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REVIEW

Clinical use of abiraterone in the treatment of metastatic castration-resistant prostate cancer

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Abstract: Prostate cancer remains the most common type of cancer among men in the United States. Treatment for metastatic prostate cancer has improved significantly over the years with more and more agents improving overall survival. This review will address the pathophysiology of prostate cancer followed by the mechanism of action and the pharmacokinetic properties of abiraterone. The review will also discuss the role of abiraterone in the treatment of metastatic castrate-resistant prostate cancer.

Keywords: glucocorticoid receptor, CYP17, pipeline, enzalutamide, sipuleucel-T, drug resistance, radium-223 dichloride

Introduction

Prostate cancer is the most common type of cancer among men in the United States with an estimated 233,000 newly diagnosed cases and an estimated 29,480 deaths in 2014.[1] The incidence of prostate cancer has been declining approximately 2.4% annually each year from 2002 to 2011.[1] In comparison, the number of deaths has declined an average of 3.3% each year over the last 10 years with an increase in the 5-year survival from 66% to 99.6% from the 1970s to today.[1] The reasons for this decline in cancer death are multifaceted and can be attributed to the increase in screening, earlier detection, the treatment of less advanced disease, and the advent of newer and more tolerable antineoplastic agents.[1,2]

Prostate cancer is dependent on hormonal stimulation for cell proliferation. In its initial stages it has an indolent course, however it may metastasize to the lymph nodes, liver, and bone if left untreated. The initial treatment for metastatic prostate cancer is the reduction of testosterone levels to less than 50 ng/dL, either through chemical or surgical castration. However, within 2 to 3 years, the cancer may develop androgen resistance, which is also known as castrate-resistant prostate cancer (CRPC).[3] The TAX 327 trial in 2004 changed the treatment landscape of metastatic CRPC, as the study showed an overall survival benefit compared to the previous gold standard treatment mitoxantrone, making docetaxel with prednisone the cornerstone of metastatic treatment in CRPC.[4,5] This was the first study to show an improvement in overall survival in a metastatic prostate cancer setting. Although this regimen improved survival by 2.4 months, significant adverse effects noted in the docetaxel arm included all grade fatigue, alopecia, diarrhea, sensory neuropathy, and grade 3/4 neutropenia.[4]

As further research is being conducted regarding the pathophysiology of metastatic CRPC, the growth and survival of these cells remains rooted in androgen stimulation. One of the trademarks of CRPC is the ability to continuously rely on androgen receptor

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signaling for tumor survival. There are data to suggest that hormone refractory prostate cells express mutations in androgen receptors, allowing for less specificity of the androgen ligand,[6] increased androgen receptor gene expression,[7] and increased androgen receptor sensitivity.[8] While docetaxel causes microtubule stabilization and subsequent apoptosis, it has also been suggested that it impairs androgen receptor transport[9] which may contribute to the cytotoxic effects of taxanes in metastatic CRPC. With this knowledge, new drugs that target other pathways of androgen development have begun to play a front line role in the treatment pathways, owing in a large part to the decrease in their side effect profile in comparison to traditional chemotherapy.

Abiraterone acetate (Zytiga®; Janssen Biotech, Inc., Horsham, PA, USA) is an orally administered, selective inhibitor of 17α-hydroxylase and the $C_{17,20}$-lysase enzymatic activities of cytochrome P450 (CYP17). It is currently approved for use in combination with prednisone for the treatment of men with metastatic CRPC. Multinational Phase III studies have shown that abiraterone acetate in combination with prednisone significantly improves overall survival in both the upfront setting prior to docetaxel and as second line therapy post docetaxel.[10,11] This article reviews the pharmacology, therapeutic efficacy, and tolerability data relevant to the utilization of oral abiraterone acetate in the treatment of patients with metastatic CRPC.

Prostate cancer pathophysiology

Androgen receptor signaling is vital in the development of primary and metastatic prostate cancer and is mediated through a series of biochemical interactions referred to as the hypothalamic-pituitary-adrenal/gonadal axis. Luteinizing hormone-releasing hormone (LHRH) released from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland. LH complexes with receptors on the Leydig cell testicular membrane and stimulates the production of testosterone and small amounts of estrogen. FSH acts on the Sertoli cells within the testes to promote the maturation of LH receptors and to produce an androgen-binding protein. This creates a negative feedback loop where circulating testosterone and estradiol influence the synthesis of LHRH, LH, and FSH.[12] The multiple steps involved in hormone regulation allow for different treatment modalities for prostate cancer including LHRH inhibitors and antiandrogens.

The testes are the primary source of testosterone in men, contributing to approximately 90% of the circulating androgens.[13] Castration mainly blocks the generation of gonadal testosterone, however androgens originating from other sources, such as the adrenal glands, may continue to drive androgen receptor signaling and thus promote prostate cancer.[14] The adrenal glands are responsible for the remaining 10% of androgens production, which are enzymatically converted to testosterone and dihydrotestosterone in the prostate and peripheral tissues.[13]

CYP17 (17α-hydroxylase/$_{17,20}$-lyase) is a key cytochrome P450 enzyme responsible for androgen biosynthesis and the rate limiting step in the production of testosterone. CYP17 is expressed in the testicular, adrenal, and prostatic tumor tissues and has been shown in metastatic CRPC to be expressed 16.9 fold higher than in primary prostate tumors.[13,15] CYP17 catalyzes two independently regulated steroid reactions involving 17α-hydroxylase and $C_{17,20}$-lyase in the androgen biosynthesis pathway.[13,14] The 17α-hydroxylase activity converts pregnenolone to 17α-hydroxypregnenolone and progesterone to 17α-hydroxyprogesterone. $C_{17,20}$-lyase converts 17α-hydroxypregnenolone to dehydroepiandrosterone and 17α-hydroxyprogesterone to androstenedione. Dehydroepiandrosterone and androstenedione are then converted to testosterone by 17α-hydroxysteriod dehydrogenase in the testis.[13,14]

In addition to catalyzing androgen biosynthesis, CYP17 is important in glucocorticoid production, with 17α-hydroxypregnenolone and 17α-hydroxyprogesterone serving as precursors to cortisol synthesis.[13,14] Cortisol acts through a negative feedback mechanism to constrain adrenocorticotrophic hormone (ACTH) production. With cortisol production inhibited, the ACTH negative feedback loop is not activated leading to an increase in ACTH levels.[13,14] ACTH therefore promotes the conversion of cholesterol to pregnenolone and progesterone, thus increasing levels of mineralocorticoids and cortisol. This results in an increase in mineralocorticoid related adverse events, manifesting as hypokalemia, hypertension, fluid retention, or edema. The imbalance in glucocorticoids and mineralocorticoid levels requires administration of a glucocorticoid or mineralocorticoid agonist, most commonly prednisone or prednisolone.[13,14]

The first agent used to target inhibition of CYP17 was ketoconazole. Ketoconazole inhibits 11β-hydroxylation, which cleaves a cholesterol side chain to pregnenolone and CYP17, thus weakly and nonspecifically inhibiting CYP17.[13] Ketoconazole has improved clinical outcomes in patients with CRPC. Its clinical use however, is limited by the high doses of ketoconazole (800–1200 mg/day) necessary to overcome the lack of specific inhibition of CYP17 that may cause hepatotoxicity, gastrointestinal toxicity, and adrenal insufficiency.

Furthermore, inhibition of cytochrome P450 enzymes creates the possibility of drug–drug interactions.[13] Limitations in ketoconazole use generated a need for a more specific mechanism of CYP17 inhibition resulting in the development of abiraterone.

Abiraterone mechanism of action

Abiraterone acetate is an oral prodrug, when hydrolyzed is converted to the active metabolite abiraterone. Both abiraterone and abiraterone acetate are selective irreversible inhibitors of CYP17.[16,17] Compared to ketoconazole, abiraterone inhibits CYP17 to a greater extent. The concentration of abiraterone required to reduce CYP17 activity by 50% in human microsomes is one tenth of that required by ketoconazole.[13] Abiraterone acetate must be taken with prednisone to address the imbalance of mineralocorticoid activity.

Abiraterone pharmacokinetics

The recommended dosing for abiraterone acetate is 1,000 mg orally once daily with prednisone 5 mg orally twice daily.[18] The maximum plasma concentration of abiraterone is reached after about 2 hours in patients with metastatic CRPC. Orally administered abiraterone is best taken without food as the presence of food may increase systemic exposure. It is also highly protein bound with excellent distribution into peripheral tissues. It is not known if abiraterone or its active compounds are distributed into semen. Therefore, patients should be advised to use a barrier protection method with a partner who is pregnant or of childbearing age.

Metabolism of abiraterone occurs mostly in the liver and involves hydroxylation, oxidation, and sulfation, leading to two major circulating active metabolites (abiraterone sulfate and N-oxide abiraterone sulfate).[17,18] The metabolism of abiraterone to abiraterone sulfate and N-oxide abiraterone sulfate are mediated by sulfotransferase and CYP3A4.[17,18] Abiraterone acetate and abiraterone were not substrates of P-glycoprotein in vitro at clinically relevant concentrations, although abiraterone acetate inhibits P-glycoprotein.[18] Abiraterone has been shown in vitro to be a strong inhibitor of CYP1A2, CYP2D6, and CYP2C8 and a moderate inhibitor of CYP2C9, CYP2C19, and CYP3A4/5.[16,17] Coadministration of abiraterone acetate with CYP2D6 substrates with a narrow therapeutic index should be used with caution or avoided.[16,17] Strong inhibitors or inducers of CYP3A4 have not been evaluated in vivo but abiraterone acetate has been shown in vitro to inhibit CYP3A4, therefore strong inhibitors or inducers of CYP3A4 should be avoided or used with caution in patients receiving abiraterone acetate.

Caution is advised in patients with severe renal impairment. Patients with end stage renal disease requiring hemodialysis receiving abiraterone acetate 1,000 mg showed no increase in serum concentrations compared to patients with normal renal function; consequently, no dosage adjustments were needed.[16,17]

Caution is advised in patients with moderate hepatic impairment but data is lacking for severe hepatic impairment therefore contraindicating its use in patients with severe hepatic impairment.[16,17] In two randomized clinical trials,[10,11] grade 3 or 4 transaminase increases were reported in 4% of patients randomized to the abiraterone acetate arm, typically during the first 3 months of starting treatment. Patients whose baseline serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were elevated were more likely to experience liver test elevation than those beginning with normal values.[10,11] Serum transaminase levels should be measured prior to initiation of abiraterone acetate, every 2 weeks for the first 3 months of therapy, and monthly thereafter. If during treatment the ALT and/or AST levels increase to greater than 5× the upper limit of normal (ULN) or if total bilirubin levels increase to greater than 3× ULN, the treatment should be interrupted and not restarted until the ALT and AST levels return to baseline, or to less than or equal to 2.5× ULN, and total bilirubin levels return to less than or equal to 1.5× ULN. Once abiraterone acetate is restarted, the recommended retreatment dosage should be 750 mg once daily. If hepatotoxicity recurs at the dose of 750 mg once daily, retreatment may be restarted at a reduced dosage of 500 mg once daily following return of liver function tests. If hepatotoxicity recurs in these patients taking abiraterone acetate 500 mg/day, the drug should be discontinued.[18]

In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with abiraterone acetate.[10,11] These side effects are a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. With the frequency of the adverse reactions of hypertension, hypokalemia, and edema, patients should be monitored at least monthly. If patients develop hypertension and hypokalemia abnormalities, they should be corrected prior to and during treatment of abiraterone acetate. Caution is advised in patients with a history of cardiovascular disease or if the patient has a medical condition (eg, heart failure, recent myocardial infarction, or ventricular arrhythmia) since safety in patients with left ventricular ejection fraction less than 50%, and New York Heart Association class III or IV have not been evaluated with abiraterone

acetate. Patients should also be monitored for symptoms and signs of adrenocortical insufficiency, especially if withdrawal from prednisone/prednisolone was experienced, their dose was reduced, or if patients experienced unusual stress during treatment. Signs and symptoms of adrenocortical insufficiency such as fatigue, nausea, vomiting, diarrhea, and loss of appetite can mimic adverse reactions associated with mineralocorticoid excess. Therefore, appropriate tests to confirm diagnosis of adrenocortical insufficiency must be performed, as indicated.[18]

Other common side effects experienced included all grade fatigue (39%), joint swelling/discomfort (30%), cough (11%), dyspnea (12%), diarrhea (18%–22%), anemia (40%), and flushing (19%–23%). Overall patients receiving metastatic CRPC therapy with abiraterone acetate plus prednisone show an acceptable tolerability profile.[18]

Abiraterone efficacy and tolerability

Historically, treatment with mitoxantrone was considered as the only treatment option for patients with hormone refractory prostate cancer. It decreased serum prostate specific antigen (PSA) levels, but showed no overall survival benefit. In 2004, the combination of docetaxel 75 mg/m^2 every 3 weeks and prednisone 5 mg twice daily was shown to significantly prolong survival compared with combination mitoxantrone and prednisone (18.9 versus 16.5 months; P=0.009).[4] It was also associated with improvement in pain and a decrease in PSA levels.[4] With this study, docetaxel became the standard first line chemotherapy for patients with symptomatic metastatic prostate cancer. However, the tolerability of chemotherapy in the elderly patient population remained a concern for treatment.

Abiraterone acetate in combination with low dose prednisone was first approved for the treatment of men with metastatic CRPC who have received prior chemotherapy containing docetaxel. COU-AA-301 was a Phase III, multinational, randomized, double-blind, placebo-controlled study which randomized individuals into either abiraterone acetate plus prednisone (n=797) or placebo plus prednisone (n=398).[10] Patients who had histologically or cytologically confirmed prostate cancer and who previously received docetaxel with disease progression were eligible for the study. Patients received 1,000 mg of abiraterone (four 250 mg tablets) or four placebo tablets orally once daily at least 1 hour before or 2 hours after a meal, with prednisone at a dose of 5 mg orally twice daily. At the time of preplanned interim analysis, the median overall survival was 14.8 months in the abiraterone acetate group and 10.9 months in the placebo group. Improvement in overall survival was found to be statistically significant leading to unblinding of the study data and patients in the placebo group were switched to active treatment with abiraterone acetate.

Secondary end points provided support for the superiority of abiraterone acetate over placebo including the confirmed PSA response rate (29% versus 6%; $P<0.001$), time to PSA progression (10.2 months versus 6.6 months), and median progression free survival on the basis of radiographic evidence (5.6 versus 3.6 months). PSA response was defined as the proportion of patients with a decrease of ≥50% in the PSA concentration from the pretreatment baseline PSA value. PSA progression was defined as an increase of at least 25%–50% over the baseline and an increase in the absolute value of the PSA level by at least 5 ng/mL. Abiraterone acetate was associated with a 42% reduction in risk of disease progression (hazard ratio, 0.58; 95% confidence interval [CI], 0.46 to 0.73; $P<0.001$) based on PSA concentration. However, regardless of PSA concentration, abiraterone acetate was associated with a 33% reduction in risk of disease progression (hazard ratio, 0.67; 95% CI, 0.58 to 0.78; $P<0.001$).

Most of the adverse reactions reported were of grade 1 or 2. There were no differences in all grade toxicity in fatigue, nausea, constipation, bone pain, and arthralgia. Grade 3 adverse reactions (fatigue, back pain, anemia, and bone pain) occurred in less than 10% of patients. Grade 4 adverse events occurred in less than 10% of both treatment groups. There were no significant differences in grade 3/4 toxicities. Discontinuation of treatment due to the adverse effects did not differ significantly between the treatment group and placebo.

Adverse events of special interest included those related to increase in mineralocorticoid activity (including hypertension, hypokalemia, and fluid retention/edema), cardiac disorders, and liver function test abnormalities. The abiraterone acetate group had a higher incidence of adverse events associated with elevated mineralocorticoid levels including edema, hypokalemia, and hypertension (55% versus 43%, $P<0.001$). Grade 1 and 2 cardiac events occurred at a higher rate in the abiraterone acetate group than in the placebo group (13% versus 11%, P=0.14). The most common adverse events were tachycardia (3% in abiraterone acetate group in comparison to 2% in placebo) and atrial fibrillation (2% versus 1%, respectively). There was no significant increase in fatal cardiac events occurring in abiraterone acetate group (1.1% versus 1.3% in the placebo group).

Abiraterone acetate treatment was associated with an elevation in aminotransferase levels versus placebo. A grade 4

elevation in an aminotransferase level early in the study led to a protocol amendment specifying more frequent monitoring of liver function tests during the first 12 weeks of treatment. However, there was no significant difference between the two groups in increased aminotransferase levels overall.

Patient death within 30 days of the last dose of study medication was reported more in the placebo group than in the treatment group of abiraterone acetate plus prednisone (11% versus 20%, respectively). A lower proportion of patients in the abiraterone acetate group, compared to the placebo group, had an adverse event that resulted in death (12% versus 15%, respectively). This trial showed that abiraterone acetate plus prednisone in comparison with placebo plus prednisone prolongs survival among patients with low frequency of additional treatment related adverse reactions.[10]

Abiraterone was also studied and approved for use in the treatment of metastatic CRPC in the predocetaxel setting with the COU-AA-302 trial.[11] Patients with histologically confirmed metastatic prostate cancer were randomized to receive abiraterone acetate plus prednisone (n=546) or placebo plus prednisone (n=542) in this randomized, multinational, Phase III trial. Patients with visceral metastatic disease or previous ketoconazole exposure were not eligible. At the time of planned interim analysis, radiographic evidence of progression free survival and overall survival were not reached in the abiraterone treatment arm. Treatment with abiraterone plus prednisone resulted in a 57% reduction in risk of radiographic progression or death (median was not reached in abiraterone acetate group versus 8.3 months in placebo; hazard ratio, 0.43; 95% CI, 0.35 to 0.52; $P<0.001$). Median overall survival for the placebo group was 27.2 months, and there was a 25% decrease in risk of death in the abiraterone group (hazard ratio, 0.75; 95% CI, 0.61 to 0.93; $P=0.01$). Although deemed not statistically significant, there was a trend toward improved overall survival with abiraterone. A second interim analysis determined that the median time to radiographic progression free survival was 16.5 months in the abiraterone group versus 8.3 months in the placebo group (hazard ratio, 0.53; 95% CI, 0.45 to 0.62; $P<0.001$). A significant delay in the median time to initiation of cytotoxic chemotherapy was observed in the abiraterone arm at 52.2 months compared to 16.8 months in the placebo arm. Other key secondary end points such as time to symptomatic deterioration, time to pain progression, and PSA progression free survival were significantly improved with abiraterone treatment. In terms of adverse events, the frequency was similar in both groups and the abiraterone arm was associated with more mineralocorticoid related effects, similar to previous studies.[10] The trial confirmed the use of abiraterone as a first line treatment option in asymptomatic or minimally symptomatic patients. However, additional studies are necessary to examine the efficacy of abiraterone in patients with visceral disease.[11] Abiraterone acetate is currently recommended by the National Comprehensive Cancer Network (NCCN) guidelines[22] for men with either asymptomatic (category 1) or symptomatic metastatic CRPC.

In both randomized trials,[10,11] abiraterone treatment was well tolerated and not only improved survival but also improved patient quality of life (QOL) by delaying skeletal related events and by pain control. In a postdocetaxel setting, abiraterone acetate was associated with longer prolonged time to skeletal events compared to placebo (9.9 versus 4.9 months). Patients in the abiraterone acetate group also had consistently improved pain palliation.[10] In the predocetaxel setting, abiraterone acetate was associated with a significantly prolonged time to initiation of cytotoxic chemotherapy (25.2 versus 16.8 months; $P<0.001$) which demonstrates a longer duration of disease control without the harsh side effects experienced with traditional chemotherapy regimens. A significant delay in the time to opiate use for cancer-related pain was observed in the abiraterone arm (median time to opiate use for cancer-related pain was not reached in the abiraterone arm, versus 23.7 months for placebo; $P<0.001$). The median time to increase in pain was 26.7 months among patients receiving abiraterone plus prednisone and 18.4 months among those receiving prednisone alone ($P<0.049$).[11] Interference with daily activities as a result of pain is a key component of pain assessments because it substantiates the effect on function and thus has clinical meaningfulness. Time to progression of pain interference was also significantly longer in the group assigned to abiraterone plus prednisone than in those assigned to placebo plus prednisone (10.3 versus 7.4 months; $P=0.005$). The abiraterone plus prednisone group also had preserved functional status as defined by the health related quality of life (HRQoL) assessment. HRQoL was measured with the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire. The FACT-P questionnaire is validated and accepted for assessing QOL in metastatic CRPC, and includes a general functional status scale consisting of physical well-being, social and family well-being, emotional well-being, functional well-being, and a prostate cancer specific subscale. The median time to HRQoL deterioration was significantly longer in patients assigned to abiraterone plus prednisone than in those assigned to placebo plus prednisone (12.7 months versus 8.3 months; $P=0.003$).[19]

New treatment options

Within the past 5 years, new treatment options have emerged for the first line treatment of metastatic CRPC. These new treatment options allow a prolonged time to initiation of chemotherapy and overall improved QOL. Treatment options currently available include immunotherapy agents such as sipuleucel-T, radiopharmaceutical therapy such as radium-223 dichloride, and new targeted, orally available, androgen deprivation therapy including abiraterone and enzalutamide. The optimal choice of therapy depends on the patients' performance status, presence of visceral disease or bone metastases, and patient preference.

Sipuleucel-T (Provenge®; Dendreon Corporation, Seattle, WA, USA) is an active cellular immunotherapy agent designed to stimulate a T-cell immune response against prostatic acid phosphatase, an antigen expressed in most prostate cancers. Sipuleucel-T involves harvesting the patient's peripheral blood mononuclear cells, culturing them with a chimeric protein containing granulocyte-macrophage colony-stimulating factor to activate antigen presentation together with prostatic acid phosphatase as a tumor-associated antigen, and then infusing the antigen-pulsed antigen-presenting cells back into the patient.[20] Each cycle therefore consists of two appointments: first, a leukapheresis procedure to collect peripheral blood mononuclear cells followed by the sipuleucel-T antigen-pulsed antigen presenting cells infusion 3 days later. The treatment is administered in three treatment cycles every 2 weeks. Sipuleucel-T was approved in April, 2010 for treatment of men with asymptomatic or minimally symptomatic metastatic CRPC based on a Phase III study[21] which showed a statistically significant advantage over placebo for overall survival. The median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group (P=0.02). The median time to disease progression was similar between both treatment groups. Sipuleucel-T however does not seem to have any effect on PSA reduction, with only 3% of patients in the sipuleucel-T group having a reduction of at least 50% in PSA level on two visits at least 4 weeks apart.[21] The controversy that remains regarding this treatment approach is how one measures disease response if there is no PSA response. Another major limitation with sipuleucel-T treatment is cost. The cost of care for men with prostate cancer has been estimated to be approximately US$1,800 per month.[20] Currently, the NCCN guidelines recommend sipuleucel-T for a very select patient population including patients with asymptomatic CRPC with good performance level (Eastern Cooperative Oncology Group Functional Status functional status 0-1) and ≥6-month life expectancy.[22] These criteria are specific to the study population since patients with visceral metastases and pathological long bone fractures were excluded. The most common adverse events in the sipuleucel-T group within 1 day after infusion were chills (51.2%), fever (22.5%), fatigue (16%), nausea (14.2%), and headache (10.7%). Adverse events of grade 3 or more within 1 day after infusion were reported in 6.8% of the sipuleucel-T group compared to 1.8% of placebo group. Grade 3 adverse events included chills, fatigue, back pain, hypertension, hypokalemia, and muscular weakness.

Enzalutamide (Xtandi®; Janssen Biotech, Inc.) is an orally available androgen receptor and nuclear translocation inhibitor that has demonstrated overall survival benefit compared to placebo. In the postdocetaxel setting, enzalutamide 160 mg orally once daily was associated with significantly improved median survival of 18.4 months compared to 13.6 months in placebo group (P<0.001).[23] Secondary end points were also improved significantly including reduction in PSA by 50% or more (54% in the enzalutamide group versus 2% in the placebo group; P<0.001), time to PSA progression (8.3 versus 3.0 months; P<0.001), and radiographic progression free survival (8.3 versus 2.9 months; P<0.001). QOL was measured using validated surveys and was improved from baseline in a higher percentage of patients in the enzalutamide group compared with placebo (43% versus 18%; P<0.001). The time to first skeletal related event was also significantly increased in enzalutamide group (16.7 versus 13.3 months; P<0.001). Enzalutamide was well tolerated with most common adverse drug reactions including fatigue, diarrhea, and hot flushes. Seizures were reported in 0.6% of patients receiving enzalutamide.[23] The results of this trial led to the incorporation of enzalutamide as a treatment option for patients with metastatic CRPC for both asymptomatic and symptomatic patients. The PREVAIL trial studied the use of enzalutamide in the predocetaxel setting and was stopped early in October, 2013 after improvement in both overall survival and radiographic progression free survival at time of interim analysis after median follow up of 20 months.[24,25] Enzalutamide showed a statistically significant benefit over placebo with 30% reduction in risk of death (P<0.0001) and 81% reduction in risk of radiographic progression or death (P<0.0001). Predicted median overall survival at time of interim analysis was estimated to be 32.4 months in the enzalutamide arm versus 30.2 months in the placebo arm. Enzalutamide was also associated with a delayed median time to chemotherapy initiation by 17 months compared to placebo (P<0.001).[24,26]

Radium-223 dichloride (Xofigo®; Bayer AG, Leverkusen, Germany) is an alpha particle emitting isotope approved in May 2013 as a first-in-class radiopharmaceutical approved for treatment of metastatic CRPC. It mimics calcium and forms complexes with the bone mineral in areas of increased

bone turnover such as in bone metastases. High energy alpha particles lead to high frequency of double-stranded DNA breaks in adjacent cells, resulting in an antitumor effect on bone metastases.[27] Radium-223 approval was based on clinical data showing a significantly improved median overall survival of 14.9 months compared to 11.3 months in the placebo arm ($P<0.001$).[28] It was also associated with a significantly prolonged time to first skeletal related events at 15.6 months versus 9.8 months in the placebo arm ($P<0.001$).[28] It is a well-tolerated agent with a mild side effect profile consisting of nausea, diarrhea, and vomiting. According to the NCCN guidelines, radium-223 is recommended only for the treatment of symptomatic bone metastases with no visceral disease.[22]

Discussion

Sipuleucel-T and radium-223 dichloride both show overall survival benefit in a select group of patients in clinical trials. Abiraterone, however, can be given to a larger subgroup of patients, particularly patients with a shorter life expectancy, worsening performance status, and visceral disease.[10] The side effect profile of abiraterone is vastly different when compared with sipuleucel-T and radium-223 dichloride mainly due to the route of administration. Radium-223 dichloride is associated with minimal side effects compared to sipuleucel-T and abiraterone. In clinical trials, the side effect profile was very similar to placebo with minimal side effects of nausea, diarrhea, and vomiting. Sipuleucel-T being administered intravenously causes infusion related reactions whereas abiraterone is associated with mineralocorticoid related effects due to its mechanism of action. Abiraterone acetate is also associated with a plethora of medication interactions, which is seen minimally with sipuleucel-T and radium-223 dichloride.

Sipuleucel-T requires a longer time commitment and may be a barrier for some patients. The treatment requires an initial visit to receive leukapheresis followed by infusion visits, taking away from day to day activities. This would be very difficult for patients with an active life style whereas abiraterone or radium-223 dichloride would provide a simpler alternative. In clinical trials, QOL was taken into consideration for both abiraterone acetate and radium-223 dichloride. In both trials[10,11,19,28] the FACT-P score was significantly decreased and associated with a better QOL compared to placebo. QOL assessment was conducted in a separate randomized controlled trial for sipuleucel-T where it was determined to be similar to placebo.[29]

Abiraterone acetate has a very similar place in therapy compared to enzalutamide where both are currently recommended in the primary and secondary treatment setting according to NCCN guidelines.[22] Abiraterone, however, is the only treatment specifically shown to have an overall survival benefit in the first line setting in patients with no previous chemotherapy exposure. Once final data are published in regards to the use of enzalutamide in the primary setting, it will be of interest to note how this will change the treatment landscape for the future.[26] Abiraterone and enzalutamide both have tolerable yet different side effect profiles. In clinical trials, enzalutamide was associated with increased risk of fatigue, diarrhea, hot flush, muscle pain, and headache in comparison to placebo.[23–25] Abiraterone, on the other hand, has an increased risk of mineralocorticoid related side effects, requiring corticosteroid supplementation.[10,11] Furthermore, the choice between use of abiraterone and enzalutamide may be preferred in different subgroups of patients. It is of special interest that patients with predisposition to seizures were excluded from clinical trials with enzalutamide, however seizures were still observed in 0.6% of patients in enzalutamide arm compared with no reported events in the placebo arm.[23] Caution is advised when using enzalutamide in patients with history of seizure disorders or other predisposing factors, in which case abiraterone may be a reasonable alternative. Significant increases in liver enzymes were reported during the first 3 months of treatment with abiraterone, hence in patients with preexisting hepatic impairment, enzalutamide may be an alternative choice.[10,11] Although side effects of treatment with abiraterone and enzalutamide have been seen, both agents have had favorable effects on QOL and significantly improved FACT-P scores in comparison to placebo.[11,23] Abiraterone significantly delayed the time to opiate use for cancer-related pain.[11] Enzalutamide has been shown to delay the time to first skeletal related event by approximately 3 months in comparison to placebo.[23]

Since abiraterone and enzalutamide have different mechanisms of action, combination therapy and also the sequencing of these agents may be of interest for future studies. A retrospective multicenter review was conducted to determine the response to abiraterone acetate after progressing on enzalutamide therapy.[31] Twenty-seven patients were suitable for analysis with 3% of patients achieving at least 50% decline in PSA with abiraterone and 11% of patients achieving at least 30% decline in PSA with abiraterone. The median duration of treatment and progression free survival for abiraterone was 16.8 and 15.4 weeks, respectively.[30] These results are consistent with a similar study (n=38) which examined 8% of patients having at least 50% decline in PSA and 18% of patients having at least 30% decline in PSA with abiraterone acetate after progressing on enzalutamide therapy.[31] While enzalutamide and abiraterone acetate have different mechanisms of action,

both target persistent androgen receptor signaling, and these data suggest that an element of cross-resistance may develop between the two therapies.[30]

To accurately evaluate the determination of the optimal sequencing of these agents, prospective trials should be conducted. Currently, the exact role of sequencing of the newer agents or their use in combination remains unknown and further data are necessary to examine such an effect. The primary selection of therapy is highly dependent on the availability of evidence on safety, efficacy, and tolerability of the agents and their application to an individual patient. Patient concerns should always be taken into consideration during the treatment decision process.

Conclusion

Historically, the treatment of metastatic prostate cancer consisted of palliative treatment until the arrival of docetaxel, which showed improved overall survival. In recent years, several new agents have been approved for use in the postdocetaxel setting, with potential for use in a first line setting. One of these agents, abiraterone acetate, is a potent and irreversible selective inhibitor of CYP17, which is involved in adrenal steroidogenesis. This inhibition provides complete blockade of the receptor for translocation of the androgen receptor to the nucleus and interaction of androgen receptor with DNA for gene transcription.[32] Abiraterone acetate in combination with prednisone has demonstrated overall survival benefit in men with metastatic CRPC who received previous docetaxel therapy and in men with no previous chemotherapy. The combination of abiraterone acetate and prednisone resulted in a significantly longer median progression free survival in both patient populations.[10,11] Furthermore, abiraterone acetate was associated with delaying the need for chemotherapy by 35 months compared to placebo while prolonging the time period of symptomatic decline in patients with no previous chemotherapy exposure.[11] Although there is much to understand regarding newer agents, including the appropriate sequence of use, abiraterone has been shown to be an appropriate option with overall survival benefit and tolerable side effect profile.

Disclosure

The authors report no conflicts of interest in this work.

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