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Abstract: While androgen-deprivation therapy can induce dramatic clinical responses in advanced and metastatic prostate cancer, refractory disease (castration-resistant prostate cancer [CRPC]) eventually emerges. In recent years, several studies have demonstrated the importance of residual intratumoral androgens in maintaining androgen receptor (AR) transcriptional activity in CRPC. The cytochrome P450 enzyme CYP17 is an obligatory step in androgen synthesis, and therefore a critical therapeutic target in CRPC. Abiraterone acetate is a selective, irreversible inhibitor of CYP17 and can suppress adrenal synthesis of androgen precursors, and possibly in situ steroidogenesis in the tumor microenvironment. In a phase III multicenter study, abiraterone in combination with prednisone improved median overall survival of men with docetaxel-refractory CRPC by 3.9 months compared to placebo plus prednisone, and also resulted in higher objective prostate-specific antigen and radiographic response rates. The study led to the FDA approval in April 2011 of abiraterone for treatment of chemotherapy-refractory CRPC patients, validating steroidogenesis and the AR axis in general as therapeutic targets in CRPC. The FDA indication for abiraterone was expanded to all CRPCs in December 2012, while evaluation in even earlier disease states is ongoing. We propose a comprehensive AR axis-targeting approach via simultaneous, frontline enzymatic blockade of several steroidogenic enzymes (eg, CYP17 and AKR1C3) in combination with gonadotropin-releasing hormone analogs and potent, second-generation AR antagonists (eg, enzalutamide) in order to improve outcomes in patients with prostate cancer.

Keywords: androgen synthesis, testosterone, dihydrotestosterone, CYP17, AKR1C3, MDV3100 (enzalutamide)

Introduction
Prostate cancer is the most common noncutaneous cancer diagnosed among US men, representing approximately 240,000 new diagnoses annually. Although many patients are diagnosed early and potentially cured with local therapy, a significant number of patients are still diagnosed with or eventually develop metastatic disease, which is currently incurable. For this reason, prostate cancer – estimated to be responsible for approximately 28,000 deaths in 2012 – is still the second-leading cause of cancer deaths in men.1 Despite this, the clinical management of advanced prostate cancer remained fairly stagnant for many years. Indeed, over the past seven decades,2 few therapeutic options beyond androgen-deprivation therapy (ADT) via gonadal suppression (orchiectomy or gonadotropin-releasing hormone [GnRH] analogs) were
available for men who were diagnosed with or developed advanced or metastatic prostate adenocarcinoma after local treatment. Unfortunately, clinical resistance to ADT eventually emerges, usually manifested as tumor regrowth associated with an increase in the serum prostate-specific antigen (PSA) levels, and this phenomenon is usually associated with fatal outcomes. Further attempts at manipulating the androgen axis with ketoconazole (an antifungal agent with activity as an androgen synthesis inhibitor) or with first-generation androgen receptor (AR) antagonists (flutamide, bicalutamide, nilutamide) are frequently successful at reducing PSA levels, but unfortunately these responses are short-lived. Moreover, ketoconazole is poorly tolerated at the doses required to inhibit androgen synthesis. In this clinical setting, the disease was traditionally considered “hormone-refractory” or “androgen-independent,” and cytotoxic chemotherapy has been used, despite only modest efficacy and limited choices of active agents. In fact, it was only in 2004 that a cytotoxic chemotherapeutic agent (docetaxel) demonstrated for the first time evidence of a statistically significant overall survival benefit, and it was only recently that a second-line cytotoxic chemotherapeutic agent (cabazitaxel) was documented to provide overall survival benefit.

It is now becoming clearer that prostate cancer growth can still remain dependent on androgen supply and sensitive to hormonal manipulation, even in the setting of disease previously called hormone-refractory or androgen-independent, and that those terms are grossly inaccurate. Newer evidence shows that even when measured serum testosterone levels are in the castrate range (<50 ng/dL), the AR axis in the prostate cancer cells can remain active and still play a significant role in their proliferation. Clinically, the increase in serum PSA (whose gene expression is critically dependent on AR activity) seen at progression after ADT, and its subsequent decline with second-line hormonal therapies, demonstrate that the AR pathway remains active regardless of the circulating levels of testosterone. Other AR target genes, including TMPRSS2 and KLK2, show similar expression patterns. Hence, the more appropriate term “castration-resistant prostate cancer” (CRPC) should be used instead. Furthermore, the AR signaling axis is hyper-sensitized to the residual levels of androgens arising from extragonadal sources. Proof of principle for this concept was provided with the introduction of abiraterone acetate, a potent CYP17 inhibitor. This highlights the importance of understanding the steroidogenic pathway(s) that operate in prostate cancer.

### Brief overview of androgen synthetic pathways

Cholesterol is the precursor for synthesis of all steroids, including androgens (Figure 1). Androgen synthesis requires two key cytochrome P450 enzymes (CYP11 and CYP17) and two hydroxysteroid dehydrogenases (3β-HSD and 17β-HSD). The expression of CYP11, CYP17, and 3β-HSD in steroidogenic tissues is regulated by the transcription factor steroidogenic factor-1 (SF-1 or NR5A1), which binds to and activates the corresponding gene promoters. In fact, SF-1 inactivation by germ-line mutations in humans or by genetic manipulation in mice leads to gonadal and adrenal failure. In the adrenal cortex (zona reticularis and zona fasciculata), adrenocorticotropic hormone activates SF-1 via the cyclic adenosine monophosphate/protein kinase A pathway.

Androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate, the main products of the androgen synthesis pathway in the human adrenal gland, are only weak AR agonists, but can become a critical source of residual AR stimulation in prostate cancer patients treated with ADT. Conversion of these weaker androgens into testosterone requires a family of enzymes with 17β-HSD activity. In prostate tissue (including adenocarcinoma), this is mediated by HSD17B5 (also known as AKR1C3).

In target tissues, testosterone is reduced to dihydrotestosterone (DHT) via 5α-reductases as DHT has a higher affinity than testosterone for AR (five- to tenfold), and the expression of 5α-reductases acts as a mechanism of in situ amplification of the androgen signal in different target tissues.

### Development of castration resistance in prostate cancer and persistence of AR signaling

GnRH agonists, the mainstay of treatment for advanced prostate cancer, suppress circulating testosterone levels usually to below 50 ng/dL and were thought, based on in vitro and animal experiments, to be capable of inducing apoptosis of prostate cancer cells. It is now clear, however, that ADT causes only a minor wave of initial apoptosis, followed by mostly growth arrest of prostate cancer cells. In fact, these cells have the ability to adapt to these castrate levels of circulating testosterone and eventually restart to proliferate. Furthermore, recent in vitro data demonstrated that a subset of the prostate cancer cells that survive after castration exhibit increased expression of stem cell markers and are subsequently able to repopulate the tumor, likely through adaptive changes in the AR axis.
Human AR is encoded by a single gene on chromosome X (Xq11–12), and when unstimulated is predominantly located in the cytoplasm. After ligand binding, the AR translocates to the nucleus, where it regulates transcription of target genes that modulate differentiation and growth of prostate epithelial cells. AR binds to androgen-response elements throughout the genome and subsequently recruits coregulators (coactivators and/or corepressors) that in turn recruit and regulate the core transcriptional complex. Importantly, these coregulators can be modified in a posttranslational fashion, allowing for the AR signal to “cross-talk” with other signaling pathways, including Src, Akt, human epidermal growth factor receptor 2, insulin-like growth factor 1 receptor, and interleukin-6, as well as potentially amplify the AR action.

For example, constitutively active AR variants have been described that lack the ligand-binding domain (LBD) and can function in a ligand-independent fashion. Such variants can originate from alternative splicing of the AR transcript. Additional AR truncated variants have been described as products of proteolytic cleavage of full-length AR to remove the carboxy-terminal LBD, in order to generate a constitutively active transcription factor.

Also, AR mRNA and protein overexpression, frequently caused by AR gene amplification, has been reported in a large subset of CRPCs, leading to an increased sensitivity to low androgen levels. Similarly, this increased sensitivity can be seen in association with gain-of-function mutations in the AR LBD, which can also lead to activation of AR by noncanonical ligands, including estrogen, progesterone, or mineralocorticoids. Both AR overexpression and gain-of-function mutations, as well as changes in the coregulators/corepressors ratio, can underlie the antagonist-to-agonist conversion of first-generation antiandrogens (flutamide, bicalutamide, and cyproterone acetate).

This phenomenon is responsible for the “antiandrogen withdrawal” responses, ie, clinical responses (decline in PSA) seen in ~20%–25% of CRPC patients upon discontinuation of first-generation antiandrogens. It could also provide an explanation for the lack of significant additional survival benefit when these medications are used up front in conjunction with ADT as “combined androgen blockade” (CAB).

Most important is, however, the fact that while GnRH agonists are very effective in achieving castrate levels of circulating testosterone, the production of androgen precursors in the adrenal glands persists. As a result, the serum levels of androstenedione, DHEA, and DHEA sulfate are only mildly suppressed after ADT, and remain more than adequate.
to serve as precursors for intratumoral conversion to testosterone and DHT (of note, in healthy, hormone-naive adult males, the circulating DHEA sulfate concentration is up to 500 times higher than that of testosterone). Treatment with GnRH agonists usually suppresses circulating testosterone and DHT by more than 90%, but the intraprostatic concentrations of these androgens decrease by only 60%–80%, which highlights the importance of the extraglandular sources of androgen. Furthermore, the intratumoral concentration of testosterone in the metastatic tissue of CRPC patients (ie, with castrate levels of circulating testosterone) has been found to be up to four times higher than its concentration in primary prostate tissue from untreated, hormone-naive patients, and in any case more than sufficient to stimulate AR-dependent gene expression. Taken together, these findings suggest that prostate cancer cells, in a castrate environment, are able to mount an adaptive response that allows using adrenal precursors to synthesize testosterone and DHT. In fact, some of the enzymes responsible for this conversion (SRD5A1, AKR1C3, CYP17A1, HSD3B1, HSD3B2, HSD17B3, and CYP19A1) have been found to be upregulated in different studies, although some variability between these studies is to be noted. The latter reflects the marked heterogeneity existing between these tumors and underscores the importance of this steroidogenic pathway as a whole. Moreover, inactivation of androgens in the prostate adenocarcinoma microenvironment is also believed to be aberrant, due to decreased expression of DHT-inactivating enzymes.

Less well established is the concept of de novo testosterone synthesis directly from cholesterol in prostate cancer cells, as conflicting data are available to date. Some investigators have reported that CYP17 is upregulated in prostate cancer cells when exposed to androgen-deprivation therapy, suggesting that prostate carcinomas may possess the complete enzymatic machinery necessary to convert cholesterol to testosterone in a cell-autonomous fashion. Others have failed to obtain the same results, and have concluded that the levels of CYP17 in prostate cancer cells are not sufficient by themselves to promote local synthesis of testosterone, therefore relying on adrenal precursors to this end. Our own findings suggest that CYP17 is overexpressed in a small but distinct subset of prostate carcinomas. These tumors are probably too few for this effect to reach statistical significance when considered as average CYP17 expression across all prostate cancers, thus explaining the negative studies mentioned above. However, these CYP17 expression outliers (overexpressors) may constitute a distinct group of prostate carcinomas that can accomplish all the steps of androgen synthesis using cholesterol as a precursor (thus being completely independent of adrenal contribution of steroids). Such observations may have treatment implications for this subset of patients.

In any case, prostate cancer cells remain dependent on the androgen supply for their survival, and are far from being “androgen-independent” or “hormone-refractory.” The response to second-line hormonal manipulations, with agents such as ketoconazole (off-label use) or more recently abiraterone is a proof of principle for this. In fact, patients with CRPC who have higher androgen levels at baseline are more likely to respond to the second-line hormonal therapies, and it has been suggested that measuring circulating adrenal androgen levels may predict response and guide treatment in these patients.

**Development of abiraterone**

Ketoconazole, an imidazole derivative, has inhibitory activity on several enzymes in the androgen synthesis pathway. However, this activity is relatively weak and unselective. Furthermore, it is usually tolerated poorly at the recommended dose. The observations that nonsteroidal 3-pyridil esters have improved selectivity for the inhibition of CYP17 led to the development of abiraterone. Structurally, abiraterone is closely related to pregnenolone, and pharmacokinetic studies in mouse models showed that it achieves several times more potent inhibition of the hydroxylase/lyase CYP17 activity than ketoconazole. In its unconjugated form, abiraterone is quickly hydrolyzed by esterases, and hence a more stable prodrug was developed – abiraterone acetate. Initial phase I studies showed that abiraterone was not only effective in further suppressing testosterone levels in castrated human individuals but was also well tolerated, without any of the significant toxicities seen with ketoconazole.

A second open-label, dose-escalation, single-center phase I study confirmed PSA decline of more than 50% in 57% of the cohort when continued administration of abiraterone was given. A dose of 1000 mg daily was recommended for phase II trials. The extension phase I/II study of 42 patients receiving this recommended dose resulted in a PSA decline of greater than 50% in 67% of patients. More importantly, a secondary decline of more than 50% in PSA levels was observed when dexamethasone was added, regardless of prior dexamethasone exposure. The mechanism proposed to explain this phenomenon is as follows: CYP17 catalyzes two enzymatic reactions (17-hydroxylase and 17,20 lyase) and is necessary for both glucocorticoid and androgen synthesis. Abiraterone completely inhibits both...
reactions and suppresses both glucocorticoid and androgen synthesis. In the absence of glucocorticoid supplementation, abiraterone leads to compensatory elevation of serum adrenocorticotropic hormone levels and increased adrenal conversion of cholesterol to pregnenolone and progesterone (which does not require CYP17). The latter can function as an AR agonist by itself, and can also be converted to 3α5α-17-hydroxy-pregnanolone, and eventually to DHT via the backdoor pathway. Moreover, because mineralocorticoids are synthesized from progesterone (Figure 1), their production is spared when CYP17 is inhibited. As a result, accumulation of progesterone promotes mineralocorticoid excess and the development of the corresponding syndrome (fluid retention, edema, hypertension, and hypokalemia) that occurs in patients treated with abiraterone in the absence of corticosteroid replacement therapy. Therefore, the use of low-dose (replacement) corticosteroids is recommended in combination with abiraterone, to suppress the accumulation of pregnenolone, progesterone, and mineralocorticoids, in order to (1) decrease the risk of mineralocorticoid side effects and (2) enhance its anticaner activity. This combination of abiraterone with replacement-dose glucocorticoids (prednisone) was used in another phase II study including 58 patients with metastatic CRPC who had previously progressed after docetaxel therapy. In this study, a decline in PSA by more than 50% was observed in 36% of the patients, with a trend towards better response in those who were ketoconazole-naive. However, a meaningful response was still seen even in patients who had previously received ketoconazole, a finding that has been corroborated by a separate phase I trial.

These preliminary findings were confirmed by the landmark phase III multicenter study by de Bono and colleagues, which compared the use of abiraterone in combination with prednisone vs placebo plus prednisone in the post-docetaxel setting. In this study, median overall survival was 14.8 months in those patients treated with abiraterone plus prednisone, compared to 10.9 months in those receiving placebo plus prednisone, representing a 35% reduction in risk of death. Higher objective PSA and radiographic responses were also evident, as well as a longer time to progression based on these parameters. The study led to the FDA approval in April 2011 of abiraterone acetate for use in chemotherapy-refractory CRPC.

**Ongoing clinical trials involving earlier clinical states**

Originally, abiraterone was approved for use only in chemotherapy (docetaxel)-refractory CRPC. However, the better understanding of its mechanism of action and its relatively well-tolerated adverse event profile make the possibility of its use before chemotherapy very attractive. Ongoing trials are addressing this question. In a recently presented abstract, Ryan and colleagues showed interim-analysis data of the COU-AA-302 study, evaluating the role of abiraterone in combination with prednisone in patients with metastatic CRPC who are chemotherapy-naive. This multicenter study included 1088 patients and showed improvement in the coprimary (overall survival, radiographic progression-free survival) and secondary end points. Based on this data, the Independent Data Monitoring Committee recommended the study to be unblinded and allowed crossover. Among the secondary end points, the use of abiraterone delayed time to chemotherapy initiation from 16.8 months to 25.2 months when compared to prednisone alone. On December 10, 2012, the US Food and Drug Administration approved an expanded indication for abiraterone acetate in combination with prednisone for the treatment of all patients with metastatic CRPC, thus including chemotherapy-naive CRPC.

As stated above, the degree of apoptosis encountered in prostate cancer cells after androgen depletion obtained with GnRH agonist monotherapy is inadequate to promote significant pathological responses. Hence, there is increasing interest in a possible role of abiraterone in combination regimens in the neoadjuvant setting. In this regard, a recent study enrolled 58 men with localized high-risk prostate cancer to receive leuprolide alone or in combination with abiraterone for the first 12 weeks followed by combination of leuprolide plus abiraterone on both arms for another 12 weeks prior to radical prostatectomy. There was a trend for a higher percentage of patients with complete or near-complete pathological response after receiving abiraterone for 24 weeks vs 12 weeks prior to prostatectomy (34% vs 15%) that did not reach statistical significance \(P = 0.0894\). Another study of 37 patients receiving GnRH agonist plus abiraterone versus GnRH agonist for 12 weeks resulted in trends towards higher rates of pathological near-complete cytoreduction (24% vs 8%) and tumor downstaging (lymph-node infiltration was 28% vs 50%), in those patients receiving abiraterone, although again the \(P\)-values did not reach statistical significance. There are additional ongoing clinical trials exploring whether more profound androgen depletion in the tumor microenvironment would be capable of inducing clinically significant cancer cell apoptosis, tumor downstaging, and possibly improving long-term outcomes.

**Adverse events of abiraterone**

Unlike ketoconazole, abiraterone is generally a well-tolerated medication. In fact, in the phase III registration trial that led
to its approval, the incidence of adverse events leading to discontinuation of treatment was not different in the group receiving abiraterone compared to those receiving placebo. Most of the side effects related to abiraterone use are secondary to mineralocorticoid excess, and include fluid retention, edema, hypertension, and hypokalemia, which are usually minimized by the concurrent administration of low-dose glucocorticoids (prednisone). Additionally, frequent monitoring of aminotransferase levels is recommended during the first few weeks of treatment, because some grade 4 elevations were observed, requiring temporary discontinuation of treatment. However, elevation of aminotransferase levels is usually reversible, and abiraterone can be safely reintroduced after dose reduction.70

**Other CYP17 inhibitors in clinical development**

As previously explained, CYP17 catalyzes two enzymatic steps (17-hydroxylase and 17,20 lyase), both of which are inhibited by abiraterone (Figure 1). Of these, the 17-hydroxylase activity is required for both androgen and glucocorticoid synthesis, while the 17,20 lyase activity is only required for androgen synthesis.41 Therefore, by blocking both steps, abiraterone requires concomitant glucocorticoid supplementation in order to avoid the side effects related to mineralocorticoid excess. A more selective inhibition of the 17,20 lyase activity would theoretically obviate this requirement. TAK-700 (ortonel) was designed to achieve this. A recent phase I study showed no added adverse effects of ortonel at a dose of 400 mg twice a day when used concomitantly with docetaxel and prednisone.74 A multicenter clinical phase III trial using ortonel at this recommended dose plus prednisone in patients that progressed after docetaxel therapy is currently ongoing, with plans to recruit 1083 patients. Additionally, the same regimen is being evaluated in chemotherapy-naïve patients.75 It is unclear whether the specificity of ortonel for the 17,20 lyase activity will be maintained at the higher dose required to obtain clinical responses (and as noted above, prednisone has already been added to these clinical trials anyway). Similarly, galetore (TOK-001 or VN/124-1), a CYP17 inhibitor and AR antagonist, is in clinical development.3

**Possible mechanisms of resistance to abiraterone**

Despite the clinical benefits obtained with abiraterone acetate in CRPC, and the encouraging results seen in early clinical trials of ortonel, disease progression eventually will occur. Prostate cancer is a markedly heterogeneous disease, with potential for multiple mechanisms of resistance to castration (see “Development of castration resistance in prostate cancer and persistence of AR signaling”). The expression of AR variants, which lack the LBD and are constitutively active in a ligand-independent manner, increases acutely after androgen ablation, and conversely is suppressed by androgen treatment.76,77 Preclinical data suggest that abiraterone treatment upregulates the expression of AR (both full-length and truncated, constitutively active variant), thus proposing one potential mechanism that may explain resistance to abiraterone.78 Other proposed mechanisms of resistance to abiraterone are (1) upregulation of steroidogenic enzyme expression, including CYP17A1 (abiraterone’s own target),78,79 and (2) accumulation of intratumoral pregnenolone/progesterone levels (that are synthesized upstream of CYP17) and can activate AR, in particular in the presence of certain LBD AR mutations79 or through conversion to 3α5α-17-hydroxyprogrenolone and eventually to 5α-dihydrotestosterone via the backdoor pathway.67 These putative mechanisms of resistance to abiraterone (or other CYP17 inhibitors) remain to be confirmed in clinical specimens of abiraterone-refractory CRPC tumors. In any case, however, these mechanisms highlight the importance of residual androgen metabolism in the presence of abiraterone, thus raising the possibility that resistance to abiraterone can potentially be overcome by using higher doses of abiraterone or additional inhibitors of other steroidogenic enzymes or by combination with potent AR antagonists, such as enzalutamide (MDV3100).78

**Enzalutamide (MDV3100), a next-generation antiandrogen with clinical activity in CRPC**

In an example of rational compound design, a chemical library of AR ligands was created by using data from a co-crystal structure of bicalutamide bound with mutant AR. This library was screened for AR antagonistic activity, and a candidate compound, MDV3100 (enzalutamide), was selected for further testing.40 Enzalutamide has high affinity for AR, but unlike the first-generation antiandrogens (eg, bicalutamide), an antagonist-to-agonist conversion has not been observed so far. It has been reported that contrary to first-generation antiandrogens, enzalutamide does not promote AR nuclear translocation and DNA binding, hence providing an explanation for its pure antagonist nature.40 Phase I/II testing suggested that enzalutamide
Combination of novel agents

Perhaps more important than the definition of the best sequence of using these novel agents individually will be their use in combination, especially in early disease states (eg, in neoadjuvant therapy and in early metastatic disease). It is reasonable to anticipate that a comprehensive AR axis-targeting approach via simultaneous, frontline enzymatic blockade of steroidogenesis (ie, via abiraterone or other emerging steroidogenesis inhibitors), in combination with GnRH analogs and novel potent AR antagonists (ie, enzalutamide), would achieve deeper AR axis inhibition. Such a powerful combination strategy could replace the current prostate cancer treatment paradigm of sequentially adding agents at the time of disease progression. Clinical testing of the abiraterone plus enzalutamide combination has already begun (ClinicalTrials.gov identifier: NCT01650194). As both agents are very well tolerated individually, with minimal overlapping toxicity, their combination is expected to be well tolerated as well.

Conclusion

Abiraterone acetate is the first of a group of rationally targeted agents to become available for the management of castrate-resistant prostate cancer. We can finally say that after 70 years of relatively few developments, the clinical management of prostate cancer is now enriched with several treatment options. The next challenge is to determine the best timing and sequence in which these drugs should be used. The use of abiraterone in combination with GnRH analogs and AR antagonists (eg, enzalutamide) up front could potentially induce higher degrees of apoptosis by means of a more potent and complete AR axis inhibition. This could result in further improvements in overall survival and progression-free survival in patients with prostate cancer, by delaying the emergence of resistance to castration. Also, the rate of pathologic complete responses seen when abiraterone is included in the neoadjuvant management of high-risk localized prostate cancer is promising, as it may form the basis of combination regimens that will result in increased cure rates. Furthermore, the lack of overlapping side effects between abiraterone acetate and MDV3100 makes the possibility of combination therapy not only conceivable but quite attractive. Our deeper understanding of the pathways involved in the growth of prostate cancer and the multiple mechanisms that lead to the development of castration resistance certainly point to the use of combination therapies as the next cornerstone in the management of this heterogeneous and complex disease.
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