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Docetaxel Rechallenge Improves Survival in Patients With Metastatic Castration-resistant Prostate Cancer: A Retrospective Study

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Abstract. *Background/Aim: Docetaxel has been widely used in metastatic Castration-resistant Prostate Cancer (mCRPC) patients for decades. The purpose of the study was to evaluate the efficacy of docetaxel rechallenge in patients with mCRPC. Patients and Methods: We retrospectively compared patients who had received either first-line docetaxel and rechallenge after Androgen Receptor-axis Targeted therapies (ARAT), to those without rechallenge docetaxel. Multivariate cox-regression analysis was used to evaluate survival. Results: Out of the 204 patients with mCRPC enrolled in the study, 24 patients received docetaxel rechallenge and 180 did not. The median overall survival was 50.11 months in the rechallenge group, as compared to 26.36 months in the non-rechallenge group (p of log rank=0.044). In the multivariate model, doxetaxel rechallenge was an independent risk factor for overall survival [hazard ratio (HR)=0.59, 95% confidence interval (CI)=0.32-0.99], together with the performance status score 2 (HR=2.46, 95%CI=1.32-4.58), hormone-sensitive state duration (HR=0.99, 95%CI=0.99-0.999), liver (HR=1.90, 95%CI=1.04-3.47) and brain metastases (HR=2.23, 95%CI=1.26-5.46). The advantage of rechallenge was addressed in the androgen receptor-axis-targeted (ARAT) non-responsive patients (HR=0.36, 95%CI=0.17-0.78). Adverse events were at 29.17% with Grade 3/4 neutropenia and at 20.83% with Grade 1/2 neutropenia in the docetaxel rechallenge group. Conclusion: The docetaxel rechallenge improved survival in patients with mCRPC failure of first-line docetaxel and subsequent abiraterone acetate or enzalutamide. Independent predictive factors for overall survival included i) the performance status, ii) hormone-sensitive state duration, iii) liver and iv) brain metastases. Patients non-responsive to ARATs will benefit from docetaxel rechallenge with regards to overall survival.*

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Chemotherapy with docetaxel was approved for its efficacy in metastatic Castration-resistant Prostate Cancer (mCRPC) by two randomized-control phase III trials (SWOG 99-16 study and TAX-327 study) in 2004, which demonstrated its advantage in prolonged overall survival and symptom control (1, 2). A combination of docetaxel and castration therapy had been the standard treatment for mCRPC for a decade until the emergence of two Androgen Receptor Axis Targeted agents (ARATs), i) Abiraterone acetate, a potent inhibitor of cytochrome P450 c17 in androgren biosynthesis, and ii) Enzalutamide, an inhibitor of nuclear translocation of the androgen receptor, which have both demonstrated the efficacy and survival improvement in a large-scale clinical trial (3-6). Despite this, there is still a lack of solid evidence surrounding the best treatment

sequence for mCRPC. Docetaxel rechallenge appears to preserve efficacy after the progression of tumor and has, therefore, been proposed as a treatment option (7, 8).

The concept of docetaxel rechallenge, previously described as the re-administration of docetaxel upon progression after a predefined number of sequential docetaxel cycles, involves preserved anti-tumor activity and good tolerability in a selected population (7, 8). In clinical practice, most patients diagnosed with mCRPC receive docetaxel as the first line of treatment, and subsequently turn to ARATs as the second line treatment after disease progression, according to the previous treatment guidelines (3, 5). The role of docetaxel rechallenge in the era of ARATs remains unclear; however, a retrospective cohort study has shown its positive outcome in improving survival and symptoms when used after the failure of frontline treatment, while partial Prostate Specific Antigen (PSA) response at rechallenge sequence and a treatment-free interval of >3 months has been associated with improved survival (9).

The aim of our study was to investigate the feasibility and tolerability of docetaxel rechallenge and to better understand the clinical factors that indicate a positive treatment response and an improved survival.

Patients and Methods

This is a retrospective chart-review study, where patients diagnosed with mCRPC at Taichung Veterans General Hospital from 2008 to 2016 were enrolled. Two hundred and four patients included in this study received informed consent forms prior to treatment, according to the certifications of the Institute Review Board of Taichung Veterans General Hospital (No CE20173B). Patients with mCRPC who met the criteria of: i) pathology confirmed prostate adenocarcinoma and ii) progression following castration (testosterone level <50 ng/dl) were enrolled. Twenty-four patients were in docetaxel rechallenge group and 180 patients in the non-rechallenge group.

Androgen deprivation therapy was used on metastasis prostate cancer and across the whole period of mCRPC and included i) surgical castration (orchiectomy) or ii) medical castration, involving LH-RH agonists or antagonists. The use of chemotherapy with docetaxel was defined as 75 mg/m^2 during a 3-week interval, in combination with 10 mg prednisone daily, while 50 mg/m^2 over a 2-week interval was also introduced at our institute, which was later transferred into standard 3-week cycle counts. ARATs included 1,000 mg abiraterone acetate (AA) with prednisolone at 5 or 10 mg per day and Enzalutamide (ENZ) at 160 mg per day. Chemotherapy with cabazitaxel was also used at 25 mg/m^2 during a 3-week interval in combination with 10 mg prednisone daily. PSA progression was defined according to the Prostate Cancer Working Group second publication (PCWG2) criteria (10).

The patients were grouped into docetaxel rechallenge and non-rechallenge groups, with characteristics, including: i) age at mCRPC, ii) Eastern Cooperative Oncology Group (ECOG) performance status, iii) PSA at initial metastatic prostate cancer, iv) nadir PSA at metastatic hormone sensitive prostate cancer (mHSPC), v) hormone-sensitive state duration (months, defined as from initial ADT to mCRPC), vi) Gleason score (G/S), vii) hypertension, viii) diabetes mellitus, ix) coronary artery disease, x) body mass index (BMI, kg/m^2), and xi) metastatic status (bone, lymph node, lung, liver and brain).

The metastatic status for mCRPC was also taken into consideration. High volume disease was defined as the presence of visceral metastases of 4 or more bone lesions, with more than 1 lesion located beyond the vertebral bodies and pelvis when compared to low volume disease (11). High-risk disease was defined as having any two of the following: i) three or more bone metastases seen on a bone scan, ii) Gleason sum ≥8, and iii) any visceral metastases (12).

Frontline treatment included i) first line docetaxel, ii) AA, iii) ENZ and iv) cabazitaxel, while the treatment courses, the cumulative dosage, and the PSA decline percentage were listed for comparison. Docetaxel rechallenge was the same as the treatment schedule described in the first-line treatment. Parameters included i) PSA, ii) PSA doubling time (months), iii) alkaline phosphate (Alk-P), iv) lactate dehydrogenase (LDH), v) hemoglobin (Hb), and vi) albumin prior to rechallenge of docetaxel, with subsequent treatment after rechallenge of docetaxel collected, possibly related to the oncological outcome.

Statistics. End point evaluation using the Kaplain-Meier survival curve and the log-rank test were used to compare the overall survival (OS) from mCRPC and PSA progression-free survival (PFS) at different sequences of docetaxel. The continuous values were analyzed by the Mann-Whitney *U*-test and Fisher's exact test *t*-test for continuous variables. A chi^2 test was used for categorical variables. Univariate and multivariate Cox hazard regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) was used for the association between the variables and OS. Subgroups for overall survival hazard ratio analysis were used when discussing the advantage of docetaxel rechallenge in the different subgroups of patients. Analyses were performed using the SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA). A *p*-Value of <0.05 was considered statistically significant.

Results

Patient characteristics are described in Table I. The median follow-up time from mCRPC was 39.71 months in the rechallenge docetaxel group and 17.38 months in the non-rechallenge docetaxel group ($p<0.001$). The age at diagnosis of mCRPC was younger in the rechallenge docetaxel group than the non-rechallenge docetaxel group (63.74 *vs.* 74.68 years, $p<0.001$). Additionally, there was no difference in the initial PSA (98.82 *vs.* 131.00, $p=0.302$), the nadir PSA at mHSPC (0.30 *vs.* 0.69, $p=0.220$), the hormone-sensitive state duration (32.07 *vs.* 28.97, $p=0.379$), the Gleason score (8.50 *vs.* 9, $p=0.843$), nor in any underlying disease or metastatic sites between the two groups.

For frontline treatment with 1st line docetaxel for mCRPC, as shown in Table I, patients received a median of 8 (range=3-21) cycles of docetaxel in the rechallenge docetaxel group and 5 (range=1-44) cycles of docetaxel in the non-rechallenge docetaxel group ($p=0.001$), while the cumulative dosage was 920 (range=405-2,800) mg and 535 (range=75-5,160) mg in each group, respectively ($p<0.001$).

Table I. *Responses and adverse events of clinical trials with sequential CD19-directed chimeric antigen receptor T-cell and immune checkpoint inhibitor therapy.*

	Rechallenge (n=24)		Non-rechallenge (n=180)		*p*-Value
Age	63.74	(48.09-81.57)	74.68	(48.73-90.97)	<0.001**
Performance (ECOG, n=24 *vs*. 179)			0.018*		
0	16	(66.67%)	70	(39.11%)	
1	8	(33.33%)	83	(46.37%)	
2	0	(0.00%)	26	(14.53%)	
PSA at initial (n=23 *vs*. 169)	98.82	(5.91-3,100)	131.00	(2.62-4,526)	0.302
Nadire PSA at mHSPC (n=24 *vs*. 175)	0.30	(0-108)	0.69	(0-812)	0.220
Hormone sensitive duration	32.07	(5.18-62.61)	28.97	(3.11-352.29)	0.379
G/S (n=20 *vs*. 146)	8.50	(7-10)	9.00	(4-10)	0.843
Hypertension	9	(37.50%)	64	(35.56%)	1.000
Diabetes mellitusf	0	(0.00%)	22	(12.22%)	0.083
Coronary artery diseasef	3	(12.50%)	21	(11.67%)	1.000
BMI (n=24 *vs*. 179)	24.39	(19.69-33.59)	24.28	(17.62-39.33)	0.367
Bone metastasesf	23	(95.83%)	177	(98.33%)	0.396
Lymph node metastasesf	12	(50.00%)	103	(57.22%)	0.652
Lung metastases[f]	2	(8.33%)	27	(15.00%)	0.540
Liver metastases[f]	2	(8.33%)	14	(7.78%)	1.000
Brain metastases[f]	1	(4.17%)	6	(3.33%)	0.589
1st line Docetaxel					
Cycle	8.00	(3-21)	5.00	(1-44)	0.001**
Cumulative dosage	920.00	(405-2,800)	535.00	(75-5,160)	<0.001**
PSA before Docetaxel	28.91	(4.41-1,563)	49.21	(1.1-5,989)	0.294
PSA after Docetaxel (n=24 *vs*. 171)	4.31	(0.08-1,837)	17.40	(0-10,625)	0.016*
PSA decline (percentage, %)	–84.52	(–99.59-147.37)	–46.48	(–100-549.58)	0.049*
Abiraterone treatment month (n=20 *vs*. 62)	6.00	(2-42)	9.00	(2-65)	0.297
Abiraterone response (n=20 *vs*. 61)	11.75	(-99.86-973.4)	–41.95	(–100-236.95)	0.216
Enzalutamide treatment month (n=11 *vs*. 18)	6.00	(2-12)	5.50	(1-38)	0.903
Enzalutamide response (n=11 *vs*. 18)	–15.22	(–89.2-118.34)	–63.01	(–99.99-33.84)	0.084
Cabazitaxel cycle (n=7 *vs*. 25)	4.00	(3-17)	4.00	(1-16)	0.771
Cabazitaxel response (n=7 *vs*. 25)	–25.48	(–94.68-75.23)	–52.00	(–99.99-142.49)	0.346
Follow up time (months, from mCRPC)	39.71	(14.86-114.32)	17.38	(0.25-111.93)	<0.001**

Mann-Whitney test. Chi-Square test. [f]Fisher's Exact test. *p<0.05, **p<0.01. Continuous data were expressed as median (Range). Categorical data were expressed in numbers and percentages. mCRPC: Metastatic castration resistant prostate cancer; G/S: Gleason Score; PSA: prostatic specific antigen; mHSPC, metastatic hormone sensitive prostate cancer; BMI: body mass index.

After treatment with 1st line docetaxel, PSA decline was –84.52% (range=–99.59-147.37) in the rechallenge docetaxel group and –46.48% (range=–100-549.58) in the non-rechallenge docetaxel group (p=0.049). Twenty patients in the rechallenge and 62 patients in the non-rechallenge group received AA with a median duration of 6 and 9 months, and a PSA response of 11.75% (range=–99.86-973.4) and –41.95% (range=–100-–236.95), both respectively. Eleven patients and 18 patients received ENZ in each group with a median of 6 months and 5.5 months duration, and a PSA response of –15.22% (range=–89.2-118.34) and –63.01% (range=–99.99-–33.84), both respectively. Cabazitaxel was also used in each group (n=7 in the rechallenge *vs*. n=25 in the non-rechallenge group) and the PSA response was –25.48% (range=-94.68-75.23) and –52.00% (range=-99.99-142.49), respectively (p=0.346).

Regarding the 24 patients who received rechallenge docetaxel (Table II), 12 of them received it at the 3rd line, 10 at the 4th line and 2 at the 5th line at mCRPC. The average number of rechallenge docetaxel cycles was 4 (range=1-17) and the cumulative dosage was 520 (range=100-2,260) mg. The PSA doubling time was 1.85 months (range=0.7-7.7) prior to treatment. Values of alkaline phosphatase (Alk-P), lactate dehydrogenase (LDH), hemoglobin (Hb), Albumin and PSA are outlined in Table II. Fourteen of these 24 patients (58.33%) achieved a PSA response (any decline of PSA after rechallenge docetaxel), while 9 of 24 patients (37.5%) achieved a PSA decline ≥20% and 3 (12.5%) achieved a PSA decline ≥50%. The median follow-up time from rechallenge docetaxel was 12.05 months (range=2.86-52.34).

Most importantly, rechallenge docetaxel significantly improved the OS from mCRPC when compared to non-

Table II. *Patients characteristics at docetaxel rechallenge (n=24).*

	Median/ number	Range/ percentage
Docetaxel rechallenge sequence		
3rd line	12	50%
4th line	10	41.67%
5th line	2	8.33%
Treatment time from mCRPC (months)	29.68	(18.71-48.82)
Interval between prior and rechallenge docetaxel (months)	17.18	(7.93-31.93)
Docetaxel cycles	4.00	(1-17)
Docetaxel cumulative dosage	520.00	(100-2,260)
PSA doubling time before	1.85	(0.7-7.7)
Alk-P (n=20)	178.50	(67-316)
LDH (n=18)	237.00	(154-708)
Hb	10.65	(7-14.9)
Albumin (n=18)	3.80	(2.7-4.5)
PSA before docetaxel rechallenge	299.50	(3.89-2,907)
PSA after docetaxel rechallenge	204.35	(3.84-2,417)
PSA decline (percentage, %)	–6.53	(–95.72-70.02)
PSA response ≥0%	14	58.33%
PSA response ≥20%	9	37.5%
PSA response ≥30%	4	16.67%
PSA response ≥50%	3	12.5%
Subsequent Abiraterone courses (n=0)		
Subsequent Enzalutamide courses (n=4)	5.00	(3-46)
Subsequent Cabazitaxel cycles (n=3)	3.00	(2-11)
Follow up time from rechallenge Docetaxel (months)	12.05	(2.86-52.43)

Categorical data were expressed in numbers and percentages. Continuous data were expressed as median (Range). mCRPC: Metastatic castration resistant prostate cancer; PSA: prostatic specific antigen; Alk-P: alkaline phosphate; LDH: lactate dehydrogenase; Hb: hemoglobin.

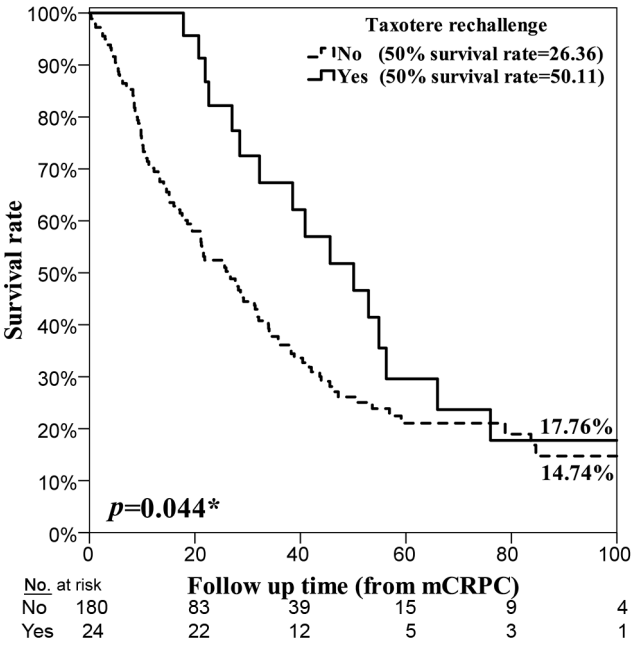

Figure 1. *Kaplan-Meier curve for overall survival (OS) from metastatic castration resistant prostate cancer (mCRPC) treated with and without docetaxel (taxotere) rechallenge (n=24 vs. 180, respectively), median 50.11 vs. 26.36 months (p for log rank test=0.044*).*

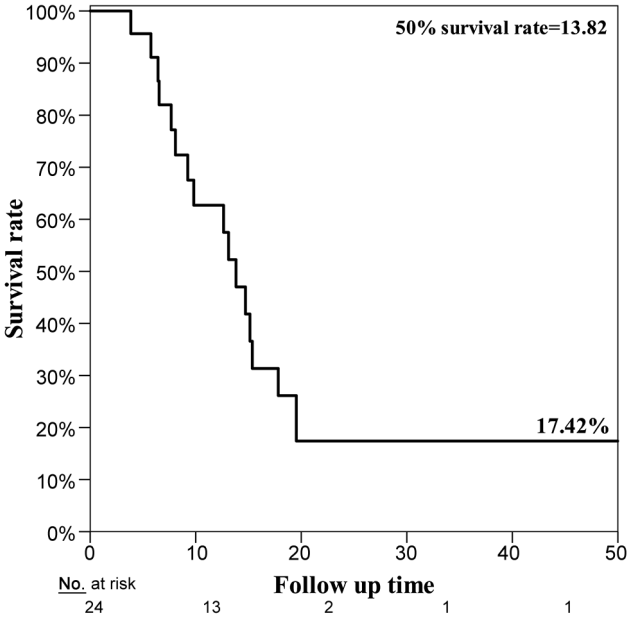

Figure 2. *Kaplan-Meier curve for overall survival (OS). In metastatic castration resistant prostate cancer (mCRPC) patients from rechallenge docetaxel (n=24) OS was 13.82 months (range=10.94-16.70).*

rechallenge docetaxel (50.11 *vs.* 26.36 months, respectively, *p* for log rank test=0.044*) (Figure 1). While discussing the treatment efficacy of docetaxel in different sequences, this appears to have a median of 5.75 months (range=4.73-6.77) PFS in the first line at mCRPC and a median of 2.79 months (2.06-3.51) in the rechallenge sequence. Figure 2 demonstrates the OS from rechallenge docetaxel with a 13.82-month (range=10.94-16.70) survival time.

Uni- and multi-variant analyses for OS from mCRPC are shown in Table III. After adjustments, we found that i) the performance status score 2 (HR=2.46, 95%CI=1.32-4.58, *p*=0.005**), ii) the hormone sensitive duration (HR=0.99, 95%CI=0.99-0.999, *p*=0.014*), iii) liver metastases (HR=1.90, 95%CI=1.04-3.47, *p*=0.036**), iv) brain metastases (HR=2.23, 95%CI=1.26-5.46, *p*=0.015**) and v) rechallenge with docetaxel (HR=0.59, 95%CI=0.32-0.99, *p*=0.046**) were the most significant factors affecting a patient's survivability.

Figure 3 shows the subgroup comparative analysis of the overall survival hazard ratio between the rechallenge docetaxel

Table III. *Uni- and Multi-variant analysis for Overall Survival (OS) from mCRPC.*

	Univariate			Multivariate		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age	1.02	(1.0002-1.04)	0.048*	1.00	(0.98-1.03)	0.830
Performance						
0	ref.			ref.		
1	1.38	(0.95-2.00)	0.091	1.29	(0.86-1.93)	0.226
2	2.94	(1.73-5.00)	<0.001**	2.46	(1.32-4.58)	0.005**
PSA at initial	1.00	(1.00-1.00)	0.405			
Nadir PSA at mHSPC	1.00	(1.00-1.00)	0.113			
Hormone sensitive duration	0.995	(0.99-0.9996)	0.031*	0.99	(0.99-0.999)	0.014*
Gleason score	0.99	(0.85-1.15)	0.896			
BMI	0.94	(0.90-0.99)	0.022*	0.95	(0.91-1.00)	0.061
Bone metastases	1.81	(0.45-7.34)	0.404			
Lymph node metastases	1.27	(0.90-1.80)	0.171			
Lung metastases	1.63	(1.00-2.67)	0.051			
Liver metastases	2.13	(1.19-3.83)	0.011*	1.90	(1.04-3.47)	0.036*
Brain metastases	3.07	(1.34-7.06)	0.008**	2.23	(1.26-5.46)	0.015*
Docetaxel rechallenge						
Non rechallenge	ref.	ref.				
Rechallenge	0.59	(0.35-0.99)	0.047*	0.59	(0.32-0.99)	0.046*

Cox regression. *$p<0.05$, **$p<0.01$. mCRPC: Metastatic castration resistant prostate cancer; PSA: prostatic specific antigen; mHSPC: metastatic hormone sensitive prostate cancer; BMI body mass index.

(left side) and non-rechallenge docetaxel (right side) group. Rechallenge docetaxel was beneficial for the overall survival in the following subgroups: i) ages (≥75 years old or <75 years old), ii) performance status (0 or 1), iii) initial PSA (≥100 or <100), iv) Gleason score (≥8 or <8), v) bone metastases only, vi) visceral metastases, vii) metastases volume (high volume or low volume), viii) metastatic risk (high or low risk), ix) hormone-sensitive state duration (≥12 months or <12 months), x) nadir PSA at mHSPC (<1 or >1), and xi) 1st line docetaxel response (response or non-response). Additionally, rechallenge docetaxel improved overall survival in the high metastases volume (HR=0.34, 95% CI=0.15-0.75, *p*=0.008**), high metastases risk (HR=0.41, 95%CI=0.17-0.96, *p*=0.040**) and ARAT non response (HR=0.36, 95%CI=0.17-0.78, *p*=0.010**) subgroups.

The adverse events are shown in Table IV. Seven patients (29.17%) suffered from Grade 3/4 neutropenia, while 5 patients (20.83%) suffered from Grade 1/2 neutropenia, both of which were tolerable and manageable. Thrombocytopenia (16.67%), anemia (25.00%), skin rash (4.17%), fatigue (45.83%), elevation of aspartate transaminase/alanine transaminase (AST/ALT) (4.17%), nausea (25.00%), diarrhea (12.5%) and nail disorder (4.17%) were also observed.

Discussion

Docetaxel for patients with mCRPC was first established in 2004 and has been widely used in them for more than ten years. Ever since the announcement of AA and ENZ in 2012, most patients have received AA or ENZ as a prior treatment, due to its favorable durability and tolerability (3, 5). Treatment options offered after failure of prior ARAT include cabazitaxel, radium-223 or another type of ARAT. Rechallenge docetaxel was meant to be an alternative to other expensive drugs, but there is not enough evidence of its usefulness. The current study is the first to have identified the efficacy of rechallenge docetaxel for mCRPC after failure of first line docetaxel and androgen receptor-axis-targeted therapies, particularly for those patients who are non-responsive to ARATs.

Docetaxel is a semisynthetic texane which binds to β-tubulin incorporated with microtubules during the G_2-M phase to trigger cell death in proliferating tumor cells (13). Several mechanisms surrounding the resistance to docetaxel include: i) the overexpression of membrane-bound efflux proteins, which decrease cellular drug accumulation; ii) altered expression of tubulin isotypes or microtubule-associated proteins (for example, overexpression of βIII-tubulin), and iii) changes to the microtubules that are induced by interactions with other cytoskeletal proteins (for example, γ-actin), causing defects in apoptotic pathways (14). Previous studies have attempted to overcome the resistance of prostate cancer to docetaxel through the simultaneous use of bevacizumab, epirubicin and carboplatin, but have been limited by their small size cohorts and inconsistent results (15-17). Furthermore, the available

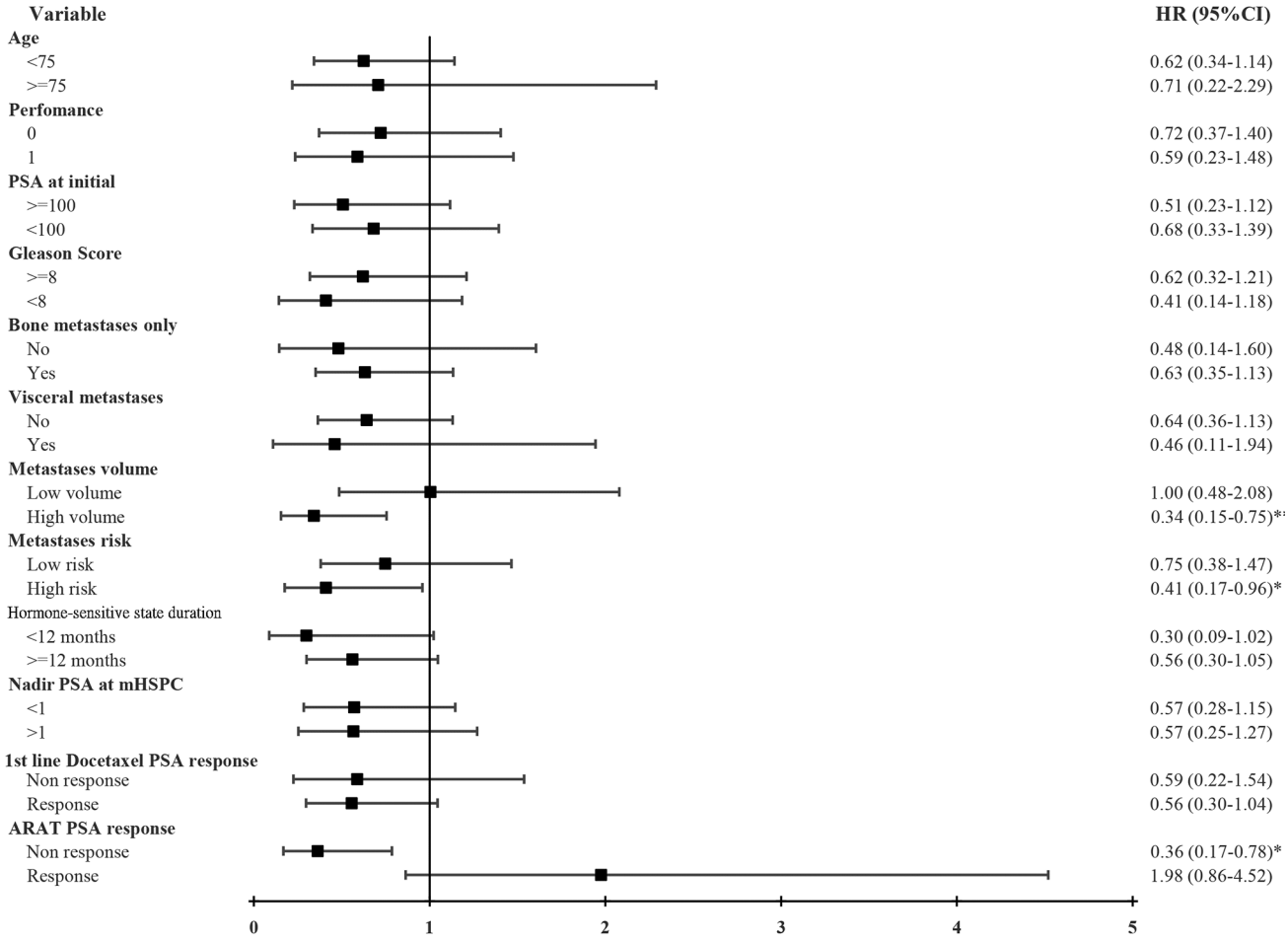

Figure 3. *Subgroup analysis for overall survival hazard ratio in metastatic castration resistant prostate cancer (mCRPC) patients received docetaxel rechallenge (left side) and without docetaxel rechallenge (right side). HR: Hazard ratio; CI: confidence interval; PSA: prostatic specific antigen; mHSPC: metastatic hormone sensitive prostate cancer.*

literature has revealed that docetaxel retreatment seems to be an option in patient response to prior line docetaxel during a minimum progression-free interval of 3-6 months, but is limited in intermittent treatment strategy in mCRPC (18).

In *in vitro* experiments, exposure of prostate cancer cells to taxane-based chemotherapy can inhibit the androgen receptor (AR) nuclear translocation by targeting the AR association with tubulin, leading to a nucleus that is significantly depleted of AR (19). The same result has also been observed in circulating tumor cells isolated from the peripheral blood of mCRPC patients, which correlates to the clinical response to taxane-based chemotherapy (20). Prior hormonal treatment may influence the docetaxel response. Marín-Aguilera *et al*., have reported that Enzalutamide can induce the expression of neuroendocrine markers, such as Chromogranin A and synaptophysin, and reduce E-cadherin, leading to reduced docetaxel-induced cytotoxicity in VCaP prostate cancer cells (21). Similarly, van Soest *et al*., have also found an impaired efficacy of docetaxel, cabazitaxel and enzalutamide in the abiraterone-resistant cell line, suggesting cells' cross-resistance in the presence of certain hormones (22).

Regarding mCRPC patient failure to prior docetaxel and ARAT treatments, several drugs offer efficacies and survival benefits. The CARD trial, a phase III randomized control study, introduced cabazitaxel as being the most effective treatment after docetaxel and progression on one line of ARTA within 12 months (23). Alpha emitter radium-223 has been another option for mCRPC patients with bone metastases, solely based upon patients' improvement in overall survival and pain relief (24). Abiraterone acetate after enzalutamide failure or *vice versa* could be a reasonable choice, but there is cross resistance between one another, and the potency is limited. Reports have stated that while there is a 36% enzalutamide response rate after abiraterone acetate failure, there is only a 4% abiraterone acetate response rate after enzalutamide failure (25-27). Other treatment options

Table IV. *Adverse events for docetaxel rechallenge (n=24).*

	Grade 1/2		Grade 3/4	
	n	%	n	%
Neutropenia	5	(20.83%)	7	(29.17%)
Thrombocytopneia	4	(16.67%)	0	(0%)
Anemia	6	(25.00%)	0	(0%)
Rash	1	(4.17%)	0	(0%)
Fatigue	11	(45.83%)	0	(0%)
Elevated AST/ALT	1	(4.17%)	0	(0%)
Nausea/vomiting	6	(25.00%)	0	(0%)
Diarrhea	3	(12.5%)	0	(0%)
Nail disorder	1	(4.17%)	0	(0%)

Categorical data are expressed in numbers and percentages. AST/ALT: Aspartate transaminase/alanine transaminase.

include the poly (adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibition using olaparib in mCRPC patients with DNA-repair gene defects (28). Nevertheless, the concern regarding the above medication is that it is expensive and has limited access. Rechallenge docetaxel in later lines could be an alternative for all these patients with advanced disease and as our previous study found, rechallenge docetaxel had a 62.5% response rate compared to AA non-responsive patients (29).

One possible reason explaining the efficacy of docetaxel rechallenge after failure of ARAT may be associated with the expression of the androgen-receptor splice variant 7 (AR-V7) in the neoplastic clones, causing resistance to novel androgen target agents (30). In contrast, expression of AR-V7 in circulating tumor cells does not appear to be associated with primary resistance to taxane-based chemotherapy (31). The presence of AR in plasma may be another explanation for the diversity of mCRPC responses to docetaxel and ARAT. Conteduca *et al*. have reported in a multi-institutional study with pooled analysis, that the normal AR status responds well to hormonal therapy whilst plasma AR-gained may have a longer response to docetaxel (32).

Several studies have also addressed the efficacy of rechallenge docetaxel in the progression of mCRPC. The retrospective extended follow up from the GETUG-AFU 15 phase III clinical trial has identified a PSA decline of ≥50% at first line rechallenge docetaxel in 4 out of 20 patients (20%), with a median 4.1-month progression-free survival period for those who had received upfront docetaxel in mHSPC (33). Di Lorenzo *et al*. have also reported a 24.5% partial PSA response in 45 patients initially responding to docetaxel in mCRPC, and then experiencing progression after a period of biochemical remission of at least 5 months (7). Additionally, Eymard *et al.,* have reported 148 mCRPC patients who responded well to first line docetaxel, received docetaxel rechallenge in second (52% of patients) and third line (48% of patients), with a 48% of patients achieving a PSA decline of ≥50% and a median overall survival of 16 months from docetaxel rechallenge. The grade 3-4 adverse events were limited to nail disorders (12%), edema/weight gain (8%), and hematological side effects (6%) (8).

Furthermore, Loriot *et al*. have reported a cohort of 39 mCRPC patients who received docetaxel rechallenge and showed a 38% PSA decline occurring in more than 50% of cases, in addition to a median of 4.3 months progression-free survival and a15.8-month overall survival. The treatment interval from the last cycle of docetaxel to rechallenge docetaxel less than three months was associated with a shorter progression-free survival (34). Thomas *et al*., have also reported 62 patients that received rechallenge docetaxel and had a PSA-response at first docetaxel-sequence at 48.4% (n=62), at rechallenge 31.6% (n=32), and at third-sequence 34.8% (n=22) docetaxel, respectively while most benefit in treatment-free interval more than three months (9). Heck *et al*., have further reported 44 patients retreated with docetaxel that had a reduction in PSA levels of ≥50% after first-line docetaxel, correlating with superior PSA progression free survival and overall survival (35). Di Lorenzo *et al*., have also reported a case of heavily pretreated mCRPC that benefited clinically from 4 cycles of docetaxel and suffered minimal toxicity (36).

There are also conflicting results about the survival benefits of mCRPC patients treated with doctaxel rechallenge. Oudard *et al*., have reported the largest cohort of 270 mCRPC patients from 2009 to 2011 and a good response (PSA decrease of ≥50%) to first line docetaxel. There was 40.4% good PSA response and a symptom relief/stable disease in the rechallenge docetaxel group (n=223); however, there was no survival benefit compared to second line non-taxane-based therapy (n=47) (37). The difference between this study and ours may be due to the fact that the former study examined a second line treatment setting whilst our data addressed the effect of docetaxel rechallenge in mCRPC patients from different treatment sequences, including patient having received abiraterone acetate and enzalutamide treatments.

One interesting study has addressed the possibility of cross resistance between abiraterone and docetaxel. Schweizer *et al*., have reported on 24 patients who received docetaxel after prior abiraterone acetate and were compared to 95 patients who received docetaxel only. Prior abiraterone acetate was associated with a shorter progression free survival (4.4 *vs*. 7.6 months, respectively) and a less frequent PSA decline ≥50% compared to docetaxel only (38% *vs*. 63%, respectively) (38).

Our study is the first one reporting on the survival benefits of rechallenge docetaxel in relation to abiraterone acetate and enzalutamide. The response rate of PSA decline of ≥30%

was found in only 16.67% of our cohort, which is less than in former studies; however, this may be due to the late sequence of rechallenge docetaxel. All our participants were exposed to at least one line of ARAT leading to a longer rechallenge interval (median of 17.18 months from the last time of first line docetaxel). Nevertheless, 58.33% of our patients benefited from rechallenge docetaxel by PSA decline at such an advanced disease stage. Our data also suggest that rechallenge docetaxel can improve overall survival when compared to the survival of patients without rechallenge, while adverse events were both few and manageable. In two clinical trial settings, there was only a 29% PSA response to abiraterone after docetaxel (COU-AA 301), and a 54% response to enzalutamide after docetaxel (AFFIRM) (3, 5). Excluding patients who respond to ARATs, rechallenge docetaxel could be a good alternative according to our findings, since rechallenge docetaxel provided a significant improvement in patients' overall survival.

Adverse events were the most concerning points for docetaxel rechallenge. The incidence of neutropenia was high in our study population but it could be managed with granulocyte colony-stimulating factor. In the largest reported data about docetaxel rechallenge, neutropenic complications usually occur at cycle 1 and the incidence decreases by treatment sequencing (37). Another study in 46 patients treated with docetaxel rechallenge reported only a limited number of major adverse events, while no patient had to stop a rechallenge because of toxicity and there were no treatment-related deaths (39). This study also concluded that docetaxel rechallenge may be safely repeated several times in mCRPC patients and suggested that in selected patients it could improve disease control. Nevertheless, cumulative toxicity associated with docetaxel should be a caution in grade 3 to 4 patients, as nail disorders increase from 4.6% to 7.9% in those receiving 1st and 2nd docetaxel rechallenge (39).

There were some limitations in our study. Inevitably, retrospective settings made a selection bias with regards to a younger age and the performance status, which offer a better response in the docetaxel rechallenge group. Our case number was small and the intergroup difference also limited the application of our results. Although the goal of our study was to try to identify the efficacy of docetaxel rechallenge in patients with mCRPC, the non-rechallenge group included patients with primary resistance, whereas patients in the rechallenge group received at least three lines of CRPC therapy. This makes the two groups imbalanced and the comparison between them possibly unjust. Additionally, the higher proportion of bone metastases and less visceral metastases in our cohort possibly expand the survival time compared to the published clinical trial with only about 90% of bone metastases (1-6). Use of ARATs as a first line treatment for mCRPC in recent years and more upfront docetaxel in mHSPC, which was excluded from our study, would restrict the application of the knowledge emerging from our data.

Finally, our real-world analysis is the first one to show evidence for the usefulness of docetaxel rechallenge in relation to ARATs. As a result, mCRPC patients receiving several lines of treatment could possibly benefit from docetaxel if novel agents are unavailable or unaffordable.

In conclusion, the docetaxel rechallenge improved the survival of patients with mCRPC after the failure of first line docetaxel and subsequent abiraterone acetate or enzalutamide. Independent predictive factors for overall survival included: i) the performance status, ii) the hormone-sensitive state duration, iii) liver and iv) brain metastases. Patients with a high metastases volume, high metastases risk and non-responsive to ARATs wound benefited from the use of rechallenge docetaxel with respect to overall survival.

Conflicts of Interest

The contributing Authors have no conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Authors' Contributions

Conceived and designed the analysis: SCH, JRL, KevinL and KYC. Data collection and statistic analysis: SCH, LWC and SSW. Contribution of study patients: SSW, CKY, CSC, SCW, CYL, CLC, YCO, KYC. Paper drift: SCH and LWC. Supervisor: KYC

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