Medical Oncology (2019) 36:18
https://doi.org/10.1007/s12032-018-1238-9

ORIGINAL PAPER

The timing of docetaxel initiation in metastatic castrate-sensitive prostate cancer and the rate of chemotherapy-induced toxicity

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Received: 9 November 2018 / Accepted: 10 December 2018 / Published online: 21 January 2019

Abstract

Docetaxel pharmacokinetics are affected by androgen deprivation therapy (ADT), which is attributed to changes in liver metabolism induced by castration. In this retrospective analysis, we assessed whether initiating docetaxel treatment in close proximity to the start of ADT therapy for metastatic castrate-sensitive prostate cancer (mCSPC) is associated with more treatment-related toxicity. We identified all patients with mCSPC treated at The Ottawa Hospital that received docetaxel chemotherapy between June 2014 and September 2017. For each patient, we calculated the time to chemotherapy (TTC) interval between the start of ADT and the first cycle of docetaxel. We checked for an association between TTC and febrile neutropenia (FN), toxicity-induced dose reduction, toxicity-induced treatment delay, and toxicity-induced treatment discontinuation. Eighty-three patients were identified. The median TTC was 67 days (range 3–189). Twenty-three patients (27.7%) experienced FN. Docetaxel toxicity resulted in 8 patients (9.6%) having their treatment delayed, 30 patients (36.1%) having their dose reduced and 18 (21.6%) having their treatment discontinued before completing the scheduled 6 cycles. No correlation was found between the TTC and FN ($P=0.99$), docetaxel dose reduction ($P=0.95$), treatment delay ($P=0.06$), and treatment discontinuation ($P=0.88$). The timing of docetaxel treatment initiation in relation to ADT initiation in patients with mCSPC did not affect the rate of treatment-related toxicity. Therefore, there is no indication for upfront chemotherapy delay from start of ADT unless clinical factors warrant a delay in starting chemotherapy. A higher than expected FN rate was identified, and primary prophylaxis should be considered.

Keywords Prostate cancer · Castrate-sensitive · Docetaxel · Toxicity

Introduction

Docetaxel is currently used to treat metastatic castrate-resistant prostate cancer (mCRPC) and recently metastatic castrate-sensitive prostate cancer (mCSPC) [1–3]. In the mCRPC space, docetaxel plus prednisone improved the median overall survival (OS) of patients by 2.4 months compared to mitoxantrone plus prednisone. In contrast, docetaxel improved OS by up to 17 months when added to androgen deprivation therapy (ADT) as first-line treatment for mCSPC with high-volume disease [1, 3, 4].

There is evidence that castration induced by ADT can affect the pharmacokinetics of docetaxel and increase its clearance by 100%. This is thought to be likely due to increased uptake of docetaxel in the liver [5]. Bruno et al. demonstrated that a 50% decrease in docetaxel clearance is associated with a threefold increase in the odds of febrile neutropenia (FN) [6]. This variation in docetaxel pharmacokinetics may explain the reports that patients with mCSPC treated with docetaxel have higher rates of FN [7].

In the CHAARTED protocol, chemotherapy for mCSPC patients was initiated within 4 months of the start of ADT, with a median time of 1.2 months between the start of ADT and first cycle of docetaxel [3]. In the STAMPEDE study, the median time from starting hormonal therapy to starting docetaxel was 8.6 weeks [2]. As it may take a few weeks until ADT treatment and consequently castration exert their effect on liver metabolism and, potentially, docetaxel

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clearance and toxicity, the timing of docetaxel treatment initiation after starting ADT (immediately versus later in the 4-month interval) may impact the rate of docetaxel-related toxicities. Therefore, in this retrospective analysis we will assess whether docetaxel treatment initiation in close proximity to start of ADT therapy for mCSPC is associated with more treatment-related toxicity.

Materials and Methods

In this retrospective analysis, we identified all patients with mCSPC treated with docetaxel chemotherapy at presentation of their disease at The Ottawa Hospital Cancer Centre between June 2014 and September 2017. Demographic and descriptive information were collected including: date of birth, the start date and type of ADT used, the start date of docetaxel, the dose of docetaxel used, number of docetaxel cycles given and chemotherapy-related complications.

For each patient, we calculated the time to chemotherapy interval (TTC) which is the time interval between the start of ADT and the first dose of docetaxel. We considered the first injection of either luteinizing hormone-releasing hormone (LHRH) agonist or antagonist as the start date of ADT. We checked for an association between TTC and febrile neutropenia (FN), toxicity-induced treatment delay or discontinuation, and toxicity-induced dose reduction. Mean and standard deviation or proportions were used to summarize the patient's characteristics of the cohort. To assess the associations between TTC and any of outcomes, the median TTC were compared between patients having the outcomes versus not having the outcomes using Wilcoxon Two-sample tests. When comparing timing cohorts (TTC $\leq$ or $>$ 60 days) Chi-squared and Fischer exact tests were used as appropriate. We used Wilcoxon Two-Sample Test to compare the median docetaxel dose used in the first cycle between patients experiencing FN during the 1st cycle versus those that did not. We used SAS 9.3 software for analyzing the data. Statistical significance was assumed at P-value ≤ 0.05. For this retrospective study, formal consent was not required. The study was approved by the Ottawa Health Science Network Research Ethics Board.

Results

Eighty-three patients treated with docetaxel chemotherapy for mCSPC were identified. The mean age (at the start of docetaxel treatment) was 69 years old with a standard deviation of 7.5. Other baseline characteristics are presented in Table 1.The median TTC was 67 days (IQR 39–94).

Twenty-three patients (27.7%) experienced FN. Their median TTC was 71 days (IQR 43–93). The median TTC in the patient population that did not suffer from FN was 64 days (IQR 38–95). This difference was not statistically significant ($P=0.99$). Most episodes of FN (68%) occurred during the 1st cycle. Only two patients suffered from more than 1 episode of FN. There was no statistically significant difference in the median dose of docetaxel used in the 1st cycle between patients experiencing FN during the 1st cycle versus those that did not (75 mg per square meter of body-surface area (IQR 75–75) versus 75 mg per square meter of body-surface area (IQR 69–75); $P=0.09$).

Thirty patients (36.1%) had chemotherapy dose reductions due to docetaxel-induced toxicity. Two-thirds of them had their 2nd cycle dose reduced. Eight patients (9.6%) had their treatment delayed and 18 (21.6%) had their treatment discontinued before completing the planned 6 cycles due to docetaxel toxicity (Table 2). This resulted in a median docetaxel relative dose intensity of 84% (IQR 67.1–96.1%). When comparing early (TTC $\leq$ 60 days) versus late (TTC $>$ 60 days) cohorts we did not see significant difference in toxicity (Table 3). No association was found between TTC and docetaxel dose reduction ($P=0.95$) or TTC and treatment discontinuation ($P=0.88$). Patients requiring chemotherapy treatment delays due toxicity had a median TTC of 34.5 days (IQR 22.5–74), while patients not suffering from treatment delays had a median TTC 68 days (IQR 42–95). This latter result demonstrated a strong trend but was not statistically significant ($P=0.06$). Detailed information is presented in Table 2.

Seven patients were treated concurrently with enzalutamide and docetaxel (as part of a clinical trial). After excluding these patients, still no correlation was found between TTC and FN ($P=0.77$), docetaxel dose reduction ($P=0.63$), toxicity-related treatment delay ($P=0.15$), and docetaxel treatment discontinuation due to toxicity ($P=0.86$).

Sixty-one patients were treated with LHRH agonist, while 22 patients were treated with LHRH antagonist. We performed separate subgroup analysis for the two groups, and no correlation between TTC and FN, docetaxel dose reduction, toxicity-related treatment delay and docetaxel treatment discontinuation due to toxicity was found.

Discussion

Docetaxel has significant pharmacokinetic variability among different patients which may explain the difference in tolerability between patients [5, 6]. In recent years, as docetaxel treatment became a standard of care for patients with newly diagnosed mCSPC, there were reports that this treatment might be associated with higher toxicity rates, mainly FN, as compared to docetaxel treatment for mCRPC patients. While in the Tax 327 trial, the rate of FN was 3% in mCRPC patients receiving docetaxel, in the CHAARTED

Table 1 Baseline disease and patient characteristics

Age (at the start of docetaxel treatment)	Years (SD)
Mean	69 (7.5)
Serum PSA	mcg/l (IQR)
Median	124 (34–356)
ECOG performance status	Number of patients (%)
0	24 (28.9)
1	24 (28.9)
2	5 (6)
3	1 (1.2)
Not available	29 (34.9)
Extent of disease	Number of patients (%)
High volume	72 (86.7)
Visceral involvement	20 (24.1)
Low volume	11 (13.3)
Gleason Score	Number of patients (%)
≤6	1 (1.2)
=7	9 (10.8)
=8	14 (16.8)
=9	45 (54.2)
=10	3 (3.6)
Not available	11 (13.2)
	Number of patients (%)
Metastatic disease at diagnosis	72 (86.7)
Recurrent disease	11 (13.3)
Prior treatment with radiotherapy	Number of patients (%)
Yes	49 (59)
No	34 (40)

SD standard deviation, *IQR* interquartile range

and STAMPEDE trials, the rate of FN was 6% and 15% in mCSPC patients receiving docetaxel [1–3, 8]. The overall rate of FN in our study is much higher (27.7%). Similar to our findings, Mahil J et al. reported that FN rate for patients with mCSPC treated with docetaxel at The Christie Hospital was 30% [7]. The high FN rates at our institution and at The Christie Hospital in comparison with CHAARTED and STAMPEDE studies may be explained by the difference between a real-world population and patients on clinical trials [9]. For example, the median age in our cohort of patients was 69 (range 49–83), while in the CHAARTED and STAMPEDE trials the median age of patients treated with docetaxel was 64 (range 36–88) and 65 (range 40–81).

As it was shown that castration status may influence the liver metabolism of docetaxel and perhaps increase its tolerability due to increased clearance rate, we assessed in this study whether the inter-patient tolerability could be related to the time of chemotherapy initiation in relation to ADT using four parameters. However, we did not find any association between the ADT-to-docetaxel time interval and FN rates, docetaxel toxicity requiring dose reduction or treatment discontinuation. The fourth parameter of treatment delays due to toxicity was more frequent in patients starting docetaxel in close proximity to ADT. However this strong trend while not statistically significant, likely due to the small sample size, suggests caution when starting

Table 2 Toxicity consequences relative to initiation of chemotherapy

	Number of patients (%)	Median (days) TTC (IQR)	*P* value
Febrile neutropenia			
Yes	23 (27.7)	71 (43–93)	0.99
No	60 (72.3)	64 (38–95)	
Toxicity-related chemotherapy treatment delay			
Yes	8 (9.6)	34.5 (22.5–74)	0.06
No	75 (90.4)	68 (42–95)	
Toxicity-induced chemotherapy dose reduction			
Yes	30 (36.1)	72.5 (35–95)	0.95
No	53 (63.9)	64 (42–93)	
Toxicity-induced chemotherapy treatment discontinuation			
Yes	18 (21.7)	63.5 (38–91)	0.88
No	65 (78.3)	67 (40–95)	

TTC time to chemotherapy (the time interval between the start of ADT and the 1st dose of docetaxel), *IQR* interquartile range

chemotherapy early in patients with little reserves to tolerate toxicity. One possible explanation to the lack of association found in the current study is that long-standing castration status could be required in order to significantly affect the liver metabolism. As mCSPC patients are starting docetaxel within 3–4 months from the start of ADT, this assumption may explain the lower FN rates in the mCRPC who may have been castrate for many months to years.

Recently a work by Rulach et al. assessed the safety profile and outcomes of docetaxel in patients with mCSPC [10]. Interestingly, they found a 9 times greater risk of FN if chemotherapy was started within 19 days of ADT initiation (out of 7 patients in risk, 3 patients suffered from FN). Although not statistically significant, in their study the risk of FN seems to decrease the later chemotherapy is started. In our study, we did not find such an association as the FN cases seems to spread more evenly. We need to take into account that the sample size in both studies is relatively small and a larger, perhaps multicenter study could solve the discrepancies between these studies.

Despite the high rates of FN and other chemotherapy-related toxicities, none of the patients died as a result of chemotherapy toxicity. It is reassuring that with appropriate toxicity management and dose reductions, most patients were able to complete the intended 6 cycles of docetaxel. Single agent docetaxel is usually considered to have an intermediate risk of FN (defined as 10–20% risk of FN) and therefore granulocyte colony-stimulating factors (G-CSF) usually are not prescribed prophylactically [11, 12]. None of the patients in our study were offered primary prophylactically G-CSF.

Both the American Society of Clinical Oncology (ASCO) and the European Organization for Research and Treatment of Cancer (EORTC) recommend to use prophylactic G-CSF from the first cycle of regimens with high likelihood for FN (defined as 20% or higher risk of FN) [12, 13]. Vogel et al. demonstrated that by adding pegfilgrastim prophylactically to women with breast cancer treated with docetaxel (at 100 mg/m^2), the rate of FN decreased considerably from 17 to 1% with subsequent decrease in the need for hospitalization and the need for antibiotics treatment [11]. Due to the unexpected high rate of FN in a real-world patient population demonstrated in our study, G-CSF should be considered for all patients with mCSPC starting docetaxel.

The timing of docetaxel initiation for patients with mCSPC is a relevant question oncologist are dealing with on daily basis. Although our study is limited by the relative small sample size and its retrospective analysis, we believe that the results are robust and can help clinicians to decide on the optimal timing of docetaxel initiation.

Conclusions

As no association was found between the timing of docetaxel initiation in relation to ADT and docetaxel-related severe toxicity in mCSPC patients, there is no role for routinely delaying chemotherapy unless clinical factors warrant a delay in starting chemotherapy. mCSPC patients treated with docetaxel have a high rate of significant toxicities, and therefore, treatment should be considered only for fit patients and close monitoring is advised. The rate of FN (27.7%) in a real-world patient population is much higher than expected, and prophylactic G-CSF should be considered for patients

Table 3 Toxicity consequences relative to initiation of chemotherapy by cohort groupings

	Days from ADH to docetaxel		*P*-value
	≤ 60 days *N* = 36	> 60 days *N* = 47	
Febrile neutropenia, *N* (%)	9 (25)	14 (29)	0.6291
Toxicity-related chemotherapy treatment delay, *N* (%)	5 (13.89)	3 (6.38)	0.2845
Toxicity induced chemotherapy dose reduction, *N* (%)	12 (33.33)	18 (38.30)	0.6408
Toxicity induced treatment discontinuation, *N* (%)	7 (19.44)	11 (23.40)	0.6644

ADH androgen deprivation therapy, *TTC* time to chemotherapy

with mCSPC receiving docetaxel, especially if other comorbidities are present.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest CC declared: Honorarium—Janssen; Advisory boards—Roche, Ipsen, Pfizer, Eisai, Merk, EMD Serono, Bayer, BMS, AstraZeneca, Janssen; Travel support—Sanofi, Amgen, Pfizer; Research funding – Eisai. DB declared: Advisory/honorarium—BMS, Pfizer, AbbVie, and AstraZenaca. NMR declared: Honoraria—Astellas, Novartis, Janssen, Roche, Pfizer, AstraZeneca. IK, KK, MO, ES declare no conflict of interest associated with this publication.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informal consent For this retrospective study formal consent was not required by the Ottawa Health Science Network Research Ethics Board.

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