who discontinued antiandrogen simultaneously and those who had previously discontinued antiandrogen therapy).

Data on the presence of androgen-receptor mutations in patient-derived specimens have provided an additional rationale for combining adrenal suppression and flutamide withdrawal (57–62). It is now clear that certain mutant androgen receptors recognize “weak” adrenal androgens, such as androstenedione, as potent androgenic agonists (4, 62). It is also clear that certain mutant receptors recognize flutamide as an agonist instead of antagonist (63, 64). Should these observations have clinical relevance, then theoretically, castrated patients with adrenal suppression should maximally benefit from flutamide withdrawal. We note that the four published studies examining this hypothesis are among the most active regimens ever reported in androgen-independent prostate cancer (21, 38, 54, 56).

In this particular study, an especially prolonged survival was noted in those individuals who received concomitant aminoglutethimide, suramin, and antiandrogen withdrawal. In fact, the median survival of this group (21.9 months) appears to be the longest in any reported trial in androgen-independent prostate cancer (see Table 4). Although the groups were not randomized, we note that patients in our cohort receiving the same regimen without antiandrogen withdrawal lived for a median of only 14.2 months. Because this was an unrandomized study, several differences might conceivably account for these findings. Differences in age at diagnosis, stage at diagnosis, time from initial diagnosis to protocol therapy, initial Gleason score, and/or number of prior treatments might explain a survival advantage for one treatment group or the other (see Table 1). We have examined each of these variables between those who did and those who did not receive antiandrogen withdrawal. No significant differences were detected between the two treatment groups. Although it is clearly premature to state that combining antiandrogen withdrawal with additional therapies confers a survival advantage, we do suggest that this concept could lead to the development of a hypothesis that could be prospectively examined in a controlled clinical trial.

In contrast to the survival results, the response rates for those receiving combination (suramin and aminoglutethimide plus antiandrogen withdrawal) therapy was lower than initially anticipated. The four trials examining combinations of adrenal suppression and flutamide withdrawal reported >50% declines in PSA for 4 or more weeks in >50% of the patients (21, 38, 54, 56). Using the same response criteria for patients receiving a combination of suramin plus aminoglutethimide, the PSA partial response rate (>50% decline in PSA) was 14.2%, whereas those patients receiving these therapies in combination with flutamide withdrawal had a PSA partial response rate of 44%. Furthermore, soft tissue responses were limited to 2 of 10 patients. Nine of those patients had PSA responses. These data suggest that suramin adds little to the response rate observed for other adrenal suppressive agents in the presence of antiandrogen withdrawal. This interpretation is in agreement with those studies controlling for adrenal suppression and flutamide withdrawal prior to suramin administration, which noted modest activity that was of short duration (21, 22). From these data, one could also hypothesize that the mechanism of action of suramin is adrenal ablation, which is supported by its response rate being equivalent to that of the other adrenal antagonists.

The grade III or greater toxicities in these trials were primarily attributable to suramin (thrombocytopenia, rash, renal dysfunction, arrhythmias, and infection). Although suramin contributed to the toxicities noted in this population, our data do not support the concept that suramin significantly enhanced the response rates.

Given that antiandrogen withdrawal is now accepted as an

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<th>Author (Ref.)</th>
<th>Investigation regimen</th>
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<td>18.8</td>
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<tr>
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<td>14.2</td>
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<tr>
<td>Simultaneous withdrawal plus suramin + aminoglutethimide</td>
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active maneuver for a subset of patients progressing after maximum androgen blockade, our limited data suggest that additional trials may benefit from antiandrogen withdrawal simultaneous with additional maneuvers. Whether or not this maneuver adds to the response rate or survival can only be determined by appropriately designed and executed randomized clinical trials.

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