Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2015

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

AR = androgen receptor

ASCO = American Society of Clinical Oncology

CRPC = castration-resistant prostate cancer

FDA = U. S. Food and Drug Administration

H&P = history and physical

mCRPC = metastatic castration-resistant prostate cancer

PCWG2 = Prostate Cancer Clinical Trials Working Group 2

PSA = prostate specific antigen

QoL = quality of life

RCT = randomized controlled trial

Purpose: The purpose of this amendment is to incorporate relevant newly-published literature to better provide a rational basis for the management of patients with castration-resistant prostate cancer.

Materials and Methods: The original systematic review and meta-analysis of the published literature yielded 303 studies published from 1996 through 2013. This review informed the majority of the guideline statements. Clinical Principles and Expert Opinions were used for guideline statements lacking sufficient evidence. In April 2014, the CRPC guideline underwent amendment based on an additional literature search, which retrieved additional studies published between February 2013 and February 2014. Thirty-seven studies from this search provided data relevant to the specific treatment modalities for CRPC. In March 2015, the CRPC guideline underwent a second amendment, which incorporated 10 additional studies into the evidence base published through February 2015.

Results: Guideline statements based on six index patients developed to represent the most common scenarios encountered in clinical practice were amended appropriately. The additional literature provided the basis for an update of current supporting text as well as the incorporation of new guideline statements for multiple index patients.

Conclusions: Given the rapidly evolving nature of this field, this guideline should be used in conjunction with recent systematic literature reviews and an understanding of the individual patient's treatment goals. Patients' preferences and personal goals should be considered when choosing management strategies. This guideline will be continually updated as new literature emerges in the field.

Key Words: prostatic cancer, castration-resistant; androgen antagonist; drug therapy

Accepted for publication October 15, 2015.

This document is being printed as submitted independent of editorial review by *The Journal of Urology®*.

No direct or indirect commercial incentive is associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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† Financial interest and/or other relationship with MDx Health.

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0022-5347/16/1955-1444/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.10.086
Vol. 195, 1444-1452, May 2016
Printed in U.S.A.

INCIDENCE AND EPIDEMIOLOGY

PROSTATE cancer is the most commonly diagnosed solid organ malignancy in the United States and remains the second leading cause of cancer deaths among American men. Approximately 220,000 new diagnoses of prostate cancer and over 27,000 deaths were estimated in the U.S. in 2015.[1] Prostate cancer deaths are typically the result of metastatic castration-resistant prostate cancer, and historically the median survival for men with mCRPC has been less than two years. The recent availability of novel treatments for mCRPC has given a resurgence of hope for these men as studies now demonstrate improved survival with a variety of new agents. However, the unfortunate reality is that mCRPC remains an incurable disease, and it is against this backdrop that we look to the future with cautious optimism and new hope for scientific discovery.

The exact mechanism of transition from castration-sensitive prostate cancer to castration-resistant disease is still not fully understood, but with recent scientific breakthroughs in basic research, there is now a greater understanding. We now know that despite castrate levels of androgens, the androgen receptor remains active and continues to drive prostate cancer progression.[2,3] This understanding has led to the development of novel agents aimed at further decreasing androgen production or blocking AR function. However, there are also many other biologic pathways that function independent of androgen signaling resulting in CRPC. With a greater understanding of the tumor biology, there is hope for continued development of innovative treatment options that improve survival for men with mCRPC.

The treatment of men with mCRPC has dramatically changed over the past decade. Prior to 2004, once patients failed primary androgen deprivation, treatments were administered solely for palliation. Landmark articles by Tannock et al.[4] and Petrylak et al.[5] demonstrated that docetaxel improved survival for these patients with mCRPC. Since the approval of docetaxel, five additional agents that show a survival benefit have been FDA-approved on the basis of randomized clinical trials. These have included enzalutamide and abiraterone, two agents designed specifically to affect the androgen axis;[6,7] sipuleucel-T, which stimulates the immune system;[8] cabazitaxel, a chemotherapeutic agent;[9] and radium-223, a radionuclide therapy.[10] These agents have been tested in multiple "disease states" of CRPC to determine if or when patients might benefit from each treatment. Other treatments for men with mCRPC have been shown to improve outcomes, but remain to be approved by the FDA.[11]

GUIDELINE PURPOSE

As a direct result of the significant increase in multiple FDA-approved therapeutic agents for use in patients with mCRPC, clinicians are challenged with a multitude of treatment options and potential sequencing of these agents that, consequently, make clinical decision-making more complex. These guidelines were developed to provide a rational basis for treatment of patients with CRPC, based on currently available published data. To assist in clinical decision-making, six index patients were developed representing the most common clinical scenarios that are encountered in clinical practice. These index patients were created based on the presence or absence of metastatic disease, the degree of symptoms, the patients' performance statuses (as defined by the ECOG scale) and the prior treatment with docetaxel-based chemotherapy.

1. Asymptomatic non-metastatic CRPC
2. Asymptomatic or minimally-symptomatic, mCRPC without prior docetaxel chemotherapy
3. Symptomatic, mCRPC with good performance status and no prior docetaxel chemotherapy
4. Symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy
5. Symptomatic, mCRPC with good performance status and prior docetaxel chemotherapy
6. Symptomatic, mCRPC with poor performance status and prior docetaxel chemotherapy

The newly incorporated literature from the 2015 amendment specifically relates to Index Patients 2, 3 and 4. A summary of the statements relating to all Index Patients can be found in Figure 1.

The goal of this guideline is to provide evidence based recommendations for the treatment of CRPC. Given that this is a rapidly evolving field, this guideline should be used in conjunction with recent systematic literature reviews and an understanding of the individual patient's treatment goals. In all cases, the patient's preferences and personal goals should be considered when choosing therapy. Although we are discussing castration-resistant disease, we support the standard of care to maintain castrate testosterone levels even in the face of castration-resistant disease.

METHODOLOGY

Process for Initial Literature Selection

Consistent with the AUA published guideline methodology framework,[12] the process started by conducting a comprehensive systematic review. The evidence report was limited to English-language, peer-reviewed literature published between January 1996 and February 2013.