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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/m^2) and nine (15.8%) received weekly docetaxel (35 mg/m^2). 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.

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 post-docetaxel 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/m^2 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/m^2) 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 $\leq$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)	P	HR (95% CI)	P
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, prostrate-specific antigen; PSADT, PSA doubling time.