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Efficacy and safety of docetaxel as first line therapy in high-risk hormone sensitive metastatic prostate cancer patients

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Abstract

Purpose: To report the survival benefit, the course of disease and side effects in high-risk patients with metastatic hormone-sensitive prostate cancer (mHSPC) treated with first-line docetaxel.

Methods: Retrospective observational study in which we analyzed patients with mHSPC treated with first-line docetaxel at National Center for Tumor disease (NCT) Heidelberg between 2014 and 2019. Data were retrieved from the NCT electronical patient charts. We analyzed the Progression-Free Survival (PFS) and overall survival (OS). We also evaluated the safety of the therapy using Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). Furthermore, we evaluated the therapy sequence in metastatic castration resistant prostate cancer (mCRPC). The median follow-up was 24.3 months.

Results: From 54 patients who underwent first-line docetaxel therapy for mHSPC, 20 progressed to mCRPC. The median PFS was 11.8 months and the median OS was 47.5 months. The study consisted of unfavourable group of patients with a high tumor burden, high Gleason score and high prostate specific antigen (PSA) at the time of diagnosis. The prognosis was particularly poor for patients who developed mCRPC within 12 months.

Conclusion: Results from this study suggest that first line docetaxel therapy is safe and well tolerated treatment choice for mHSPC patients. Even the high-risk patients can profit from this therapy regime compared to androgen deprivation monotherapy. The optimal sequencing for first- and further line therapies for mCRPC is still unknown.

Introduction

Androgen Deprivation Therapy (ADT) for prostate cancer has been the standard of care for over 70 years now and represents one of the most effective systemic treatments known for solid tumors and although palliative, it can normalize serum levels of Prostate-Specific Antigen (PSA) in over 90% of patients and can produce objective tumor responses in 80-90% of cases [1,4]. The role of androgens in prostate cancer growth was described in 1941. By Charles Huggins whose results led to the development of ADT for patients with advanced prostate cancer [2]. Patients that suffer from prostate cancer have had just a few treatment options for a very long period of time [3]. A well-established regime with six cycles of docetaxel + ADT results in significantly longer OS than that with ADT alone as a first line therapy in mHSPC [5]. During the last decade a number of new drugs have

been tested and consequently approved and are currently being implemented into oncological routine [6-10]. This extends the treatment options considerably. We analyzed all applicable patients treated at NCT Heidelberg for PFS and OS under first-line docetaxel treatment for mHSPC. We further analyzed the safety of the first line docetaxel therapy and sequence of further line therapies in mCRPC. The study was approved by local ethics committee (S-690/2015).

Materials and methods

In this retrospective observation study we identified patients treated with first line docetaxel therapy for mHSPC and their records were assessed through their electronic charts saved in Heidelberg Tumor Database [11]. All of the patients received docetaxel first line therapy within 120 days of initiating ADT. There were several parameters that were assessed, including initial PSA value, Gleason score, metastatic spread, tumor stage, time to castration resistance, PSA at the time of castration and finally the further therapy lines in mCRPC. Progression free survival (PFS) was evaluated using the Prostate Cancer Working Group 2 criteria [12]. Overall survival (OS) was calculated from the date of the first docetaxel cycle application to the date of death or the date of last follow-up. Side effects were classified according to CTCAE dictionary version 5.0. Survival and progression were calculated using Kaplan–Meier estimates and compared using log-rank tests. Statistical analyses were conducted using the SPS Sv 23 software.

Results

The final study population consisted of 54 patients that were treated with first line docetaxel therapy between 2014 and 2019. Median PSA value at initial diagnosis was relatively high at 85.8 ng/ml and 87% of patients had a Gleason Score ≥8. Furthermore, 89% of patients had bone metastasis, 55% of whom had ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis. Additionally, 8 patients had distal metastasis. The main patient characteristics are shown in Table 1. The most frequent imaging tool used for staging was CT combined with skeletal scintigraphy (54%) followed by PSMA-PET-CT (26%), MRI (13%) and skeletal scintigraphy alone (7%). The vast majority of patients (93%) had LHRH agonist as a form of prior-to-chemo androgen deprivation therapy. Other forms of ADT included subcapsular orchidectomy and a complete androgen blockade. Docetaxel was administered at a dose of 75 mg/m^2 every 3 weeks. The first line treatment was generally well tolerated with an average of 5,7 docetaxel cycles administered. Majority of patients (74%) were asymptomatic or with mild symptoms (CTCAE Grade 1), with neither intervention nor hospitalization needed. The therapy was discontinued after 4th cycle due to GI bleeding for three patients. Two patients developed a strong allergic reaction with flushes associated with hypotension and tachycardia which resulted in therapy discontinuation after 2nd cycle. Nonetheless, the median PSA nadir was relatively low at 0,87 ng/ml. Median PSA value at mCRPC was 30.9 ng/ml and 20 patients developed castration resistance. Figure 1 shows the median PFS, which was 11.8 months. The first line treatment options for mCRPC patients included: abiraterone, enzalutamide, cabazitaxel, cisplatin/etoposid and nivolumab/docetaxel. Further therapies in mCRPC included cabacitaxel after abiraterone, enzalutamid after abiraterone and docetaxel after enzaludamide. The administration of abiraterone as first-line therapy for mCRPC followed by cabazitaxel has provided the best survival rates in this study and 60% of mCRPC patients had a stable disease after this treatment sequence. The median OS was 47.5 months, as represented by Figure 2. Furthermore, the patients were stratified into two groups, patients who developed mCRPC in less than 12 months and those who developed mCRPC in more than 12 months. For these two groups, the median OS (7.9 vs 47.3 months) was statistically significant ($p<0.001$, CI 95%) and is shown on Figure 3.

Table 1: Patient characteristics.

Parameter	N	% (Range)
Number of patients	54	100
deceased	14	25,93
alive	40	74,07
Age, median	65,55	(39-81)
Gleason Score		
≤7	7	12,96
≥8	47	87,04
Clinical nodal status at the time of first diagnosis		
N0	19	35,19
N1	35	64,81
Metastatic spread at first diagnosis		
regional (pelvic) lymph nodes	22	40,74
non-regional lymph nodes	8	14,81
bones	48	88,89
other sites	8	14,81
liver	2	3,70
adrenal gland	1	1,85
lungs	5	9,25
Androgen deprivation therapy		
subcapsular orchidectomy	2	3,70
complete androgen blockade	2	3,70
LHRH agonists	50	92,60
Median PSA value at initial diagnosis	85.81	(3.7-2726)
Median PSA nadir	0.87	(0.01-82.0)
Median PSA value at the point of castration resistance	30.91	(0.07-1500)
Bone protective therapy		
zelodronic acid	2	3,70
denosumab	17	31,48
none	35	64,82

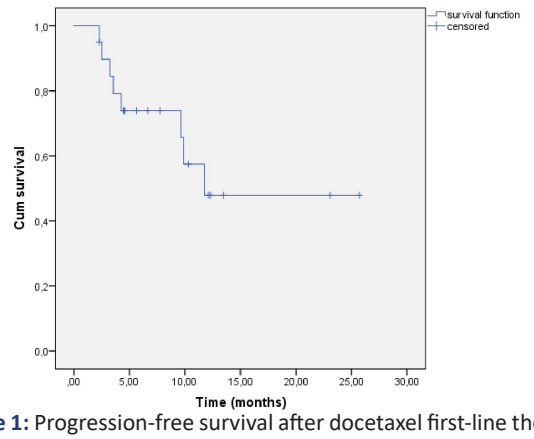

Figure 1: Progression-free survival after docetaxel first-line therapy for mHSPC (95% Confidence interval).

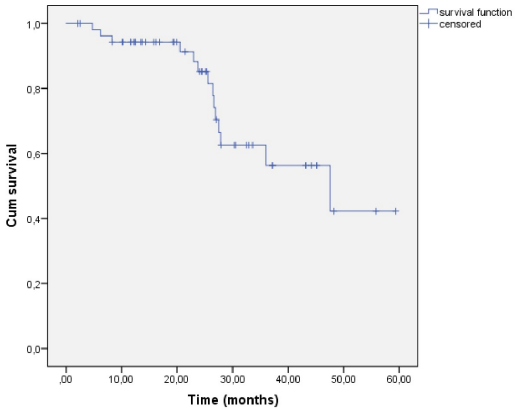

Figure 2: Overall survival after docetaxel first line therapy for mHSPC (95% Confidence interval).

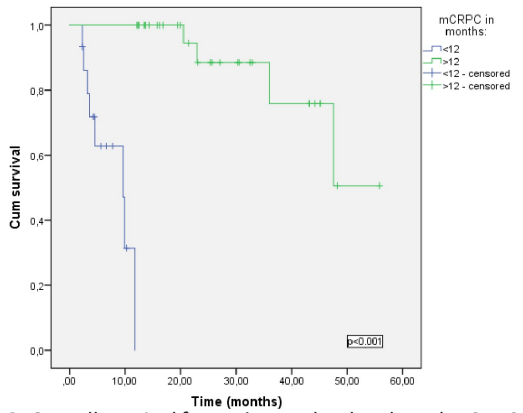

Figure 3: Overall survival for patients who developed mCRPC within and in more than 12 months (p<0.001, 95% Confidence interval).

Discussion

Although initial research on adding docetaxel to ADT for mHSPC could not show advantages of this therapy option [13], a clinical benefit was indeed observed with longer follow up [5,14]. This study showed that docetaxel is a safe first line therapy option for mHSPC and the results obtained demonstrate a better cancer control than that with ADT alone, as reported in the literature [5]. During the last decade, especially in the last couple of years, a number of new drugs have been tested, consequently approved and are currently being implemented into oncological routine [6-10]. This extends the treatment options considerably. A taxan chemotherapy (cabaxitaxel) and New Antihormonal Agents (NAA) have all been approved and shown to be active after failure of docetaxel as a first line therapy [15-17]. Cabazitaxel is also used relatively often as a 3rd or 4th line therapy after previously Abiraterone or Enazalutamide therapy, being efficient in those settings [18-21]. Contradicting results have been reported for the optimal sequence of substances for 2nd and further lines in mCRPC. Some retrospective single- and multicentric studies as well as meta-analyses showed no significant differences between the different agents used in 3rd or 4th line [22]. On the other hand, some other retrospective single- and multicentric studies as well as meta-analyses suggested a survival benefit when administrating the sequence Docetaxel-Cabacitaxel-Abiraterone or the sequence Cabazitaxel-NAA (or vice versa) compared to NAA-NAA after Docetaxel [23-25]. Based on the data from CHAARTED and STAMPEDE trials, it can be anticipated that an increasing number of patients will have received Docetaxel as a first line therapy to ADT in the hormone-sensitive setting. Consequently, new questions of optimal therapeutic sequencing once castration resistance developed will be raised. There have been a number of previously published studies that reported a correlation between longer duration of remission on first line docetaxel for Gleason Sore ≥8 [26-29]. Considering the fact that the vast majority of our patients were high-risk patients with 87% of them having Gleason Score ≥8, the median OS of 47.5 months represents a very good result, particularly compared to ADT monotherapy [5]. Nevertheless, our study also shows that one year as cut-off value for developing mCRPC after docetaxel appears to be predictive of OS. Interestingly, the cut-off value of 12 months has also been reported in mCRPC therapy sequencing. The results from a prospective randomized phase III study show that patients who had received docetaxel as first line therapy for mHSPC and the following therapy for mCRPC with either abiraterone or enzalutamide lasted less than 12 months have a benefit from further cabazitaxel therapy independently whether abiraterone or enzalutamide were administrated [30]. Our study showed that the therapy sequence abiraterone followed by chemotherapy for mCRPC achieved the best results in terms of OS. Limitations of our study are its retrospective character and small sample size. Results from this study suggest that first line docetaxel therapy is safe and well tolerated treatment choice for mHSPC patients with neither intervention nor hospitalization needed in vast majority of cases. Even the high-risk mHSPC population can benefit from chemotherapy with acceptable side effects. The optimal sequencing for second- and further line therapies is still unknown and prospective studies are needed in order to identify the optimal treatment sequence. In the future, the therapy sequence for mCRPC will be significantly influenced by the choice of therapy in previous stages (mHSPC, nmCRPC).

Declarations

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Ethical consideration

- Approval of the research protocol by an Institutional Reviewer Board (S-690/2015)
- Informed Consent
- Registry and the Registration No. of the study/trial (N/A.)
- Animal Studies (N/A.)

Conflict of interest: The author declares no conflict of interest.

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