Abiraterone in Prostate Cancer: A New Angle to an Old Problem

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Abstract
Abiraterone acetate is an orally administered potent inhibitor of cytochrome P450, family 17, subfamily A, polypeptide 1 (CYP17), which is essential for synthesis of testosterone from cholesterol. Although decreasing serum testosterone through inhibition of testicular function is the first line of treatment for men with metastatic prostate cancer, residual androgens may still be detected in patients treated with luteinizing hormone-releasing hormone agonists or antagonists. Treatment with abiraterone results in rapid, and complete, inhibition of androgen synthesis in the adrenal glands and potentially within the tumor itself. An overall survival benefit of maximal androgen suppression was recently shown in a randomized placebo-controlled phase III clinical trial of abiraterone with prednisone versus prednisone in men with metastatic castrate-resistant prostate cancer previously treated with docetaxel chemotherapy. Abiraterone’s efficacy shows the importance of androgen signaling in patients with castrate-resistant metastatic disease, with additional confirmation from recent studies of other novel agents such as MDV3100, an androgen receptor signaling inhibitor. These promising results now pose a new angle to an old problem about hormonal therapy and raise new questions about how resistance develops, how to best sequence therapy, and how to optimize combinations with other emerging novel agents.

Introduction
“To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science” —Albert Einstein

Solving a key problem of androgen growth stimulation in prostate cancer, the findings by Huggins and Hodges in 1941, with a subsequent Nobel Prize, forever changed our approach on the treatment of prostate cancer and improved the lives of thousands of men diagnosed with prostate cancer. With some improvement on the use of androgen ablation therapy at different points of disease progression, more than 70 years passed without a distinctly new angle in the hormonal treatment of prostate cancer. With the approval of abiraterone acetate (abiraterone) for the treatment of castrate-resistant prostate cancer (CRPC), there is now evidence that targeting the androgen receptor axis in men with advanced CRPC can lead to improved survival. This finding has substantially changed our central assumptions of CRPC progression and opened the potential for multiple advances, as we better understand additional targets, agents, and mechanisms of resistance to maximal castration therapy.

Rationale for Targeting CYP17
Although it would seem that the rationale of targeting cytochrome P450, family 17, subfamily A, polypeptide 1 (CYP17) would be obvious, the importance of androgen dependence for prostate tumor growth has been understood in the past through a framework of prior studies of castrating therapies (1, 2). Unfortunately, surgical and medical castrating therapies that decrease the synthesis of testosterone or dihydrotestosterone (DHT) are only temporarily effective in patients with advanced disease and do not abrogate all sources of androgen exposure to tumor tissue (3, 4). Although the dominant source of ligand for the androgen receptor is testosterone produced by the testicular Leydig cells, approximately 10% of circulating androgen is synthesized in the adrenal gland (5). Accumulating evidence shows that intratumoral synthesis of the potent androgen receptor ligands testosterone and DHT may occur using weak adrenal androgens as substrates (6–8). Additional studies suggest that castrate tumors can synthesize intratumoral androgens de novo from cholesterol (9–11) and can oxidize the progesterone derivative androstenediol directly to DHT via the “backdoor pathway” (12). Therefore, inhibiting androgen synthesis, despite inhibition of testicular function, has a compelling rationale in the treatment of CRPC.

As an approach to inhibiting androgen synthesis, a focus on the essential role of CYP17 in sex steroid synthases...
provided the rationale needed for developing agents to treat men with CRPC. The pathway for synthesis of testosterone and DHT is well characterized, as shown in Fig. 1. The cytochrome P450 system is a superfamily of enzymes responsible for catalyzing numerous biosynthesis and detoxification pathways. CYP17 is a dual-function enzyme with activity as a 17-α-hydroxylase and a 17,20 lyase. Activity of CYP17 is essential for synthesis of testosterone and DHT from cholesterol (13, 14). The physiologic consequences of abrogating CYP17 activity is shown in children with congenital adrenal hyperplasia who lack sex steroid and cortisol production while experiencing adrenocorticotropic hormone (ACTH)–mediated overproduction of mineralocorticoids leading to hypertension and hypokalemia (14, 15).

As proof of principle, it has long been recognized that ketoconazole decreases the levels of multiple CYP enzymes involved in steroid synthesis, including CYP17, but with a relatively weak IC_{50} while being associated with significant toxicity (13). The clinical activity of ketoconazole has been shown in multiple phase II studies (reviewed in Yap and colleagues; ref. 16) and a phase III trial (CALGB 9583) in men with castrate-resistant disease randomized to antiandrogen withdrawal or antiandrogen withdrawal plus ketoconazole (17). Prostate-specific antigen (PSA) response (decrease in PSA by 50% from baseline) was achieved in 11% and 27%, respectively. No significant difference in overall survival was noted, although this analysis was limited by the substantial crossover to ketoconazole by patients in the control arm. Ketoconazole toxicities include fatigue, hepatotoxicity, nausea, and rash. Its utility is often limited by drug interactions owing to the nonspecific inhibition of CYP450-mediated drug metabolism.

Clinical Development of Abiraterone

Given the compelling rationale for development of more potent and specific inhibitors of CYP17, medicinal chemists explored a variety of compounds to inhibit the CYP17 activity.
enzyme (14). Abiraterone acetate was synthesized at the Institute for Cancer Research in London and is structurally related to pregnenolone, a natural substrate of CYP17 (18). Placement of a nitrogen-containing pridyl group at carbon 17 of pregnenolone led to potent inhibition of CYP17, whereas a double bond at the 16,17 position led to irreversible binding and inhibition of CYP17. An acetate prodrug of abiraterone was developed to increase oral bioavailability (14). Early phase I studies showed good bioavailability at doses of greater than 200 mg, a half-life of approximately 28 hours, and significantly increased absorption with food (19). Abiraterone is metabolized by CYP3A4 and is an inhibitor of CYP2D6. Therefore, caution with coadministration of abiraterone and other drugs is important, especially for drugs that inhibit or induce CYP3A4, which may alter abiraterone levels, and for drugs that are substrates of CYP2D6, which may be affected by abiraterone. Included in the initial studies were men who were not on a luteinizing hormone-releasing hormone (LHRH) agonist. In this population, a compensatory surge in luteinizing hormone led to an increase in testosterone by day 4 of treatment with abiraterone in some men, suggesting the need for abiraterone to be given concomitantly with suppression of testicular function (19).

These early proof-of-principle studies were followed by a continuous dosing, phase I dose escalation trial in chemotherapy-naive men with CRPC who had not received prior ketoconazole (20). Doses of up to 2,000 mg per day were well tolerated. Testosterone became rapidly undetectable within 8 days at all dose levels and remained undetectable, even at the time of disease progression, indicating durable CYP17 inhibition by abiraterone. PSA decline of >50% occurred in 57% of patients. As anticipated, on the basis of knowledge from patients with congenital CYP17 deficiency, absence of CYP17 led to loss of feedback-mediated ACTH suppression by cortisol. ACTH-driven synthesis of deoxycorticosterone and corticosterone, upstream from CYP17, prevented adrenocortical insufficiency and led to excess mineralocorticoid effects of hypertension, hypokalemia, and edema. These effects could be reversed by administration of dexamethasone to restore ACTH suppression. In 4 of 15 patients who developed progression while on the study, dexamethasone caused a PSA response, suggesting, as one possibility, that promiscuous androgen receptor activation by steroids upstream of CYP17 led to abiraterone resistance in some patients. A second phase I trial also included patients who had received prior ketoconazole (21). A 50% decrease in PSA was seen in 9 (47%) of 19 patients with prior ketoconazole therapy and 9 (64%) of 14 patients without prior ketoconazole therapy.

Phase II Studies

Phase II trials of abiraterone in men with CRPC were conducted in chemotherapy-naive (22, 23) and chemotherapy-resistant patients (24, 25), with either prednisone or the mineralocorticoid antagonist eplerenone to manage mineralocorticoid excess. In the studies of patients with no prior chemotherapy, PSA decline of ≥50% ranged from 67% (23) to 79% (22), with a median time to progression of 32 to 71 weeks, respectively. In the trials of patients with prior chemotherapy, declines of ≥50% were seen in 36% and 51% of subjects (24, 25), with a notable ≥90% decline in approximately 15% of patients. Median time to PSA progression was 24 weeks in both trials. Correlative studies in the phase II trials included evaluation of circulating tumor cells (CTC), providing important preliminary data for use of CTCs as a biomarker. CTC number, using the Cell Search System (Veridex), has previously been shown to be an independent prognostic factor for survival (26). In 2 trials of abiraterone after chemotherapy, CTC counts of ≥5 cells/7.5 mL were seen in 70% to 79% of subjects. While on treatment with abiraterone, 34% to 41% of patients converted to the more favorable subgroup with <5 cells/7.5 mL, providing a rationale for incorporating CTC into randomized phase III trials with abiraterone (24, 25). Molecular profiling of CTCs was also done, showing the feasibility of detecting TMPRSS2–ETS-related gene (ERG) fusions in CTC (27). In one study, the presence of an ERG rearrangement in CTC or archival tissue was associated with an increased chance of having ≥90% decrease in PSA, suggesting an association between ERG rearrangement and benefit from abiraterone (28). In a recent study of 48 men treated with abiraterone after chemotherapy, TMPRSS2-ERG status did not predict for a decline in PSA or improved survival, leading the authors to suggest that TMPRSS2-ERG fusion status may have a limited role as a biomarker in this setting (29). Additional ongoing studies will be important to better understand predictive biomarkers.

Phase III Results

The clinical utility of abiraterone was definitively shown in a randomized phase III trial in which 1,195 men with CRPC, previously treated with docetaxel chemotherapy, were randomized in a 2:1 ratio to receive 5 mg of prednisone daily with either 1,000 mg of abiraterone acetate or placebo (30). Patients treated with prior ketoconazole, uncontrolled hypertension, and cardiac ejection fraction <50% were excluded. The primary endpoint of the study was overall survival, and the planned interim analysis done after 67% of on-study deaths occurred (median follow-up of 12.8 months) showed that median survival improved from 10.9 months to 14.8 months (HR = 0.646; P < 0.0001) for patients treated with abiraterone (30). In an updated survival analysis done after 775 deaths, median overall survival was 15.8 months versus 11.2 months (31). Patients receiving abiraterone also had an increase in confirmed PSA response (29.1% vs. 5.5%; P < 0.0001) and progression-free survival as determined by PSA increase of ≥25% (10.2 vs. 6.6 months; P < 0.0001). Recent data presented at the American Society of Clinical Oncology in 2011 confirmed that abiraterone doubled the time to the first skeletal-related event (10 vs. 5 months; P = 0.0006; ref. 32).

Abiraterone side effects were primarily related to elevated mineralocorticoid effects, as a result of CYP17 inhibition.
Common toxicities included fluid retention and edema (31%, all grades), hypokalemia (17%, all grades), increased hepatic transaminases (10%, all grades), hypertension (10%, all grades), and cardiac events (13%, all grades, 3%, grade 3/4). Cardiac events included tachycardia (3%, all grades) and atrial fibrillation (2%, all grades); however, there was no significant increase in fatal cardiac events in the abiraterone group. Abiraterone was not tested in patients with baseline ejection fraction <50%. A postbaseline ejection fraction of <50% was seen in 7.7% of patients on abiraterone and 5% of patients on placebo, leading the U.S. Food and Drug Administration to recommend caution when using abiraterone in patients with a history of cardiovascular disease, with monitoring of blood pressure, serum potassium, and symptoms of fluid retention at least monthly (33).

The approval of abiraterone for treatment of metastatic CRPC has encouraged new questions that may lead to additional future options. Although initially tested and proven to improve survival in men with disease that progressed with chemotherapy, the benefit of abiraterone in castrate-resistant men prior to chemotherapy is of great interest. This question is the subject of a phase III trial of abiraterone in men with asymptomatic or mildly symptomatic castrate-resistant disease without prior chemotherapy or ketoconazole (NCT00887198). Accrual to this trial, with progression-free and overall survival endpoints, has been completed, and results are pending. In the absence of phase III data, the completed phase II trial by Ryan and colleagues with abiraterone plus prednisone prior to chemotherapy (with time to PSA progression of 71 weeks) showed promising activity in the prechemotherapy space (22). Recent consensus guidelines appropriately recognize that patients with significant comorbidities, who may not be suitable for cytotoxic chemotherapy, could be considered for treatment with abiraterone if they have castrate-resistant metastatic disease, as it has substantially less toxicity than cytotoxic chemotherapy (34). Currently, studies are also comparing neoadjuvant castration with abiraterone/prednisone plus leuprolide to single-agent leuprolide prior to prostatectomy in men with localized high-risk prostate cancer (NCT01088529 and NCT00924469). These studies will be important to compare changes in levels of androgens and other potential biomarkers of androgen signaling (before, during, and after treatment) in the serum, primary tumor microenvironment, and bone marrow.

Mechanisms of Resistance to Abiraterone

Our current understanding of mechanisms of resistance to abiraterone remains in the early stages; however, relevant preclinical and clinical data are beginning to emerge. In the majority of patients in the phase II studies, published data showed that PSA increased at the time of disease progression. Expression of PSA, which is under control of the androgen receptor, implies that progression while on abiraterone is related to ongoing activity of the androgen receptor. Activation of the androgen receptor, in turn, may occur through ligand-dependent and ligand-independent mechanisms (3). Although abiraterone activity may be related to inhibition of intratumoral synthesis of testosterone and DHT, it also seems that abiraterone resistance may be mediated through upregulation of intratumoral CYP17 (9, 11). In a castrate-resistant VCap xenograft model, treatment with abiraterone resulted in an initial tumor response and decreased androgen receptor gene activation followed by relapse at 4 to 6 weeks. In all relapsing xenografts, CYP17 expression markedly increased. These data imply that the abiraterone exerts a selective pressure leading to abiraterone resistance via intratumoral androgen synthesis (9). Using 2 LuCap prostate xenografts treated with abiraterone, Mostaghel and colleagues, likewise, showed that the abiraterone resulted in induction of CYP17 and other genes involved in de novo synthesis of intratumoral androgens (11). Additionally, some tumors showed increases in expression of the full-length androgen receptor as well as androgen receptor variants lacking the c-terminal ligand-binding domain.

Taken together, these data suggest that resistance to abiraterone may be overcome by direct targeting of the androgen receptor. MDV3100 is a potent androgen receptor antagonist that may be able to overcome the effects of increased transcription of the full-length androgen receptor (35, 36), as well as of androgen receptor splice variants that function to potentiate the effect of the full-length androgen receptor (37). Recently, a phase III trial of MDV3100 versus placebo in men with CRPC previously treated with docetaxel was halted and unblinded when a planned interim analysis showed that MDV3100 treatment led to an increase in overall survival from 13.6 to 18.4 months (HR = 0.631; P < 0.0001), and was well tolerated (38). These data provide support to now include MDV3100 among agents such as abiraterone and cabazitaxel that improve survival in men with CRPC following progression after docetaxel. Additional studies of MDV3100 effects on bone marrow androgen levels in patients with bone metastases suggest that MDV3100 caused a compensatory increase in bone marrow testosterone, a potential surrogate for intratumoral testosterone (39). Thus, individually, abiraterone and MDV3100 induce antagonistic changes in the androgen axis that could potentially be abrogated with combination therapy, supporting studies of combined abiraterone and MDV3100. Another androgen receptor antagonist in development is EPI-001. This drug disrupts activity of the androgen receptor N-terminal domain, thereby maintaining activity against androgen receptor splice variants with c-terminal ligand-binding domain deletions as well as inhibiting full-length androgen receptors (40).

On the basis of the promising activity of ketoconazole given in combination with dutasteride, which inhibits conversion of testosterone to the more active DHT (41), it could be hypothesized that the combination of abiraterone plus a second drug targeting DHT synthesis may help to overcome abiraterone resistance. Drugs targeting other enzymes involved in DHT synthesis, such as AKR1C3, are also in development (42). Other potential mechanisms for
targeting the androgen receptor include inhibiting androgen receptor chaperone proteins such as clusterin (43). In preclinical models, treatment with the clusterin antisense molecule OGX-011 in combination with MDV3100 led to accelerated androgen receptor degradation and repressed androgen receptor transcriptional activity, as well as significantly delayed time to progression compared with treatment with MDV3100 alone. Finally, an emerging appreciation of the role of c-met signaling in the castrate-resistant state, based on the clinical experience with the dual c-met/VEGF-R2 inhibitor cabozantinib, will likely drive evaluation of combined androgen receptor and c-met blockade in patients with CRPC (44).

In addition to upregulation of ligand synthesis, nonligand-based mechanisms of androgen receptor activation and true androgen receptor–independent carcinogenesis are both clinically relevant mediators of androgen independence. A druggable target that may potentially activate the androgen receptor in a ligand-independent manner includes Src kinase (45). In this regard, dasatinib, a Src kinase inhibitor, is currently being evaluated in combination with abiraterone as a means of overcoming resistance to abiraterone (NCT01254864). Recent data also suggest that continued blockade of the androgen receptor is necessary when targeting the phosphoinositide 3-kinase (PI3K) signaling pathway, an important mediator of castrate resistance (46). In PTEN-negative prostate cancer with resultant activation of the PI3K-AKT-mTOR-signaling pathway, pharmacologic inhibition of mTORC1 (everolimus) or PI3K and mTORC1/2 (BEZ225) resulted in reciprocal increase in androgen receptor protein levels and androgen receptor signaling, whereas inhibition of androgen receptor led to increased activation of AKT by inhibition of an AKT phosphatase. Therefore, dual androgen receptor/PI3K pathway inhibition will be an important area of investigation. The optimal combination strategy for abiraterone may also be informed by our emerging understanding of the role of the high frequency gene fusion between the androgen receptor–regulated TMPRSS2 gene and the ETS family of transcription factors. The TMPRSS2-ETS fusion is the most common of the fusions and is found in approximately 50% of localized prostate cancers (47). Multiple lines of evidence have shown that overexpression of the ETS-related transcription factors increases prostate cancer development and invasiveness. In an effort to target ETS transcription factors by identifying essential proteins that interact with ETS, the DNA repair protein PARP was found to interact with ERG, implying that PARP1 inhibitors may block ETS-mediated transcription (48). In support of this finding, pharmacologic inhibition of PARP1 blocked ETS-positive, but not ETS-negative, prostate cancer xenograft growth. Therefore, abiraterone-mediated inhibition of androgen receptor and downstream TMPRSS2-ETS transcription combined with PARP1 inhibition may overcome the deleterious effects of ETS transcription. Furthermore, preliminary data suggest that inhibition of PARP1 enzymatic activity suppresses ligand-dependent androgen receptor transcriptional activity. Therefore, coordinate PARP and androgen receptor inhibition may be a means of maximal androgen receptor inhibition (49). Finally, as other mechanisms of general resistance to tumor cell stress, such as autophagy, are better understood in the context of androgen ablation in prostate cancer, targeting these mechanisms may also hold promise to improve upon current results (50).

Considerations of Sequence and Space

At the current time, abiraterone is approved for use after treatment with docetaxel-based chemotherapy. Therefore, it remains to be determined whether earlier initiation of treatment with abiraterone will result in an increased duration of benefit compared with treatment after chemotherapy. Similarly, it is also not known whether treatment with abiraterone and subsequent progression will affect response to docetaxel chemotherapy. Recent studies have shown that some of the benefit from taxane-based therapy may be due to taxane-mediated suppression of androgen receptor, raising the possibility of cross-resistance to maximal castration therapy and taxane-based therapy (51, 52). Trials sequencing or combining taxane-based therapy with second-generation hormonal agents such as abiraterone, TAK-700, or MDV-3100 may be informative in this regard. Furthermore, it remains unclear whether there is a detrimental effect from discontinuing abiraterone or other second-generation hormonal agents, such as MDV3100 or TAK-700, as opposed to continuing these agents in the setting of progression, as is routinely done with LHRH agonists. Other considerations about the use of abiraterone prior to chemotherapy relate to optimal integration with sipuleucel-T, which was approved on the basis of prolongation of survival in men who received this therapy prior to chemotherapy. The immune implications of maximal castration therapy are of potential interest, given studies that suggest a benefit of vaccination in conjunction with hormonal therapy. A phase II trial in men with castrate nonmetastatic prostate cancer showed a median survival of 6.2 years for patients who received vaccine prior to nilutamide, compared with 3.7 years for patients who started on nilutamide followed by vaccine ($P = 0.045$). This study suggested that vaccine therapy initiates a host immune response that can be augmented by subsequent complete androgen blockade (53). Finally, the metabolic implications of maximal androgen suppression on bone health, insulin resistance, and cardiovascular health remain to be determined. Of particular interest will be the long-term metabolic effects of maximal castration therapy on patients who receive LHRH agonists and maximal androgen suppression in the early-disease setting with high-risk localized disease or PSA relapse after definitive therapy.

Summary

The compelling survival benefit seen with abiraterone use in patients with heavily pretreated, castrate-resistant disease has refocused attention on the value of inhibition of the androgen receptor axis throughout the entire natural history of the prostate cancer disease process, a real
advance in the treatment of prostate cancer. As a result of dramatic advances in our understanding of prostate pathogenesis, regulation of the androgen receptor, and novel drug development, rationally designed abiraterone combination studies hold great additional promise. At the same time, fundamental questions about integration of abiraterone into our current treatment paradigms present multiple quandaries for the practicing oncologist and provide the impetus for expedient development of clinical trials to optimize our use of abiraterone for improvement of patient care. Additional challenges include prioritizing among multiple compelling trial concepts and the potential need for integration of new agents such as MDV3100, targeting the androgen axis, resulting in an urgent need for increased cooperation among investigators, industry, and regulatory agencies to bring the greatest benefit to the patients in the most efficient manner possible. Finally, as we continue to look for strategies to develop innovative options to continue to win the war on cancer, it is important to reflect on how our 70-year-old view of an old problem about hormonal therapy and resistance changed with a creative new angle and approach that led to an important advance and positive impact on countless lives.

Disclosure of Potential Conflicts of Interest

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