METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: THE TREATMENT ALGORITHM REDESIGNED

A newsletter from the 2014 Annual Meeting of the American Urological Association

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CONTINUING EDUCATION

TARGET AUDIENCE
This educational activity is specifically designed to meet the needs of practicing urologists, medical oncologists, and other healthcare professionals involved in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

LEARNING OBJECTIVES
Upon completion of this educational activity, participants should be able to:

• Employ current guidelines and recent evidence when developing treatment plans for mCRPC that incorporate novel agents and strategies
• Evaluate new data regarding how best to incorporate standard treatments, such as immunotherapy, bone-targeted therapy, and androgen suppression, into the care of men with mCRPC
• Explain the variables involved in sequencing therapies during the management of mCRPC

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1. Metastatic Castration-Resistant Prostate Cancer: The Treatment Algorithm Redesigned • A Prime Oncology Educational Activity
On May 19, 2014, over 400 urologists and oncologists gathered for a symposium titled “Metastatic Castration-Resistant Prostate Cancer: The Treatment Algorithm Redesigned,” held in conjunction with the American Urological Association’s annual meeting in Orlando, Florida. Participants heard 5 experts discuss how treatment of metastatic castration-resistant prostate cancer (mCRPC) has evolved as novel agents have been added to the therapeutic armamentarium over the past several years.

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: MANY OPTIONS/CHALLENGING DECISIONS

The chair of the symposium, Mark Soloway, MD, PhD, from the University of Miami, opened the meeting with a discussion of the current dilemmas in treating mCRPC. From 1990-2007, patients with high-risk prostate cancer accounted for approximately one-third of the total prostate cancer population.1 Although in recent years there has been a decline (to 24% of the total population) in numbers of patients with metastatic prostate cancer, the good news is that outcomes for these patients are improving, and they can often expect to live for many years after diagnosis. Even for those patients who eventually develop metastatic disease, they have typically been treated with androgen deprivation therapy for 5 to 15 years after PSA progression following primary treatment. The question of when urologists should refer their patients with prostate cancer to an oncologist is important, particularly with the rapidly expanding options for treatment. Most urologists tend to refer their patients to medical oncology once they note a PSA rise following androgen deprivation, and they almost always refer after discovering objective disease progression. Urologists and urologic oncologists have little experience managing the side effects of newer systemic therapies, which can include neuropathy and myelosuppression from chemotherapy, and hypertension, fatigue, and seizures from some of the newer nonchemotherapy agents. These side effects may be unfamiliar to urologists, but for those who choose to manage care of their patients beyond a PSA rise, they need to know the safety profiles of these newer therapies, particularly the oral agents abiraterone and enzalutamide, when counseling patients about their treatment options. In his discussion, Dr Soloway also encouraged urologists to prescribe these newer agents regardless of specialized ordering requirements. Any allied professional on a urologist’s staff can order abiraterone or enzalutamide from a specialty pharmacy. Furthermore, patients prescribed the radiopharmaceutical radium-223 can be sent to a certified radiation oncologist or nuclear medicine radiologist for administration of the agent, and urologists can concomitantly manage their care.

Patients with low-risk prostate cancer are increasingly being managed with active surveillance, while high-risk prostate cancer is treated more aggressively. Patients with high-risk prostate cancer are treated initially with radical prostatectomy or androgen deprivation therapy and external beam radiotherapy. The good news is that outcomes for these patients are improving, and they can often expect to live for many years after diagnosis. Even for those patients who eventually develop metastatic disease, they have typically been treated with androgen deprivation therapy for 5 to 15 years after PSA progression following primary treatment.

Figure 1. Natural history of prostate cancer and available therapies at each stage of disease

Docetaxel became the standard of care for mCRPC in 2004, when it was shown to produce a survival advantage over mitoxantrone + prednisone.24 Key side effects include myelosuppression, nausea, vomiting, diarrhea, fatigue, and sensory neuropathy.4 Dr Soloway stated that he finds docetaxel to be generally well tolerated and effective in this patient population, although his bias is to limit the number of doses (typically a maximum of 6 or 7 doses) and to discontinue treatment once the patient responds, because toxic side effects increase dramatically with prolonged docetaxel administration. Abiraterone, which needs to be administered in combination with prednisone, causes fluid retention and requires potassium and blood pressure monitoring.5 In addition, liver function tests may be needed and some patients experience cardiac disorders,6 complications that urologists may not want to manage. Enzalutamide, which was approved in 2012 for the treatment of prostate cancer, is similar to the more familiar antiandrogen bicalutamide, but it has a higher binding affinity to the androgen receptor.4 One of the side effects of this agent is seizure, but the risk is extremely small,7 particularly if a patient has never had a prior seizure. Fatigue is another risk,7 but this can be managed with dose reductions. Dr Soloway shared his belief that urologists can confidently prescribe this agent.

In the past, urologists immediately referred patients to a medical oncologist once they became ‘hormone refractory’. Now, however, urologists can be much more involved, thanks to the advent of these newer agents. The key is for urologists to decide what type of side effects they are willing to manage in their practices, because several of these newer agents have distinct safety profiles. Ideally, these mCRPC cases will be reviewed by a multidisciplinary team. Such a team would include a medical oncologist, neurologic oncologist, radiologist, urologist, and pathologist, and should meet weekly or biweekly.

CONTINUED TARGETING OF ANDROGEN SIGNALING BEYOND CASTRATION RESISTANCE

Adam Kibel, MD, from the Dana-Farber Cancer Institute, provided a historical perspective of prostate cancer, reminding everyone that androgen deprivation therapy has been the gold standard of treatment for advanced prostate cancer for decades, although eventual androgen independence by the cancer cells leads to metastasis and death. Reducing serum testosterone levels, and even reducing testicular and peripheral androgens, is insufficient to control disease because testosterone-producing enzymes in the metastatic tissue create high testosterone levels despite castrate conditions.8

The upregulation of these enzymes in the cancer cell provides a focus for therapeutic research efforts. Currently, two approaches have been exploited: (1) CYP17 lyase inhibition to reduce testosterone production within the cancer cell and (2) antiandrogen administration to block the binding site of the androgen receptor. Abiraterone is a CYP17 inhibitor that is already approved for use in prostate cancer, and orteronel is an investigational CYP17 inhibitor. Likewise, enzalutamide is an androgen approved by the US Food and Drug Administration (FDA), and ARN 509, a similar agent, is currently under investigation.

Unlike the widely used ketoconazole, which inhibits the production of glucocorticoids and mineral corticoids in addition to testosterone, abiraterone primarily functions...

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to block testosterone production. In COUGAR 301, one of the pivotal trials for abiraterone, patients with mCRPC who had already received docetaxel were randomized 2:1 to abiraterone + prednisone/prednisolone or placebo + prednisone/prednisolone. Results demonstrated a 2.0-month improvement (hazard ratio [HR] = 0.67; P < .001) in median progression-free survival (PFS) with abiraterone and a 3.9-month improvement in median overall survival (OS; HR = 0.65; P < .001). Many of the adverse effects associated with abiraterone are due to mineralocorticoid excess because the increased amount of adrenocorticotropic hormone, caused by inhibition of testosterone production, is funneled through the mineralocorticoid pathway. For example, fluid retention and hypokalemia also were more frequent in the abiraterone group than the placebo group (31% vs 22%). Hypokalemia also appears to be more common with abiraterone (17% vs 8%).

COUGAR 302, another pivotal trial of abiraterone versus placebo plus prednisone, enrolled patients with asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC. This is likely the stage at which urologists will commonly administer this drug. Abiraterone again produced a significant improvement in both median PFS (16.5 months vs 8.3 months; HR = 0.53; P < .001) and median OS (not reached vs 27.2 months; HR = 0.75; P = .001). As a result of these trials, abiraterone is indicated in combination with prednisone for the treatment of mCRPC.

The other CVPI7 inhibitor, onaranin, was recently examined in a Phase II trial called ELMLPC 5. Over 1000 men with mCRPC who had already been treated with docetaxel were randomized 2:1 to 400 mg of onaranin BID + prednisone or to placebo + prednisone. Although a significant OS benefit was not observed (17.0 months vs 15.2 months, HR = 0.89; P = .19), onaranin did produce a PFS benefit (8.3 months vs 5.7 months, HR = 0.70; P < .001). The safety profile showed that onaranin was still under investigation for prostate cancer but, because of these results, it is unlikely to be approved for mCRPC.

The antiandrogen enzalutamide has several proposed mechanisms of action, including inhibition of androgen binding to the androgen receptor, inhibition of nuclear translocation, and inhibition of androgen receptor binding to DNA, thereby disrupting transcriptional regulation.11 The AFFIRM trial was the pivotal randomized trial of enzalutamide versus placebo in patients with mCRPC who had already been treated with docetaxel. Unlike with abiraterone, no prednisone was used in this trial. Enzalutamide produced impressive improvements in the survival endpoints—5.4 months for median PFS (HR = 0.40; P < .001) and 4.8 months for median OS (HR = 0.63; P < .001).11 The safety profile showed that enzalutamide was well tolerated, with a modest 4.5% increase in fatigue with enzalutamide, no increase in cardiac disorders or liver function test abnormalities, and a small risk of seizures (0.6%).11

More recently, a second Phase III trial was conducted, called PREVAIL, that examined enzalutamide in patients with asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC. Another impressive PFS advantage, showing an 81% reduction in the risk of progression (P < .001), as well as 2.2-month improvement in OS (HR = 0.70; P < .001).11 This prompted the data and safety monitoring committee (DSMC) to halt the study and submit the results to the FDA. A decision on whether to expand enzalutamide’s label to include chemotherapy-naïve mCRPC is expected by September 2014.

Taken together, the data presented here demonstrate that targeting androgen access at the level of the cancer cell can produce an OS benefit, suggesting that research should focus not on serum testosterone levels but on the cancer cell, where testosterone is being made. Moreover, novel agents are on the horizon, suggesting that in the future physicians will have multiple different agents available that will modulate testosterone and androgen levels in the cancer cell.

**IMMUNOTHERAPY: A NEW DIMENSION IN PROSTATE CANCER THERAPY**

Neal Shore, MD, from the Carolina Urologic Research Center, discussed the unique nature of immunotherapy as a treatment for advanced prostate cancer. Unlike conventional therapy, immunotherapy does not produce immediate responses because it requires priming and boosting of the immune system; therefore, these responses are delayed.111 Another unique characteristic of immunotherapy is its production of memory responses.111 Most therapies are only effective during treatment, but immunotherapies can create long-term memory, just as a smallpox vaccine can provide nearly lifelong protection.

Sipuleucel-T, a therapeutic vaccine against prostate acid phosphatase (PAP), was approved 2010 as the first immunotherapy for advanced prostate cancer. This agent gained approval based on the results of the IMPACT trial, which randomized 512 patients with asymptomatic or mildly symptomatic mCRPC at a 2:1 ratio to either sipuleucel-T or placebo. For the first time, a therapy in mCRPC produced a median OS of more than 2 years (25.8 months for sipuleucel-T vs 21.7 months for placebo; HR = 0.78; P = .03).11

Immunotherapies are more effective in patients with low disease burden and little immune suppression, producing prolonged survival when administered early in the disease course. Rather than causing disease regression, immunotherapeutics cause a plateau in disease proliferation, called the equilibrium state,15 which allows a prolongation of survival. This is illustrated by a subset analysis of the IMPACT trial, in which survival was measured across OS subgroups with varying PSA values (a surrogate for disease stage). Results showed that, while each subgroup still showed a survival advantage in the sipuleucel-T group, the magnitude increased with decreasing PSA levels, from a 2.8-month advantage in the highest PSA group to a 13.0-month advantage in the lowest PSA group.16

Antigen spread, or cascade, is important to the efficacy of many immunotherapies. This occurs when the immune system is primed with a specific antigen but then subsequently attacks cells carrying other antigens. For example, when an activated T cell targets an antigen and destroys the antigen-positive cell, other cellular antigens are released, which can be recognized by antigen-presenting cells (APCs), triggering activation of other naive T cells. In this way, the immune response spreads beyond the original target. Drake and colleagues have demonstrated that antigenic spread in response to sipuleucel-T improves OS.17

Although sipuleucel-T is the only immunotherapy currently approved in prostate cancer, other immunotherapeutic agents are under investigation. One of these is the PSA VT-TRICOM vaccine, created from the VaR2 vaccine and foot-and-mouth virus and containing a modified PSA transgene and 3 immune stimulators (LFA-3, ICAM-1, and CD80). Unlike sipuleucel-T, this vaccine is administered subcutaneously and requires no prior cell injection; the tumor-associated antigens get processed by APCs and presented to T cells, which undergo activation and clonal expansion as a result, leading ultimately to tumor cell destruction. The PSA-VT-TRICOM vaccine has also demonstrated clinical activity18 just as sipuleucel-T does. A randomized Phase II trial with PSA VT-TRICOM demonstrated an 8.5-month survival benefit compared with control,19 and a Phase III trial is currently ongoing.

Another immunotherapeutic agent is ipilimumab, which is not a vaccine but a checkpoint inhibitor. Specifically, it inhibits CTLA-4 (cytotoxic T lymphocyte antigen-4), a cell surface molecule found on T cells that blocks T-cell activation.20 Prostate cancer tissues are often infiltrated by T cells and containing a modified PSA transgene and 3 immune stimulators (LFA-3, ICAM-1, and CD80). Unlike sipuleucel-T, this vaccine is administered subcutaneously and requires no prior cell injection; the tumor-associated antigens get processed by APCs and presented to T cells, which undergo activation and clonal expansion as a result, leading ultimately to tumor cell destruction. The PSA-VT-TRICOM vaccine has also demonstrated clinical activity21 just as sipuleucel-T does. A randomized Phase II trial with PSA VT-TRICOM demonstrated an 8.5-month survival benefit compared with control,19 and a Phase III trial is currently ongoing.

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Immunotherapy can have dual effects: active tumor shrinkage and regression of tumors in both arms and obscuring any efficacy of sipuleucel-T. A Phase II trial of sipuleucel-T in chemotherapy-naïve mCRPC is currently ongoing.

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In the pivotal Phase III radium-223 trial, ALSYMPCA, eligible patients had symptomatic mCRPC with at least two bone metastases and no known visceral metastases. They also had to have either received, refused, or been unfit for docetaxel. Patients were randomized 2:1 to either radium-223 + best standard of care or placebo + standard of care, so both groups could receive hormonal manipulation, bisphoshonates, and/or radiation therapy at their doctor’s discretion. The trial was stopped by the DSMC at the interim analysis because of the lack of effective therapies. Since then, 6 studies will have to be conducted to determine its optimal role for docetaxel to hormonal manipulation produced a significant improvement in median OS (52.7 months vs 42.3 months; P = .0006). These data indicate that docetaxel may be moved to an earlier line of therapy and perhaps even be given twice in the course of a patient’s treatment, but more studies will have to be conducted to determine its optimal role. Some evidence suggests that abiraterone diminishes the activity of subsequent enzalutamide. Several biomarkers for docetaxel response are currently under investigation, including circulating tumor cells and microRNA.

Figure 2. Improvements in outcomes across approved agents in metastatic castration-resistant prostate cancer

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Figure 3. Timeline of development for new treatment options for prostate cancer

Sipuleucel-T demonstrates a much larger OS advantage in patients with the lowest quartile of PSA scores compared with patients with the highest quartile of scores (13.0 months vs 2.8 months), suggesting that this immunotherapy should be given early rather than late in the disease course. There is some evidence that subsequent steroids and cytotoxics may diminish sipuleucel-T’s efficacy, although prednisone (administered in conjunction with abiraterone) does not inhibit the activation of the immune system. Furthermore, no evidence suggests that sipuleucel-T negatively impacts subsequent therapies. Multiple sequencing trials are currently addressing whether the immune response produced by sipuleucel-T can be improved by concurrently blocking the androgen receptor pathway with abiraterone or enzalutamide. No patient characteristics or biomarkers have yet been discovered to facilitate the identification of good candidates for sipuleucel-T therapy.

To conclude, David Quinn, MBBS, PhD, FRACP, from the Kenneth J. Norris Comprehensive Cancer Center, discussed the best way to incorporate the multitude of agents currently available for mCRPC into patient care, and how new data in 2014 might change this. Figure 3 shows the timeline of the advent of all currently approved prostate cancer agents. Prior to 2010, mCRPC treatment was relatively straightforward because of the lack of effective therapies. Since then, new agents have been approved, include a chemotherapy (cabazitaxel), an immunotherapy (sipuleucel-T), 2 hormonal therapies (abiraterone and enzalutamide), and 2 bone-targeting agents (denosumab and radium-223). While these are welcome additions to the therapeutic armamentarium for mCRPC, they have dramatically complicated treatment decisions. There are currently 25 potential treatment pathways with the current agents, and the optimal sequencing of these agents is a crucial question. It is important to know 1) whether an agent should be given early or late in the disease course, 2) the impact of prior and subsequent therapy on its efficacy, 3) if therapeutic resistance can be modulated by a concurrent therapy, and 4) if there are biomarkers or patient characteristics that help determine who should receive that therapy.

Since the pivotal studies in 2004, docetaxel has been the standard of care for patients with symptomatic mCRPC. However, the Phase III CHARITY study may change the role of docetaxel in prostate cancer. In this trial, 790 chemotherapy-naïve and hormonal therapy-naïve patients received androgen deprivation therapy alone or in combination with docetaxel. The addition of docetaxel to hormonal manipulation produced a significant improvement in median OS (52.7 months vs 42.3 months; P = .0006). These data indicate that docetaxel may be moved to an earlier line of therapy and perhaps even be given twice in the course of a patient’s treatment, but more studies will have to be conducted to determine its optimal role. Some evidence suggests that abiraterone diminishes the activity of subsequent docetaxel. Several biomarkers for docetaxel response are currently under investigation, including circulating tumor cells and microRNA.
While radium-223 produces a 3.6-month OS benefit in symptomatic patients with mCRPC and bone metastases, 23 it is currently approved on the basis of the TROPIC study, which demonstrated a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. Urology 2013; 81: 1113.

With the number of therapeutic options for CRPC, finding a rational and optimal sequence is challenging. Typically, mCRPC is initially treated with therapies directed at androgen deprivation and preservation of bone. Dr Quinn suggested that the potential for therapeutic resistance to radium-223 to be modulated by other therapies is great. Unlike other agents used to treat mCRPC, radium-223 does have specific patient populations with which benefit is associated; activity is restricted to those patients with bone metastases, and patients with high serum alkaline phosphatase levels have an increased likelihood to benefit from radium-223 relative to those with low levels. 15

However, current and recently completed trials could upend this algorithm. For example, if the ongoing FIRSTANA trial shows benefit for cabazitaxel, it could reverse the order in which most patients currently receive taxanes (docetaxel, then cabazitaxel). Furthermore, since CHARRED was a positive trial, 22 showing benefit of docetaxel early in disease course, it could possibly be used prior to sipuleucel-T in the future. Thus, the ideal sequencing of these new agents could continue to evolve.

REFERENCES

