Similar Clinical Outcomes in African-American and Non-African-American Males Treated With Suramin for Metastatic Prostate Cancer

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African-American males have a higher incidence of prostate cancer than non-African-American males and an overall poorer prognosis. Environmental factors such as socioeconomic status and biological factors such as an increased frequency of androgen receptor mutation have been identified as causal. As androgen ablation therapy is ubiquitous in the treatment of metastatic prostate cancer, little information is available on clinical outcome independent of hormone therapy. Our experience at the Warren G. Magnusson Clinical Center, National Institutes of Health with the anticancer agent, suramin, offers the opportunity to study clinical outcome in patients treated with an agent whose tumoricidal activity is not dependent on androgen receptor function.

Clinical outcome was examined retrospectively in 43 patients treated on a single suramin-based protocol and evaluated as a function of ethnic background. No significant difference in time to disease progression or survival was observed between African Americans (n=4) and the other 39 patients. These findings are consistent with the hypothesis that therapies that work through mechanisms independent of the androgen receptor may result in similar outcomes across ethnic groups. (*J Natl Med Assoc.* 1997;89:622-628.)

Key words: prostate cancer ◆ suramin ◆ African Americans ◆ ethnic groups ◆ clinical outcome

Prostate cancer will be diagnosed in approximately 317,100 men in the United States in 1996, accounting for 41% of all male cancers.[1] It will cause death in approximately 41,400, accounting for 14% of all male cancer deaths. It is now the number two cause of cancer death among American males. African-American males have shown a significantly higher risk for developing prostate cancer than non-African-American males.[2-4] Furthermore, age-adjusted incidence and mortality rates have been rising dramatically since 1955, with the United States having the highest incidence of prostate cancer in the world.

When compared with other ethnic groups (ie, Hispanics, whites, and Asians), African Americans have a poorer prognosis.[4,5] African-American men have a lower 5-year survival rate (49%) compared with US whites (60%), are more likely to have an initial diagnosis of metastatic disease (29.3% versus

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Table 1. Patient Characteristics

Characteristic	No. (%) African Americans*	No. (%) Non-African Americans†
Age at diagnosis (years)	57.8‡	61.5§
Age at initiation of suramin (years)	63.8‖	66.3¶
Previous treatments		
Surgery/medical castration	4 (100)	39 (100)
Secondary hormonal treatment	4 (100)	31 (79)
Chemotherapy	2 (50)	2 (5)
Radiotherapy (bone or prostate)	3 (75)	33 (85)
Metastatic disease sites		
Bone involved only	3 (75)	33 (85)
Measurable soft tissue	2 (50)	17 (44)
Histology		
Gleason grades 1 to 4	1 (25)	2 (5)
Gleason grades 5 to 7	2 (50)	20 (51)
Gleason grades 8 to 10	1 (25)	17 (44)
Unknown	0 (0)	0 (0)

*n=4.
†n=39.
‡Range: 51 to 61 years.
§Range: 42 to 76 years.
‖Range: 60 to 66 years.
¶Range: 48 to 80 years.

Table 2. Mean (±Standard Deviation) Serum Prostate Specific Antigen (PSA) Levels on Suramin Therapy

PSA Levels (ng/mL)	African Americans	Non-African Americans	*P* Value
Before suramin	897.5±750.7	289.7±412.1	.027
At completion of suramin	650.1±685.4	303.4±330.7	.21
% change	28% reduction	5% increase	

17.8%), and are more likely to present at an earlier age (70.3 years versus 72.3 years).[6] Several studies also have shown that, at the time of diagnosis, African-American patients have significantly higher clinical stages and tumor grades than US whites.[4,5,7] While the reasons for these findings are unclear, socioeconomic factors, health-care access, and biological differences based on ethnicity have all been identified.[8,9]

If prostate cancer in African-American men is more aggressive biologically, differences in biological markers of disease also would be expected. Emerging reports are, in fact, consistent with this hypothesis. Several authors have shown that even after adjusting for grade and stage, mean prostate specific antigen (PSA) values were significantly higher in African-American males compared with US whites.[1-11] Abnormalities in the CAG repeat region of the androgen receptor gene have been shown to occur more frequently in African-American males than in men of other ethnic groups.[12-14] This finding may offer a potential molecular explanation for ethnic-based differences in prostate cancer outcome. Indeed, recent studies suggest that CAG repeat status has a major impact on cellular response to antiandrogens, and consequently, clinical tumor response to hormonal therapy.[15]

There are mitigating factors, however, in considering these findings. A recent study suggests that even within the same stage, African Americans may have a greater volume of disease.[9] As serum PSA values correlate with disease volume, the higher PSA values seen in African Americans may reflect larger tumor burdens, which may reflect intrinsic alterations in prostate cancer biology.[11] Other authors have suggested that the increased incidence of

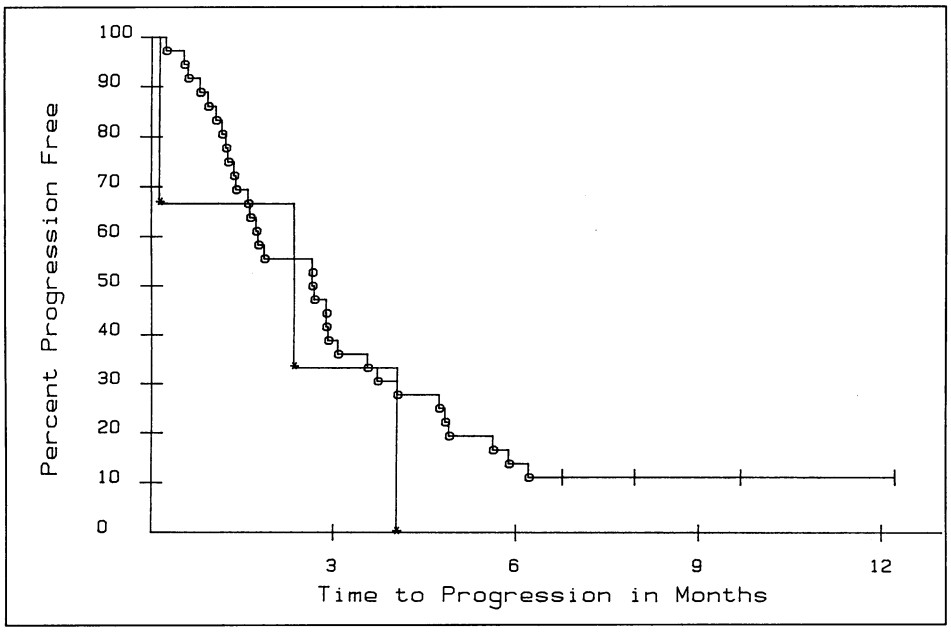

Figure 1.
Time to disease progression in patients with metastatic prostate cancer as a function of ethnic background. Time to disease progression was determined from the first day of suramin therapy in patients beginning part 2 of the study. The probability of remaining progression free in African-American (*) or non-African-American (□) patients was calculated according to the method of Kaplan and Meier.

prostate cancer in African-American males is due to higher circulating testosterone levels in this population.[16,17] Testosterone is a prostate cancer growth stimulatory hormone, and Ross et al[16] have proposed that the risk of prostate cancer is determined by the cumulative exposure to circulating testosterone.

If clinical outcomes are dependent, at least in part, on differences in prostate cancer biology, and if the sole biological difference is related to alterations in the androgen receptor, similar outcomes should be seen in nonendocrine-based therapies. Systemic therapy with the antiproliferative agent suramin has been reported to show activity in both hormone-sensitive and hormone-resistant metastatic prostate cancer.[18,19] This is consistent with a molecular basis of activity that is not dependent on interaction with the androgen receptor. Potential molecular mechanisms include inactivation of growth factors such as basic FGF, PDGF, VEGF, and possibly others, which affect prostate cancer cell growth.[20-24]

As suramin therapy is not necessarily dependent on androgen receptor status, a retrospective analysis of African-American males treated with suramin at the Warren G. Magnusson Clinical Center, National Institutes of Health was undertaken. To minimize variables, the analysis focused on one specific treatment regimen and compared the clinical outcome in African Americans with that of the remainder of the cohort, which was primarily US whites. This study provides insightful information on the biology of prostate cancer and its potential relationship to ethnic background.

MATERIALS AND METHODS

All patients were treated with suramin as previously reported,[18] on an approved experimental therapy protocol of the National Cancer Institute, in Bethesda, Maryland, after informed consent was obtained. All therapy took place at the Warren G. Magnusson Clinical Center, National Institutes of Health. The treatment regimen, eligibility criteria, and criteria for assessment of response and toxicity have been described in detail elsewhere.[18,25] Patients were eligible if they had metastatic histologically confirmed prostate cancer and had failed primary combined hormonal therapy. Combined therapy consisted of castration (medical or surgical) plus coadministration of flutamide. Intact end-organ function was documented, and patients must have stopped previous therapy at least 4 weeks prior to starting suramin. If patients were on a luteinizing hormone-releasing hormone agonist prior to study entry (ie, medically castrated), such therapy was continued while on this study.

Suramin was manufactured by Mobay Pharmaceutical Co and distributed by the Cancer Treatment Evaluation Program of the National Cancer Institute. Suramin was supplied in 10-mL vials containing 1 g of sodium suramin as a sterile freeze-dried powder. Each vial was reconstituted with

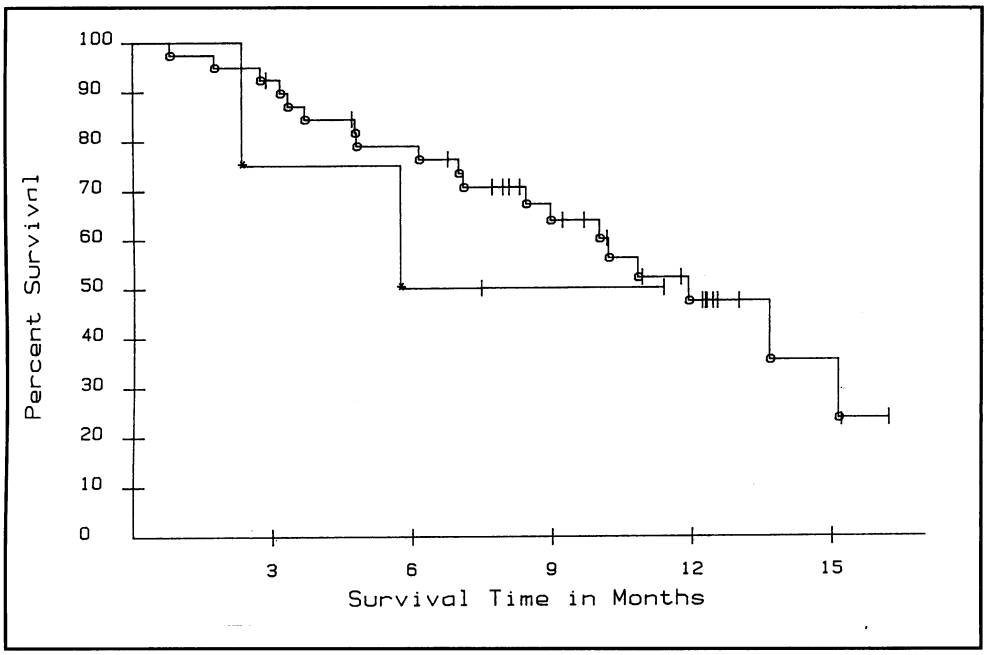

Figure 2.
Survival of patients with metastatic prostate cancer as a function of ethnic background. Survival was determined from the first day of suramin therapy in patients beginning part 2 of the study. The probability of survival in African-American (*) or non-African-American (□) patients was calculated according to the method of Kaplan and Meier.

10 mL of sterile water for injection to yield a final concentration of 100 mg/mL. The individual dose for each patient was diluted in 5% dextrose to a total volume of 150 mL and administered over 1 hour.

Suramin was administered on an outpatient basis. The first five doses of suramin were fixed based on the patients' ideal body weight (day 1=16.1 mg/kg, day 2=11.4 mg/kg, day 3=9.4 mg/kg, day 4=8.2 mg/kg, and day 5=7.5 mg/kg). Plasma suramin concentrations were determined using the method described by Supko and Malspeis.[26] The initial pharmacokinetic parameters were determined by linear least squares fitting a three-compartment open-linear model (using the objective function incorporated with the means and coefficients of variation of our previous suramin study) to determine new parameters for this study.[27] Bayesian modification was done using the Marquardt-Levenberg iterative algorithm as computed by Abbottbase Laboratories, Abbott Park, Illinois, with version 1.0 for DOS.

After characterization of the patients' pharmacokinetic parameters during the initial five doses, suramin dosing was guided by a three-compartment open-linear model using an adaptive feed-back control, as previously described.[27] Doses were adjusted to maintain suramin plasma concentrations between 175 and 300 µg/mL, administered Monday through Friday as needed. Patients also received replacement doses of hydrocortisone of 30 mg/day.

Patients were treated with suramin for either 6 or 8 weeks; no further cycles of suramin therapy were administered. If during the initial 6 weeks of suramin therapy, patients experienced disease progression or achieved a complete response, therapy would be stopped at 6 weeks; otherwise, patients were treated for a total of 8 weeks. Complete response to therapy required complete disappearance of all evaluable sites of disease, lasting for at least 1 month, along with a documented negative biopsy of the prostate in those individuals who had never undergone prostatectomy.

A partial response required a ≥50% reduction in serum PSA level for at least 1 month, disappearance of lesions on bone scan, or ≥50% reduction in the sum of the product of the largest perpendicular diameters of all measured lesions for at least 1 month. Progressive disease required a ≥50% increase in the serum PSA level, new lesions on bone scan, a ≥25% increase in the sum of the product of the largest perpendicular diameters of all measured lesions, or the development of new lesions. All other situations were defined as stable disease. Toxicities were assessed according to the criteria of the Cancer Therapy Evaluation Program of the National Cancer Institute.

The probability of survival or time to progression was calculated using the Kaplan-Meier method, and the difference between the two racial categories was

Table 3. Mean (±Standard Deviation) Pharmacokinetic Parameter Estimates of Suramin Therapy

Parameter	Units	African Americans	Non-African Americans
Total clearance	L/hr	0.0244±0.0125	0.0229±0.0096
Microrate constants	hr^{-1}		
K12		0.157±0.022	0.159±0.020
K21		0.1253±0.0216	0.1181±0.0136
K13		0.0279±0.0041	0.0278±0.0055
K31		0.0052±0.0019	0.0060±0.0020
K10		0.0059±0.0034	0.0081±0.0130
Macrorate constants	hr^{-1}		
Alpha		0.0181±0.0013	0.0182±0.0036
Beta		0.0006±0.0002	0.0008±0.0006
Gamma		0.303±0.005	0.298±0.012
Volume of distribution	L	34.6±9.1	30.3±7.9
Terminal half-life	hr	1344±841	1135±476

compared using the Mantel-Haenszel technique.[28,29] Survival duration was calculated from the date therapy was initiated, until death or last follow-up. Time to progression was defined from the start of suramin until progression or last follow-up.

RESULTS

Table 1 summarizes patient characteristics. Five African-Americans were accrued into the protocol, and four went on to receive suramin; their characteristics were similar to the cohort as a whole. Specifically, there were no meaningful differences between patient subsets with respect to age at original diagnosis or age at time of initiation of suramin therapy. Likewise, there were no meaningful differences with respect to prior therapy, sites of metastatic disease, or Gleason grade of tumor specimens. Bulk of tumor could not be assessed retrospectively.

Patient serum PSA levels are depicted in Table 2. While pre- and posttreatment PSA levels were generally higher in African-American patients, a significant difference only was observed between pretreatment groups (P=.027, Wilcoxon rank sum test). While a 28% reduction in PSA level was seen in African-American patients, no African-American patient experienced an objective response while on suramin therapy. A 5% increase in PSA level was seen with non-African-American patients while on suramin therapy. However, within this subgroup, 10 patients experienced an objective PSA response (≥50% decrease in the PSA lasting at least 4 weeks).

No differences were observed in more important measures of clinical outcome. Time to disease progression for both patient subsets is shown in Figure 1. The curves essentially overlapped and were not statistically different (P=.43), suggesting no differences between groups. Overall survival is shown in Figure 2; again, no differences were observed between African-American and non-African-American patients (P=.57). No meaningful differences in treatment-related toxicity profiles were observed between African-American and non-African-American patients (data not shown).

Table 3 shows mean pharmacokinetic parameters for suramin in the two patient subsets. There were no differences between groups with respect to total body clearance, rate constants (micro or macro), volume of distribution, or terminal half-life.

DISCUSSION

One consistent observation from a large number of studies is that African-American patients do less well after treatment for prostate cancer than other ethnic groups.[4,5] Whether this is due to differences in biology, health-care access, or other factors still is not clear. In vitro studies have identified molecular changes in the CAG repeat region of the androgen receptor gene that may be related to ethnic origin.[12-14] As the primary form of therapy for prostate cancer relates to androgen ablation, differential receptor-related responses could translate into differences in clinical outcomes.[30] Indeed, other studies have identified mutations in the body of the androgen receptor that serve to alter its response to receptor antagonists.[15,31]

As androgen ablation therapy is ubiquitous in the

treatment of prostate cancer, it is difficult to evaluate clinical outcomes separate from hormonal manipulation. Our studies involving suramin treatment of patients with androgen-independent prostate cancer provide an unique cohort of patients. Numerous studies indicate that suramin acts by modulating prostate cancer cell growth factor interactions, possibly by altering the constituency of extracellular proteoglycans (a reservoir for numerous growth factors).[20-24] These actions are not dependent on androgen receptor binding. Thus, response to suramin therapy is not necessarily dependent on androgen receptor function.

In this study, our institutional experience with suramin administration was examined as it related to treatment outcome as a function of ethnic origin. While this study was limited by its retrospective nature and the small number of African-American patients, it provides a measure of insight into an important area in which little information exists. Within the confines of this study, suramin therapy appears to be associated with similar clinical outcomes in both African-American and non-African-American patients with metastatic prostate cancer. This finding suggests that therapies that work through mechanisms independent of the androgen receptors may result in similar outcomes across ethnic groups.

This finding also supports the possibility that the poor outcome observed in African-Americans in studies involving prostate cancer may be related to hormonal manipulation and differential cell response to such. This hypothesis would be consistent with other emerging studies. Shortening of the CAG repeat length in prostate cancer tissues may be associated with a worse prognosis. Abnormalities in CAG repeat length are more frequent in African Americans compared white Americans, who in turn have a higher frequency of abnormalities than Asian Americans.[12,14] Interestingly, this relationship (African Americans > white Americans > Asian Americans) is also true for the respective death rates from metastatic prostate cancer.[32] Therefore, it is possible that the observed differences in survival after therapy for metastatic prostate cancer may indeed be related to ethnic origin, have a biological basis, and affect multiple ethnic groups.

CONCLUSION

Further studies into the relationship between ethnic origin, androgen receptor gene mutations, and clinical outcome in patients with prostate cancer are needed before definitive conclusions can be made. Such studies hopefully can lead to the development of more effective therapies for African Americans with prostate cancer. Measures to mitigate the effect of low socioeconomic status-related factors will improve prostate cancer outcome in African Americans irrespective of the outcome of these studies.

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