Advances in the Treatment of Metastatic Prostate Cancer

Jong Chul Park, MD, and Mario A. Eisenberger, MD

From the Genito-Urinary Oncology Program, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Johns Hopkins University, Baltimore, MD.

CME Activity

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Abstract

During the past several years, there has been substantial progress in the development of treatments for advanced prostate cancer with the approval of multiple new life-prolonging agents using different mechanisms of action. Such progress was attainable because of advances in our understanding of the biology behind mechanisms of androgen receptor pathway activation, complex tumor-microenvironment interaction of bone metastasis, antitumor immunology, and new oncogenic pathways. Continuous efforts are being made to develop new therapeutics with novel mechanisms of action, define the optimal sequences and/or combinations of current agents, and identify reliable surrogate end points to facilitate new drug development.

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Prostate cancer is the most common malignancy in men in the United States, with an estimated 220,800 new cases in 2015.[1] Since the introduction of the serum prostate-specific antigen (PSA) test and the wide acceptance of routine PSA screening, there has been a substantial stage shift with a dramatic decrease in the proportion of advanced stage disease at diagnosis; approximately 80% of prostate cancer cases are diagnosed as localized disease and only 4% as metastatic disease.[1-3]

In the past decade, the landscape of treatments for metastatic prostate cancer had drastic changes from treatments with mostly palliative benefits to a number of new life-prolonging therapeutics approved by the Food and Drug Administration (FDA) (Figure 1). Despite such advances, metastatic prostate cancer remains a lethal disease and accounts for approximately

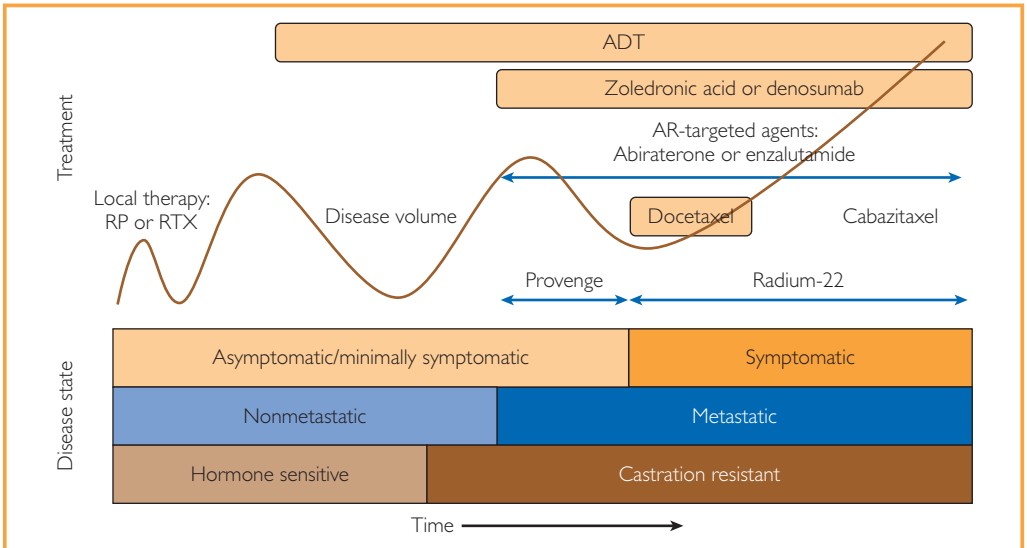

FIGURE 1. Natural history and management landscape of prostate cancer. ADT = androgen deprivation therapy; AR = androgen receptor; RP = radical prostatectomy; RTX = radiation therapy.

27,000 cancer-related deaths annually. In this review, we discuss the treatment of metastatic prostate cancer focusing on recent advances, challenges in new drug development, and promising ongoing research.

TREATMENT OF METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

For patients with newly diagnosed, hormone-naive, metastatic disease, androgen deprivation therapy (ADT) either by bilateral orchiectomy (surgical castration) or by testicular androgen synthesis (medical castration) suppression using luteinizing hormone-releasing hormone agonists or antagonists remains the cornerstone of initial treatment. The ADT of both modalities reduces serum testosterone levels to less than 50 ng/dL and results in PSA and/or radiographic response as well as symptomatic improvement in most patients.[4]

The addition of first-generation antiandrogens to ADT (combined androgen blockade) as the initial therapy has shown minimal clinical benefit at the expense of more toxicity and higher cost in comparison with ADT alone.[5-7] The benefit of combined androgen blockade using more potent second-generation antiandrogens such as enzalutamide and orteronel is under evaluation, but the routine use of combined androgen blockade is not generally recommended.

More recently, multiinstitutional prospective trials evaluating the role of upfront docetaxel chemotherapy in addition to hormone therapy have been reported (Table 1).[8-11] Although the survival benefit did not reach statistical significance in the French Genitourinary Tumor Group (GETUG-AFU) 15 trial,[8] the following 2 larger trials, ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease (CHAARTED)[12] and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE),[10] found significant survival improvements of early docetaxel use in newly diagnosed metastatic disease. A small sample size with a relatively low proportion of high-volume disease and a higher proportion of patients receiving salvage chemotherapy in the GETUG-AFU 15 trial may have contributed to the negative survival benefit. Subset analysis in the CHAARTED study suggests that patients with high-volume disease derive greater benefits from this combined approach, whereas more follow-up is needed to evaluate the benefits in patients with lower tumor burden.[12] The STAMPEDE study evaluated a mixed population of both high-risk locally advanced and metastatic disease and the specifics on the disease volume status is not available, which may explain the difference in the magnitude of survival benefit between CHAARTED and STAMPEDE studies.[10] At the present time,

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