Sequencing of Cabazitaxel and Abiraterone Acetate After Docetaxel in Metastatic Castration-Resistant Prostate Cancer: Treatment Patterns and Clinical Outcomes in Multicenter Community-Based US Oncology Practices

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Abstract

The optimal treatment sequence for metastatic castration-resistant prostate cancer (mCRPC) is undetermined. Retrospective assessment of 350 patients with mCRPC receiving different sequences of cabazitaxel (C) or abiraterone acetate (A), or both, after docetaxel (D) treatment suggested that receipt of all 3 agents was associated with improved overall survival (OS) versus the use of 2 agents ($P = .0002$) in a multivariable analysis. OS was increased with DCA versus DAC ($P = .0210$).

Background: Optimal sequencing of cabazitaxel (C) and abiraterone acetate (A) after docetaxel (D) for metastatic castration-resistant prostate cancer (mCRPC) is unclear. We assessed treatment patterns and outcomes in patients with mCRPC receiving different sequences of A or C, or both, after administration of D. **Methods:** Retrospective analysis was conducted of US Oncology Network iKnowMed (iKM) electronic health record (EHR) data to assess patients with mCRPC who received treatment with D and were subsequently treated with C or A, or both, between April 2011 and May 2012. Patients received 2 or 3 drugs: DA, DC, DAC, or DCA. Overall survival (OS) and time to treatment failure (TTF) were analyzed by the Kaplan-Meier method from the start to the end of second-line therapy after administration of D (TTF1) and to the end of combined second- and third-line therapy (TTF2) for 3-drug sequences. Multivariable Cox proportional hazard models evaluated the impact of baseline clinical prognostic factors and treatment sequence on OS and TTF. **Results:** Of 350 patients who were treated with D and subsequent therapies, 183 (52.3%) received DA, 54 (15.4%) received DC, 77 (22.0%) received DCA, and 36 (10.3%) received DAC. In a multivariable analysis, adjusted comparisons suggested that 3-drug sequences were associated with improved OS versus 2-drug sequences (hazard ratio [HR], 0.21; 95% confidence interval [CI], 0.092-0.476; $P = .0002$). There were no statistically significant differences in OS and TTF for DC versus DA, and OS was significantly greater for DCA versus DAC (HR, 0.13; 95% CI, 0.022-0.733; $P = .0210$). More cycles of C were administered in DCA than in DAC (median 6 vs. 4; t test $P < .0001$), whereas the duration of A treatment was similar. **Conclusion:** Administration of 3 agents in the DCA sequence was more optimal for treating mCRPC in this hypothesis-generating study.

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Keywords: Clinical outcomes, Electronic health record, mCRPC, Retrospective, Treatment sequence

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Introduction

First-line chemotherapy for metastatic castration-resistant prostate cancer (mCRPC) with docetaxel (D) every 3 weeks plus prednisone yields a median overall survival (OS) of nearly 19 months.[1-3] Recent approval of many new promising treatments for prostate cancer has led to a marked expansion of the therapeutic arsenal in this clinical setting. Cabazitaxel (C), abiraterone acetate (A), and enzalutamide improve OS when administered after treatment with D.[4-6] Treatment with A and enzalutamide have also extended survival in chemotherapy-naive patients.[7,8] Moreover, sipuleucel-T prolonged survival in minimally symptomatic patients and radium-223 prolonged survival in patients after administration of D or in chemotherapy-ineligible patients with symptomatic bone metastases.[9,10] Further complicating decisions around sequencing of agents in the metastatic prostate cancer setting is the release of interim data from the National Cancer Institute–sponsored Eastern Cooperative Oncology Group 3805 (ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer [CHAARTED]) study, which revealed an OS advantage in patients with hormone-sensitive prostate cancer and extensive metastatic disease who received D plus androgen-deprivation therapy (ADT) versus ADT alone.[11]

Given the rapid proliferation of systemic therapies for mCRPC, optimal sequencing after administration of D is an important treatment consideration; however, the influence of sequencing on OS remains unknown. Prospective trials comparing all possible sequences of agents are unlikely to be conducted. McKesson Specialty Health's iKnowMed (iKM) electronic health record (EHR) system offers an opportunity to analyze and compare outcomes for different sequences of therapy and may offer useful insights and generate hypotheses when controlling for other known clinicopathologic prognostic factors.

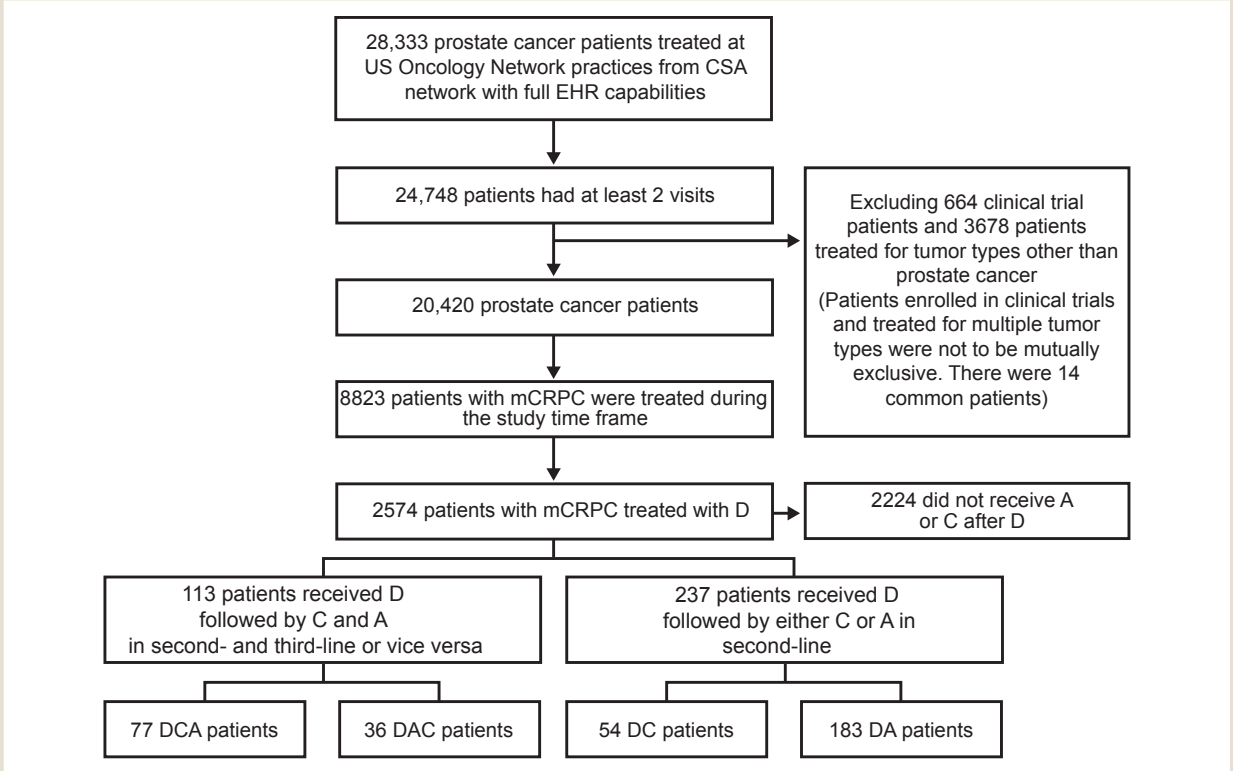
The first objective of the current retrospective study was to characterize patients receiving different sequences of C and A after D, and the second objective was to estimate and compare clinical outcomes in patients receiving these different sequences of therapy. At the time this study was conceived, only C and A were approved for the treatment of mCRPC after administration of D. We evaluated treatment patterns, OS, and time to treatment failure (TTF) among patients with mCRPC receiving A or C, or both, after administration of D and report the influence of number of lines of therapy after treatment with D and the potential effect of specific prognostic factors on outcomes.

Patients and Methods

Study Design and Patient Population

This study consisted of 350 men with mCRPC who had received D and were subsequently administered C or A, or both, from April

Figure 1 Consort Diagram



Abbreviations: A = abiraterone acetate; C = cabazitaxel; CSA = Comprehensive Strategic Alliance; D = docetaxel; DA = docetaxel followed by abiraterone; DAC = docetaxel followed by abiraterone acetate and then cabazitaxel; DC = docetaxel followed by cabazitaxel; DCA = docetaxel followed by cabazitaxel and then abiraterone acetate; EHR = electronic health record; mCRPC = metastatic castration-resistant prostate cancer.

2011 (when both C and A were commercially available in the United States) to May 2012. For inclusion in this study, patients within the McKesson Specialty Health/US Oncology Network database were required to have had at least 2 visits within the US Oncology Network and to have received care at a Comprehensive Strategic Alliance practice using the full EHR capacities of the iKM database. Patients were excluded if they were enrolled in a clinical trial or diagnosed with other tumors during the index period.

Data Sources

Data were primarily abstracted from McKesson Specialty Health's iKM EHR, which receives input from more than 1000 medical oncologists from 350 oncology centers in 19 US states. This database includes more than 850,000 patients (12% of the US cancer population). The data obtained consisted of demographics and clinical, laboratory, and treatment data. Chart review was conducted by clinical staff, which included nurses and pharmacists, to supplement data captured by programmatic queries of the iKM EHR. Documented vital status identified in iKM was supplemented with date of death data from the Social Security Death Master File. The patients' Social Security numbers were used for data linkage between iKM and the Social Security Death Master File.

Statistical Analysis

OS was measured from the date of initiation of second-line therapy after administration of D to date of death, censoring patients who were still alive at last contact. TTF was assessed in 2 ways: TTF1 was the time from initiation to the end of second-line treatment or death, whichever came first, and TTF2 was the time from the initiation of second-line treatment to the end of third-line treatment or death, whichever came first. Descriptive statistics with 95% confidence intervals (CIs) were used to describe patient demographics and clinical characteristics and frequency counts and percentages were used to evaluate the reasons for treatment discontinuation. A Fisher test/χ^2 test for categorical data or a *t* test/Kruskal-Wallis test for continuous variables was conducted to determine statistically significant differences in patient characteristics by treatment group. Median time to OS and TTF end points were analyzed by the Kaplan-Meier method. A multivariable Cox proportional hazards model was used to examine OS and TTF end points, adjusting for the effect of covariate prognostic factors, which were selected based on accessibility of measurements and their usefulness for clinical prognostication or subject stratification, or both, in clinical trials.[12]

The primary variable for comparison was drug treatment sequence, specifically within the 2-drug cohort comparing DC versus DA and in the 3-drug cohort comparing C followed by A after D (DCA) versus A followed by C after D (DAC), and then comparing results from the 2- versus 3-drug sequences. Covariates analyzed for effects on OS and TTF included age (in years) at the initiation of second-line therapy, the Prostate Cancer Clinical Trial Working Group subtype based on location of metastasis (bone with or without lymph node metastasis and visceral or other metastasis), use of narcotics, duration of baseline D treatment, duration of second-line therapy in the 3-drug cohort, Charlson comorbidity index (CCI) score, interaction of treatment and time, Gleason score, and baseline prostate-specific antigen (PSA), alkaline phosphatase, hemoglobin (considered anemic if < 13 g/L), and lactate dehydrogenase levels.

Results

Baseline Demographic and Clinical Characteristics

After screening 28,333 individuals with prostate cancer in the US Oncology Network EHR, 350 patients with mCRPC who received treatment with D met study eligibility criteria; 113 of these patients were treated with both C and A, and 237 patients were treated with only 1 of these agents (Figure 1). Among patients using 3 lines of therapy, 77 received DCA and 36 received DAC. Within the 2-drug cohort, 183 patients received A after D (DA) and 54 received C after D (DC). The median duration of D treatment (6 cycles) was

Table 1 Drug Exposure and Treatment Discontinuation Rates

	Two-Drug Sequence				Three-Drug Sequence			
	Total (N = 237)	DC (n = 54)	DA (n = 183)	*P* Value	Total (N = 113)	DCA (n = 77)	DAC (n = 36)	*P* Value
Docetaxel cycles, n								
Mean (SD)	7.72 (6.14)	7.44 (4.29)	7.80 (6.59)		8.08 (5.72)	8.01 (5.72)	8.25 (5.79)	
Median	6	6.5	6		6	6	6.5	
Range	1-45	2-19	1-45		1-32	1-30	2-32	
95% CI	6.93-8.50	6.27-8.61	6.84-8.76	.7484	7.02-9.15	6.71-9.31	6.28-10.21	.5712
Cabazitaxel cycles, n								
Mean (SD)	–	5.98 (4.93)	–		6.51 (4.22)	7.58 (4.25)	4.22 (3.13)	
Median	–	5	–		5	6	4	
Range	–	1-20	–		1-19	1-19	1-17	
95% CI	–	7.32-4.63	–		5.72-7.30	6.61-8.54	3.16-5.28	<.0001
A discontinuation rates within 3 mo, n (%)	–	–	39 (21.3)		46 (40.7)	32 (41.6)	14 (38.9)	.7878

Abbreviations: CI = confidence interval; DA = docetaxel followed by abiraterone acetate; DAC = docetaxel followed by abiraterone acetate and then cabazitaxel; DC = docetaxel followed by cabazitaxel; DCA = docetaxel followed by cabazitaxel and then abiraterone acetate; SD = standard deviation.

Table 2 Demographic and Clinical Characteristics

	Two-Drug Sequence			Three-Drug Sequence			Two- vs. Three-Drug *P* Value
	Total (N = 237)	DC (n = 54)	DA (n = 183)	Total (N = 113)	DCA (n = 77)	DAC (n = 36)	
Age, years	n = 237	n = 54	n = 183	n = 113	n = 77	n = 36	
Mean (SD)	72.7 (9.1)	71.2 (9.8)	73.1 (8.9)	68.5 (9.1)	68.1 (9.2)	69.3 (8.7)	
Median	73	72.5	73	69	69	68	
Range	39-94	39-88	49-94	46-89	46-86	51-89	
95% CI	71.5-73.9	68.5-73.9	71.8-74.4	66.8-70.2	66.0-70.2	66.3-72.3	<.0001
CCI, n (%)	n = 193	n = 50	n = 143	n = 113	n = 77	n = 36	
6	107 (55.4)	29 (58.0)	78 (54.6)	68 (60.2)	50 (64.9)	18 (50.0)	
7-8	68 (35.2)	16 (32.0)	52 (36.4)	40 (35.4)	22 (28.6)	18 (50.0)	
9-10	17 (8.8)	5 (10.0)	12 (8.4)	3 (2.7)	3 (3.9)	0	
≥11	1 (0.5)	0	1 (0.7)	2 (1.8)	2 (2.6)	0	.1089
Missing	44	4	40	0	0	0	
Metastatic Location, n (%)	n = 237	n = 54	n = 183	n = 113	n = 77	n = 36	
Bone	209 (88.2)	49 (90.7)	160 (87.4)	100 (88.5)	66 (85.7)	34 (94.4)	
Liver	19 (8.0)	5 (9.3)	14 (7.7)	13 (11.5)	8 (10.4)	5 (13.9)	
Lung	31 (13.1)	6 (11.1)	25 (13.7)	13 (11.5)	11 (14.3)	2 (5.6)	
Lymph nodes	69 (29.1)	15 (27.8)	54 (29.5)	40 (35.4)	26 (33.8)	14 (38.9)	
Visceral	16 (6.8)	3 (5.6)	13 (7.1)	16 (14.2)	13 (16.9)	3 (8.3)	
CNS/not brain	3 (1.3)	0	3 (1.6)	0	0	0	
Other	15 (6.3)	4 (7.4)	11 (6.0)	12 (10.6)	9 (11.7)	3 (8.3)	
Gleason Score, n (%)	n = 166	n = 32	n = 134	n = 86	n = 60	n = 26	
≤6	28 (16.9)	4 (12.5)	24 (17.9)	6 (7.0)	6 (10.0)	0	
7	43 (25.9)	11 (34.4)	32 (23.9)	23 (26.7)	16 (26.7)	7 (26.9)	
8-10	95 (57.2)	17 (53.1)	78 (58.2)	57 (66.3)	38 (63.3)	19 (73.1)	.0296
Missing[a]	65	21	44	27	17	10	
Second-Line Therapy Duration, days				n = 113	n = 77	n = 36	
Mean (SD)	–	–	–	524.4 (308.8)	555.7 (325.6)	455.3 (260.1)	
Median	–	–	–	445	487	394.5	
Range	–	–	–	77-1755	77-1755	77-1183	
95% CI	–	–	–	466.8-581.9	482.8-630.6	367.3-543.3	
Narcotic Use, n (%)	172 (72.6)	40 (74.1)	132 (72.1)	93 (82.3)	66 (85.7)	27 (75.0)	
Stage at Diagnosis, n (%)	n = 237	n = 54	n = 183	n = 113	n = 76	n = 37	
I	3 (1.3)	1 (1.9)	2 (1.1)	0	0	0	
II	31 (13.1)	6 (11.1)	25 (13.7)	15 (13.3)	11 (14.5)	4 (10.8)	

Table 2 Continued

	Two-Drug Sequence			Three-Drug Sequence			Two- vs. Three-Drug *P* Value
	Total (N = 237)	DC (n = 54)	DA (n = 183)	Total (N = 113)	DCA (n = 77)	DAC (n = 36)	
III	28 (11.8)	5 (9.3)	23 (12.6)	18 (15.9)	11 (14.5)	7 (18.9)	
IV	141 (59.5)	32 (59.3)	109 (59.6)	70 (61.9)	50 (65.8)	20 (54.1)	
Unknown	34 (14.3)	10 (18.5)	24 (13.1)	10 (8.8)	4 (5.3)	6 (16.2)	
Prostate-Specific Antigen, ng/mL	n = 228	n = 52	n = 176	n = 107	n = 71	n = 36	
Mean (SD)	313.4 (818.6)	494.4 (1183.2)	259.9 (669.8)	392.9 (1156.0)	515.1 (1397.1)	152.0 (230.1)	
Median	67.1	159.7	57.0	97.1	111.8	76.7	
Range	0.09-8250	3.6-8250	0.09-6323	0.80-8755	0.87-8755	0.80-1116	
95% CI	206.5-420.2	165.0-823.8[b]	160.2-359.5[b]	171.4-614.5	184.4-845.8	74.1-229.8	.1383
Lactate dehydrogenase, U/L	n = 72	n = 12	n = 60	n = 32	n = 19	n = 13	
Mean (SD)	232.8 (113.6)	243.8 (57.6)	230.6 (121.9)	215.0 (83.2)	204.7 (99.4)	229.9 (51.7)	
Median	207	234.5	201	199	180	226	
Range	4-718	161-358	4-718	114-502	114-502	176-363	
95% CI	206.1-259.4	207.2-280.3	199.1-262.1	185.0-245.0	156.8-252.6[b]	198.7-261.2[b]	.4725
Alkaline phosphatase, U/L	n = 230	n = 51	n = 179	n = 111	n = 76	n = 35	
Mean (SD)	177.6 (264.6)	190.6 (250.9)	173.9 (269.0)	196.2 (285.6)	208.8 (326.8)	168.7 (165.0)	
Median	102	113	99	100	100	101	
Range	3.78-2495	31-1649	3.78-2495	34-2342	34-2342	44-914	
95% CI	143.2-212.0	120.0-261.1	134.2-213.6	142.4-249.1	134.1-283.5	112.0-225.4	.7290
Hemoglobin, g/dL	n = 229	n = 51	n = 178	n = 111	n = 76	n = 35	
Mean (SD)	11.5 (1.8)	11.3 (2.1)	11.5 (1.7)	11.6 (1.8)	11.5 (1.8)	12.0 (1.8)	
Median	11.6	11.3	11.6	11.7	11.6	12.0	
Range	3.6-19.1	3.6-15.6	8.1-19.1	7.3-17.5	8.1-15.9	7.3-17.5	
95% CI	11.2-11.7	10.7-11.9	11.3-11.8	11.3-12.0	11.0-11.9	11.4-12.7	.4638

Abbreviations: CCI = Charlson comorbidity index; CI = confidence interval; CNS = central nervous system; DA = docetaxel followed by abiraterone acetate; DAC = docetaxel followed by abiraterone acetate and then cabazitaxel; DC = docetaxel followed by cabazitaxel; DCA = docetaxel followed by cabazitaxel and then abiraterone acetate; SD = standard deviation.

[a]Unknown/missing combined for 3-drug cohort.

[b]$P < .05$ within cohort.

similar in all groups of patients (Table 1). In comparing baseline characteristics between groups and cohorts, parameters were generally well matched with few exceptions (Table 2). Specifically, in the 2-drug cohort, the median PSA level was significantly higher with DC than with DA (159.7 vs. 57.0 ng/mL; $P = .0014$). In the 3-drug cohort, the median baseline lactate dehydrogenase level was significantly higher in patients receiving DAC compared with those receiving DCA (226 vs. 180 U/L; $P = .0301$). Patients receiving all 3 drugs were significantly younger (median 69 vs. 73 years; $P < .0001$) and had a higher frequency of visceral metastasis ± other site clinical subtype (42.3% vs. 29.4%), whereas the 2-drug group had a higher frequency of bone ± lymph node clinical subtype (70.6% vs. 57.7%; $P = .0204$).

Clinical Outcomes

In the 2-drug cohort, crude estimates indicated a significantly higher median OS for the DA sequence compared with the DC sequence (17.0 vs. 7.0 months; $P = .0002$) and a numerically higher TTF with DA compared with DC, although this did not reach statistical significance (4.0 vs. 3.0 months; $P = .7635$) (Table 3). However, when comparing the DC sequence using DA as reference in a multivariable analysis, adjusted comparisons did not indicate treatment sequence as a significant covariate, suggesting no difference in the risk of mortality ($P = .1183$) or TTF ($P = .6480$) between the DA and DC cohorts. Other covariates that appeared to be associated with OS in this multivariable analysis included narcotic use (hazard ratio [HR], 2.48; 95% CI, 1.167-5.277), baseline hemoglobin level (HR, 0.72; 95% CI, 0.593-0.872), and baseline D treatment duration (HR, 0.95; 95% CI, 0.915-0.987) (Table 3). The latter result was observed despite the median number of D cycles not significantly differing between groups (DC, 6.5 [range, 2-19] cycles; DA, 6.0 [range, 1-45] cycles; $P = .7484$) (Table 3). None of the covariates in the multivariable analysis were associated with TTF.

In the 3-drug cohort, crude estimates indicated a significantly higher median OS with DCA than with DAC (18.2 vs. 11.8 months; $P = .0023$) (Figure 2A). In addition, when comparing the DCA sequence using DAC as the reference in a multivariable analysis, adjusted comparisons of OS indicated that treatment sequence was a significant covariate, suggesting a lower risk of mortality in the DCA versus DAC cohorts ($P = .0210$). Other covariates—including the CCI (HR, 1.33; 95% CI, 1.060-1.674), duration of second-line therapy (HR, 1.00; 95% CI, 0.992-0.998), and baseline PSA level per 100 ng/mL (HR, 1.02; 95% CI, 1.006-1.041)—appeared to be associated with OS in this multivariable analysis (Table 3). The crude

Table 3 Summary of Effectiveness Outcomes and Multivariable Analysis Results[a]

Outcome			Multivariable Analysis		
			Significant Covariates	HR (95% CI)	*P* Value
Two-Drug Sequence[b]	DC (n = 54)	DA (n = 183)			
Median OS,[c] months (95% CI)	7.0 (5.0-12.0)	17.0 (14.0-NE)	Narcotic use	2.48 (1.167-5.277)	.0182
			Baseline treatment duration	0.95 (0.915-0.987)	.0082
			Baseline hemoglobin	0.72 (0.593-0.872)	.0008
Median TTF, months (95% CI)	3.0 (2.0-4.0)	4.0 (3.0-5.0)			
Three-Drug Sequence[d]	DCA (n = 77)	DAC (n = 36)			
Median OS,[c] months (95% CI)	18.2 (16.0-22.0)	11.8 (9.8-14.4)	Sequence (DCA vs. DAC)	0.13 (0.022-0.733)	.0210
			CCI	1.33 (1.060-1.674)	.0141
			Second-line treatment duration	1.00 (0.992-0.998)	.0006
			PSA/100 ng/mL	1.02 (1.006-1.041)	.0072
Median TTF1,[c] months (95% CI)	5.2 (4.3-7.0)	4.3 (2.4-5.1)	Narcotic use	1.86 (1.012-3.408)	.0457
Median TTF2,[c] months (95% CI)	10.4 (9.2-12.1)	7.1 (5.6-8.1)	Sequence (DCA vs. DAC)	0.18 (0.050-0.644)	.0084
Three versus Two-Drug Sequence[e]	Three-Drug (n = 113)	Two-Drug (n = 237)			
Median OS, months (95% CI)	17.0 (14.0-20.0)	17.0 (13.0-NE)	Treatment (3-drug vs. 2-drug)	0.21 (0.092-0.476)	.0002
			Narcotic use	2.01 (1.240-3.259)	.0046
			Baseline PSA level	1.01 (1.001-1.027)	.0369
			Baseline AP level	1.00 (1.000-1.001)	.0038
			Time on sequence	0.87 (0.806-0.946)	.0009

Abbreviations: AP = alkaline phosphatase; CCI = Charlson comorbidity index; CI = confidence interval; DA = docetaxel followed by abiraterone acetate; DAC = docetaxel followed by abiraterone acetate and then cabazitaxel; DC = docetaxel followed by cabazitaxel; DCA = docetaxel followed by cabazitaxel and then abiraterone acetate; HR = hazard ratio; NE = not estimated; OS = overall survival; PSA = prostate-specific antigen; TTF = time to treatment failure; TTF1 = TTF from start of second-line therapy after docetaxel treatment to end of second-line therapy; TTF2 = TTF from start of second-line therapy after docetaxel treatment to end of combined second- and third-line therapies.

[a]Only significant covariates shown.

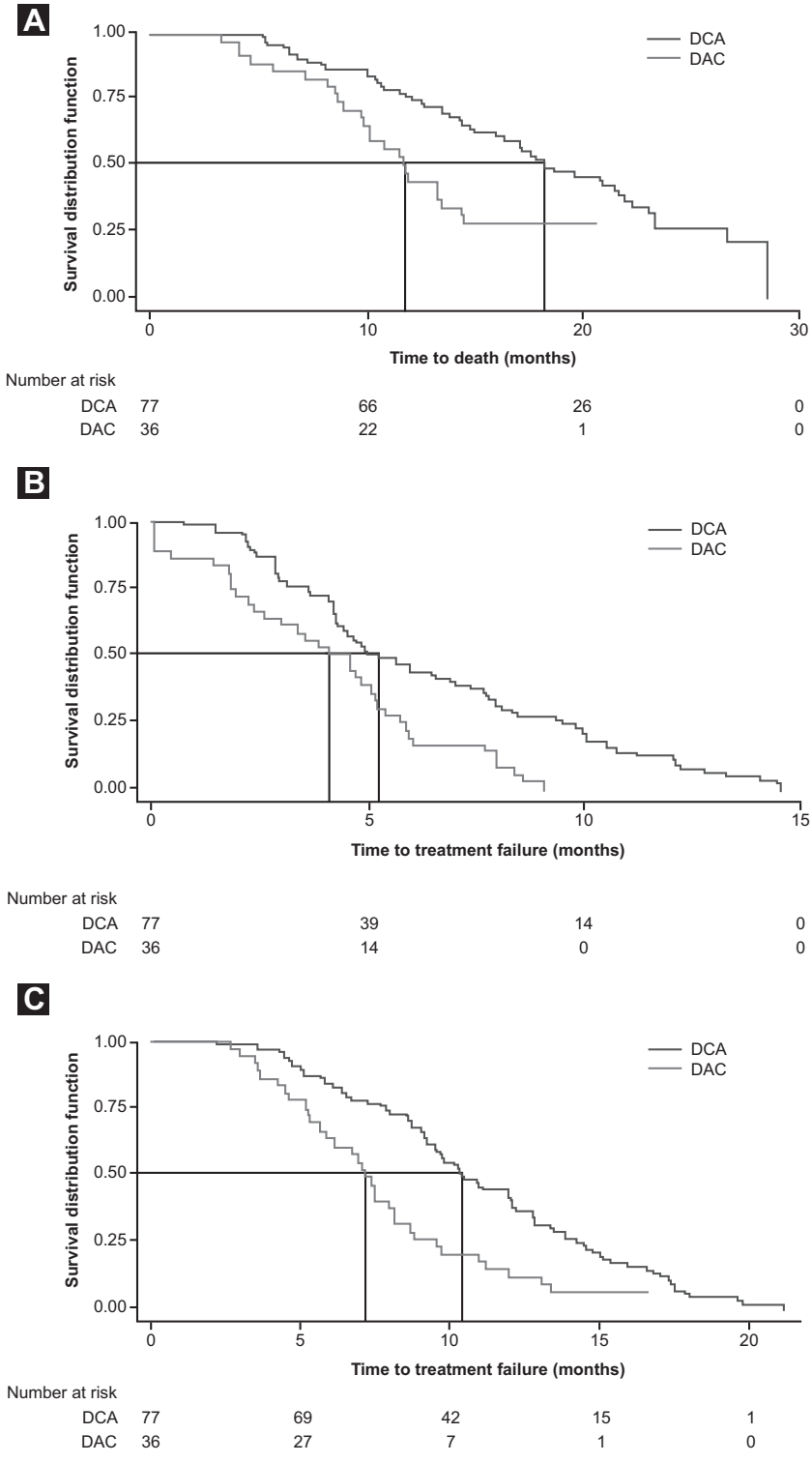
[b]Total covariates included sequence (DC vs. DA), Charlson comorbidity index, bone ± lymph node metastasis (vs. visceral/other metastasis), anemia, narcotic use, age, baseline PSA level, baseline (docetaxel) treatment duration, Gleason score, baseline AP level, baseline hemoglobin value, and treatment versus time interaction.

[c]$P < .01$.

[d]Total covariates included sequence (DCA vs. DAC, Charlson comorbidity index, bone ± lymph node metastasis (vs. visceral/other metastasis), anemia, narcotic use, duration of second-line therapy, age, baseline PSA level, baseline treatment duration, and treatment versus time interaction.

[e]Total covariates included drug cohort (3 vs. 2 medications), Charlson comorbidity index, bone ± lymph node metastasis (vs. visceral/other metastasis), anemia, narcotic use, age, baseline PSA level, baseline (docetaxel) treatment duration, baseline AP level, and treatment versus time interaction.

Figure 2 Three-Drug Sequence Results. Unadjusted Kaplan-Meier Plots Show Results for (A) Overall Survival, (B) Time to Treatment Failure From Start to End of Second-Line Therapy, and (C) Time to Treatment Failure From Second-Line to the End of Third-Line Therapy



Abbreviations: DAC = docetaxel followed by abiraterone acetate and then cabazitaxel; DCA = docetaxel followed by cabazitaxel and then abiraterone acetate.

Table 4 Drug Discontinuation Rates and Reason by Cohort and Sequence

	Two-Drug Sequence		Three-Drug Sequence			
	DC (n = 54)	DA (n = 183)	DCA (n = 77)	DAC (n = 36)	DCA (n = 77)	DAC (n = 36)
Drug Discontinued, n (%)	C	A	C		A	
Death	2 (3.7)	12 (6.6)	0	0	3 (3.9)	1 (2.8)
No response to treatment	0	2 (1.1)	2 (2.6)	0	2 (2.6)	1 (2.8)
Patient choice	2 (3.7)	5 (2.7)	2 (2.6)	2 (5.6)	2 (2.6)	0
Physician choice	3 (5.6)	1 (0.5)	3 (3.9)	0	0	0
Progression or relapse	22 (40.7)	86 (47.0)	43 (55.8)	21 (58.3)	33 (42.9)	26 (72.2)
Toxicity	8 (14.8)	8 (4.4)	7 (9.1)	3 (8.3)	3 (3.9)	1 (2.8)
Other	3 (5.6)	12 (6.6)	2 (2.6)	2 (5.6)	5 (6.5)	2 (5.6)
Treatment completed as scheduled	4 (7.4)	0	6 (7.8)	0	0	1 (2.8)
Insurance/finance	0	2 (1.1)	0	0	0	0
Unknown/missing	10 (18.5)	55 (30.1)	12 (15.6)	8 (22.2)	29 (37.7)	4 (11.1)

Abbreviations: A = abiraterone acetate; C = cabazitaxel; DA = docetaxel followed by abiraterone acetate; DAC = docetaxel followed by abiraterone acetate and then cabazitaxel; DC = docetaxel followed by cabazitaxel; DCA = docetaxel followed by cabazitaxel and then abiraterone acetate.

estimate of median TTF1 was significantly greater with DCA than with DAC (5.2 vs. 4.3 months; $P = .0003$) (Figure 2B), although adjusted comparisons in a multivariable analysis did not identify treatment sequence as a significant covariate, suggesting no difference in TTF1 between the DCA and DAC cohorts. Narcotic use was the only covariate associated with TTF1 identified in this multivariable analysis (HR, 1.86; 95% CI, 1.012-3.408; $P = .0457$). The crude estimate of median TTF2 was also significantly greater with DCA than with DAC (10.4 vs. 7.1 months; $P = .0002$) (Figure 2C), and adjusted comparisons in a multivariable analysis identified treatment sequence as a significant covariate, suggesting that the DCA sequence was associated with a lower risk of TTF2 compared with the DAC sequence (HR, 0.18; 95% CI, 0.050-0.644; $P = .0084$).

In comparing outcomes between the 2- and 3-drug groups, crude estimates for median OS were similar for both groups (both 17.0 months). However, adjusted comparisons in a multivariable analysis comparing the 3-drug cohort using the 2-drug cohort as reference identified the number of treatments administered as a significant covariate, suggesting a lower risk of mortality in the 3-drug group compared with the 2-drug group (HR, 0.21; 95% CI, 0.092-0.476; $P = .0002$). Other covariates associated with mortality in this multivariable analysis were narcotic use (HR, 2.01; 95% CI, 1.240-3.259; $P = .0046$), baseline PSA level (HR, 1.01; 95% CI, 1.001-1.027; $P = .0369$), baseline alkaline phosphatase level (HR, 1.00; 95% CI, 1.000-1.001; $P = .0038$), and interaction of treatment and time (HR, 0.87; 95% CI, 0.806-0.946; $P = .0009$) (Table 3).

Treatment Patterns

Drug exposure and discontinuation rates in patients from the 2- and 3-drug cohorts are presented in Table 1. Exposure to C treatment was significantly higher in patients receiving DCA compared with those receiving DAC (median 6 vs. 4 cycles; $P < .0001$). Exposure to A treatment was similar for the DCA and DAC groups. Reasons for treatment discontinuation were also evaluated and are presented in Table 4.

Discussion

In this retrospective study of 350 patients with mCRPC receiving C or A, or both, after treatment with D, A was administered more frequently overall compared with administration of C (84.6% vs. 47.7%). In the 2-drug group, adjusted comparisons indicated that treatment with C (n = 54) or A (n = 183) after D did not significantly impact OS outcomes in a multivariable analysis. Receipt of both C and A (3-drug group) occurred in 32.3% of patients after treatment with D and was independently associated with an improved OS compared with patients receiving only C or A (2-drug group [67.7%]) in an adjusted multivariable analysis ($P = .0002$). DCA (n = 77) was administered more frequently than DAC (n = 36) in the 3-drug group. Additionally, OS and TTF2 were significantly greater with DCA compared with DAC in a multivariable analysis. Improved outcomes with DCA may be partly attributable to more cycles of C administered in DCA than in DAC (median 6 vs. 4; $P < .0001$), whereas the duration of A treatment was similar for both the DCA and DAC groups. These data suggest that the sequence of C followed by A may be more feasible, allowing delivery of more C after D, thereby resulting in improved survival. Indeed, a modest decrement in delivery of chemotherapy may compromise survival, as observed in the MAINSAIL phase III trial (evaluating the safety and effectiveness of lenalidomide in combination with docetaxel and prednisone for patients with castrate-resistant prostate cancer) in which a median of 2 fewer cycles of D delivered in the D plus lenalidomide arm because of toxicities from the combination may have contributed to lower survival in this arm compared with the D plus placebo arm.[13]

The validity of our data is supported by the significance of recognized prognostic factors in the multivariable models, such as CCI, second-line treatment duration, and baseline PSA levels in the 3-drug group (in addition to specific sequence) and baseline anemia, narcotic use (ie, pain), and previous duration of D treatment in the 2-drug group. However, it is difficult to determine the clinical significance of these factors and covariates and whether the results are clinically meaningful.

We selected a period (April 2011-May 2012) when both C and A were commercially available. Moreover, we excluded patients enrolling in clinical trials during the study period, because such patients are more likely to be a good prognostic group, which may confound outcomes, as demonstrated in another recent study.[14]

There were several limitations to the current study, including the retrospective design and relatively modest sample size. All community oncology practices are not included in the iKM dataset because not all US Oncology Network clinics use the full EHR capabilities of iKM. Furthermore, although data quality checks were conducted, it is possible that some variables of interest such as toxicity profiles and reasons for treatment discontinuation and switching of therapy may not be complete. Missing values may result in exclusion from the study or analysis or imputation of a value that was captured after treatment. Finally, problems with inadequate or inaccurate codes in databases may introduce some level of misclassification bias.

Other retrospective studies have suggested that treatment with C followed by androgen axis inhibitors might lead to improved outcomes compared with treatment with androgen axis inhibitors followed by C.[15] Patients whose disease progresses after treatment with A may have a larger tumor burden and poorer performance status, precluding the institution or optimal delivery of C. Conversely, patients whose disease progresses after treatment with C may still be eligible for treatment with A, given its probable higher tolerability.

Given the rapid proliferation of agents for mCRPC, there exists a need for tailored therapy. Some potential clinical factors exist. Patients with a < 16-month response to initial ADT may respond better to chemotherapy than to subsequent hormonal therapies.[11,16]

The survival benefit obtained with D or C treatment may be most pronounced in patients with high Gleason score tumors,[17,18] whereas patients with Gleason scores of 8 to 10 have shown a poor response to A treatment.[19] Moreover, the resistance mechanisms engendered by each line of therapy remain poorly defined, although all these agents exhibit some element of cross-resistance.[20-22] Although data suggest that targeted androgen axis inhibitors are effective in the chemotherapy-naive mCRPC setting, recent data from the CHAARTED study suggest a role for earlier administration of chemotherapy.[11] However, in the absence of validated predictive biomarkers, consideration should probably be given to the strategy of administering the most feasible sequence of agents.

Conclusion

Based on the findings of this retrospective analysis, exposure to all 3 agents in the DCA sequence may be a more optimal sequence of treatment for mCRPC than the DAC sequence. However, these results are exploratory, and prospective validation in a randomized trial or prospective observational study, or both, is necessary.

Clinical Practice Points

- First-line treatment with D for mCRPC yields a median OS of nearly 19 months. Recent years have seen a marked expansion in available treatment options for mCRPC.
- C, A, and enzalutamide all improve OS when administered after D treatment. However, in the absence of prospective trials comparing sequences of agents administered after treatment with D, the optimal sequence is unknown, and there is no clear evidence to support clinical decisions.
- McKesson Specialty Health's iKM EHR allows analysis and comparison of different treatment sequences in patients with mCRPC. In the current retrospective study of 350 patients with mCRPC receiving C or A, or both, after D treatment, adjusted comparisons in a multivariable analysis suggested that clinical outcomes for D followed by A only were not significantly improved compared with D followed by C only.
- In a multivariable analysis, administration of both C and A after treatment with D was associated with improved OS compared with administration of only C or A after treatment with D. For the 3-drug regimens, OS and TTF were significantly greater with the DCA sequence compared with DAC in the multivariable analysis.
- Given the rapid growth of agents for mCRPC, there is a need for tailored therapy. Without predictive biomarkers, consideration should be given to the strategy of administering the most feasible sequence of agents.
- Based on this retrospective analysis, DCA may be a more optimal treatment sequence for mCRPC compared with DAC. These results are exploratory and require prospective validation.

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