Clinical Roundtable Monograph

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The Relationship Between Symptomatology and Treatment Selection in Metastatic Castrate-Resistant Prostate Cancer

PART 2 OF A 3-PART SERIES

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Abstract: Metastatic castrate-resistant prostate cancer (CRPC) can occur in a patient with de novo metastatic disease who has received androgen-deprivation therapy. The initial evaluation of a patient who may have CRPC should include measurement of testosterone levels at the time of progression to confirm the presence of castrate levels of testosterone. Components of the workup include a baseline bone scan, a computed tomography scan, and a full blood panel. The follow-up of patients with metastatic CRPC should include measurement of prostate-specific antigen (PSA) levels as well as imaging studies. The most important clinical endpoint for these patients is survival, but others include symptoms, such as pain and fatigue; biochemical factors; and radiographic progression. Physicians must help manage symptoms, regardless of whether they arise from the treatment or the disease itself. For patients with metastatic CRPC, choice of treatment is driven primarily by whether the patient has asymptomatic or minimally symptomatic, versus symptomatic, disease. In this clinical roundtable monograph, experts discuss the diagnosis, prognosis, and management of patients with CRPC, with a focus on the best utilization of 4 recently approved agents: abiraterone acetate, sipuleucel-T, cabazitaxel, and denosumab.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and other healthcare professionals who treat patients with prostate cancer.

Statement of Need/Program Overview

Of the approximately 50,000 patients per year who develop metastatic prostate cancer, it is estimated that between 25,000–30,000 have castration-resistant disease. In the sequence of the disease continuum, castrate-resistant prostate cancer (CRPC) begins as asymptomatic nonmetastatic disease. Asymptomatic nonmetastatic CRPC is followed by asymptomatic or minimally symptomatic metastatic CRPC. Symptomatic metastatic CRPC is considered the final disease state in this progression. In addition to survival, important clinical endpoints include symptoms, such as pain and fatigue; biochemical factors; and radiographic progression. The therapeutic options to treat metastatic CRPC have vastly increased in the past few months, with the introduction of abiraterone acetate, sipuleucel-T, cabazitaxel, and denosumab. These new agents are intended for specific subpopulations of metastatic CRPC patients.

Educational Objectives

After completing this activity, the participant should be better able to:

- Define components of the initial workup of patients with castrate-resistant prostate cancer (CRPC)
- List tests included in the follow-up of CRPC patients
- Describe mechanisms of action and clinical trial data for newly approved therapies in CRPC
- Identify patient subsets most likely to benefit from new CRPC therapies

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Assessment of Patients With Castrate-Resistant Prostate Cancer

David F. Penson, MD, MPH

The Prostate Cancer Clinical Trials Working Group (PCWG2) has defined prostate cancer as a continuum, with key classifications based on the presence or absence of clinically detectable metastases, as well as whether the serum testosterone level is in the castrate range.[1] Patients develop castrate-resistant prostate cancer (CRPC) via 1 of 2 routes. In some cases, the patient has de novo metastatic disease that has progressed through androgen-deprivation therapy (ADT), and he then becomes castrate-resistant, developing metastatic (M1) CRPC. Perhaps more commonly, patients are initially treated for localized or locally advanced disease, progress and experience a biochemical failure, and are treated with ADT. They then demonstrate a rising prostate-specific antigen (PSA) level while on ADT; these patients will be diagnosed with nonmetastatic (M0) CRPC.

Of the approximately 50,000 patients per year who develop metastatic disease, it is estimated that between 25,000–30,000 have CRPC. This estimate includes a key assumption that there is a median time to progression (TTP) of 18–24 months for a patient on ADT.

The initial evaluation of a patient who may have CRPC should include measurement of testosterone levels at the time of progression to confirm that he really does have castrate levels of testosterone. In some cases, a rise in PSA level can be explained simply by a late or inadequate dose of hormonal agent or even a change in the hormonal regimen.

Disease progression in patients with CRPC is defined using any of 3 parameters. A rising PSA level should be considered after 2 increases, not just 1 increase. Some physicians use an indicator—such as an absolute rise of 5 ng/mL in PSA level—to help define this rise. The second parameter is radiologic evidence of new metastasis, generally shown on a bone or computed tomography (CT) scan. Third, patients with worsening pain or other symptoms should be considered to have progressive disease.

In the sequence of the disease continuum, CRPC begins as asymptomatic nonmetastatic disease. Asymptomatic nonmetastatic CRPC is followed by asymptomatic or minimally symptomatic metastatic CRPC. In general, when determining if a patient should be categorized as minimally symptomatic, the physician should consider whether the patient consistently requires opiate analgesics for pain control. If he does, he likely should be considered symptomatic and not minimally symptomatic. Symptomatic metastatic CRPC is considered the final disease state in this progression (Figure 1).

Initial Workup

There are no specific guidelines regarding the workup of patients identified as having CRPC. However, several assessments are guided by an understanding of the disease. A baseline bone scan is essential to determine the presence or absence of bone lesions. In fact, this need was especially emphasized in findings from a recent report by Yu and colleagues, which demonstrated that of 2,516 CRPC patients included in a clinical trial, 30% exhibited a current metastasis on a baseline bone scan.[2] Bone scans can also provide information about bone-related metastases that may be clinically important, such as pathologic fractures, spinal cord compression, and bone marrow failure.

In most cases, a CT scan is indicated as well. A CT scan is especially important for CRPC patients, in whom PSA levels are not necessarily a reliable predictor of tumor volume. Simply put, in CRPC patients, the degree or extent of disease does not necessarily correlate with PSA levels.

A full blood panel, including complete blood count, a comprehensive metabolic panel, liver function enzymes, and coagulation factors, can also provide a great deal of useful information for the physician. These laboratory results can help to diagnose important cancer-related disorders such as anemia, weight loss, fatigue, hypocoagulability, and increased susceptibility to infection.

Follow-Up of Patients With CRPC

The follow-up of patients with nonmetastatic CRPC can be complicated by the fact that in most cases, these patients do not feel ill. Regular PSA level assessments, as well as bone scans to check for the development of bone metastases, should be performed. Although a change in PSA levels by itself may not be enough to initiate therapy (as the indications for most therapies include

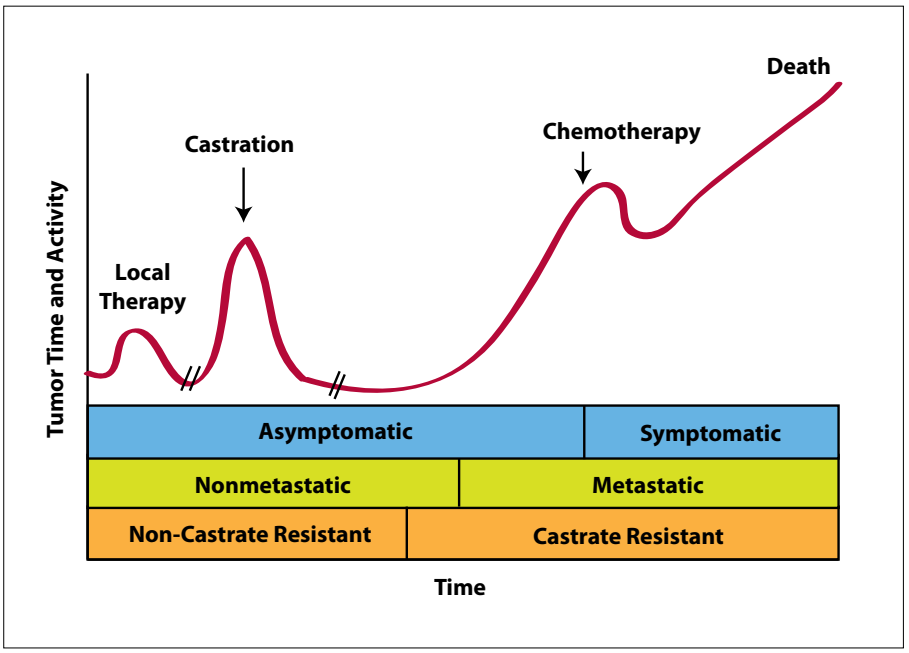

Figure 1. Natural history of metastatic prostate cancer.

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documented evidence of metastases), a persistent rise in PSA level can help the physician to more carefully consider changes in imaging studies in these patients. In our practice, we try to assess PSA levels in these patients quarterly. We test more frequently in patients who request it. The bone scan is repeated approximately every 6 months, in an attempt to catch bone metastases as early as possible.

Compared with the numerous agents that have been approved for the treatment of metastatic CRPC, the treatment options for nonmetastatic CRPC are far fewer. These options are limited to secondary hormonal manipulations with agents such as ketoconazole and diethylstilbestrol (DES). For nonmetastatic CRPC patients, enrollment in an appropriate clinical trial should be considered.

The follow-up of patients with metastatic CRPC is very similar. Although PSA levels are not necessarily reliable in this setting, they should be measured regardless. Traditionally, a 50% or greater decline in PSA levels has been considered a good response to therapy. However, the definition of progression in this state is less exact. One example of disease progression that would prompt initiation of second-line therapy would be a PSA level increase of 25% or more, or an absolute increase in PSA level of 5 ng/mL or more. PSA levels should not be the only criteria considered for disease progression. Imaging studies can be used to monitor patients, with any increase in measurable metastases considered disease progression. Further, any change or worsening of symptoms upon patient assessment should also be considered progression.

Discussion

H&O Is there a discrete difference between nonmetastatic and metastatic CRPC? Or between asymptomatic or minimally symptomatic and symptomatic disease?

David F. Penson, MD, MPH Although these disease states are considered discrete for regulatory purposes and for drug approval, in clinical practice it is difficult to consider them as distinct disease states. For example, what may be considered minimally symptomatic in one patient may be maximally symptomatic in another. In the clinic, these disease states should instead be considered a continuum. However, to properly use agents indicated for CRPC according to the label, one must categorize the patient into a discrete disease state. This approach can be challenging to explain to patients. Specifically, it can be difficult to tell a man with nonmetastatic CRPC who has undetectable metastases that he is ineligible for agents indicated only for metastatic CRPC. However, these distinctions are necessary in order to make appropriate treatment choices.

H&O In patients with nonmetastatic CRPC, how do you determine the sequencing of hormonal therapy?

David F. Penson, MD, MPH If the patient is not on monotherapy, the first treatment I use is a combined

androgen blockade. Anti-androgen withdrawal or ketoconazole can be used after this. In our office, DES is not readily available. Because abiraterone is not yet indicated for this stage, this is where we decide to stop therapy and wait until further disease progression.

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Prognosis of Patients With Castrate-Resistant Prostate Cancer

Oliver Sartor, MD

For the patient, just the concept of having nonmetastatic CRPC is confusing. Many patients know that at one point they had "metastatic disease," as evidenced by their positive lymph nodes at surgery. However, they are now being told that they have nonmetastatic CRPC. In these cases, the physician should be sure to explain to the patient that he in fact does have metastatic disease, but that the metastases are not detectable using the current radiographic imaging methods. It may be helpful to further explain that the limits of detection of these imaging methods is usually approximately 1 cm, which represents approximately 1 billion tumor cells. At present, we do not have a reliable means of detecting a metastasis that is smaller than that (eg, 500 million cells).

Nonmetastatic CRPC With a Rise in PSA

We have now learned some of the natural history of asymptomatic nonmetastatic CRPC, defined only by a rise in PSA levels. Some of this information comes from placebo-controlled trials that specifically enrolled patients with these disease characteristics. For example, Nelson and colleagues conducted a phase III, randomized, placebo-controlled trial that enrolled 941 prostate cancer patients with castrate testosterone levels and no radiographic evidence of metastases, but rising PSA levels.[1] A total of 474 patients were randomized to receive placebo (the remaining 467 patients were randomized to receive the investigational agent atrasentan). At baseline, the median PSA level of placebo-treated patients was 13.1 ng/mL (range: 0.8–672.2 ng/mL). Overall, no significant differences were noted between the 2 treatment arms. However, among the placebo-treated patients, the median TTP from randomization was approximately 22 months (671 days). The median overall survival (OS) was 46.1 months (1,403 days) for placebo-treated patients. Thus, one can infer from this study several points regarding the natural history of patients with asymptomatic nonmetastatic CRPC, including that the median time to development of metastatic disease is approximately 22 months.

In another study, Smith and coworkers further described the natural history of nonmetastatic CRPC with rising PSA levels using data from 201 patients in a placebo control group included in an aborted randomized controlled trial.[2] In that study, patients were randomized to receive either placebo or zoledronic acid, in order to determine the time to first bone metastasis. At baseline, the median PSA level of placebo-treated patients was 13.8 ng/mL (range: 0.9–630 ng/mL). Analyzing just the patients in the placebo arm showed that the median bone metastasis–free survival was 30 months, with the median time to first bone metastasis and median OS not reached. Interestingly, both baseline PSA level above 10 ng/mL (relative risk [RR], 3.18; 95% confidence interval [CI], 1.74–5.80; $P<.001$) and PSA velocity (RR, 4.34 for each 0.01 increase in PSA velocity; 95% CI, 2.30–8.21; $P<.001$) independently predicted a shorter time to first bone metastasis. Baseline PSA level greater than 10 ng/mL and PSA velocity were also significantly associated with shorter OS (RR, 3.19; 95% CI, 1.51–6.73; $P=.002$ and RR, 1.39; 95% CI, 1.15–1.69; $P<.001$, respectively). Tertiles of baseline PSA levels (<7.7, 7.7–24, and >24 ng/mL) and PSA doubling time (<6.3, 6.3–18.8, and >18.8 months) were associated with significantly different bone metastasis-free survival ($P<.001$). Thus, it appears that higher (>10 ng/mL) baseline PSA levels and PSA velocity are important prognostic factors in men with nonmetastatic CRPC with rising PSA levels.

Smith and associates recently presented updated data from the phase III Study 147, which compared denosumab with placebo in men with nonmetastatic CRPC.[3] Other inclusion criteria included a baseline PSA value of 8.0 ng/mL or higher that was obtained within 3 months prior to randomization, and/or a PSA doubling time within 10.0 months. This study was positive, showing significant improvements with denosumab in terms of bone metastasis–free survival, delayed time to first bone metastasis, and delayed time to symptomatic bone metastasis. Patients in the placebo arm of this study experienced a median bone metastasis–free survival of 25.2 months compared with 29.5 months in the denosumab arm (hazard ratio [HR], 0.85; 95% CI, 0.73–0.98; $P=.028$). There was also a delayed time to first bone metastasis with denosumab versus placebo (HR, 0.84; 95% CI, 0.71–0.98; $P=.032$), as well as a delayed time to symptomatic bone metastasis (HR, 0.67; 95% CI, 0.49–0.92; $P=.01$). There was no difference in the OS between the 2 treatment groups, however

(HR, 1.01; 95% CI, 0.85–1.20; *P*=.91). It should be noted that PSA levels were not reported in this study.

Despite the fact that nonmetastatic CRPC with a rise in PSA levels has begun to be addressed in clinical trials, there are currently no approved therapies for this stage of disease. Thus, the question remains regarding how to best treat these patients. In my practice, I typically rely on serial secondary hormone manipulations. In this setting, I tend to rely heavily on both rises and declines in PSA, as well as the kinetics of PSA levels, to help guide therapeutic decisions. In addition, I weigh progression-free survival (PFS) more heavily than a single time point treatment response; for example, a 90% decline in PSA level that lasts for only 6 weeks may be less meaningful than more minor declines that last for much longer.

Metastatic CRPC

Patients with nonmetastatic CRPC and a rise in PSA levels will eventually progress to metastatic CRPC. The distinction of these patients into those with asymptomatic or minimally symptomatic versus symptomatic disease is very important in this disease state, as there are certain therapies indicated only for the former condition.

A recent addition to the treatment arsenal for patients with metastatic CRPC is abiraterone acetate, an inhibitor of androgen synthesis. Results of the international, randomized, phase III COU-AA-301 study, which evaluated abiraterone acetate in patients previously treated with docetaxel, were recently reported.[4] This study randomized 1,195 previously treated patients in a 2:1 fashion to receive either abiraterone acetate or placebo; both arms also received daily prednisone. With a median follow-up of 12.8 months, a statistically significant improvement in OS was observed among patients in the abiraterone arm compared with the placebo arm (14.8 vs 10.9 months, HR, 0.65; 95% CI, 0.54-0.77; *P*<.001). Additionally, patients in the abiraterone arm achieved significant improvements in time to PSA progression (10.2 vs 6.6 months; *P*<.001), PFS (5.6 vs 3.6 months; *P*<.001), and PSA response rate (29% vs 6%; *P*<.001). A similarly designed phase III study, COU-AA-302, is evaluating abiraterone acetate in chemotherapy-naïve metastatic CRPC patients.[5] The results of this trial are still maturing and are eagerly awaited.

Updated guidelines from the National Comprehensive Cancer Network (NCCN) now include abiraterone acetate as a category 1 recommendation (based on high-level evidence and uniform NCCN consensus) for patients with metastatic CRPC following failure of docetaxel chemotherapy.[6] The NCCN guidelines also include a category 2B recommendation (based on lower level evidence and non-uniform NCCN consensus) for the use of abiraterone acetate in patients who are not candidates for docetaxel chemotherapy, but they discourage the routine use of abiraterone in the pre-docetaxel setting, pending the results of the COU-AA-302 trial.

The immunotherapeutic therapy sipuleucel-T was the first-in-class autologous vaccine approved in men with asymptomatic or minimally symptomatic CRPC. This approval was largely based on the IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) study, a pivotal multicenter, randomized, double-blind, phase III trial.[7] In this study, a total of 512 patients with asymptomatic or minimally symptomatic metastatic CRPC were randomized in a 2:1 fashion to receive either sipuleucel-T or placebo, both administered as 3 infusions every 2 weeks. Significantly, patients in the sipuleucel-T arm experienced an improvement in median OS compared with patients in the placebo arm (25.8 vs 21.7 months), which equated to a 22% relative reduction in the risk of death (HR, 0.78; 95% CI, 0.61–0.98; *P*=.03). Despite the significant survival benefit associated with sipuleucel-T, there was no difference between the 2 treatment arms in the time to objective disease progression (3.7 vs 3.6 months in the sipuleucel-T vs placebo arms, respectively; HR, 0.95; 95% CI, 0.77–1.17; *P*=.63). Sipuleucel-T was also demonstrated to significantly improve median OS compared with placebo in a similarly designed, second phase III trial (25.9 vs 21.4 months; HR, 1.70; 95% CI, 1.13–2.56; *P*=.01).[8] However, the primary endpoint of that study, TTP, did not achieve statistical significance (11.7 vs 10.0 weeks; HR, 1.45; 95% CI, 0.99–2.11; *P*=.052).

Clinical Endpoints

The discussion of acceptable clinical endpoints is an important conversation between the physician and the patient with CRPC. There are several potential endpoints that can be assessed. The most important of these are symptoms, such as pain and fatigue. In addition, biochemical endpoints may also provide useful information. For example, several factors have been found to be prognostically important in this disease, including PSA, lactate dehydrogenase, hemoglobin levels, and alkaline phosphatase. Radiographic progression, including bone scan progression, visceral disease, or enlarging lymph nodes, may also be used as a clinical endpoint.

The ultimate endpoint for both patients and physicians is survival. It is notable that in recent years, the US Food and Drug Administration (FDA) has placed a much greater emphasis on OS results in prostate cancer clinical trials. This is evident in the agents approved for CRPC since 2004 (excluding those approved to treat

skeletal-related events). Docetaxel, sipuleucel-T, cabazitaxel, and abiraterone were approved after an improvement in OS was demonstrated. However, despite the obvious importance of OS as an endpoint, it is not the only endpoint that patients are concerned with; they are also concerned with achieving and maintaining good PSA responses, preventing radiographic progression, and limiting their symptoms and treatment-related toxicity. These endpoints all enter into a determination of the patient's overall quality of life. Physicians need to be concerned with helping to manage the patient's symptoms, regardless of whether they arise from the treatment used or the disease itself. This can be best accomplished by listening to patients, and then addressing their concerns in the best way possible.

Discussion

H&O What options are there for the CRPC patient who presents with no documented metastases but evidence of lymph node enlargement on a CT scan? How do you counsel this patient?

Oliver Sartor, MD Some patients may present with a lymph node that measures 1.4 cm, which does not meet the criteria for what would be designated as metastatic disease. However, the presence of this enlarged lymph node is somewhat worrisome. Fortunately, you can inform the patient that in this setting, he is mostly likely to be in an asymptomatic stage of the disease. In terms of the treatment of such a patient, I generally would refer to the treatment history and the kinetics of his disease (ie, how fast the disease is progressing) to decide on a course of therapy. Secondary hormonal therapy is feasible in these patients, and it can be accomplished with an anti-androgen, ketoconazole, steroids, or other estrogens. These hormone therapies may be manipulated somewhat, depending on the patient's characteristics. For example, the introduction of steroids would need to be done in a very cautious manner in diabetic patients, as these agents can worsen the patient's diabetes.

Eric J. Small, MD Interestingly, most of the secondary hormone therapies included in the NCCN guidelines are not approved for this setting, and are used off-label.

H&O As treatment advances, is it always clear when a symptom is from the disease and when it is related to therapy?

Oliver Sartor, MD Certain symptoms can be difficult to distinguish. Fatigue, for example, can be associated with both disease progression as well as a number of therapies, such as docetaxel and ketoconazole. Physicians should carefully question the patient and try to determine the sequence of events in order to establish where the symptoms are coming from. However, this can be difficult even for the best of clinicians.

Eric J. Small, MD I agree, and would also add that truly distinguishing between disease-related and treatment-related symptoms may often require trials on and off therapy. One of the few treatments in which it is relatively easy to discern between the 2 is sipuleucel-T; the toxicity profile of this agent is generally related to its administration (ie, infusion reactions) and therefore does not reflect typical symptoms of disease progression.

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Current Treatment Options in Castrate-Resistant Prostate Cancer

Eric J. Small, MD

As has been discussed earlier, CRPC represents a continuum of disease states in which patients have nonmetastatic PSA-only CRPC, then advance through asymptomatic or minimally symptomatic disease, and, finally, develop symptomatic disease. It is important to note that to a certain extent, these categories are relatively arbitrary—although each is very real, they are not very distinct. Instead, they reflect regulatory issues in how to best target a disease state. However, there is some clinical evidence supporting these disease categories. For example, Halabi and colleagues evaluated pain as a prognostic factor in men with CRPC, which is known to be a common event in these patients.[1] Pooled data from 3 randomized, multicenter, phase III clinical trials were combined from 599 men with progressive CRPC. It was shown that the pain interference score was significantly associated with the risk of death in these patients. The median OS was 17.6 months (95% CI, 16.1–19.1) and 10.2 months (95% CI, 8.6–11.3) in men with low (<17) and high (≥17) pain scores, respectively (P<.001). Furthermore, pain was found to be inversely associated with the likelihood of PSA decline, objective response, and time to bone progression.

Patients with symptomatic metastatic CRPC should be treated according to the needs of their disease. Agents that require several months to develop a response or elicit a biologic effect are likely not the best choice of therapy for these patients with symptomatic and rapidly progressive disease.

The final disease state to consider is that of pre-docetaxel exposure versus docetaxel-resistant disease. This distinction is in some ways a regulatory construct. Abiraterone, while currently approved only in the post-docetaxel state, from a physiologic perspective, can certainly be used in the prechemotherapy state. By contrast, a drug like cabazitaxel, which has demonstrated preclinical activity in docetaxel-resistant models, does make sense in the post-docetaxel state.

Mechanisms of New Therapies

The androgen receptor is an exciting target in the current era of drug discovery for prostate cancer. In prostate cancer patients, androgens help to drive the growth and progression of tumor cells. It is for this reason that ADT is a standard of care for the treatment of recurrent prostate cancer. However, although ADT mainly inhibits testicular androgen production, prostate tumors utilize additional sources of androgen produced by both the adrenal glands as well as the prostate tumor cells themselves. In metastatic CRPC, androgens are supplied from 3 sources: the testes, the adrenal glands, and the tumor tissue itself. Abiraterone acetate is an inhibitor of the 17a-hydroxylase/C17,20-lyase (CYP17) enzyme, a key protein in the conversion of pregnenolone and progesterone into the testosterone precursors dehydroepiandrosterone (DHEA) and androstenedione, respectively. Abiraterone acetate therefore is able to target all 3 sources of androgen production.

The immune system is another important avenue of approach in CRPC treatment. It has been demonstrated to be a viable approach with the success of the immunotherapy sipuleucel-T. Like most malignancies, prostate cancer has been considered to be immunoevasive, meaning that it can escape normal immune surveillance. Sipuleucel-T is a novel therapy that uses the patient's own antigen-presenting cells (APC) to stimulate the body's immune system to recognize and mount an immune response to the prostate tumor cells. The immune cells, including APC, but also including lymphocytes and other mononuclear cells, are first collected from the patient. Ex vivo, these cells are then exposed to a targeting cassette, which is composed of the ubiquitous prostate cancer-associated antigen, prostatic acid phosphatase (PAP), linked to what is believed to be a targeting molecule, granulocyte macrophage colony stimulating factor (GM-CSF), which allows uptake of PAP into the APCs. It is important to note that sipuleucel-T does not have significant innate GM-CSF activity. Following incubation of the PAP-GM-CSF cassette with the patient's antigen-presenting cells, there is uptake, processing, and presentation of PAP-derived antigens on the APC cell surface. This process results in antigen-presenting cell maturation. It is thought that when reintroduced back into the patient, the mature antigen-presenting cells, along with any lymphocytes present, activate T cells, rendering them capable of recognizing PAP-expressing prostate cancer cells. The T cells then multiply and target prostate tumor cells. (This is the presumed mechanism of action of sipuleucel-T, but it has not yet been proven.)

The novel cytotoxic agent cabazitaxel is a semisynthetic taxane derivative and antimitotic chemotherapeutic agent. Like several other cytotoxic chemotherapeutic agents, cabazitaxel inhibits microtubules by binding to the tubulin protein and promoting microtubule stabilization. Cabazitaxel does this by promoting tubulin assembly and simultaneously inhibiting tubulin disassembly. As a result, cabazitaxel leads to inhibition of microtubule-dependent cellular functions, including mitosis.

Bone-targeting agents such as denosumab have also been investigated for their potential anticancer activity. In CRPC, Smith and coworkers recently presented updated data from the phase III Study 147, which compared denosumab with placebo in men with nonmetastatic CRPC (previously discussed).[2]

Changes in the Treatment Landscape

Just a few years ago, the treatment landscape for CRPC was vastly different than it is now. Previously, the only widespread accepted option for men with CRPC was docetaxel plus prednisone, based on results from the Southwest Oncology Group (SWOG) 9916 and the TAX 327 randomized phase III studies. The SWOG 9916 trial randomized 770 men with metastatic CRPC to treatment with either docetaxel plus estramustine and dexamethasone or mitoxantrone plus prednisone.[3] Among the intent-to-treat population, a significant improvement in median OS was achieved in the docetaxel arm versus the mitoxantrone arm (17.5 vs 15.6 months, HR, 0.80; 95% CI, 0.67–0.97; *P*=.02). Other improvements in efficacy endpoints were also noted, including the median TTP (6.3 vs 3.2 months; *P*<.001), declines in PSA of 50% or more (50% vs 27%; *P*<.001), and objective tumor responses (17% vs 11%; *P*=.30). The TAX327 trial randomized 1,006 men with metastatic CRPC to 3 arms, receiving either mitoxantrone, docetaxel (75 mg/m^2) every 3 weeks, or docetaxel (30 mg/m^2) weekly; all 3 arms also received prednisone.[4] Patients in the docetaxel every-3-weeks arm achieved the best median OS compared with the docetaxel weekly and mitoxantrone arms (18.9 vs 17.4 and 16.5 months, respectively; HR, 0.76; 95% CI, 0.62–0.94; *P*=.009 for men in the docetaxel every-3-weeks arm; HR, 0.91; 95% CI, 0.75–1.11; *P*=.36). Other important achievements in efficacy included a 50% or higher decline in the serum PSA level (45%, 48%, and 32% for the docetaxel every-3-weeks, docetaxel weekly, and mitoxantrone arms, respectively; *P*<.001 for both comparisons with mitoxantrone) and a predefined reduction in pain (35%, 31%, and 22%, respectively; *P*=.01 for comparison of docetaxel every 3 weeks with mitoxantrone; *P*=.08 for comparison of docetaxel weekly with mitoxantrone). An updated survival analysis of TAX327 demonstrated a continued benefit in median OS with docetaxel every 3 weeks compared with mitoxantrone (19.2 vs 16.3 months; *P*=.004).[5] Based on these 2 pivotal trials, docetaxel plus prednisone was previously considered the standard of care for men with metastatic CRPC.

Now in 2011, the therapeutic options to treat CRPC have vastly increased. The past several months have seen the introduction of 4 major new agents—abiraterone acetate, sipuleucel-T, cabazitaxel, and denosumab—to treat this disease. As has been discussed, with the exception of denosumab, the approval of these agents was primarily based on their significant prolongation of OS in men with CRPC. Although it is important to consider that other endpoints could be important in this disease, it is remarkable that so many agents have been approved with the potential to improve patient survival.

Making Treatment Decisions

None of these newer agents are currently approved for men with nonmetastatic CRPC. However, as a reflection of the continuum of this disease, it is likely that these agents will be increasingly tested and used in this setting. The use of agents that target the androgen receptor in the prechemotherapeutic setting has yet to be established as an approved treatment option. However, it does make physiologic sense that targeting the androgen receptor would be an effective strategy even prior to initiation of chemotherapy. Results from a completed phase III trial (COU-AA-302) testing abiraterone in the prechemotherapy space are eagerly awaited.[6]

For patients with metastatic CRPC, choice of treatment is often driven by whether the patient has symptomatic disease. For example, the immunotherapeutic agent sipuleucel-T is currently indicated only for patients with asymptomatic or minimally symptomatic disease, and therefore its use should be restricted to earlier in the course of metastatic CRPC. It is possible (but not tested) that for patients with more advanced metastatic CRPC, the disease is progressing too quickly to allow benefit from the immune reaction.

The question of administering a therapy such as sipuleucel-T with steroids has not yet been resolved. Steroids are lymphotoxic, which can be problematic when they are delivered with sipuleucel-T because activated lymphocytes are an important component of the immune response. Whether low-dose replacement steroids used with agents like abiraterone or ketoconazole impair the efficacy of sipuleucel-T is not known. There is also a question of how much time should elapse between time of chemotherapy and sipuleucel-T administration. Currently, in our practice, we follow the protocol described

in the pivotal clinical trials, which is to provide at least a 3-month interval between the 2 therapies.

Another important point regarding the administration of sipuleucel-T is that there is not yet a clearly defined population of patients who are most likely to benefit from therapy. In lieu of this, sipuleucel-T is used in the asymptomatic or minimally symptomatic metastatic CRPC population as a whole.

Finally, in the symptomatic CRPC state, docetaxel has been shown to have an impact on pain, making it an appropriate treatment choice. Some of the androgen receptor targeting agents have also been shown to be active even in patients with active pain, and therefore these agents should not be excluded from consideration in this setting.

Cabazitaxel is also an appropriate choice for selected patients with metastatic CRPC following docetaxel therapy. However, it is important to remember that this drug is not well-suited for everyone. Patients should have a reasonable performance status as well as resolution of toxicities. Although there are several examples in which cabazitaxel is used as a last-option salvage therapy—when the patient has explosively progressive disease—this use may be asking too much from this agent. Instead, initiating the agent sooner and before the patient is on a downward spiral may make more sense.

Both denosumab and zoledronic acid are recommended by the NCCN to prevent or delay disease-associated skeletal-related events in men with CRPC and bone metastases.[7] In a direct comparison, denosumab resulted in a longer median time to first on-study skeletal-related event than zoledronic acid (20.7 vs 17.1 months; HR, 0.82; 95% CI, 0.71–0.95; *P*=.008 for superiority), although it was associated with a slight increase in osteonecrosis of the jaw (ONJ) (2% vs 1%).[8] It is important to understand that although the indication for denosumab is somewhat broader—in that it does not specify administration only in CRPC—the pertinent clinical studies of its activity were restricted to patients with CRPC. Thus, these agents should not be used for prevention or delay of skeletal-related events in patients who do not have CRPC (ie, in patients with metastatic, but hormone-sensitive, prostate cancer).

Although the introduction of these agents has brought about a very exciting time in the field, it is becoming increasingly apparent that the work has really just begun. Major challenges and unanswered questions still remain, such as: How do we choose and sequence these agents? Can we tailor therapy to specific subsets of patients? Can agents with non-overlapping toxicity profiles be continued, or do they need to be stopped before we move to the next one? What is the utility of these therapies in earlier disease states?

Discussion

H&O There has previously been evidence suggesting that patients who received sipuleucel-T may actually respond better to docetaxel. What are your thoughts on this?

Eric J. Small, MD This fascinating observation came from an exploratory analysis of 2 phase III studies, presented by Petrylak.[9] This analysis demonstrated a prolonged OS benefit for CRPC patients initially treated with sipuleucel-T who then went on to receive docetaxel chemotherapy following disease progression. Data from 82 patients showed that the median OS was significantly prolonged among patients who received sipuleucel-T versus placebo, and then subsequently received docetaxel (34.5 vs 25.4 months; HR, 1.90; *P*=.023). Further, 68% of the patients who were randomized to receive placebo subsequently took part in a crossover salvage protocol, which allowed them to receive treatment with an active cellular immunotherapy (APC8015F) generated from cryopreserved cells. As was the case in patients receiving sipuleucel-T, among these patients, the median OS was higher for those who received APC8015F followed by subsequent docetaxel compared with patients who received placebo only followed by docetaxel (25.7 vs 20.2 months). Notably, this equated to a 14.3-month difference between the median OS of patients who received initial treatment with sipuleucel-T followed by docetaxel versus patients who continually received placebo followed by docetaxel (34.5 vs 20.2 months). While exploratory, these data raise the question that immune priming with sipuleucel-T followed by cytotoxic therapy might be a way of enhancing efficacy of these agents.

This observation may have some biologic basis. The presence of activated memory cells and dendritic cells may prove to be a benefit with docetaxel treatment, providing further cell death. However, this question is complicated by a lack of understanding of the true mechanism of action of sipuleucel-T. Although this study was an exploratory analysis, it was provocative and really emphasized the question of sequencing and timing of therapy.

H&O Is there any future role in CRPC for the other immunotherapeutic agent, ipilimumab?

Eric J. Small, MD Ipilimumab is a monoclonal antibody directed against CTLA-4, an immune-inhibitory T-cell surface molecule that is important in dampening the immune response. By blocking CTLA-4, ipilimumab can augment the T-cell response against a tumor. Currently, ipilimumab is approved only for the treatment of late-stage melanoma, but it has been investigated in

men with CRPC. Ipilimumab has proven to be more toxic than an agent such as sipuleucel-T, but it has the added benefit of a unique mechanism of action, and fairly impressive anti-cancer activity in selected CRPC patients. Therefore, there is potential that ipilimumab could be used in combination with another agent with a different target.

H&O How do you address the issue of the use of prednisone in the setting of sipuleucel-T therapy?

Eric J. Small, MD Most certainly, studies investigating the safety of steroid use in conjunction with sipuleucel-T need to be performed. Associated with this is the issue of optimal sequencing of therapy, especially with new agents such as abiraterone that are still given with prednisone. Until these issues are addressed, I think it is best to avoid the concomitant use of sipuleucel-T with steroids.

David F. Penson, MD, MPH Another important point is that many of the androgen-inhibiting agents that are currently in the investigational stage have the advantage of not requiring coadministration of prednisone. Therefore, these agents may obviate this discussion in the future.

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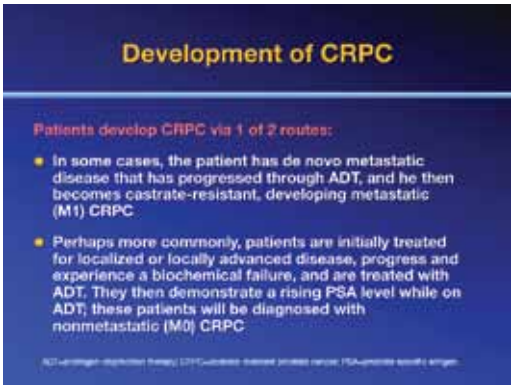

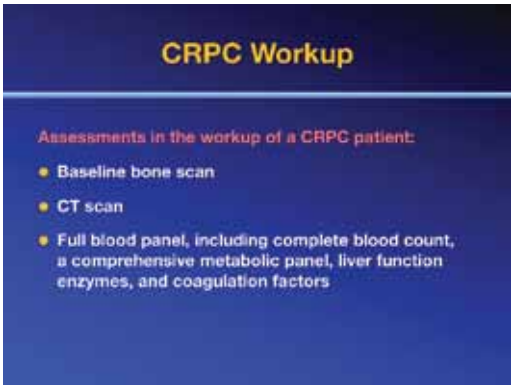

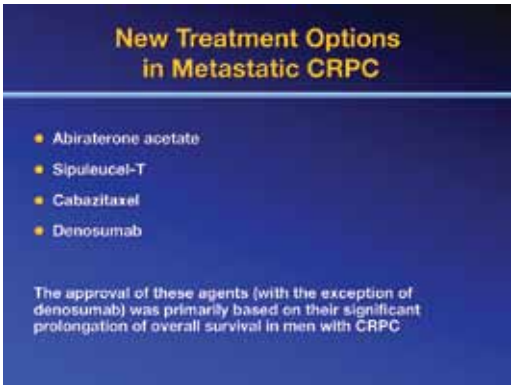

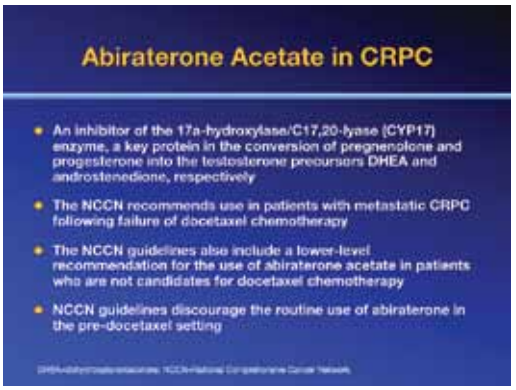

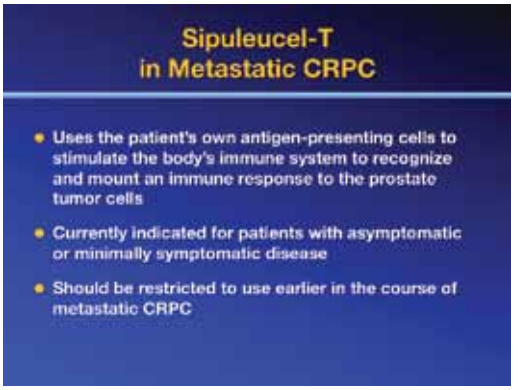

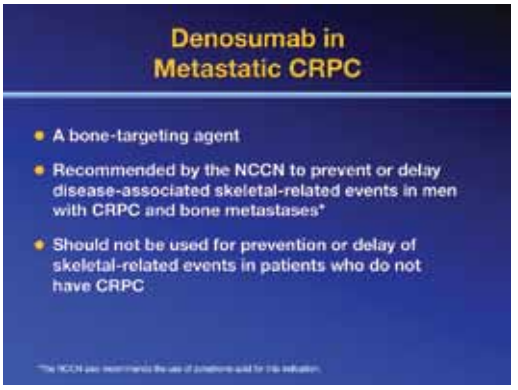

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