New Strategies in Metastatic Prostate Cancer: Targeting the Androgen Receptor Signaling Pathway

Gerhardt Attard, Juliet Richards, and Johann S. de Bono

Abstract

Recent data report that abiraterone acetate, a specific inhibitor of CYP17 that is key to androgen and estrogen synthesis, improves survival in metastatic castration-resistant prostate cancer (CRPC), confirming the continued dependency of CRPC on the androgen receptor (AR) signaling pathway. MDV3100 is a novel antagonist of AR that is also in phase III clinical trials. In addition, several other agents targeting the AR axis are undergoing evaluation in early clinical studies. CRPC patients progress on these therapies with an increasing prostate specific antigen (PSA), suggesting that repeated therapeutic interventions targeting the AR signaling axis could induce secondary responses and achieve prolonged clinical benefit for a subgroup of patients. These exciting results are good news for patients but introduce a number of treatment paradigm dilemmas for physicians. Clinical studies evaluating the ideal sequence of administration of these new agents, best timing for initiation, combination strategies, discontinuation beyond progression and after commencement of subsequent therapies, and coordination with other treatments have not been done. Predictive biomarkers could allow patient selection for a specific treatment, but in their absence, most physicians will rely on a trial of treatment with a preferred agent and substitute for an alternative therapy on objective progression. Current data suggest that the response rate to drugs targeting the AR ligand-binding domain decreases with each treatment, but we hypothesize that a significant proportion of CRPC remains dependent on the AR axis and, therefore, novel strategies for disrupting AR signaling merit evaluation. Clin Cancer Res; 17(7): 1649–57. ©2011 AACR.

Background

The mainstay of first-line treatment for patients with metastatic prostate cancer is suppression of gonadal androgens by medical or surgical castration, a strategy that was described 7 decades ago by Charles Huggins and colleagues (1). This original observation that prostate cancer is a hormone-dependent cancer remains critically important, especially after recent reports of significant antitumor activity with the novel endocrine treatments abiraterone acetate and MDV3100 in castration-resistant prostate cancer (CRPC) patients progressing after multiple prior hormonal manipulations including estrogens, steroids, antiandrogens, and the nonspecific CYP inhibitor ketoconazole (2–5). Significant antitumor activity was also reported in patients previously treated with docetaxel or other chemotherapies (2, 6). The primary endpoint used to evaluate antitumor activity in early clinical studies of abiraterone acetate and MDV3100 was a decline in prostate specific antigen (PSA). Notably, declines in PSA were associated with declines in circulating tumor cell (CTC) count, symptomatic improvements, radiologic regression, and, in the phase I-II study of MDV3100, inhibition of 14Fi-fluoro-5alpha-dihydrotestosterone on PET imaging (2, 4–7). These data led to the conduct of pivotal phase III studies of abiraterone acetate and MDV3100 in both chemotherapy-naive and chemotherapy-treated CRPC patients. The postchemotherapy study of abiraterone acetate was recently reported and confirmed that targeting of the androgen receptor (AR) is a valid therapeutic strategy in CRPC, imparting overall survival (OS) benefit in advanced prostate cancer. Expression of PSA is predominantly regulated by upstream promoter and enhancer androgen response elements (ARE; ref. 8). An increasing PSA implies transcription of genes regulated by an ARE and, arguably, suggests activation of the AR or other steroid receptor signaling pathways (9). This hypothesis is important as an increase in PSA seems to be associated with cancer progression in the majority of patients receiving treatment with abiraterone acetate as well as MDV3100, suggesting that the biological mechanisms causing treatment resistance are associated with reactivation of the AR. We therefore hypothesize that targeting of the AR through multiple approaches, for example MDV3100 and abiraterone acetate in combination or sequentially, could improve patient outcome. This review outlines how these results could change the treatment paradigms for CRPC and

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doi: 10.1158/1078-0432.CCR-10-0567
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discusses the challenges now faced in the development of novel therapeutics for this disease.

**Suppression of androgens and estrogens that bind the androgen receptor**

Gonadal androgens account for up to 80% of serum androgenic steroids (10). Castration, therefore, does not suppress adrenal androgens and achieves a "hormone-reduced" rather than a "hormone-free" state, hence, the recent renaming of this stage of the disease as castration-resistant in preference to hormone-refractory. CRPC cells undergo a number of genomic and expression changes involving the AR and its associated coactivators and corepressors that could allow continued activation of the AR signaling axis by castrate levels of androgens (11). Moreover, intratumoral hormone synthesis associated with overexpression of key enzymes, including CYP17, could cause resistance to castration (12–14). Although the latter remains a very challenging phenomenon to unequivocally prove, the body of circumstantial evidence for suggesting tumors synthesize their own androgens is compelling and introduces the interesting possibility of therapeutically directly targeting tumor hormone synthesis. In 2005, we hypothesized that continuous, specific inhibition of CYP17, a key enzyme in androgen and estrogen biosynthesis, could induce secondary responses in progressing CRPC patients (10). Ketoconazole, a nonspecific CYP inhibitor that weakly inhibits CYP17 at high doses and has definite antitumor activity in CRPC, was routinely used in a number of academic centers to treat CRPC as an off-license indication (15). However, the significant toxicities in up to two thirds of patients limit its widespread use and prevent escalation to doses that irreversibly inhibit CYP17. In fact, resistance to ketoconazole was associated with rebound increases in circulating androgens (15). A number of specific CYP17 inhibitors that could test our hypothesis had been developed; abiraterone acetate was developed by chemists in our institution a decade earlier (10, 16), but because of concerns about drug safety and an absence of interest in targeting AR signaling, continuous administration was only tested for a maximum of 12 days in noncastrate men (17). We hypothesized that CYP17 blockade would not result in adrenal insufficiency and would have important antitumor activity in CRPC. With renewed support from Cougar Biotechnology, we designed the first clinical studies to confirm the safety and antitumor activity of continuous, daily, single-agent abiraterone acetate (without concurrent steroids) in chemotherapy-naive patients (3, 4). The latter patient population was not dependent on steroids to maintain their fitness, and, as they generally had a better performance status, we hypothesized that they could tolerate the predicted toxicities of secondary mineralocorticoid excess. In keeping with reports of teenagers with familial CYP17 deficiency who present with delayed puberty and are found to be hypertensive (18), single-agent abiraterone acetate was not associated with adrenocortical insufficiency as a result of a compensatory increase in adrenocorticotropic hormone (ACTH), which drives up levels of the weak glucocorticoids deoxycorticosterone and corticosterone 10- to 40-fold, thus maintaining the glucocorticoid requirements of patients (4). However, the mineralocorticoid properties of steroids upstream of CYP17 caused side-effects in two thirds of patients characterized by hypokalemia, hypertension, and fluid overload (3, 4). As spironolactone was reported to bind and activate wild-type AR, the more specific mineralocorticoid receptor antagonist eplerenone (which was previously shown not to bind wild-type AR) was used to treat these toxicities (19). With prompt and careful use of eplerenone (commencing at 50 mg and dose escalating to 200 mg daily), exogenous glucocorticoids were only required to control side-effects associated with mineralocorticoid excess in a minority of patients (20). However, because of the risks associated with hypokalemia, especially in older men with concurrent heart disease and taking antiarrhythmic medication, regular monitoring of serum electrolytes and blood pressure is required until the commencement of a mineralocorticoid antagonist or glucocorticoid and may limit the administration of single-agent abiraterone acetate by non-specialist centers.

In phase I and II clinical studies of abiraterone acetate, 50 to 60% of chemotherapy-naive patients had a decline in PSA by ≥50%, and the median time to PSA progression (as defined by the Prostate-Specific Antigen Working Group I; ref. 21) was about 230 days (3, 5). Importantly, 20 to 30% of patients had a ≥90% PSA decline that was associated with a patient subgroup that had near complete radiologic responses, normalization of CTC count, and PSA progression-free survival lasting longer than 1 year. Antitumor activity was reported at all doses from 250 mg to 2,000 mg daily, but 1,000 mg once daily was selected for phase II development owing to a plateau in the feedback-driven increase of steroids upstream of CYP17 at 750 mg, 1,000 mg, and 2,000 mg daily (4). Addition of dexamethasone or prednisone to patients on single-agent abiraterone acetate significantly extends the time on treatment and could also reinduce sensitivity (defined in our study as a decline in PSA ≥50% after commencing steroids) in 25% of patients irrespective of prior treatment with steroids (4, 5). The improved tolerability and efficacy of abiraterone acetate when administered in combination with low dose steroids, which prevent a compensatory ACTH increase, have led to its development in metastatic CRPC in combination with prednisone. We initiated a study of single-agent abiraterone acetate in postdocetaxel patients, confirming single-agent antitumor activity in this setting, but because of the long-term use of low dose steroids by the majority of these patients prior to receiving abiraterone, we allowed continuation of steroids from the start of study in about half of patients to maintain their general fitness (6). Two separate phase II studies reported significant antitumor activity in chemotherapy-treated patients, with a time to PSA progression of about 170 days, suggesting that docetaxel-treated CRPC remained hormone dependent (6, 7). Although the rate of PSA decline is ≥50% and time to PSA progression is less than in chemotherapy-naive patients, direct compar-
isons are not possible due to the significant heterogeneity between the 2 patient populations accrued to these studies. These data led to the conduct of 2 pivotal phase III trials in metastatic CRPC. Abiraterone acetate has been combined with prednisone 10 mg daily (prednisolone 10 mg daily in the United Kingdom) to minimize toxicity and maximize efficacy. The first study, which was reported recently (22), accrued 1,197 CRPC docetaxel-pretreated CRPC patients randomized 2 to 1 to receive abiraterone acetate and prednisone. As mitoxantrone is not universally used and has not been reported to improve median survival, the control arm used prednisone (and placebo). Accrual was initiated in April 2008 and completed in July 2009. Although significant antitumor activity has been reported in ketoconazole-treated patients (a significant number of whom would have stopped treatment because of toxicity rather than resistance; refs. 3, 7), the data on cross-resistance between ketoconazole and abiraterone acetate are confounding, and prior treatment with ketoconazole was therefore an exclusion criterion. Fifteen percent of patients had received 2 prior lines of chemotherapy, and the median OS of the placebo and prednisone arm was 10.9 months. The median survival of patients treated with abiraterone acetate and prednisone was 14.8 months [hazard ratio = 0.646 (0.54 to 0.77), P < 0.0001; ref. 22].

Abiraterone acetate in combination with prednisone has also been evaluated in a randomized, placebo-controlled, double-blind phase III study in metastatic chemotherapy-naive CRPC patients (NCT00887198; Table 1). The primary endpoints are OS and progression-free survival. On the basis of the phase II data, one would expect abiraterone acetate and prednisone to have equivalent or greater efficacy in the predocetaxel setting, and, because of its better tolerability when compared with taxanes, abiraterone acetate may be increasingly used prior to chemotherapy (Table 2). In patients who are asymptomatic from their metastatic prostate cancer, the Cushingoid side-effects of long-term ACTH suppression by prednisone may become problematic. The combination of abiraterone acetate with alternative oral steroid dosing regimens or mineralocorticoid receptor antagonists merits further evaluation in this patient population.

The significant antitumor activity reported with abiraterone acetate has led to the clinical development of other CYP17 inhibitors (Table 1). Owing to the postulated similarity in the CYP17 domain that catalyses the C17,20-lyase and 17α-hydroxylase functions of this enzyme, therapies with hundred-fold specificity for the C17,20-lyase activity have not yet been reported. It is, therefore, possible that, because of intra- and interpatient pharmacokinetic variation, it may not be feasible to irreversibly inhibit C17,20-lyase while avoiding any inhibition of cortisol synthesis. However, novel CYP17 inhibitors with different properties may have slightly different clinical benefits. For example, TOK-001, which was originally identified in a drug screen at the University of Maryland to identify compounds that are dual CYP17 inhibitors and AR antagonists (23), is in phase I-II development (NCT00959959). Also, a placebo-controlled, randomized phase III study (primary endpoint: OS) of orteronel (TAK-700), another specific CYP17 inhibitor, in combination with prednisone recently commenced accrual of chemotherapy-treated CRPC patients (NCT01193257).

### Persistence of ligands that could activate a promiscuous androgen receptor in abiraterone-treated patients

Studies to date suggest that there is no increase in serum androgens at progression on abiraterone acetate (4, 5), although comprehensive evaluation of androgen levels in tumors before treatment and after progression is ongoing. Although resistance does not seem to be a result of pharmacologic failure, tumoral changes in CYP17 expression could overcome drug effect. Androgens are the most effective agonists of wild-type AR signaling, but point mutations, increased expression of the AR, and alterations in the AR-coactivator–repressor complex may occur with increasing frequency in patients after sequential hormone treatments and allow activation of the AR in preclinical models.

### Table 1. Agents Targeting AR in Clinical Development for Metastatic CRPC

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drug</th>
<th>Patient population</th>
<th>Phase of development</th>
<th>Clinicaltrials.gov registration number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationally designed</td>
<td>Abiraterone</td>
<td>Chemotherapy-treated</td>
<td>Phase III: reported at ESMO annual meeting 2010 (19)</td>
<td>NCT00638690</td>
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<tr>
<td>specific CYP 17</td>
<td>acetate</td>
<td></td>
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<tr>
<td>inhibitors</td>
<td>Orteronel (TAK-700)</td>
<td>Chemotherapy-naive</td>
<td>Phase III</td>
<td>NCT00887198</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
<td>Phase III</td>
<td>NCT01193257</td>
</tr>
<tr>
<td>Novel AR antagonists</td>
<td>MDV-3100</td>
<td>Chemotherapy-naive</td>
<td>Phase III</td>
<td>NCT01193244</td>
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<tr>
<td></td>
<td></td>
<td>Chemotherapy</td>
<td>Phase III</td>
<td>NCT00974311</td>
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<tr>
<td></td>
<td></td>
<td>treated</td>
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<tr>
<td></td>
<td>AZD3514</td>
<td>Chemotherapy-naive</td>
<td>Phase I-II</td>
<td>NCT01162395</td>
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<tr>
<td></td>
<td>ARN-509</td>
<td>Chemotherapy-naive</td>
<td>Phase I-II</td>
<td>NCT0117898</td>
</tr>
<tr>
<td>Dual CYP 17</td>
<td>TOK-001</td>
<td>Chemotherapy-naive</td>
<td>Phase I-II</td>
<td>NCT00959959</td>
</tr>
<tr>
<td>inhibitors</td>
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models by alternative ligands, such as deoxycorticosterone, corticosterone, and cortisol (Fig. 1; refs. 24–26). Mutations of AR could be clonally selected for by sequential hormonal treatments conferring a survival advantage on cells with a promiscuous AR, with mutations that allow activation by nonsuppressed ligands becoming increasingly prevalent in advanced disease. Current treatment strategies may therefore fail to achieve *in vivo* a tumor environment that is entirely free of potential AR ligands.

**Small molecule antagonists of the androgen receptor ligand-binding domain**

Nonsteroidal AR antagonists (most commonly bicalutamide, nilutamide, or flutamide) have been standard treatment for advanced prostate cancer for 3 decades (Fig. 1). Several studies have investigated combination of antiandrogens with castration, and a meta-analysis of randomized studies suggested a modest survival benefit (27). Also, the duration of response to these antiandrogens is often less than 4 months; their AR binding is reversible, and paradoxical agonism of the AR occurs in 10 to 15% of patients (15). The Sawyers laboratory, therefore, established a drug discovery program to screen for novel small molecules that inhibited PSA transcription in a bicalutamide-resistant model of LNCaP cells engineered to overexpress wild-type AR (28, 29). The screen started off with a chemical structure known to have exceedingly high affinity for the AR, and, through iterative structural changes, they identified a number of candidates that potently inhibited PSA in cells overexpressing AR (28). Moreover, this series of candidates also inhibited structurally promiscuous AR (for example with the W751C point mutation) that bicalutamide was agonistic to (29). One of the clinical leads (MDV3100) was licensed to Medivation and underwent evaluation in a 140-patient phase I-II study conducted by the U.S. Prostate Cancer Clinical Trials Consortium (2). In this study, treatment with MDV3100 at doses ≥60 mg resulted in PSA declines ≥50% in 50 to 60% of chemotherapy-naive or docetaxel-treated CRPC patients, most of whom had previously progressed on treatment with an antiandrogen and multiple other lines of hormone treatments (2). This outcome was associated with other objective endpoints of antitumor activity, including declines in CTC counts and radiologic progression; the median time to PSA progression in these chemotherapy-pretreated patients was 189 days (2). Declines in PSA ≥90% were also reported in 10 to 30% of patients. Epileptic seizures and severe fatigue were reported at doses ≥340 mg, which may be a class effect of antiandrogens that cross the blood-brain barrier (30). Nonetheless, the significant antitumor activity and absence of serious adverse events at doses <240 mg led to the initiation of a double-blind, placebo-controlled, randomized phase III study in docetaxel-treated patients of MDV3100 160 mg/day in combination with prednisone (NC100974311). The primary endpoint is OS. Comparing different clinical studies is fraught with caveats, but the data suggest that the declines in PSA and CTC count, radiologic responses, duration of response, and time on treatment in phase I-II studies of MDV3100 are similar to studies with abiraterone acetate. Moreover, MDV3100 is also undergoing evaluation in a large, placebo-controlled study in chemotherapy-naive

<table>
<thead>
<tr>
<th>Table 2. Predicted Castration-Resistant Prostate Cancer Treatment Dilemmas for Physicians in 2012</th>
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<tr>
<td>Treatment dilemma</td>
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<tr>
<td>What is the frequency of cross-resistance between abiraterone acetate and MDV3100, and is there a benefit in sequential use?</td>
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<tr>
<td>How does one decide whether to use abiraterone acetate or MDV3100 first?</td>
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<tr>
<td>Are abiraterone acetate or MDV3100 best used before docetaxel, and is there a patient subgroup that should be offered chemotherapy before either agent?</td>
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<tr>
<td>How does one select patients for cabazitaxel in preference to abiraterone acetate or MDV3100 after treatment with docetaxel?</td>
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<tr>
<td>How does one coordinate treatment with Sipuleucel-T with initiation of treatment with abiraterone acetate or MDV3100?</td>
</tr>
<tr>
<td>Should abiraterone acetate be continued or stopped at disease progression?</td>
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patients (NCT01212991). Predictably, these data have led to significant investment in the development of novel AR antagonists, and several are now undergoing evaluation in early clinical studies, including another clinical candidate from the same screening program as MDV3100 (ARN-509; Table 1). A multitude of novel AR antagonists with different pharmacologic and pharmacodynamic properties achieving regulatory approval may translate into significant benefits for our patients, with the possibility of sequential, albeit potentially less frequent and of shorter duration, secondary responses. However, in the absence of head-to-head studies, physicians are going to be unable to select the best sequence and type of agent to use.

**New treatment paradigms for metastatic prostate cancer**

**Castration-resistant prostate cancer.** The current phase III studies have been designed to confirm the efficacy of

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Figure 1. Strategies for therapeutically targeting the AR. The hypothalamus-pituitary-gonadal axis controls androgen synthesis as part of a negative feedback loop. Luteinizing hormone (LH) is released from the pituitary following stimulation by luteinizing hormone releasing hormone (LHRH) and stimulates testicular androgen production, whereas ACTH secreted by the anterior pituitary stimulates the adrenal production. Androgens or alternative ligands bind to wild-type or mutant AR, causing dissociation from HSPs and translocation of the AR to the nucleus. The AR binds to AREs on androgen responsive genes, including TMPRSS2:ERG and PSA, and coregulatory proteins are recruited for transcriptional activation. The 3 main structural components of the AR, the N-terminal domain (NTD), DNA-binding domain (DBD), and the LBD, are shown separately. Strategies with marketing approval or in late stages of clinical development involve targeting of the LBD or androgens; other potential ligands exist. Microtubules may also be essential to AR function and could be disrupted with taxanes. More novel strategies involve targeting of the NTD or chaperone proteins.
abiraterone acetate and MDV3100, but no attempt has yet been made to develop an evidence-based paradigm for the best treatment schedule. Moreover, the recent U.S. Food and Drug Administration (FDA) approval for metastatic CRPC of Sipuleucel-T (chemotherapy-naive and treated) and cabazitaxel (docetaxel-treated patients only), based on significant improvements in OS in randomized phase III studies (31, 32), introduces a number of treatment dilemmas for physicians if both abiraterone acetate and MDV3100 achieve regulatory approval in the pre- and postchemotherapy space (Table 2). It is possible that most physicians and patients would prefer to use abiraterone acetate or MDV3100 prior to docetaxel because of a perceived better tolerability, although the results of phase III studies in this setting will ultimately inform this decision. In the absence of combination or sequential data from randomized studies of abiraterone acetate and MDV3100, most physicians will probably use both agents sequentially with personal preference or local guidelines dictating the order of treatment. A proportion of patients who progress on these treatments with an increase in PSA are likely to benefit from further hormonal manipulations with agents such as estrogens or novel AR-targeting therapeutics (multiple novel agents are anticipated to be in clinical trials over the next few years; Table 1), although it is probable that the response rate will decrease owing to cross-resistance. Moreover, the survival benefit from docetaxel or cabazitaxel after treatment with abiraterone acetate or MDV3100 will remain unknown in the absence of the appropriate studies, although this may be impacted if the mechanism of action of taxanes are related to their effects on AR signaling (Fig. 1; ref. 33). Another critical challenge for physicians that currently occurs when PSA increases is when to discontinue or change treatments (Table 2). Patients may continue to derive benefit from ongoing maximal inhibition of AR as they do from continuous castration, and studies are urgently required to evaluate the benefit of continuing treatment with drugs such as abiraterone acetate or MDV3100 beyond progression, including, for example, after initiation of taxane chemotherapy.

Hormone-naive prostate cancer and other settings. No clinical studies have yet evaluated the benefit of combining a novel hormonal treatment with castration for hormone-naive patients. However, it is possible that the improved inhibition of AR will translate into a greater benefit than was observed with flutamide and nilutamide (27). Such phase III trials are now being planned that will address long-term safety concerns in addition to improved efficacy. Novel hormonal agents may also be critically important in the adjuvant setting to improve the outcome in the setting of high risk locally advanced disease.

On the Horizon

Intermediate endpoints of treatment effect

PSA is a useful pharmacodynamic biomarker of AR signaling, but changes in PSA are not approved by the regulatory authorities as an intermediate endpoint (surrogate) of OS in clinical studies. Although PSA is routinely used in patient practice to identify failure of treatment effect, cases in which PSA change is discordant from other endpoints of antitumor activity are well described. In particular, drugs targeting AR signaling may have a significant effect on PSA transcription but have minimal cytotoxic effect on resistant tumors. We and others have reported a significant association between CTC count and OS (34–36), and the recently reported abiraterone acetate phase III study included as a coprimary endpoint the evaluation of CTC count as an intermediate endpoint of survival. CTC enumeration has also been included in a number of other phase III studies, and this will allow evaluation of CTC count as an intermediate endpoint using a meta-analysis of several studies of effective agents. The studies to date used CellSearch for CTC enumeration; this is the only platform with FDA clearance, and it is robust with minimal interoperator variability and uses a well-established protocol for CTC identification. If multiple prospective randomized studies confirm a significant association between CTC count and treatment effect, CTC enumeration may become increasingly used to inform early treatment discontinuation.

Using predictive biomarkers to identify patient subgroups enriched for endocrine sensitive disease

We reported an increased prevalence of patients with hormone-regulated ERG gene rearrangements in the subpopulation who had >90% PSA declines with abiraterone acetate (37). However, a significant number of patients with an underlying hormone-regulated gene fusion were resistant (37). Moreover, the majority of prostate cancer patients respond by PSA measurements to first-line hormone treatment, suggesting that the underlying biology of treatment-naive disease may be hormone driven; however, even in the first-line setting, a decrease in PSA does not necessarily equate to antitumor activity. There seem to be mechanisms of cross-resistance between different treatments as the response rate to second-line and subsequent hormonal manipulations declines. However, resistance to one treatment may not necessarily denote resistance to other treatments. Predictive biomarkers of resistance will, therefore, allow patient selection for a specific treatment on the basis of an understanding of the underlying biology, rather than a trial of treatment. As CRPC tissue is often impossible to sequentially acquire, we have used CTC to molecularly characterize CRPC (37). Genomic evaluation of loss of PTEN and gain of AR in these studies in a limited number of patients failed to identify an association with response to abiraterone acetate, possibly in part because of intrapatient heterogeneity. Other groups have sequenced DNA from CTC for commonly occurring mutations of the AR; these analyses are now required in the context of clinical studies (38). CTC are not reliably identified in all patients, and CTC isolation can be costly and time consuming. The isolation and study of nucleic acids in plasma could, therefore, be an alternative strategy for characterization of patients using a blood sample (39).
Disrupting the androgen receptor transcription complex

Targeting of chaperones such as HSP90, which include key oncogenes such as HER2 (erbB2) as client proteins, is a therapeutic strategy that has been undergoing evaluation in several tumor types for close to a decade. Steroid receptors exist in complexes that include coactivator and corepressor proteins and chaperones. The understanding of the role of different members of this complex is incomplete. Some studies suggest HSP90 is predominantly cytoplasmic, and, as activated AR in progressing prostate cancer is predominantly nuclear, it has been proposed that other chaperones, such as HSP27, may be better therapeutic targets (40, 41). We and others have tested several HSP90 inhibitors in early clinical studies and with limited antitumor activity reported to date in CRPC, although we have reported a durable response lasting more than a year in a patient treated with 17DMAG (42, 43). It is unclear whether this limited antitumor activity is due to poor drug pharmacology, incomplete or transient target inhibition, continued coexistent ligand activation of AR, or significant redundancy of chaperone proteins. As HSP27 is not ATP dependent, no specific small molecule inhibitors have been developed to date, but an HSP27-targeting locked antisense (OGX-427) in combination with prednisone is currently undergoing evaluation in a randomized phase II study in CRPC (NCT01120470; Fig. 1). Another strategy that could be employed for disrupting the AR transcriptional complex is the inhibition of histone deacetylases (HDAC) that regulate AR transcriptional activity in vitro (44); however, HDAC inhibitors tested in clinical studies to date have failed to reproduce this effect (45).

Ligand-binding domain–independent targeting of the androgen receptor

Current hormonal therapies target the AR ligand-binding domain (LBD), and, predictably, most molecular changes that develop with castration resistance predominantly involve aberrations of the AR LBD. The AR amino-terminal domain is responsible for ARE binding and regulation of gene transcription, and this introduces the possibility of improving therapeutic efficiency by targeting this domain (Fig. 1). A drug discovery screen identified candidate small molecule inhibitors of the AR amino-terminal domain (46), but these data require further preclinical validation prior to consideration for clinical testing. Also, as the technologies for developing antisense or RNA-silencing therapeutics to silence genes such as AR improve, one could envision the design of species targeting amino-terminal domain sequences.

Targeting steroid-receptor–regulated gene fusions

The discovery of chromosomal rearrangements or part deletions in prostate cancer that result in overexpression of oncogenes by AR or other steroid receptors introduced the possibility of directly targeting gene fusions and avoiding the side effects of and resistance to hormone treatments. The 3’ constituents of gene fusions described to date include members of the ETS family, most commonly ERG and ETV1, and the RAf kinase family, B-RAF and RAF-1 (47, 48). Gene fusions involving ERG, most commonly with the serine protease TMPRSS2 following deletion of the 2.1-Mb region between ERG and TMPRSS2 on chromosome 21(q), occur in 30 to 50% of prostate cancers (48). Several 5’ gene fusion partners have been described (49). A functional ARE sequence has been shown in silico to be in proximity of the majority of promoter genes (50), and expression of the majority of partners has also been confirmed in vitro or in animal models to be regulated by androgens or other steroid ligands (49). These could include estrogens as shown in the AR-negative prostate cancer cell line NCI-H660, in which transcription of the TMPRSS2:ERG gene fusion is modulated by estrogen receptor signaling (51). Therapeutics targeting the RAF-MEK axis are undergoing evaluation in non–tumor-specific early clinical studies. However rearrangement-dependent overexpression of RAF kinases occurs in <3% of prostate cancers (47), and, therefore, drug discovery programs to identify therapeutic strategies targeting the commonly rearranged ETS transcription factors are ongoing.

Conclusion

The increase in prostate cancer research funding 2 decades ago is bearing fruit with new scientific discoveries allowing a better understanding of the biology that underlies the disease and a consequent exponential increase in novel prostate cancer therapeutics entering clinical trials. 2010 saw the unprecedented publication of 2 positive phase III trials (Sipuleucel-T and cabazitaxel; refs. 31, 32) with FDA approval and the presentation of a third positive phase III trial (abiraterone acetate; ref. 22). However, despite 7 decades of hormonal treatments for prostate cancer, it is generally accepted that treatments to date fail to achieve indefinite complete inhibition of AR signaling and repeated sequential therapeutic targeting of the AR in metastatic prostate cancer remains necessary to maintain remission.

Disclosure of Potential Conflicts of Interest

G. Attard, J. Richards, and J.S. de Bono are employees of The Institute of Cancer Research, which has a commercial interest in the development of abiraterone acetate. J.S. de Bono has served as a paid consultant for Johnson & Johnson, Medivation, Astellas, Dendreon, and AstraZeneca. G. Attard has served as a paid consultant for Millennium Pharmaceuticals and as an uncompensated advisor for Johnson & Johnson. G. Attard is on The Institute of Cancer Research list of rewards to inventors of abiraterone acetate.

Grant Support

G Attard, J. Richards, and J.S. de Bono are employees of the Section of Medicine at The Institute of Cancer Research, which is supported by a Cancer Research UK program grant and an Experimental Cancer Medical Centre (ECMC) grant from Cancer Research UK and the Department of Health (CS/AT/001). G. Attard holds a Prostate Cancer Foundation (Santa Monica, CA) Young Investigator Award. G. Attard and J.S. de Bono also acknowledge NHS funding to the NHBR biomedical research center.

Received December 7, 2010; revised January 20, 2011; accepted January 24, 2011; published OnlineFirst March 3, 2011.
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Clin Cancer Res; 17(7) April 1, 2011

Clinical Cancer Research

1656

Published OnlineFirst March 3, 2011; DOI: 10.1158/1078-0432.CCR-10-0567

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Clinical Cancer Research

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