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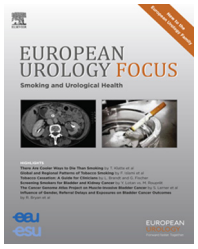

Platinum Priority – Prostate Cancer
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Individual Patient Data Analysis of Randomized Clinical Trials: Impact of Black Race on Castration-resistant Prostate Cancer Outcomes

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Abstract

Background: Population data suggest that black men have a higher risk of dying from prostate cancer (PCa) than other racial ethnicities.
Objective: To examine the impact of black race on progression-free survival (PFS) and overall survival (OS) among men with metastatic castration-resistant PCa (mCRPC) enrolled in randomized controlled trials (RCTs).
Design, setting, and participants: A pooled analysis was performed on individual patient data from five modern PCa RCTs available from Project Data Sphere.
Outcome measurements and statistical analysis: Adjusted hazard ratios (HRs) were calculated to compare black and white race regarding PFS and OS. Subgroup analyses of mCRPC trials were performed based on the control arm treatments (mitoxantrone or docetaxel). Relevant covariates were used for adjustment in all analyses.
Results and limitations: A total of 1613 patients were included; 77 were black (4.7%). No significant differences between black and white men's baseline characteristics were noted regarding age, performance status, or pretreatment prostate-specific antigen. The pooled HRs for black race for OS and PFS were 1.01 (95% confidence interval [CI], 0.73–1.35) and 1.29 (95% CI, 0.95–1.76), respectively. The median OS for black compared with white men was 254 versus 238 d ($p = 0.92$), respectively, with mitoxantrone and 581 versus 546 d ($p = 0.53$), respectively, with docetaxel. The primary limitation was the relatively small number of black men enrolled in mCRPC clinical trials.
Conclusions: In the context of RCTs, in which patients receive generally uniform treatment, a significant difference in OS for black men could not be detected in mCRPC. Black men continue to be dramatically underrepresented in RCTs, and efforts are needed to increase minority accrual to these trials.
Patient summary: We looked at the outcomes of men treated in randomized controlled trials to determine the impact of black race on survival. We found that in the context of modern clinical trials, there does not appear to be a significant difference in survival between black and white races; however, a trend for greater progression in black men was noted.

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1. Introduction

A disparity is defined as "a great difference," and within the field of oncology, the disparity seen in prostate cancer (PCa) outcomes across racial ethnicities is exactly that, a great difference. Of the 319 million people in the United States, approximately 13% (42 million) are black; however, among the 220 000 men diagnosed with PCa each year in the United States, approximately 25% (56 000) are black [1]. The likelihood of dying from PCa is 2.5 fold higher in black men compared with white men [1]. The etiology of this difference is multifactorial, complex, and under active investigation [2,3].

Multiple societal-level factors clearly exist that affect oncologic outcomes for racial minorities. These include socioeconomic, geographic, and educational disparities, among others, that ultimately have been linked to differences in cancer prevention, incidence, screening, diagnosis, treatment, and access to and enrollment in clinical trials [3]. The increased incidence of advanced PCa among Hispanic men, for example, appears to be related principally to barriers in health care access [4]. In contrast, studies to date for black men have not been able to demonstrate clearly that societal-level factors account for the entirety of the disparate PCa survival outcomes, suggesting the potential for intrinsic biological differences.

One potential method to better delineate the impact of social and biological differences would be to evaluate the impact of race on outcomes from men treated on randomized controlled trials (RCTs). Enrollment in an RCT would intrinsically reduce the impact of societal disparities because issues relating to staging, treatment, and follow-up are more standardized. However, of patients enrolled in recent practice-changing RCTs of castration-resistant PCa (CRPC), only 3.3% were black men [5]; therefore, comparison of outcomes by race in any single trial is generally uninformative and not performed. We pooled individual patient data from five RCTs to investigate the impact of black race on overall survival (OS) in men with mCRPC.

2. Methods

2.1. Study selection and data acquisition

Project Data Sphere was leveraged to obtain deidentified individual patient-level data from the comparator arms (ie, control arms) of phase 3 RCTs (Project Data Sphere is an initiative to provide public access to individual patient data from control arms of RCTs across numerous cancer types from industry and academia). The subject of the included trials was required to be PCa within the mCRPC disease state. Trials were excluded if they did not investigate PCa, did not report progression-free survival (PFS) or OS, or if no information on race was provided. Five clinical trials were included for analysis. Trials were conducted in both the United States and in Europe. Specific eligibility criteria for each trial can be found in their respective published articles [6–10]. Nonwhite and nonblack participants were excluded from all analyses.

2.2. Study design and end point definitions

This study is a pooled analysis of prospective RCTs. The primary end point was OS; the secondary end point was PFS. Preplanned subgroup analyses included combinations of like control arm treatments and disease state. Five trials were conducted in mCRPC patients: two treated with mitoxantrone, two treated with docetaxel, and the fifth was with prednisone alone and not included in the subgroup analyses (Table 1).

All studies were included in the OS pooled analyses. OS was defined from the date of randomization to the date of death due to all causes. The sunitinib trial did not report PFS and was excluded from the PFS analyses. Definitions of PFS varied by clinical trial, and the trial definition of PFS was used (Table 2).

2.3. Statistical analysis

Categorical variables are listed as frequencies and percentages, and continuous variables are listed as means with 95% confidence intervals (CIs) or medians with interquartile ranges. To compare baseline characteristics between black and white patients, the chi-square test was used for categorical variables and the Wilcoxon rank sum test or Student t test for continuous variables. All analyses compared the outcome for black versus white men. Other racial ethnicities were excluded from analyses. In each trial, we used Cox regression models to estimate the adjusted hazard ratios (HRs) of OS and PFS comparing black versus white after adjusting for age, prostate-specific antigen (PSA) level, and Eastern Cooperative Oncology Group (ECOG) performance score (if available). For meta-analysis, both a fixed-effects model and a random-effects model were considered. The extent of heterogeneity was minimal, thus a fixed-effects model was reported for all analyses. Extent of heterogeneity between studies was performed with the Cochran Q test and an I^2 test. Subgroup analyses were performed using the Kaplan-Meier method and compared using a log-rank test. Adjustments were made for each trial using the covariates race, age, ECOG performance status, and PSA (Table 1). Statistical analyses were performed using SAS software v.9.4 (SAS Institute Inc., Cary, NC, USA), and forest plots were plotted with Stata software v.13.1 (StataCorp, College Station, TX, USA). We used a two-sided p value <0.05 in all analyses as criteria for statistical significance.

3. Results

3.1. Patient and study characteristics

A total of 1613 patients of either black or white race were identified from five randomized PCa trials (Fig. 1). From the entire cohort, 77 men (4.7%) were of black race. The mean age was similar across trials (range: 66.7–67.8 yr). The median follow-up ranged from 209 to 637 d; the median PSA ranged from 76 to 217.5 ng/ml.

No significant differences between black and white men's baseline characteristics were noted in each trial with regard to age (p values: 0.31–0.59), ECOG performance status (p values: 0.30–0.87), or pretreatment PSA (p values: 0.10–0.67). However, the median baseline PSA was higher in black patients compared with white patients in each trial, although this difference was not statistically significant (Table 3).

3.2. Primary and secondary end points

The pooled HR for black race for OS was 1.01 (95% CI, 0.73–1.35) (Fig. 2a). There were no significant differences in OS across any individual trial or the pooled data set. The pooled HR for black race for PFS was 1.29 (95% CI, 0.95–1.76)

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