

Original Article

Importance of cycles of chemotherapy and postdocetaxel novel therapies in metastatic castration-resistant prostate cancer

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ABSTRACT

Purpose: With the emergence of various novel therapies including new generation taxane and androgen-targeted therapies, the optimal sequence of systemic treatment in metastatic castration-resistant prostate cancer (mCRPC) patients remains to be defined. Our aim is to investigate the impact of duration of docetaxel-based chemotherapy and postdocetaxel treatment in mCRPC patients.

Methods: The medical data of 57 Chinese mCRPC patients who received docetaxel-based chemotherapy in two oncology centers between 2003 and 2012 were reviewed. The treatment efficacy and toxicity were determined. The potential determinants of efficacy were also determined.

Results: Fifty-seven patients (median age 66 years, range 51–82 years) were given docetaxel-based chemotherapy, of whom 48 (84.2%) received 3-weekly docetaxel (52.5–75 mg/m²) and nine (15.8%) received weekly docetaxel (35 mg/m²). Postdocetaxel treatments were received by 31 (57.4%) patients, including abiraterone in 13 patients and cabazitaxel in one patient. The median follow-up time was 14.3 months. The median overall survival (OS) and progression-free survival were 20.8 months and 5.8 months, respectively. In multivariate analysis, eight cycles or more of chemotherapy [hazard ratio (HR) = 0.151, $P < 0.0358$], use of postdocetaxel treatment (HR = 0.346, $P = 0.0005$), and hemoglobin level of < 10 (HR = 5.224, $P < 0.0001$) were independent determinants of OS. Patients who had received abiraterone and cabazitaxel as postdocetaxel treatment had significantly longer OS compared with those who received other postdocetaxel treatments (including rechallenge of docetaxel) and those who did not receive any postdocetaxel treatment (35.3 months vs. 20.8 months vs. 15.3 months, $P = 0.00057$).

Conclusions: The results suggest that maximizing exposure to docetaxel-based chemotherapy followed by novel therapies would have a favorable survival impact on mCRPC patients.

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1. Introduction

Based on the results of two landmark studies, Southwest Oncology Group (SWOG) 9916 and TAX-327, docetaxel-based chemotherapy is currently widely administered for patients with metastatic castration-resistant prostate cancer (mCRPC) worldwide.^{1,2} Previous studies have shown that the treatment outcome would be improved by maximizing the exposure of mCRPC patients to docetaxel-based chemotherapy, as long as the tolerance and biochemical response are favorable. The optimal number of cycles of docetaxel-based chemotherapy, however, has not been defined.^{3,4}

The more recent emergence of novel therapeutic agents including abiraterone, cabazitaxel, and enzalutamide, has opened up new research questions.^{5–8} Studies are ongoing to determine the optimal sequence of these novel agents for use in the postdocetaxel setting, and in the chemotherapy-naïve setting.⁹

While results of these studies are awaited, retrospective data may provide hints to these issues. In the present study, we investigated the relation of the number of cycles of docetaxel chemotherapy and postdocetaxel therapies to the survival of mCRPC patients.

2. Methods

In this retrospective study, it was noted that 57 consecutive Chinese mCRPC patients had received docetaxel-based chemotherapy at two oncology centers in Hong Kong between April 2003

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and December 2012. All study participants had histologically proven adenocarcinoma of the prostate with metastatic disease that had progressed despite the castration level of testosterone that was achieved after any mode of castration. The definition of clinical, biochemical, or radiological progressive disease was based on the Prostate Cancer Clinical Trials Working Group (PCWG-2) criteria.¹⁰ The study was approved by the Institutional Review Board of the Chinese University of Hong Kong (CRE-2012.395-T) and conducted in accordance with the Helsinki Declaration of 1975.

Docetaxel was given either as a weekly (35 mg/m² on Day 1, Day 8, Day 15, Day 22, and Day 29 of a 6-week cycle) or a 3-weekly (52.5–75 mg/m²) regimen, with 5 mg prednisone twice per day. The choice of treatment schedule was left to the discretion of the attending oncologists. Treatment with docetaxel was continued until disease progression, unacceptable toxicities, or patient's refusal to continue. Granulocyte colony stimulating factor prophylaxis was administered to patients at the discretion of the attending oncologist. The prostate-specific antigen (PSA) response was defined according to the PCWG-2 criteria. Patients who showed reduction or withdrawal of the World Health Organization (WHO) Class II or III analgesics according to the WHO analgesics ladder during or after the chemotherapy were regarded as having improvement in pain control. Postdocetaxel treatments were given at progression after docetaxel. The choice of postdocetaxel treatment is determined by several factors including the patient's clinical condition, physician's preference, and patient affordability (abiraterone and cabazitaxel being self-financed items). Abiraterone and cabazitaxel only became available to our institutions since April 2010.⁸

Statistical analysis was performed using SPSS (Windows version 17.0.1.80; SPSS Inc., Chicago, IL, USA). The updated database as of July 1, 2013 was used for the analysis. Kaplan–Meier plots of progression-free survival and overall survival (OS) were obtained for subsets of patients segregated by each of the variables (potential prognosticators) listed in Table 1. The log rank test was used to assess the difference in outcome between subsets. The variables were also subject to multivariate analyses using the Cox proportional hazards regression model. A *P* value ≤0.05 was considered

significant. The hazard ratio (HR) and the corresponding 95% confidence interval (CI) were calculated.

3. Results

3.1. Characteristics of patients and treatments

Table 2 summarizes the characteristics of the patient cohort. The median follow-up duration was 14.3 (range, 4.3–42.6) months. The median age at the commencement of treatment was 66 (range, 51–82) years. The median prechemotherapy PSA is 168 (range, 6–2189). Thirty-four patients (59.6%) required WHO Class II or III analgesics at the time of commencement of chemotherapy. Forty-eight (84.2%) and nine (15.8%) patients received docetaxel as a 3-weekly and a weekly regimen, respectively. Ten patients required dose modifications: nine owing to hematological toxicity and one owing to both hematological and neurological toxicities. Primary and secondary granulocyte colony stimulating factor prophylaxis was administered to three patients (5.3%) and one patient (1.8%), respectively. The median number of cycles of chemotherapy was six (range, 1–12), with 19 (33.3%) patients receiving eight or more cycles of chemotherapy. The reasons for discontinuation of chemotherapy are summarized in Table 3. Early discontinuation of chemotherapy owing to progressive disease and poor tolerance occurred in seven and nine patients, respectively, and they are regarded as nonresponders in our study (28%). The other responding patients (responders) received a median of six cycles of chemotherapy.

3.2. Clinical efficacy

Disease progression occurred in 54 patients (94.7%), seven during chemotherapy and 47 after discontinuation of chemotherapy. Postdocetaxel therapies were administered to 31 patients (57.4%), including abiraterone in 13 patients and cabazitaxel in one patient (Table 3). The median OS and progression-free survival time of the cohort were 20.8 months and 5.8 months, respectively (Fig. 1). The 1-year OS rate was 77.8%. As a whole group,

Table 1
Univariate and multivariate analyses of overall survival.

Predictors	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age (y)	1.337 (0.454–3.937)	0.5972	NA	
PSA response	0.272 (0.081–0.915)	0.0243	0.106 (0.016–0.713)	0.1381
Performance status	1.980 (0.852–4.604)	0.1059	NA	
Gleason score	1.856 (0.805–4.279)	0.1408	NA	
Prechemotherapy PSA	1.184 (0.539–2.605)	0.6738	NA	
PSADT	2.341 (0.929–5.901)	0.0635	NA	
Docetaxel schedule	2.016 (0.472–8.607)	0.3338	NA	
Symptomatic disease (yes vs. nil)	1.697 (0.575–5.005)	0.3325	NA	
ALP	3.752 (1.596–8.822)	0.0012	2.000 (0.496–8.070)	0.2105
Severe anemia	6.472 (2.779–15.071)	0.0001	5.224 (2.119–12.881)	<0.0001
Visceral metastasis (yes vs. nil)	1.299 (0.427–3.956)	0.6443	NA	
Cycles of chemotherapy (≥8 cycles)	0.365 (0.135–0.986)	0.0385	0.151 (0.044–0.517)	0.0358
Postdocetaxel treatment (yes vs. nil)	0.098 (0.03–0.316)	<0.0001	0.346 (0.124–0.967)	0.0005
Time to biochemical failure after chemotherapy <3 mo	0.238 (0.056–1.017)	0.0356	0.591 (0.232–1.507)	0.2529
Time to castration failure >1 y	0.366 (0.156–0.862)	0.0167	0.393 (0.147–1.054)	0.393
Time to chemotherapy from castration failure <6 mo	1.386 (0.508–3.776)	0.5224	NA	
Palliative radiotherapy (yes vs. nil)	1.131 (0.764–1.281)	0.7323	NA	

Age, <70 years versus ≥70 years; PSA response, <90% versus ≥90% PSA decline from the baseline; performance status, ECOG 0–1 versus 2; Gleason score, <8 versus ≥8; prechemotherapy PSA, <200 versus ≥200; PSADT, <3 months versus >3 months; Docetaxel schedule, q1wk versus q3wks; ALP level >200; severe anemia, hemoglobin level <10; cycles of chemotherapy, ≥8 versus <8; Time to biochemical failure after chemotherapy, <3 versus ≥3 months; Time to castration failure, >1 versus ≤1 year; Time to chemotherapy from castration failure, <6 months versus ≥6 months.

ALP, alkaline phosphatase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NA, nonapplicable; PSA, prostate-specific antigen; PSADT, PSA doubling time.

Table 2

Patient demographics and treatment details.

	No. (%)
Performance status (ECOG)	
0	32 (56.1)
1–2	25 (43.9)
Gleason score	
≥8	32 (56.1)
≤7	18 (31.6)
Unknown	7 (12.3)
Involved organs	
Bone	53 (93)
Lymph node	28 (49.1)
Liver	3 (5.3)
Lung	7 (12.3)
Dose and schedule of docetaxel	
3-weekly	48 (84.2)
52.5 mg/m ²	1 (1.8)
60 mg/m ²	8 (14)
67.5 mg/m ²	3 (5.3)
75 mg/m ²	36 (63.2)
Weekly (35 mg/m ²)	9 (15.8)
Dose modification	
Total	10 (17.5)
Due to hematological toxicities	10
Due to neurological toxicities	1

ECOG, Eastern Cooperative Oncology Group.

nonresponders had significantly shorter OS than responders (16.2 months vs. 27.2 months, $P = 0.028$).

Overall, ≥50% PSA decline from the baseline value was observed in 33 (57.9%) of 57 patients. Of these patients, 16 (28.1%) showed a PSA decline of ≥90% from the baseline. Improvement in pain control was observed in 22 (64.7%) of 34 patients. Palliative radiotherapy to painful bony metastasis and bisphosphonates was received by 11 patients (11/22, 50%) within 3 months of chemotherapy.

3.3. Adverse events

Hematological toxicities were the most common Grade 3–4 toxicities in this cohort (Table 3). Febrile neutropenia occurred in

Table 3

Treatment-related toxicities and posttreatment status.

Grade 3 or 4 treatment-related toxicity	Grade 3 or 4 treatment-related toxicity	
	Grade 3	Grade 4
Anemia	5 (8.8)	1 (1.8)
Leukopenia	1 (1.8)	5 (8.8)
Neutropenia	6 (10.5)	15 (26.3)
Febrile neutropenia	7 (12.3)	1 (1.8)
Stomatitis	1 (1.8)	0
Diarrhea	1 (1.8)	0
Peripheral edema	1 (1.8)	0
Chemotherapy suspension reason		
Progressive disease		7 (12.3)
Treatment-related toxicities		9 (15.8)
Chemotherapy break		18 (26.3)
Financial constraint		4 (7)
Maximum disease response achieved		19 (33.3)
Postchemotherapy treatment		
None		23 (43.6)
Yes		31 (57.4)
Abiraterone		13
Cabazitaxel		1
Docetaxel rechallenge		2
Estramustine		3
Mitoxantrone		4
Antiandrogen		6
Prednisolone		5
Ketoconazole		2

Data are presented as n or n (%).

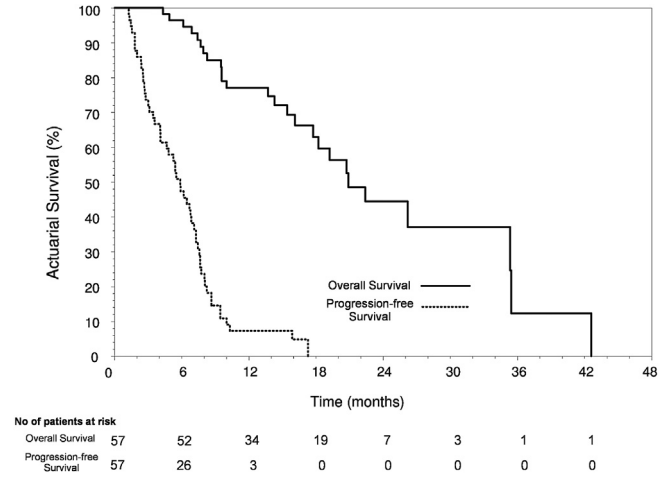


Fig. 1. Progression-free survival and overall survival.

eight patients (14.0%). Other Grade 3 toxicities were stomatitis, diarrhea, and peripheral edema. None of the patients in this cohort died from treatment-related toxicities, but treatments were discontinued in nine (15.8%) patients because of treatment-related toxicities. No statistically significant clinical factors (including age, extent of bone metastases, or chemotherapy schedule) were associated with febrile neutropenia.

3.4. Univariate and multivariate analyses

Univariate analysis revealed six significant predictors of OS (Table 1). Significant anemia (hemoglobin level < 10) (HR = 5.224; 95% CI, 2.119–12.881; $P < 0.0001$), eight or more cycles of chemotherapy (HR = 0.151; 95% CI, 0.044–0.517; $P = 0.0358$), and use of postdocetaxel treatment (HR = 0.346; 95% CI, 0.124–0.967; $P = 0.0005$) are significantly associated with OS in the multivariate analysis (Table 1). Notably, significant differences in median OS were observed in patients who received abiraterone and cabazitaxel (novel agents), received other postdocetaxel treatments (including rechallenge of docetaxel), and did not receive any postdocetaxel treatment (35.3 months vs. 20.8 months vs. 15.3 months, $P = 0.00057$; novel agents vs. other postdocetaxel treatment, $P = 0.00314$; Fig. 2).

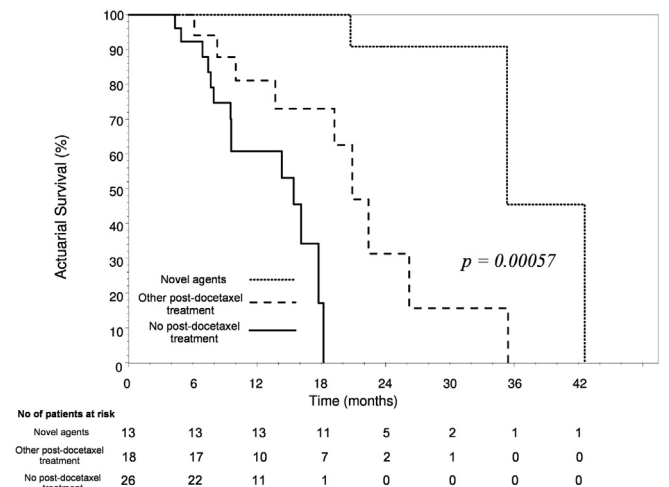


Fig. 2. Overall survival stratified by postdocetaxel treatment.

4. Discussion

This study illustrated the importance of postdocetaxel treatment and duration of docetaxel-based chemotherapy (≥ 8 cycles) in mCRPC patients, based on the statistically significant positive correlation with OS in the multivariate analysis. Additionally, patients who had received postdocetaxel novel agents including abiraterone and cabazitaxel had significantly longer OS compared with those who did not receive any postdocetaxel treatment and those who received other postdocetaxel treatments including rechallenge of docetaxel. The superiority of postdocetaxel novel agents over other postdocetaxel treatments including rechallenge of docetaxel in terms of survival benefit is supported by the robust evidence for the former in contrast to the lack of supporting evidence for the latter.^{5,6} In this privileged era of plentiful novel agents available in the market, the optimal sequence of systemic treatment in mCRPC remains to be defined, and the importance of docetaxel in mCRPC is being challenged by the promising results of the COU-AA-302 study.⁹ Although the results of studies addressing the optimal sequence and agents in managing mCRPC are still being eagerly awaited, this study has consolidated the approach of maximizing exposure to docetaxel-based chemotherapy followed by novel agents, a sensible strategy with exceptional additive survival results.

The intricate interaction between taxane and androgen signaling pathway has been the subject of extensive research previously.^{11–15} Taxanes are shown to interact with androgen signaling in prostate cancer cells at both the cytoplasmic level (via microtubules) and the nuclear level, affecting the transcriptional regulators of androgen-responsive gene expression.^{12,16–18} Data from clinical trials suggest that prior new generation hormonal therapies, particularly abiraterone or enzalutamide, can potentially decrease the subsequent efficacy of taxanes in treating prostate cancer. Mezynski et al.¹⁹ demonstrated that the activity of docetaxel post-abiraterone setting is unexpectedly lower than anticipated, with only 26% of participants showing a $\geq 50\%$ PSA decline rate, in contrast to rates of 45% in the TAX327 study. Meanwhile, Schweizer et al.²⁰ illustrated that mCRPC patients receiving abiraterone prior to docetaxel were more likely to progress on docetaxel and less likely to achieve a PSA response than abiraterone-naïve patients. The underlying hypothesis is that abiraterone, an androgen synthesis inhibitor, may modify the tumor biology into a more androgen-insensitive condition. This would lead to the development of acquired cross-resistance to the subsequent taxane, which exerts its antitumorogenic effect via inhibition of the androgen signaling pathway, in patients with prior abiraterone. This hypothesis is supported by van Soest et al.'s²¹ preclinical study, in which the impaired efficacy of docetaxel and cabazitaxel in the abiraterone-resistant cell line was found. Conversely, results from clinical trials, COU-AA-301 and AFFIRM, have highlighted the persistent responsiveness to androgen-targeted therapy with prior chemotherapy, which might imply that these novel androgen-targeted therapies should suitably be reserved after taxane treatments.^{5,7} In our study, postdocetaxel novel agents were found to be significantly associated with enhanced OS, and this finding is in line with the substantial improvement in survival with novel agents after chemotherapy in the aforementioned studies. The potential additive survival benefit with the sequence of taxane followed by novel agents, as illustrated in our study, may not be achieved if the sequence is reversed.

In our study, the duration of chemotherapy (≥ 8 cycles) had a significant impact on OS. In the pivotal studies establishing the survival advantage of docetaxel-based chemotherapy, patients

received up to 10 cycles of treatment if no progression or no prohibitive toxicities were noted.¹ To date, however, the optimal number of cycles of docetaxel chemotherapy remains unclear. Retrospective studies had compared the survival results among patients receiving ≥ 10 cycles and < 10 cycles of chemotherapy.^{3,4} The results are conflicting, but owing to their retrospective features, confirmatory data in regard to the optimal number of cycles of chemotherapy are lacking. Our findings of significant favorable impact on OS with eight or more cycles of chemotherapy may just be a reflection of the patient's tolerability and biochemical response. Nonetheless, unless untoward treatment-related complications and discouraging response are encountered, our results suggest that patients having eight or more cycles of chemotherapy may lead to a more favorable clinical outcome.

Meanwhile, this study has also affirmed the tolerability and efficacy of docetaxel-based chemotherapy in Chinese mCRPC patients. In our study, the median cycle of chemotherapy is comparatively smaller than that of TAX 327 (6 in the current study vs. 9 in TAX 327), and a certain proportion of patients require a modified starting dose of docetaxel. These findings can be attributed to the significant differences between Asian and Caucasian patients regarding the intrinsic pharmacokinetics and pharmacodynamics, which could influence the tolerability of docetaxel-based chemotherapy.²² The incidence of febrile neutropenia in this cohort is slightly higher than in previous reports (14% in the current study vs. 3–5% in TAX 327 and SWOG 9916 studies). This is in concordance with the findings that Asians are susceptible to chemotherapy-induced myelosuppression.^{23,24} Preemptive primary G-CSF should be considered in Chinese mCRPC patients when docetaxel-based chemotherapy is initiated.

The efficacy of docetaxel-based chemotherapy in this study is comparable to that in TAX 327 and SWOG 9916 studies. The PSA response ($\geq 50\%$ PSA decline from the baseline) in this study is 57.9%, which is similar to the rates found in the cited studies (45% in TAX 327, 50% in SWOG 9916). The magnitude of pain alleviation after chemotherapy is unexpectedly better than in a previous report (64.7% in the current study vs. 35% in TAX 327), and this could be explained by the fact that half of the patients with improvement in pain control had received palliative radiotherapy or bisphosphonates within 3 months of docetaxel-based chemotherapy. The median OS in the current study (20.8 months) is comparable to that of TAX 327 (18.9 months) and SWOG 9916 studies (17.5 months). Because our study had included patients who received novel agents such as abiraterone and cabazitaxel, which were not available when TAX 327 and SWOG 9916 studies were ongoing, the duration of the median OS in our study might numerically lengthen them.

Our study has several limitations. First, despite the fact that novel agents are demonstrated to have a significant impact on survival in our study, they only became accessible since 2010, and longer follow-up is mandatory in order to validate their robustness. Second, the number of patients included in this study is not large enough, and the results may be subject to patient selection bias. Third, we understand that the longer cycle of chemotherapy that led to better survival in this study may simply be a reflection of the good response (lead-time bias) and is subject to selection bias. Finally, the survival results may not be mature enough, and further follow-up is required to validate the study results. In conclusion, our study has illustrated that docetaxel-based chemotherapy is tolerable and efficacious in Chinese mCRPC patients. Meanwhile, our findings suggest that maximizing exposure to docetaxel-based chemotherapy followed by novel therapies would have a favorable survival impact on mCRPC patients.

Conflicts of interest

No conflict of interests was declared by the authors.

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