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REVIEW ARTICLE

Docetaxel in the treatment of castrate resistant advanced prostate cancer: a paradigm in change

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Summary

Until last year, the international guidelines recommended the use of docetaxel in advanced prostate cancer (PC) at the time of progression following androgen deprivation therapy (ADT). Nevertheless, two randomized phase III trials, CHAARTED and STAMPEDE, delivered level I evidence showing that upfront introduction of docetaxel, during the androgen sensitive course of disease, is able to significantly improve the patients' overall survival. As such, this strategy was rapidly included in the current guideline recommendations, with slightly different indications in the ESMO as compared to the NCCN version. Side effects of chemotherapy along with the possible higher benefit in high vs low-volume metastatic disease should be taken into consideration when choosing this alternative. The present paper makes a review of the current data supporting the new indication of docetaxel, and provides detailed information in order to assist the clinician in deciding the best treatment for patients with advanced PC.

Key words: *castrate sensitive, docetaxel, prostate cancer*

Introduction

Until very recently docetaxel was recommended in advanced PC, at the time of progression following ADT. This strategy was based on the assumption that castrate resistant cell clones are emerging due to therapeutic pressure of hormone deprivation. Two papers published in the same issue of The New England Journal of Medicine provided clinical evidence in support of this strategy, showing a significant overall survival (OS) improvement with docetaxel compared to mitoxantrone [1,2]. However, recent results of several randomized trials challenged this paradigm, providing evidence that starting docetaxel up front, concurrently with ADT in the setting of hormone sensitive PC may substantially improve patient outcome.

The CHAARTED trial randomized 790 patients with metastatic PC to ADT alone or ADT + docetaxel [3]. Docetaxel was administered at 75 mg/m^2 every 21 days for a maximum of 6 cycles. Daily prednisone was not required. After a median follow-up of 28.9 months , the median time to clinical progression (increasing symptoms of bone metastases or radiographic progression) was 33 months for the combination therapy vs 19.8 months for ADT alone (HR 0.61, p<0.001). The median OS was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 vs 44.0 months; HR 0.61, p<0.001). The benefit was more consistent in the high-volume disease subgroup (65%), with an OS difference of 17.0 months (49.2 vs 32.2 months; HR 0.60, p<0.001). High-volume disease was defined as presence of visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis or vertebral column. In the subgroup with low-volume disease

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the median survival had not been reached, and despite the same reduction in the hazard for death, the difference was statistically not significant (HR 0.60, p=0.11). The authors speculated on this discrepancy, considering that men with extensive disease may benefit more due to the higher risk of death, while patients with low-volume disease are adequately treated with ADT alone. Moreover, patients with low-volume disease are more likely to live longer in general and are prone to die due to non–prostate cancer causes (mainly cardiovascular disease). Subsequently, the effect of initial therapy might have been diluted. The incidence of grade 3-4 toxicity was low in the combination arm, i.e febrile neutropenia 6.2%, infection with neutropenia 3%, and the rate of grade 3 sensory neuropathy and of grade 3 motor neuropathy was 0.5%. Noteworthy, patients in arm A (ADT + docetaxel) reported -2.7 ± 0.9 decline in quality of life evaluated by FACT-P at 3 months (p=0.003), but did not differ significantly from baseline at 12 months (-0.7 ± 1.1). In contrast, patients in arm B (ADT alone) did not differ significantly at 3 months. FACT-P scores differed significantly between arm A and B at 3 months (p=0.02) and 12 months (p=0.04), with arm A lower at 3 months and higher at 12 months [4].

The STAMPEDE trial included patients with newly diagnosed PC that was either metastatic, node positive, or contained two or more of the following features: Gleason score 8-10, stage T3/4, or prostate-specific antigen (PSA) > 40 ng/mL. Patients with relapsed disease after surgery or radiation were included, provided they had at least one of the followings: a PSA of at least 4 ng/mL and a PSA doubling time of less than 6 months, PSA > 20 ng/mL, node-positive disease, or metastatic disease [5]. A number of 2962 patients were randomized 2:1:1:1 to standard of care (SOC), SOC+docetaxel, SOC+zoledronic (ZA) or SOC+docetaxel+ZA. Four mg ZA were given for six 3-weekly cycles then 4-weekly until 2years. Docetaxel was given as 75mg/m^2 for six 3-weekly cycles with prednisolone 10mg daily. Results were presented at ASCO 2015 meeting [6]. In the overall study population, including all patients with high-risk nonmetastatic or regional (lymph node) metastatic (M0) and distant metastatic (M1) prostate cancer, the median OS was improved by 10 months in the docetaxel arm compared with SOC (77 vs 67months; HR 0.76 p =0.003). The beneficial effect on survival was restricted to the M1 subpopulation (61%), with a remarkable 22 months difference in OS favoring the docetaxel arm (65 vs 43 months HR 0.73, p=0.002). For M0 patients there was no survival advantage (HR 1.01, 95% CI 0.65–1.56). However, improved failure-free survival for M0 disease (HR 0.57, 95% CI 0.42–0.76) as well as for M1 disease (HR 0.62, 95% CI 0.54–0.73) was noted. Grade 3–5 adverse events were reported for 399 (32%) patients receiving SOC, 197 (32%) receiving SOC+ZA, 288 (52%) receiving SOC+docetaxel, and 269 (52%) receiving SOC+ZA+docetaxel.

Interestingly, an updated analysis of another trial using ADT+docetaxel upfront, GETUG-AFU 15, did not support the above presented data. In this trial 192 patients with metastatic PC were randomly allocated to receive ADT plus docetaxel and 193 to receive ADT alone [7,8]. After a median follow up 82.9 months the biological progression-free survival was significantly improved (HR 0.7, p=0.0021), while only a trend towards OS improvement on the docetaxel arm was noted (HR 0.9, p=0.44). Even when assessed by tumor volume as in CHAARTED trial, there was no OS benefit: high-volume disease 39 vs 35.1 months (HR 0.8, p=0.35); low-volume disease 83.1 months vs not reached (HR 1.0, p=0.87). Discrepancies were explained by the high salvage rate with docetaxel in the ADT arm of the GETUG-15 vs CHAARTED trial (62 vs 35%) as well as by trial being underpowered to specifically assess the high volume subgroup.

An overview of the most important data of CHAARTED, STAMPEDE and GETUG-AFU 15 trial are presented in Table 1.

In order to build a clear picture of the evidence pertaining to the addition of docetaxel to ADT in castrate sensitive PC, a recent meta-analysis was performed [9], pooling the results of all randomized trials. For men with metastatic disease, the addition of docetaxel to standard of care was shown to convey an OS benefit, with a HR 0.77 (p<0.0001). This finding translated into a 10% absolute improvement in survival at 4 years (from 40 to 50%). Docetaxel also improved failure-free survival, with HR 0.64 (p<0.0001), which translated into a 15% absolute reduction of 4-year failure-free survival (from 80 to 65%) [3,5,6]. In men with non-metastatic disease, for failure-free survival, the effect of adding docetaxel was statistically significant, with a HR of 0.70 (p<0.0001), yielding an 8% absolute reduction of 4-year failure-free survival (from 70% to 62%). However, the evidence was insufficient for finding a survival benefit: HR 0.87 (p=0.218), which translates into a 5% potential improvement in survival (from 80 to 85%) at 4 years [5,6,10-12].

Table 1. Overview of CHAARTED, STAMPEDE and GETUG-AFU 15 trials

	CHAARTED [3]		STAMPEDE [5,6]		GETUG-AFU 15 [7,8]	
	DOC+ADT	ADT	DOC+ADT	ADT	DOC+ADT	ADT
Patients, N	397	393	600	1200	192	193
Age, median, years	64		65		66	
Stage	M1		M1+M0		M1	
Docetaxel cycles, N	6		6		9	
OS	57.6 vs 44 months HR=0.61 (95% CI 0.47-0.80) p<0.001		77 vs 67 months HR=0.76 (95% CI 0.63-0.91) p=0.003		60.9 vs 46.5 months HR=0.9 (95% CI 0.7-1.2) p=0.44	
OS High-volume[a]	49.2 vs 32.2 months HR=0.60 (95% CI 0.45-0.81) p<0.001		NA		39 vs 35.1 months HR=0.8 (95% CI, 0.6-1.2) P=0.35	
OS Low-volume	HR= 0.60 (95% CI 0.32-1.13) p=0.11		NA		HR=1.0 (95% CI 0.6-1.5) p=0.87	
OS in M1	NA		65 vs 43 months HR=0.73 (95% CI 0.59-0.89) p=0.002		NA	
OS in M0	NA		HR=1.01 (95% CI 0.65-1.56); p not stated - data not mature			
Subsequent therapies	Total =238 (60%) Docetaxel, 14%	Total 287 (73%) Docetaxel, 35%	Total 135 (23%) Docetaxel, 14%	Total 372 (31%) Docetaxel, 41%	Total 86 (45%) Docetaxel 28%	Total 150 (78%) Docetaxel 62%

Doc: docetaxel, ADT: androgen deprivation therapy, M1: metastatic stage, M0: non-metastatic stage, OS: overall survival, HR: hazard ratio, NA: not available

[a] High-volume disease: presence of visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis or vertebral column

The previously presented practice of changing data has already being incorporated in the recommendations of the current guidelines. As such, ADT plus docetaxel is recommended as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy (1, A: not documented in the ESMO guidelines [13]), while the last NCCN version included the addition of docetaxel to ADT among other classical options with the amendment that "patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT [14]. No guideline recommends docetaxel for patients with non-metastatic disease.

Last but not least, it is encouraging to note that even in the era of molecular targeted therapy and immune check points inhibitors, important improvements in cancer care may be achieved without prohibitive associated costs, by intelligently use of common drugs , making the innovative new standard immediately accessible for all patients around the world.

Conflict of interests

The authors declare no confict of interests.

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