ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Prostate Cancer In Focus

Recent Advances in the Management of Castration-Resistant Prostate Cancer

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H&O What are the cornerstones of castration-resistant prostate cancer (CRPC) management?

DG The management of CRPC focuses primarily on the goals of extending life and maintaining quality of life for as long as possible. Unfortunately, today we are unable to cure the vast majority of men who present with metastatic CRPC. Nonetheless, there have been tremendous improvements in both quality of life outcomes and overall survival among men with this disease. The management of CRPC has changed dramatically in the past 2–3 years. Historically, the only treatment that had been known to prolong survival for this disease was docetaxel and prednisone chemotherapy, which still remains a cornerstone of management. In recent years, however, the US Food and Drug Administration (FDA) has approved the novel immunotherapy sipuleucel-T (Provenge, Dendreon), which has been shown to improve overall survival for this population. Another agent recently approved by the FDA is the secondary hormonal therapy abiraterone acetate (Zytiga, Janssen Biotech), which is used in combination with prednisone. Abiraterone acetate specifically targets androgen synthesis occurring anywhere in the body, not just in testosterone, an approach that has shown significant improvement in overall survival. Enzalutamide (Xtandi, Astellas Pharma) is an androgen-receptor signaling inhibitor with unique activity that has been shown to improve overall survival in men with metastatic CRPC. Cabazitaxel (Jevtana, sanofi-aventis) chemotherapy in combination with prednisone has been shown to improve overall survival in men who have previously been treated with docetaxel chemotherapy, again demonstrating the survival benefit seen with chemotherapy and solidifying this approach as a cornerstone of management.

In the future, there may be additional cornerstones. Radiopharmaceuticals have been shown to improve palliative care. Alpharadin, also known as radium-223, is a new radiopharmaceutical agent that appears to improve overall survival. It is undergoing review by the FDA for approval.

H&O How has the management of CRPC changed in recent years?

DG The management of metastatic CRPC has changed dramatically due to new therapies and improvement in survival. The natural history of the disease has changed because of the prolonged survival associated with these therapies. Patients are now living longer than ever, so it is important that metastatic CRPC is diagnosed early. There is more screening for metastases among men who have a rising prostate-specific antigen (PSA) level while receiving primary hormonal therapy in order to diagnose asymptomatic metastatic disease. Sipuleucel-T is specifically indicated for patients who have asymptomatic or minimally symptomatic metastatic CRPC, so for that group of patients, it is important to diagnose metastatic disease before it becomes symptomatic. There is therefore a need to screen more regularly for metastases among patients with rising levels of PSA.

In addition, 2 therapies have been shown to prevent and delay the onset of skeletal-related events. Zoledronic acid and denosumab (Xgeva, Amgen), an antibody to the RANK ligand, are FDA-approved for prophylaxis of skeletal-related events, which are defined primarily as a new bone metastasis that causes pain, results in core compression, or requires intervention with radiation or surgery. Skeletal-related events can significantly alter quality of life, so the ability to prevent and delay them is very significant for this population. Zoledronic acid and denosumab are indicated for patients with osseous metastasis, which is found in the vast majority of patients with metastatic CRPC.

H&O Have these new drugs shed light on the mechanisms of prostate cancer?

DG Throughout the past 10 years, studies in animal models and preclinical cell lines have demonstrated the importance of the androgen-receptor signaling pathway in the progression of metastatic CRPC. Clinical data, however, were missing. With the significant overall survival advantage seen with both abiraterone acetate and enzalutamide, it is now clear that those mechanisms are indeed driving disease progression among a significant proportion of patients with metastatic CRPC. The success of these agents has clearly identified the androgen-receptor signaling pathway as an important component in this disease.

It is not entirely clear how the androgen-receptor signaling pathway remains active in the setting of primary hormonal therapy. There may be multiple mechanisms, including overproduction of androgens, overexpression of the androgen receptor, variations or mutations of the androgen receptor, or other signaling mechanisms that could crosstalk with this pathway on some level. The mechanisms of resistance to primary hormonal therapy may involve 1 or more of these possible biologic alterations, but it is clear that this pathway remains the critical central biology to CRPC.

H&O Are there novel treatments in development?

DG As we recognize the importance of androgen and the androgen receptor, there are several newer drugs that can target the inhibition of androgen biosynthesis differently from abiraterone acetate, as well as agents that may block the androgen receptor differently from enzalutamide. Other agents in development target the tumor microenvironment. A randomized phase III study of alpharadin, or radium-223, has shown a survival advantage in a patient population with symptomatic metastatic CRPC and predominant bone metastases. The mechanism of this effect is largely due to the deposition of a radiopharmaceutical agent into areas where there is active bone turnover and uptake of the radium as a calcimimetic. This uptake results in the release of an alpha particle, which is a high-energy, short track length radiation particle that induces double-stranded DNA breaks and cell death in the tumor microenvironment around the radium deposition. The primary targets of the alpha particle are the tumor microenvironment and the tumor cells that are in direct contact with the microenvironment, which represents a novel mechanism in prostate cancer treatment.

In addition, several targeted therapies are blocking signaling pathways that may be important in the tumor microenvironment. The multi-targeted agent cabozantinib (Cometriq, Exelixis) blocks both vascular endothelial growth factor receptors and the c-Met receptor, among other receptors. In a single-arm, phase II study, cabozantinib demonstrated pharmacodynamic changes on bone scans as well as dramatic improvement in pain control. We await results from ongoing phase III studies that are evaluating whether cabozantinib reduces pain and improves overall survival.

H&O What are some areas of unmet need?

DG There is clearly a lot of work still to be done in this field. Although there has been a dramatic improvement in the overall survival of these patients, they are still going on to die from disease progression and complications from metastatic castration-resistant disease. Much of the mortality is due to resistance of the pathways that are being targeted, including the androgen-receptor pathway as well as alternative signaling pathways that may become dominant drivers in the absence of androgens and androgen-receptor biology. In order to develop new therapies, it will be critical to recognize those pathways and identify the key drivers in truncal events related to this biology.

There is an increasing awareness of the histologic subtypes of CRPC, including a small-cell variant, a ductal variant, and an anaplastic variant. These variants can manifest clinically through different patterns of metastases, such as more visceral or hepatic metastases. They can also be associated with very low PSA levels or with the production of other biomarkers, including chromogranin or carcinoembryonic antigen, suggesting an alternative biology. There is a need to understand the heterogeneity that drives metastatic CRPC and to develop a better appreciation of the histologic and biologic subtypes of the disease to identify therapies that specifically target their underlying biologies.

There are also improvements to be made in immunotherapy. Sipuleucel-T is a great start in terms of being able to target and harness the immune system against

prostate cancer, but there is room to improve with additional agents. There is excitement in the field of oncology regarding checkpoint inhibitors and similar strategies, and there will be an opportunity for advancements in prostate cancer management, particularly with immunotherapy.

H&O What are some promising areas of research?

DG Research is needed to develop a better understanding of the underlying biology of prostate cancer, not necessarily as a monolithic disease but as disease subtypes. One of the critical limitations here has been access to tissue. At my institution and others, researchers have performed tumor-directed biopsies of bone or other soft tissue to access prostate cancer tissue, but a more concerted effort will be needed to improve access to allow for better somatic characterization of the disease biology. One promising area of research appears to be circulating tumor cells and the ability to collect tumor samples from the blood in a serial manner. The FDA has approved a test to monitor circulating tumor cells. It will be critical to build upon this technology—or develop other technologies—to improve upon the collection rate, the number of cells collected, and the characterization of these cells to understand the biology of this disease.

In addition, the ability to better image prostate cancer and perhaps the biologic phenotypes of prostate cancer will be an important aspect to both selecting patients for targeted therapies as well as monitoring response and benefit to treatment. Another important area is profiling, in which sequencing and other approaches are used to differentiate the subtypes of prostate cancer and evaluate how they respond to therapy in order to identify the critical targets for this disease. These areas of research have the potential to impact the field in the next 5 years, and I look forward to seeing how they become integrated into our standard practice.

Suggested Readings

De Bono JS, Fizazi K, Saad F, et al. Primary, secondary, and quality-of-life endpoint results from the phase III AFFIRM study of MDV3100, an androgen receptor signaling inhibitor. *J Clin Oncol* (ASCO Annual Meeting Abstracts) 2012;30(18 suppl): Abstract 4519^.

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Sartor O, Heinrich D, Helle SI, et al. Radium-223 chloride (Alpharadin) impact on overall survival and skeletal-related events in patients with castration-resistant prostate cancer with bone metastases: a phase III randomized trial (ALSYMPCA). Abstract presented at: the 2012 American Urological Association Annual Meeting; May 19-23,2012; Atlanta, GA. Abstract 684.

Smith M, Saad F, Shore N, et al. Denosumab delays development of multiple bone metastases in men with castrate-resistant prostate cancer. Abstract presented at: the 2012 American Urological Association Annual Meeting; May 19-23, 2012; Atlanta, GA. Abstract 681.

Smith MR, Sweeney C, Rathkopf DE. Cabozantinib (XL184) in chemotherapy-pretreated metastatic castration resistant prostate cancer (mCRPC): results from a phase II nonrandomized expansion cohort (NRE). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30(18 suppl): Abstract 4513.