Review

Systemic treatment for metastatic prostate cancer

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Abstract   The management of metastatic prostate cancer (mPCa) has changed over the past ten years. Several new drugs have been approved with significant overall survival benefits in metastatic castration resistant prostate cancer (PCa) including chemotherapy (docetaxel, cabazitaxel), new hormonal therapies (abiraterone, enzalutamide), Radium-223 and immunotherapy. The addition of docetaxel to androgen deprivation therapy (ADT) versus ADT alone in the castration sensitive metastatic setting has gained significant overall survival benefit particularly for high volume disease. More recently two phase III trials have assessed the efficacy of abiraterone plus prednisone plus ADT over ADT alone in newly high risk castrate sensitive mPCa. Determination of the appropriate treatment sequence using these therapies is important for maximizing the clinical benefit in castration sensitive and castration resistant PCa patients. Emerging fields are the identification of new subtypes with molecular characterization and new therapeutic targets.

1. Introduction

Prostate cancer (PCa) is one of the most commonly diagnosed cancers among men in the Western industrialized nations and the second leading cause of death [1]. The majority of patients have localized disease (80%) or loco-regional disease (12%). Patients with metastatic disease at the time of PCa diagnosis present fewer than 5% of all PCa diagnoses, but account for about one third of PCa deaths in recent years [2].

Androgen deprivation therapy (ADT) is the standard treatment for metastatic disease, which includes surgical castration, luteinizing hormone-releasing hormone (LHRH) agonist with or without anti-androgen treatment and/or LHRH antagonists. The goal of castration is to lower

testosterone levels to less than 50 ng/dL. Significant biochemical response is obtained in almost all patients, but responses are only transient with a median duration of 18 months when patients will develop castration resistant disease [3]. Different mechanisms lead to castration resistance: Amplification, overexpression or mutation of the androgen receptor (AR), constitutive activation of AR, alternative splicing events, intra-tumoral androgen synthesis or androgen synthesis by the adrenal glands, activation of other ligands, proliferation of prostate tumor cells independent of androgens [4].

2. Docetaxel

2.1. Metastatic castrate resistant PCa (mCRPC) (Table 1)

Docetaxel was the first agent to show significant survival improvement in two phase III trials. In the TAX 327, 1006 patients were randomized between docetaxel 75 mg/m^2 every 21 days and in the SWOG9916 patients received docetaxel and estramustine [5,6]. In both studies the control arm was mitoxantrone. The median survival for docetaxel in the TAX 327 study was 18.9 months (range 17.0–21.2 months) versus 16.5 months for mitoxantrone (hazard ratio [HR]: 0.76, 95% confidence interval [CI]: 0.62 to 0.94; $p = 0.009$) with a significant reduction in pain and improvement of quality of life [7].

2.2. Metastatic castrate sensitive PCa (mCSPC) (Table 2)

Until 2004, docetaxel with prednisone was the only treatment that could improve survival of castrate resistant disease. The benefit of this drug in mCRPC suggested that early chemotherapy might improve the overall outcome of patients with mCSPC.

The GETUG-AFU 15 study was the first study performed to assess the efficacy and safety of docetaxel combined with ADT versus ADT alone in patients with mCSPC [8]. This European trial evaluated docetaxel 75 mg/m^2 every 21 days for up to nine cycles with castration over castration alone. Biochemical and clinical progression free survival were improved with docetaxel and were 23 months versus 13 months (HR: 0.72, $p = 0.0052$) and 23 months versus 15 months (HR: 0.75, $p = 0.0147$). They did not show a statistically significant survival benefit, after a median follow up of 50 months, the median survival was 58.9 months in docetaxel arm versus 54.2 months in androgen deprivation arm (HR: 1.01, 95% CI: 0.75–1.36). An updated analysis after 82.9 months of follow-up with a retrospective analysis of volume disease did not show any difference of the median survival between the docetaxel and control arm [9]. In the high volume disease patients, a non-significant difference in median survival of 4 months was observed favoring docetaxel (39 months vs. 35.1 months, HR: 0.8, $p = 0.35$). In this study the majority of patients had low volume disease (53%) and up to 80% of patients in the ADT alone arm received docetaxel at time of mCRPC.

Table 1 Phase III mCRPC.

Study	n	Agents	Indication	HR (95% CI)	OS
Tax-327 [6]	1006	Docetaxel + P vs Mitoxantrone + P	mCRPC	0.76 (0.62–0.94)	18.9 vs. 16.5
D9901 and D9902 [27,28]	225	Sipuleucel T vs. Po	mCRPC pre docetaxel	1.5 (1.10–2.05)	32.2 vs. 18.9
IMPACT [29]	512	Sipuleucel T vs. Po	mCRPC pre docetaxel	0.78 (0.61–0.98)	25.8 vs. 21.7
COU-AA-301 [17]	1195	Abiraterone + P vs. P	mCRPC post docetaxel	0.65 (0.54–0.77)	14.8 vs. 10.9
COU-AA-302 [18,19]	1088	Abiraterone + P vs. p	mCRPC pre docetaxel	0.75 (0.61–0.93)	NR vs. 27.2
AFFIRM [22]	1199	Enzalutamide vs. Po	mCRPC post docetaxel	0.63 (0.53–0.75)	18.4 vs. 13.6
PREVAIL [23]	1717	Enzalutamide vs. Po	mCRPC pre docetaxel	0.71 (0.60–0.84)	32.4 vs. 30.2
TROPIC [24]	755	Cabazitaxel + P vs. Mitoxantrone + P	mCRPC post docetaxel	0.70 (0.59–0.83)	15.1 vs. 12.7
ALSYMPCA [30]	Po921	Radium-223 vs. Po	mCRPC pre docetaxel	0.7 (0.55–0.88)	14 vs. 11.2
FIRSTANA [25]	1168	Cabazitaxel 25 mg/m^2 (C25) vs. 20 mg/m^2 (C20) vs. docetaxel 75 mg/m^2 (D75)	mCRPC pre docetaxel	C20 vs. D75 1.01 (0.85–1.20) C25 vs. D75 0.97 (0.82–1.16)	24.5 C20 25.2 C25 24.3 D75
PROSELICA [26]	1200	Cabazitaxel 25 mg/m^2 (C25) vs. 20 mg/m^2 (C20)	mCRPC post docetaxel	1.024	13.4 vs. 14.5

HR: hazard ratio; mCRPC, metastatic castrate-resistant prostate cancer; NR, not reached; OS, overall survival; P, prednisone; Po, placebo; CI, confidence interval.

Table 2 Phase III mCSPC.

	DOCETAXEL + ADT vs. ADT			Abiraterone + prednisone + ADT vs. ADT	
	GETUG-15 [8,9]	CHAARTED [11,12]	STAMPEDE [13,34]	STAMPEDE [21]	LATITUDE [20]
Period of inclusion	10/2004—12/2008	07/2006—11/2012	10/2005—03/2013	11/2011—01/2014	02/2013—12/2014
n	385	790	2962 (M0/M1)	1917 (M0/M1)	1199
ECOG, PS					
0	357 (98%)	549 (69.5%)	662 (72%) ADT arm	1489 (77.7%)	
1—2	9 (2%)	241 (30.5%)	225 (28%) ADT arm	428 (22%)	NA
Metastatic at diagnosis	71% (272)	73% (575)	61% (1817)	49% (941)	100% (1199)
Burden of metastases					
HVD	48% (183)	65% (513)	NA	NA	100% (1199)
LVD	52% (202)	35% (277)	NA	NA	0
Gleason Score ≥8	56%	61.2%	64% ADT arm	75%	98%
Number of cycles of Docetaxel/median duration of abiraterone + p	9	6	6 + prednisone 10 mg/day	23.7 months	NA
Median follow-up (months)	84	54	43	40	30.4
Median OS (months) ADT/ADT + D (or abiraterone + prednisone)	48.6/62.1 HR 0.88 (0.68—1.14)	47.2/57.6 HR: 0.73 (0.59—0.89)	45/60 HR: 0.76 (0,62—0,92)	3-year survival 76%/83% HR: 0.63 (0.52—0.76)	34.7/NR HR: 0.62 (0.51—0.76)
Median OS HVD (months) ADT/ADT + D	35.1/39.8 HR: 0.78 (0.56—1.09)	34.4/51.2 HR: 0.63 (0.50—0.79)	NA	NA	34.7/NR HR: 0.62 (0.51—0.76)
Median OS LVD (months) ADT/ADT + D	83.4/NR HR: 1.02 (0.67—1.55)	NR/63.5 HR: 1.04 (0.70—1.55)	NA	NA	NA
Median PFS (months) ADT/ADT + D (or abiraterone + prednisone)	12.9/22.9 HR: 0.67 (0.54—0.84)	11.7/19.4 HR: 0.61 (0.52—0.73)	M1: HR: 0.61 (0.53—0.71)	3-year failure-free survival 45%/75% HR: 0.29 [0.25—0.34]	radiographic PFS 14.8/33.0 HR: 0.47 (0.39—0.55)

ADT, androgen deprivation therapy; D, docetaxel; HR, hazard ratio; HVD, high volume disease (for CHAARTED and GETUG-15 were defined as visceral metastases or 4 or more bone metastases with >1 bone lesion beyond pelvis or axis, for Latitude patients were considered high risk if they met at least two of the following requirements: Gleason score of at least 8, presence of at least three lesions on a bone scan, or presence of measurable visceral metastasis); LVD, low volume disease; mCRPC, metastatic castrate-resistant prostate cancer; NA, not applicable; NR, not reached; OS, overall survival; PFS, progression free survival; PS, performance status; P, prednisone; M0, no metastatic; M1, metastatic.

Multivariate analysis showed volume disease and alkaline phosphatase as independent prognostic factors for survival [10].

The ECOG-CHAARTED study evaluated the benefice of six cycles of docetaxel 75 mg/m^2 with ADT versus ADT alone in 790 men [11]. Patients were stratified by extent of metastatic disease; high volume disease (HVD) was defined as visceral metastases or four or more bone metastases with >1 bone lesion beyond pelvis or axis. The median survival was significantly longer for patients treated with docetaxel plus ADT over ADT alone (57.6 months vs. 44 months, HR: 0.61 [95% CI: 0.47–0.80, $p < 0.001$]). The median survival benefit reached 17 months in the HVD subgroup comparing docetaxel + ADT vs. ADT alone (overall survival [OS]: 49.2 months vs. 32.2 months, HR: 0.60; 95% CI: 0.45–0.81; $p < 0.001$). The updated results were presented at the ESMO meeting in 2016, after a median follow-up of 54 months [12]. Overall survival was significantly increased (median: 58 months vs. 47 months, HR: 0.73, 95% CI: 0.59–0.89). For HVD (513 patients), the major gain in overall survival of 17 months was confirmed (median: 51 months vs. 34 months, HR: 0.63, 95% CI: 0.50–0.79). For low volume disease (LVD) (277 patients), there was no significant difference in overall survival (median: 64 months vs. not reached, HR: 1.04, 95% CI: 0.70–1.55).

The STAMPEDE multi-arm multi-stage randomized study compared ADT to ADT plus docetaxel (75 mg/m^2 every 3 weeks for six cycles) and/or zoledronic acid in 2962 men with advanced or metastatic CSPC [13]. At a median follow-up of 43 months, the addition of docetaxel to ADT improved OS in metastatic disease (HR: 0.8, 95% CI: 0.65–0.99) and for docetaxel plus zoledronic acid plus ADT (HR: 0.92, 95% CI: 0.75–1.12) versus ADT alone. Subgroup analysis of mCSPC patients demonstrated an overall survival benefit with docetaxel (65 months vs. 43 months, HR: 0.73, 95% CI: 0.59–0.89; $p = 0.002$) but patients with M0 disease did not appear to derive benefit (HR: 1.01, 95% CI: 0.65–1.56). The addition of zoledronic acid did not confer any survival benefit.

A meta-analysis of these trials has been realized, which has provided substantial and reliable evidence that the addition of docetaxel to ADT improves survival of patients with metastatic castration-sensitive disease, and the HR of 0.77 (95% CI: 0.68–0.87; $p < 0.0001$) translates to an absolute improvement in 4-year survival of 0.09 (95% CI: 0.05–0.14) [14]. Docetaxel in addition to ADT also improved failure-free survival, with the HR of 0.64 (95% CI: 0.58–0.70; $p < 0.0001$) translating into a reduction in absolute 4-year failure rates of 0.16 (95% CI: 0.12–0.19).

3. Abiraterone

Abiraterone acetate (AA) is an irreversible, highly selective Cytochrome p450 (CYP) 17 inhibitor that targets its 17α-hydroxylase and C17,20-lyase activities resulting in reduced in intratumoral production of androgens reducing as well their synthesis in the adrenal glands and the testes [15].

3.1. Abiraterone in mCRPC

The COU-AA-301 trial was a randomized, double-blind, placebo-controlled phase III study of AA administered with prednisone in mCRPC patients previously treated with docetaxel [16]. In this study, 1195 patients were randomized between AA (1 g orally once daily) plus prednisone (5 mg orally twice daily) and placebo plus prednisone. Interim analysis revealed a median OS of 14.8 months in the AA group and 10.9 months in the placebo group. Study data were unblinded and patients in the placebo group were switched over to AA if they met criteria for crossover treatment. The final analysis of the COU-AA-301 trial showed that the median OS in the AA group was significantly longer than in the placebo group (15.8 months vs. 11.2 months, HR: 0.74, 95% CI: 0.64–0.86; $p < 0.0001$) [17]. Common adverse events of abiraterone included: Fatigue, hypokaliemia, hypertension, fluid retention and elevated amino transferase.

COU-AA-302 was a placebo-controlled trial in chemotherapy naïve asymptomatic or minimally symptomatic mCRPC. Patients ($n = 1088$) were randomly assigned at a 1:1 ratio to receive AA (1000 mg/day) + prednisone (5 mg twice daily) or placebo + prednisone [18]. At the interim analysis a 25% reduction in the risk of death with abiraterone was observed (HR: 0.75, 95% CI: 0.61–0.93; $p = 0.01$). There was a clear benefit in radiological progression free survival (PFS) favoring abiraterone (16.5 months vs. 8.3 months, HR: 0.53, 95% CI: 0.45–0.62; $p < 0.001$). After a median follow up of 49.4 months, the benefit in OS with abiraterone was statistically significant (34.7 months vs. 30.3 months, HR: 0.81, 95% CI: 0.70–0.93; $p = 0.0033$) [19].

3.2. Abiraterone in mCSPC

AA was evaluated earlier in mCSPC. Latitude is a Phase III trial of abiraterone prednisone + ADT versus placebo + ADT in newly diagnosed and high-risk mCSPC [20]. Patients were considered high-risk if they met at least two of the following requirements: Gleason score of at least 8, presence of at least three lesions on a bone scan, or presence of measurable visceral metastasis. The trial had accrued 1199 patients with a median follow-up of 30.4 months. The abiraterone prednisone + ADT arm showed a 38% reduction in risk of death when compared to the control arm (OS: not reached vs. 34.7 months, HR: 0.62, 95% CI: 0.51–0.76; $p < 0.0001$). Overall survival benefit persisted across all of the pre-specified subgroups (ECOG status and visceral disease). Radiographic progression-free survival, the co-primary endpoint, was significantly improved with the addition of abiraterone (median 33.0 months vs. 14.8 months, HR: 0.47, 95% CI: 0.39–0.55). Significantly better outcomes in all secondary end points were observed in the abiraterone group, including the time until pain progression, next subsequent therapy for PCa, initiation of chemotherapy, and prostate-specific antigen (PSA) progression ($p < 0.001$ for all comparisons), along with next symptomatic skeletal events ($p = 0.009$).

The STAMPEDE phase III trial was conducted in patients with locally advanced or metastatic PCa (mPCa) [21]. A total of 1917 patients were randomized between abiraterone plus prednisone plus standard of care (SOC) versus SOC alone. The median follow-up was 40 months, and there was a 37% relative improvement in overall survival (HR: 0.63, 95% CI: 0.52−0.76) favoring SOC + AA + prednisone. The HR was 0.75 in patients with non-metastatic disease and 0.61 in those with metastatic disease. There was a 55% reduction in skeletal related events (HR: 0.45, 95% CI: 0.36−0.58). The failure free survival was the main secondary end point with a 71% improvement in time to failure for the abiraterone arm as compared with the SOC arm (HR: 0.29, 95% CI: 0.25−0.34; $p < 0.001$); the HR was 0.21 in patients with non-metastatic disease and 0.31 in those with metastatic disease.

4. Enzalutamide

Enzalutamide targets the AR and blocks the intracellular effects of androgens, preventing nuclear translocation, DNA binding and transcription without AR agonistic effects.

The AFFIRM study is a phase III randomized, double-blind, placebo-controlled, multicenter trial assessing the efficacy and safety of enzalutamide in patients with mCRPC who had previously received docetaxel [22]. A total of 1199 male patients were included in the study and were randomized (2:1), to receive 160 mg enzalutamide orally once daily or placebo. The primary end point was overall survival. Enzalutamide provided a median 4.8-month improvement in overall survival (18.4 months *vs.* 13.6 months, HR: 0.63, 95% CI: 0.53−0.75; $p < 0.001$), with a 37% reduction in risk of death. Enzalutamide was better than placebo for secondary endpoints including PSA reduction by 50% or more (54% *vs.* 2%, $p < 0.001$), the soft-tissue response (29% *vs.* 4%, $p < 0.001$), the quality-of-life response (43% *vs.* 18%, $p < 0.001$), the time to PSA progression (8.3 months *vs.* 3.0 months, HR: 0.25; $p < 0.001$), radiographic PFS (8.3 months *vs.* 2.9 months, HR: 0.40; $p < 0.001$), and the time to the first skeletal-related event (16.7 months *vs.* 13.3 months, HR: 0.69; $p < 0.001$). Most frequent adverse events reported included, fatigue, diarrhea, hot flushes, musculoskeletal pain, headaches, and 0.96% were reported to have a seizure.

The Prevail Study is a double-blind phase III study where 1717 patients with chemotherapy naïve mCRPC were randomly assigned to receive either enzalutamide (at a dose of 160 mg) or placebo once daily [23]. Enzalutamide treatment provided 29% reduction in the risk of death (HR: 0.71, 95% CI: 0.60−0.84; $p < 0.001$). The radiological PFS at 12 months was better in the enzalutamide treated patients (65% *vs.* 14%, HR: 0.19, 95% CI: 0.15−0.23) and time to initiation of chemotherapy and time until the first skeletal-related event were significantly delayed in the enzalutamide arm.

5. Cabazitaxel

Cabazitaxel, is a semi-synthetic member of the taxane family and was developed as a derivative of docetaxel. The TROPIC phase III trial randomized men with mCRPC and

prior exposure to a docetaxel-containing regimen to receive cabazitaxel (25 mg/m^2 every 3 weeks) or mitoxantrone (12 mg/m^2 every 3 weeks), with both groups receiving prednisone [24]. Cabazitaxel significantly improved the overall survival by 2.4 months (median OS: 15.1 months *vs.* 12.7 months, HR: 0.70, 95% CI: 0.59−0.83; $p < 0.0001$), which was the primary endpoint of the study. The most common adverse events with cabazitaxel were neutropenia (82% *vs.* 58%) and febrile neutropenia (8% *vs.* 1%) and diarrhea (grade 3: 6% *vs.* <1%).

FIRSTANA was a phase III randomizing 1168 patients with chemotherapy-naïve mCRPC to three treatment arms: Cabazitaxel 20 mg/m^2 (C20), cabazitaxel 25 mg/m^2 (C25), or docetaxel 75 mg/m^2 (D75) every 3 week [25]. The results showed that cabazitaxel was not superior to docetaxel for overall survival (24.5 months for C20 [HR *vs.* docetaxel = 1.01; $p = 0.997$] *vs.* 25.2 months for C25 [HR *vs.* docetaxel = 0, $p = 0.757$] *vs.* 24.3 months for D75) which was the primary end point. However, cabazitaxel given at 25 mg/m^2 yielded a significant improvement in radiological tumor response compared to docetaxel (41.6% *vs.* 30.9%, $p = 0.037$). In the PROSELICA trial in patients progressing after docetaxel, 200 patients were randomized between cabazitaxel 20 mg/m^2 and 25 mg/m^2 [26]. The results demonstrated the non-inferiority for overall survival of 20 mg/m^2 *vs.* 25 mg/m^2 (median OS were 13.4 months and 14.5 months [HR: 1.024]), with better safety profile. Patients treated with C20 had fewer serious adverse events than patients treated with C25 (grade ≥3 adverse events, 39.7% *vs.* 54.5%, respectively).

5.1. Immunotherapy

Sipuleucel-T is an autologous dendritic cell vaccine. Peripheral blood mononuclear cells are obtained through leukapheresis and incubated with recombinant fusion protein with prostatic acid phosphatase and granulocyte macrophage colony-stimulating factor and are reinfused into patients as three intravenous infusions at two-week intervals. Asymptomatic or minimally symptomatic mCRPC without visceral metastasis and with good performance status, were randomized between Sipuleucel-T or placebo, given as three intravenous perfusion [27,28]. Sipuleucel-T demonstrated a 33% reduction in the risk of death (median survival of 23.2 months *vs.* 18.9 months, HR = 1.50, 95% CI: 1.10−2.05; $p = 0.011$) compared to the placebo arm. However no significant difference was observed for PFS between the two arms. The more frequent adverse events were chills, pyrexia, and myalgia and were mild to moderate. The results were confirmed in a phase II trial with 512 patients enrolled [29]. Sipuleucel-T arm demonstrated a 22% reduction in the risk of death (median survival 25.8 months, while the placebo arm had a median survival of 21.7 months, HR: 0.78, 95% CI: 0.61−0.98; $p = 0.03$) compared to the placebo arm.

5.2. Radium-223

Radium-223 dichloride is an alpha-emitting radioisotope which acts as calcium mimetic and is readily taken up at sites of bone metastases. The phase III ALSYMPCA trial

compared six cycles of radium-223 to placebo in 921 patients with CRPC and symptomatic bone metastases without lymph node and/or visceral metastases [30]. Radium-223 led to an increase in 5.1 months overall survival benefit versus placebo (14 months *vs.* 11.2 months, HR: 0.7; $p = 0.002$). In addition radium-223 is demonstrated improvement into palliating bone pain, in QoL, and prolonging time to skeletal-related events (SRE).

6. The future

Recent discoveries of germline mutations are driving the research of new therapeutics. Advances in genome analyzing techniques have provided profound insight into PCa biology and have identifier potential drug targets for PCa treatment [31]. A recent study of the genomic landscape of mCRPC has demonstrated that $\sim 90\%$ of PCas harbor genomic aberrations which may present a potential target of tailored drugs [32]. The AR, erythroblast transformation-specific (ETS) gene rearrangement, phosphoinositide 3-kinase (PI3K)—AKT signaling, and DNA repair defects are the most prevalent genetic aberrations in mCRPC. Due to high intra- and inter-patient heterogeneity at diagnosis and also during treatment in this disease, these advances will enable personalized treatments.

7. Conclusion

The treatment landscape for patients with mPCa is evolving, since the superiority of mitoxantrone plus prednisone over best supportive was shown in 1996 in terms of palliative response [33]. A growing number of treatment options with chemotherapy and new hormonal therapy improve survival. The challenge is how to use optimal sequencing. Better knowledge of the disease, the molecular alteration of the tumor and mechanisms of treatment resistance, could give more opportunities to select the most appropriate treatment. Improving our accuracy of our assessment with better prognostic and predictive factors will allow giving the best treatment to the right patients.

Conflicts of interest

The author declares no conflict of interest.

Acknowledgements

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