Translating Scientific Advancement into Clinical Benefit for Castration-Resistant Prostate Cancer Patients

Gerhardt Attard and Johann S. de Bono

Abstract

In the past 12 months, three novel therapeutics—sipuleucel-T, cabazitaxel, and abiraterone acetate—were granted Food and Drug Administration regulatory approval for the treatment of metastatic castration-resistant prostate cancer (CRPC) patients based on phase III studies that showed a survival advantage. Other agents, including the novel antiandrogen MDV3100, are at an advanced stage of clinical phase III evaluation. The treatment paradigm for CRPC has now changed significantly, and this has introduced new challenges for physicians, including selecting patients for specific therapies, developing the best sequencing and combination regimens for the several new effective agents that have recently been approved or are in development, and dissecting mechanisms of resistance that will inform the development of a new generation of therapeutics. This Focus issue reviews the results obtained with immunotherapies, taxane cytotoxics, and androgen receptor targeting therapeutics for CRPC, as well as the postulated mechanisms of resistance to these protocols and proposed strategies for improvement. The use of biomarkers for patient selection, monitoring of treatment activity, and acceleration of drug approval will be critical for achieving further improvements in the treatment for CRPC, and is also discussed in detail. Clin Cancer Res; 17(12); 3867–75. ©2011 AACR.

Introduction

The publication of this Focus issue of Clinical Cancer Research was instigated by the recent report of 3 positive registration phase III studies in metastatic castration-resistant prostate cancer (CRPC; Table 1). Reporting of a fourth registration phase III trial, of the novel antiandrogen MDV3100, is expected within the next 12 months. The total improvement in median survival for an individual patient treated with 3 or 4 novel effective agents is unlikely to be cumulative, but it is probable that most patients with CRPC will live significantly longer compared with 5 years ago. A decade of scientific discoveries driven by increased funding for prostate cancer research has improved our understanding of the molecular biology underlying prostate cancer progression and driven the development of new therapies. The finding that aberrations of the androgen receptor (AR) develop with sequential hormone treatments (1–3), and in vitro and in vivo evidence that increased AR expression induces resistance to hormone therapies (4) led to efforts to improve on therapeutics targeting the AR axis [recently reviewed in ref. 5 and by Massard and Fizazi (6) in this Focus issue]. However, CRPC remains a fatal disease and patients invariably develop drug resistance. A long list of other therapeutic candidates have been proposed and targeted clinically, mostly with limited success. For example, phase II trials of therapeutics targeting HER2 in CRPC, which was shown in robust preclinical experiments to modulate the AR and induce castration resistance (7–9), failed to identify antitumor activity (10). However, the use of declines in prostate-specific antigen (PSA) as the primary endpoint in phase II studies has increased the risk of early drug attrition for potentially effective therapies. In the future, the use of endpoints that are independent of AR signaling, such as changes in circulating tumor cell (CTC) count or bone imaging, could be critical for identifying active treatments in early clinical trials. Moreover, strategies that reverse resistance to androgen deprivation in preclinical models may only be effective when AR signaling has been effectively abrogated in patients, and novel agents may therefore prove to be most effective when combined with effective CYP17 inhibition of AR antagonism (Table 1).

This Focus issue concentrates on discussing the results and potential for improvement of strategies with proven efficacy in CRPC, namely, AR-targeting therapeutics (6),...
taxane cytotoxics (11), and immunotherapy (12). Given the important role biomarkers could have in accelerating cancer drug development and improving patient management, a fourth article in this series reviews the biomarker landscape beyond PSA (13). Several other novel therapeutic strategies that target prostate cancer aberrations are in late preclinical and early clinical development, and a comprehensive review of all of these approaches is beyond the scope of this series. Table 2 summarizes molecular aberrations that have been identified in prostate cancer and are targeted by therapeutics currently undergoing clinical evaluation. The discovery in 2005 by Tomlins and colleagues (14) of hormone-regulated ERG and ETV1 gene fusions led to a search for therapeutic strategies that inhibit either ERG or ETV1 or interacting proteins that are key to the function of ERG or ETV1. Gene fusions involving BRAF and RAF-1 (15) are significantly less common, but could be inhibited by therapeutics already in clinical trials (Table 2). Similarly, the identification of overexpression of SPINK1 in a subset of prostate cancers with no underlying ETS gene rearrangement introduced the possibility of efficacy in therapeutically targeting SPINK1 (16, 17).

Table 1. Failure of active treatments for CRCP in early clinical trials: causes and possible solutions

<table>
<thead>
<tr>
<th>Problem</th>
<th>Cause</th>
<th>Possible solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of declines in PSA as the primary endpoint in phase II studies.</td>
<td>Active agents may fail due to an early rise in PSA.</td>
<td>Use of AR-independent activity endpoints, including changes in CTC count and bone imaging.</td>
</tr>
<tr>
<td>Incomplete abrogation of AR signaling in CRPC patients tested.</td>
<td>Antitumor activity observed in preclinical models with effective inhibition of AR signaling may not be effective in the presence of activated AR.</td>
<td>Clinical trial combinations with novel treatments targeting AR, including abiraterone acetate and/or MDV3100.</td>
</tr>
<tr>
<td>Failure to include patient subpopulations in which a treatment would be active.</td>
<td>Therapeutics targeting an aberration present in &lt;30% of the population may not recruit sufficient patients in phase II trials to reject the null hypothesis.</td>
<td>Biomarker-driven patient selection for clinical trial recruitment.</td>
</tr>
</tbody>
</table>

Table 2. Molecular aberrations, therapeutic strategies, and biomarker profiles currently under evaluation

<table>
<thead>
<tr>
<th>Molecular aberration</th>
<th>Therapeutic strategy</th>
<th>Biomarker profiles that could be used to identify sensitive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation of the PI3K/AKT pathway</td>
<td>Small-molecule inhibitors of PI3K or AKT</td>
<td>Loss of PTEN, expression of phospho-AKT</td>
</tr>
<tr>
<td>DNA repair defects</td>
<td>PARP inhibitors and other therapies that exploit synthetic lethality</td>
<td>Loss of PTEN, chromosomal rearrangements</td>
</tr>
<tr>
<td>Overexpression of IGF-1R</td>
<td>Monoclonal antibodies and small-molecule inhibitors of IGF-1R</td>
<td>IGF-1R overexpression</td>
</tr>
<tr>
<td>Amplification of c-Myc</td>
<td>Inhibitors of PIM kinase</td>
<td>Increased c-Myc copy number</td>
</tr>
<tr>
<td>Gene fusions involving RAF family of oncogenes</td>
<td>Small-molecule inhibitors of RAF or MEK</td>
<td>Detection of BRAF or RAF-1 gene fusions by fluorescence in situ hybridization (break-apart assays) or RT-PCR</td>
</tr>
</tbody>
</table>

Treatment of Metastatic Prostate Cancer: A Historical Perspective

High doses of estrogens were shown to induce tumor responses in metastatic prostate cancer seven decades ago (5). This strategy was superseded by medical or surgical castration, and the use of estrogens for...
hormone-therapy–naïve disease is no longer recommended (Fig. 1). The efficacy of castration was improved upon by the development of small-molecule AR antagonists. In 2000, a meta-analysis of clinical trials published between 1983 and 1987 that evaluated the combination of initiation of castration with either the nonsteroidal antiandrogens nilutamide or flutamide or the steroidal compound cyproterone acetate showed a 5-year improvement in overall survival (OS) of 2% to 3%, although the range of uncertainty was 0% to 5%, compared to castration alone (18). The limited improvement in OS observed when antiandrogens are combined with castration may be a result of the pharmacologic limitations of the agents used, and does not necessarily mean that the strategy of combining androgen deprivation with AR antagonism is ineffective. For example, currently approved antiandrogens are reversible inhibitors of the AR, have a several-fold lower affinity for the AR compared with androgens, and mutations in the AR that cause these drugs to become agonistic have been detected in at least 15% to 30% of patients after development of resistance (3). In fact, the previously used term "maximum androgen blockade" could now be replaced by a more appropriate definition, such as "dual targeting of the AR," to reflect the current limitations of this strategy. Nonetheless, antiandrogens are currently a common addition to castration at disease progression (indicated by a rise in PSA or clinical or radiological worsening of disease) and are associated with declines in PSA in 40% to 60% of patients. They can also be used as monotherapy in preference to castration as a first-line treatment for metastatic patients in whom avoidance of the side effects of castration is important. A series of phase II and phase III trials that were not powered to detect improvements in OS reported tumor responses with estrogens, steroids, and ketoconazole in CRPC resistant to antiandrogens; however, none of these strategies...
has shown a survival benefit (19). Mitoxantrone chemotherapy in combination with prednisone received regulatory approval for treatment of CRPC based on an improvement in quality of life for CRPC patients. Two large randomized studies that compared 3-weekly docetaxel and daily prednisone with 1-weekly docetaxel and daily prednisone or 3-weekly mitoxantrone and prednisone (TAX-327) and 3-weekly docetaxel and estramustine with mitoxantrone and estramustine (SWOG-9916) were the first therapeutic studies to show an improvement in OS for CRPC patients (2.5 months for TAX-327, later updated to 2.9 months; Table 3; refs. 20–22). Bisphosphonates and, more recently, inhibitors of receptor activator of NF-κB ligand (RANKL) achieved registration for the treatment of CRPC based on a reduction in first on-study skeletal-related events: a composite endpoint that included pathologic fracture, radiation therapy, surgery to bone, or spinal cord compression (23, 24). This treatment scheme is summarized in Fig. 1.

**Targeting AR Signaling in CRPC**

The past decade witnessed a paradigm shift in CRPC treatment with the clinical confirmation that a significant proportion of CRPCs remain dependent on ligand activation of the AR (6). Inhibition of CYP17-dependent hormone synthesis, which was initially attempted using the nonspecific CYP inhibitor ketoconazole (25), has now been proven to be a valid therapeutic approach with the use of the selective and potent CYP17 inhibitor abiraterone acetate. The recently reported placebo-controlled, registration phase III study of abiraterone acetate and prednisone in docetaxel-treated patients confirmed a significant survival advantage with minimal toxicity, leading to FDA approval of this agent for the treatment of patients in the postdocetaxel setting (April 2011; ref. 26). Also, as discussed by Massard and Fizazi (6) in this issue of Clinical Cancer Research, phase I and II clinical trials of abiraterone acetate reported significant activity in chemotherapy-naïve CRPC patients (27–29), and abiraterone acetate may be as effective in the chemotherapy-naïve setting as it is postchemotherapy (as evaluated in a multicenter, global, placebo-controlled phase III study [NCT00887198] due for reporting in the next 24 months; Table 4). Similarly, the novel antiandrogen MDV3100, which was rationally designed and selected for significant activity in bicalutamide-resistant preclinical models (30), is highly active in chemotherapy-naïve and docetaxel-treated CRPC patients who previously progressed on the antiandrogens bicalutamide or flutamide and other hormonal therapies (31). Phase III survival data for MDV3100 in both chemotherapy-naïve and docetaxel-pretreated patients are expected within the next 24 months, and it is hoped that MDV3100 will become another therapeutic option.
for treating this disease (Table 4). Evaluation of the long-term combination of AR blockade with abiraterone acetate and/or MDV3100 in combination with castration at development of metastases or adjuvantly in nonmetastatic, high-risk, locally advanced disease is now required. In both registration phase III trials, abiraterone acetate was combined with prednisone or prednisolone to maximize efficacy and minimize toxicity from secondary mineralocorticoid excess. Abiraterone acetate can be administered alone with mineralocorticoid receptor antagonists to minimize toxicity from mineralocorticoid excess (32), a strategy that may be required in early disease when long-term use of steroids may not be tolerated. However, spironolactone potently activates AR signaling (33) and should therefore be avoided in this patient population.

The division of patients with CRPC into chemotherapy-naive and docetaxel-treated populations for evaluation of AR-targeting agents has been driven more by practical considerations than by scientific logic, namely, the requirement to select a population that will minimize the lead time for obtaining regulatory approval for a novel agent. However, emerging evidence that the mechanism of action of taxanes in prostate cancer may be due at least in part to the disruption of membrane-to-nucleus shuttling of steroid receptors (34, 35) suggests that one may observe cross-resistance between hormone therapies and taxanes, with response rates to either agent decreasing after sequential treatment. This may introduce important considerations for treatment sequencing that have not been suitably studied to date. Similarly, the combination of hormone therapies such as abiraterone acetate and MDV3100 with docetaxel in CRPC patients warrants evaluation, but improved efficacy from such a combination is certainly not a foregone conclusion. Predictably, following reporting of the phase I and II results for abiraterone acetate and MDV3100, a variety of novel agents targeting AR entered clinical evaluation for CRPC (recently reviewed in ref. 5). We previously proposed that continued activation of the AR and/or other steroid receptor signaling pathways results in drug resistance in a significant proportion of CRPC patients progressing on abiraterone acetate and/or MDV3100, and further targeting of this pathway is a valid approach (reviewed in ref. 1). However, as is the case with all new agents targeting the AR ligand-binding domain that are currently under clinical evaluation, cross-resistance could be high, and novel approaches such as direct inhibition of the AR amino-terminal domain (36) may be required to achieve the next significant improvement in outcome for CRPC patients.

Defining a Role for Immunotherapy in the Treatment of CRPC

The year 2010 saw the publication of the positive IMPACT phase III study of sipuleucel-T (ref. 37; Table 3). This was soon followed by the publication of a phase II study of a PSA-targeted poxviral vaccine, which also reported an improvement in median survival, a secondary endpoint in this study (38). Other immunotherapy approaches are also being evaluated in CRPC phase III studies, including the monoclonal antibody to CTLA4, ipilimumab, which is being investigated in both chemotherapy-naive and docetaxel-treated patients (http://clinicaltrials.gov, identifier numbers NCT01057810 and NCT00861614, respectively; Table 4). CTLA4 is a negative regulator of T cells, and ipilimumab has been reported to confer a survival advantage in malignant melanoma.

### Table 4. Treatments in advanced phase III development for progressive metastatic CRPC

<table>
<thead>
<tr>
<th>Experimental arm</th>
<th>Comparator arm</th>
<th>Disease state</th>
<th>clinicaltrials.gov Identifier number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily MDV-3100 and prednisone (AFFIRM)</td>
<td>Placebo and prednisone</td>
<td>Docetaxel-treated</td>
<td>NCT00974311</td>
</tr>
<tr>
<td>Daily abiraterone acetate and prednisone (COU-302)</td>
<td>Placebo and prednisone</td>
<td>Chemotherapy-naive</td>
<td>NCT00887198</td>
</tr>
<tr>
<td>Daily MDV-3100 (PREVAIL)</td>
<td>Placebo</td>
<td>Chemotherapy-naive</td>
<td>NCT01212991</td>
</tr>
<tr>
<td>Daily orteronel and prednisone</td>
<td>Placebo and prednisone</td>
<td>Chemotherapy-naive</td>
<td>NCT01193257</td>
</tr>
<tr>
<td>Daily orteronel and prednisone</td>
<td>Placebo and prednisone</td>
<td>Chemotherapy-naive</td>
<td>NCT01193244</td>
</tr>
<tr>
<td>Alpharadin</td>
<td>Placebo and prednisone</td>
<td>Chemotherapy-naive and docetaxel treated</td>
<td>NCT00699751</td>
</tr>
</tbody>
</table>

NOTE: See Table 4 in ref. 11 for a list of phase III trials evaluating the pairing of novel agents with docetaxel. Also see Fig. 1 for placement of trials in the CRPC-management paradigm.
through postulated enhancement of the immune response (39). The majority of patients tolerate treatment well, but side effects can be very severe, with a treatment-related mortality of 2% (39). In contrast, minimal toxicity has been reported with vaccine therapy. Other approaches for stimulating antitumor immunity are also undergoing evaluation, including blockade of PD-1, an inhibitory receptor expressed on the surface of activated T cells (40). As proposed by Gulley and Drake (12) in this Focus issue, the most appropriate time to use immunotherapy is probably when the tumor load is lowest and the induced immune response has the best chance of significantly affecting the upward slope of tumor growth. This introduces the possibility of using an approved vaccine therapy, such as sipuleucel-T, at development of castration resistance, thus allowing a significant time interval from initiation of steroids or chemotherapy (Fig. 1). Gulley and Drake also discuss the combination of more than one immunotherapy agent or of immunotherapy with other treatments.

In the absence of biomarkers of response or robust pharmacodynamic endpoints for immunotherapy, it is not clear whether the significant improvements in median survival reported to date are due to very prolonged responses in a small subpopulation of patients or a more modest improvement across all patients. Also, physicians face challenges in continuing immunotherapy in patients with a rising PSA and no objective evidence of benefit, in terms of both justification of cost and patient reassurance. Greater efforts to understand the mechanism of action underlying treatment and to develop pharmacodynamic endpoints will be required in future immunotherapy clinical trials if significant improvements are to be made in antitumor efficacy and cost-effectiveness. Immunotherapy approaches for hormone-sensitive disease are also undergoing evaluation, but in the absence of surrogates of response, the long lead time to meet a primary endpoint of OS and the impact of cross-over to other agents after the trial therapeutic intervention will make such studies challenging to conduct and interpret.

**Chemotherapy for CRPC: Beyond Single-Agent Docetaxel**

After the publication of the TAX327 and SWOG-9916 registration phase III studies (20, 21), docetaxel replaced mitoxantrone as the first-line cytotoxic choice for palliation of symptoms in metastatic CRPC patients. The TAX327 and SWOG-9916 studies aimed to give patients 10 cycles of treatment; however, patients who show an ongoing response and tolerate treatment are often administered several more cycles of docetaxel. Moreover, a number of retrospective analyses have reported secondary responses in re-treated patients who had progressed after stopping first-line docetaxel (41). However, the absence of robust biomarkers of response and progression for CRPC makes it difficult to select patients who continue to be docetaxel-sensitive for readministration of this taxane. Most studies used PSA-based criteria, e.g., by rechallenging patients who showed a decline in PSA of ≥50% with no increase for at least 3 months after stopping treatment. In the absence of robust survival data for re-treatment with docetaxel, it is hard to interpret these findings. The recently reported TROPIC study (Table 1) showed that the use of cabazitaxel in patients previously treated with docetaxel is effective and improves median survival by 2.4 months (42). Significant response rates were reported for patients who had previously progressed during docetaxel treatment as well as within 12 weeks of completing docetaxel. This suggests that in addition to the secondary responses one would expect from re-treatment with docetaxel, the pharmacologic properties of cabazitaxel might further improve on the antitumor activity of docetaxel. This approach is now undergoing clinical evaluation in a direct comparison of docetaxel and cabazitaxel. In view of the risks reported for this agent, cabazitaxel should be administered with the appropriate precautions by oncologists with expertise in managing neutropenic sepsis.

Nonetheless, taxane resistance is inevitable for most patients with CRPC, and remains one of the key challenges in the treatment of this disease. As discussed by Madan and colleagues (11), it may be possible to delay the time-to-progression on taxanes by interrupting treatment after an arbitrary measure of tumor response is achieved, by combining it with another novel or established drug, or by combining both of these strategies. The first strategy is limited by the unavailability of a suitable surrogate of tumor response that could indicate the correct time to interrupt treatment. Tumor responses in the absence of a decline in PSA are well described, and declines in PSA may not truly represent a tumor response. The second strategy is undergoing extensive evaluation, with at least 7 different novel agents in phase III docetaxel-combination clinical trials (see Table 4 in ref. 11). The mechanisms underlying taxane resistance are not completely understood, although a number of hypotheses exist (see Table 1 in ref. 11). These mechanisms could be CRPC-specific, such as alterations in inhibition of AR signaling, or cancer-generic, such as tubulin mutations. Interestingly, castrated patients show increased clearance of docetaxel compared with noncastrated patients, which could explain the relatively good tol-
erability of docetaxel in CRPC but may also contribute to treatment failure (43).

Biomarker-Driven Therapeutic Development for CRPC

As discussed by Danila and colleagues (13) in this issue, robust intermediate endpoints or surrogate biomarkers of treatment response are urgently needed for CRPC. A number of novel biomarkers are undergoing evaluation as potential surrogates of response, probably foremost among which is the CTC count. A CTC count of <5, compared with ≥5, respectively, before or after one or more cycles of cytotoxic treatment for CRPC is associated with longer survival (44). Demonstration of surrogacy requires evaluation of CTC in several positive therapeutic phase III trials. These studies are ongoing, including the recently reported phase III study of abiraterone acetate in docetaxel-treated patients. An improved understanding of the molecular biology underlying CRPC is also driving the evaluation of predictive biomarkers that could be used to enrich for patients who are more likely to respond to a specific treatment. The discovery of hormone-driven ERG gene fusions in 50% to 70% of prostate cancers provided a compelling explanation for the hormone-driven nature of prostate cancer (14). Genomic changes, such as rearrangements of ERG or gain of AR, can be robustly evaluated in CTC and tissue via fluorescence in situ hybridization (45), allowing the stratification of patients into different molecular subgroups that could have differential responses to specific therapies. In a recent study, massively parallel, high-resolution, deep sequencing of prostate tumors was used to identify multiple novel somatic mutations and chromosomal rearrangements (46). As deep-sequencing technology and other whole-genome and expression-analysis platforms become more cost-effective, strategies involving comprehensive molecular evaluations, subclassification of all patients, and targeted selection for treatments will become more appealing.

Future Strategies

As is evident from this Focus issue, significant advances have been made in prostate cancer research in the past decade. We propose a new treatment pathway for CRPC that includes agents in advanced phase III development (Fig. 1). In addition to the continuing requirement for novel effective drugs and therapeutic strategies, several new challenges now confront physicians treating CRPC. These challenges include developing the best sequencing and combination regimens for the several new effective agents that have recently been approved or are in development, dissecting mechanisms of resistance that will inform the development of a new generation of therapies, and conducting well-powered, hypothesis-testing studies (5).

Disclosure of Potential Conflicts of Interest

G. Attard 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 Veridex 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

Cancer Research UK and the Department of Health [Cancer Research UK program grant and Experimental Cancer Medical Centre grant (C51/ A7401) to Section of Medicine, Institute of Cancer Research]; Prostate Cancer Foundation Young Investigator Award (G. Attard); and National Health Service funding to the Royal Marsden Hospital National Institute for Health Research Biomedical Research Centre.

Received April 12, 2011; revised April 28, 2011; accepted April 28, 2011; published online June 16, 2011.

References

7. Craft N, Shostak Y, Carey M, Sawyer CL. A mechanism for hormone-independent prostate cancer through modulation of...


Translating Scientific Advancement into Clinical Benefit for Castration-Resistant Prostate Cancer Patients

Gerhardt Attard and Johann S. de Bono

*Clin Cancer Res* 2011;17:3867-3875.

Updated version  Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/17/12/3867

Cited articles  This article cites 46 articles, 21 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/17/12/3867.full#ref-list-1

Citing articles  This article has been cited by 11 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/17/12/3867.full#related-urls

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.