Original Article

Factors Influencing Treatment of Veterans With Advanced Prostate Cancer

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BACKGROUND: Treatments for metastatic castration-resistant prostate cancer (CRPC) differ in toxicity, administration, and evidence. In this study, clinical and nonclinical factors associated with the first-line treatment for CRPC in a national delivery system were evaluated. **METHODS:** National electronic laboratory and clinical data from the Veterans Health Administration were used to identify patients with CRPC (ie, rising prostate-specific antigen [PSA] on androgen deprivation) who received abiraterone, enzalutamide, docetaxel, or ketoconazole from 2010 through 2017. It was determined whether clinical (eg, PSA) and nonclinical factors (eg, race, facility) were associated with the first-line treatment selection using multilevel, multinomial logistic regression. The average marginal effects (AMEs) were calculated of patient, disease, and facility characteristics on ketoconazole versus more appropriate CRPC therapy. **RESULTS:** There were 4998 patients identified with CRPC who received first-line ketoconazole, docetaxel, abiraterone, or enzalutamide. After adjustment, increasing age was associated with receipt of abiraterone (adjusted odds ratio [aOR], 1.07; 95% credible interval [CrI], 1.06-1.09) or enzalutamide (aOR, 1.10; 95% CrI, 1.08-1.11) versus docetaxel. Greater preexisting comorbidity was associated with enzalutamide versus abiraterone (aOR, 1.53; 95% CrI, 1.23-1.91). Patients with higher PSA values at the start of treatment were more likely to receive docetaxel than oral agents and less likely to receive ketoconazole than other oral agents. African American men were more likely to receive ketoconazole than abiraterone, enzalutamide, or docetaxel (AME, 2.8%; 95% CI, 0.7%-4.9%). This effect was attenuated when adjusting for facility characteristics (AME, 1.9%; 95% CI, −0.4% to 4.1%). **CONCLUSIONS:** Clinical factors had an expected effect on the first-line treatment selection. Race may be associated with the receipt of a guideline-discordant first-line treatment. ***Cancer*** **2021;127:2311-2318**.

KEYWORDS: care delivery, novel agents, prostate cancer, variation, veterans.

INTRODUCTION

Prostate cancer is a leading cause of cancer death in men in the United States and the most common nonskin malignancy among US Veterans.[1] Several treatment options exist for men with metastatic castration-resistant prostate cancer (CRPC), including chemotherapy (mitoxantrone, docetaxel, and cabazitaxel), oral androgen inhibitors (ketoconazole, abiraterone, and enzalutamide), immunotherapy (sipuleucel-T), and a radiopharmaceutical (radium-223). Each varies in side-effect profile, mechanism of action, and resource use. Although most improve survival and palliate symptoms for patients with metastatic CRPC, mitoxantrone and ketoconazole are considered palliative only and thus are not generally used as a first-line treatment.[2-10]

The extent to which clinical and nonclinical factors impact variation in these treatments has implications for quality and consistency of care. There are some studies that show age, income, and region of the country may impact treatment patterns for these expensive drugs among commercially insured patients.[11-13] However, claims-based studies have limited disease-specific information because they lack laboratory or imaging results and thus cannot adjust for disease status or delineate castration-resistant from castration-sensitive disease. We also have limited understanding of racial differences in the treatment of advanced prostate cancer as African American men are underrepresented in population-based studies and account for only 6% of clinical trial enrollment.[12] A better understanding of the contributions of clinical and nonclinical factors in CRPC may guide priorities for clinical quality improvement.

In this context, we used the Veterans Health Administration (VA) national electronic laboratory and clinical data infrastructure to examine CRPC treatment patterns among a diverse group of men with differing clinical and nonclinical factors. Importantly, the proportion of Veterans who are African American is higher than the general

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population, allowing us to better illuminate the implications of race on CRPC treatment patterns within a national system.

This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for cohort studies.[14] This study was approved by the Veterans Affairs Ann Arbor Healthcare System Internal Review Board.

MATERIALS AND METHODS

Cohort Identification

Using the VA Corporate Data Warehouse, consisting of aggregated medical record data from 130 facilities, we identified men with a diagnosis of prostate cancer using *International Classification of Diseases, Ninth Revision* (*ICD-9*) code 185 for 2010 through 2015, and *ICD-10* code C61 for 2016 and 2017. Using pharmacy claims, we identified men with prostate cancer who received at least 1 of 8 medications used for CRPC treatment during this period: mitoxantrone, ketoconazole, docetaxel, cabazitaxel, sipuleucel-T, abiraterone, enzalutamide, or radium-223. Because some patients enroll in the VA system while already receiving CRPC treatment, we further restricted the cohort to men confirmed to be receiving their prostate cancer care (ie, androgen-deprivation therapy [ADT]) within the VA system.

To ensure patients were castration-resistant, we required patients to be receiving ADT for at least 6 months before first therapy and to have a rising PSA while receiving ADT. Identifying castration-resistance has been challenging in claims data because ICD codes do not specify castration-sensitivity or resistance; thus, our utilization of PSA values allowed us to be confident in the identification of men with CRPC. ADT was defined as at least 2 injections of a gonadotropin-releasing hormone analogue within the 8 months before receipt of the first CRPC treatment or an orchiectomy in the prior 12 months. Medications were identified using inpatient and outpatient pharmacy data, the Healthcare Common Procedure Coding System, and the *Current Procedural Terminology* codes. Finally, because only 29 patients (0.6%) received cabazitaxel, mitoxantrone, sipuleucel-T, or radium-223 as the first-line CRPC treatment, we excluded these patients in the final analysis. Figure 1 illustrates the development of the final cohort.

Exposure

By the rigorous approach detailed above to ensure patients had castration-resistant disease, our primary exposure was the first-line therapy for CRPC. The first-line CRPC treatment is generally the most effective, given the relative naiveté of CRPC.

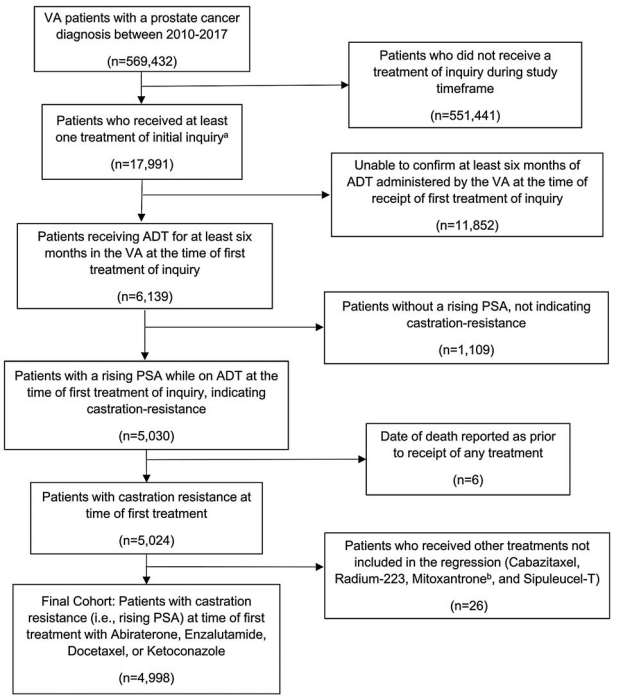

Figure 1. Final cohort of Veterans with castration-resistant prostate cancer. ADT indicates androgen-deprivation therapy; PSA, prostate specific antigen; VA, Veterans Health Administration. [a]Treatment of inquiry: abiraterone, cabazitaxel, docetaxel, enzalutamide, ketoconazole, mitoxantrone, radium-223, sipuleucel-T. [b]Mitoxantrone: No patients received mitoxantrone as a first-line treatment of inquiry

Clinical and Nonclinical Factors

To determine nonclinical factors associated with first-line treatments, we collected information on race, year of treatment, and the facility where the patient was treated. Race was self-reported. Prior work among commercially insured patients showed African American men may be less likely to receive docetaxel than abiraterone or enzalutamide.[12] The year of treatment was assigned based on the first administration of a treatment of inquiry. We expected patients would receive more docetaxel and ketoconazole in the earlier years of study, with an increasing use of abiraterone and enzalutamide in later years as they were approved midway through data collection.[11] Patients were assigned to a facility based on where the patient's first treatment was dispensed. The VA is divided into 130 health systems over 18 regional networks. We identified workforce capacity at the facility as the ratio of clinical full-time equivalent units of physicians in a specialty clinic

divided by the total number of patients in that specialty clinic. We expected patients treated in facilities with a lower workforce capacity would use more ketoconazole or docetaxel and have less access to the novel oral therapies abiraterone and enzalutamide.

The clinical factors we expected to affect CRPC treatment selection included age, Charlson Comorbidity Index, and PSA indicators of cancer severity. We used the patient's age at the time of the first-line treatment initiation. Comorbidities were determined from those reported within the year before the start of the first treatment. We expected patients who were older and had more comorbid conditions would be less likely to receive docetaxel than the oral therapies because docetaxel has more associated toxic side effects. Finally, we used the PSA level at time of treatment and PSA doubling time as biomarkers of disease severity.[15,16] The PSA at the start of the first-line treatment was determined by the PSA most proximal to the time of first treatment. The PSA doubling time was calculated using the PSA most proximal to the first-line treatment and the lowest PSA value within the 6 months before first treatment. We expected patients with more aggressive disease based on higher PSA values and faster PSA doubling time would be more likely to receive docetaxel than oral therapies.

Statistical Analysis

We evaluated the association of different patient, facility, and time variables upon the receipt of first-line CRPC treatment. We first fit a Bayesian multilevel multinomial regression model to calculate odds ratios (ORs) and 95% credible intervals (CrIs) for each variable in the model. We included the treating facility in the model as a random intercept. Weakly informative normal priors were chosen for each regression coefficient. Trace plots were checked to ensure parameter convergence.

To better understand the differences in treatments observed by race and disease status after multivariable analysis, we conducted a series of sensitivity analyses. We first assessed whether disease status at the start of the first-line treatment differed by race. In addition, because of effects observed by race with regard to treatment with ketoconazole (considered a suboptimal comparator to the other first-line therapies based on a lack of evidence for a survival benefit), we conducted a univariate logistic regression identifying patient, disease, and facility variables associated with ketoconazole versus other first-line CRPC therapies. To determine whether additional variables affected the association of race with treatment with ketoconazole, we then used an innovative analytic method of calculating the average marginal effects (AMEs) by sequentially adding covariates back into the model.[17] Finally, because ketoconazole and docetaxel were used most commonly in the earlier years, we conducted a similar analysis limited to the years 2013-2017 when all therapies were available for use.

We used R version 3.6.0 for our analyses; the Bayesian multilevel modeling was done using the brms R package.[18]

RESULTS

Among 569,432 Veterans identified with prostate cancer between 2010 and 2017, 3.16% (n = 17,991) received at least 1 of the CRPC treatments. After cohort restriction to patients with a rising PSA receiving ADT within the VA system (ie, considered castration-resistant), and excluding the <1% of patients who received the less commonly used first-line therapies, our final cohort included 4998 men with CRPC at 127 facilities who received abiraterone, enzalutamide, docetaxel, or ketoconazole as the first-line treatment (Fig. 1).

The mean age was 73 years (range, 42-100 years), with 3197 patients (64.0%) identified as White, 1424 (28.5%) as African American, and 377 (7.6%) as other or an unidentified race (Table 1). Supporting Figure 1 illustrates the marked shift in treatments used throughout the years, with ketoconazole and docetaxel used most commonly in earlier years (2010-2011) and a gradual substitution of abiraterone and enzalutamide for docetaxel and ketoconazole in later years.

Clinical and Nonclinical Factors Associated With First-Line CRPC Treatment

After adjustment for other covariates, patients who were older had greater odds of receiving first-line abiraterone (adjusted odds ratio [aOR], 1.07; 95% CrI, 1.06-1.09 for every year of age) or enzalutamide (aOR, 1.10; 95% CrI, 1.08-1.11 for every year of age) compared with docetaxel. There was also a preference for enzalutamide versus abiraterone in patients who were older (aOR, 1.02; 95% CrI, 1.01-1.03).

As shown in Table 2, patients with a Charlson Comorbidity Index of 2 or greater were more likely to receive enzalutamide compared with any of the other therapies (aOR, 1.79; 95% CrI, 1.31-2.45 vs docetaxel; aOR, 1.53; 95% CI, 1.23-1.91 vs abiraterone; and AaR, 1.50; 95% CrI, 1.08-2.08 vs ketoconazole).

TABLE 1. Patient Characteristics

	First Drug[a]								Total	
	Abiraterone (N = 2073)		Docetaxel (N = 876)		Enzalutamide (N = 936)		Ketoconazole (N = 1113)		4998	
Age at first drug, mean (range), y	74.6 (51-100)		69.3 (42-94)		75.8 (53-100)		74.9 (51-98)		73.0 (42-100)	
Race, No. (%), by drug										
White	1377	(66.4)	541	(61.8)	586	(62.6)	693	(62.3)	3197	(64.0)
African American	565	(27.3)	256	(29.2)	290	(31.0)	313	(28.1)	1424	(28.5)
Other	30	(1.4)	13	(1.5)	18	(1.9)	23	(2.1)	84	(1.7)
Unknown	101	(4.9)	66	(7.5)	42	(4.5)	84	(7.5)	293	(5.9)
CCI, No. (%), by drug										
0	1156	(55.8)	522	(59.6)	462	(49.4)	649	(58.3)	2789	(55.8)
1	468	(22.6)	195	(22.3)	204	(21.8)	223	(20.0)	1090	(21.8)
2+	449	(21.7)	159	(18.2)	270	(28.8)	241	(21.7)	1119	(22.4)
Starting PSA, median (IQR), ng/mL	39.9 (14.6-119.0)		84.9 (22.1-272.8)		29.6 (11.7-88.0)		36.8 (13.9-102.6)		41.2 (14.4-126.1)	
PSA doubling time, median (IQR), mo	6.2 (4.9-8.4)		5.7 (4.4-7.5)		6.2 (4.8-8.3)		6.4 (5.0-8.5)		6.1 (4.8-8.2)	
PSA doubling time, No. (%), by drug										
<3 mo	111	(5.4)	75	(8.6)	44	(4.7)	42	(3.8)	272	(5.4)
3-<6 mo	870	(42.0)	414	(47.3)	386	(41.2)	428	(38.5)	2098	(42.0)
6-<10 mo	736	(35.5)	275	(31.4)	371	(39.6)	462	(41.5)	1844	(36.9)
≥10 mo	356	(17.2)	112	(12.8)	135	(14.4)	181	(16.3)	784	(15.7)
Year at time of first treatment, No. (%), by year										
2010	0	(0.0)	162	(37.9)	0	(0.0)	266	(62.1)	428	
2011	58	(9.4)	182	(29.5)	0	(0.0)	376	(61.0)	616	
2012	154	(28.1)	146	(26.6)	1	(0.2)	248	(45.2)	549	
2013	356	(63.3)	70	(12.5)	21	(3.7)	115	(20.5)	562	
2014	420	(63.3)	98	(14.8)	87	(13.1)	58	(8.7)	663	
2015	351	(52.1)	66	(9.8)	229	(34.0)	28	(4.2)	674	
2016	348	(48.5)	81	(11.3)	277	(38.6)	12	(1.7)	718	
2017	386	(49.0)	71	(9.0)	321	(40.7)	10	(1.3)	788	
Regional health network, No. (%), by facility										
A	223	(50.8)	72	(16.4)	44	(10.0)	100	(22.8)	439	
B	164	(42.3)	62	(16.0)	86	(22.2)	76	(19.6)	388	
C	162	(44.1)	48	(13.1)	55	(15.0)	102	(27.8)	367	
D	150	(42.1)	70	(19.7)	54	(15.2)	82	(23.0)	356	
E	100	(29.5)	111	(32.7)	56	(16.5)	72	(21.2)	339	
F	147	(46.2)	40	(12.6)	70	(22.0)	61	(19.2)	318	
G	133	(42.1)	37	(11.7)	76	(24.1)	70	(22.2)	316	
H	136	(43.3)	39	(12.4)	63	(20.1)	76	(24.2)	314	
I	123	(40.5)	71	(23.4)	27	(8.9)	83	(27.3)	304	
J	106	(35.6)	56	(18.8)	79	(26.5)	57	(19.1)	298	
K	93	(36.5)	57	(22.4)	51	(20.0)	54	(21.2)	255	
L	115	(46.9)	13	(5.3)	45	(18.4)	72	(29.4)	245	
M	75	(35.5)	25	(11.8)	60	(28.4)	51	(24.2)	211	
N	59	(28.4)	38	(18.3)	65	(31.2)	46	(22.1)	208	
O	109	(54.0)	48	(23.8)	24	(11.9)	21	(10.4)	202	
P	80	(43.7)	39	(21.3)	28	(15.3)	36	(19.7)	183	
Q	57	(42.9)	32	(24.1)	12	(9.0)	32	(24.1)	133	
R	41	(33.6)	18	(14.8)	41	(33.6)	22	(18.0)	122	

Abbreviations: CCI, Charlson Comorbidity Index; IQR, interquartile range; PSA, prostate-specific antigen.
[a]Cabazitaxel, mitoxantrone, radium-223, and sipuleucel-T are not included.

We also found treatment year had an expected effect on the first-line treatment, with docetaxel and ketoconazole more likely to be used than abiraterone or enzalutamide in earlier years, and abiraterone more likely to be used than enzalutamide in years before enzalutamide approval, as shown in Table 2.

Prostate cancer characteristics were associated with first-line therapy selection. Patients with a higher starting

TABLE 2. Bayesian Multilevel[a] Multinomial Regression of First-Line Treatment Among Patients Treated From 2010 to 2017

	Abiraterone vs Docetaxel		Enzalutamide vs Docetaxel		Enzalutamide vs Abiraterone		Abiraterone vs Ketoconazole		Enzalutamide vs Ketoconazole		Docetaxel vs Ketoconazole	
	aOR	95% CrI	aOR	95% CrI	aOR	95% CrI	aOR	95% CrI	aOR	95% CrI	aOR	95% CrI
Age at first treatment, y	**1.07**	**(1.06- 1.09)**	**1.10**	**(1.08-1.11)**	**1.02**	**(1.01-1.03)**	0.99	(0.98-1.00)	**1.02**	**(1.00-1.03)**	**0.92**	**(0.91-0.93)**
Race												
White	1.00		1.00		1.00		1.00		1.00		1.00	
African American	1.07	(0.85-1.36)	1.12	(0.84-1.50)	1.05	(0.84-1.31)	0.83	(0.64-1.08)	0.86	(0.62-1.19)	0.78	(0.60-1.02)
Other	0.92	(0.41-2.15)	1.29	(0.48-3.51)	1.38	(0.66-2.89)	0.68	(0.30-1.53)	0.95	(0.36-2.60)	0.78	(0.34-1.71)
CCI												
0	1.00		1.00		1.00		1.00		1.00		1.00	
1	1.11	(0.86-1.43)	1.18	(0.87-1.62)	1.06	(0.84-1.34)	1.22	(0.92-1.61)	1.30	(0.93-1.82)	1.06	(0.80-1.40)
2+	1.16	(0.90-1.51)	**1.79**	**(1.31-2.45)**	**1.53**	**(1.23-1.91)**	0.98	(0.74-1.28)	**1.50**	**(1.08-2.08)**	0.82	(0.61-1.10)
Starting PSA, ng/mL	**0.89**	**(0.83-0.95)**	**0.82**	**(0.75-0.89)**	**0.92**	**(0.86-0.99)**	**1.27**	**(1.18-1.37)**	**1.17**	**(1.06-1.28)**	**1.44**	**(1.33-1.55)**
PSA-doubling time												
<3 mo	1.00		1.00		1.00		1.00		1.00		1.00	
3-<6 mo	**1.51**	**(1.01-2.27)**	**1.85**	**(1.09-3.15)**	1.22	(0.80-1.88)	0.91	(0.55-1.52)	1.11	(0.60-2.02)	**0.61**	**(0.37-0.98)**
6-<10 mo	**1.85**	**(1.23-2.80)**	**2.31**	**(1.35-3.97)**	1.25	(0.82-1.93)	0.86	(0.51-1.42)	1.07	(0.58-1.98)	**0.46**	**(0.28-0.75)**
≥10 mo	**1.74**	**(1.09-2.76)**	1.64	(0.91-3.00)	0.95	(0.59-1.51)	1.02	(0.60-1.75)	0.96	(0.48-1.86)	0.58	(0.34-1.00)
Year at time of first treatment												
2017	1.00		1.00		1.00		1.00		1.00		1.00	
2016	0.94	(0.64-1.39)	0.81	(0.55-1.22)	0.87	(0.68-1.12)	1.17	(0.49-2.83)	1.02	(0.41-2.53)	1.26	(0.50-3.33)
2015	0.96	(0.65-1.43)	0.81	(0.54-1.22)	0.83	(0.65-1.08)	**0.32**	**(0.16-0.66)**	**0.27**	**(0.13-0.55)**	**0.34**	**(0.15-0.74)**
2014	0.91	(0.63-1.30)	**0.19**	**(0.12-0.29)**	**0.21**	**(0.16-0.29)**	**0.18**	**(0.09-0.35)**	**0.04**	**(0.02-0.08)**	**0.20**	**(0.10-0.42)**
2013	1.00	(0.67-1.50)	**0.06**	**(0.03-0.10)**	**0.06**	**(0.03-0.09)**	**0.07**	**(0.04-0.13)**	**0.00**	**(0.00-0.01)**	**0.07**	**(0.03-0.15)**
2012	**0.19**	**(0.13-0.28)**	**0.00**	**(0.00-0.01)**	**0.00**	**(0.00-0.03)**	**0.01**	**(0.01-0.02)**	**0.00**	**(0.00-0.00)**	**0.07**	**(0.03-0.14)**
2011	**0.05**	**(0.03-0.08)**	**0.00**	**(0.00-0.00)**	**0.00**	**(0.00-0.02)**	**0.00**	**(0.00-0.01)**	**0.00**	**(0.00-0.00)**	**0.06**	**(0.03-0.12)**
2010	**0.00**	**(0.00-0.00)**	**0.00**	**(0.00-0.00)**	0.01	(0.00-55.6)	**0.00**	**(0.00-0.00)**	**0.00**	**(0.00-0.00)**	**0.07**	**(0.04-0.15)**
Site-level urologist FTE ratio[b]	0.99	(0.92-1.06)	1.06	(0.96-1.16)	1.05	(0.96-1.14)	0.94	(0.88-1.01)	1.01	(0.92-1.12)	0.97	(0.89-1.06)
Site-level HemeOnc FTE ratio[b]	1.00	(0.98-1.01)	1.00	(0.98-1.02)	1.00	(0.98-1.02)	1.02	(1.00-1.05)	1.02	(0.99-1.05)	**1.03**	**(1.00-1.06)**

Abbreviations: CCI, Charlson Comorbidity Index; CrI, credible interval; FTE, full-time equivalent; HemeOnc, hematology/oncology; aOR, adjusted odds ratio; PSA, prostate-specific antigen.

These are the results of Bayesian multilevel multinomial regression of first-line treatment among patients with castration-resistant prostate cancer. This model includes 4685 patients from the 118 facilities for which complete information on race and FTE ratio could be used. Patients from 9 sites (n = 313) were not included in this regression analysis because of incomplete information on race or FTE ratio. The bolded numbers are statistically significant.

[a]Facility was included in the model as a random intercept.

[b]Site-level FTE ratio defined as FTE per 10,000 patients in specialty.

PSA (ie, more severe disease) were more likely to receive docetaxel (aOR, 1.44; 95% CrI, 1.33-1.55), abiraterone (aOR, 1.27; 95% CrI, 1.18-1.37), or enzalutamide (aOR, 1.17; 95% CrI, 1.06-1.28) compared with ketoconazole. Those with higher starting PSA values were less likely to receive oral therapies abiraterone (aOR, 0.89; 95% CrI, 0.83-0.95) or enzalutamide (aOR, 0.82; 95% CrI, 0.75-0.89) compared with docetaxel. Similarly, Table 2 demonstrates patients with a slower PSA doubling time (ie, >3 months), suggesting less aggressive disease, had greater odds of receiving oral therapies abiraterone or enzalutamide versus docetaxel.

After adjusting for clinical and facility-level variables, race was not associated with first-line abiraterone, enzalutamide, or docetaxel over the others. There was a trend toward African American men having lower odds of receiving docetaxel or abiraterone over ketoconazole first-line (aOR, 0.78, 95% CrI, 0.60-1.02 for docetaxel; aOR, 0.83; 95% CrI, 0.64-1.08 for abiraterone), but the credible intervals crossed 1.

We further characterized whether the disease state of patients in our cohort at the time of first treatment differed by race. The median PSA at the time of first treatment was 41.2 ng/mL (interquartile range [IQR], 14.4-126.1) for all patients and 58.8 ng/mL (IQR, 18.2-180.2) for African American men, suggesting that the disease state at the time of the first CRPC treatment may be more advanced in African American men. In the entire cohort,

men with higher PSA at the start of the first treatment were more likely to be started on docetaxel, abiraterone, or enzalutamide than ketoconazole. We saw a trend for the opposite effect among African American men even though African American men had higher starting PSA values. To understand why we were observing this opposite effect in African American men, we conducted additional sensitivity analyses with a multivariable logistic regression to determine the marginal effects of an African American man receiving ketoconazole, as a presumably less effective or guideline-discordant comparator versus any of the other 3 therapies, with the stepwise addition of the different therapies into the model.

The results of these sensitivity analyses show the change in predicted probability of an African American man receiving ketoconazole versus 1 of the other evidence-based treatments (Table 3). Patient characteristics, such as age and comorbidities and the year of treatment, had little effect on whether African American men were more likely to receive ketoconazole. However, after adjusting for severity of disease, African American men were more likely than White men to receive ketoconazole versus other first-line treatments (AME, 2.8%; 95% CI, 0.7%-4.9%). This effect was partially attenuated by accounting for facility characteristics (AME, 1.9%; 95% CI, 0.4%-4.1%). These effects remained when we limited this analysis to the years 2013-2017, but were not statistically significant (Supporting Table 1).

TABLE 3. Average Marginal Effect of an African American Man Receiving Ketoconazole as the First-Line CRPC Treatment Versus Other Therapies (Abiraterone, Enzalutamide, or Docetaxel Therapy)

	Model	AME	95% CI
Patient characteristics and year	Unadjusted	0.3%	–2.3% to 2.9%
	Race + year	0.8%	–1.3% to 2.9%
	Race + year + age	1.6%	–0.5% to 3.7%
	Race + year + age + CCI	1.6%	–0.6% to 3.7%
Disease characteristics	Race + year + age, + CCI + starting PSA	**2.8%**	**0.8%-4.9%**
	Race + year + age + CCI + starting PSA + PSA-doubling time	**2.9%**	**0.8%-5.0%**
Facility characteristics	Race + year + age + CCI + starting PSA + PSA-doubling time + HemeOnc FTE ratio	**2.8%**	**0.7%-4.9%**
	Race + year + age + CCI + starting PSA + PSA-doubling time + HemeOnc FTE ratio[a] + facility random intercept[b]	1.9%	–0.4% to 4.1%

Abbreviations: AME, average marginal effect; CCI, Charlson Comorbidity Index; CRPC, castration-resistant prostate cancer; HemeOnc FTE, hematology/oncology clinical full-time equivalent; PSA, prostate-specific antigen.
This model includes 4685 patients from the 118 facilities for which complete information on race and FTE ratio could be used. Patients from 9 sites (n = 313) were not included in this regression analysis because of incomplete information on race or FTE ratio. The AME is defined as the change in the predicted probability when additional variables are added. The bold numbers indicate statistical significance.
[a]Site-level FTE ratio defined as FTE per 10,000 patients in specialty.
[b]Facility was included in the model as a random intercept.

DISCUSSION

In this cohort of US men with CRPC, we found that clinical and nonclinical factors were associated with the first-line treatment. Patients who were older or had more comorbidities were more likely to receive less toxic oral therapies compared with docetaxel and more likely to receive enzalutamide versus abiraterone. Overall, patients with more aggressive prostate cancer characteristics were more likely to receive a first-line treatment with docetaxel versus an oral therapy such as abiraterone, enzalutamide, or ketoconazole. However, despite having a higher starting PSA suggesting more advanced disease at the start of a first treatment, African American men were more likely to receive ketoconazole (a drug with no known survival benefit) than the other first-line therapies, a treatment decision that may be partly explained by the patient's treating facility. Taken together, these results identify the complexities in understanding CRPC care delivery, even in a national system aiming to mitigate financial and other access to care issues, including those impacted by race.

Older patients and those with more comorbidities receiving abiraterone or enzalutamide over docetaxel supports previous work among commercially insured patients.[12] Docetaxel chemotherapy is more toxic and can be more difficult to administer in elderly patients or those with more comorbid conditions. Less expected was that older and sicker patients were more likely to be prescribed enzalutamide over abiraterone. Because abiraterone has more potential cardiovascular complications and is administered with prednisone, providers may view this therapy with trepidation in patients with preexisting hypertension or diabetes mellitus, measureable comorbid conditions commonly included in comorbidity indices. Interestingly, abiraterone was found to be better

tolerated than enzalutamide in a recent study,[19] so this propensity for enzalutamide over abiraterone in older and sicker populations may change in the coming years.

Because abiraterone and enzalutamide were not approved for first-line use in CRPC until 2013 and 2014, respectively, our temporal effects were also expected.[3,5] Moreover, it is generally common for patients with higher PSA values or faster PSA doubling time, and thus more aggressive disease, to be prescribed docetaxel as the first-line treatment rather than an oral agent. None of these treatments have been compared head to head, so it is unknown whether disease factors such as PSA doubling time should impact the first-line treatment for CRPC. However, chemotherapy is generally expected to work more quickly in crisis situations with more aggressive disease, and oncologists may be less likely to wait for an oral therapy to take effect.

More concerning was the observed racial differences in both the disease state at the start of treatment and in subsequent prescribing patterns. Prior research among commercially insured men with prostate cancer found that African American men were more likely to be prescribed an oral agent over docetaxel compared with White men, but the reasons for this are not known and could be based on unmeasured factors such as patient preference.[12] In this study, we did not see that African American Veterans were more likely to receive abiraterone or enzalutamide over docetaxel, but we did see a trend by race in the use of ketoconazole over the other 3 evidence-based treatments. Ketoconazole is an oral antifungal agent that was found to have antiandrogen effects, and thus was used traditionally for treatment of CRPC before other more effective agents were available. Unlike docetaxel, abiraterone, and enzalutamide, ketoconazole has not been shown to improve overall survival in patients with CRPC and is not included in the guidelines for the treatment of CRPC. The 2010 National Comprehensive Cancer Network guidelines, before abiraterone or enzalutamide were available, list ketoconazole as a potential strategy to lower PSA but indicate that there is no known benefit to survival, unlike docetaxel.[20] When we looked at this association in a stepwise manner and adjusted for PSA, African American men appeared more likely to receive ketoconazole than the other guideline-concordant therapies. That the unadjusted model did not show this difference likely reflects the fact that African American men in our cohort had higher PSA values at the time of the first-line treatment. If African American men were being prescribed therapies based on their starting PSA alone, we should have seen in the unadjusted model that African American men were less likely to be prescribed ketoconazole than the other 3 therapies. Adjusting for treating facility and less so for workforce capacity, mitigated some of the effect, suggesting that facility characteristics beyond workforce may explain this difference. Prior work has shown that the hospital where a patient is treated, including demographics of the hospital patient population can affect treatment and the quality of treatment a patient receives, even within the VA.[21-24] The quality of care associated with the racial composition of a facility is an example of structural racism within the health care system.[25] Furthermore, though total drug costs and out-of-pocket expenses in the civilian setting may be higher for abiraterone and enzalutamide compared with ketoconazole, differences in out-of-pocket costs do not apply in an integrated single-payer system such as the VA, where all medications have minimal copay.

A strength of this analysis was the high proportion of African American patients in our cohort. African American men account for 17% of men in the VA system, and 20% of men with prostate cancer in the VA. Yet, close to 30% of patients in our final cohort were African American. This large cohort of African American men may reflect the increased rates of advanced disease among African American men because we only included men with CRPC. Furthermore, this analysis included ketoconazole, a therapy that was commonly used off-label to treat prostate cancer, but which is frequently not discussed in the current era of advanced therapeutics and not included in prior trials. A limitation, however, is that unlike abiraterone and enzalutamide, docetaxel and ketoconazole have indications for use other than CRPC. Because all patients included in this cohort started their treatment after being identified to have newly castration-resistant disease, we believe that treatment with these therapies was most likely directed at their CRPC. Another limitation was that we did not include diagnosis codes for metastatic disease, so it is possible that patients may have had nonmetastatic CRPC. Considering median PSA values at the start of any of the treatments were similar, we did not expect the presence of metastases to differ by the first-line treatment. We did, however, consider the potential that coding for metastases may have been affected by pharmacy formulary restrictions for more expensive abiraterone or enzalutamide. For these reasons, we chose not to include a metastatic variable. Finally, all patients included in our final analysis received 1 of the treatments of inquiry and thus did not include patients with CRPC for which no treatment is given. Whether patient and facility-level factors influence whether a patient is offered treatment at all deserves further study. These limitations notwithstanding, our investigation highlights some of the

important CRPC treatment predictors in a diverse cohort of men with advanced prostate cancer.

In conclusion, comorbidity, age, and starting PSA were factors that accounted for some of the variation in how men were treated for CRPC in the US. Importantly, African American race may be associated with a guideline-discordant first-line treatment for CRPC. Some of this disparity was partially mediated through site of care; thus, future work should explore how structural racism impacts facility- and individual-level mediators of racial disparities. Furthermore, considering the disproportionately high number of African American patients in our cohort and the imbalance in PSA between African American men and White men at the start of treatment, further study must be done to understand the extent to which race impacts the development and severity of CRPC. Now that additional therapies are being used in the metastatic castration-sensitive setting for longer periods, a better understanding of the disparities in treatment will be critical to ensuring that all Veterans and nonveterans are receiving optimal care.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Megan E. V. Caram: Conceptualization and design, data analysis and interpretation, writing–original draft, and writing–review and editing. **Jennifer Burns:** Conceptualization and design, collection and assembly of data, data analysis and interpretation, writing–original draft, and writing–review and editing. **Kyle Kumbier:** Conceptualization and design, collection and assembly of data, data analysis and interpretation, writing–original draft, and writing–review and editing. **Jordan B. Sparks:** Collection and assembly of data, and writing–review and editing. **Phoebe A. Tsao:** Data analysis and interpretation, and writing–review and editing. **Christina H. Chapman:** Conceptualization and design, data analysis and interpretation, and writing–review and editing. **Jordan Bauman:** Data analysis and interpretation, and writing–review and editing. **Brent K. Hollenbeck:** Conceptualization and design, data analysis and interpretation, and writing–review and editing. **Vahakn B. Shahinian:** Data analysis and interpretation, and writing–review and editing. **Ted A. Skolarus:** Conceptualization and design, data analysis and interpretation, and writing–review and editing.

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