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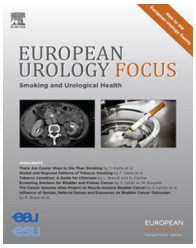

Review – Prostate Cancer

The Natural History and Outcome Predictors of Metastatic Castration-resistant Prostate Cancer

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Abstract

Context: Biomarkers for the treatment of metastatic castration-resistant prostate cancer (mCRPC) are urgently needed by clinicians to facilitate treatment decisions.
Objective: To review current prognostic and predictive biomarkers in mCRPC.
Evidence acquisition: We performed a nonsystematic review of the literature from 2004 to August 2016 by searching in Medline. Cross-matching references were used to search for additional articles. We reviewed clinical research and review articles written in the English language.
Evidence synthesis: Nomograms of prognostic factors (eg, albumin, lactate dehydrogenase) enable clinicians to estimate the prognosis of men with mCRPC. These prognostic tools may aid with when to trigger treatment, therapeutic monitoring, and follow-up. However, validated predictive biomarkers in mCRPC are still lacking. Androgen receptor (AR) splice variants (ie, AR-V7), gene fusions, and point mutations determined using liquid biopsies such as circulating tumor cells (CTCs) or cell-free DNA (cfDNA) are promising biomarkers that are the subject of ongoing research. Patient biomarkers (eg, neutrophil-to-lymphocyte ratio) are readily available and come with no extra cost but need further validation before their implementation in clinical practice.
Conclusions: Determination of AR-V7 in CTCs is a big step towards a more personalized treatment approach in mCRPC. Genomic characterization of liquid biopsies such as CTCs, cfDNA, and circulating RNA are noninvasive tools to further personalize treatment in prostate cancer. Clinical parameters are readily available, but are derived from retrospective studies and should be interpreted with care. Only by conducting biomarker-driven studies, rather than large *one-size-fits-all* trials, will we be able to improve prostate cancer treatment.
Patient summary: Several biomarkers are currently under investigation that may predict which patients will respond to specific therapies in the future of metastatic castration-resistant prostate cancer treatment.

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1. Introduction

The treatment of metastatic castration-resistant prostate cancer (mCRPC) has changed considerably over the past years with the advent of several life-prolonging therapies. Docetaxel chemotherapy was the first approved agent for men with mCRPC, following reports of improvement in survival and quality of life in the pivotal TAX327 and SWOG 99-16 trials in 2004 [1,2]. In the following years, the treatment landscape rapidly evolved with the development

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and subsequent regulatory approval of cabazitaxel, abiraterone, enzalutamide, radium 223, and sipuleucel-T [3–9]. Despite these rapid therapeutic advances, mCRPC is still a lethal disease that is characterized by a heterogeneous natural history. Prognostic models and nomograms have been developed to estimate the prognosis of men with mCRPC, which ranges between 1 yr and 3 yr [10]. Although the prognosis of patients can be estimated accurately using these nomograms, we are not able to predict response to the available therapies for mCRPC. Since there is a lack of Level one evidence to tailor therapy, treatment decisions are largely based on personal preferences, reimbursement policies, and toxicity profiles. Therefore, predictive biomarkers are urgently needed by clinicians to guide treatment choices for individual patients, in order to better select therapy. This will ultimately define which patients will benefit from treatment, can help to avoid overtreatment, and improve quality of life by obtaining better responses and limiting drug-related toxicity.

In this article, we will give an overview of prognostic and potential predictive biomarkers in mCRPC, and recommendations for the future.

2. Evidence acquisition

We performed a nonsystematic review of the literature from 2004 to August 2016 by searching Medline with the keywords metastatic castration-resistant prostate cancer, novel therapies, androgen receptor, docetaxel, cabazitaxel, abiraterone, enzalutamide, radium-223, prognostic biomarkers, predictive biomarkers. Cross-matching references were used to search for additional articles. We reviewed clinical research and review articles written in the English language. Conference abstracts were not included. Because of its very limited use in Europe, articles on immunotherapy were not included. We did not include bone-specific biomarkers.

3. Evidence synthesis

Only articles that clearly defined the mCRPC study population, clinical endpoints, and methods were included in this review. We included 38 articles that investigated the prognostic and predictive biomarkers in mCRPC. We, herein, review articles focused on the use of these biomarkers in the management of men with mCRPC.

3.1. Clinical and biochemical markers

3.1.1. Prognostic factors and models

Prognostic factors have been developed to predict the overall survival (OS) of men with mCRPC in clinical practice and have been used for risk stratification in clinical trials. Over the past years, databases from large phase 3 trials have been of value to develop several prognostic nomograms. In the TAX327 registration trial of docetaxel, several independent prognostic factors for survival were identified [2]. These factors included: performance status, the presence of liver metastases, number of metastatic sites, clinically significant pain, type of progression, prostate-specific antigen (PSA) doubling time, baseline PSA, tumor grade, alkaline phosphatase, and hemoglobin [11]. Three prognostic models, each of which incorporated some of these prognostic markers, were initially developed by the Cancer and Leukemia Group B [12] by Smaletz et al [13] and Armstrong et al [11]. More contemporary nomograms using similar readily available clinical parameters have been recently constructed. Halabi et al [10] have used data from the phase 3 trial Cancer and Leukemia Group B-90401, comparing docetaxel to docetaxel plus bevacizumab to improve the prognostic model for men receiving first-line chemotherapy (Fig. 1). Data from the TROPIC trial, comparing cabazitaxel with mitoxantrone, and the SPARC trial comparing satraplatin with a placebo, were used to improve the prognostic model for men receiving second-line chemotherapy [14]. Likewise, clinical factors have been identified for men receiving abiraterone in the postdocetaxel setting including: lactate dehydrogenase, performance score, alkaline phosphatase, albumin, and duration of initial hormonal therapy [15].

In practice, they can help the clinician to estimate survival and decide when to initiate treatment. These prognostic models can also be used to derive a prognostic score, which may serve as an eligibility criterion in clinical trials, to derive an individualized predicted survival probability, and to classify patients into risk groups on the basis of validated cut points in future trials of mCRPC. The relevance of these models in the changing landscape of mCRPC environment has become questionable. Following the publication of the data of STAMPEDE and CHAARTED trials, docetaxel is often administered together with androgen deprivation therapy in newly diagnosed metastatic hormone-sensitive prostate cancer patients [16]. In other patients, the results of PREVAIL and COU-AA-302 studies and the consensus that followed, established enzalutamide and abiraterone as a first-line treatment in most mCRPC patients [3,8,16]. Novel nomograms are currently being developed based on these modern data.

3.2. Neutrophil-to-lymphocyte ratio

An emerging and readily available biomarker in mCRPC and other tumor types is the neutrophil-to-lymphocyte ratio (NLR). NLR, a marker for host inflammation, was associated with clinical outcome in several malignancies such as hepatocellular, gastric, renal cell, colorectal, and prostate cancer [17]. In a prognostic model of two large phase 3 trials of 2230 men with mCRPC receiving first-line chemotherapy, an elevated NLR was an independent predictor of shorter OS (hazard ratio [HR]: 1.29, $p < 0.001$ in the training set and 1.43, $p < 0.001$ in the validation set) [18]. A similar prognostic value for NLR was found for men receiving second-line chemotherapy [19].

This marker was also explored for predictive properties [18]. Although men with an elevated NLR had a shorter OS, the OS benefit in men treated with docetaxel was 4.3 mo with PSA response rates of 53–67% in this patient population. Similarly, cabazitaxel showed an OS benefit irrespective of NLR in a posthoc analysis of the TROPIC trial