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Navigating the evolving therapeutic landscape in advanced prostate cancer

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Abstract

Prostate cancer is the most common cause of cancer in men, with 137.9 new cases per 100,000 men per year. The overall 5-year survival rate for prostate cancer is very high. Up to 20% of men who undergo state-of-the art treatment for prostate cancer will develop castration-resistant prostate cancer (CRPC) within 5 years, with median survival for those with metastatic CRPC ranging from approximately 15 to 36 months in recent studies. With the advent of several new drugs in the past 5 years to treat CRPC, the challenge facing clinicians is how to best sequence or combine therapies or both to optimize outcomes. A better understanding of the disease process and the role of the androgen receptor as a target for both therapy and resistance have led to the consideration of biomarkers as an approach to aid in selecting the appropriate agent for a given patient as patients respond to or tolerate different drugs differently. Research to identify new prognostic biomarkers, which are associated with outcome measures, as well as predictive biomarkers, which predict response or resistance to therapy is ongoing. The treatment of advanced prostate cancer and the research related to biomarkers are discussed.

Keywords: Androgen receptor; Biomarkers; Metastatic; Prostate cancer; Treatment

1. Introduction

Prostate cancer is the most common cancer in men, with 137.9 new cases per 100,000 men per year [1]. Although still the most common cancer in men, the number of new cases per year has steadily declined since the early 1990s. An estimated 21.4 deaths per 100,000 men per year are due to prostate cancer, which also represents a decline from approximately 40 deaths per 100,000 men in the early 1990s. The overall 5-year survival rate for prostate cancer is very high: 98.9% for the period from 2005 to 2011. Most men have localized (80%) or regional (12%) prostate cancer at the time of diagnosis, and their 5-year survival is nearly 100%. For the 4% of men who have distant (metastatic) prostate cancer at the time of diagnosis, their 5-year survival, although improved from 2 decades ago, is still only 28.2%. These statistics are of importance and concern to both urologic and medical oncologists. Early detection and treatment of prostate cancer is associated with better outcomes. However, both urologists and medical oncologists share concerns about overdiagnosis and overtreatment.

Advanced prostate cancer is broadly categorized as nonmetastatic, metastatic, and castration-resistant prostate cancer (CRPC). Defining prostate cancer clinical states is a rapidly changing paradigm. One model categorizes the disease continuum based on whether metastases are detectable and whether the serum testosterone level is in the castrate range [2,3]. Characteristics of CRPC include a conventionally defined testosterone level of <50 ng/dl, a rise in prostate-specific antigen (PSA) levels for 3 consecutive tests, a PSA nadir >2 ng/ml, a rise in PSA despite androgen deprivation therapy (ADT), and often, a progression of disease after antiandrogen withdrawal (≥ 4 weeks for flutamide and ≥ 6 weeks for bicalutamide). We note that the definition of a testosterone level ≤ 50 ng/dl is arbitrary;

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there is now clear evidence that even lower amounts of testosterone can stimulate tumor growth.

Approximately 10% to 20% of men with advanced prostate cancer will develop CRPC within 5 years, and ≥84% of those will have metastases at the time of CRPC diagnosis [4]. Of those with no metastases present at the time of CRPC diagnosis, 33% likely will develop metastases within 2 years. Median survival of men with metastatic CRPC ranges from approximately 15 to 36 months depending on the study cited. Detection of metastases is highly dependent on the imaging modality used, and new techniques such as prostate-specific membrane antigen positron emission tomography scans can dramatically alter the extent of disease visualized [5,6].

There are a number of guidelines by different groups for diagnosing and treating metastatic disease in prostate cancer, but they differ in their recommendations. After a review of currently available imaging guidelines and relevant clinical validation studies for metastatic disease, the prostate cancer radiographic assessments for detection of advanced recurrence (RADAR) group found no consensus regarding eligibility criteria, type of imaging modality, and the frequency of scanning for detecting metastatic disease [7]. The resulting recommendations of RADAR I to improve early detection of metastatic disease with imaging in clinical practice—stratified patients were to categorize them into 3 groups (Fig. 1) [7].

As mentioned, early diagnosis and treatment of prostate cancer is associated with better outcomes, as evidenced by the 100% 5-year survival rate in patients with localized or regional disease. Hormone therapy (e.g., gonadotropin-releasing hormone agonists and androgen receptor [AR] antagonists) exerts selective pressure on tumor cells causing cell death or cell cycle arrest, which leads to tumor regression [8]. However, it may also lead to CRPC due to adaptations by tumor cells (e.g., mutation, aberrant modification, alternate splicing, cofactor perturbation, and intracrine androgen synthesis) that restore AR signaling leading to a rise in PSA levels and recurrent tumor growth (Fig. 2) [8]. With the advent of many new drugs for CRPC in the past 5 years (Table 1), physicians must exercise

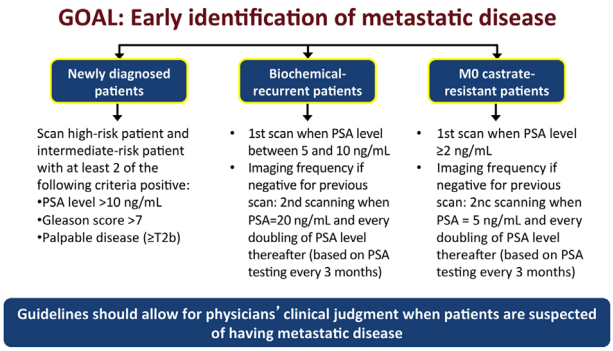

Fig. 1. Recommendations from the RADAR I group for imaging metastatic disease in patients with prostate cancer [5]. (Color version of figure is available online.)

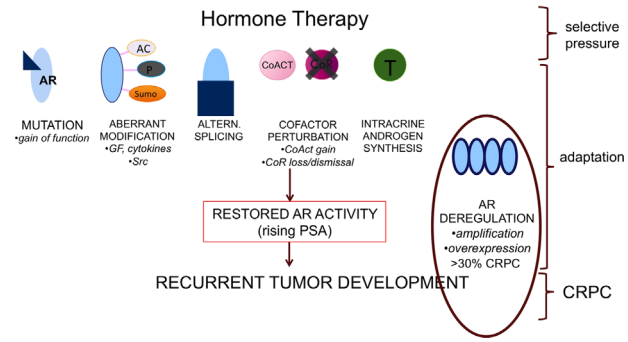

Fig. 2. Development of castrate-resistant prostate cancer (CRPC) [7]. Hormone therapy of prostate cancer results in tumor cell death or cell cycle arrest. This selective pressure on androgen receptor (AR) activity leads to adaptation events (amplification or overexpression of AR, gain of function, somatic mutation of AR, aberrant AR posttranslational modification, and alternative splicing events) that result in hyperactive receptors, cofactor dysregulation, or intracrine androgen synthesis or all of these, which can restore AR signaling. Resurgent AR activity, marked by a rise in PSA (biochemical failure), induces CRPC. (Color version of figure is available online.)

clinical judgment when selecting treatment (Fig. 3). Consideration of the mechanism of action, dosing, cautions, and adverse events for each of the newer treatments is important for determining which therapy is right for an individual patient. Other factors to consider are prior therapy, symptom burden, type of metastasis, performance status, and treatment sequence [9]. Nonetheless, it remains difficult to precisely tailor optimal therapy for an individual patient. Ongoing research shows promise that selected biomarkers may be a useful tool for individualizing prostate cancer therapy.

2. Treatment of advanced prostate cancer

2.1. Androgen deprivation therapy

ADT, which blocks the interaction of androgen with the AR, has been the mainstay of advanced prostate cancer since the 1940s. Yet, as noted by Dr. Charles Huggins in his 1966 Nobel Lecture, "there are many failures of endocrine therapy to control the disease." Our understanding of the natural history of prostate cancer has changed over time from a linear model to a more dynamic one, and the use of biomarkers will enhance treatment decisions along the continuum.

Indications for ADT include newly diagnosed metastatic disease, adjuvant therapy of node-positive disease discovered at prostatectomy, and combined with radiotherapy in patients with intermediate or high-risk disease (Fig. 3). The most common use of ADT in the United States is in patients with biochemical progression; however, there is no level 1 evidence to support this indication. There are several types of conventional ADT, including luteinizing hormone (LH)-releasing hormone (LHRH) agonists (leuprolide and goserelin), LHRH antagonists (degarelix) that provide a