

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Research in Drug Development for Advanced Prostate Cancer



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H&O What are the standard approaches for the treatment of advanced prostate cancer?

ME There are several treatments approved by the US Food and Drug Administration (FDA) that can be considered standard, such as hormonal therapy and medical castration with luteinizing hormone-releasing hormone agonists and antagonists. Abiraterone acetate (Zytiga, Janssen) and enzalutamide (Xtandi, Astellas/Medivation) have both been approved by the FDA for the treatment of metastatic castration-resistant disease. However, evidence suggests a potential role in combination with standard

These systemic approaches were approved throughout the past 13 years. At this time, the best way to sequence them remains undefined.

H&O What are the unmet needs in this setting?

ME The most important need remains the development of effective new treatments. One of the critical issues as we enter the era of precision medicine is the identification and utilization of new biomarkers that may provide important prognostic information and assist in the selection of treatments for individual patients.

Genomics is likely to become an important tool for treatment selection. New research shows that gene alterations can be applied for specific selection of treatments; for example, mismatch repair (MMR) or DNA repair genes could support the use of specific modalities, such as immunotherapy or drugs/modalities that damage DNA. As in other fields of oncology, this research is evolving.

Genomics is likely to become an important tool for treatment selection.

H&O Are there particular challenges to drug development for prostate cancer?

gonadal ablation for the initial treatment of patients with metastatic hormone-sensitive disease. The combination of standard taxane-based chemotherapy (see below) and conventional gonadal suppression has also shown major survival benefits in patients with extensive hormone-sensitive prostate cancer. Other options for the treatment of advanced prostate cancer include docetaxel and cabazitaxel (Jevtana, Sanofi Genzyme), the radiopharmaceutical agent radium-223 (Xofigo, Bayer), and the cell-based immunotherapy sipuleucel-T (Provenge, Dendreon).

ME In patients with advanced disease, the regulatory criteria for drug approval continue to focus on improvement in survival. It can be difficult to ascribe improvements to a new drug/modality when patients are also receiving additional life-extending treatments. If a therapy is tested in the frontline setting, then it is necessary to control for the treatments that follow. The FDA and clinical trialists alike need to review outcomes that reflect meaningful clinical benefit to justify drug approval. An important step will be to identify

intermediate endpoints showing clinically meaningful improvement to serve as surrogates for outcomes, such as survival.

The ICECaP study (Intermediate Clinical Endpoint in Cancer of the Prostate) analyzed patient-level clinical data involving several thousand patients with early prostate cancer enrolled in trials of adjuvant chemotherapy or hormonal therapy after radical prostatectomy, surgery, or radiation. The analysis found that the development of bone metastasis was an important and potentially meaningful clinical endpoint that correlated with survival. Another important challenge is the management of patients with a rising prostate-specific antigen (PSA) level, but who have not yet developed bone metastasis. The standard treatment approach for these patients remains undefined, and the methodology of clinical trials for them is also unestablished.

H&O What is the impact of bone metastases?

ME Bone metastases can lead to pain and fractures, and delaying their development is a clinically meaningful endpoint. Early treatment for patients with asymptomatic disease clearly extends the time to symptomatic disease and possibly improves survival. Initiation of hormonal therapy in patients who are asymptomatic but who have evidence of metastatic disease is a reasonable approach and the one most commonly employed in the clinic today. There is an evolving interest in evaluating a potential role for stereotactic radiation among patients with oligometastatic disease (<5 metastatic sites on conventional radiology). The optimal time to begin hormonal therapy in patients with no evidence of metastasis is unknown.

H&O Are patients with prostate cancer at risk for certain toxicities?

ME Men with prostate cancer can experience symptoms caused by chronic androgen deprivation. Early male menopause can lead to symptoms such as bone changes, muscle weakness, and fatigue, as well as cognitive deficiencies. Some of these events are treatment-related. Men with prostate cancer tend to be older, so there are also age-related issues.

H&O Are there new biomarkers to guide treatment?

ME The androgen receptor variant 7 (AR-V7) is an RNA mutation of the androgen receptor that has significant management implications. It was discovered and developed at Johns Hopkins. The mutation is seen

in patients who are managed with long-term hormonal therapy, who usually receive prior AR-targeting drugs (eg, abiraterone, enzalutamide). AR-V7 is a truncated receptor, but still constitutively active. It does not have a hormone-binding domain. Therefore, the standard hormonal therapies enzalutamide and abiraterone acetate are unlikely to have a beneficial effect in these patients.

Algorithms incorporating expression of various tissue base biomarkers (eg, Ki-67, neuroendocrine markers) may also identify patients with aggressive subtypes, who are best treated with chemotherapy rather than hormonal therapy.

H&O What are some promising therapies in development?

ME Several compounds appear uniquely active in tumors with alterations in DNA repair genes, which occur in 10% to 25% of patients with metastatic disease. Many trials are evaluating poly(ADP-ribose) polymerase (PARP) inhibitors in patients with these mutations, which can be germline or somatic. Other compounds that damage DNA include radiopharmaceuticals and the standard platinum chemotherapy compounds. This approach appears promising.

Another interesting strategy involves targeting the prostate-specific membrane antigen (PSMA), which is expressed in 99% of patients with prostate cancer, most prominently in those who are castration-resistant. PSMA conjugate compounds with radiopharmaceuticals, such as lutetium (Lu177), have been used successfully to target this antigen. Several years ago, my colleague Dr Martin Pomper led development of a small molecule that binds only to PSMA. I would anticipate that other conjugates, such as chemotherapy compounds and immunotherapies, will soon be in clinical trials.

Approximately 2% of patients with prostate cancer express somatic gene alterations of *MMR*. These patients have microsatellite instability, which is also seen in other tumors, such as colorectal cancer. They can be successfully treated with conventional immunotherapies, such as checkpoint inhibitors. Subsets of patients with more aggressive disease may have a higher mutational load.

The field of immunotherapy is moving slowly in prostate cancer. Good responses to immunotherapy are less common in patients with bone metastases. However, preliminary observations show that it is possible for patients with soft tissue disease to demonstrate remarkable responses to checkpoint inhibitor treatment, and suggest that the tumor microenvironment may be an important factor.

Another interesting area is the way testosterone modulates androgen receptor function. Some patients

who have received long-term hormonal therapy with testosterone suppression develop molecular changes in the androgen receptor. In some patients, these changes can be modified or restored by the administration of testosterone at supraphysiologic doses. Evolving experience in clinical trials suggests that at least 25% of these patients may respond well to the administration of intermittent high-dose testosterone.

H&O Is it known how newer therapies might be combined with older therapies?

ME The issue of combined therapy is pertinent to nearly every modality available, as well as immunotherapy. Combinations and sequencing of immunotherapy agents may be important in terms of antigen presentation or immune response. My previous comments regarding combinations of AR-targeted drugs and standard hormonal therapy with chemotherapy also apply here.

Disclosure

Dr Eisenberger is a consultant to Pfizer, Sanofi, and Astellas.

Suggested Readings

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