Prostate Cancer: Evolution or Revolution?

Eric J. Small, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA
Johann Sebastian de Bono, The Royal Marsden National Health Services Foundation Trust; and The Institute of Cancer Research, Sutton, Surrey, United Kingdom

In this issue of *Journal of Clinical Oncology*, we present a special series on prostate cancer that illustrates how our understanding of the biology and therapy of this disease has changed over the last few years. This series comes on the heels of the 2011 Genitourinary Cancers Symposium (held February 17 to 19, 2011, in Orlando, FL), jointly sponsored by the American Society of Clinical Oncology, the American Society for Therapeutic and Radiation Oncology, and the Society of Urologic Oncology. It is instructive to consider how the field has evolved, as articulated in the review articles in this issue, compared with the state of the art described in a special edition of the *Journal* published shortly after the first Prostate Cancer Symposium in 2005.1

**The Landscape in 2005**

In 2005, the treatment paradigm for prostate cancer was relatively simple. Patients with clinically localized disease were generally offered definitive local therapy; patients with locally advanced or locoregional disease were often treated with androgen deprivation, just as if they were patients with metastatic disease; and patients who developed hormone resistance were considered candidates for docetaxel therapy. The docetaxel/prednisone regimen was approved in 2004 for the management of patients with metastatic castration-refractory prostate cancer (CRPC) after two phase III trials (TAX 327 and Southwest Oncology Group 9916) demonstrated a survival advantage of this combination over the prior cytotoxic standard, mitoxantrone.2,3 The approval of docetaxel in 2004 brought the number of agents approved for use in patients with advanced prostate cancer to six; docetaxel joined strontium 89, estramustine phosphate, samarium 153, zoledronic acid, and mitoxantrone.4-7 Notably, none of the other five agents had been approved on the basis of prolonging life in this group of patients, and three (strontium, samarium, mitoxantrone) were explicitly developed and approved as palliative agents. The year 2004 also marked the publication of results from Cancer and Leukemia Group B (CALGB) 9583, which demonstrated the superior activity of ketoconazole together with antiandrogen withdrawal compared with antiandrogen withdrawal alone in this group of patients.8 At the time of the publications of results with docetaxel and ketoconazole, these patients were still said to have developed hormone-resistant prostate cancer. Our increased understanding of this disease state from preclinical data, clinical trials, and translational studies has now led to this disease being more accurately defined as CRPC, although the term “advanced prostate cancer” may be more acceptable to both clinicians and patients.9

**The Landscape in 2011**

**Biology.** In 2011, the therapeutic spectrum has changed dramatically, and our understanding of the biology of patients with prostate cancer is far more sophisticated. It is gratifying to observe that research dedicated to understanding the biology of prostate cancer has exploded exponentially. In no small measure, the development of many of the novel agents being tested in patients with advanced disease reflects a change in the understanding of the biology of CRPC. There have been considerable strides in understanding biologic events in CRPC, from the mechanisms driving continued androgen receptor signaling, the engagement of bone remodeling mechanisms, immunobiology including the role of immune checkpoints, and an understanding of the ETS fusion proteins.

This issue of *Journal of Clinical Oncology* focuses on several critical biologic observations. First, as outlined by Ryan and Tindall,10 the androgen receptor is recognized as an ongoing critically important driver (and validated target) in prostate cancer that has progressed despite androgen deprivation therapy. Unlike other malignancies, however, activating mutations in the receptor probably play only a small role in disease pathogenesis, although this may have an important role in treatment resistance. Moreover, although overexpression of the androgen receptor is a common event, this is frequently linked to a commensurate increase in intratumoral ligand. In addition, not only do adrenal androgens play a critical role in prostate cancer pathogenesis, but it is now appreciated that prostate cancer cells themselves can serve as a paracrine and autocrine organ, developing all the synthetic machinery to produce multiple steroids, including androgens and estrogens. Thus, given an environment in which disease progression is mediated by an increase in both receptor and ligand, it is not surprising that agents that target the receptor (such as the novel antiandrogens MDV3100 and ARN509), and ligand synthesis inhibitors (such as abiraterone acetate, TAK700), or both (TOK001) have been tested. Several of these agents have been shown to have considerable activity in CRPC. As discussed in the review by Ryan and Tindall,11 the first such positive trial was reported in patients with metastatic CRPC who had progressed after docetaxel chemotherapy and who were randomized to abiraterone plus prednisone versus placebo plus prednisone.11 This trial demonstrated a significant overall survival advantage with abiraterone of 3.9 months. These data have unambiguously validated the androgen receptor as a target in advanced prostate cancer progressing despite castration and once and for all have established that patients with “hormone-resistant prostate” cancer are, in fact, not always resistant to hormonal manipulations targeting the androgen...
receptor, and led to US Food and Drug Administration approval of abiraterone acetate. Moreover, this study has proven that hormonal treatment can still have important antitumor activity after chemotherapy administration, despite the treatment of patients with late-stage and visceral disease.

The second major biologic observation is described by Rubin et al.12 These and other authors have made the seminal observation that fusion proteins, once felt to be pertinent largely in hematologic malignancies are a common event in prostate cancer.13,14 These rearranged oncogenes—including ERG, ETV1, ETV4, ETV5, and BRAF—have emerged as critically important driver genomic changes that probably occur early in prostate carcinogenesis, possibly as a direct result of the impact of ligand binding to the androgen receptor and topoisomerase IIb–induced double-strand DNA breaks at androgen receptor DNA binding sites/response elements. It is hoped that these rearranged oncogenes will prove to be important therapeutic targets that lead to effective therapies that do not induce androgen deprivation. Moreover, the observation that androgens induce the ETS gene rearrangements further increase the biologic plausibility of androgen synthesis inhibition in prostate cancer prevention, although this remains challenging and controversial research.15 A key question that remains to be addressed is whether DNA repair defects, perhaps resulting from Nkx3.1 or PTEN loss early in prostate carcinogenesis, are required to permit the generation of these rearrangements.16 This is a particularly important question given that BRCA2 mutations expedite prostate carcinogenesis, and cancer with homologous recombination DNA repair defects are sensitive to poly(adenosine diphosphate) ribose polymerase17 inhibitors. The development of molecular diagnostics evaluating these rearranged genes may also be critically important to delivering molecularly stratified and more personalized prostate cancer medicine.

Therapeutics. Critically important changes in the way patients with prostate cancer are treated have occurred at both ends of the natural history continuum. Although dramatic advances have been made in the treatment of patients with advanced disease, equally important observations have been made in patients with low-risk localized prostate cancer. The dictum first popularized by Dr. Whitmore, who famously asked: “Is cure possible? Is cure necessary? Is cure possible only when it is not necessary?” has gained traction with the growing understanding of the role of active surveillance. Cooperberg et al19 update the available data on active surveillance. Ironically, the broader understanding of active surveillance and its off-uptake among patients and physicians proved a barrier to accrual to a high-priority surveillance versus intervention phase III trial, leading to its premature closure in May 2011. A critically important mandate remains the development of molecular biomarkers that can identify patients with good prognosis who merit this conservative treatment approach.

At the other end of the disease state spectrum, the development of novel approaches for patients with progressive disease despite androgen deprivation therapy has been even more dramatic. Thus, in 2011, therapeutic options for patients with metastatic CRPC include four new agents approved by the US Food and Drug Administration in 2010 and 2011, providing a total of 10 approved agents. These new agents include an immunotherapeutic product (sipuleucel-T), a bone-targeting agent (denosumab), a cytotoxic agent (cabazitaxel),20–22 and as discussed, an androgen receptor–targeting agent, abiraterone acetate. Three of these agents were approved on the basis of prolonging life in patients with CRPC (sipuleucel-T, abiraterone, and cabazitaxel).

As pointed out by Cha and Fong23 in their review of immunotherapy, the approval of sipuleucel-T by the US Food and Drug Administration is a landmark event that marks the first immunotherapeutic in prostate cancer and one of few active immune agents in oncology. However, as Cha and Fong point out, although sipuleucel-T prolongs life in patients with CRPC, its mechanism of action is not fully understood and the role of checkpoint inhibition with drugs like ipilimumab, recently approved for melanoma, is not fully understood. By contrast, although the mechanism of action of cabazitaxel in patients with CRPC previously treated with docetaxel is more clear, as Sergua and Tannock24 point out in their review of chemotherapy, several questions remain. With evidence emerging that taxanes have a large impact on androgen receptor signaling, studies to evaluate whether taxanes primarily have antitumor activity in ETS gene–rearranged cancers are now needed. The optimal sequence of drug administration also needs to be interrogated. Does it matter whether abiraterone is given before taxanes? Another important question that needs to be addressed is the issue of whether cabazitaxel is superior to docetaxel in the first-line setting. Moreover, it is important for the practitioner to appreciate the difference between docetaxel-exposed and docetaxel-refractory patients. A consensus definition of what defines docetaxel-refractory is required. Importantly, however, this pivotal phase III trial enrolled a selected group of patients; for an agent with a significant risk of neutropenic sepsis, its careful introduction into the unselected real-world population is critically important.

Of interest, in 2005, the overview accompanying the prostate cancer special series in the Journal pointed out that “the increasing use of docetaxel will result in a growing number of docetaxel-resistant or docetaxel-treated patients” and commented on the “scant literature describing therapeutic options in this new disease state, which represents a clinical state with unmet needs, and which offers the opportunity for future interventions.”25 In 2011, it is clear that the prostate cancer research community has risen to the occasion. Two agents are specifically approved for use in the postdocetaxel state (cabazitaxel and abiraterone acetate), and several more (eg, MDV3100, TAK700) are being tested in this setting.

However, many challenges remain for prostate cancer researchers. It is clear that prostate cancer is a molecularly heterogeneous disease with evidence that it may be comprised of more than twenty different clonal subtypes.14 Many of these clonal subtypes can be categorized into classes, such as the ERG rearranged subgroup. It is critical that future trials attempt to prospectively stratify this disease. It is envisioned that this will result in bigger gains for individual patients and minimize the use of drugs that are ineffective in certain disease subtypes. Molecular classification may also decrease the risk of late drug development attrition in phase III trials.

Another major challenge that comes with the approval of multiple novel agents is the urgent need to develop analytically validated and clinically qualified intermediate end points (surrogate biomarkers) for overall survival. This is particularly crucial given that progression free survival end points in this disease remain biased by the biochemical evaluation of prostate-specific antigen, with overall survival remaining the primary drug approval end point. This makes the study of drugs in earlier disease stages with overall survival end points a high-risk strategy in view of the considerable crossover to (approved or unapproved) novel agents for patients treated on the control arm.
Scher et al\textsuperscript{25} summarize the crucially important effort to clinically qualify circulating tumor cells and other biomarkers as intermediate end points of overall survival.

**Translating the Results of Clinical Trials into Practice**

How these (and future) novel agents are deployed clinically is an evolving field. Large questions remain about how these agents are used in earlier disease states. Although postdocetaxel is clearly a valid disease state in which to test new agents, the group of patients in that state represents a group of patients with quite advanced disease and begs the question of whether patients with less extensive disease burden might benefit even more from these agents. With several new agents now approved or soon-to-be approved, questions about concurrent or sequential therapy remain. If sequential therapy is to be used, practical issues about the order of sequencing need to be addressed. Moreover, questions remain about whether patients slowly progressing on abiraterone should have this agent continued to maintain the blockade of intratumoral hormone synthesis. Drug costs may prohibit this, but it remains a vital clinical dilemma that clinicians have to face because this disease may remain androgen receptor driven at the time of abiraterone resistance. Although these kind of questions can ultimately only be answered by clinical trials, practical generalizations can be made.

Use of androgen receptor targeting agents in hormone sensitive prostate cancer is not yet indicated. Although androgen receptor targeting agents like abiraterone acetate have only been tested in the castration-resistant environment (ie, targeting the amplified androgen receptor), it is completely reasonable to assume that they will have efficacy in earlier disease states. Several trials using androgen receptor targeting agents in patients with hormone-sensitive disease are either underway or under development. It is tempting to think that more complete abrogation of androgens may ultimately be shown to provide more durable control of disease. These agents have particular promise in the treatment of patients with high-risk, early-stage disease, and the pursuit of such trials is now a major priority.

Use of androgen receptor targeting agents in the prechemotherapy space seems to be almost a foregone conclusion. Although these agents are clearly active in patients with metastatic CRPC that has progressed despite chemotherapy, their physiological space is probably after androgen deprivation. Two pivotal trials in patients with metastatic CRPC prior to chemotherapy treatment (one with abiraterone acetate, one with MDV3100) have been fully enrolled and are maturing. The favorable toxicity profile of these agents will likely lead to their use before the use of chemotherapy. Trials pursuing the development of these agents in even earlier disease states, for example to prevent the development of metastases in patients with nonmetastatic CRPC, are either planned or underway.

Immunotherapy with sipuleucel-T can be used relatively early in the course of metastatic CRPC. Sipuleucel-T is approved for use in patients with metastatic CRPC that are asymptomatic, or minimally symptomatic, and without evidence of visceral disease. Immunotherapy takes time to kick in, and although minor objective and prostate-specific antigen responses have been reported with sipuleucel-T, this should not be viewed as an agent that will provide rapid responses. Thus, sipuleucel-T may be considered almost an adjunctive therapy, given early, and followed by other therapies as needed. It is unknown whether therapies administered after immune therapy have an additive or synergistic effect, given that induced immune responses generally persist after the immune therapy has been discontinued. Retrospective data suggest that patients treated with docetaxel after sipuleucel-T had a longer survival than patients treated with docetaxel after placebo,\textsuperscript{26} which generates the hypothesis that treatment with immunotherapy before chemotherapy may represent appropriate sequencing. The optimal amount of time after (or before) the administration of sipuleucel-T before subsequently administering potentially immunosuppressive therapy (such as chemotherapy or steroids) is not known. However, because the trials of sipuleucel-T required that patients be off chemotherapy for at least 3 months before receiving the immune therapy, as a practical matter, that landmark can potentially be adopted.

The practical dilemma of the appropriate sequence of use of the two new noncytotoxic agents (sipuleucel-T and abiraterone) is being addressed by trials that are under development. For now, given the broader window of applicability of abiraterone and the longer time required to develop an immune response with sipuleucel-T, if both agents are to be used, it seems reasonable to administer sipuleucel-T first with Abiraterone after additional disease progression. Biomarkers to help define the optimal use of immunotherapy are needed.

*Use of immunotherapy in hormone-sensitive prostate cancer is not yet indicated.* Although the argument has been made that immune mechanisms may be more active in lower disease burden scenarios, it does not necessarily follow that the progression from one disease state to another is associated with the same antigenic profile. Thus, the development of seemingly efficacious therapy in patients with advanced metastatic CRPC may or may not be relevant to the treatment of patients with earlier-stage and/or androgen deprivation–responsive (hormone-sensitive) prostate cancer. Protocols testing immunotherapy in earlier disease states are underway.

**Cabazitaxel is an appropriate choice for selected patients with metastatic CRPC after docetaxel therapy.** It should be remembered that the patients treated on the cabazitaxel registration trial were selected and had to have been fit enough to have either not developed or recovered from the adverse events of docetaxel, most notably neutropathy. Because of this and the risk of neutropenic sepsis associated with this drug, cabazitaxel should be administered by oncologists with expertise in handling neutropenia and sepsis, possibly with granulocyte colony-stimulating factor. Whether cabazitaxel can be substituted for front-line docetaxel is the subject of a prospective phase III trial.

**Bone-targeting therapy is indicated for metastatic CRPC.** Both denosumab and zoledronic acid are approved for use in the prevention of skeletal-related events (SREs). In a head-to-head comparison, the use of denosumab resulted in a lower incidence of SREs than zoledronic acid. The slightly higher incidence of osteonecrosis of the jaw and hypocalcemia is postulated by Saylor et al\textsuperscript{27} in their review article to reflect more effective osteoclast inhibition. Although the denosumab label is somewhat broader in that it doesn’t specify whether patients need have castration-resistant disease; in fact, the head-to-head comparison of denosumab to zoledronic acid was undertaken in patients with metastatic CRPC and not in hormone-sensitive disease. Consequently, until trials evaluating the use of these agents in metastatic hormone-sensitive disease are completed and reported, it is appropriate to not routinely use these agents for SRE prevention in patients who have not yet developed castration-resistant disease.
Vision for the Future

Compared with 2004, the issues confronting us as a prostate cancer community are considerably more complex and, in some ways, reminiscent of issues that faced some of our colleagues in other areas of oncology in years past. How do we choose and sequence agents? Can we tailor therapy to specific patient subsets? Can agents with nonoverlapping toxicity be combined, and if so, how do we rationally develop, test, and implement these combinations? If active in more advanced disease, which of these agents make sense in earlier-stage disease? Can mechanisms of action (and resistance) be elucidated? Another major societal challenge will be meeting the fiscal challenges of funding multiple new agents for this common disease, particularly as evidence accumulates about the use of these novel agents in high-risk, locally advanced disease in which drugs like abiraterone will now be evaluated.

Perhaps the most important change in 2011 relative to 2005 is a cultural one. In 2005, therapeutic nihilism was the norm. The approval of docetaxel, although hailed as a milestone, was quite frankly met with skepticism by practitioners who were not fully immersed in the treatment of patients with metastatic, castration-resistant disease. The approvals of sipuleucel-T, denosumab, cabazitaxel, and abiraterone acetate are a wake-up call. Patients with CRPC respond to therapy, and available therapeutic interventions confer important benefit. One hopes that the incidence of patients with metastatic CRPC automatically being relegated to hospice care is diminishing among urologists, radiation oncologists, and medical oncologists. These data now need to be incorporated into the training of primary care practitioners, so that the former nihilism associated with this disease is replaced by the recognition that there are many therapeutic options; the challenge is predicting which ones are appropriate for an individual patient.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about relationships marked with a “U” are those for which no compensation was received; those

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES


DOI: 10.1200/JCO.2011.37.8653; published online ahead of print at www.jco.org on August 22, 2011