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Risk of febrile neutropenia and early treatment cessation in men receiving standard and dose-reduced 3-weekly docetaxel for metastatic castration-resistant prostate cancer

Running Title: Docetaxel dose and toxicity outcomes in metastatic castration-resistant prostate cancer.

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Abstract

BACKGROUND:

Docetaxel is effective therapy for metastatic castration-resistant prostate cancer (mCRPC) however many patients experience febrile neutropenia (FN) and cease treatment early due to toxicity. It is not known whether lower dose q3-weekly docetaxel impacts toxicity or efficacy.

METHODS:

Multicenter retrospective study included 166 patients with mCRPC who received q3-weekly docetaxel between 2010-2015. Demographic, disease, chemotherapy (standard dose, SD>60mg/m^2 vs lower dose, LD≤60mg/m^2) and toxicity data were collected. Univariable and multivariable logistic and competing risk regression models evaluated docetaxel dose association with FN and early treatment cessation (ETC) due to toxicity. Associations between dose and efficacy end points were also evaluated. Analyses were repeated employing inverse propensity score weights.

RESULTS:

Patients who received LD docetaxel (28.9%) were older with poorer ECOG status. 15% of patients experienced FN, with a non-significant trend to lower incidence in the LD group (multiple adjusted OR=0.42; p=0.21). No baseline patient nor prior treatment factors were predictive of FN. ETC due to toxicity occurred in 35%, with risk associated with increasing age, co-morbidity count and poorer ECOG. There was no difference between LD and SD with respect to ETC due to toxicity, in unweighted and weighted analyses (LD vs SD, multivariable weighted HR=1.47; p=0.08). LD was associated with

reduced PSA response (50% vs 66.1%, multivariable weighted HR=0.54; p=0.03) and overall survival (median 7.9 vs 13.8 months, multivariable weighted HR=2.19; p<0.0001).

CONCLUSIONS:

LD docetaxel for mCRPC did not mitigate risk of FN or ETC due to toxicity. Dose reduction may result in poorer PSA response and survival.

Abstract word count: 250

Keywords: metastatic prostate cancer; castration-resistant; docetaxel; febrile neutropenia; chemotherapy toxicity

1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is associated with significant morbidity, impaired quality of life and poor prognosis (1). Whilst the adoption of novel antiandrogens such as enzalutamide and abiraterone acetate has changed the therapeutic landscape of castration-resistant disease, docetaxel plus prednisolone has remained the treatment standard for appropriately selected patients since the seminal TAX-327 study demonstrated improved survival compared to mitoxantrone plus prednisolone (2). Tolerability of docetaxel, however, remains a significant clinical challenge. Survival improvements come at the expense of increased treatment toxicities including febrile neutropenia (FN), sensory neuropathy, nausea, fatigue and nail dystrophy (2, 3). In a typically older

population of patients with co-morbid diseases, early discontinuation (<10 cycles) of docetaxel due to toxicity alone occurs in 10-25% of patients (4), potentially curtailing palliative benefit.

Baseline clinical predictors of docetaxel toxicity – manifested as FN and need for early treatment cessation (ETC) – remain poorly defined in the mCRPC population. Concerns regarding the lack of predictability of docetaxel intolerance administered at a standard dose schedule (75mg/m2, q3-weekly) have prompted efforts to explore the efficacy and safety of alternative treatment schedules. A prospective randomized trial of lower-dose q2-weekly docetaxel versus standard-dose q3-weekly treatment demonstrated improved time to treatment failure and lower rates of myelosuppression and febrile neutropenia with lower-dose treatment (5). Cabazitaxel given at 20mg/m^2 compared to the conventional 25mg/m^2 results in a non-inferior overall survival (13.4 vs 14.5 months) but with significantly less grade 3-4 adverse events (6). It is unclear however if commonly-adopted 'empiric' dose reductions when commencing q3-weekly docetaxel lead to lower rates of toxicity, improved rates of therapy completion or comparable efficacy.

Therefore we studied whether dose-dependent treatment factors and/or baseline patient factors predict for FN and ETC due to toxicity and whether these factors impact prostate specific antigen (PSA) response and survival in a retrospective cohort of men receiving q3-weekly docetaxel for mCRPC.

2. Patients and Methods

2.1. Study Population

All men who received at least one dose of docetaxel for mCRPC between 2010 and 2015 inclusive and subsequently completed or ceased planned therapy were identified through hospital patient databases and pharmacy records across four institutions – three public tertiary center and one private

center. Patients receiving weekly docetaxel or re-treatment with docetaxel after failure of alternative therapy for mCRPC were excluded. Patients who received docetaxel in the context of a clinical trial were also excluded. Prior alternative chemotherapy for mCRPC (such as cabazitaxel) was permitted. Prophylactic antibiotics and growth factor support (such as granulocyte-colony stimulating factor) were not administered routinely when commencing docetaxel. The study was approved by the institutional research ethics committee of participating centers.

2.2. Data Collection

Docetaxel treatment dates and doses were obtained from pharmacy and electronic medical records (EMR). Historical and baseline demographic and clinical variables, baseline (defined as time of docetaxel commencement) laboratory values, PSA values, toxicity outcomes, subsequent therapies and survival status were obtained individually from patient EMR and pathology/radiology records.

2.3. Outcomes

The primary objective was to compare rates of FN and ETC due to toxicity in men with mCRPC receiving standard dose (SD) versus lower-dose (LD) q3-weekly docetaxel and to study associations with baseline demographic, clinical and laboratory variables. Secondary objectives were to compare PSA response, time to next treatment (TTNT) and overall survival (OS) between SD and LD groups.

2.4. Statistical Methods

Date of enrolment was defined as the date of administration of the first cycle of docetaxel. Where the exact date of prostate cancer diagnosis or initiation of continuous androgen deprivation therapy (ADT) was not specified, the approximated date used for analysis was midway in the specified month or year. LD docetaxel was defined as a dose at enrolment of $\leq 60 mg/m^2$ q3-weekly and SD docetaxel $>60 mg/m^2$ q3-weekly. Overall survival (OS) was calculated from the date of enrolment to death with

censoring at date of last contact for alive patient at cut-off date June 2015. Time to next treatment (TTNT) was calculated from date of enrolment to date of subsequent therapy for mCRPC or death. Defined PSA response (≥50% decrease in PSA from baseline value at enrolment) was consistent with the Prostate Cancer Working Group 2 (PCWG2) criteria (7). Demographic variables are presented using median and ranges for age and frequencies and percentages for other factors. Differences in demographic distributions were tested using Kolmogorov-Smirnov (KS) tests. The associations between treatment dose (LD vs SD) and (A) occurrence of FN, (B) early stopping due to toxicity, (C) time to new treatment, (D) PSA response and (E) overall survival were assessed using binomial logistic regression (A&D), Fine and Gray competing risk regression (B) and Cox proportional hazard regressions (C&E). In the competing risk regression for early stopping, toxicity was considered an event and progression the competing risk. Time-to-event survival-type curves are presented using the Kaplan-Meier technique. Multivariable analyses adjust for baseline patient age and Eastern Cooperative Oncology Group Performance Status (ECOG-PS), number of major comorbidities (congestive cardiac failure; ischemic heart disease; chronic kidney disease; chronic obstructive pulmonary disease; dementia) and presence of visceral metastases as variables. In addition, due to the large imbalance in baseline covariates between LD and SD treated cohorts we repeated the analyses using inverse propensity score (PS) weights. Propensity for LD treatment was assessed using binomial logistic regression with the same four baseline covariates as predictors. Significance was taken at the 0.05 threshold using two-sided tests where appropriate. Analyses were conducted in R v3.3.3 (8) using the *twang*, *cmprsk* and *rms* packages.

3. Results

3.1. Patients and treatment

A total of 166 men who received docetaxel for mCRPC between Jan 2010 and Dec 2015 were identified, of whom 118 received SD and 48 received LD docetaxel respectively. Demographic and oncological factors are presented in Table 1. Men who received LD docetaxel were older (mean 80.4 vs 69.6 years, $p < 0.0001$) and had poorer ECOG-PS (mean 1.0 vs 0.7; $p = 0.0002$) compared to those who received standard dosing. There was no difference in number of major co-morbid conditions nor presence of visceral metastases at baseline, as markers of adverse prognosis. Patients in the SD group received a median of 7 cycles (vs 5 cycles for LD group). 35 (30%) patients receiving SD docetaxel were subsequently dose-reduced. Docetaxel dose was modified in 11 LD patients during treatment – 6 (12.5%) were escalated and 5 (11.4%) underwent further dose reduction. When employing PS weights, LD and SD groups were balanced with regard to baseline factors, including age (p=0.96) and ECOG-PS (p=0.47).

3.2. Febrile neutropenia

Overall 25 (15%) patients experienced febrile neutropenia during docetaxel treatment. Although the point estimate odds ratio indicates a reduction of FN with LD docetaxel (rate 10.4% vs 17% in SD group) the differences were not significant between the groups (multiple adjusted OR = 0.42; 95% CI 0.10- 1.55; $p = 0.21$), PS weighting did not change this conclusion (OR = 0.69; 95% CI 0.32-1.4; $p = 0.33$) (Table S1). There were no patient nor prior treatment factors (age p=0.95; baseline albumin p=0.83; baseline lymphocyte count p=0.57; any previous radiotherapy p=1.00) that were identified as predictive for FN.

3.3. ETC due to toxicity

58 of the 166 patients (35%) ceased treatment early due to toxicity for varied reasons including fatigue, gastrointestinal intolerance, infection and other intercurrent illness. Other reasons for treatment cessation were disease progression (31.3%) and unspecified in 2.4%. Overall 31.1% completed planned therapy. Men treated with LD docetaxel were twice as likely to cease therapy early (p = 0.02), however when adjusting for differences in age and co-morbidities this hazard was attenuated (multivariable weighted HR = 1.47; 95% CI 0.96-2.24, p = 0.08) (Table S2; figures 1A & S1A). Fine and Gray competing risk regression model for baseline variables of interest revealed three factors significantly associated with ETC due to toxicity: increasing age (per decade; sHR 1.5; 95% CI 1.2-2.0, p = 0.002), more co-morbidities (sHR 1.4; 95% CI 1.2-1.7, p < 0.0001) and poorer ECOG-PS (score 2-3 vs 0-1; sHR 1.8; 95% CI 1.0-3.1, p = 0.05) (Table 2; Figure 2). These factors retained significance on multivariable analysis with the exception of ECOG-PS (sHR 1.4; 95% CI 0.8-2.5, p = 0.29).

3.4. Time to next treatment

Time to subsequent treatments after docetaxel was not significantly different between SD and LD groups (multivariable weighted HR = 0.85; 95% CI 0.60-1.21, p = 0.36), though patients treated with LD docetaxel exhibited higher risk of starting new treatment in the first 9 months after enrolment (figures 1B & S1B). This risk subsequently fell below the SD group, however notably there were few patients beyond this time point.

3.5. PSA response and overall survival

Overall 102 of 166 (61.4%) patients achieved a PSA response with docetaxel. LD treatment was associated with a significant reduction in the probability of achieving a PSA response compared to standard dosing (50% vs 66.1%, LD vs SD respectively) in both weighted and unweighted multivariable analyses (weighted HR = 0.54; 95% CI 0.31-0.93, p = 0.03). Men treated with LD docetaxel had poorer overall survival (median 7.9 vs 13.8 months, LD vs SD respectively) (figures 1C & S1C) and this was significant despite adjustment with PS weights (multivariable, weighted HR = 2.19; 95% CI 1.55-3.08, p < 0.0001).

4. Discussion

In this study, men who received dose-reduced docetaxel for mCRPC were older and frailer compared to those receiving standard dose. Although the estimated odds ratio of FN was half that in the LD group as compared to the SD group, this was not statistically significant and may be related to a lack of power. By way of comparison, LD cabazitaxel led to a significant reduction (OR = 2.0) in FN compared to SD cabazitaxel in the 1200-patient PROSELICA trial (6). We were unable to identify other baseline clinical predictors for FN among all patients, including factors previously shown to be associated with FN in patients receiving docetaxel for mCRPC – age, previous radiotherapy and lymphopenia (9, 10). Approximately one third of patients ceased planned therapy early due to chemotherapy toxicity, however a dose relationship was not observed. Unsurprisingly older patients with more co-morbidities and poorer ECOG-PS were significantly at risk of ETC due to toxicity. The overall PSA response rate of 61% was comparable to previous prospective studies and real-world reports of q3-weekly docetaxel for mCRPC, varying between 45% to 69% (2, 4, 11-13). Despite adjustment for imbalanced baseline covariates of adverse prognosis, treatment with LD docetaxel was associated with significantly poorer PSA response rate and overall survival. However we acknowledge

that despite use of PS weights to adjust for imbalances in baseline variables, significant unmeasured confounders may be present, which limits the ability to draw definitive conclusions comparing SD and LD groups.

Exploring the efficacy of LD or adapted chemotherapy regimens to minimize toxicity while maintaining efficacy is not a novel proposition in mCRPC. Indeed a prospective trial of LD cabazitaxel after failure of docetaxel demonstrated non-inferior survival outcomes with a significantly improved safety profile (neutropenic infection; Grade 3-4 adverse events) compared to SD therapy (6). Multiple studies have addressed a similar question with respect to docetaxel, exploring dose- and frequency-modified regimens. LD weekly (14, 15), 2-weekly (16), 3-weekly (17) regimens demonstrate activity as well as comparable responses and tolerability to standard dosing in retrospective analyses. A Japanese study (18) of docetaxel dose and dose-intensity dichotomized the study population to <60mg/m^2 vs ≥60mg/m^2. Patients who received LD therapy were significantly older and had adverse prognostic features including higher lactate dehydrogenase and lower hemoglobin levels. Higher dose therapy resulted in superior PSA response rate (62.3% vs 36.4%) at the expense of more frequent severe leukopenia. Although other toxicities were not documented, there was no difference in mean number of docetaxel cycles nor mean cycle dose. Cancer-specific survival did not differ by dose (<60/≥60mg/m^2) nor dose intensity (<13.8/≥13.8mg/m^2/week) in an unweighted univariable analysis. The TAX-327 study included a weekly docetaxel 30 mg/m^2 arm, which while not demonstrating survival improvement over mitoxantrone plus prednisolone, did result in meaningful PSA responses (48%) and reductions in pain (23%) which were comparable to 3-weekly docetaxel (PSA response, 48%; pain reduction, 22%) (2). Similarly the randomized PROSTY II study of 2-weekly 50mg/m^2 vs 3-weekly 75mg/m^2 docetaxel had encouraging findings. 2-weekly treatment was associated with longer time to treatment failure, prolonged OS, similar PSA response rate as well as significantly lower rates of grade 3-4 toxicities (including febrile neutropenia and neutropenic infection)(5).

Febrile neutropenia occurred more frequently among patients in this study compared to historical trial controls, which highlights a differential observed between trials and clinical practice (4). Previous studies have identified age ≥ 75 years old, previous external beam radiotherapy, increased co-morbidities, lymphopenia and low albumin as pre-treatment risk factors for development of FN on docetaxel for mCRPC (9, 10). Liebowitz-Amit and colleagues found in their study comparing octogenarians to younger patients receiving docetaxel, that while PSA response rate, OS and most toxicities did not differ, rates of FN were significantly higher in the very elderly (16% vs 7%) (19). This difference was particularly notable given the greater use of lower dose intensity and weekly therapy among the octogenarian cohort. Our study does not confirm these findings nor does it support the notion that dose reduction necessarily mitigates risk of FN during therapy. However the low FN event rate limits our findings.

Elderly patients and those with greater co-morbidities are vulnerable to docetaxel toxicity and experience more severe adverse events and dose reductions on treatment (20-22). A model predicting risk for chemotherapy toxicity in the elderly has been proposed (23), incorporating tumor/treatment variables, laboratory results and geriatric assessment variables. Our observation that both advanced age and greater major co-morbidity count independently predict for ETC due to toxicity is clinically relevant, as these factors can inform patient selection for docetaxel. Several retrospective and post hoc analyses have suggested a docetaxel cycle number-dependent survival association in mCRPC (24-26), however prospective studies are lacking. LD treatment did not reduce ETC due to toxicity nor improve time to next treatment. Therefore in the absence of randomized data, careful consideration needs to be made regarding the merits of LD q3-weekly treatment in light of potentially inferior PSA responses and survival outcomes.

There are several limitations to this study, the most important of which are its inherent retrospective nature and the potential for inaccuracy with manually recorded clinical data. Variables such as history of FN, co-morbidities, ECOG-PS and reason for ETC rely on investigator assessment of medical records and therefore these data are at risk of reporting bias and over- or under-estimation of outcomes. Our findings also lack formal CTCAE grading of adverse events, although we have used ETC as a surrogate marker for grade 3-4 adverse events which may prompt early treatment cessation.

In conclusion, our results support careful patient selection when considering docetaxel for mCRPC, particularly in at-risk groups (elderly; greater co-morbidities; borderline performance status) in order to balance the potential palliative benefits of therapy against emergent and limiting toxicities. The present study adds to a body of literature investigating tolerability and efficacy outcomes of alternative (primarily dose-reduced) chemotherapy schedules in mCRPC. Routine dose reduction in the absence of risk factors cannot currently be recommended based on our data, as it may result in poorer PSA responses and survival outcomes with a non-significant reduction in febrile neutropenia.

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Figure 1. Kaplan-Meier curves for (A) cycles of docetaxel until ETC due to toxicity, (B) time to starting new treatment and (C) OS, by docetaxel dose (SD vs LD).

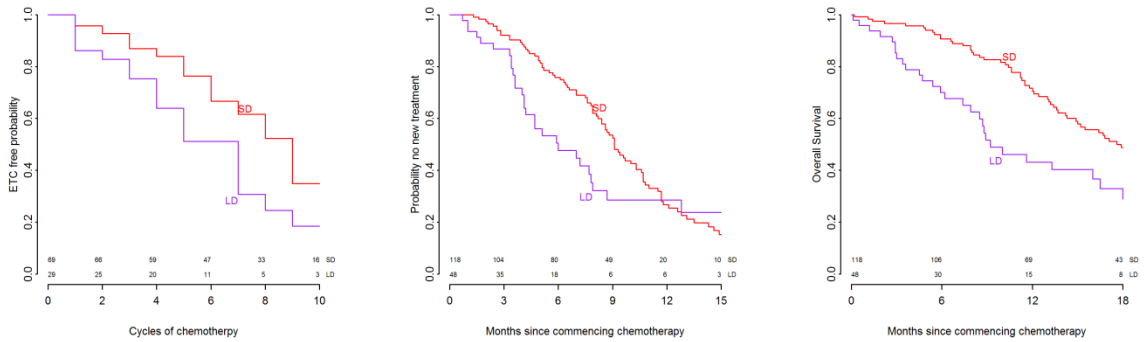

Figure 2. Kaplan-Meier curves for cycles of docetaxel until ETC due to toxicity by baseline patient variables. Individuals with progression are censored at the time of progression.

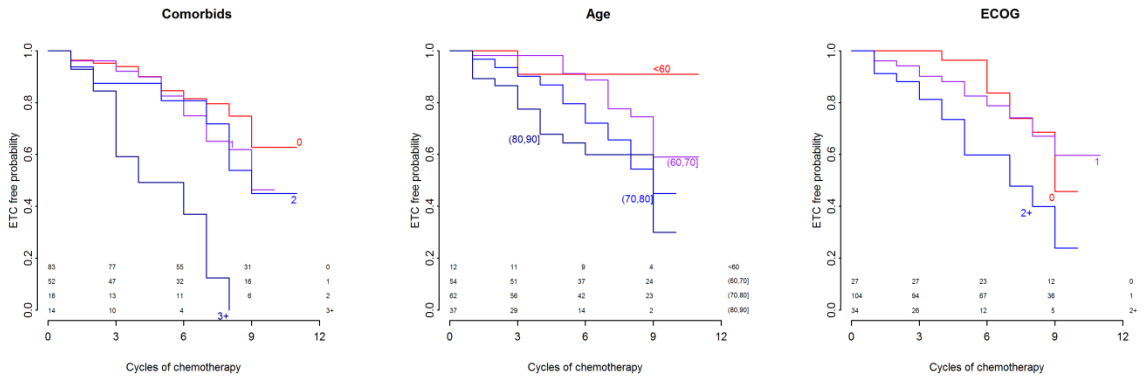

Table 1. Patient characteristics for SD and LD groups.

	SD docetaxel N = 118	LD docetaxel N = 48	p-value*
Age (years)			
Median (range)	70 (40, 84)	82 (65, 89)	<0.0001
Co-morbidities (count)			
0	61 (52%)	22 (46%)	0.42
1	40 (34%)	13 (27%)	
2	12 (10%)	4 (8%)	
3+	5 (4%)	9 (19%)	
ECOG-PS score			
0	24 (20%)	3 (6%)	0.0002
1	82 (69%)	23 (48%)	
2	12 (10%)	20 (42%)	
3	0 (0%)	2 (4%)	
Visceral metastases			
Absent	101 (86%)	41 (85%)	1.00
Present	17 (14%)	7 (15%)	

* Kolmogorov Smirnov test.

Table 2. Predictors of ETC due to toxicity. Fine & Grey competing risk regression estimated (subdistribution) sHR (95% confidence intervals) and p-values. The competing risk is disease progression.

		Univariable		Multivariable	
		sHR (95% CI)	***p* value**	*sHR (95% CI)*	***p* value**
Age (years)	*per decade*	1.5 (1.2-2.0)	0.002	1.5 (1.1-2.0)	0.006
Dose of docetaxel	*LD vs SD*	1.4 (0.8-2.4)	0.21		
Baseline albumin level (g/L)	*per count*	1.0 (1.0-1.0)	0.33		
Baseline lymphocyte count (x1000/mcL)	*per count*	1.0 (0.6-1.5)	0.86		
Prior radiotherapy	*Yes v No*	1.1 (0.7-1.9)	0.69		
Co-morbidities	*per count*	1.4 (1.2-1.7)	<0.0001	1.4 (1.2-1.6)	<0.0001
ECOG-PS	*2-3 vs 0-1*	1.8 (1.0-3.1)	0.05	1.4 (0.8-2.5)	0.29
Visceral metastases	*present v absent*	1.0 (0.5-2.1)	0.96		