ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 999–1005

UROLOGIC ONCOLOGY

Clinical-Prostate cancer

Comparative assessment of docetaxel for safety and efficacy between hormone-sensitive and castration-resistant metastatic prostate cancer

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Received 14 April 2019; received in revised form 4 June 2019; accepted 8 July 2019

Abstract

Objective: To compare toxicity and response of docetaxel chemotherapy between metastatic hormone-sensitive prostate cancer (mHSPC) and castration-resistant metastatic prostate cancer (mCRPC) patients of the same therapeutic era for assessing of upfront docetaxel against the benchmark of docetaxel in the castrate resistant stage in the setting outside of clinical trials.

Methods: A prospectively collected database of real-world prostate cancer patients receiving docetaxel was divided in mHSPC and mCRPC cases and retrospectively analyzed. Principal objectives were toxicity measured by the common criteria of adverse events terminology and response characterized by Prostate specific antigen decline and radiographic progression-free disease at restaging. The prognostic value of suspected variables for grade 3 to 5 toxicity and response was investigated by logistic regression analysis.

Results: Of 72 patients 34 (47%) were treated for mHSPC and 38 (53%) for mCRPC. Patients with mCRPC were older and had worse performance status ($P< 0.01$). In mHSPC total number of grade 3 to 5 adverse events (24, median 0, interquartile range 0−1) was significantly less than in mCRPC (46, median 1, interquartile range 1−2) ($P = 0.01$). Multivariable analysis revealed age as independent predictive variable for grade 3 to 5 toxicity ($P = 0.03$) but not disease stage, Prostate specific antigen predocetaxel, volume of disease, and Eastern Cooperative Oncology Group performance status ($P > 0.05$). Objective response was significantly higher in mHSPC compared to mCRPC patients ($P < 0.01$). Multivariable analysis confirmed mHSPC stage as independent prognostic factor for radiographic progression free disease at restaging ($P < 0.01$).

Conclusions: The association of age with toxicity and of mHSPC stage with response resulted in significantly fewer grade 3 to 5 adverse events but higher response rates for upfront docetaxel in mHSPC compared with docetaxel in the later mCRPC stage.

Keywords: Metastatic; Prostate cancer; Hormone-sensitive; Castration-resistant; Docetaxel; Chemohormonal therapy

1. Introduction

Recently, chemohormonal therapy conferred prolonged survival in CHAARTED and STAMPEDE (arm C) trials in metastasized hormone-sensitive prostate cancer (mHSPC) [1,2]. This was reinforced by several meta-analyses including also GETUG-AFU 15 trial, which previously had failed to demonstrate survival benefit itself [3−5]. Treatment-associated grade 3 to 5 toxicity among mHSPC study population was reported in 30% to 52% of patients. In particular, the rate of febrile neutropenia grade 3 to 5 was as high as 6% to 15%. However, real-world data of safety and efficacy of docetaxel in mHSPC patients are still sparse. So far, reported rates of grade 3 to 5 adverse events ranged between 34% and 40% [6,7]. Thus, concerns regarding toxicity might be a hurdle in widely implementing upfront cytotoxic treatment,

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

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https://doi.org/10.1016/j.urolonc.2019.07.005
1078-1439/

since docetaxel was associated with a lower toxicity rate in the mCRPC setting in the TAX 327 trial (26%) [8].

Later, LATITUDE and STAMPEDE (arm G) randomized controlled trials investigated abiraterone in mHSPC patients and demonstrated significantly improved median overall (53.3 vs. 36.5 months) as well as 3-year survival (83% vs. 76%), which was similar to the survival benefit that previously had been reported for docetaxel (57.6 vs. 44 months, 81 vs. 71 months) in CHAARTED and STAMPEDE trials [1,2,9−11]. A similar burden of grade 3 to 5 events (47%−63%) was reported [10,11]. Most recently, ARCHES trial yielded advantage for enzalutamide by reducing the risk of radiographic progression or death by 61% vs. androgen deprivation therapy (ADT) alone, while ≥ grade 3 adverse events were encountered in 24% [12]. Taking into account ongoing trials with apalutamide (NCT02489318) and darolutamide (NCT02799602), further expansion of the therapeutic armamentarium in mHSPC is warranted.

Only one direct comparison for efficacy and safety between docetaxel and abiraterone in mHSPC patients between STAMPEDE arms has been conducted, which demonstrated no difference in outcomes [13]. Several network meta analyses sought to increase the evidence for the decision whether to start with docetaxel or with abiraterone in mHSPC, but no definitive conclusion favoring one over the other could be drawn [5,13−15].

As a result, real-life data might contribute to the understanding of a better patient stratification outside clinical trials. In this setting, a gap of routine data exists for evaluation of docetaxel-associated toxicity in patients with mHSPC in comparison to mCRPC. Therefore, the objective of this study was to compare toxicity as well as clinical response of docetaxel utilized in mHSPC vs. mCRPC disease during the same therapeutic era.

2. Material and methods

A retrospective analysis of a prospectively collected database of the university cancer center Mainz of prostate cancer patients receiving docetaxel was performed. Data acquisition and analysis adhered to local ethical standards ((REC/IRB 83755015 (10318)). Groups of treatment for mHSPC and mCRPC were formed as follows: To represent the same therapeutic era, characterized by an equal availability of approved cancer therapies to both groups, inclusion of mCRPC patients required start of treatment not before 2013. All patients who had consecutively received docetaxel from 2013 to 2018 for metastasized prostate cancer at our institution were included and assigned to the mHSPC or mCRPC group. Metastasized CPRC was defined by histologically documented metastatic prostatic adenocarcinoma with radiographically measurable disease progression or biochemical progression despite castrate serum testosterone levels (<50 ng/dl). In mCRPC, the indication for docetaxel was symptomatic disease, bone scan progression or visceral metastases following the principle of sequential monotherapies. In patients presenting with mHSPC, docetaxel treatment was indicated according to the CHAARTED trial's inclusion criteria.

Docetaxel standard dose was 75 mg/m^2 body surface area every 3 weeks for 6 cycles. Clinical visits were on day 1 and day 8 of each cycle. Daily 5 mg prednisone orally was given. On days 0, 1, and 2, dexamethasone 8 mg was added. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (Version 4.0) of the National Cancer Institute. All adverse events of each administered cycle of docetaxel were recorded. Definition of the volume of disease adhered to the E3805 (CHAARTED) trial [2].

In case of neutropenia ≥ grade 2 during the first or subsequent cycle, Granulocyte-colony stimulation factor (G-CSF) was routinely prescribed for the following cycles as secondary prophylaxis.

To depict clinical response, Prostate specific antigen (PSA) response, defined by PSA decline ≥50% [6,16] and ≥30% [17,18] and radiographic evidence of progression-free disease at restaging [19], were used. Restaging was performed within 8 weeks after last application of docetaxel and comprised standard imaging with computed tomography and bone scan.

Variables were tested for normal distribution using Lilliefors test. As a result, descriptive analysis required median and interquartile range (IQR) and continuous variables were tested using Wilcoxon-Mann-Whitney-U test. Categorical variables were analyzed using Chi-Square test. The prognostic value of suspected variables for response and Common Terminology Criteria for Adverse Events grade 3 to 5 toxicity was investigated by logistic regression analysis. Selected variables were mHSPC vs. mCRPC, age, PSA pre-docetaxel, high volume of disease vs. low volume of disease, and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. ≥1). Level of significance was set to $P < 0.05$. Bias software (Bias. 10.12, epsilon, Frankfurt, Germany) was used for statistical analyses [20].

3. Results

Of 72 patients receiving docetaxel from 2013 to 2018, 34 (47%) were treated for mHSPC and 38 (53%) for mCRPC. Patients' baseline characteristics are presented in Table 1. Compared to mHSPC patients, mCRPC patients were older, had worse performance status, lower hemoglobin value, and were locally pretreated more often ($P < 0.01$). Median time from initiation of ADT to docetaxel in mHSPC patients was 23 (IQR 1−58) days. In the group of mCRPC, patients' median time from antihormonal treatment to first dose of docetaxel was 41 (IQR 20−72) months. Docetaxel was administered as first-line treatment for mCRPC in 13 (34%), as second-line in 20 (53%), and as third-line in 5 (13%) patients after therapy with abiraterone (n= 20, 53%), enzalutamide (n = 8, 21%), or ketoconazole (n = 1, 3%).

Table 1
Patients' baseline characteristics at initiation of docetaxel

	mHSPC $n = 34$ (47%)	mCRPC $n = 38$ (53%)	P value
Age (Median, IQR)	66 (58–72)	74 (68–78)	<0.01
ECOG performance status = 0	24	10	<0.01
ECOG performance status ≥ 1	10	28	
PSA predocetaxel (Median, IQR)	32.5 (9–50)	42.5 (14–146)	0.07
Epstein/ISUP grade (Median, IQR)	5 (3.5–5)	4 (4–5)	0.5
Hb predocetaxel (Mean ± SD)	14.4 ± 1.2	12.4 ± 1.4	<0.01[a]
High volume disease	13 (38%)	35 (92%)	<0.01
Bone metastases	27 (79%)	33 (87%)	0.6
Visceral metastases	5 (14%)	11 (29%)	0.1
Prior treatment for prostate cancer			
No local treatment	29 (85%)	16 (42%)	<0.01
Primary radiation	1 (3%)	2 (5%)	0.6
Prostatectomy	4 (12%)	20 (53%)	<0.01
Comorbidities			
CCI (Median, IQR)	6 (6–7)	6 (6–7)	0.5
Cardiovascular	2	8	0.1
Cerebrovascular	2	1	0.6
Peripheral vascular/aneurysm	4	4	1.0
Thromboembolic events	3	4	1.0
Arterial hypertension	20	23	1.0
Diabetes	6	7	1.0
COPD	0	1	0.5
History of sepsis/immunodeficiency	1	4	0.4

Data presented as absolute values or median described by interquartile range (IQR).
[a] T test used and data presented as mean value described by standard deviation (SD) since data were of normal distribution. CCI = Charlson comorbidity index.

Treatment administration, toxicity, and response are summarized in Table 2. Two (6%) mHSPC and 8 (21%) mCRPC patients discontinued treatments resulting in 99% and 87% completion of planned cycles ($P < 0.01$). The total numbers of adverse events over all administered cycles were 188 in mHSPC and 256 in mCRPC patients. In mHSPC, 44% of patients had at least one grade 3 to 5 adverse event. At the same time, 76% of mCRPC patients suffered from at least one grade 3 to 5 event. The median cumulative number of grade 3 to 5 adverse events over all administered cycles added up to 24 in mHSPC and 46 in mCRPC ($P = 0.01$). A detailed breakdown of frequent adverse events, which occurred at least in 1% of administered cycles, is presented in Table 3. Except for gastrointestinal disorders ($P < 0.01$), there were no significant differences of adverse events between mHSPC and mCRPC. G-CSF therapy for acute management or secondary prophylaxis of high grade neutropenia was conducted in

Table 2
Administration, toxicity and clinical response

	mHSPC $n = 34$ (47%)	mCRPC $n = 38$ (53%)	P value
Administration			
Dose reduction[a]	5 (15%)	12 (32%)	0.2
Discontinuation	2 (6%)	8 (21%)	0.1
Administered cycles/planned cycles	201/204	199/228	<0.01
Toxicity			
Any AE: Total number, Median (IQR)	188, 5 (4–7)	256, 6 (3–9)	0.3
Grade 3–5 AE: Total number, Median (IQR)	24, 0 (0–1)	46, 1 (1–2)	0.01
Grade 3–5 AE: Number of patients	15 (44%)	29 (76%)	<0.01
Clinical response			
PSA (≥50%) response	28 (82%)	17 (44%)	<0.01
PSA (≥30%) response	30 (88%)	22 (58%)	<0.01
Radiographic progression free disease at restaging	32 (94%)	15 (39%)	<0.01

[a] Dose reduction to 60 mg/m^2 body surface area every 3 weeks or to 35 mg/m^2 weekly with a one week rest every 4 weeks was at the discretion of the treating urologist.

Table 3
Breakdown of adverse events (AE) of more than 1% occurrence at least in one AE subgroup over delivered cycles.

	mHSPC		mCRPC	
Cycles	201		199	
Adverse event	Grade 1–2	Grade 3–5	Grade 1–2	Grade 3–5
Neutropenia	34 (17%)	11 (5.5%)	42 (21%)	18 (9%)
Febrile Neutropenia	n/a	1 (0.5%)	n/a	3 (1.5%)
Diarrhea	13 (6.5%)	0	26 (13%)	5 (2.5%)
All gastrointestinal disorders[a]	21 (10.5%)	1 (0.5%)	40 (20%)	6 (3%)
Fatigue	32 (16%)	1 (0.5%)	35 (17.5%)	2 (1%)
Peripheral neuropathy	9 (4.5%)	0	7 (3.5%)	0
Dygeusia	10 (5%)	0	8 (4%)	0
All nervous system disorders	56 (28%)	0	53 (27%)	0
Diabetes mellitus (development/aggravation)	2 (1%)	0	1 (0.5%)	2 (1%)
Renal & urinary disorders including UTI	17 (8.5%)	0	7 (3.5%)	3 (1.5%)
Respiratory disorders including infections	3 (1.5%)	4 (2%)	7 (3.5%)	3 (1.5%)
Skin & subcutaneous tissue disorders	10 (5%)	0	11 (5.5%)	1 (0.5%)
Cardiac disorders	1 (0.5%)	2 (1%)	4 (2%)	1 (0.5%)
Musculoskeletal disorders	9 (4.5%)	0	14 (7%)	0
Vascular disorders	4 (2%)	0	3 (1.5%)	2 (1%)
Eye disorders	5 (2.5%)	0	2 (1%)	0

[a] Except for gastrointestinal disorders ($P < 0.01$), there were no significant differences of adverse events between mHSPC and mCRPC ($P > 0.05$).

31% and 26% over all administered cycles in mHSPC and mCRPC patients (nonsignificant). In univariable logistic regression analysis mCRPC disease, older age, high volume disease, a higher ECOG performance status and a lower hemoglobin level were significant predictive variables for grade 3 to 5 toxicity. In the multivariable analysis, only age has been shown to independently predict for this outcome. To further investigate age dependency of toxicity a ROC analysis was conducted revealing a cut-off value of 67.5 years (Area under the curve = 0.73, 95% confidence intervals [0.613876; 0.852033], SD(Area under the curve) = 0.06; False negative + false positive/total population = 28.6%; Fig. 1).

PSA (≥50%) and PSA (≥30%) responses to docetaxel were significantly predicted by mHSPC status, younger age, better ECOG performance status, and higher hemoglobin values in univariable analysis, whereas in multivariable analysis none was of independent predictive value. Radiographic progression-free disease at restaging as a feature of clinical response was significantly predicted by mHSPC status and high volume disease in univariable analysis, whereas in multivariable analysis only mHSPC status was of independent predictive value (Table 4).

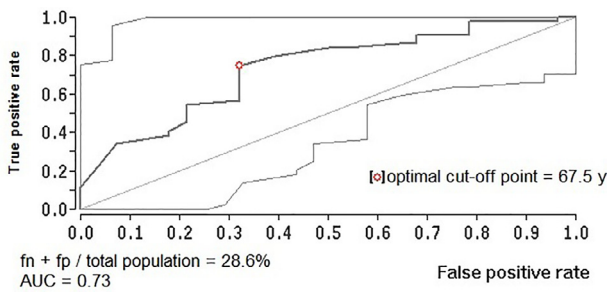

Fig. 1. ROC analysis of age as predictor of grade 3 to 5 toxicity of docetaxel. Thin gray lines represent the simultaneous 95%-confidence bounds according to Campbell.

4. Discussion

In prostate cancer, therapeutic landscape has been revolutionized since impressive phase 3 data of CHAARTED, STAMPEDE and LATITUDE trials demonstrated that upfront addition of docetaxel or abiraterone to antihormonal treatment in newly diagnosed metastatic disease significantly improves survival [1,2,10,11]. On the basis of these phase 3 trials, several further follow-up data and network meta-analyses sought to define whether abiraterone should be preferred instead of docetaxel or vice versa and if patients could be identified which benefit most from either approach. However, except for the current common sense that upfront systemic therapy should be restricted to patients with high-volume or high-risk disease [3,21], no definitive recommendation for or against docetaxel or abiraterone can be made for individual patients [5,13–15,22,23].

In this context, our prospectively collected observational cohort study provides additional insight in chemohormonal therapy of mHSPC and mCRPC patients of the same therapeutic era. Since we provide a complete report of all adverse events over all administered cycles, we comprehensively depict real-world clinical data.

Thus, patients receiving docetaxel in the mHSPC setting were significantly younger than their counterparts in the later mCRPC stage. Median age of our mHSPC cohort (66 years) was similar to STAMPEDE or CHAARTED participants (65 and 64 years) and comparable to a real-world

Table 4
Logistic regression analysis of predictive variables for grade 3–5 toxicity and for clinical response

Variable	OR (95%-CI)	*P* value
Grade 3–5 toxicity		
Univariable analysis		
mHSPC	0.24 (0.09–0.68)	<0.01
Age	1.10 (1.03–1.16)	<0.01
PSA predocetaxel	1.00 (0.99–1.01)	0.2
High volume disease	4.49 (1.56–12.92)	<0.01
ECOG performance status	3.15 (1.16–8.57)	0.03
CCI	2.37 (0.99–5.65)	0.05
Hb	0.67 (0.48–0.95)	0.02
Visceral metastases	1.53 (0.46–5.09)	0.5
Multivariable analysis		
mHSPC	1.09 (0.22–5.33)	0.9
Age	1.09 (1.01–1.17)	0.03
PSA predocetaxel	1.00 (0.99–1.00)	0.7
High volume disease	3.13 (0.74–13.12)	0.1
ECOG performance status	2.09 (0.59–7.41)	0.3
CCI	2.52 (0.88–7.19)	0.1
Hb	1.17 (0.69–1.99)	0.6
Visceral metastases	0.75 (0.16–3.40)	0.7
Clinical response – PSA (≥50%) response		
Univariable analysis		
mHSPC	5.76 (1.91–17.40)	<0.01
Age	0.92 (0.86–0.98)	<0.01
PSA predocetaxel	0.99 (0.99–1.00)	0.2
High volume disease	0.43 (0.14–1.29)	0.1
ECOG performance status	0.17 (0.06–0.52)	<0.01
CCI	0.87 (0.45–1.68)	0.7
Hb	1.57 (1.12–2.20)	<0.01
Visceral metastases	0.51 (0.16–1.61)	0.3
Multivariable analysis		
mHSPC	2.37 (0.46–12.12)	0.3
Age	0.93 (0.87–1.00)	0.1
PSA predocetaxel	0.99 (0.99–1.00)	0.5
High volume disease	1.22 (0.24–6.19)	0.8
ECOG performance status	0.29 (0.08–1.01)	0.05
CCI	1.12 (0.49–2.58)	0.8
Hb	1.02 (0.62–1.68)	0.9
Visceral metastases	0.71 (0.17–2.85)	0.6
Clinical response – PSA (≥30%) response		
Univariable analysis		
mHSPC	5.45 (1.57–18.89)	<0.01
Age	0.92 (0.86–0.99)	0.03
PSA predocetaxel	1.00 (0.99–1.00)	0.9
High volume disease	0.40 (0.11–1.39)	0.1
ECOG performance status	0.18 (0.05–0.64)	<0.01
CCI	0.73 (0.37–1.45)	0.4
Hb	1.56 (1.10–2.20)	0.01
Visceral metastases	0.27 (0.08–0.89)	0.03
Multivariable analysis		
mHSPC	1.78 (0.31–10.18)	0.5
Age	0.93 (0.86–1.01)	0.1
PSA predocetaxel	0.99 (0.99–1.00)	0.5
High volume disease	0.85 (0.15–4.74)	0.8
ECOG performance status	0.27 (0.07–1.09)	0.1
CCI	0.97 (0.40–2.40)	0.9
Hb	1.19 (0.70–2.02)	0.5
Visceral metastases	0.37 (0.09–1.62)	0.2
Clinical response – radiographic progression free disease at restaging		
Univariable analysis		
mHSPC	40.53 (4.77–342.55)	<0.01
Age	0.99 (0.93–1.04)	0.6
PSA predocetaxel	1.00 (0.99–1.00)	0.8
High volume disease	0.06 (0.01–0.50)	<0.01
ECOG performance status	0.47 (0.16–1.42)	0.2
CCI	1.34 (0.59–3.04)	0.5
Hb	1.32 (0.95–1.83)	0.1
Visceral metastases	0.33 (0.09–1.12)	0.1
Multivariable analysis		
mHSPC	57.14 (3.75–871.89)	<0.01
Age	1.07 (0.99–1.19)	0.1
PSA predocetaxel	1.00 (0.99–1.00)	0.5
High volume disease	0.22 (0.02–2.60)	0.2
ECOG performance status	1.74 (0.33–9.12)	0.5
CCI	2.99 (0.83–10.78)	0.1
Hb	0.72 (0.39–1.35)	0.3
Visceral metastases	0.09 (0.01–1.02)	0.05

CCI = Charlson comorbidity index, Hb = hemoglobin value.

cohort of mHSPC patients receiving docetaxel (67 years) recently published by Lavoie et al., who considered their mHSPC patients to be older than those included in the aforementioned trials [6]. Median age of the mCRPC cohort (74 years) was older than that of the participants in the TAX 327 (Suppl. Table) and SWOG 99-16 docetaxel phase 3 trials (67 and 70 years) [8,24] indicating the anticipated bias toward more fit patients in clinical trials [6,25].

In our data, mCRPC patients suffered significantly more often from grade 3 to 5 adverse events compared to mHSPC patients. Since the STAMPEDE study authors discussed possibly higher toxicity for docetaxel use in mHSPC patients compared to previously reported mCRPC study participants, this concern has been taken up by the LATITUDE trial authors to support the strategy of abiraterone treatment in mHSPC patients [1,10]. However, our real-life data are not in line with this concern. In our series of mHSPC patients, 56% had at least one grade 3 to 5 adverse event which is in the range of grade 3 to 5 adverse events reported in the STAMPEDE standard of care (SOC) plus docetaxel and the STAMPEDE SOC plus docetaxel plus zoledronic acid arms (51% and 53%). In contrast 76% of our mCRPC patients suffered from at least one grade 3 to 5 event, which was 3-fold higher than 26% in the TAX 327 trial [8]. Rates of febrile neutropenia were only 0.5% in mHSPC and 1.5% in mCRPC patients of our real-world cohort, which is in contrast to 6% to 15% in the CHAARTED and STAMPEDE data for mHSPC and almost in the range of 3% for mCRPC in the TAX 327 trial [2,8,11]. This result was unanticipated, since evidence for an increased hepatic clearance of docetaxel in castrated compared to noncastrated prostate cancer patients has been found in a recently published pharmacokinetic study [26]. The liberal indication for G-CSF in our treatment algorithm might be an explanation for this result, since no mandatory requirements on the use of G-CSF were given by protocol and no numbers of G-CSF usage were later reported in STAMPEDE or CHAARTED trials.

Interestingly, multivariable analysis revealed that this significant difference of grade 3 to 5 toxicity between mHSPC and mCPRC could not be attributed to tumor associated (PSA, volume of disease) and comorbidity associated (ECOG performance status) factors but only to age. This finding is in line with data from a project data sphere analysis of the control arms of 6 randomized controlled trials including 2,449 mCRPC patients receiving docetaxel, where only age was independently associated with the occurrence of ≥ grade 3 adverse events in a multivariable model including age, BSA (body surface area), albumin, creatinine, Lactate dehydrogenase, Alkaline phosphatase, lymphocytes, pain or fracture, and urea [27]. Furthermore, the strong association between age and toxicity might be the reason for the high percentage of grade 3 to 5 adverse events of our relatively old mCRPC group compared to the younger cohorts of the docetaxel phase 3 trials [8,24].

Grade 5 adverse events represent the most unfavorable condition considering the relatively long time of survival of a typically low symptomatic mHSPC patient starting with antihormonal treatment only. In our cohort one grade 5 adverse event (3%) occurred when a patient died from pneumonitis. This was in the range of grade 5 adverse events (2%) in other real-world data reported by Rulach et al. [7].

Lacking robust evidence on comparison between docetaxel and abiraterone in mHSPC disease, decision on which agent to start treatment with should be made on individual base implicating shared decision making and addressing clinical aspects like age, comorbidities as well as patient‘s preferences. The latter might weigh between undergoing 6 cycles of chemotherapy and then being followed up or receiving abiraterone treatment on daily base, which is not free of adverse events as well and was accompanied by 1% to 5% treatment related deaths and 47% to 63% of grade 3 to 5 events in the both aforementioned milestone trials [10,11]. Furthermore, efforts to compare docetaxel with abiraterone in mHSPC patients by several network meta-analyses and by analyzing data of the STAMPEDE SOC plus abiraterone arm revealed either no significant difference [13,22] or, at best, slight advantages in terms of failure-free survival in some patients receiving abiraterone [5,14]. In contrast to docetaxel, the association of age and toxicity has never been demonstrated for abiraterone [28]. Thus, further research is warranted to more extensively elucidate which patient in clinical routine would benefit most from which systemic approach.

Clinical response to docetaxel treatment differed significantly between the 2 groups favoring mHSPC patients simultaneously commencing on ADT over their mCRPC counterparts. Apparently, combining ADT with cytotoxic treatment in mHSPC disease concurrently targeting prevailing hormone-sensitive as well as -insensitive tumor cell clones results in a higher clinical efficacy than attacking prevailing hormone-insensitive clones by chemotherapy in mCRPC stage. PSA response was observed in 82% of mHSPC patients which was in line with previously published real-world data of mHSPC demonstrating 85% [6]. In contrast, in mCRPC disease, in line with the TAX 327 trial, response in terms of PSA decline ≥50% was limited to 44% [8].

The present study is limited by its retrospective and thus non-randomized nature. Thus, mHSPC patients starting upfront docetaxel in early 2016 at our institution were compared to patients, who had been diagnosed with metastasized prostate cancer before CHAARTED or STAMPEDE data were available and who subsequently got castration resistant and received docetaxel. However, by only including mCRPC patients having started docetaxel treatment not before 2013, the 2 cohorts run in the same therapeutic era with regard to both approved cancer therapies and concepts of supportive oncologic care. Therefore, we feel that our cohort is representative for contemporary patients with prostate cancer being confronted with the question whether to start with docetaxel treatment at first diagnosis of metastatic disease or to postpone cytotoxic therapy until castration resistant state is reached.

5. Conclusions

The present work evaluated toxicity and response of upfront docetaxel in mHSPC patients against the long-established benchmark of docetaxel in mCRPC patients analyzing robust real-life data of a contemporary population of metastasized prostate cancer patients of our tertiary referral center. Early docetaxel treatment in the mHSPC stage demonstrated significantly fewer grade 3 to 5 adverse events but significantly improved clinical response compared to later docetaxel in mCRPC stage. Age was the only variable of independent predictive value for toxicity whereas clinical response was associated with mHSPC status. Our findings suggest the importance of critical weighting patient's age when considering upfront docetaxel therapy and might imply to integrate docetaxel at the beginning of sequential therapy in metastasized prostate cancer.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.07.005.

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