Published in final edited form as:

Med Oncol. 2016 July ; 33(7): 77. doi:10.1007/s12032-016-0793-1.

Docetaxel-Related Toxicity in Metastatic Hormone-Sensitive and Metastatic Castration-Resistant Prostate Cancer

Michael T. Schweizer^{1,2,*}, Roman Gulati³, Elahe A. Mostaghel^{1,2}, Peter S. Nelson^{1,4}, R. Bruce Montgomery^{1,2}, Evan Y. Yu^{1,2}, and Heather H. Cheng^{1,2}

¹Department of Medicine, Division of Oncology, University of Washington, Seattle, WA 98109, USA

²Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

³Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

⁴Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

Abstract

Background—Docetaxel plus androgen deprivation therapy (ADT) offers a survival benefit in metastatic hormone-sensitive prostate cancer (mHSPC). However, one trial evaluating docetaxel in mHSPC (GETUG-AFU15) showed unexpected toxicity; raising concerns that docetaxel may carry increased toxicity when used to treat mHSPC compared to metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods—We conducted a retrospective analysis evaluating differences in toxicity based on the clinical state (i.e. mHSPC vs. mCRPC) docetaxel was used. Patients initiating docetaxel between 1/1/2014—7/15/2015 were included, with the former date chosen to coincide with the press release for the first mHSPC study that showed a survival benefit with early docetaxel; ensuring contemporary docetaxel-treated cohorts.

Results—Thirty-nine mCRPC and 22 mHSPC patients were included. Compared to mCRPC, mHSPC patients were younger (median years: 66.3 vs. 71.8, $P=0.007$); had better performance status (ECOG 0–1: 100% vs. 62%, $P<0.0001$); and used opiates less frequently (29% vs. 66%, $P=0.04$). Neutropenic fevers occurred in 9% and 5% ($P=0.95$) of men with mHSPC and mCRPC, respectively. Other toxicities also occurred at similar rates between cohorts. The incidence of any toxic event was 73% and 67% ($P=0.84$) for men with mHSPC and mCRPC, respectively. Within the mHSPC cohort, neutropenic fevers occurred at a similar rate regardless of the time interval between initiating ADT and the start of docetaxel.

Conclusions—We did not observe a significant difference in toxicity between mHSPC and mCRPC patients receiving docetaxel. However, the small sample size and retrospective nature of this study limits our ability to draw definitive conclusions.

*Correspondence: schweize@uw.edu.

Conflict of interest: None

Introduction

In 2004, docetaxel was approved by the Food and Drug Administration for the treatment of metastatic castration-resistant prostate cancer (mCRPC) on the basis of two Phase III studies demonstrating that it afforded an overall survival (OS) advantage compared to mitoxantrone. [1, 2] Recently, three large randomized trials have evaluated docetaxel in combination with androgen deprivation therapy (ADT) (i.e. LHRH agonists or antagonists) in men with newly diagnosed, hormone-sensitive metastatic prostate cancer. The CHAARTED and STAMPEDE trials demonstrated a statistically significant improvement in OS, with a median improvement of 13.6 and 15 months (M1 subgroup only), respectively, while the GETUG-AFU15 trial reported a smaller, non-significant improvement in survival of only 4.7 months.[3–5] Based on these aggregate findings, docetaxel has become a standard treatment option for metastatic hormone-sensitive prostate cancer (mHSPC).

As docetaxel is increasingly used in the upfront treatment of mHSPC, concerns over increased toxicity have emerged.[6] The authors of the GETUG-AFU15 trial noted that, prior to an amendment allowing the use of granulocyte colony stimulating factor (G-CSF) support, Grade 3–5 neutropenia occurred in nearly 1/3 of the patients enrolled in that trial, with 7% of patients developing febrile neutropenia, and two deaths resulting from neutropenia-related complication.[3] Cross-trial comparisons between the TAX-327 trial, which tested docetaxel plus prednisone in the mCRPC setting, and the GETUG-AFU15, CHAARTED, and STAMPEDE trials revealed that rates of febrile neutropenia were lower in TAX-327 at 3% vs. 16% in GETUG-AFU15, 13% in STAMPEDE, and 6% in CHAARTED. [3–5] Data regarding the use of growth factors in the CHAARTED and STAMPEDE studies were not collected. Cross-trial comparisons are prone to introducing bias and in general should not be used to guide decision-making, but do raise the possibility there may be clinically relevant differences in toxicity.

To address the uncertainty of whether docetaxel-based regimens may be more toxic when used to treat mHSPC compared to mCRPC, we conducted a retrospective analysis on contemporary cohorts of prostate cancer patients receiving docetaxel to treat mHSPC or mCRPC. Our primary goal was to determine if docetaxel was associated with more toxicity when used to treat mHSPC compared to the mCRPC.

Patients and Methods

Patients

This was a retrospective, single-institution analysis that included metastatic prostate cancer patients treated with standard docetaxel chemotherapy (i.e. 75 mg/m² every 21 days). Patients with small cell or neuroendocrine prostate cancer and those receiving docetaxel in combination with other cytotoxic agents (e.g. carboplatin) were excluded. Clinical data for consecutive patients with metastatic prostate cancer who received treatment with docetaxel were obtained from the Genitourinary Cancer CAISIS database maintained by the Fred Hutch Cancer Center Consortium and with Institutional Review Board approval. Only those who initiated docetaxel between 1/1/2014 and 7/15/2015 (the date our database was locked) were included, with the interval start date chosen to coincide with the press release

announcing the results of the CHAARTED study – thus ensuring that patients receiving docetaxel for mCRPC were contemporaneous to those receiving docetaxel for mHSPC.[7]

Statistical Analysis

The primary objective was to determine if there were differences in toxicity associated with docetaxel chemotherapy when used to treat mHSPC compared to mCRPC. Metastatic castration-resistant prostate cancer was defined as metastatic prostate cancer that had progressed on continuous LHRH agonist or antagonist therapy or after surgical castration. Progression was determined by the treating physician. Patients with metastatic prostate cancer not meeting criteria for mCRPC were defined as having mHSPC. Potential docetaxel-related toxicities were pre-defined as neutropenia (absolute neutrophil count $<1000/\mu\text{l}$), fever (temperature $>38.3^{\circ}\text{C}$), neutropenic fever (fever in the presence of neutropenia), neuropathy, mucositis and hospitalization for any reason. These data elements were gathered through chart review. Because of the retrospective nature of this study, details regarding the severity of any given event were generally unavailable. Lab parameters that were likely to be impacted by docetaxel were also collected. These labs included: white blood cell (WBC) and absolute neutrophil counts, hemoglobin, platelet count, albumin, alkaline phosphatase, lactate dehydrogenase (LDH). Serum testosterone levels were not available for most patients included in this database. Data regarding the use of growth factors (i.e. G-CSF) and prophylactic antibiotics was also collected.[8]

Summary statistics of selected patient characteristics at initiation of chemotherapy were calculated and stratified by hormone-sensitive or castration-resistant settings. Differences in continuous measures were tested using t-tests and differences in categorical measures were tested using χ^2 test or 2-sided 2-sample tests of proportions as appropriate. To test differential risks of toxicity events in the hormone-sensitive and castration-resistant settings, and to account for different numbers of patients at risk and differential follow-up, we estimated Kaplan-Meier survival curves for each toxic event and for the composite endpoints of any toxic event and time to neutropenia or receipt of G-CSF. Differences were tested using log-rank tests.

Results

Patients

Between January 1, 2014 and July 15, 2015, 61 patients with metastatic prostate cancer received docetaxel chemotherapy. Thirty-nine of these patients had mCRPC and 22 had mHSPC. The median time from initiating androgen deprivation therapy (ADT) to the first dose of docetaxel was 16 days (range, 0 to 211) in the mHSPC cohort and 1,098 days (range, 98 to 3352) in the mCRPC cohort ($P<0.0001$). The median number of cycles of docetaxel received was 6 (range, 1 to 6) and 6 (range, 1 to 14) for patient with mHSPC and mCRPC, respectively.

Patients with mHSPC had better ECOG performance status (ECOG 0–1: 100% vs. 62%, $P<0.0001$) and less frequent opiate use (29% vs. 66%, $P=0.04$) at the start of chemotherapy. Additional baseline characteristics for these two cohorts were similar (Table 1).

Toxicity

The number of patients whose course was complicated by neutropenia, fever, neutropenic fever, neuropathy, mucositis or hospitalization was similar for patients with mHSPC and mCRPC (Table 2). Similarly, these toxicities did not differ across docetaxel cycles when stratified by disease state (Table 3). Time to event analysis also revealed no significant difference in the rates for each toxic event between groups (Figure 1).

A number of additional toxicities occurred in our cohort of patients, which were captured as ‘other’ toxicities. For mHSPC patients, these included: nail changes (N=2), rash (N=1), soft tissue infection (N=1), zoster infection (N=1), non-anaphylactic infusion reaction (N=1), rhinorrhea (N=1), headache (n=1), joint pain (N=1), hyperglycemia (N=1) and vision changes (N=1). For mCRPC patients, these included: soft tissue infection (N=1), nail changes (N=1), nausea and vomiting (N=1), diarrhea/loose stool (N=2), edema (N=1), thrush (N=1), pneumonia (N=1), bladder stones (N=1), hematochezia (N=1) and pulmonary embolus (N=1). There was a trend toward more ‘other’ toxicities in men with mHSPC (41% vs. 18%, $P=0.10$).

We also found no differences between groups for the composite endpoints of ‘any toxic event’ and ‘time to neutropenia or receipt of G-CSF’ (Figure 2). The use of G-CSF was similar between groups, with 7 (32%) of patients with mHSPC and 16 (42%) of mCRPC patients receiving G-CSF at any time during the course of their treatment with docetaxel ($P=0.43$). The rate of prophylactic antibiotic use at anytime during the course of treatment was also similar between the mHSPC and mCRPC groups at 10% and 16% ($P=0.477$), respectively. Change in lab parameters (i.e. albumin, alkaline phosphatase, hemoglobin, LDH, neutrophil count, platelets and WBC) over the course of treatment did not differ between groups.

Conclusion

This single-institution retrospective analysis did not demonstrate that docetaxel is more toxic in the mHSPC setting compared to the mCRPC setting. The small sample size and retrospective nature of this study prevent us from drawing definitive conclusions; however, our findings suggest that a dramatic difference in docetaxel-related toxicity between groups is unlikely. It is notable that we observed neutropenic fever in 9% of mHSPC patients. Given that primary prophylaxis with growth factors has been proposed to be most appropriate when the risk of febrile neutropenia is $>20\%$, our findings alone do not support the use of primary prophylaxis with growth factors for most mHSPC patients.[9]

The retrospective nature of this study limited our ability to detect differences in on-treatment lab values between groups. Because lab values were ordered at the discretion of the treating physician rather than at predefined time points, some differences in lab abnormalities may have simply been undetected. For instance, neutropenia was likely underappreciated in this analysis given that blood counts were not routinely obtained mid-treatment cycle (i.e. at the time of count nadir). That said, clinically significant toxicities resulting from neutropenia (e.g. neutropenic fevers and hospitalizations) did not occur more frequently in the mHSPC group and would almost certainly garner mention in the medical record. Moreover, there was

no apparent difference in the composite endpoint of neutropenia or G-CSF use; again, pointing toward the absence of a substantial difference in bone marrow toxicity in the mHSPC vs. mCRPC setting.

An important issue not addressed by this analysis, is whether differences in toxicity may have been present depending on the time elapsed between the start of ADT and initiation of docetaxel in the mHSPC group. In a prior pharmacokinetic study, it was reported that docetaxel clearance increased by approximately 100% in castrate compared to non-castrate men with prostate cancer.[10] That study found no difference in CYP3A4 activity (the main docetaxel-metabolizing enzyme) between cohorts; however, subsequent rat studies demonstrated that increased docetaxel clearance was associated with increased expression of rOat2 (*Slc22a7*), an organic anion transport protein (OATP). Therefore, it is plausible that differences in docetaxel toxicity exist between castrate and non-castrate men as a result of variable hepatic uptake and clearance.

The timeframe by which OATP transporters are upregulated in humans following castration is not clear, and it is possible that men who start docetaxel at the same time as ADT may have more toxicity than those who delay docetaxel initiation. It is notable that in the GETUG-AFU15 trial the median time from initiating ADT to study enrollment was approximately 15 days.[3] While testosterone levels were not captured in that study, it seems likely that many men were not castrate at the time they received their first dose of docetaxel given that median time to castration following receipt of an LHRH agonist is approximately one month.[11] Whether this point explains the relatively high rate of febrile neutropenia observed in that trial is not clear. Interestingly, in our mHSPC cohort, the median time from initiating ADT to the first dose of docetaxel was similarly short at 16 days, while the observed rate of febrile neutropenia was low compared to GETUG-AFU15 (9% vs. 16%). Because our mHSPC cohort was relatively small at 22 patients, there was inadequate power to formally evaluate for differences in toxicity within this group based on time from initiating ADT to the first docetaxel dose; however, when our mHSPC cohort is dichotomized based on median time from initiating ADT to first dose of docetaxel, there is no clear difference in the rate of febrile neutropenia (Table 4). In addition, none of the five patients that initiated docetaxel within one month of ADT had a neutropenic fever during their course of treatment.

Given the combined experience from the GETUG-AFU15, CHAARTED, and STAMPEDE trials, additional studies are justified to evaluate for potentially clinically meaningful differences in toxicity when docetaxel is used in a hormone-sensitive vs. castration-resistant setting.[3–5] Moreover, the aforementioned data regarding the impact of androgens on expression of hepatic OATPs provide motivation for reanalyzing these Phase III trials to assess for differences in toxicity based on the time from the start of ADT to docetaxel initiation. To overcome the limitations of retrospective analyses and the bias associated with cross-trial comparisons, additional prospective studies will be needed. These studies should follow mCRPC and mHSPC patients at prespecified timepoints and capture toxicity based on accepted criteria such as the Common Terminology Criteria for Adverse Events (CTC AE). Strict inclusion/exclusion criteria will be essential in order to control for baseline differences in patient health and disease severity. Ideally, these studies should also

interrogate testosterone kinetics following the initiation of ADT alongside the pharmacokinetics of docetaxel.

Acknowledgments

This work was supported by NCI award number P50CA097186, the University of Washington/Fred Hutchinson Cancer Research Center Institute for Prostate Cancer Research, and the Prostate Cancer Foundation. The authors would like to acknowledge Agnes Gawne for her help with the genitourinary cancer CAISIS database.

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Figure 1. Kaplan-Meier estimates of time to toxic event

P-value (log-rank test) for all comparisons is >0.1 . mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer.

Figure 2. Kaplan-Meier estimates of time to composite toxic event endpoints
P-value (log-rank test) for both comparisons is >0.1.

Table 1

Baseline features.

	mCRPC (N=39)	mHSPC (N=22)	P-value
Age at start of docetaxel, years, median (min-max)	72 (49 – 89)	66 (51 – 84)	0.0099
Time from starting ADT to initiating docetaxel, days, median (min-max)	1098 (98 – 3352)	16 (0 – 211)	<0.0001
PSA at start of ADT, ng/ml, median (min-max)	32.9 (0.2 – 1989.2)	37.9 (2.5 – 1948.7)	0.43
Gleason grade, number (%)			
6–7	15 (43)	4 (20)	0.14
8	20 (57)	16 (80)	
Disease burden, number (%) *			
High	29 (85)	14 (67)	0.18
Low	5 (15)	7 (33)	
ECOG performance status, number (%)			
0–1	21 (62)	22 (100)	0.0007
2–4	13 (38)	0 (0)	
Concurrent prednisone given with docetaxel	22 (63)	8 (44)	0.39
Opiate use at start of docetaxel, number (%)	21 (66)	5 (29)	0.04

Note: For Gleason grade, disease burden, and ECOG performance status the total number of subject in each subcategory does not equal the total number of subjects for the given disease state. This discrepancy is because data was unavailable for all subjects included in this study. Similarly, data on the concurrent use of prednisone at the start of docetaxel was unavailable for 4 patients in the mHSPC and mCRPC groups, and for baseline opiate use in 5 and 7 patients in the mHSPC and mCRPC groups, respectively.

* Disease burden was categorized as high if a subject had 4 bone metastases with at least one extra-axial skeletal metastasis or at least one lung/liver metastasis.

mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; ECOG, Eastern Cooperative Oncology Group.

Table 2

Toxic events during treatment with docetaxel.

	mCRPC, N (%)	mHSPC, N (%)	P-value
Neutropenia	10 (26)	7 (32)	0.83
Fever	3 (8)	1 (5)	1
Neutropenic Fever	2 (5)	2 (9)	0.95
Neuropathy	7 (18)	6 (27)	0.60
Mucositis	4 (10)	4 (18)	0.63
Hospitalization	10 (26)	6 (27)	1
Other	7 (18)	9 (41)	0.10
Any Toxicity	26 (67)	16 (73)	0.84

mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

Table 3

Cumulative toxicities for patients with metastatic castration-resistant prostate cancer (mCRPC) and metastatic hormone-sensitive prostate cancer (mHSPC) receiving docetaxel.

	Disease state	Cycle Number					
		1	2	3	4	5	6
Number at risk	mCRPC	39	37	34	27	27	26
	mHSPC	22	21	20	19	19	17
Toxicity, N (%)							
Fever	mCRPC	0 (0%)	1 (3%)	0 (0%)	1 (4%)	2 (7%)	2 (8%)
	mHSPC	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	P-value	0.77	1	NA	1	0.63	0.67
Hospitalization	mCRPC	2 (5%)	2 (5%)	3 (9%)	2 (7%)	3 (11%)	4 (15%)
	mHSPC	3 (14%)	2 (10%)	4 (20%)	4 (21%)	4 (21%)	3 (18%)
	P-value	0.50	0.96	0.45	0.36	0.61	1
Mucositis	mCRPC	2 (5%)	3 (8%)	3 (9%)	1 (4%)	1 (4%)	1 (4%)
	mHSPC	3 (14%)	4 (19%)	3 (15%)	3 (16%)	3 (16%)	3 (18%)
	P-value	0.50	0.42	0.80	0.37	0.37	0.32
Neuropathy	mCRPC	1 (3%)	3 (8%)	5 (15%)	4 (15%)	4 (15%)	5 (19%)
	mHSPC	1 (5%)	3 (14%)	3 (15%)	3 (16%)	5 (26%)	5 (29%)
	P-value	1	0.77	1	1	0.55	0.69
Neutropenia	mCRPC	5 (13%)	9 (24%)	9 (26%)	9 (33%)	9 (33%)	9 (35%)
	mHSPC	5 (23%)	6 (29%)	5 (25%)	5 (26%)	5 (26%)	6 (35%)
	P-value	0.52	0.97	1	0.85	0.85	1
Neutropenic Fever	mCRPC	0 (0%)	1 (3%)	0 (0%)	1 (4%)	1 (4%)	1 (4%)
	mHSPC	2 (9%)	2 (10%)	1 (5%)	1 (5%)	1 (5%)	1 (6%)
	P-value	0.24	0.61	0.79	1	1	1
Other	mCRPC	1 (3%)	3 (8%)	5 (15%)	5 (19%)	6 (22%)	6 (26%)
	mHSPC	0 (0%)	3 (14%)	6 (30%)	5 (26%)	8 (42%)	8 (47%)
	P-value	1	0.77	0.32	0.79	0.26	0.19

Only data through the first six cycles of chemotherapy are provided given that no patient with mHSPC received more than six cycles.

Table 4

Toxic events during treatment with docetaxel for patients with metastatic hormone-sensitive prostate cancer (mHSPC); stratified by median time from initiating androgen deprivation therapy (ADT) to first dose of docetaxel.

	Time from ADT initiation to start of docetaxel	
	At or below the median	Above the median
Neutropenia	4 (33)	3 (30)
Fever	0 (0)	1 (10)
Neutropenic Fever	1 (8)	1 (10)
Neuropathy	5 (42)	1 (10)
Mucositis	3 (25)	1 (10)
Hospitalization	4 (33)	2 (20)
Other	8 (67)	1 (10)
Any Toxicity	10 (83)	6 (60)