Feasibility and efficacy of early docetaxel plus androgen deprivation therapy for metastatic hormone-sensitive prostate cancer in a rural health care setting

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Abstract

Aim/Background: The aim of this study was to evaluate the feasibility and efficacy, in terms of overall survival, of intensified upfront systemic therapy in patients with metastatic hormone-sensitive prostate cancer who lived in rural Nordland County, Norway.

Patients and Methods: Overall 117 patients were included in this retrospective study. Three cohorts were created: early docetaxel and androgen deprivation therapy (ADT; the CHAARTED regimen; n=37), ADT only during the same time period (2014-2020; n=33), and ADT only in the years 2009-2014 (n=47).

Results: Four patients (11%) did not complete 6 cycles of docetaxel, one of these due to early progression of cancer. During follow-up, 8 patients (22%) progressed to castration-resistant disease (mCRPC), compared to 24 (73%) with ADT only and 35 (75%) in the historical cohort, p=0.000001. Such progression occurred within 12 months in 3 patients (8%) treated with docetaxel and 9 patients (27%) treated with ADT only during the same time period, p=0.05. Median survival was 56 months (95% CI 40-72 months), compared to 30 months in both other cohorts. Three-year survival rates were 79, 38 and 37%, respectively (p=0.016). In multivariate analysis, the CHAARTED regimen was associated with significantly improved survival.

Conclusion: In this rural health care setting, early docetaxel was feasible and effective in reducing progression to mCRPC and prolonging survival. Median survival was very close to the 58 months reported in the CHAARTED trial.

Keywords: prostate cancer, distant metastases, chemotherapy, systemic therapy, survival, pattern of care

Introduction

Despite the fact that prostate cancer commonly is diagnosed in early, non-metastatic stages, a proportion of patients presents with symptomatic distant metastatic disease (for example, bone pain leading to a diagnosis of prostate cancer) [1, 2]. In others, staging reveals asymptomatic metastases. The management of patients with de novo, hormone-sensitive metastatic prostate cancer has changed after publication of the landmark CHAARTED study, which established early chemotherapy with docetaxel as a new treatment paradigm [3]. Previously, docetaxel was prescribed after development of metastatic castration-resistant cancer (mCRPC). The second analysis of the CHAARTED study also included results for the prospectively defined low- and high-volume disease subgroups [4]. High-volume disease was defined as presence of visceral metastases and/or ≥ four bone metastases with at least one outside of the vertebral column and pelvis. The median OS was 58 months for the chemohormonal therapy arm versus 47 months for ADT only (HR, 0.72; 95% CI, 0.59 to 0.89; p = 0.0018). For patients with low-volume disease, no significant survival benefit was observed. In 2016, a systemic review and meta-analysis of three studies also showed benefit of early chemotherapy with docetaxel in patients with low-volume disease [5].

Stimulated by the initial publication of the CHAARTED data at oncology meetings, the authors' institution in Bodø has offered this regime of early docetaxel to patients with high-volume disease who did not present with contraindications since autumn 2014. Later, selected patients with extensive lymph node metastases outside of the pelvis in the absence of bone or other metastases also received early docetaxel. The aim of the present study was to compare own results to those from the CHAARTED trial, because it has been shown that real-world outcomes in rural health care settings might deviate

from those observed in the pivotal randomized clinical trials [6-8]. Earlier, a comparable study was performed in patients with mCRPC [9].

Material and Methods

This retrospective study included 117 consecutive men (all Caucasian) with newly diagnosed, metastatic hormone-sensitive prostate cancer who received oncology care at Nordland Hospital Trust's hospital in Bodø (academic teaching hospital in rural North Norway). All patients presented with distant metastases at initial diagnosis and none were managed with radical approaches in an oligometastatic or initially curative setting. The metastases were diagnosed with traditional staging methods, such as radionuclide bone scan, computed tomography or magnetic resonance imaging, rather than routine positron emission tomography. Histological verification was obtained on a case-by-case basis, e.g. in liver metastases without simultaneous bone metastases. A weekly multidisciplinary tumor board (urologists, oncologists, pathologists, radiologists) provided the diagnostic and treatment recommendations. In all cases, systemic treatment with ADT was started between 2009 and 2020. Three cohorts were created: 1) treatment before the CHAARTED regimen was available (2009-2014), 2) treatment with the CHAARTED regimen (2014-2020), 3) treatment during the CHAARTED era, but with ADT only (2014-2020). In line with National guidelines, enzalutamide or abiraterone acetate were never instituted for hormone-sensitive disease. Docetaxel was administered according to the CHAARTED protocol, i.e. every 3 weeks for 6 cycles (75 mg/m^2). The regional electronic patient record (EPR) system, named DIPS®, was used to collect all follow-up, treatment and baseline data. Actuarial survival from the day of cancer diagnosis was calculated with the Kaplan-Meier method and compared between subgroups with the log-rank test. In the historical cohort 1), 46 of 47 patients

had died at the time of the analysis in July 2021. In the docetaxel cohort 2), 8 patients had died and 29 patients were censored at the time of their last follow-up (minimum 7 months, median 23 months). In the ADT only cohort 3), 20 patients had died and 13 were censored (minimum follow-up 7 months, median 26). Associations between different variables of interest were assessed with the chi-square or Fisher's exact probability test (two-tailed). The impact of continuous variables such as age and blood test results on survival was examined in univariate Cox analyses. A multivariate forward conditional Cox analysis of prognostic factors for survival was then performed. A p-value <0.05 was considered statistically significant. Due to limited patient numbers, a p-value <0.15 was selected in the initial analyses, e.g. when deciding which parameters to include in the multivariate Cox model.

Results

Patient characteristics

In the docetaxel cohort 2), median age was 68 years, range 48-79 years. The patients in the other cohorts were significantly older and also less likely to be married or partnered. Further patient characteristics are shown in Table 1, also in comparison to the other cohorts.

Treatment details

Four patients (11%) did not complete 6 cycles of docetaxel, one of these due to early progression of cancer, the others due to toxicity/quality of life issues. Treatment-related death did not occur. As shown in Figure 1, the utilization of ADT only has decreased in the second half of the study period.

During follow-up, 8 patients (22%) in the docetaxel cohort progressed to mCRPC. The corresponding figures were 24 (73%) with ADT only and 35 (75%) in the historical cohort 1), p=0.000001. Seven of the eight patients who progressed to mCRPC after ADT and early docetaxel received active treatment with drugs approved for mCRPC, e.g., enzalutamide, abiraterone acetate or cabazitaxel. In the historical cohort 1), 60% of the patients had received mCRPC drugs (docetaxel, enzalutamide or abiraterone acetate alone or in sequence, sometimes also cabazitaxel or Ra-223). Supplementary Table 2 shows detailed information about all 8 patients who progressed to mCRPC. These data illustrate the connection between short time to mCRPC and short overall survival. All three patients who had developed mCRPC within 12 months had extensive bone metastases (>10) together with extra-osseous metastases at the time of prostate cancer diagnosis.

Overall survival

Median survival was 56 months (95% CI 40-72 months), compared to 30 months in both other cohorts. Three-year survival rates were 79, 38 and 37%, respectively. The survival curves are shown in Figure 2 (p=0.016). Potentially relevant baseline differences were observed with regard to age, serum hemoglobin, prostate-specific antigen (PSA), previous other cancer and being married or partnered (all p<0.15 as indicated in Table 1). Therefore, the impact of all these parameters on survival was examined in univariate analyses. A potential impact was found for lower hemoglobin (p=0.036), higher age (p=0.07) and higher PSA (p=0.08). The multivariate model with these 3 parameters (entered as continuous variables) indicated that lower hemoglobin (p=0.002) and higher PSA (p=0.01) were associated with shorter survival, whereas age was not. A further analysis including early docetaxel as the fourth parameter

showed that higher PSA (p=0.008), lower hemoglobin (p=0.016) and lack of early docetaxel treatment (p=0.028) were associated with shorter survival (Table 2).

Discussion

In the present observational study, the median overall survival of 56 months after ADT plus early docetaxel was very close to the 58 months reported in the randomized CHAARTED trial. In the two remaining cohorts of our study, median survival was 30 months each. Thus, the expected prolongation of survival could be confirmed. We observed that patients treated with ADT plus early docetaxel were significantly younger and more often married or partnered, compared to their counterparts managed with ADT only. Comorbidity was largely comparable, except for a history of previous treatment for other types of cancer, e.g. bowel, kidney and lung cancer. When interpreting the results, one should note that 19% of our ADT plus docetaxel patients harbored nodal distant metastases alone, without bone or other visceral involvement. The majority had high-volume bone metastases without any visceral involvement. Due to the non-randomized treatment assignment in our study, several imbalances in baseline characteristics existed. Therefore, a multivariate analysis included such baseline parameters in addition to the treatment approach. Also in this analysis, ADT + early docetaxel was associated with significantly improved survival.

An observational study from Australia included men diagnosed from 2014 to 2018 (Prostate Cancer Outcomes Registry-Victoria) [10]. Predictors of docetaxel utilization were identified in 1014 men, 25% of whom received docetaxel with ADT. Uptake of docetaxel increased from 20% in 2014 to 33% in 2018. Predictors of higher usage of docetaxel were younger age and treatment in a private hospital, with both remaining

significant on multivariable analysis. The proportion of men under 70 receiving docetaxel increased from 54% to 64%, while in men aged 70 and over the corresponding figures were 15% and 22% respectively. A study from Scotland included 103 patients treated with ADT plus docetaxel, of whom 83 completed all 6 cycles [11]. Their median age was 68 years (range 45-85). Patients who received ADT only had a HR of 5.9 for death (95% CI: 2.5–13.7; p=0.001). Unfortunately, the Kaplan-Meier curves were truncated after 20 months of follow-up.

STAMPEDE was a widely known multi-arm multi-stage trial, which included six cycles of docetaxel plus ADT in one arm (n = 592) [12]. This trial showed a 10-month survival benefit with ADT and docetaxel (median 81 vs 71 months in the ADT only arm, HR 0.78, 95% CI: 0.66–0.93; p=0.006). Vale et al. performed a meta-analysis of STAMPEDE, CHAARTED and GETUG-15 trial data [13]. The HR of 0.77 (95% CI 0.68–0.87; p<0.0001) translated to an absolute improvement in 4-year survival of 9% (95% CI 5–14) when adding docetaxel to ADT. Both, observational studies and randomized trials showed consistent survival improvements.

Recently, chemotherapy-free and less toxic options such as abiraterone acetate have emerged, which might diminish such age-related disparities [14]. Such treatment alternatives were not available in Norway during the time period of the present study. For patients who can tolerate docetaxel, combination androgen receptor inhibition and chemotherapy might represent a new option leading to further prolongation of survival in metastatic hormone-sensitive prostate cancer [15].

The present study provided other relevant information, beyond survival data and a confirmation of the feasibility in a rural region with long travel distances. The cross-over rate, i.e. treatment with docetaxel later during the course of the disease (in the mCRPC state) was limited in patients managed with initial ADT only. It was 45% in the historical cohort and 21% in the contemporary cohort. Also overall, only 60% of the patients in the historical cohort had received mCRPC drugs (docetaxel, enzalutamide or abiraterone acetate alone or in sequence, sometimes also cabazitaxel or Ra-223). A large Swedish study of mCRPC showed comparable trends [16]. Despite treatment availability, the Swedish group found treatment utilization to remain low. Docetaxel was used in 39%, abiraterone acetate in 15%, enzalutamide in 13%, cabazitaxel in 11% and Ra-223 in 5% of treatments. Treatment increased from 22% in 2006-2009 to 50% in 2013-2015 ($p < 0.001$). As mentioned above, the present study found a rate of 60% in the time period 2009-2014. In contrast to the Swedish study, ours might not have included the complete population in the region, due to possible referral bias. It is possible that mainly younger and fitter patients in our health care region were referred to the Department of Oncology and Palliative Medicine in Bodø (the only provider), while others were managed by the local primary healthcare sector.

Further limitations of the present study include the number of patients, statistical power of subgroup analyses, and retrospective design. The lack of randomization might have resulted in a negative selection of patients with contraindications for docetaxel in the respective cohort, and in imbalances in baseline factors that were not included in the data collected for this study. For example, information about performance status was not available. Finally, the follow-up was more mature in the historical cohort.

Conclusions

In this rural health care setting, early docetaxel was feasible and effective in reducing progression to mCRPC and prolonging survival. Median survival was very close to the 58 months reported in the CHAARTED trial.

References

1. Kaipia A, Riikonen J. Contemporary and past challenges of prostate cancer diagnostics. Scand J Urol. 2017;51:193-201. doi: 10.1080/21681805.2017.1329902.

2. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: Treatment of relapsing and metastatic prostate cancer. Eur Urol. 2021;79:263-282. doi: 10.1016/j.eururo.2020.09.046.

3. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373:737-746. doi: 10.1056/NEJMoa1503747.

4. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol. 2018;36:1080-1087. doi: 10.1200/JCO.2017.75.3657.

5. Tucci M, Bertaglia V, Vignani F, et al. Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive metastatic prostate cancer: A systematic review and meta-analysis. Eur Urol. 2016;69:563-573. doi: 10.1016/j.eururo.2015.09.013.

6. Levit LA, Byatt L, Lyss AP, et al. Closing the rural cancer care gap: Three institutional approaches. JCO Oncol Pract. 2020;16:422-430. doi: 10.1200/OP.20.00174.5.

7. Charlton M, Schlichting J, Chioreso C, et al. Challenges of rural cancer care in the United States. Oncology (Williston Park). 2015;29:633-640.

8. Baade PD, Yu XQ, Smith DP, et al. Geographic disparities in prostate cancer outcomes - review of international patterns. Asian Pac J Cancer Prev. 2015;16:1259-1275. doi: 10.7314/apjcp.2015.16.3.1259.

9. Nieder C, Dalhaug A, Haukland E. Feasibility and efficacy of sequential systemic therapy for metastatic castration-resistant prostate cancer in a rural health care setting. Scand J Urol. 2020;54:110-114. doi: 10.1080/21681805.2020.1730435.

10. Azad AA, Tran B, Davis ID, et al. Predictors of real-world utilisation of docetaxel combined with androgen deprivation therapy in metastatic hormone-sensitive prostate cancer. Intern Med J. 2021 Mar 12. doi: 10.1111/imj.15288.

11. Rulach RJ, McKay S, Neilson S, et al. Real-world uptake, safety profile and outcomes of docetaxel in newly diagnosed metastatic prostate cancer. BJU Int. 2018;121:268-274. doi: 10.1111/bju.14025.

12. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387:1163-1177. doi: 10.1016/S0140-6736(15)01037-5.

13. Vale CL, Burdett S, Rydzewska LHM, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol. 2016;17:243-256. doi: 10.1016/S1470-2045(15)00489-1. Erratum in: Lancet Oncol. 2016;17:e46.

14. Rydzewska LHM, Burdett S, Vale CL, et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis. Eur J Cancer. 2017;84:88-101. doi: 10.1016/j.ejca.2017.07.003.

15. Adashek JJ, Reed JP, Tandon A, et al. Combination androgen receptor inhibition and docetaxel in metastatic castration-sensitive prostate cancer: The next step in first-

line treatment? Clin Genitourin Cancer. 2020;18:425-428. doi: 10.1016/j.clgc.2020.05.003.

16. Vigneswaran HT, Warnqvist A, Andersson TML, et al. Real world treatment utilization patterns in patients with castration-resistant prostate cancer. Scand J Urol. 2021:1-8. doi: 10.1080/21681805.2021.1936626.

Figure Legends

Figure 1. Proportion of men who were treated with androgen deprivation therapy (ADT) only in the first and second half of the study period, respectively (p=0.13).

Figure 2. Actuarial Kaplan-Meier survival curves for patients treated with androgen deprivation therapy (ADT) only (n=33), ADT plus docetaxel (n=37) and a historical cohort (also ADT only, n=47). The median was 56, 30 and 30 months, respectively (p=0.016, log-rank test over all three strata). The vertical bars at 2 and 4 years indicate the 95% confidence intervals.

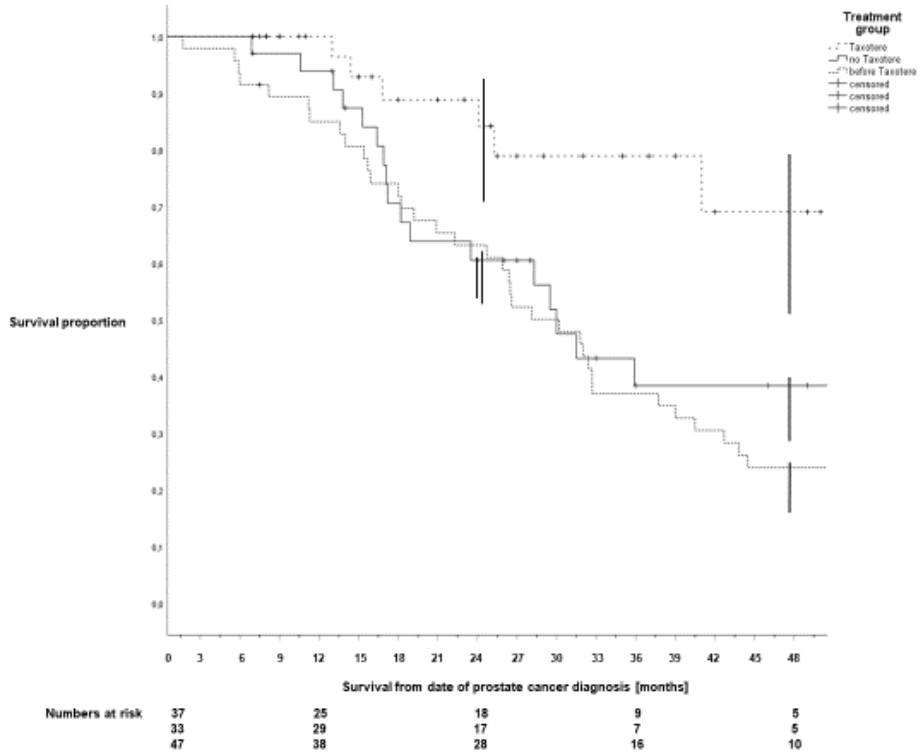

Table 1. Patient characteristics stratified by treatment approach (n=37 (ADT + docetaxel), 33 (ADT only) and 47 (historical cohort); time period 2009-2020; Nordland Hospital Trust, Bodø, Norway; all patients had newly diagnosed, metastatic hormone-sensitive prostate cancer, i.e. distant metastases at initial diagnosis)

Parameter	ADT + docetaxel		ADT only		Historical cohort		Comments
	n	(%)	n	(%)	n	(%)	
Gleason 5 component	27	(73)	22	(67)	27	(57)	difference n.s.
Visceral metastases only	1	(3)	0	(0)	0	(0)	
Visceral metastases + others	4	(11)	1	(3)	2	(4)	
Distant nodal metastases only	7	(19)	3	(9)	1	(2)	*
No comorbidity	19	(51)	15	(45)	23	(49)	difference n.s.
Diabetes mellitus	8	(24)	6	(18)	8	(17)	difference n.s.
Previous other cancer	2	(5)	7	(21)	3	(6)	p=0.07
Cardiac comorbidity	10	(27)	10	(30)	13	(28)	difference n.s.
Married or partnered	33	(89)	20	(61)	29	(62)	p=0.01
Docetaxel for mCRPC[1]	1	(3)	7	(21)	21	(45)	p=0.0005
ENZ/AA for mCRPC[2]	6	(16)	6	(18)	7	(15)	difference n.s.
Median age, range (years)	68, 48-79		76, 59-90		71, 56-89		p<0.001
Median PSA, range (ng/ml)	77, 4-3500		84.5, 4-3486		157, 5-5000		p=0.13
Median Hb, range (g/dl)	14.1, 11.2-17.2		14.0, 6.2-17.7		13.4, 8.2-16.7		p=0.09

*numbers too small

PSA: prostate specific antigen, Hb: hemoglobin, mCRPC: metastatic castration-resistant prostate cancer, ENZ/AA: enzalutamide or

abiraterone acetate, n.s. not significant (due to small group sizes, p≥0.15 was employed in these initial univariate analyses)

[1]some patients had additional drugs before or after, e.g. ENZ/AA

[2]none of these patients had docetaxel in the mCRPC setting

Table 2. Factors associated with risk of death from any cause in uni- and multivariate analyses (ADT only as reference, both groups combined)

Parameter	Hazard ratio and 95% confidence interval (univariate)	Univariate p-value	Hazard ratio and 95% confidence interval (multivariate)	Multivariate p-value
Age, continuous	1.03, 1-1.06	0.07	1.03, 0.97-1.09	0.17
PSA, continuous	1.04, 1-1.08	0.08	1.07, 1.04-1.11	0.012
Hemoglobin, continuous	0.86, 0.74-0.98	0.036	0.82, 0.70-0.96	0.014
ADT plus docetaxel	0.54, 0.28-0.80	0.005	0.72, 0.49-0.95	0.047

PSA: prostate specific antigen, ADT: androgen deprivation therapy