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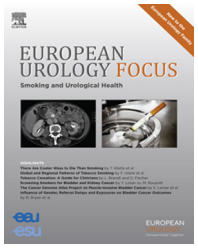

Clinical Consultation Guide

Treatment of Castration-naive Metastatic Prostate Cancer

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1. Introduction

The incidence of de novo metastatic prostate cancer at diagnosis is highly variable across the globe and ranges from about 5% of newly diagnosed prostate cancer in some Western countries to about 60% in large countries from Eastern Asia. For these patients, the outcome is less favorable, with a recently reported median survival of 42 mo [1,2]. In the last decade, pre-clinical and clinical research focused on metastatic castration-resistant prostate cancer (mCRPC), and options of treatment for this lethal form greatly expanded. However, until recently, androgen deprivation therapy (ADT) administered alone was the cornerstone of treatment for patients with metastatic castration-naive prostate cancer (mCNPC). The last 5 yr saw a great shift in the treatment of de novo metastatic prostate cancer. Docetaxel, used customarily in mCRPC, together with ADT, became the standard of care for men presenting with mCNPC, based on findings from three major trials [1,3,4]. Finally, abiraterone acetate (AA), a selective CYP17A1 inhibitor that proved a survival benefice in pre- and post-docetaxel mCRPC has also been moved forward in the treatment of these patients [5,6].

Hereby, we seek to review the evidence behind the evolution of treatment of mCNPC. Relevant studies discussed in the current review are summarized in Table 1.

2. Chemotherapy

Starting in 2004, it was the first GETUG-AFU15 phase III trial that randomized 385 men with mCNPC to receive ADT alone or ADT + docetaxel (75 mg/m^2 every 3 wk, up to nine cycles) with a primary endpoint of overall survival (OS) [7]. Almost a decade later, in 2013, it concluded in a non-significant increase in median OS of 4.7 mo in the favor of those receiving ADT + docetaxel. Both biochemical and clinical progression-free survival (PFS) were also improved with the addition of docetaxel: 22.9 mo (95% confidence interval [CI] = 19.6–28.4) versus 12.9 mo (11.9–17.7); hazard ratio (HR) = 0.72, 0.57–0.91; $p = 0.005$, and 23.5 mo (20.5–31.9) versus 15.4 mo (12.5–19.8); HR = 0.75, 0.59–0.94; $p = 0.015$, respectively.

Only a year later, CHAARTED became the first trial supporting survival improvement with docetaxel for mCNPC [4]. This phase III trial randomized 790 patients between ADT alone or ADT + docetaxel (75 mg/m^2 every 3 wk, up to six cycles). Patients were stratified prospectively according to tumoral burden ("high-risk", ie, with one or more visceral metastases and/or four bone metastases with at least one appendicular localization vs "low-risk"). The first results reported an increase of 13.6 mo in the median OS with the addition of docetaxel (57.6 mo vs 44.0 mo; HR = 0.61; 95% CI 0.47–0.80, $p < 0.0001$) largely driven by the high-risk group with a 17-mo increase in OS. In contrast, there was no difference in OS in the low-risk group, but the median survival had not been reached at the time of analysis. Long-term efficacy data have been presented at ESMO 2016 with OS still significantly longer in patients receiving ADT + docetaxel but with a smaller benefit (median = 57.6 mo vs 47.2 mo; HR = 0.73; $p = 0.0018$) [8].

Finally, the multi-arm multi-stage STAMPEDE trial included 3000 patients with high-risk locally advanced and mCNPC between 2005 and 2014 [3]. With the addition of docetaxel, the median OS was 15.0 mo longer than that with ADT alone (45 mo vs 60 mo; HR = 0.76, 95% CI = 0.62–0.92; $p = 0.005$) in the cohort of patients with mCNPC. A meta-analysis of available trials confirmed a survival benefit

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Table 1 – Clinical characteristics of patients and overall survival outcomes.

	Patients	Treatment		Primary endpoint	No. of patients		Median follow-up (mo)	Median OS (mo)		HR (95% CI)
		Comparator	Experimental		ADT alone	Experimental		ADT alone	Experimental	
GETUG-AFU 15	Metastatic PCa	ADT (both arms)	Docetaxel (75 mg/m^2 IV day 1 every 3 wk); up to nine cycles. No daily prednisone	OS	193	192	82.9	46.5	60.9	0.9 (0.7–1.2)
CHAARTED	Metastatic PCa	ADT (both arms)	Docetaxel (75 mg/m^2 IV day 1 every 3 wk); up to six cycles. No daily prednisone	OS	393	397	28.9	44.0	57.6	0.61 (0.47–0.80)
STAMPEDE (only metastatic subgroup)	Metastatic PCa	ADT (both arms)	Docetaxel (75 mg/m^2 IV day 1 every 3 wk); up to six cycles. Daily prednisolone 10 mg	OS	724	362	NA	45	60	0.76 (0.62–0.92)
LATITUDE	Metastatic PCa with two of the three following factors: • Gleason score ≥8 • At least three bone lesions • Measurable visceral metastasis	ADT (both arms)	Abiraterone acetate (1000 mg/d, given once daily as four 250 mg tablets) plus prednisone (5 mg daily)	OS and rPFS	602	597	30.4	34.7	NR	0.62 (0.51–0.76)
STAMPEDE (only metastatic)	Metastatic PCa	ADT (both arms)	Abiraterone acetate (1000 mg/d) plus prednisolone (5 mg/d)	OS	502	500	40	NA	NA	0.61 (0.49–0.75)

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo = months; NA = not available; NR = not reached; OS = overall survival; PCa = prostate cancer; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival.

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