Review

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Changes in Metastatic Castration Sensitive Prostate Cancer

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Abstract

Prostate cancer is the second most common cancer in men worldwide, with approximately 1,276,106 new patients and 358,989 new deaths. Metastatic castration-sensitive prostate cancer may be *de novo* metastatic, but also it may be in the localized disease stage at the time of diagnosis, and may present as biochemical relapse and later metastatic disease over time. Purposes of metastatic castration-sensitive prostate cancer treatment are prolonging survival, improving quality of life and reducing complications. In this review, it is aimed to evaluate the current developments in metastatic castration-sensitive prostate cancer treatment.
Keywords: Prostate cancer, castration sensitive, treatment, chemotherapy

Introduction

Overview of Prostate Cancer

Prostate cancer (PC) is the second most common cancer in men worldwide, with nearly 1,276,106 new patients and 358,989 new deaths worldwide (1). PC is responsible for one out of every 5 cancers in men in the United States of America (USA), and is the second most common cause of cancer-related deaths (2). In the USA, according to the Surveillance, Epidemiology and End Results (SEER) database, an estimated 174,650 new patients (9.9% of all newly diagnosed cancers) and 31,620 deaths (5.2% of cancer related deaths) are expected in 2019. Again, according to the SEER database, 5-year survival in PC is 98%, the majority of patients are diagnosed at an early stage and the median age at diagnosis is 66, and the median age at death is 80. Incidence and mortality in PC decrease or stabilize in many parts of the world (3).

In our country, according to 2015 Turkey cancer statistics of the Cancer Agency Presidency, PC is the second most common cancer after lung cancer in men with frequency of 33.1/100,000 according to given standardized rate of 10 cancers by age while in the second frequency; while it is the second most common cancer with 13.2% among men between the ages of 50-69 (4).

Treatment of Metastatic Castration Sensitive Prostate Cancer

Metastatic castration sensitive PC (mCSPC) may be *de novo* metastatic, or may be in the localized disease stage at the time of diagnosis and may present as biochemical relapse and later as metastatic disease over time. The aim of mCSPC treatment is to prolong survival, improve quality of life and reduce complications. The properties of some agents used in mCSPC are summarized in Table 1.

Androgen Deprivation Therapy in mCSPC

PC is a hormone-dependent disease like breast cancer. Androgens are hormones that play a key role in the growth of cancer cells (5). Testosterone and dihydrotestosterone (DHT) are the two main androgens in men. Of testosterone 90-95% is synthesized from testis Leydig cells and 5-10% from the adrenal glands (6). Circulating testosterone is converted into the active form DHT in the cell by the 5-α reductase enzyme, and DHT acts on the androgen receptor (7).

Huggins and Hodges (8) showed that PC was an androgen sensitive disease and that the disease could regress by lowering the testosterone level by performing bilateral orchiectomy. Androgen deprivation therapy (ADT) is the standard treatment in mCSPC. ADT can be performed with surgical castration (bilateral orchiectomy) or it can be performed medically. In medical castration; gonadotropin releasing hormone (GnRH) agonists (e.g., leuprolide, goserelin, buserelin, triptorelin…) or GnRH antagonists (degarelix) can be used. Testosterone synthesis is suppressed through the hypothalamus-pituitary-gonad axis with medical castration (9). Although the majority of patients respond to ADT, resistance to castration develops in most of the patients within 1-3 years (10).

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Table 1. Properties of some agents used in metastatic CSPC				
	Docetaxel	**Abiraterone acetate**	**Enzalutamide**	**Apalutamide**
Route of administration	intravenous	oral	oral	oral
Dosage	75 mg/m^2	1000 mg/d	160 mg/d	240 mg/d
Need for prednisone	√	√		
Decrease in seizure threshold			√	
Liver toxicity		√	Lesser	
Risk of hypertension		√	√	√
Febrile neutropenia	√			
Neuropathy	√			
Rash				√
Treatment duration	6 cures	Until progression	Until progression	Until progression
CSPC: Castration sensitive prostate cancer				

Antiandrogens used in PC treatment are divided into two as steroidal and non-steroidal ones. Steroidal anti-androgens are synthetic derivatives of hydroxyprogesterone. In addition to blocking androgen receptors in the periphery, these agents have testosterone-lowering and progestational properties with pituitary inhibition. In addition to inhibiting gonadotropin release, they also suppress adrenal activity. They are not recommended for use as monotherapy. They are associated with lower overall survival (OS) rate than luteinizing hormone-releasing hormone (LHRH) analogues (11). Non-steroidal antiandrogens (e.g., bicalutamide, nilutamide, flutamide) are agents with better quality of life and compliance as they do not lower testosterone levels. Bone mineral density, physical performance and libido are protected with these agents. In a meta-analysis including 2717 patients with advanced stage PC, it was shown that non-steroidal antiandrogens were associated with lower OS rate compared to LHRH agonists (12). In a randomized study comparing steroidal and nonsteroidal anti-androgens, survival data of flutamide and cyproterone acetate were found to be similar (13).

Chemotherapy in mCSPC

The addition of cytotoxic chemotherapy (CT) to the standard treatment in mCSPC has resulted in improvements in survival and quality of life (14,15). In studies investigating the role of CT in mCSPC, it has been tried to find an answer to the question of whether there is a survival benefit.

In the CHAARTED study by Sweeney et al. (16), 790 patients with mCSPC were randomized one-on-one to either the ADT arm or ADT + docetaxel (75 mg/m^2 every 21 days, 6 cycles) arm. The primary endpoint of the study was OS. In the CHAARTED study, the presence of 4 or more bony lesions, at least one of which was extra-vertebrae or extrapelvic, or extranodal visceral metastasis was defined as a high-volume disease. The median OS was 57.6 vs 49.2 months when all patients were evaluated [95% confidence interval (CI)=0.47-0.80; p<0.001]. Median OS in patients with high volume disease was 49.2 and 32.2 months [hazard ratio (HR)=0.61, 95% CI=0.45-0.81; p<0.001] and there was no statistically significant difference between treatment arms in terms of median OS in patients with low-volume disease (p=0.11). Among grade 3-4 side effects; neutropenia was detected in 12.1%, febrile neutropenia in 6.1% and fatigue in 4.1% of the patients in the combination arm. As a result, adding docetaxel to ADT provided a statistically significant benefit in OS in high-volume disease (16).

In the open-label, randomized, phase 3 GETUG-AFU 15 study, 385 patients with a diagnosis of mCSPC were randomized one-on-one to either the ADT arm or ADT + docetaxel (75 mg/m^2 every 21 days, 9 cycles) arm. The primary endpoint of the study was OS, and the secondary endpoint was biochemical and radiological progression-free survival (PFS). The median follow-up period was 50 months. The median OS was 58.9 vs 54.2 months (95% CI=0.75-1.36) in the treatment groups. Three-year OS was 64.2% in the ADT arm and 62.9% in the combination arm. The most common grade 3-4 side effects in the combination arm were neutropenia, febrile neutropenia, and fatigue. Consequently, the OS benefit of adding docetaxel to standard therapy could not be demonstrated in this study (17).

In arm C of the multi-arm STAMPEDE trial, patients were randomized one-on-one to either standard therapy or standard therapy + docetaxel (6 cycles of 75 mg/m^2 every 21 days). The primary endpoint of the study was OS. The median follow-up period was 43 months. The median OS was 71 months in the standard treatment arm and 81 months in the combination arm (HR=0.78; 95% CI=0.66-0.93; p=0.006). Of the patients, 77% were able to complete 6 cycles of docetaxel treatment in the combination arm. Grade 3-5 side effects were observed in 32% of the standard treatment arm and 52% of the standard treatment + docetaxel arm. The most common grade 3-5 side effects in the combination arm were neutropenia and febrile neutropenia. Similar to the CHAARTED study, in this study, the survival benefit of adding docetaxel to ADT was shown (18).

A meta-analysis of 5 studies investigating the benefit of adding docetaxel CT to standard treatment in patients with PC was published in Lancet Oncology in 2016. In this meta-analysis, the OS benefit of adding docetaxel to standard therapy was demonstrated (HR=0.77, 95% CI=0.68-0.87; p<0.0001). Absolute improvement in four-year survival was 9% (95% CI=5-14). Addition of docetaxel to standard treatment also provided a statistically significant benefit in disease-free survival (DFS) (HR=0.64; p<0.0001). Absolute improvement in four-year DFS

was 16% (95% CI=12-19) (19). Phase 3 ADT + CT studies in mCSPC are shown in Table 2.

mCSPC and Abirateron Acetate

Abiraterone acetate (AA) is an inhibitor of the cytochrome P-450c17 (CYP17) enzyme, which is a critical enzyme in extragonadal and testicular androgen synthesis. It inhibits both 17α-hydroxylase and C17-20-lyase by dual function. Testosterone precursors inhibit the formation of dehydroepiandrosterone and androstenedione (20). Various studies have been carried out to demonstrate the survival benefit, efficacy, and side effects of AA in mCSPC (21,22).

In the double-blind, phase 3, placebo-controlled LATTITUDE study, 1199 patients were randomized one-on-one to either the ADT + AA + prednisolone arm or ADT + placebo arm. The primary endpoint of the study was OS and radiological PFS. Patients with mCSPC who were aged 18 years or older, had an ECOG performance score of 0-2, and had 2 of 3 high risk factors (Gleason's score ≥8, ≥3 bone metastasis, visceral metastasis) were included in the study. While OS endpoint could not be reached in the combination arm, it was 34.7 months (HR=0.62; 95% CI=0.51-0.76; p<0.001) in the ADT arm. Radiological PFS was 33 months in the combination arm and 14.7 months in the ADT arm (HR=0.47; 95% CI=0.39-0.55; p<0.001). All secondary endpoints were statistically significant in favor of the combination arm. Grade 3 or above side effects including hypertension, hypokalemia, increase in alanine aminotransferase and aspartate aminotransferase, and hyperglycemia were more in the AA arm. With this study, the addition of AA + prednisolone to the standard treatment ADT statistically prolonged OS and radiological PFS in patients with a diagnosis of mCSPC (21).

In the multi-arm STAMPEDE study, 1917 patients were randomized individually to either the ADT or ADT + AA + prednisolone arm. The primary endpoint of the study was OS. The median age at diagnosis was 67, the median PSA level was 53 ng/mL, and 52% of the patients were metastatic. The median follow-up period was 40 months. The three-year OS was 76% vs 83% and was in favor of the combination arm (HR=0.63; 95% CI=0.52-0.76; p<0.001). Three-year event-free survival was 75% vs 45% in favor of the AA arm (HR=0.29; 95% CI=0.25-0.34; p<0.001). Grade 3-5 side effects were observed in 47% of the combination arm and 33% of the monotherapy arm. Hypertension, cardiovascular and hepatic disorders were more common in the combination arm. Symptomatic skeletal related events were less common in the combination arm (HR=0.46; 95% CI=0.37-0.58; p<0.001) (22).

There are no studies directly comparing AA with docetaxel, but in a meta-analysis of seven studies, AA + ADT provided a 19% reduction in the risk of death compared to docetaxel + ADT (HR=0.81; 95% CI=0.66-1.00) (23). In the multi-armed, multi-center STAMPEDE study, 189 (14%) of 1348 patients received docetaxel + ADT and 377 (28%) received AA + ADT. In the indirect comparison of docetaxel + ADT and AA + ADT in the STAMPEDE study; median age was 66, median PSA was 56 ng/mL. HR was 1.16 (95% CI 0.82-1.65) for OS; HR was 0.51 (95% CI 0.39-0.67) for event free survival; and HR was 0.65 (95% CI=0.48-0.88) for PFS (24).

mCSPC and Enzalutamide

Enzalutamide, a new generation androgen receptor blocker, blocks the DHT receptor both on the target cell surface and on the nucleus, thanks to its high receptor affinity. It is an orally used agent that has been shown to be effective in patients who have developed resistance to first generation non-steroidal antiandrogens such as bicalutamide, nilutamide, and flutamide (25).

In the double-blind, phase 3 ARCHES study in which the benefit of enzalutamide on survival was investigated, 1150 patients with a diagnosis of mCSPC were randomized either to the enzalutamide + ADT arm or placebo + ADT arm. The primary endpoint of the study was radiological PFS. The risk of radiological progression and death was statistically significantly lower in the enzalutamide + ADT arm (HR=0.39; 95% CI=0.30-0.50; p<0.001). Enzalutamide + ADT therapy reduced the risk of PSA progression, initiation of new antineoplastic therapy, skeletal related events, and CSPC and pain progression. The frequency of grade 3 or above side effects was 24.3% in the enzalutamide + ADT arm and 25.6% in the placebo + ADT arm (26).

In another open-label, phase 3, randomized ENZAMET study in which the survival benefit of enzalutamide was investigated, 1125 patients with mCSPC were randomized either to the ADT + standard non-steroidal antiandrogen (bicalutamide, nilutamide, flutamide) arm or ADT + enzalutamide arm. The primary endpoint of the study was OS. The median follow-up duration was 34 months. There were 102 deaths in the enzalutamide arm and 143 deaths in the standard non-steroidal antiandrogen arm (HR=0.67; 95% CI=0.52-0.86; p=0.002). Three-year OS rate was 80% vs 72%, which was in favor of the enzalutamide arm. Three-year PFS rate was 67% vs 37%, which was in favor of the enzalutamide arm (HR=0.39; 95% CI=0.33-0.47; p<0.001). Treatment discontinuation due to side effects was more in the enzalutamide arm. Seizures were seen in 7 (1%) patients in the enzalutamide arm. In that study, the addition of enzalutamide provided a statistically significant advantage in terms of OS and PFS in patients with a diagnosis of mCSPC (27).

Table 2. Phase 3 ADT + CT trials in mCSPC

Trial name	Number of patients	CT regimen	Primary end point	OS duration	HR (95% CI)
CHAARTED	790	Docetaxel 75 mg/m^2, 6 cures	OS	Median 57.6 vs 44 months	0.61 (0.47-0.80)
GETUG-AFU 15	385	Docetaxel 75 mg/m^2, 9 cures	OS	Median 58.9 vs 54.2 months	1.01 (0.75-1.36)
STAMPEDE- C arm	1776	Docetaxel 75 mg/m^2, 6 cures	OS	Median 81 vs 71 months	0.78 (0.66-0.93)

ADT: Androgen deprivation therapy, CT: Chemotherapy, mCSPC: Metastatic castration sensitive prostate cancer, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval

In a study comparing enzalutamide with AA + prednisone indirectly, in the predosetaxel and postdosetaxel periods, better results were obtained with enzalutamide in terms of radiological PFS, PSA response rate and time until PSA progression; while there was no difference between the two agents in terms of OS (28).

mCSPC and Apalutamide

Apalutamide is a non-steroidal antiandrogen agent used in the treatment of PC. Apalutamide binds directly to the ligand binding portion of the androgen receptor and prevents androgen receptor translocation, DNA binding, and androgen receptor-mediated transcription (29).

In the phase 3, randomized, double-blind, placebo-controlled TITAN trial, 1052 patients with mCSPK were randomized one-on-one either to ADT + apalutamide arm or ADT + placebo arm. Apalutamid was given orally with a dose of 240 mg/day. The primary endpoints were radiologic PFS and OS. Demographic and clinical characteristics of the patients were well balanced. The median age in both groups was 68. Of the patients, 10.7% previously received docetaxel treatment; 62.7% had high-volume disease, and 37.3% had low-volume disease. One of the primary endpoints, the radiologic PFS at 24 months, was 68.2% in the apalutamide arm and 47.5% in the placebo arm (HR=0.48; 95% CI=0.39-0.60; p<0.001). The first interim analysis for OS was performed after 200 deaths were observed (83 in the apalutamide group and 117 in the placebo group). Another primary endpoint, OS at 24 months, was 82.4% in the apalutamide arm versus 73.5% in the placebo arm (HR=0.67; 95% CI=0.51-0.89; p=0.005). The risk of death in the apalutamide arm was lower by 33%. The frequency of grade 3-4 side effects was 42.2% in the apalutamide arm compared to 40.8% in the placebo group, and rash was more common in the apalutamide arm. Forty two patients (8.0%) in the apalutamide arm and 28 patients (5.3%) in the placebo arm could not continue treatment because of adverse effects. As a result, adding apalutamide to ADT significantly prolonged OS and radiologic PFS in patients with a diagnosis of mCSPC, and no significant difference was found between the two arms in terms of side effect profile (30). Phase 3 studies of hormonal treatment agents used in mCSPC are shown in Table 3.

Should Zolendronic Acid be Used in the mCSPC?

Bisphosphonates, which are synthetic pyrophosphate analogues, accumulate in bone binding to hydroxyapatite crystals and suppress the function of osteoclasts (31). Zolendronic acid, a powerful third generation bisphosphonate, has been shown to reduce the incidence of skeletal related events in patients with a diagnosis of mCSPC (32).

In the multi-arm STAMPEDE study, the contribution of adding zolendronic acid to standard therapy was investigated. Patients were randomized either to the standard therapy arm or standard therapy + zolendronic acid arm. The median OS was 71 months in the standard treatment arm and was not achieved in the standard therapy + zolendronic acid arm (HR=0.94, 95% CI=0.79-1.11; p=0.450). There was also no statistical difference in terms of event-free survivals. In this study, the skeletal related event, OS and event-free survival benefits of adding zolendronic acid to standard therapy could not be demonstrated. In a meta-analysis published in Lancet Oncology, the benefit of skeletal related events and OS [95% CI=0.94 (0.83-1.07); p=0.323] of zolendronic acid in mCSPC could not be demonstrated (19).

The Role of Local Treatment in Metastatic Disease

Radical prostatectomy (RP) or radiotherapy (RT) are the standard treatment options in PC with a life expectancy of ≥10 years and organ limited PC (33). ADT + RT is widely used in locally advanced disease. The effect of local treatment to the prostate on survival in patients with metastatic PC has been searched for a long time.

In the multi-center HORRAD study; 432 patients with PC with primary bone metastasis and PSA >20 ng/mL were randomized one-on-one to either the standard ADT arm or ADT + RT arm. In the RT arm, a total of 70 Gy RT was given in 35 fractions within 3 months after ADT. Primary endpoint was OS. The secondary endpoint was time to PSA progression. The median OS was 45 months in the ADT + RT arm and 43 months in the ADT arm (HR=0.90; 95% CI=0.70-1.14; p=0.4), and there was no statistically significant difference. The time to median PSA progression was 15 months in the RT arm and 12 months in the ADT arm (HR=0.78; 95% CI=0.63-0.97; p=0.02), and a statistically significant difference was found (34).

In the phase 3 STAMPEDE study in which 2061 patients with newly diagnosed metastatic PC were included, patients were randomized individually to either the ADT arm or ADT + RT arm. Primary endpoint was OS. Of the patients, 40% had low-volume disease and 54% had high-volume disease. Three-year OS was 62% in the ADT arm and 65% in the RT arm (HR=0.92;

Table 3. Phase 3 trials of hormonal treatment agents used in mCSPC

Trial ame	Number of patients	Agent used	Primary end point	Duration for radiological PFS	OS duration	HR of OS (95% CI)
LATTITUDE	1199	abiraterone acetate	OS Radiological PFS	33 vs 14.8 months	While the median value could not be reached in the AA arm, the median value was 34.7 months in the control arm.	0.62 (0.51-0.76)
STAMPEDE	1917	abiraterone acetate	OS		OS at 36th month %83 vs %76	0.63 (0.52-0.76)
ENZAMET	1125	enzalutamide	OS		OS at 36th month 80% vs 72%	0.67 (0.52-0.86)
TITAN	1052	apalutamide	OS Radiological PFS	At 24th month 68.2% vs 47.5%	OS at 24th month 68.2% vs 47.5%	0.67 (0.51-0.89)

mCSPC: Metastatic castration sensitive prostate cancer, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, PFS: Progression-free survival, AA: Abiraterone acetate

95% CI=0.80-1.06; p=0.266). The 3-year event-free survival was 23% in the ADT arm and 32% in the RT arm (HR=0.76; 95% CI=0.68-0.84; p<0.0001). When subgroup analyzes were evaluated, it was shown that adding RT to ADT in low-volume disease significantly prolonged OS (HR=0.68; 95% CI=0.52-0.90; p=0.0098) (35). Phase 3 prostate RT studies in metastatic PC are shown in Table 4.

Table 4. Phase 3 prostate RT trials in metastatic PC

Trial name	Number of patients	Primary end point	OS duration	HR (95% CI)
HORRAD	432	OS	45 vs 43 months	0.90 (0.70-1.14)
STAMPEDE	2061	OS	65% vs 62% for 36 months	0.76 (0.68-0.84)

PC: Prostate cancer, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, RT: Radiotherapy

In a meta-analysis evaluating the results of 3 studies investigating the effect of RT to the prostate on survival in patients with mCSPC, there was no statistically significant difference in terms of OS (HR=0.92; 95% CI=0.81-1.04, p=0.195) and PFS (HR=0.94; 95% CI=0.84-1.05, p=0.238), while there was improvement in terms of biochemical progression (HR=0.74; 95% CI=0.67-0.82) and in event-free survival (HR=0.76, 95% CI=0.69-0.84) in RT arm (36).

The role of local treatment for primary tumor in patients with metatastic PC was investigated in a reprospective study by Culp et al. (37). In the study, data of 8185 patients were scanned. Of those, 7811 patients did not receive local treatment, 245 patients received RP and 129 patients received brachytherapy. Five-year OS was 67.4% in the RP arm and 52.6% in the non-treated arm (p<0.001). In another retrospective study conducted by Gratzke et al. (38), while 1464 of 1538 patients with metastatic PC did not receive local treatment, 245 patients received RP. Five-year OS was 55% in the RP arm and 21% in the non-locally treated arm (p<0.01).

Cost

Various therapeutic agents can be used in the treatment of mCSPC and there is a financial toxicity brought by these agents. The cost of docetaxel CT for 6 cures is approximately 6000 Turkish Liras (TL), but the treatment of conditions such as febrile neutropenia that may arise due to CT-related toxicities may increase this cost. Monthly costs of new generation antiandrogen treatments range between 6,000 and 10,000 TL.

Conclusion

The treatment of PC has been changing rapidly in recent years. Many therapeutic agents are started to be used in the early period of the disease, and the survival results of our patients are happily improving. Since the introduction of docetaxel in 2004, many agents in the groups of CT, new hormonal therapies, immunotherapy and radionuclides have been approved in various stages of PC and have entered clinical use. However, there are no head-to-head randomized controlled trials with these agents. For this reason, many features such as patient characteristics, efficacy, accessibility to treatment, experience, toxicity, drug-drug interactions, expected side effects and cost should be evaluated together in treatment selection.

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Ethics

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