

Exploratory Analysis on the Effect of Race on Clinical Outcome in Patients With Advanced Prostate Cancer Receiving Bicalutamide or Flutamide, Each in Combination With LHRH Analogues

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BACKGROUND. Black race has been associated with a significantly increased risk of prostate cancer mortality. This exploratory analysis investigated the effect of race on the clinical outcome of combined androgen blockade (CAB).

METHODS. Data for analysis were obtained from a double-blind, randomized, multicenter trial comparing CAB in the form of bicalutamide (50 mg once daily) or flutamide (250 mg three times daily) plus luteinizing hormone-releasing hormone analogs (LHRHa; goserelin acetate 3.6 mg, or leuprolide acetate 7.5 mg) in 813 patients with stage D₂ prostate cancer (median follow-up, 160 weeks). Patients were analyzed according to race (African American [AA], white, or other). The primary clinical events were disease progression and survival.

RESULTS. Four hundred and four patients received bicalutamide/LHRHa and 409 received flutamide/LHRHa. Although treatment with bicalutamide/LHRHa resulted in slightly

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The interim results of this exploratory analysis were first presented in poster form in 1996 at the American Society of Clinical Oncology Annual Meeting in Philadelphia, Pennsylvania.

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longer time to progression and survival time in white and AA males than treatment with flutamide/LHRHa, the differences between the treatment groups were not statistically significant.

CONCLUSIONS. No marked effect of race on clinical outcome was observed regardless of antiandrogen, suggesting that similar treatment benefits are to be expected in either race. *Prostate* 40:218–224, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS: bicalutamide; flutamide; combined androgen blockade; clinical outcome; racial differences

INTRODUCTION

Prostate cancer is a major burden on the healthcare systems of Western societies, where it is one of the most commonly diagnosed cancers in men, with an estimated 179,300 new cases in the US during 1999 [1]. Even in Japan, which has one of the lowest age-adjusted death rates from prostate cancer in the world, the incidence of, and death rate from, prostate cancer are rising rapidly [2].

Within the affected population, African-American (AA) males are more likely to be diagnosed with metastatic prostate cancer than white males and are less likely to have undergone a prostatectomy or radiation treatment [3], and thus are more likely to have been treated only with hormonal therapy [4]. Although there was a trend towards more aggressive treatment (e.g., radical prostatectomy) of prostate cancer during the period 1984–1991, the proportion of African-American men who received such treatment was substantially lower than in white men [3–5]. Even for those patients (white and AA) who received radical prostatectomy in an equal-access setting, the poorer outcome in AA men was still evident [6]. In a recent analysis of data from the Surveillance, Epidemiology and End Results (SEER) program, black race was independently associated with a significantly increased risk of prostate cancer mortality [7]. Indeed, the 5-year survival rates were lower among AA than white males [4,8].

The reasons for the difference in prostate cancer mortality between white and AA men are not well-documented. Prostate-specific antigen (PSA) is a powerful predictor of tumor volume and pathologic stage [9], and AA men have both a significantly higher PSA production per tumor volume compared with white males [10,11], and a larger tumor burden [10,12].

These findings highlight the issue of earlier detection, including PSA screening in AA men. Indeed, there are some preliminary data indicating that the proportion of tumors confined to the prostate increases with PSA screening, and that a reduction in mortality via screening [13,14] is feasible. It has been

suggested that race should be a stratification factor in clinical trials, particularly if recurrence-free survival is an endpoint [6].

In the National Cancer Institute (NCI) Intergroup Study #0036, an unexpected finding was that the median survival rate was lower in AA compared with white males (26.4 vs. 33.6 months), regardless of therapy, which included leuprolide and placebo or combined androgen blockade (CAB) with leuprolide and flutamide [15]. However, no other studies have reported the relationship between race and the outcome of CAB.

This exploratory analysis further investigated the effect of race on clinical outcome in patients with advanced prostate cancer who had received CAB in the form of bicalutamide plus luteinizing hormone-releasing hormone analog (LHRHa) or flutamide plus LHRHa. Data for the analysis were obtained with a median follow-up of 160 weeks in a double-blind, randomized, multicenter trial comparing these two regimens in 813 patients with stage D₂ prostate cancer [16].

MATERIALS AND METHODS

Patients

The methodology of this investigation has been published in detail [16–18]. In brief, patients aged 18 or over with confirmed adenocarcinoma (stage D₂) of the prostate gland and evaluable bone metastases or at least one measurable nonskeletal lesion were included. Patient's race was recorded at baseline. Patients were excluded if they had had previous systemic therapy for prostate cancer, an additional malignancy, or an Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4. Written, informed consent was obtained from all patients, and the study was approved by the appropriate Institutional Review Boards.

Design

The investigation was a randomized, multicenter study with a 2 × 2 factorial design. Antiandrogen treatment was randomized in a double-blind manner.

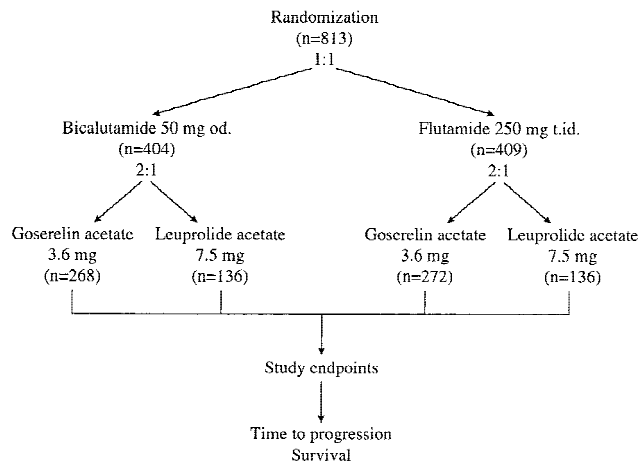


Fig. 1. Treatment arms after randomization.

The antiandrogens, bicalutamide 50 mg once daily (Casodex, Zeneca Pharmaceuticals, Wilmington, DE) and flutamide 250 mg three times daily (Eulexin, Schering Corporation), and the LHRH analogs, goserelin acetate 3.6 mg (Zoladex, Zeneca Pharmaceuticals) and leuprolide acetate 7.5 mg (Lupron Depot, TAP Pharmaceuticals), were allocated 1:1 and 2:1, respectively (Fig. 1). Bicalutamide and flutamide were supplied in a double-dummy pack which contained active antiandrogen and a placebo that matched the other antiandrogen. Treatment was initiated within 2 weeks of randomization; antiandrogen and LHRHa were started on the same day.

Measurements

Data were obtained at a median follow-up of 160 weeks. The clinical endpoints for this exploratory analysis by race were disease progression and survival. Race was recorded at baseline. Patients were analyzed retrospectively according to race (AA, white, or other race), and the effect on primary and secondary events was evaluated in each treatment group.

Objective evaluation of tumors took place 1 month before and every 6 months after randomization; assessment included baseline radionuclide bone scan, serum PSA level, and, if required, pelvic and abdominal computed tomography and chest X-ray. Progression was defined as the appearance of one or more new bone metastases or worsening of existing bone metastases on bone scan, the appearance of at least one new extraskelatal metastasis, or an increase by 25% or more of any existing measurable extraskelatal metastases.

Statistics

Time to progression and survival were calculated from time of randomization to time of progression or

death. Data were collected from all randomized patients and from all patient visits made by the date the last recruited patient completed 18 months of follow-up.

The relative effects of the antiandrogens were assessed using Cox's proportional hazards regression model, adjusted for covariates such as LHRHa, baseline extent of disease, and baseline ECOG status. The hazard ratios (HR), with 95% two-sided confidence intervals (CI), of bicalutamide/LHRHa to flutamide/LHRHa were calculated.

RESULTS

In all, 813 patients were randomized in the trial [16]. Of these, 404 received the bicalutamide/LHRHa combination and 409 received flutamide/LHRHa. The two patient groups were well-balanced with respect to baseline characteristics, including race and extent of disease (Table I). Each treatment group included a higher but consistent proportion of white males relative to AA males. There were approximately three times as many white as AA males in each treatment group (71% and 24% for bicalutamide/LHRHa and 72% and 22% for flutamide/LHRHa, respectively).

The effect of CAB on clinical events was assessed in the cohort as a whole at a median follow-up of 160 weeks. While overall there was a higher rate of events (progression and deaths) in AA men, the differences were not statistically significant (Table II). The incidences of disease progression or death were lower in the bicalutamide/LHRHa group compared with the flutamide/LHRHa group, resulting in HR of less than 1 (Table III), but the differences between treatment groups were not statistically significant.

In white males, there was little difference between bicalutamide/LHRHa and flutamide/LHRHa in terms of disease progression or survival, as shown by HR of 0.95 and 0.88, respectively (Table III). In AA males, there was a larger difference between treatments with respect to survival (HR of 0.79). Although this suggested a benefit for bicalutamide/LHRHa, the difference was not statistically significant, and the CI was wide (0.54–1.15). The Kaplan-Meier survival curve according to treatment and race is shown in Figure 2.

Despite the lower mean (SD) baseline value in whites, PSA levels fell by 98% from baseline to the nadir in both white and AA males (from 580 (1,368) to 11 (74) ng/ml in white males, and from 942 (1,473) to 23 (106) ng/ml in AA males).

Overall, no major tolerability differences were found during the study [16]; however, the flutamide/LHRHa combination was associated with a significantly higher frequency of diarrhea than bicalutamide/LHRHa (26% vs. 12%, $P < 0.001$). Hematuria

TABLE I. Patient Characteristics

	Number of patients			
	White		African American	
	Bicalutamide/ LHRHa	Flutamide/ LHRHa	Bicalutamide/ LHRHa	Flutamide/ LHRHa
Total number of patients	287	294	95	91
Mean age and range (years)	70 (43–91)	70 (42–93)	70 (54–86)	71 (48–88)
Extent of disease				
Minimal	157	148	42	42
Extensive	119	128	52	47
Extent not available	11	18	1	2
Metastases				
None	28	22	8	6
≤5	129	126	34	36
≥6	101	112	47	39
Superscan	18	16	5	8
Not available	11	18	1	2
Histologic differentiation				
Well	45	33	11	9
Moderate	146	145	47	43
Poor	87	101	34	37
Other	8	13	3	2
Not available	1	2	0	0

TABLE II. Number of Events Observed in 813 Patients*

	Number of events			
	Bicalutamide/LHRHa		Flutamide/LHRHa	
	White	African American	White	African American
Number of patients	287	95	294	91
Disease progression	207 (72)	65 (68)	210 (71)	71 (78)
Death	147 (51)	53 (56)	163 (55)	59 (65)

*Percentages in parentheses.

occurred significantly more frequently in the bicalutamide/LHRHa group than in the flutamide/LHRHa group (12% vs. 6%, $P = 0.007$).

Table IV shows the adverse events which occurred with a frequency greater than 10% in each treatment arm. When these results were analyzed regardless of treatment (Table V), adverse events seemed to be more frequent in white males than in AA males. Diarrhea and asthenia were numerically more common in white than in AA men, whereas anemia and hypertension were more common in AA than white males. The reason for these differences is not known.

DISCUSSION

In the present exploratory analysis involving 813 patients with advanced prostate cancer, the incidences

of disease progression and of death were lower in the bicalutamide/LHRHa group compared with the flutamide/LHRHa group, resulting in hazard ratios of less than 1, but the differences between treatment groups were not statistically significant. We observed no significant effect of race on clinical outcome, regardless of antiandrogen. Both treatments were well-tolerated, although flutamide/LHRHa was associated with a significantly higher incidence of diarrhea than bicalutamide/LHRHa (26% vs. 12%, $P < 0.001$), resulting in more withdrawals due to diarrhea in the flutamide/LHRHa group compared with the bicalutamide/LHRHa group [16].

Significant improvements in progression-free survival and survival have been demonstrated for CAB (flutamide plus leuprolide) compared with leuprolide

TABLE III. Hazard Ratios for Disease Progression and Survival by Race*

	Hazard ratio (bicalutamide + LHRHa/flutamide + LHRHa) (95% CI)		
	White (n = 581)	African American (n = 186)	Overall (n = 813)
Disease progression	0.95 (0.78–1.15)	0.89 (0.63–1.25)	0.93 (0.79–1.10)
Death	0.88 (0.70–1.11)	0.79 (0.54–1.15)	0.87 (0.72–1.05)

*HR, hazard ratio; CI, two-sided confidence interval.

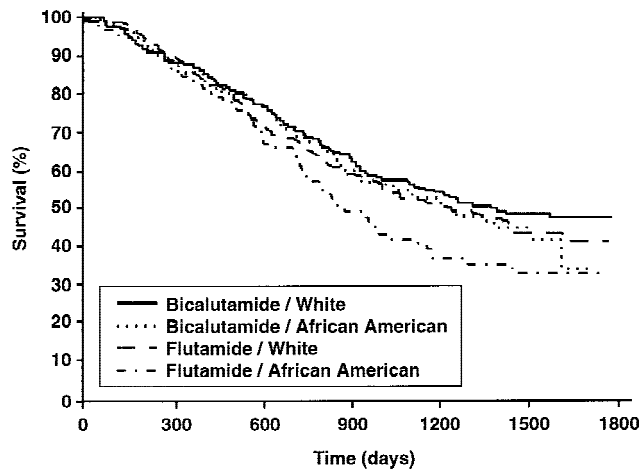


Fig. 2. Overall survival according to treatment and race.

in 617 patients with stage D₂ prostate cancer in the NCI Intergroup Study #0036 [19]. This study and the present investigation included a similar ratio of white to AA men who were well-balanced demographically. In the NCI study, the median survival of the 107 AA men was 26.4 months compared with 33.6 months in the 442 white men [15], and it was calculated that black race was a significant adverse prognostic factor in relation to survival [19]. However, it is not known if there was any difference between the two subgroups in response to CAB compared with LHRHa alone, or how many of the AA men in the NCI study had severe disease. In the present study, a higher proportion of AA men presented with extensive disease or with poorly differentiated tumors compared with white men; however, this difference may have been greater in the NCI study, which could have resulted in the significantly inferior survival of AA men in the NCI study. Any future study to compare racial differences may need to account for such baseline differences in the trial design.

Epidemiological studies confirm that there is a difference in survival between AA and Caucasian men with prostate cancer [3,4]. Other high-risk racial

groups are Hispanic American [20] and Asian American men [21]. Due to the small number of patients in these ethnic groups enrolled in our trial, treatment effects were not explored.

While there is some disagreement [22], AA men seem to have higher normal PSA levels than white men in every age group [23] and higher PSA levels at every stage of prostate cancer [10], as found in stage D₂ cancer in the present study. The higher normal PSA levels possibly indicate a higher number of undiagnosed prostate tumors in AA men than in white men, or higher PSA concentrations in AA men compared with white men [23].

It has been suggested that resources should be focused on early detection of prostate cancer in AA men, as they represent a high-risk group; however, there are controversies over this issue, including benefit and cost [24,25]. While a negative attitude to digital rectal examination among AA men does not seem to be a factor for the observed racial differences, a negative attitude towards the healthcare system has been proposed [26]. More intensive efforts to increase access to, and utilization of, healthcare resources, together with educational programs targeted at AA men, have been recommended [27].

Socioeconomic status may also be an important factor in the development of prostate cancer, but further research is needed [28]. However, even when equal access to healthcare is taken into account [6,26] or adjustment is made for socioeconomic status [27], AA men in the US still have a poorer outcome than white men.

The reasons for the poorer outcome in AA compared with white men with prostate cancer are not well-defined; however, the approach to tumor detection and management may need to be reconsidered. In the previous NCI study, treatment with CAB resulted in longer survival in the white subgroup than in the AA subgroup [15]. Although in this present study the incidence of disease progression or death was lower in

TABLE IV. Adverse Events in Racial Subgroups, Regardless of Causality*

	White		African American	
	Bicalutamide/ LHRHa	Flutamide/ LHRHa	Bicalutamide/ LHRHa	Flutamide/ LHRHa
Hot flashes	162 (57)	168 (58)	42 (45)	42 (46)
Pain	105 (37)	94 (32)	26 (28)	23 (25)
Diarrhea	41 (14)	92 (32)	6 (6)	13 (14)
Back pain	77 (27)	80 (27)	21 (22)	17 (19)
Asthenia	75 (26)	70 (24)	10 (11)	13 (14)
Pelvic pain	66 (23)	55 (19)	13 (14)	17 (19)
Constipation	65 (23)	51 (17)	14 (15)	5 (5)
Infection	48 (17)	49 (17)	21 (22)	7 (8)
Nausea	46 (16)	49 (17)	14 (15)	12 (13)
Anemia	26 (9)	36 (12)	16 (17)	10 (11)
Nocturia	42 (15)	43 (15)	6 (6)	8 (9)
Dyspnea	37 (13)	24 (8)	13 (14)	8 (9)
Peripheral edema	40 (14)	33 (11)	10 (11)	12 (13)
Hypertension	25 (9)	16 (5)	7 (7)	5 (5)
Hematuria	36 (13)	21 (7)	7 (7)	8 (9)
Abdominal pain	32 (11)	36 (12)	11 (12)	10 (11)
Increased liver function tests	19 (7)	34 (12)	8 (9)	7 (8)
Bone pain	29 (10)	32 (11)	7 (7)	7 (8)

*Events occurring in >10% of patients. Percentages in parentheses.

white males compared with AA males, the difference was not statistically significant.

TABLE V. Overall Incidence of Adverse Events (%) by Race, Regardless of Treatment Group (Events Occurring With a Frequency >10%)

	Race	
	White (n = 581)	African American (n = 186)
Hot flashes	330 (57)	84 (45)
Pain	199 (34)	49 (26)
Diarrhea	133 (23)	19 (10)
Back pain	157 (27)	38 (20)
Asthenia	145 (25)	23 (12)
Pelvic pain	121 (21)	26 (14)
Constipation	116 (20)	31 (17)
Infection	97 (17)	26 (14)
Nausea	95 (16)	21 (11)
Anemia	62 (11)	28 (15)
Nocturia	85 (15)	16 (9)
Dyspnea	61 (11)	21 (11)
Peripheral edema	73 (13)	18 (10)
Hypertension	41 (7)	19 (10)
Hematuria	57 (10)	12 (6)
Abdominal pain	68 (12)	19 (10)
Increased liver function tests	53 (9)	18 (10)
Bone pain	61 (11)	14 (8)

CONCLUSIONS

In conclusion, we were unable to find any marked effect of race on clinical outcome in patients receiving CAB, regardless of antiandrogen. The combination of bicalutamide/LHRHa resulted in slightly longer time to progression and survival time in both white and AA males than treatment with flutamide/LHRHa, but the differences between treatment groups for either endpoint and for both races were not statistically significant. Therefore, similar treatment benefits are to be expected with CAB in either race.

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