ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Drugs and Treatment Strategies in Prostate Cancer

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H&O How has the therapeutic landscape for prostate cancer changed over recent years?

MG The therapeutic landscape has had several dramatic changes over the years. More drugs have been approved for advanced prostate cancer in the past few years than there had been in the preceding 30 years. Importantly, approvals have involved drugs with multiple and different mechanisms of action, including drugs that target the androgen receptor signaling axis, agents that capitalize on the immune system, and other treatments that specifically target bone metastases.

H&O Why is symptomatic improvement important, and what have clinical trials shown?

MG How patients feel from the drugs used to treat cancer is of critical importance. However, it has not been a major area of focus in terms of cancer drug development. How patients feel is difficult to measure, especially when compared with how long patients live, which is an established and meaningful clinical endpoint that has generally been favored by both investigators and regulatory agencies.

How patients are feeling when they are on treatment is critical in terms of weighing the risks vs the benefits of treatments. Some treatments may offer only modest extensions in quantity of life but might provide more meaningful improvements in quality of life. There has been a push to focus on patient-reported outcomes in drug development in order to ensure that we are rigorously capturing patients' symptoms, such as pain-related issues that are associated with bone metastases. Of the agents approved for the treatment of advanced prostate cancer over the past several years, the majority of studies have included at least some endpoints related to quality of life, typically as secondary endpoints. Such findings have shown that not only do these drugs improve the length of patients' lives, but they also improve symptoms, decrease the need for narcotic medicines, and decrease the time to worsening of pain—all of which are critically important to patients with this disease.

An interesting development approach is being taken with cabozantinib (Cometriq, Exelixis), a small-molecule tyrosine kinase inhibitor that inhibits both the vascular endothelial growth factor (VEGF) receptor and MET. That drug development plan in the phase 3 setting involves 2 parallel phase 3 trials. One of the trials has a primary endpoint of survival—a very traditional phase 3 design in oncology—and the other has a primary endpoint of improvement in pain. To my knowledge, this is the first time in oncology where there have been 2 large randomized trials exploring the same drug with different endpoints, 1 investigator-assessed and 1 patient-reported.

H&O What changes have been made in trial designs and endpoints? What advances have occurred as a result?

MG There has been an understanding that a post-treatment decline in prostate-specific antigen (PSA) is an acceptable intermediate endpoint for screening the activity of some drugs with certain mechanisms of action; however, this approach may not reveal all the necessary information to make decisions about moving drugs from

the phase 2 setting to the phase 3 setting. Focusing on progression endpoints is much more important. This has been difficult because prostate cancer is typically a bony metastatic disease, and bone metastases are hard to measure with conventional imaging.

Over the past few years, a lot of work has been integrated into phase 3 trials focused on how to interpret progression on bone scans. It is rather tedious work and it can be viewed as trivial work, but I think it has made a critical difference in ensuring that patients have been maintained on these drugs long enough to show their full therapeutic efficacy.

H&O What progress has been made in redefining certain types of disease?

MG Much progress has been made in redefining castration-resistant disease, which used to be known as hormone-refractory disease. Tumors that were previously considered hormone refractory are not in fact hormone refractory, and it is now known that the androgen receptor still plays a major role in driving disease progression in such patients. As a result, treatments directed against the androgen receptor may still provide a benefit to patients with that disease state, and we have certainly witnessed that with some of the drugs recently approved for the treatment of advanced prostate cancer. That was a major shift in the nomenclature and in the understanding of the disease. Although it occurred many years ago, we are still seeing its ramifications.

More recently, there has been a focus on and a shift in the understanding of what has been called neuroendocrine prostate cancer. In the past, neuroendocrine prostate cancer was recognized as a rare variant of prostate cancer. However, it is now appreciated that treatment-induced neuroendocrine prostate cancer may be occurring with increasing frequency, owing to the selective pressure of much better therapies targeting the androgen receptor signaling axis. The androgen receptor is probably not a critical therapeutic target in these neuroendocrine prostate cancers, and new approaches are needed for this disease phenotype.

H&O What key agents have recently been approved, and how are they likely to alter treatment options?

MG Abiraterone acetate (Zytiga, Janssen Biotech) is an androgen-biosynthesis inhibitor. It was the first drug targeting androgen receptor signaling that demonstrated activity and the ability to prolong survival in patients who had already received chemotherapy. Subsequently, a shift in thinking emerged regarding the role of targeting the androgen receptor signaling axis in patients who were castration resistant and had already progressed on cytotoxic drugs. Abiraterone essentially opened up the floodgates for a variety of new treatments targeting androgen-receptor signaling. This drug has now moved to the prechemotherapy setting, based on a prolongation in time to disease progression and a prolongation in other clinically relevant endpoints in that disease state.

Enzalutamide (Xtandi, Astellas/Medivation) is an androgen receptor inhibitor that also inhibits translocation of the androgen receptor from the cytoplasm to the nucleus and binds with much greater potency than older androgen receptor inhibitors, such as bicalutamide. Enzalutamide has also been shown to improve survival in patients who have received chemotherapy and, according to a recent press release, in patients who are chemotherapy-naive.

These are 2 new hormonal treatments that can be applied before patients receive chemotherapy. Both agents are well tolerated and have significant activity. As such, they will impact the timing and, ultimately, the role of chemotherapy in this disease.

Cabazitaxel (Jevtana, Sanofi-Aventis) is the first cytotoxic chemotherapy drug to improve survival in patients with metastatic hormone-refractory prostate cancer who have received treatment with a docetaxel-containing regimen. Sipuleucel-T (Provenge, Dendreon) is an active cellular immune therapy vaccine that has been shown to improve survival in men with metastatic prostate cancer; it is frequently being administered in the prechemotherapy setting, particularly in men with an indolent disease course.

The most recent agent to receive approval is radium-223 (Xofigo, Bayer/Algeta). This is the first radiopharmaceutical to improve survival in patients with metastatic prostate cancer, as well as improving pain and decreasing skeletal-related events.

We now have a host of new therapies with differing and potentially complementary mechanisms of action that can be used at different times during the treatment course of the disease.

H&O What are some promising agents in development?

MG There are a few agents in development that look promising. Cabozantinib, which I already mentioned, showed very striking activity on bone scans in early clinical trials in prostate cancer and is now being evaluated in 2 large randomized phase 3 trials. Galeterone (TOK-001) is a very interesting hormonal therapy that has 3 main mechanisms of action, which makes it slightly different from abiraterone and enzalutamide. This drug not only inhibits the androgen receptor and blocks androgen biosynthesis, but has also been shown in nonclinical studies to degrade the androgen receptor. Thus, it could potentially have activity

in cancers that have become resistant to currently available hormonal therapies, in which resistance is mediated by a number of factors that retain androgen receptor signaling.

ARN-509 is another promising androgen receptor inhibitor that appears to be more potent than enzalutamide and potentially offers a different safety profile.

H&O What are the biggest remaining challenges in this disease?

MG One of the biggest challenges is understanding whether completely obliterating androgen receptor signaling will offer a potential cure for prostate cancer, or if optimal blockade of androgen receptor signaling will result in resistance pathways that are not mediated by androgen receptor signaling. We will likely need to focus on other targets as well, as evidenced by the increasing importance of neuroendocrine differentiation and potentially the progression of androgen receptor–nonexpressing cancer.

H&O What is your outlook for the future?

MG Overall, I believe that the outlook for the future is positive. Historically, advanced prostate cancer was not thought to be a chemotherapy-sensitive disease, and there was thus a lack of rigorous investigation into the molecular and biologic underpinnings of the disease and its progression.

Fortunately, investigator and industry interest in recent years has changed the course of therapeutic options by gaining a better understanding of the biology of the disease, which has led to a marked increase in the number of new treatment options. With the large number of investigators and the incredible work that is being done in both the laboratory and the clinic, I believe we will soon have a better understanding of prostate cancer, prostate cancer progression, and mechanisms of resistance to currently available drugs.

Suggested Readings

de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011;364(21):1995-2005.

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