Treatment patterns and clinical effectiveness in metastatic castrate resistant prostate cancer after first-line docetaxel

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Background Treatment for metastatic castrate-resistant prostate cancer in community settings is not well understood.
Objective To examine treatment patterns, sequencing, and outcomes in patients receiving second- and third-line treatment after first-line docetaxel.
Methods We used a community oncology database to identify patients who progressed after line 1 docetaxel (D) and received line 2 cabazitaxel (DC), abiraterone (DA), or other therapy (DO). Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier and Cox regression models. Line 3 included subsets DCA and DAC.
Results Line 2 groups (DC = 60 patients, DA = 71, DO = 153) did not differ significantly on demographic and clinical characteristics or median PFS on docetaxel therapy. Cox regression for OS by line 2 groups showed increased risk for DA compared with DC (HR, 1.69; $P = .026$) when 24 untreated DO patients were excluded. A similar nonsignificant pattern was observed when the 24 untreated patients were included. Of patients receiving DC in line 2, a nominally greater proportion received A in line 3 (57%, 34 of 60 patients) than did patients who received DA in line 2 followed by C in line 3 (25%, 18 of 71).
Limitations There was a small sample for line 3, and unexamined confounds and selection biases in observational research.
Conclusions Treatment patterns in community settings following docetaxel are complex and may involve multiple hormonal agents prior to disease progression. Cabazitaxel may not be optimally used in advanced disease. Although Cox regression showed increased risk of death for DA compared with DC, results need to be validated prospectively.
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Prostate cancer is the most common cancer, excluding skin cancer, and the second leading cause of cancer-related death for men in the United States. It is estimated that in 2014 there will be 233,000 new cases and 29,480 deaths from prostate cancer.[1] More than 90% of all prostate cancers are discovered in the local or regional stages for which the 5-year relative survival rate approaches 100%. In contrast, the prognosis for advanced and metastatic disease is less favorable, with 5-year survival of less than 30%.[1] First-line treatment for advanced prostate cancer typically includes androgen deprivation therapy (ADT), either achieved surgically, or medically with gonadotropin-releasing hormone agonists or antagonists. Remissions occur in about 80%-90% of patients. Patients being managed with ADT who have evidence of disease progression (increasing serum prostate-specific antigen [PSA], new clinical metastases, progression of existing metastases) are considered to have castrate-resistant prostate cancer (CRPC).[2]

In May 2004, the US Food and Drug Administration (FDA) approved docetaxel as first-line chemotherapy treatment for metastatic CRPC (mCRPC) based on the TAX 327[3,4] and SWOG 9916[5] trials. For those patients who can tolerate taxane therapy, docetaxel has become standard of care for mCRPC.[6] Patients with mCRPC who have a progression after docetaxel therapy may receive re-challenge with docetaxel or be considered for other subsequent therapies. After docetaxel failure, the 2013 National Comprehensive Cancer Network

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(NCCN) treatment guidelines[7] included the use of the following treatment options: abiraterone acetate[8] or enzalutamide,[9] cabazitaxel,[10] radium 223,[11] docetaxel re-challenge, mitoxantrone, salvage chemotherapy, sipuleucel-T,[12] and participation in a clinical trial. These guidelines also include further secondary hormonal manipulations such as: antiandrogen, antiandrogen withdrawal, ketoconazole, and diethyl stilbestrol or other estrogen.

The array of treatments available for mCRPC is increasing but little is known about the pattern of treatment after docetaxel in real world settings such as the community oncology practice, where most of the patients are treated after they develop advanced disease. The present study was conducted as a retrospective observational study of real world treatment of community oncology patients with mCRPC who either progressed after or failed first-line docetaxel and who went on to receive subsequent treatment through December 31, 2012. Given the time frame of this study, the focus was on cabazitaxel and abiraterone because approval for enzalutamide (August 2012) and radium Ra 223 dichloride (May 2013) after docetaxel occurred outside this time frame. The principle objectives of this investigation were to: describe demographic and clinical characteristics of mCRPC patients who progressed during or after first-line docetaxel (D); describe differences among patients who received second-line cabazitaxel (DC) and those who received abiraterone (DA) or other treatment (DO); describe overall treatment patterns among second-line DC and DA patients, including sequencing of treatments through third-line therapy (DCA and DAC); and examine efficacy (progression-free survival [PFS] in line 1, line 2, and line 3, and overall survival [OS]) by treatment group.

Methods

Study design

This was a retrospective observational study conducted with data from the ACORN Data Warehouse, a comprehensive cancer patient database comprising demographic, medical, treatment, and patient-reported outcome (PRO) variables. All of the information was collected as part of routine care from 12 geographically diverse community oncology sites in the United States. Study protocol and procedures were approved by the institutional review board of IntegReview (Austin, Texas).

Inclusion and exclusion criteria

Patients selected for inclusion were patients in the ACORN Data Warehouse who met the following criteria:

- Confirmed diagnosis of mCRPC stage IV as indicated by ICD-9 diagnostic code of 185.x and statement within the medical record that the patient was hormone resistant or refractory or castration resistant, or evidence within the medical record that the patient had progressed on or following ADT.
- Received first-line docetaxel-based therapy as treatment for mCRPC. The first administration of docetaxel following mCRPC diagnosis was defined as first-line docetaxel-based therapy. This permitted inclusion of patients who may have received, for example, immunetherapy or some other therapy prior to receiving docetaxel.
- Experienced progression of disease during or following receipt of first-line docetaxel-based therapy.
- Progression on or after first-line docetaxel may have occurred at any point up to 60 days before the date of data abstraction, to provide sufficient time to classify patients based on subsequent treatment.
- Medical record had to identify the start and end dates of docetaxel therapy.
- Age 18 years or older as of date of diagnosis with mCRPC.
- Patients with other concurrent cancer (excluding basal cell carcinoma) or receiving therapy for another cancer were excluded.

Procedures

Emphasis was placed on patients who received either cabazitaxel or abiraterone at any point after progression either while on or following first-line treatment with docetaxel. All such patients were included. Among patients who had no record of cabazitaxel or abiraterone treatment at any point after progression on or after first-line docetaxel, a subset of patients was randomly selected so as to reach the planned study sample size. This sampling approach permitted better generalization to the population of patients within treatment groups or treatment sequence groups.

Statistical analyses

Descriptive statistics were used to describe demographic and clinical characteristics by line 2 (DC, DA, DO) and line 3 (DCA, DAC) treatment groups. Differences in the distribution of categorical variables across levels of comparison groups were assessed by chi-square tests of independence or Fisher's exact tests. T-tests, analyses of variance, or nonparametric equivalents were used to test the association of comparison group with continuous variables. Kaplan-Meier analysis with the log rank test was used to compare relevant groups on time to event outcomes (PFS, OS). Initial Cox regression models compared treatment groups on PFS and OS controlling for significant demographic and disease characteristics (ADT duration, age, race, body mass index, disease stage at initial diagnosis, Gleason score, performance status, number of comorbid conditions, and presence of each of bone, liver, and lung metastases. Final Cox regression models used stepwise deletion for covariate

selection with alpha = 0.05, two tailed.

Results

In all, 403 charts were reviewed, with 119 patients screened out and 284 in the final sample used for analysis. Of those screened out, 60 patients met other inclusion criteria but failed to have documented progression following line 1 docetaxel. Another 41 had insufficient documentation. Finally, 18 otherwise eligible cases were screened out because they had another cancer in addition to mCRPC. For the 284 patients in the study sample, dates for the start of first-line docetaxel treatment ranged from June 2003 to August 2012.

Table 1 shows demographic and clinical characteristics of the 3 line 2 groups comprised of 60 patients with DC, 71 with DA, and 153 with DO. Note that Table 1 includes 24 DO patients with no second-line treatment. There were no statistically significant differences between the 3 groups on baseline characteristics (all *P*'s > .20). Median patient age was 70 years, with 65% being white and 29% black. ECOG ratings of ≥ 2 or a Karnofsky score < 80% indicated impairment. In the absence of specific ratings, text reference to impairment consistent with ECOG of 2 or higher also indicated impairment. Derived classification indicated that about 15% of patients were impaired. The proportion of patients initially diagnosed with stage IV disease was nominally higher in the DC group (37%) than in the DA group (24%) or the DO group (27%) but not significantly higher. Metastatic disease occurred predominantly in bone (88%), with specific other sites at much lower rates. The most common comorbidity was diabetes (23%), followed by chronic obstructive pulmonary disease (COPD) and history of myocardial infarction (7% each), and is consistent with the overall tendency toward overweight, where median body mass index (BMI) was 27.93. Patients had a median of 2.82 previous years (mean, 3.84) of ADT.

PFS line 1 treatment

Median PFS for line 1 docetaxel treatment was not significantly different by the line 2 treatment group (DC, 7.51 months [95% CI, 5.79, 9.44]; DA, 7.76 [95% CI 5.98, 9.34]; DO, 7.97 [95% CI 6.84, 8.98], log rank chi square (2, 283) = 2.283, *P* = .560). Across lines of therapy and considering other methods used

TABLE 1 Baseline patient characteristics

Characteristics[a]	Treatment group DC n = 60	DA n = 71	DO n = 153	Total N = 284
Median age, y	70	71	70	70
Ethnic background, n (%)[b]				
White	41 (68)	46 (65)	98 (64)	185 (65)
Black	17 (28)	23 (32)	41 (27)	81 (29)
Hispanic	1 (2)	0 (0)	1 (1)	2 (1)
Other	0 (0)	1 (1)	0 (0)	1 (< 1)
Not available	1 (2)	1 (1)	13 (9)	15 (5)
Median body mass index	28.57	27.72	27.80	27.93
Performance status, n (%)[c]				
Impaired	8 (13)	12 (17)	23 (15)	43 (15)
Not indicated impaired	52 (87)	59 (83)	130 (85)	241 (85)
Stage at initial diagnosis, n (%)				
I-III	11 (18)	16 (23)	28 (18)	55 (19)
IV	22 (37)	17 (29)	42 (27)	81 (29)
Unknown	27 (45)	38 (54)	83 (54)	148 (52)
Metastatic Sites, n (%)				
Bone	57 (95)	61 (86)	131 (86)	249 (88)
Brain	0 (0)	1 (1)	2 (1)	3 (1)
Liver	4 (7)	5 (7)	18 (12)	27 (10)
Lung	3 (5)	8 (11)	18 (12)	29 (10)
Other	16 (27)	19 (27)	57 (37)	92 (32)
Median Gleason score	8.00	8.00	8.00	8.00
No. comorbidities, median (mean)	0 (0.60)	0 (0.62)	0 (0.63)	0 (0.62)
Comorbidity frequencies, n (%)				
AIDS	0 (0)	0 (0)	0 (0)	0 (0)
Alzheimer disease	0 (0)	1 (1.41)	2 (1)	3 (1)
Cerebrovascular accident	4 (7)	4 (6)	7 (5)	15 (5)
COPD	0 (0)	5 (7	16 (10)	21(7)
Cirrhosis	0 (0)	1 (1)	0 (0)	1 (< 1)
Congestive heart failure	0 (0)	3 (4)	5 (3)	8 (3)
Connective tissue disease	0 (0)	1 (1)	0 (0)	1 (< 1)
Diabetes	14 (23)	16 (23)	36 (24)	66 (23)
Hemiplegia	1 (2)	0 (0)	0 (0)	1 (< 1)
Leukemia	0 (0)	0 (0)	1 (< 1)	1 (< 1)

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(eg, measurable tumor, bone scan), the most commonly used method for documenting disease progression among physicians was PSA (71% in line 1, 50% line 2, 44% line 3).

TABLE 1 *continued*

Characteristics[a]	Treatment group DC n = 60	DA n = 71	DO n = 153	Total N = 284
Lymphoma	1 (2)	0 (0)	0 (0)	1 (< 1)
Metastatic solid tumor	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial infarction	6 (10)	6 (8)	9 (6)	21 (7)
Peripheral vascular disease	2 (3)	3 (4)	2 (1)	7 (2)
Renal disease	6 (10)	3 (4)	11 (7)	20 (7)
Ulcer disease	2 (3)	1 (1)	7 (5)	10 (4)
Prior ADT duration, median y	2.66	2.92	2.78	2.82
Alkaline phosphatase, median U/L	117.00	99.00	117.00	114.50
Hemoglobin, median g/dL	11.10	11.30	11.55	11.40
PSA, median ng/mL	221.00	82.00	111.45	112.00

ADT, androgen deprivation therapy; COPD, chronic obstructive pulmonary disease; PSA, prostate-specific antigen

[a]Characteristics assessed at start of line 2 treatment. [b]Percentages do not = 100 because of rounding. [c]Performance status classification based on Eastern Cooperative Oncology Group (ECOG) or Karnofsky if available, otherwise based on text information in the medical record. ECOG > 2,Karnofsky < 80%, and text reference to impairment were considered indicators of impairment.

No significant differences between groups on any baseline characteristics (all *P*'s > .20).

PFS line 2 treatment

There were 24 patients in the DO group who never received line 2 treatment. These patients were excluded from the analyses for line 2 treatment outcomes, which reduced the number of patients in the DO group from 153 to 129. The most common other therapies in the DO group were: ketoconazole, mitoxantrone, platinum combinations, and docetaxel re-challenge. Kaplan-Meier analysis showed that median PFS in line 2 by line 2 treatment group was not significantly different (DC, 5.23 months [95% CI 3.39, 6.08]; DA, 6.05 [95% CI 3.91, 7.83]; DO, 4.93 [95% CI 3.91, 5.69], log rank chi square (2, 260) = 0.97, *P* = .616). Cox regression analysis for PFS using significant covariates showed no overall treatment effect (*P* = .701), and larger BMI was associated with reduced risk, whereas stage IV at initial diagnosis and impaired performance status were associated with higher risk.

OS by line 2 treatment

Figure 1 shows the results of Kaplan-Meier analysis of OS from start of line 2 therapy by line 2 treatment group. As shown, there were no significant differences in OS by treatment group (log rank, *P* = .271). However, Cox regression analyses of these same data, controlling for other patient characteristics, showed a significant overall treatment group effect (*P* = .0338), with specific group effects as shown in Table 2. DA-treated patients were at higher risk of death than were DC patients (HR, 1.6934 [95% CI 1.0658, 2.6906]; *P* = .0258; Table 2), and compared with DC-treated patients, DO-treated patients were not at any significantly different risk. Other significant covariates associated with higher risk included: older age, presence of stage IV disease at first diagnosis, presence of bone metastasis, presence of liver metastasis, and a greater number of comorbidities. Higher BMI was associated with reduced risk. The race effect was modeled as a 3 level, white versus minority versus unknown race, but nearly all (81 of 84 minority patients were black (Table 1). Although the overall race effect was significant, it was driven mainly by the patients with unknown race (n = 15), most of whom were in the DO group, and for whom risk of death was significantly higher than for whites (HR, 3.7447; *P* = .0000). The risk for minority patients was nominally lower than for whites (HR, 0.9475; *P* = .7677).

Similar Cox regression modeling was conducted including the 24 untreated DO patients in line 2 (not shown). The pattern of results was similar to the model that included the 24 untreated DO patients, but the overall effect of treatment group fell short of significance (*P* = .1179) with DA having nominally higher risk compared with DC (HR, 1.4547; *P* = .1044), and DO similar to DC. Risk was significantly higher for older patients, with shorter ADT exposure, of unknown race compared with white patients, with lower BMI, performance impaired, and with liver metastasis. The differences in the 2 models were owing to changes in parameter estimates when the 24 untreated patients were included compared with when they were excluded. These 24 untreated DO patients tended to be older and have more comorbidities, and it is likely that they did not go on to receive line 2 treatment after docetaxel failure for those reasons.

Patterns of selected adverse events and supportive care treatment

Tracking of selected adverse events during line 2 treatment showed significantly more: anemia in the DC group (18%) compared with the DO group (7%), *P* = .0191, and neu-

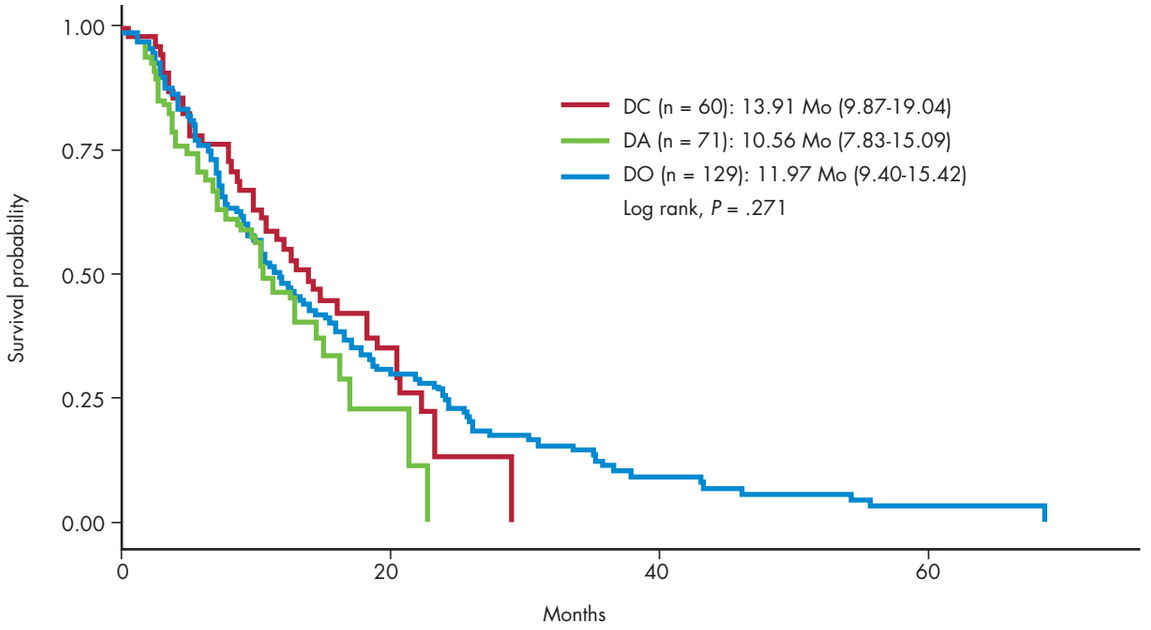

FIGURE 1 Overall survival by line 2 treatment group[a,b]

DA, docetaxel followed by abiraterone; DC, docetaxel followed by cabazitaxel; DO, docetaxel followed by other; mo, months

[a]Line 1 treatment = docetaxel (D). [b]Survival interval begins at line 2 of treatment. Excludes 24 untreated DO patients.

tropenia in the DC group (15%) compared with the DA group (1%), $P = .0096$. Proportionately more DC patients got granulocyte-colony stimulating factor (G-CSF; 77%) than either DA (3%) or DO (19%) patients, all Ps < .0001. In general, use of G-CSF was therapeutic rather than prophylactic.

Pain severity was recorded as either mild or moderate/severe based on examination of the medical record. Figure 2 shows rates of the 2 pain severity types by second-line treatment group both at the start of line 2 treatment and any point following. Differences between rates at baseline and at any point following reflect onset of pain after the start of line 2 treatment. At the start of line 2 treatment significantly more DA patients had mild pain compared with either DC or DO patients (all Ps < .024). At baseline, differences for moderate/severe pain were not significant ($P = .289$). Assessed any point after baseline neither the rates of mild pain nor the rates of moderate/severe pain differed significantly by treatment group ($P = .062$ and 0.126, respectively).

Hospitalization incidence was also recorded over the entire medical record. Measured from the start of second-line therapy to the end of the medical record, there appeared to be no significant differences among the treatment groups – DC (50%), DA (48%), DO (56%) – in terms of patients hospitalized or number of hospitalizations.

Efficacy and treatment sequencing pattern in line 3

Among patients who received either C or A following D, there was a limited subsample that went on to receive line 3 treatment (DCA, n = 34; DAC, n = 18). Comparison of demographic and clinical characteristics for these 2 subsamples showed no significant differences (all Ps > .28). Kaplan-Meier analysis of PFS in line 3 treatment showed no significant group differences (DCA, 4.64 months [95% CI, 3.42,6.02]; DAC, 4.87 [95% CI, 2.30,7.10], log rank chi square (1, 52) = 0.048, $P = .4884$), nor did Cox regression analyses controlling for other covariates. Presence of bone metastasis was the only significant predictor of disease progression in this limited sample (HR, 7.7932; $P = .0126$).

There was a tendency for C to be underused in line 3 treatment compared with A (Figure 3). Of patients receiving DC in second-line, a nominally greater proportion received A in the third line (57%, 34 of 60 patients), compared with second-line DA patients who received C in the third line (25%, 18 of 71 patients).

Discussion

This retrospective observational study of mCRPC patients treated in the community oncology setting after first-line exposure to docetaxel shows that treatment patterns and treatment sequencing in the postdocetaxel setting is fairly

TABLE 2 Cox regression for overall survival from line 2 treatment by line 2 treatment group with significant covariates[a,b]

Effect	HR	95% LCL	95% UCL	*P* value
Treatment (vs DC)				
DA	1.6934	1.0658	2.6906	.0258
DO	1.0286	0.7024	1.5062	.8849
Age	1.0288	1.0102	1.0478	.0023
Race (vs white)				
Minority	0.9475	0.6623	1.3554	.7677
Unknown	3.7447	2.0258	6.9223	.0000
BMI	0.9242	0.8940	0.9554	.0000
Stage at diagnosis (vs I-III)				
IV	2.0604	1.2863	3.3003	.0026
Unknown	1.0514	0.6910	1.5999	.8150
Metastasis				
Bone	1.7307	1.0228	2.9284	.0410
Liver	2.2931	1.4252	3.6895	.0006
No. of comorbidities	1.2298	1.0186	1.4847	.0314

BMI, body mass index; DA, docetaxel followed by abiraterone; DC, docetaxel followed by cabazitaxel; DO, docetaxel followed by other; LCL, lower confidence limit; UCL, upper confidence limit.

[a]Reference level: Treatment = DC; white = Yes; Stage at diagnosis = I-III; Impaired performance = No; Bone metastasis = No; Liver metastasis = No; Lung metastasis = No [b]Survival interval begins at line 2 of treatment. 24 DO patients with no line 2 treatment are excluded. Significant covariates selected by backward deletion alpha = 0.05, two tailed.

complex. We focused on patients who received either cabazitaxel (DC) or abiraterone (DA) in line 2 treatment and compared their clinical efficacy with a random sample of patients who received other therapies (including no treatment; DO) in the postdocetaxel setting. In regard to demographic and clinical characteristics, our overall patient sample was generally comparable with the patient samples in the TROPIC (cabazitaxel)[10] and COU-301 (abiraterone)[8,13] trials. Line 1 docetaxel was frequently followed by hormonal agents before disease progression, and docetaxel re-challenge was one of the more common treatments after progression for DO patients. When we excluded 24 untreated cases in the DO sample, Cox regression analyses of OS showed that patients receiving DA were at greater risk for death (HR, 1.69; $P = .026$) than were DC patients who did not differ significantly from DO patients. The pattern of findings was similar but was not statistically significant in a comparable analysis that included the 24 untreated DO cases. The 24 untreated DO cases seemed to carry significant weight in the second analysis because they were older and had more comorbid conditions that might have been associated with them being "selected" for nontreatment in the postdocetaxel setting. Although we observed a greater risk of death in the DA group compared with the DC group, these results need to be validated in a prospective study before assigning a high degree of confidence in the results.

In this community oncology sample, we did not observe much use of experimental agents (4%), and most of that occurred in line 1 treatment. In line 2 treatment, use of G-CSF was more common in DC patients than either DA or DO patients, and most of that use occurred as postneutropenia intervention rather than preventive or prophylactic treatment. Line 2 toxicities (anemia, neutropenia, diarrhea, nausea, renal failure) tended to occur more often in DC patients than in the other 2 groups, as expected from the phase 3 study results. Our sample for line 3 treatment was limited, but we did observe that proportionately more patients getting DC went on to get abiraterone in line 3 than did DA patients who went on to get cabazitaxel after line 2 DA. It is possible that treating physicians perceived cabazitaxel as being less tolerable for patients who go on to receive line 3 treatment, but we could not find enough documentation of that type of reasoning from the medical records. In general documentation for preferring one treatment over another in line 3 was poor.

We did observe that more patients who received abiraterone in line 2 had a record of mild pain compared with either DC or DO patients. The incidence of moderate/severe pain was comparable across all 3 groups. One might speculate that patients with mild pain may be preferred for abiraterone in light of recent findings that support more sustained quality of life maintenance and pain management in patients treated with abiraterone and prednisone compared with placebo and prednisone for mCRPC.[14,15]

The clinical implications of this investigation are interesting from the standpoint of undertreatment of some patients. We found a subset of patients who received first-line docetaxel but did not go on to receive additional treatment. More information is needed about this phenomenon using larger samples of patients. For example, are these patients at higher risk for toxicities? Are some of these patients opting not to pursue further treatment and if so, what are their reasons for opting out of further treatment? Is cost a factor in these decisions? We also found that among patients who went on to a third line of therapy, cabazitaxel seemed to be less frequently used than was abiraterone, but we were not able to ascertain if that was due to actual or perceived differences in the tolerability of the 2 drugs.

A major limitation of our study was the small sample of patients, at the time of the study, available for analysis in

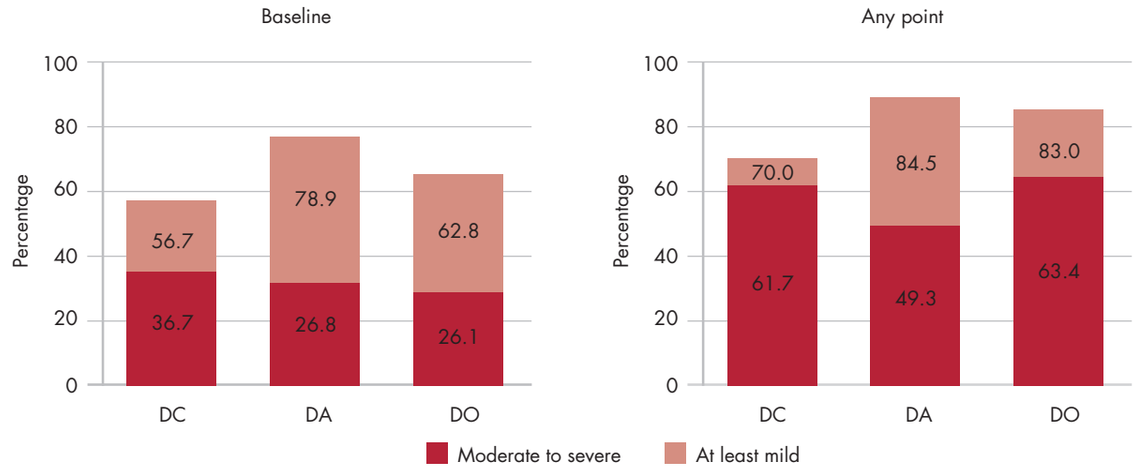

FIGURE 2 Pain severity during line 2 treatment by treatment group at baseline and any point following[a]

DA, docetaxel followed by abiraterone; DC, docetaxel followed by cabazitaxel; DO, docetaxel followed by other

[a]Line 1 treatment = docetaxel (D)

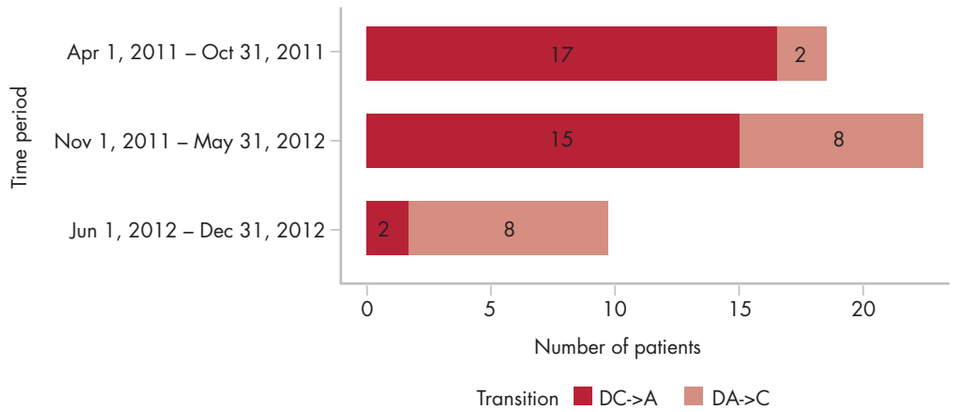

FIGURE 3 Treatment patterns for patients receiving line 3 treatment with cabazitaxel (C) and abiraterone (A), by time period[a]

DA, docetaxel followed by abiraterone; DC, docetaxel followed by cabazitaxel

[a]Line 1 treatment = docetaxel (D)

line 3 treatment. It is likely that with the advent of more treatments coming on line, increasing numbers of mCRPC patients will go on the third-line treatment. This certainly needs further examination to evaluate how actual practice is conducted beyond progression on or after first-line docetaxel. We also found that medical records even those including physician notes are not sufficient to provide information about certain decision processes such as reasons for the choice of one treatment over another and reasons for recommending no further treatment. Methods for collecting patient-reported information about treatment decision making could add valuable information to medical records. We believe that our sample is representative of community oncology practice in the United States, but the results might not generalize to other settings such as academic centers and hospital based care. Finally, unexamined confounding variables and selection biases can be assumed to be present in observational research, and these factors may have affected the study findings in unknown ways.

Retrospective observational research of this type offers valuable insights into real world practice and treatment effectiveness in community oncology settings, the place where most cancer patients receive treatment.[16] Further research should examine recent trends toward use of hormonal agents such as abiraterone prior to docetaxel, the use of radium 223, and the impact of these on the timing of

cabazitaxel use. Future work should also include evaluation of patient reported symptom burden and health related quality of life across the continuum of care in order to provide better evidence for the impact of available treatments from the perspective of patient experience. Given the poor outcomes associated with mCRPC that has progressed after docetaxel treatment, all active agents should be considered and evaluated in this patient population.

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