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Proceeding Article

Drug Protocols on Prostate Cancer Clinic Studies

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Abstract

In this review article, used drug protocols on prostate cancer clinical studies. The review cover the possible treatment options include surgery, radiotherapy (RT), hormonal therapy, chemotherapy (CT), immunotherapy or a combination of these depending on the stage of the disease or the medical condition of the patient in prostate cancer cases.

Keywords: Prostate cancer, PCA, drug, protocol, case, anti carcinogen

Introduction

Of 175,000 new cases of prostate cancer (PCa) diagnosed in the United States (USA) in 2019, 6% presented with metastatic disease, and every year, despite the growing number of treatments, more metastases cases emerge. It is estimated that the global PCa-related mortality will be 385.560 in 2020 (1). The single PCR incidence study reported from Turkey was conducted in Izmir. In that study, PCa was determined as the fifth most common cancer with an incidence of 13.8 per 100000 based on the data from 1998 to 2002 (2).

In PCa, treatment options include surgery, radiotherapy (RT), hormonal therapy, chemotherapy (CT), immunotherapy or a combination of these depending on the stage of the disease or the medical condition of the patient.

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Anticarcinogenic Medical Agent Groups

Luteinizing hormone-releasing hormone (LHRH) agonists *(leuprolide, goserelin, buserelin,* and*triptorelin)* exhibit their effect by down-regulating LHRH receptors, thereby reducing follicle stimulating hormone (FSH), luteinizing hormone (LH) release and testosterone (T) production (Schally et al.,1971).

LHRH agonists have become a standard in the hormonal treatment of PCa due to their recyclability, compliance with intermittent androgen deprivation therapy (ADT), and causing no physical or mental problems related to orchiectomy, as well as their efficacy in oncological treatment (Mc Leod et al.,2003; Seidenfeld et al.,2000).

LHRH antagonists *(degarelix, abarelix, cetrorelix)*, competitively bind to LHRH receptors in the pituitary, resulting in a rapid decrease without causing an increase in LH, FSH and T levels (Debruyne et al.,2006; Klotz et al., 2008; Tombal et al., 2010).

However, despite their low cost, clinical trials with a large series are needed before they can be routinely used.

Antiandrogens: Male sex hormones in steroid structure consisting of T and dihydrotestosterone (DHT) are from the testicle at 90-95% and adrenal gland at 5-10%. Ninety-five percent of T, which enters the prostate cell, turns into DHT through the enzyme 5α-reductase. Antiandrogens compete with T and DHT in the binding sites of receptors in the prostate cell nucleus. Thus, while stimulating apoptosis, they also inhibit the growth and development of cancer cells. According to their chemical structure, antiandrogens are divided into two groups as steroidal and non-steroidal (Kokontis et al.,1999).

Steroidal antiandrogens are synthetic derivatives of hydroxyprogesterone (*cyproterone acetate, megestrol acetate, medroxyprogesterone acetate*). In addition to blocking androgen receptors (AR) in the periphery, they exhibit central effects, reducing the levels of LH, and thus lowering T. They also suppress adrenal activity by inhibiting gonadotropin release. They are not recommended for use in monotherapy (Moffat et al.,1990).

Since they lower the T level, their main side effects include loss of libido, erectile dysfunction, cardiovascular toxicity, hepatotoxicity, and gynecomastia.

Non-steroidal antiandrogens *(flutamide, nilutamide, bicalutamide, apalutamide, enzalutamide, daralutamide)* show their effects by blocking T receptors and do not reduce the T level; therefore, they preserve libido, physical performance, and bone mineral intensity, thus providinga better quality of life than after castration. Common side effects of these agents include gynecomastia, chest pain, hot flashes, and hepatotoxicity (McLeod et al.,1997; Dalaere et al.,1991).

Suppressants of adrenal androgens *(ketoconazole, aminoglutethimide, glucocorticoids)*: The serum T level decreases by about 90% after medical or surgical castration. Until the 1970s, bilateral adrenalectomy was implemented to suppress adrenal androgens today the same effect is achieved with drugs (Lam et al.,2006).

Ketoconazole, an antifungal, reduces androgen biosynthesis by P450 demethylase inhibition (De Coster et al.,1996).

Aminoglutethimide blocks adrenal steroid synthesis by inhibiting both enzymes involved in corticosteroid synthesis and aromatase enzyme (Shaw et al.,1988).

Glucocorticoids suppress adrenal androgens by providing negative feedback to the pituitary and hypothalamus in the central nervous system(Lam et al.,2006).

Estrogens are effective through the basic mechanisms of reducing LHRH and LH release by negative feedback, suppressing T production by direct testicular and adrenal effects, and direct cytotoxic effects on PCa cells (13). The most used estrogen is *diethylstilbestrol* (DES); however, its use is limited due to serious cardiovascular side effects.estrogenic preparations, such as *PC-SPES*, *Premarin*, and *transdermal estradiol* or estrogen receptor inhibitors, such as *tamoxifen* and *raloxifene* can also be used in PCa (Lam et al.,2006; Zhang et al.,2015; Salata et al.,2019).

Chemotherapeutics have been investigated by the National Prostate Cancer Project (NPCP) in several randomized studies as single agents or in combination in PCa patient groups and were first called 'hormone-resistant', then referred to as 'castrate-resistant' (CRPCA). Agents, such as *cyclophosphamide*, *cisplatin*, *carboplatin*, *satraplatin*, *5-fluorouracil* (5-FU), *doxorubicin*, *vinblastine*, *etoposide*, *methotrexate*, *estramustine*, *docetaxel*, and *mitoxantrone* have been tested, with some earning their place in routine treatment (Naderet al.,2018).

Immunologicagents (e.g., *Spilucel-T*, *Prostvac, Gvax, ipilimumab, tremelimumab, nivolumab*, *cabozantinib, pembrolizumab, lambrolizumab, avelumab*, *atezolizumab*, *durvalumab)* and therapeutic anti-cancer vaccines, including those that are dendritic cell-based, whole cell-based, and vector-based are the main immunotherapeutic strategies used in the treatment of PCa (Harris et al.,2018).

TREATMENTS IN LOCALIZED PROSTATE CANCER

In the American Association of Urology (AUA) guidelines, clinicians are advised not to administer neoadjuvant systemic therapy other than neoadjuvant ADT or clinical trials if the localized PCa case has chosen to undergo radical prostatectomy (RP) (Sanda et al.,2018).

Localized high-risk or local advanced stage PCa: Of newly diagnosed PCa cases, 17–31% present with localized high risk or locally advanced disease, for which curative treatment is required (Cooperberg et al.,2008).

If these cases are not treated, 10 and 15 year PCa-specific mortality rates can reach 28.8% and 35.5%, respectively (Rider et al.,2013).

Combined local or systemic applications are used in treatment modalities. ADT alone should not be considered as a viable treatment option in high-risk and locally advanced PCa. Currently, the European Association of Urology (EAU) PCa guidelines recommend a multimodal approach in pelvic lymph node dissection and RP, and possibly adjuvant RT ± ADT after surgery or 76-78 Gy external beam RT (EBRT) or long-term ADT combined with brachytherapy (BT) and EBRT in patients with a life expectancy of more than 10 years (Mottet et al.,2019).

Evidence pertaining to treatment methods is still lacking, and patients are treated on the basis of clinical experience rather than receiving evidence-based treatment.

Treatments in addition to radical prostatectomy: Studies reveal that post-RP early ADT is more beneficial than delayed ADT. In some studies comparing RP and RT, there was no statistical difference in terms of distant metastasis-free survival between RP and EBRT + ADT, whereas the superiority of RP was reported in relation to overall mortality, PCa-specific mortality, overall survival (OS), and cancer-specific survival (CSS) data (Boorjian et al.,2011; Yamamoto et al., 2014).

When the results of literature studies are examined, it is seen that early EBRT after RP provides improvement in biochemical and clinical disease-free survival in addition to OS in patients with locally advanced PCa. In a study comparing RP without any

additional treatment with MaxRT (EBRT + BT + ADT), the former resulted in higher PCa-specific mortality and overall mortality rates, but no difference was observed in the results when compared to RP + adjuvant RT and/or maxRP (RP + RT + ADT) (Tilki et al.,2018).

In a study applying adjuvant bicalutamide after RP, OS or CSS advantage was not shown after an average of follow-up of 11.2 years (Iversen et al.,2010).

In another study, after 10 years of follow-up with neoadjuvant ADT, both biochemical disease-free survival and positive contributions to OS were reported (Fujita et al.,2017).

In another study, neoadjuvant LHRH analog was compared with pre-RP CT (estramustin, oral etoposide, and paclitaxel) and its positive contributions to overall mortality and biochemical disease-free survival were noted (Ferris et al.,2018).

CT applications before RP: Recently, there has been a growing interest in neoadjuvant therapy in order to eliminate micrometastases and improve surgical outcomes in a variety of cancers. However, there are only limited data due to the absence of mature Phase III studies evaluating the role of neoadjuvant CT in PCa and the use of different CT agents and a limited number of patients in Phase II studies. The use of neoadjuvant CT before RP is still under investigation and is currently not a standard part of treatment in patients with PCa.

CT after RP: In the GETUG 12 trial, stage T3-T4 disease, Gleason score ≥8, PSA level >20 ng/ml or lymph node dissection positive disease were accepted as high-risk features. The 8-year disease-free survival was 50% in the ADT arm, and they showed that the ADT + docetaxel and estramustin combination arm was superior with 62% (Fizazi et al.,2015).

In a study conducted by the Scandinavian Prostate Cancer Group (SPCG) overa mean follow-up of 56.8 months, the biochemical progression rate was 44.8% in the study arm containing docetaxel and 38.9% in the surveillance arm, and the authors concluded that there was no benefit or potential harm of adding docetaxel to the treatment of high-risk PCa patients after RP (Ahlgren et al., 2016).

Combined hormone-radiotherapy: Many controlled randomized trials have shown that combined ADT + EBRT therapy has a survival advantage over the use of these treatment options alone. In studies comparing EBRT alone with EBRT + ADT, the positive results of combined therapy have also been reported (29,34,35). In the comparison of the groups formed by the addition of EBRT + ADT and docetaxel, it was determined that although the docetaxel group provided superior results in terms of OS, the rate of toxicity associated with CT and mortality associated with treatment were significantly higher (Rosenthal et al., 2015;Carles et al.,2019).

CT after radiotherapy: One of the most promising studies evaluating CT after RT is the phase III study conducted by Sandler et al., who randomized 563 high-risk PCa patients to ADT+RT or ADT+RT, followed by docetaxel and prednisone treatments, respectively. The four-year OS increased from 93% in the ADT + RT arm to 93% with the addition of docetaxel. Furthermore, there was a 10% increase in the six-year disease-free survival rate in the docetaxel group. In light of these results, adjuvant docetaxel in addition to RT for the treatment of PCa cases with high-risk disease was included in the treatment proposal of appropriately selected patients in the National Comprehensive Cancer Network (NCCN) guidelines (Sandler et al.,2015).

TREATMENTS IN METASTATIC PROSTATE CANCER

LHRH agonists and antagonists: In studies comparing an LHRH agonist *leuprolide acetate* and an LHRH antagonist *degarelix*, the latter was found to reduce T similar to but faster than the former and without exacerbation. Furthermore, using degarelix, PSA progression and PCa-specific death were less common in advanced-stage patients (Klotz et al., 2008; Tombal et al., 2010).

However, the use of this agent is limited due to the serious and life-threatening side effects mediated by histamine in 5% of cases during treatment. Another LHRH antagonist, *abarelix*, has not been widely adopted due to rapid onset allergic reactions caused by histamine release (Debruyne et al.,2006).

Antiandrogen monotherapy: Compared with goserelin, the use of *steroidal antiandrogens* alone has poorer survival data. Among *non-steroidal antiandrogens*, *nilutamide* and *flutamide* applied as monotherapy have contradictory results. *Bicalutamide* monotherapy can be the treatment option for locally advanced or carefully selected patients with low PSA (Tyrrell et al.,1998 a,b).

In a study comparing flutamide and orchiectomy, no difference was found between the two groups in terms of survival; however, side effects were more common in the flutamide group (Boccon et al.,1997).

In another study comparing flutamide and DES, the authors reported the time to progression similar in both groups but OS time was shorter in the former (Chang et al.,1996).

In another study by Schröder et al. comparing *flutamide* and *cyproterone acetate*, the results of the groups were similar in terms of OS and progression-free period, while side effects were more common in the flutamide group (Schröder et al.,2004).

In a meta-analysis conducted with advanced stage PCa patients, non-steroidal antiandrogens were reported to be associated with lower OS compared to LHRH agonists (Seidenfeld et al.,2000).

Similarly, in a study conducted with 1,453 locally advanced and metastatic PCa patients, 150 mg/day bicalutamide was compared with surgical or medical castration, and it was determined that bicalutamide was not as effective as castration in terms of OS results. However, quality of life parameters were found to be better in the bicalutamide group, but gynecomastia and breast sensitivity were also higher among these patients (Tyrrell et al.,1998 b).

In the only randomized study comparing steroidal and non-steroidal antiandrogens as monotherapy, *cyproterone acetate* and *flutamide* were found to be equally effective in CSS and OS over an 8.5-year follow-up (Schröder et al.,2004).

Estrogens: DES, a synthetic estrogen, affects LHRH or the pituitary gland and suppresses the release of LH, thereby lowering the T level. However, the interest in this drug diminished beginning with the publication of the Veterans Administration Cooperative Urological Research Group (VACURG) study, which showed an increased risk of cardiovascular death after DES treatment at a 5.0 mg dose (Bailar et al.,1970).

In terms of efficacy, many studies comparing DES with primary hormonal therapy in patients with metastatic PCa compared with other ADTs did not detect any difference in patient survival. However, most studies have shown that DES is associated with severe cardiovascular toxicity requiring discontinuation of therapy, especially at 3.0 and 5.0 mg/day doses. These results suggest that DES should no longer be used at doses higher

than 1 mg per day. Recent clinical data also strongly suggest that parenteral administration of estrogen can overcome the thromboembolic cascade of events related to oral administration(Reis et al.,2018).

Maximal androgen blockage (MAB): The goal of this treatment is the suppression of not only androgens originating from the testicles, but also adrenal androgens. In addition to castration (surgical/LHRH agonist), both biochemical and clinical improvements are achieved in more than 90% of cases with the use of antiandrogen. In a study by Labrie et al., 97% positive objective response was achieved with *buserelin* and *nilutamide* therapy over an average of 4.2-month follow-up. The authors suggested that with MAB, only 25-30% more responses would be obtained against testicular androgen blockade (Labrie et al.,1983).
Crawford et al. compared *leuprolide* + placebo with *leuprolide* + *flutamide* treatments, and after four years of follow-up, they determined the time to progression as 13.9 months versus 16.5 months and survival times as 22.3 months and 35.6 months, respectively, indicating statistically significant differences between the two groups (Schröder et al.,2004).

Denis et al., compared orchiectomy + placebo with *goserelin* + *flutamide* treatments, reporting that MAB was significantly more effective in terms of the duration of progression and survival (Denis et al.,1998).

In contrast, in other studies comparing *goserelin* + *placebo* with *goserelin* + *flutamide*, and comparing orchiectomy alone with *orchiectomy*+ *flutamide* treatments, the authors did not observe any significant difference between the groups (Fourcade et al.,1990; Eisenberger et al.,1998).

Intermittent androgen deprivation is a form of treatment in which tolerance and quality of life are better and costs are reduced through the discontinuation of treatment at times when serum androgens reach their normal levels (Abrahamsson et al.,2010).
When PSA is reduced by 80% from its basal value, the drug is interrupted, and the treatment is restarted when there is a 50% increase in PSA compared to the level at the time the drug is stopped. In a study by Leval et al., groups receiving continuous and intermittent treatments were compared. After a three-year follow-up, the progression rates were 7% in the intermittent treatment group and 39% in the continuous treatment group (De Leval et al.,2002).

Early or delayed treatment: The time to start hormonal therapy in patients with advanced PCa remains controversial. In studies comparing early and late treatments in advanced-stage patients, it was concluded that early treatment had better results in terms of complications related to progression and disease progression, but no improvement was observed in cancer-specific survival (Byar et al.,1973; Jordan et al.,1977).

There is no definite consensus on when to start hormonal treatment in asymptomatic advanced stage patient (Morgan et al.,2009).

Addition of CT to first-line treatment in metastatic disease: For metastatic hormone-sensitive PCa, the cornerstone of treatment targets the androgen tract, but most of these patients progress to CRPCA within one to two years. The mechanism of action of *docetaxe* has led to the idea that it may also be beneficial for hormone-sensitive PCa, which has opened the way for new research (Shenoy et al.,2016).

In a study conducted by the Genitourinary Group and the French Association of Urology (GETUG-AFU), the role of

docetaxel was evaluated in 385 men with metastatic hormone-sensitive PCa. The patients were randomized into groups to receive *ADT alone* or *docetaxel + ADT*. The result was that there was no difference between the groups in OS, and side effects were more common in the combined treatment group. The authors concluded that the study did not support the use of docetaxel in the first-line treatment of patients with metastatic hormone-sensitive PCa (Gravis et al.,2013).

In another larger study (the CHAARTED study with ECOG), docetaxel + ADT treatment in patients diagnosed with de-novo castration-sensitive prostate cancer prolongs the time to castration resistance and results in better cancer control, especially for the high-volume disease group (Sweeney et al.,2015).

To date, the STAMPEDE study the largest work to investigate the efficacy of various treatments, including *docetaxel* and *zoledronic acid* as pretreatment with hormonal therapy in men diagnosed newly diagnosed with PCa. Improvements in survival were achieved in patients receiving docetaxel with standard therapy. However, subgroup analyses showed that patients with non-metastatic disease did not benefit from this additional treatment. The authors concluded that standard care should include docetaxel treatment for those with disease metastatic, castrate-sensitive disease(James et al.,2016).

Cyclophosphamide is an alkylating agent that affects cell division by crosslinking deoxyribonucleic acid (DNA) strands, and thereby reducing DNA synthesis. In an NPCP study, full response was reported in none of the patients, and partial response was achieved only in 7%, with stable disease being observed in 26-46% of patients (Yagoda et al.,1993).

Later, although cyclophosphamide was reused with an interest in its role in angiogenesis inhibition via the metronomic cycle, this drug was mainly discussed in terms of its use in cases where docetaxel had failed (Ladoire et al.,2010).

Cisplatin inhibits DNA synthesis by crosslinking DNA strands. Studies have reported the partial remission rate as 12%, which indicates a moderate antitumor activity, and therefore cisplatin is still being investigated in terms of its effects as a single agent and in combination with other treatments (Yagoda et al.,1993).

Carboplatin has been studied as a single agent with minimal effects. However, when combined with other CT drugs, such as paclitaxel and estramustine, significant decreases in serum PSA levels were seen (Kelly et al.,2001).

Satraplatin, a fourth-generation platinum analog, has been found to be effective against cisplatin- and carboplatin-resistant cell lines. It has also been shown to be beneficial to relieve pain in patients with CRPCA, but no positive contribution to OS has been reported in Phase III trials (Figg et al., 2013; Sternberg et al.,2009).

5-fluorouracil, is a pyrimidine analog that suppresses DNA synthesis by inhibiting thymidylate synthetase. Studies have shown the modest antineoplastic activity of this agent. *Doxorubicin* intercalates between DNA base pairs and inhibits replication and transcription, disrupting the function of topoisomerase II. In an NPCP study, it was reported to have clinical benefits with a response rate reaching 84%, including stable disease (Eisenberger et al.,1985).

Subsequent studies using *vinblastine* and *etoposide* alternating with additional *ketoconazole* with doxorubicin did not show any additional benefit compared with hormonal therapy alone (68). In one of the studies comparing *doxorubicin* with *5-FU*, 25% clinical response was achieved with doxorubicin, while this rate remained at 8% in those treated with 5-FU alone (DeWys et al.,1983).

Methotrexate is a dihydrofolic acid reductase inhibitor that inhibits purine and thymidyl acid synthesis and serves to interfere with DNA synthesis. Studies have shown that it can provide stable disease at a rate of 20% (Murphy et al.,1988).

Etoposide replaces DNA replication, induces G2 phase stop, and kills cells in G2 and late synthesis phases. Studies have shown the overall response rate to bepoor at 3% (Trump et al.,1984).

Vinblastine is a vinca alkaloid that prevents microtubule formation. The few available studies have shown a 21% remission rate(Eisenberger et al.,1988).

Estramustine is an estradiol with antiandrogen and antimicrotubule effects and a combination of nor-nitrogen mustard carbamate. It has been extensively studied by NPCP and reported to have an effect on CRPCA patients, but an objective response has been rarely seen in studies. Similarly, when estramustine was examined in combination with *prednimustin*, *vincristine* and *cisplatin*, no noteworthy additional benefit was shown (Eisenberger et al.,1988).

While subsequent studies combining estramustine with *docetaxe* provided promising results, it was noted that the efficacy of treatment was higher due to docetaxel, and the use of estramustine was almost completely abandoned due to its side effect profile (Figg et al., 2007).

Mitoxantrone is an anthracenedione that serves to interfere with DNA intercalation and damage and a Type II topoisomerase inhibitor. On the other hand, it produces negative feedback on the pituitary gland, which prevents the release of prednisone, reduced dehydroepiandrosterone (DHEA), and dehydroepiandrosterone-sulfate (DHEAS), which can be metabolized to a small amount of T. In patients who no longer respond to primary androgen ablation, symptoms, especially bone pain can be improved with low-dose prednisone and mitoxantrone in up to 30% of cases (Tannock et al., 1989).

Other attempts have also been made to assess the role of mitoxantrone in OS, but no benefit has been shown. Today, mitoxantrone is used to improve quality of life and control pain beyond secondary or tertiary treatment or CT.

When transition to **second-line hormone therapy** is inevitable in metastatic PCa (if there is disease progression despite primary hormonal therapy),different hormonal treatments are applied, such as withdrawal of antiandrogen, replacement of antiandrogen or increasing its dose, estrogen therapy, switching to progestational agents, use of glucocorticoids, or adrenal androgen synthesis inhibitors.

TREATMENTS IN CASTRATE-RESISTANT PROSTATE CANCER

Metastatic PCa becomes CRPCA by developing resistance to ADT within an average of 18-24 months. According to the guidelines, despite serum testosterone being at the castrate level (<50 ng/dl or 1.7 nmol/l), the presence of one of the following criteria is defined as CRPCA: a) biochemical progression referring to more than a 50% increase in two of three consecutive PSA measurements and PSA >2 ng/ml and b) radiological progression referring to two or more new bone lesions or soft tissue lesions in bone screening based on response evaluation criteria in solid tumors (Cornford et al., 2017).

Many mechanisms are considered to be effective in resistance development, including AR overexpression, AR hypersensitivity, AR mutation, mutations in coactivators, androgen-independent receptor activation, and AR variants (Chandrasekar et al., 2015).

Before 2018, the treatment options for non-metastasis CRPCA (nm-CRPCA) were observation, first-generation AR

antagonists, such as bicalutamide and flutamide, estrogens, or ketoconazole, but none was associated with survival benefits (Lodde et al., 22010).

The development of a new second-generation AR antagonist in recent years has altered the treatment scheme for nm-CRPCA and provided new prospects for prolonged life expectancies in patients with advanced PCa.

Apalutamide is an antiandrogen that directly binds to the ligand binding domain of AR and prevents AR translocation, DNA binding, and AR-mediated transcription (Clegg et al., 2012).

For nm-CRPCA therapy, apalutamide is an FDA-approved agent that was shown to have the benefit of non-metastatic survival in a phase III study (SPARTAN) (Smith et al., 2018).

Enzalutamide, a new-generation AR blocker approved by FDA in 2013, inhibits DHT receptors both on the target cell surface and on the nucleus. Enzalutamide shows higher affinity for AR compared to older-generation antiandrogens, such as bicalutamide and flutamide. In addition to direct AR inhibition, it reduces AR translocation in the nucleus and the binding of AR to DNA, leading to a decrease in transcriptional activity. Non-steroidal antiandrogens still allow ARs to be transferred to the nucleus, while enzalutamide blocks AR transfer, and therefore suppresses possible agonist-like activity (Tran et al., 2009).

In the PREVAIL study, a placebo was compared with enzalutamide, and OS was reported to be 32.4 months in the enzalutamide group and 30.2 months in the placebo group. Enzalutamide was statistically significantly superior in terms of radiological progression-free survival rate and time to CT, time to first skeletal event, response rates in soft tissue lesions, time to PSA progression, PSA response rates, and quality of life scores (Beer et al., 2014).

Darolutamide is a second-generation antiandrogen and a non-steroidal AR antagonist similar to enzalutamide and apalutamide. Although it differs from enzalutamide and apalutamide in structure, it causes the decrease of the growth of PCa cells (Borgman et al., 2018).

Preclinical studies have shown that darolutamide inhibits AR more strongly than other second-generation antiandrogens in a pre-clinical CRPCA model characterized by AR amplification and over-expression compared to enzalutamide. Furthermore, darolutamide has the additional ability to inhibit some mutations of AR, which occur as a result of the use of enzalutamide or apalutamide. In addition, the power of darolutamide to cross the blood-brain barrier is at a negligible level. Therefore, it theoretically causes a much lower risk of cerebral side effects than enzalutamide or apalutamide (Moilanen et al., 2015).

There is no study directly comparing enzalutamide, apalutamide and darolutamide; therefore a direct comparison between studies is not valid. However, all the results from the ARAMIS, PROSPER and SPARTAN trials provide positive results for primary endpoint metastasis survival (Smith et al., 2018; Fizazi et al., 2019; Hussain et al., 2018).

Docetaxel is a taxane derivative, and studies using it as a single agent or in combination with estramustine showed objective response rates in 38% of patients and a PSA decrease by more than half in 69% of patients (Picus et al., 2018; Berry et al., 2001).

In light of studies performed after these findings, cytotoxic CT, especially docetaxel with prednisone has been accepted to significantly prolong OS in CRPCA, and

FDA has confirmed the use of docetaxel in treatment (Tannock et al., 2004).

In another study, it was concluded that treatment with estramustine and docetaxel in CRPCA not only moderately increased survival but also had side effects, and therefore it is rarely used (Petrylak et al., 2004).

Cabazitaxel is a third-generation semi-synthetic taxane developed after PCa resistance to other taxanes was observed (Mita et al., 2009).

Cabazitaxel was found to be as strong as docetaxel in cell lines and have antitumor activity in paclitaxel and docetaxel resistant models. In a phase III study in patients with CRPCA with progressive disease after docetaxel treatment, an evaluation was performed in *mitoxantrone + prednisone* and *cabazitaxel + prednisone* groups. There was a 30% risk of death in the cabazitaxel arm compared to the mitoxantrone arm. However, cabazitaxel showed higher side effects, with the most common being neutropenia, leukopenia, and anemia (De Bono et al., 2010).

In a later study comparing 20 mg and 25 mg cabazitaxel in order to reduce side effects and evaluate their efficacy, the efficacy rates were found to be similar, and side effects were less in the 20 mg arm (De Bono et al.,2016).

As a result, cabazitaxel remains an option for CRPCA cases, in which docetaxel treatment has been unsuccessful. However, there is no data to support that it is more effective than docetaxel.

Abirateron acetate (AA) blocks cytochrome p450c17. Thus, 17-alpha-hydroxylase and 17-20-lyase enzymes are inactivated and suppress androgen synthesis. Following AA intake, it transforms into its active metabolite of abiraterone, suppressing androgen production from testicular, adrenal and tumor tissues, providing an effective androgen blockade. It should be used with prednisone/prednisolone to prevent drug-induced hyperaldosteronism. The COU-AA-302 study, investigating the efficacy of CT-naïve CRPCA patients, included asymptomatic or mildly symptomatic patients without visceral metastasis. One study arm was given *AA + prednisolone* while the other arm received *placebo + prednisolone*. Survival without radiological progression was 16.5 months in the AA group and 8.2 months in the placebo group. Furthermore, a 25% reduction was achieved in the mortality risk of AA. Since this value did not reach the predefined value, it was not accepted as significant and was interpreted as a tendency in OS in favor of AA (Ryan et al., 2013).

In patients who cannot tolerate docetaxel treatment, the use of AA may be an appropriate approach. In addition, the use of AA in the asymptomatic or minimal symptomatic period before the deterioration of patient performance provides more advantages compared to its use in the advanced symptomatic period. However, Schweizer et al. reported that the use of AA before docetaxel in CRPCA led to the inhibition of AR pathways by taxanes and the formation of cross-resistance and limited antitumor activity (Schweizer et al., 2014; Van Soest et al., 2013).

Radium-223(Ra-223) is a calcimimetic agent and causes DNA breaks with α-particles it emits by forming complexes with hydroxyapatite in bone mineral tissue. Ra-223 is the only bone-specific treatment with confirmed efficacy demonstrated by a phase III study (ALSYMCA) published in 2013 (Parker et al., 2013).

This study included CRPCA patients with two or more bone metastases but no visceral metastasis, who had an ECOG performance score of 0-2, who had disease progression after docetaxel, or were not suitable for docetaxel treatment. Patients were randomized to the Ra-223 and placebo arms. Meanwhile, patients continued their

standard treatment. OS was 14.9 months in the Ra-223 treatment group and 11.3 months in the placebo group. Concerning all the results, Ra-223 was significantly superior to the placebo in terms of the time to first skeletal event, time to alkaline phosphatase increase, and time to PSA increase. In addition, it was determined that Ra-223 treatment positively affected OS and was found to be safe in both the group that had used docetaxel and the group that had not previously received this treatment (Hoskin et al., 2014).

In another study comparing the activity of AA and AA + Ra-223, it was determined that OS did not increase and skeletal events were at a higher rate in the combination arm, and the authors emphasized that these two agents should not be used together (Smith et al., 2019).

Zoledronate is a bisphosphonate effective in bone metastases and pain relief in patients with CRPCA. In vitro and in vivo models revealed that it also has antitumor activity, which prevents apoptosis, tumor cell growth, adhesion, invasion, and angenesis, extending beyond its antiosteoclastic activity. Studies have also investigated the possible synergistic activity of zoledronate when combined with CT regimens in various tumors, especially PCa. More positive results have been obtained in metastatic CRPCA cases, in which zoledronate was administered metronomically after docetaxel. Thus, there is a growing interest in combining zoledronic acid with various therapeutic agents in PCa in larger studies **(**Finianos et.al.,2019)

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