New Developments in the Management of Prostate Cancer

Presented by Philip W. Kantoff, MD, and James L. Mohler, MD

Abstract
Rapid progress was recently made in the treatment of prostate cancer, especially metastatic castration-resistant prostate cancer. At the NCCN 18th Annual Conference, Dr. Philip W. Kantoff reviewed the data supporting the use of abiraterone acetate, enzalutamide, cabazitaxel, sipuleucel-T, and radium-223 (pending approval), and offered recommendations for their sequential use in different settings. Dr. James L. Mohler described factors that dictate who should receive treatment, when they should receive it, and how to treat in the setting of prostate-specific antigen elevation. He explained how better treatment decisions will result from individualized estimation of threat-to-life posed by prostate cancer, chance of cure by treatment, and treatment risks. (JNCCN 2013;11:653–657)

Almost one-third of men who undergo local treatment for prostate cancer will experience relapse and most will receive androgen-deprivation therapy. Most treated patients will eventually become resistant, however, and will develop metastatic castration-resistant or castration-recurrent prostate cancer (mCRPC). For years, docetaxel was the only treatment option for these patients; now, however, the landscape has changed and a variety of new agents are extending remission and survival for these patients.

Androgen Signaling Pathway Remains Important
“We have learned a great deal in the past 10 years about the importance of androgen signaling, even in CRPC,” said Philip W. Kantoff, MD, Director of The Lank Center for Genitourinary Oncology and Chief of Solid Tumor Oncology at the Dana-Farber Cancer Institute/Brigham & Women’s Hospital, Boston. CRPC shows persistence of androgen receptor expression, genes downstream of the androgen receptor, and intratumoral ligand, he said, which means “the androgen signaling pathway is still important.”

Two drugs targeting this pathway were recently approved—abiraterone acetate, an androgen synthesis inhibitor, and enzalutamide, an anti-androgen—and these have changed the treatment landscape, he said. Abiraterone plus prednisone was shown to improve overall survival (OS) by almost 4 months in the COUGAR 301 trial (N = 1158) in patients with mCRPC previously treated with docetaxel (hazard ratio [HR], 0.646; P <.0001).1 In COUGAR-302 (N = 1082), abiraterone was given before chemotherapy. It delayed the time to progression by 50% and was associated with a trend toward improved OS.2 Data updated at the 2013 Genitourinary Cancers Symposium showed a near doubling in radiographic progression-free survival (PFS), from 8.3 to 16.5 months (HR, 0.53; P <.0001), and again a trend toward improved OS, from 30.1 to 35.3 months with the combination (HR, 0.79; P =.0151).3

Enzalutamide, which binds to the androgen re-
Targeting Bone Metastases

The NCCN Panel stated that for protecting bones, zoledronic acid and denosumab are both reasonable alternatives. Although the optimal scheduling of these agents has not been determined, clinicians can consider convenience for the patient (intravenous vs subcutaneous administration, and schedule), side effects, cost, and patient copay.

Both agents are associated with a small risk of osteonecrosis of the jaw (1% with zoledronic acid, 2% with denosumab), and hypothetically, they may be unnecessary when other active agents are on board. This may allow patients a break from treatment or the possibility of avoiding these agents altogether in patients with poor dentition. More hypocalcemia is seen with denosumab (13% vs 6%), but calcium and vitamin D will decrease this risk, and acute phase reactions are more likely with zoledronic acid (18% vs 8%).

Radium-223

FDA approval is expected soon for radium-223 dichloride, which uses alpha-particles to kill tumor cells in a highly localized manner, with minimal damage to surrounding normal tissue. In the phase III ALSYMPCA study (N = 922), men with symptomatic mCRPC and bone metastases received radium-223 after docetaxel (or before chemotherapy, if not fit for treatment), leading to an OS benefit of 3.6 months (HR, 0.695; P < .001). A survival benefit was noted across all patient subgroups, and the drug significantly delayed time to skeletal-related event by 5.8 months (HR, 0.63; P < .001). Further follow-up continues to show a highly favorable safety profile, Dr. Kantoff noted. Dr. Kantoff also showed updated data from the ASCO Genitourinary meeting upholding an OS benefit and demonstrating a delay in time to skeletal-related events. Interestingly, patients with higher alkaline phosphatase levels (for which patients were stratified) seem to derive greater benefit.

Immunotherapy

Sipuleucel-T became available in 2010 as the first immunotherapy approved for any malignancy. The randomized phase III IMPACT trial (N = 512) in asymptomatic or minimally symptomatic mCRPC, which was led by Dr. Kantoff, showed a 4.1-month improvement in OS (HR, 0.78; P = .03). This improvement persisted at 3 years (HR, 0.77 P = .02) despite a 50% crossover rate; however, time to disease progression was similar to that of control patients.

Interestingly, patients with lower prostate-specific antigens (PSAs) appear to benefit more than those with advanced disease, which is contrary to the results seen with drugs with different mechanisms of action. Dr. Kantoff maintained that the best candidates for this agent are men with asymptomatic, indolent mCRPC, rather than those with rapidly progressing disease.

Chemotherapy

Cabazitaxel is a semi-synthetic taxane that is potent against taxane-sensitive and -resistant cell lines. In the global phase III TROPIC study (N = 755) of mCRPC after docetaxel, cabazitaxel plus prednisone was associated with an OS advantage of 2.4 months (HR, 0.70; P < .0001). Because of the occurrence of

ceptor, demonstrates potency comparable to abiraterone. Its clinical benefit was borne out in the phase III AFFIRM trial (N = 1199) in patients with mCRPC after docetaxel. The OS endpoint was reached, for a difference of 4.8 months (HR, 0.63; P < .0001). The incidence of seizure (0.9% at follow-up) was concerning, but enzalutamide was otherwise well tolerated and is now being evaluated in the pre-chemotherapy mCRPC setting in the PREVAIL trial (N = 1680).

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for prostate cancer include abiraterone/prednisone as a category 1 recommendation (uniform consensus based on high-level evidence) in both before and after chemotherapy settings and enzalutamide as a category 2A recommendation (consensus based on lower-level evidence) for docetaxel-naive men and a category 1 recommendation after chemotherapy.

“The studies are proof of principle that the androgen signaling pathway is still important in mCRPC, and these drugs have a clinically meaningful impact on survival,” Dr. Kantoff said. “Their impact earlier in disease, in men with locally advanced high-grade cancer, or early in the evolution of recurrence, has yet to be tested.”

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granulocytopenia, growth factor support should be considered.

Clinicians can now prescribe a number of agents shown to have an OS benefit in mCRPC (Figure 1), but OS benefit remains elusive in the non-metastatic CRPC setting. The optimal sequencing of these new agents is not yet known, and head-to-head comparisons cannot be made. Figure 2 shows new options and indications.

**Sequencing Recommendations**

In summary, Dr. Kantoff offered these recommendations for sequential treatment:

- In non-metastatic CRPC, observation is reasonable for patients with slow PSA velocity, and secondary hormonal therapies can be considered. Trials with androgen-signaling inhibitors and immunotherapies will soon open.
- For mCRPC before chemotherapy in asymptomatic patients with slowly progressing disease, sipuleucel-T, abiraterone, enzalutamide (depending on insurance approval), and clinical trials are options.
- For mCRPC before chemotherapy in asymptomatic patients whose disease is progressing rapidly, abiraterone, enzalutamide (depending on insurance approval), and clinical trials are options, and docetaxel is “not unreasonable.”
- For mCRPC before chemotherapy in the symptomatic patient, docetaxel or radium-223 (when approved) are options.
- For mCRPC after chemotherapy, patients can undergo retreatment if their disease is still sensitive to docetaxel. If it is resistant, enzalutamide or abiraterone are options. Cabazitaxel, clinical trials, mitoxantrone, and sipuleucel-T (only in asymptomatic patients with good prognosis) can also be considered.

### Treatment Versus Active Surveillance

James L. Mohler, MD, Chair of the NCCN Panel on Prostate Cancer, discussed 4 areas of controversy in

<table>
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<th>Trial (Agent) Approved</th>
<th>Disease State</th>
<th>Comparator</th>
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<th>Hazard Ratio</th>
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<td>ALSYMPCA</td>
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<td>COU 301 (Abiraterone+ Prednisone) 2011</td>
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<td>Prednisone</td>
<td>3.9</td>
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*Figure 1* Agents with overall survival benefit in metastatic castration-resistant prostate cancer (mCRPC).
prostate cancer in 2013: early detection, over-treatment, active surveillance, and salvage radiation. Dr. Mohler is Associate Director for Translational Research and Chair of Urology at Roswell Park Cancer Institute.

Panel concerns have influenced the NCCN Guidelines recommendations; these concerns include the high prevalence of prostate cancer on autopsies and high frequency of prostate cancer on biopsy—even when PSA and digital rectal examination results are normal. Additional concerns are the low mortality rate (1 in 6 prostate cancer diagnoses) and the overtreatment of screen-detected cancers (up to 50%), Dr. Mohler said.

In 70% of men, elevated PSA occurs in the absence of a positive biopsy. Because PSA levels fluctuate daily, the rate of rise (velocity, doubling time) is a better reflection of risk than an “absolute snapshot,” he maintained. The average PSA doubling time is 4 years. In 2010, the NCCN Panel “was ahead of its time” in recommending active surveillance for men with a low risk of prostate cancer and life expectancy less than 10 years and those with a very low risk of cancer and a life expectancy less than 20 years, he said.

In 2011, the NCCN Guidelines for prostate cancer that discuss active surveillance were updated to recommend PSA as often as every 3 months but at least every 6 months, digital rectal exam as often as every 6 months but at least every 12 months, and repeat needle biopsy within 6 months of diagnosis if the initial biopsy contained less than 10 cores (within 18 months if 10 or more cores). Criteria to define progressive disease warranting treatment are still undefined, and the Panel has called for more research on this issue.

In general, active surveillance is appropriate for clinically localized cancer when PSA doubling time is greater than 5 years. Cure rates are no worse for men who undergo active surveillance for a period of time before converting to treatment, and in the absence of biomarkers of aggressive disease, PSA kinetics are informative. Active surveillance is an appropriate option for men with clinically localized prostate cancer when the PSA doubling time exceeds 5 years, he said.

In determining treatment (and in discussions with patients), Dr. Mohler recommends the following steps:

- Estimate life expectancy.
- Stratify risk using stage, Gleason sum, and PSA.
- Consider active surveillance as the first option discussed, against which the benefits (potential and need for cure) and risks (mortality, urinary incontinence, and impotence) of treatment should be compared.
- Recommend active surveillance for very low- and low-risk prostate cancer when life expectancy is less than 20 and 10 years, respectively.

Life expectancy is estimated through conversation with the patient and use of tables provided by the Minnesota Metropolitan Life insurance and the Social Security Administration (Figure 3). “You and the patient decide whether he is in the best, worse, or middle two quartiles, then adjust for overall health status,” Dr. Mohler explained.

He noted that, for example, active surveillance would be a good option for a 65-year-old man whose health is poor and who has a PSA of 7.2, clinical stage T1c disease, Gleason score of 6 (3+3), and prostate cancer in 10% of 12 biopsies. On the other hand, the same patient in excellent health would be advised to have radiotherapy or prostatectomy; with average health, his options would be a matter of opinion.
that PSA elevation after radical prostatectomy does not necessarily lead to clinical recurrence, and salvage radiotherapy shows little benefit for patients with PSA recurrence with a slow PSA doubling time (>1–3 years) and older age (>65 years). Online tools are available for predicting cure after radical prostatectomy and predicting the benefit of salvage radiation, he said.

**References**