Multi-institutional Analysis of the Clinical and Genomic Characteristics of Black Patients with Metastatic Hormone-Sensitive Prostate Cancer

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Abstract

Background: The outcomes of metastatic hormone-sensitive prostate cancer (mHSPC) have significantly improved through treatment intensification, yet Black representation in those studies is suboptimal.

Methods: A multi-institutional, retrospective analysis of Black men with mHSPC was conducted, focusing on baseline demographics, treatment patterns, genomic profiles, clinical outcomes including prostate-specific antigen response, time to castrate-resistant prostate cancer (CRPC), and subsequent treatments.

Results: A total of 107 patients, median age 64 years, 62% with de novo metastases at diagnosis and 64% with high-volume disease, were included. Twenty-nine patients (27%) were treated with androgen deprivation therapy (ADT) with and without first generation anti-androgens, while 20%, 38% and 5% received chemotherapy, abiraterone, and enzalutamide, respectively. At time of data cut-off, 57 (54%) patients had developed CRPC, with a median time to CRPC of 25.4 months (95% CI 20.3-30.4). The median time to CRPC was 46.3 months (18.9-73.7) and 23.4 months (18.6-28.2) for patients who received ADT with or without first-generation anti-androgens and treatment intensification, respectively. The 2-year survival rate was 93.3%, and estimated median overall survival of was 74.9 months (95% CI, 68.7-81.0). Most patients (90%) underwent germline testing; the most frequent known alterations were found within the DNA repair group of genes. Somatic testing revealed pathogenic alterations of interest, notably TP53 (24%) and CDK12 (12%).

Conclusion: In our cohort, Black men with mHSPC presented with a high proportion of de novo metastases and high-volume disease. Treatment outcomes were very favorable with ADT-based regimens. The genomic landscape suggests different molecular profile relative to White patients with potential therapeutic implications.

Key words: prostatic neoplasms; androgen deprivation therapy; health care disparities; African Americans, steroid synthesis inhibitors, DNA sequence analysis.

Implications for Practice

Racial disparities unfortunately play a role in clinical trial enrollment, treatment implications, and clinical outcomes between Black and White patients with prostate cancer. In this multi-institutional study of Black patients with hormone-sensitive prostate cancer, the observed clinical outcomes were very favorable with androgen deprivation therapy-based regimens. The genomic testing revealed different germline and somatic mutations with significant impact in the management of these patients.
Introduction

The incidence of metastatic prostate cancer in the United States has been rising, from 4% in 2003 to 8% in 2017. Approximately 7% of patients with prostate cancer present with de novo distant metastases, and up to 30% of patients initially diagnosed with and treated for localized prostate cancer develop metastases. With more treatment options now available, the 5-year survival rate of metastatic prostate cancer has slightly increased in recent decades but still hovers around 30%. Virtually all patients with metastatic disease initially respond to castration; however, progression is inevitable, leading to metastatic castrate-resistant prostate cancer (CRPC).

Until 2015, the standard treatment for metastatic hormone-sensitive prostate cancer (mHSPC) was based on castration alone or combined with first-generation anti-androgens. Since then, the standard of care has rapidly evolved to include novel hormonal therapies or chemotherapy based on the positive results from phase III trials. When combined with androgen deprivation therapy (ADT), docetaxel, abiraterone, enzalutamide, and apalutamide improved all efficacy endpoints irrespective of tumor volume. However, Black patient representation in these studies was very low, ranging from 1.4% to 9.6% of enrolled participants. This underrepresentation is ubiquitous across mainstream prostate cancer trials, as shown in an analysis of 72 global phases 3 and 4 trials involving prostate cancer, in which an astounding 809,978 of 544,002 participants (96.0%) with available race data were White. This discrepancy is more concerning given that compared with non-Hispanic White men, non-Hispanic Black men have a much higher chance of developing prostate cancer and dying from prostate cancer. Socioeconomic factors, access to health care, baseline medical conditions, and underlying genetic factors may all play a role. Nevertheless, Black men with low-risk prostate cancer were found to have a higher risk of dying compared to non-Black men with similar disease burden. Intriguingly, when comparing CRPC treatment outcomes by race, Black patients may have better outcomes with docetaxel, radium-223, and sipuleucel-T. The Black patient underrepresentation along with these paradoxical findings warrants further investigation. Recent advancements to improve the accessibility of germline and somatic sequencing provide a unique opportunity to evaluate the potential role of genetics in these disparities. Our group with collaborators has previously revealed differences in the tumor genomic profile of Black versus White men with advanced prostate cancer.

This multi-institutional, retrospective study aimed to report clinical and treatment outcomes and provide additional insights on the somatic and germline profile of Black men with mHSPC.

Methods

Study Design and Patient Population

A retrospective study was conducted with data from 7 academic institutions across 7 states treating Black men with mHSPC, with year of stage 4 diagnosis ranging from 2008 to 2021 (with 87% of patients diagnosed with stage 4 disease in the year 2015 or later). Participants included male patients who self-identified as Black, with known mHSPC, for whom somatic and/or germline genome sequence data were available.

Patients were divided into 2 main treatment groups: ADT ± first-generation anti-androgen and treatment intensification. Treatment intensification included ADT plus chemotherapy and/or a novel hormonal therapy such as abiraterone acetate, enzalutamide, and/or apalutamide.

Somatic testing was gathered using Guardant360 (Redwood City, CA), and germline data was gathered primarily using Invitae Multi-Cancer Panel (San Francisco, CA). Other sources of germline data included Common Hereditary Cancers Panel (San Francisco, CA), Prostate Cancer Panel (Gaithersburg, MD), and Ambry Genetics/CancerNext + RNA (Aliso Viejo, CA). All genomic tests were obtained as system on chip through Clinical Laboratory Improvement Amendments certified labs.

The primary objective was to describe the baseline patient and disease characteristics and treatment patterns of mHSPC Black male patients. Variables of interest included Gleason score, pathology, prostate-specific antigen (PSA) level, age at diagnosis, and disease volume at time of stage 4 diagnosis. “Disease volume” was defined by CHAARTED criteria (presence of 4 or more bone metastases with at least one outside the pelvis and spine, and/or visceral metastases). “High-risk” status was defined by LATITUDE criteria (presence of at least 2 of the following: 3 or more bone metastases, visceral metastases, Gleason 8 or higher). Treatment for mHSPC and subsequent lines of treatment for CRPC (when available) were captured.

Secondary objectives included time to CRPC, overall survival, PSA response, as well as the germline and somatic data. Time to CRPC was defined as the time to PSA progression, radiographic evidence of disease progression, or time to clinical progression per local investigator’s assessment. Overall survival was calculated using time from diagnosis to death or last follow-up. Undetectable PSA was defined as <0.1 ng/mL. For germline data, pathogenic alterations and variants of uncertain significance (VUS) were collected. Somatic data were examined for pathogenic alterations (both the gene and the genomic alteration). Data were also collected relating to mortality, first-line treatment and number of subsequent treatments for CRPC, and the need for palliative radiation to metastatic sites.

Statistical Analysis

Microsoft Excel and SPSS (IBM Corp©, version 23.0.0.0) were used to calculate summary statistics for baseline characteristics, treatment, and genetic data. Time-to-event analysis was calculated using the Kaplan-Meier estimator. PSA progression, scan progression, or clinical progression, time to CRPC, and survival data were calculated based on dates given by the collecting site.

Results

Baseline Characteristics

A total of 107 patients (median age 64 years, range 41-84) were included in the final analysis. The median follow-up time from stage 4 diagnosis was 2.2 years (IQR 1.5 years to 3.6 years). Sixty-three patients (59%) had Gleason 8-10, 66 patients (62%) had newly diagnosed metastatic disease, and the median initial PSA at diagnosis was 97.8 ng/mL (range 0.9-650). Sixty-nine patients (66%) had high-volume disease based on CHAARTED criteria, including 17 (16%) of patients with visceral disease and 60 patients (58%) with...
Clinical Outcomes
We evaluated the clinical outcomes on 106 patients (1 patient was excluded due to missing data). Overall, 27% of patients (N = 29) were treated with ADT with or without first-generation anti-androgens; most of the cases (88%) were prior to the year 2015. Treatment intensification with either chemotherapy or novel hormonal therapies was used in most cases (73%, N = 77); 20% received a chemotherapy-based regimen. Eight patients received triplet therapy (8%) with ADT plus docetaxel and abiraterone (N = 2) or enzalutamide (N = 6), and 1 patient was treated with carboplatin plus etoposide plus ADT. The treatment intensification cohort had a significantly higher number of patients with de novo metastatic disease (P = .038), a numerically higher number of high-volume disease (P = .094) and higher initial median PSA at time of advanced disease (PSA = 435 vs 64.8 ng/mL) compared with the ADT cohort.

Eleven patients (10%) received radiation to the prostate gland after diagnosis of stage 4 disease, and 5 patients had low-volume disease. Undetectable PSA was achieved in 42 patients (40%), more commonly with abiraterone acetate (N = 24/40) and enzalutamide (N = 3/5). At time of cut-off, 57 patients (54%) developed CRPC, and the median time to CRPC was 25.3 months (95% CI, 21.4-29.3). Patients treated with ADT with or without first-generation anti-androgens had a median time of CRPC of 46.3 months (18.9-73.7). Those in the ADT ± anti-androgen group were less likely to present with de novo disease than patients in the treatment intensification group (P = .006) but not statistically less likely to have high-risk disease (P = .527) or high-volume disease (P = .102).

Patients with either high-volume disease (CHAARTED criteria), with treatment intensification, or with detectable nadir PSA while on HSPC therapy were associated with a significantly shorter time to CRPC (18.9 vs 99.6 months, P < .001; 23.3 vs 46.3 months, P = .031; 13.5 vs 46.3 months, P < .001, respectively). Patients with visceral disease also had shorter time to CRPC although this was not statistically significant (28.0 vs 19.8 months, P = .079). Neither newly diagnosed metastatic disease (22.6 vs 33.1 months, P = .096) nor Gleason score 8-10 (24.0 vs 26.0 months, P = NS) were associated with shorter time to CRPC.

Subsequent Treatments for CRPC and Overall Survival
Among the 55 patients who developed CRPC with data available, the subsequent therapy was most commonly abiraterone acetate (38%), followed by enzalutamide (27%), chemotherapy (7%), Radium-223 (7%), and no subsequent treatment (7%). Of the 17 patients who underwent treatment with abiraterone originally, 10 (59%) were treated with another novel hormonal therapy in the CRPC stage. Of these 10, half were continued on a form of abiraterone and half were switched to enzalutamide. Of the 4 patients who underwent treatment with ADT + NHT + chemotherapy in the CRPC stage, 2 were switched to an NHT. In both cases, patients went from ADT + Enzalutamide + chemotherapy in the HSPC stage to Abiraterone in the CRPC stage. Patients underwent a median of 2 lines (range 0-7) of treatment for CRPC (Fig. 1). The 2-year survival rate from time of initial diagnosis of mHSPC was 93.3%. The estimated median overall survival (OS) in this cohort was 74.9 months (95% CI, 68.7-81.0; Table 2).

Genomic Germline and Somatic Data
Most patients (78%) had genetic testing done in the HSPC stage, a median of 14 days after stage 4 diagnosis (range 0 days and 11 years). Germline data were available for 96 patients (90%). Among these, 12% tested positive for at least 1 pathogenic/likely pathogenic mutation in a prostate cancer genetic panel. BRCA2 was found most frequently (N = 3) followed by BRCA1 (N = 2) and PALB2 (N = 2). Other pathogenic mutations included RAD54L, PM52, HOXB13, FANCA, and APC (Fig. 2). Among VUS, the most frequently seen were in RECQL4, ATM, and POLE (N = 6). Additionally, somatic testing was available for 50 patients (47%) after excluding 2 due to insufficient quality. Next
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The generation sequencing results included tissue sample (40%), ctDNA (52%), and both in 3 patients. This most often revealed at least one pathogenic genomic alteration (median = 1), most commonly $TP53$ (24%), $CDK12$ (12%), $TMPRSS2-ERG$ fusion (10%), and $SPOP$ (8%) (Table 3). Patients with $TP53$ mutated tumors were associated with a higher number of de novo disease, high-volume disease, development of CRPC, and inferior PSA response rate, although without statistical significance (Table 4).

Discussion

This study evaluated the outcomes of Black patients with mHSPC from different academic institutions with an interest in racial disparities. This study focused exclusively on patients with available genomic data because we were interested in assessing the molecular profile in this setting. To our knowledge, this is the largest cohort of Black patients reported since the incorporation of chemotherapy and novel hormonal
therapies as the standard of care for patients with mHSPC. We reported favorable clinical outcomes in terms of time to CRPC and OS including patients treated with ADT with or without first generation anti-androgens, and we noted a heterogenous management of this patient population in terms of systemic therapies used and the type and panel of the genomic testing performed.

In mHSPC, Black men represented <5% of all patients enrolled in the randomized phase III trials in this setting, except for the SWOG S1216 study which enrolled 10% of Black patients.10,16-18,27 When compared with the trial population included in those studies, our cohort consisted of patients with a lower median age and similar rate of Gleason score 8-10 at time of mHSPC, but with a higher proportion of high-volume disease, an increased number of visceral metastases, and a higher initial PSA at time of stage 4.10,12,14-16,27

In our dataset, only a small fraction of patients (19%) who were treated for mHSPC after 2015 were offered ADT alone. However, real-world data suggest the opposite in that most patients with mHSPC—and more Black than White patients—are currently receiving ADT regimens without treatment intensification.28 Of note, the time to CRPC of almost 4 years in this ADT subgroup was approximately twice as long as the observed progression-free survival in the control arms of all phase III trials.10-16,27 This may be skewed as patients with recurrent (non-de novo) were overrepresented in this cohort. The time to CRPC in this study was defined by PSA, radiographic, or clinical progression. Most patients met serologic criteria, which typically precedes the time of radiographic progression in several months.29 Thus, this difference in time to CRPC seems to suggest that Black patients achieve better treatment outcomes, requiring further validation.

Notably, the median time to CRPC was much shorter in patients who received treatment intensification compared with ADT with and without first-generation anti-androgen, which might be explained by the over-representation of high-volume disease in this first group. In fact, the factors associated with shorter time to CRPC such as disease volume and detectable nadir PSA have been reported in previous studies and support these findings.30-34 Additionally, the differences

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Table 3. Somatic alterations in mHSPC patients with somatic available testing performed (N = 50), as well as frequency and assay used.

| Somatic alteration | N (%) | Next-generation sequencing assay (N) |
|--------------------|-------|-------------------------------------|
| None               | 14 (28%) | Tissue (4); ctDNA (7); unknown (1) |
| TP53               |       |                                     |
| Q167: splice site SNV; R267fs; c.578A>G p.H193R; c.743G>A; p.R248Q; R175H; N239S + R248Q; H179Q; N131 del; R342; K132R; 1 unspecified |
| CDK12              | 6 (12%) | Tissue (3); ctDNA (2); Both (1)     |
| S133fs+p.S133fs+p.D121fs+p.M972fs; c.1086T>G p.Y362; 162delG+1066A>T; 2 unspecified |
| TMPRSS2            | 5 (10%) | Tissue (3); ctDNA (1); Both (1)     |
| 4 ERG-fusion; 1 unspecified |
| SPOP               | 4 (8%)  | Tissue (4)                           |
| p.F133L; p.F125V; c.305T>G p.F102G; W131R |
| AR                 | 3 (6%)  | Tissue (2); ctDNA (1)                |
| 1 amplification; 2 AR-V7 |
| CTNNB1             | 3 (6%)  | Tissue (1); ctDNA (2)                |
| D32Y; p.D32N; S45P-subclonal |
| PIK3CA (H1047R; amplification) | 2 (4%) | Tissue (1); ctDNA (1) |
| CCNE1 amplification | 2 (4%) | ctDNA (2)                             |
| PTEN (130Q; deletion) | 2 (4%) | Tissue (1); ctDNA (1)                |
| TMB (high)         | 1 (2%)  | Tissue (1)                           |

ctDNA (circulating tumor DNA): Guardant 360, Strata; Tissue: Foundation One, Caris. TMB (tumor mutational burden); high defined as ≥10 Mb.

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Figure 2. Pathogenic and likely pathogenic germline mutations (N = 12) in mHSPC patients with available germline test (N = 96).
observed by type of agent (chemotherapy vs novel hormonal therapy) seem to favor the addition of a novel hormonal agent in this setting, but more studies are needed to confirm these findings.\textsuperscript{33,36}

The access to emergent life-prolonging therapies during advanced disease significantly impacts the outcomes of prostate cancer patients. We observed an encouraging 2-year OS (>90%) that compares favorably with trial data with any combination regimen in this space. Additionally, we confirmed the access to subsequent effective and emergent therapies of patients who progressed to CRPC. Considering the ADT-only subgroup of patients, the relatively fewer number of patients with newly diagnosed and low volume disease might help to explain the long time to CRPC of almost 4 years. A longer follow-up is required to confirm these encouraging results.

Almost all our patients (90%) had germline testing. Germline mutations were found in a subset of patients, with many that involved DNA repair genes; this has also been previously reported.\textsuperscript{25} The BRCA2 germline mutation was found to be the most prevalent DNA repair gene alteration, which was similar to a large germline study involving mostly White men with metastatic prostate cancer.\textsuperscript{37} Poly(ADP-ribose) polymerase inhibitors have demonstrated success in treating patients with cancer with germline BRCA mutations, with olaparib and rucaparib now FDA-approved treatments in the setting of CRPC with these mutations.\textsuperscript{38,39} Black patients with these germline mutations discovered in the mHSPC setting may warrant targeted therapy, and there is an ongoing study testing this hypothesis.\textsuperscript{40}

Fewer patients had somatic testing done, using 4 different assays. Liquid biopsy was used more frequently than tissue-based sequencing test, which is often due to the lack of tissue samples available. The relatively low number of genomic alterations, including in the AR gene, is consistent with low exposure to systemic therapies including castration.\textsuperscript{41} In this sample, some patients underwent genetic testing before exposure to systemic therapies, but others received testing later during treatment. The high frequency of CDK12 genomic alterations is again confirmed in this patient population as shown by our group recently,\textsuperscript{42} with prognostic and therapeutic implications at time of progression to CRPC.\textsuperscript{43} TP53 was the most common somatic alteration detected; this is consistent with low \(S\) somatic alteration though without statistical significance.

Published studies have revealed that Black patients are diagnosed at a younger age, have more aggressive disease, yet clinical outcomes in this cohort do not appear to be inferior.\textsuperscript{44-47} Prospective studies with approved therapies for metastatic disease have suggested Black patients may respond better than White patients, as suggested with docetaxel (meta-analysis of nine phase II/III trials)\textsuperscript{22} and sipuleucel-T (PROCEDURE, NCT01306890).\textsuperscript{44}

These findings emphasize the increasing effort to investigate racial disparities in prostate cancer and several clinical trials and registries are actively enrolling Black patients. As an example, the PANTHER trial (NCT03098836) is testing the combination of abiraterone acetate with apalutamide (meta-analysis of nine phase II/III trials)\textsuperscript{22} and sipuleucel-T (PROCEDURE, NCT01306890).\textsuperscript{44}

The limitations of this study include its retrospective nature and the relative short follow-up to explore treatment sequencing and outcomes at time of progression to CRPC. There was a selection bias since all patients were included from academic cancer centers in the US, most of which are in urban areas which may not be generalizable to patients in more rural environments, or environments outside of the USA. Furthermore, this study identified patients with genetic testing data available (despite the short interval between the diagnosis of stage 4 disease and genetic test) which might have contributed to the selection bias. Although the majority of patients received genetic testing close to initial stage 4 diagnosis, not every patient received somatic testing at the same time; therefore, there is potential immortal time bias as patients with less severe disease may have lived longer and been able to receive somatic testing later in the disease course. African ancestry was not confirmed with genetic testing, which may create heterogeneity of the genomic samples and therefore skew or dilute the genetic results. Despite being one of the largest cohorts in this patient population, the genomic data are limited by the scope of and differences between the gene panels of choice, which limits definitive conclusions.

Conclusions

In this cohort of Black patients with HSPC, the observed clinical outcomes were very favorable with ADT-based regimens. The genomic testing revealed different germline and somatic mutational with significant impact in the management of these patients.
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Conflict of Interest
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Data Availability Statement
The data underlying this article will be shared on reasonable request to the corresponding author.

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