Prescribing Patterns of Oral Antineoplastic Therapies Observed in the Treatment of Patients With Advanced Prostate Cancer Between 2012 and 2014: Results of an Oncology EMR Analysis

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ABSTRACT

Purpose: The purpose of this study was to examine, using a US electronic medical records (EMR) database, the clinical characteristics and real-world treatment sequences in men with advanced prostate cancer who initiated treatment with abiraterone acetate or enzalutamide.

Methods: This retrospective, observational study evaluated adult male patients with a diagnosis of prostate cancer (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 185) in the EMR database between July 1, 2011, and March 31, 2014, who had initiated first-line treatment with abiraterone acetate or enzalutamide between September 1, 2012, and March 31, 2014. The first record for a patient initiating abiraterone acetate or enzalutamide was the index date. Patients had 6 months of pre-index medical record history and a variable length follow-up period, extending from the index date to the end of medical record data availability or date of the end of the study (March 31, 2014). The sequence of first- and second-line therapies for advanced prostate cancer therapy was reported.

Findings: A total of 809 patients met study inclusion and exclusion criteria. This study found that the majority of patients who initiated treatment with either abiraterone acetate or enzalutamide between September 1, 2012, and March 31, 2014, received a single line of therapy (72%); abiraterone acetate was the most common first-line treatment (74% of first-line patients). A subset of patients treated first-line with either abiraterone acetate or enzalutamide were transitioned to an oral second-line agent (17% of first-line abiraterone acetate–treated patients transitioned to second-line enzalutamide, and 16% of first-line enzalutamide-treated patients transitioned to second-line abiraterone acetate). Chemotherapy with docetaxel was also a commonly observed second-line treatment selection, occurring in 8% of first-line abiraterone acetate–treated patients and in 7% of first-line enzalutamide-treated patients.

Implications: This EMR study is among the first to present evidence of US physician practice prescribing patterns regarding initiation of oral antineoplastic agents and use of subsequent therapies in patients with advanced prostate cancer. (*Clin Ther.* 2016;38:1817–1824) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: abiraterone acetate, enzalutamide, metastatic castration-resistant prostate cancer.

INTRODUCTION

After skin cancer, prostate cancer is the most common cancer diagnosed among men in the United States.[1] Approximately 220,000 incident cases of prostate cancer were diagnosed in 2015, which is decreasing over time due to changes in screening for prostate cancer with prostate-specific antigen (PSA).[1] In male patients, metastatic, castration-resistant prostate cancer (mCRPC) is the second deadliest cancer after lung cancer, resulting in ~30,000 deaths per year in the United States.

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Although there is no cure for mCRPC, docetaxel, a member of the taxane class, has historically been the standard of care for treating advanced prostate cancer. A clinical trial in patients with mCRPC reported a 2.4-month improvement in overall survival for docetaxel in combination with prednisone, compared with mitoxantrone plus prednisone.[2] In the past 5 years, several additional treatment options have emerged that offer novel mechanisms of action, side effect profiles, modes of administration, and survival benefits to patients with mCRPC.[3–6] Sipuleucel-T, first in the class of autologous cellular immunotherapies indicated for prostate cancer, involves harvesting and priming the patient's CD54+ cells with prostatic antigen phosphatase-granulocyte macrophage colony-stimulating factor and infusion of these cells in three 60-minute infusions at 2-week intervals (over a total of 6 weeks). In 2 randomized controlled trials of men with asymptomatic or minimally symptomatic mCRPC, sipuleucel-T treatment led to 4.5 and 4.1 months of improvement in overall survival versus placebo, respectively.[7,8] Abiraterone acetate, given orally in combination with prednisone, was the first androgen biosynthesis inhibitor approved by the US Food and Drug Administration for the treatment of mCRPC. Abiraterone acetate acts by inhibiting cytochrome p450 17A1, an enzyme in the androgen synthesis pathway, and blocks androgen production at the testes, adrenal, and tumor.[9,10] Phase III studies in men with asymptomatic or mildly symptomatic mCRPC found a 4.4- month improvement in overall survival for abiraterone acetate plus prednisone versus prednisone alone.[11] Another oral agent, enzalutamide, inhibits the androgen receptor, preventing androgen signaling.[9,10] Phase III studies in men with asymptomatic or mildly symptomatic chemotherapy-experienced mCRPC exhibited a 4-month improvement in overall survival for enzalutamide versus placebo.[12] Both abiraterone acetate and enzalutamide increased overall survival in patients with mCRPC in the prechemotherapy setting.[13,14] Another agent, cabazitaxel, administered intravenously, exhibited a median overall survival benefit of 2.4 months compared with mitoxantrone alone.[15]

Because of this rapid expansion in the number of mCRPC treatment options, few studies have investigated how clinicians are selecting treatments in clinical practice, particularly orally administered therapies.[16] The aim of the current study was to describe patient characteristics and treatment sequences in patients with mCRPC recorded in an electronic medical records (EMR) database drawn from US community oncology practices.

MATERIALS AND METHODS

Data Source

The Truven Health MarketScan Oncology EMR Database was used to conduct this study. The oncology EMR database contains medical record data for $>500{,}000$ patients actively seen in >100 community oncology practices throughout the United States at any time from July 2011 through March 2014, as well as all historical data for patients captured during this period. The database contains information on patient demographic characteristics, diagnoses, cancer stage, histology, treatments, outcomes, and other clinical information contained in the digital fields of the EMR. All geographic regions of the United States are represented, with 38% of patients coming from the South, 25% from the Northeast, 20% from the West, and 17% from the North Central region. All age groups are included; 53% of the patients are aged ≥ 65 years. The data contained in these databases were processed by statistical de-identification and were certified to satisfy the conditions set forth in Sections 164.514 (a)-(b)(1)ii of the Health Insurance Portability and Accountability Act. Institutional review board approval and written informed consent were therefore not required for this study.

Subject Selection and Follow-up

Patients were retrospectively selected for the study and had a diagnosis of prostate cancer, as indicated by *International Classification of Diseases, Ninth Revision, Clinical Modification* code 185 in the medical record at any time between July 1, 2011, and March 31, 2014, and had their first prescription for abiraterone acetate or enzalutamide between September 1, 2012, and March 31, 2014; this time coincides with a period when both medications were commercially available in the Unites States. The first EMR record for a patient initiating abiraterone acetate or enzalutamide between September 1, 2012, and March 31, 2014, was designated as the index date. To ensure patients were newly initiating treatment, patients were required to have 6 months of pre-index medical record history and to have no abiraterone acetate or

enzalutamide treatment in the 6-month pre-index period. Study patients were excluded if they were aged <18 years on the index date, had other cancer as their first occurring primary cancer, had invalid medical record data, or had evidence of concurrent use of abiraterone acetate or enzalutamide on the index date. The follow-up period varied in length and extended from the index date to the last date of medical record data availability in the oncology EMR database or to the date of the end of the study (March 31, 2014), whichever occurred earliest.

Outcomes

A line of therapy was defined as the period from the first to the last medical record indicating a study medication of interest before a switch to a subsequent line of therapy or the end of the study period. Individual flags were created to identify subsequent lines of therapy for the following medications of interest, using all variations in generic and brand name to identify each drug: abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, and sipuleucel-T. Treatment sequences ranging from first to third lines of treatment were reported. For example, a patient who initiated abiraterone acetate and then switched to enzalutamide was categorized as abiraterone acetate followed by enzalutamide. A patient who initiated abiraterone acetate and then switched to enzalutamide and then switched back to abiraterone acetate was categorized as abiraterone acetate followed by enzalutamide followed by abiraterone acetate.

Concurrent treatment with hormone therapy (luteinizing hormone-releasing hormone [LHRH] agonists, LHRH antagonists, antiandrogens, and diethylstilbestrol), corticosteroids, and other biologic and chemotherapy treatments was identified during the first line of therapy.

Patient Demographic and Clinical Characteristics

Patient demographic and clinical characteristics were collected to describe the patient population. Demographic characteristics were measured on the index date and included patient age in years, US Census Bureau geographic region of residence, and insurance plan type. Clinical characteristics were measured during the pre-index period from available EMR data fields, including disease stage, metastasis status, sites of metastasis, indicators for previous prostate cancer procedures (eg, surgical castration, radiation therapy), and previous prostate cancer treatments (hormone therapies [LHRH agonists, LHRH antagonists, antiandrogens, and diethylstilbestrol], corticosteroids, and other biologic and chemotherapy treatments). PSA scores were measured in the pre-index period by using the PSA test result that was most proximate to the index date.

Table I. Study attrition.

Inclusion and Exclusion Criteria	Patients	
	No.	%
Patients ≥18 years of age with prostate cancer between July 1, 2011, and March 31, 2014 and abiraterone acetate or enzalutamide treatment between September 1, 2012, and March 31, 2014	1586	100.0
Evidence of prostate cancer as first occurring primary cancer type	1518	95.7
No abiraterone acetate or enzalutamide treatment in the preindex period	1433	90.4
Medical record history with valid study start and end dates	1379	86.9
No evidence of any other primary cancers	1338	84.4
At least 180 days of preindex medical record history	830	52.3
No evidence of concurrent use of abiraterone acetate and enzalutamide on index date or during the line of therapy	809	51.0
Final patient count	809	51.0
First-line abiraterone acetate	602	74.4
First-line enzalutamide	207	25.6

Table II. Demographic and baseline clinical characteristics. Unless otherwise indicated, values are given as number (%).

Characteristic	First-Line Abiraterone Acetate (n = 602)	First-Line Enzalutamide (n = 207)
Age, mean (SD), y	75.2 (9.7)	75.2 (10.3)
Age group		
46–55 y	17 (2.8)	8 (3.9)
56–65 y	85 (14.1)	29 (14.0)
66–75 y	201 (33.4)	66 (31.9)
76–84 y	181 (30.1)	68 (32.9)
≥85 y	118 (19.6)	36 (17.4)
Geographic region		
Northeast	129 (21.4)	36 (17.4)
North Central	71 (11.8)	26 (12.6)
South	257 (42.7)	100 (48.3)
West	139 (23.1)	45 (21.7)
Unknown	6 (1.0)	0
Disease stage		
Early stage (stage I/II)	2 (0.3)	0
Stage III	3 (0.5)	2 (1.0)
Stage IV	402 (66.8)	152 (73.4)
Unknown/missing	195 (32.4)	53 (25.6)
Metastatic sites		
Bone	315 (78.4)	124 (81.6)
Lung	6 (1.5)	0
Lymph nodes	41 (10.2)	24 (15.8)
Other	13 (3.2)	7 (4.6)
Unknown/missing	61 (15.2)	18 (11.8)
PSA test result category		
Normal (0–4 ng/mL)	65 (10.8)	23 (11.1)
Elevated (>4 ng/mL)	460 (76.4)	155 (74.9)
Unknown/missing	77 (12.8)	29 (14.0)
Surgical castration	3 (0.5)	2 (1.0)
Preindex medications		
LHRH agonists	250 (41.5)	75 (36.2)
LHRH antagonists	10 (1.7)	6 (2.9)
Antiandrogens	236 (39.2)	62 (30.0)
Diethylstilbestrol	1 (0.2)	0
Corticosteroids	234 (38.9)	97 (46.9)
Chemotherapy*	155 (25.7)	92 (44.4)
Docetaxel	105 (17.4)	72 (34.8)
Cabazitaxel	53 (8.8)	26 (12.6)
Sipuleucel-T	12 (2.0)	5 (2.4)

LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen.
*In addition to agents listed here, includes mitoxantrone, estramustine, doxorubicin, etoposide, vinblastine, paclitaxel, and vinorelbine.

Statistical Analyses

Summary statistics were used to describe the demographic characteristics, baseline clinical characteristics, and study outcomes. No formal statistical tests were performed to compare data between mCRPC treatment groups.

RESULTS

A total of 1586 patients were identified with a prostate cancer diagnosis and an order for either abiraterone acetate or enzalutamide. Fifty-one percent (n = 809) met all study inclusion and exclusion criteria as shown in Table I.

Patient Clinical Characteristics

Patients treated with first-line abiraterone acetate or enzalutamide had a mean age of 75 years. A slightly higher proportion of first-line enzalutamide-treated patients were observed in the Southern region (Table II). The patient groups had similar disease stage at the index date, with the majority of patients in both groups having some notation of stage IV disease (67% and 73% of the abiraterone acetate and enzalutamide groups, respectively). The primary metastatic site noted was bone. Approximately three quarters of each group had elevated PSA scores in the 6-month pre-index period. Approximately 50% to 60% of patients had a record of previous treatment with LHRH agonists, LHRH antagonists, antiandrogens, or other hormonal agents. Preindex corticosteroid use was observed in a slightly higher proportion of patients with first-line enzalutamide (47%) compared with patients with first-line abiraterone acetate (39%). Similarly, a higher proportion of first-line enzalutamide-treated patients had pre-index docetaxel exposure compared with first-line abiraterone acetate–treated patients (35% and 17% of the enzalutamide and abiraterone acetate groups, respectively).

Observed Treatment Sequences

Seventy-two percent of patients in this study received 1 line of therapy (Figure 1). The most commonly observed first-line therapy was abiraterone acetate (74% of first-line patients). First-line enzalutamide was observed in 26% of patients. Use of a second-line agent was observed in 28% of patients overall (Table III). Among first-line abiraterone acetate–treated patients, 27% continued to a second-line therapy. Among first-line enzalutamide-treated patients, 31% continued to a second-line therapy. An oral medication was observed commonly for a second-line treatment; 17% of first-line abiraterone acetate–treated patients transitioned to second-line enzalutamide, and 16% of first-line enzalutamide-treated patients received second-line abiraterone acetate. Chemotherapy with docetaxel was also commonly observed as a second-line treatment selection, occurring in 8% of first-line abiraterone acetate–treated patients and in 7% of first-line enzalutamide-treated patients. Approximately 6% of first-line enzalutamide-treated patients (10 of 207 patients) received cabazitaxel as a second-line agent, and 2% of abiraterone acetate–treated patients received cabazitaxel as a second-line agent (10 of 602).

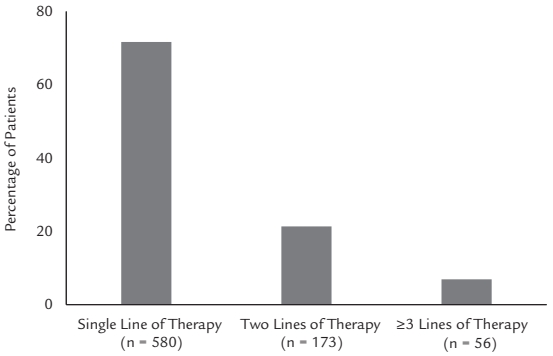

Figure 1. Distribution of first-line, second-line, and subsequent lines of therapy.

Concurrent medication use was higher among abiraterone acetate–treated patients, with slightly greater use of concurrent hormone therapy (31% vs 25% for abiraterone acetate vs enzalutamide, respectively). Likewise, concurrent corticosteroid use was observed in a higher proportion of abiraterone acetate–treated patients (76%) compared with enzalutamide-treated patients (13%) (Figure 2). Most patients in the 2 groups did not receive concurrent chemotherapy (0.5% vs 2% for abiraterone acetate vs enzalutamide, respectively).

DISCUSSION

To the best of our knowledge this study is among the first to report real-world treatment sequencing of oral antineoplastic agents for advanced prostate cancer. This retrospective EMR study found that the majority

Table III. First to second line of therapy.

First to Second-Line Treatment Sequence	All First-Line Patients (N = 809)	
	No.	%
Abiraterone acetate only	438	54.1
Abiraterone acetate followed by cabazitaxel	10	1.2
Abiraterone acetate followed by docetaxel	50	6.2
Abiraterone acetate followed by enzalutamide	100	12.4
Abiraterone acetate followed by sipuleucel-T	4	0.5
Enzalutamide only	142	17.6
Enzalutamide followed by abiraterone acetate	33	4.1
Enzalutamide followed by abiraterone acetate/enzalutamide*	2	0.2
Enzalutamide followed by cabazitaxel	12	1.5
Enzalutamide followed by docetaxel	15	1.9
Enzalutamide followed by sipuleucel-T	3	0.4

*Abiraterone acetate and enzalutamide treatment were identified on the same date and reported as a separate treatment sequence.

of patients prescribed either abiraterone acetate or enzalutamide between September 2012 and March 2014 received only a single line of therapy (72%), with abiraterone acetate being the most commonly prescribed first-line therapy. Although previous prostate cancer medication use was generally similar between the abiraterone acetate–treated and enzalutamide-treated groups, a higher proportion of first-line enzalutamide-treated patients had received corticosteroids and a prior taxane-based chemotherapy compared with first-line abiraterone acetate–treated patients. Although this finding is not surprising given that during the study period, the indication for enzalutamide according to the US Food and Drug Administration approval specified use only in patients with previous docetaxel treatment, it should be noted that nearly one half of first-line enzalutamide use was observed in patients who had not received previous chemotherapy. This finding, combined with the observation that an oral treatment was chosen as the second-line treatment in the majority of patients receiving a second-line agent, may be an indicator of patient or physician preference for oral-based therapies versus existing chemotherapy strategies. This finding may also be due, at least in part, to patient preferences for more convenient oral treatments.[17]

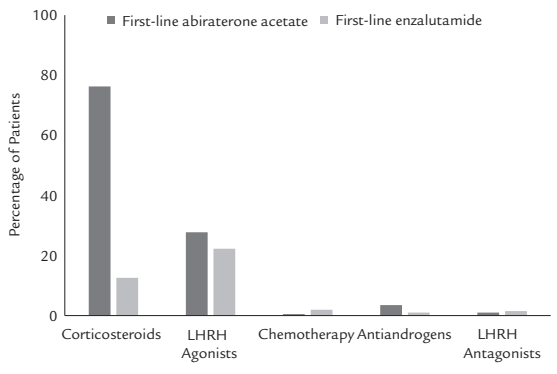

Figure 2. Concomitant medication use in the first line of therapy. LHRH = luteinizing hormone-releasing hormone.

Docetaxel was the only therapy available to treat mCRPC up until 2010, but the changing landscape of prostate cancer treatment with the addition of novel therapies has increased overall survival in patients with mCRPC from an average of 6 to 10 months to a new average of 18 to 24 months.[18] Due to this evolving treatment landscape, treatment sequencing has not yet been well defined.[19,20] Ongoing trials are resulting in updated package labeling expanding the indications for existing therapies. Physicians and

patients will need to consider a multitude of factors aside from survival benefit, including adverse events, contraindications, and patient preference, when choosing which treatment to initiate first-line and which treatments to use after progression.

This study is subject to several limitations. First, the oncology EMR database contains only health care services provided inside the oncologist's office. Medical records for services provided outside the oncologist's office may not be captured in the EMR. In particular, oral medications prescribed or refilled outside of the oncologist's office may be missing. For example, the rate of concurrent corticosteroid use during first-line abiraterone acetate treatment (76%) and during first-line enzalutamide treatment (13%) was lower than recently seen in an analysis of patients with prostate cancer in 3 claims databases.[21] In the claims database analysis, concurrent first-line corticosteroid use ranged from 81% to 86% and 32% to 38% for abiraterone acetate–treated patients and enzalutamide-treated patients, respectively. Second, abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, and sipuleucel-T were the only treatments assessed in this analysis. To better understand the utilization of other mCRPC treatments, various potential concurrent medications such as hormone therapy (LHRH agonists, LHRH antagonists, antiandrogens, and diethylstilbestrol), corticosteroids, and other biologic and chemotherapy treatments were assessed in the pre-index period and during the first line of therapy. Standard comorbidities and clinical characteristics, as well as observations about patient disposition, may be missing from the EMR database. Oncologists may not record comorbidities in the EMR that do not affect treatment decisions. Clinical information about mortality was not captured. Longer follow-up may have provided insights regarding second and subsequent lines of therapy. Finally, because indications for PC treatments have been expanding over time, this study may not reflect the most current prescribing patterns.

CONCLUSIONS

This study provides an initial description of real-world treatment sequencing patterns in patients with advanced prostate cancer treated with drugs typically used in the mCRPC setting. As indications for mCRPC treatments expand over time, this study should be re-visited with additional longitudinal data as the treatment landscape continues to evolve.

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All of the authors contributed to the conceptualization of the analysis and study design, provided critical review of the data, and participated in the development of the manuscript. All authors contributed to and approved the final manuscript.

CONFLICTS OF INTEREST

Dr. Ellis and Dr. McKenzie are employees of Janssen Scientific Affairs and are stockholders in Johnson & Johnson. Ms. Malangone-Monaco, Ms. Varker, and Ms. Wilson are employees of Truven Health Analytics, and Dr. Foley was an employee of Truven Health Analytics at the time the study was conducted. Truven Health Analytics was compensated to perform this work on behalf of Janssen Pharmaceuticals, LLC.

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