Review – Prostate Cancer

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

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Abstract

\textbf{Context:} Biomarkers for the treatment of metastatic castration-resistant prostate cancer (mCRPC) are urgently needed by clinicians to facilitate treatment decisions.

\textbf{Objective:} To review current prognostic and predictive biomarkers in mCRPC.

\textbf{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.

\textbf{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.

\textbf{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.

\textbf{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. \textbf{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 1 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.
Fig. 1 – Nomogram predicting overall survival probability. Instructions to physicians: All of the eight prognostic factors should be available before using this model. An online calculator is available at: https://www.cancer.duke.edu/Nomogram/firstlinechemotherapy.html. Please start from the second top axis by identifying the opioid analgesic use. Draw a vertical line to the points axis (top line) to represent the number of prognostic points the patients will receive for opioid analgesic use. Do the same for the other prognostic variables. Once all prognostic points for the predictors have been determined, add up the prognostic points for each prognostic variable. On the basis of the total points, one can determine the 18-mo survival probability by drawing a vertical line from the total points x-axis to the survival probability. The same process can be performed to estimate the 24-mo, 30-mo, 36-mo, and 48-mo survival probability or the median survival.


[19]. In contrast, a retrospective study exploring the role of NLR in mCRPC patients treated with abiraterone revealed that men with an elevated NLR showed low PSA response rates (16%) and shorter survival [20].

Taken together, NLR is a readily available and a cheap clinical parameter which can be used for risk stratification in future clinical trials and may provide direct prognostic information for patients in daily practice. NLR is not predictive of response to treatment with docetaxel chemotherapy, but might predict modest PSA response in men receiving abiraterone. Further research should define whether NLR could be a biomarker of response to androgen receptor (AR)-targeted agents or chemotherapy.

3.2.1. Duration of response to initial hormonal therapy
A clinical factor of interest that might aid treatment selection for men with mCRPC in clinical practice is the duration of response to prior hormonal therapy. In a retrospective study in 173 men treated with AR-targeted drugs including abiraterone and enzalutamide, patients...
were stratified according to response to initial hormonal therapy [21]. It was observed that men with a short duration of response to initial hormonal therapy (<12 mo) had inferior PSA response rates as compared with men with durable response to initial hormonal therapy (≥12 mo; 16% vs 41%, respectively, p = 0.005). A similar clinical parameter—time to development of mCRPC—was negatively associated with PSA-progression-free survival (PFS; HR: 0.99, p = 0.02) and PFS (HR: 0.99, p = 0.01) in a retrospective study of 126 men treated with abiraterone and enzalutamide [22]. In contrast, in posthoc analyses of phase 3 trials of mCRPC men treated with docetaxel, the treatment benefit of chemotherapy was irrespective of duration of initial androgen deprivation therapy [18]. These hypothesis-generating findings might suggest that men with only a short response to initial hormonal therapy respond better to chemotherapy compared with AR-targeted agents. Further research is warranted to define whether duration of initial androgen deprivation therapy might be used as parameter for further personalizing treatment.

3.2.2. Gleason score
In a posthoc analysis of the TAX327 trial, greater OS was observed in men with high Gleason score tumors (OS benefit 4.4 mo vs 2.9 mo in the total patient population) [23]. A similar analysis stratified by Gleason score (≥8 vs <8) was performed with data of the COU-AA-301 and COU-AA-302 trials of abiraterone postchemotherapy and prechemotherapy [24]. In men treated with abiraterone prechemotherapy, abiraterone and prednisone significantly improved PFS over prednisone alone irrespective of Gleason score. In a subgroup of men with a high Gleason score (≥8), a trend in improvement of OS was observed (HR: 0.82, p = 0.06). However, there was no treatment interaction of Gleason score for OS in men treated with abiraterone both predocetaxel and postdocetaxel. In summary, Gleason score might be useful in identifying men who derive the most benefit from treatment with docetaxel, but should not be used to predict benefit of other mCRPC treatments.

3.3. Genomic markers: liquid biopsy

3.3.1. Circulating tumor cells
Circulating tumor cells (CTC), cell-free DNA (cfDNA), and RNA offer the potential for noninvasive characterization of disease and molecular stratification of patients. The development of metastases likely involves a period of circulatory spread of invasive carcinoma cells in target organs, typically lymph nodes, bone, lung, and liver in mCRPC. The measurement of these rare tumor cells in the circulation of patients with cancer has been studied for many years, but only recently has technology advanced to the point of regulatory approval as an epithelial cell adhesion molecule-based cell capture commercially available prognostic biomarker. CTCs are not detectable in people without cancer, and the enumeration of CTCs from whole blood has been shown to be prognostic for OS in mCRPC [25]. CTC count has demonstrated to be a strong predictor of OS, with a shorter survival in men with a baseline CTC count of ≥5 (HR: 3.6–6.5, p < 0.0001) [25]. Furthermore, a CTC decline at 12 wk has been associated with increased survival in men with mCRPC treated with abiraterone and chemotherapy in several studies [26–28]. This makes CTC enumeration a useful parameter to predict clinical outcome at baseline and after 12 wk during treatment. The only Food and Drug Administration-approved platform for CTC enumeration is the Cellsearch system (Janssen Diagnostics, NJ, US). CTCs, however, will reveal their full potential if they will be extensively characterized and used as liquid biopsies. Several platforms have been developed for this purpose. Beltran et al [29] have used the EPIC Sciences platform (San Diego, CA, USA) to demonstrate that CTC characterization is able to accurately detect transition of mCRPC toward an aggressive neuroendocrine phenotype less likely to respond to AR pathways inhibitors.

3.3.2. CTC characterization: AR splice variants
Androgen receptor-V7 (AR-V7) is a splice variant of the AR which lacks the ligand-binding domain, and remains constitutively active in the absence of ligand. Since abiraterone and enzalutamide share the AR as their therapeutic target, it was hypothesized that men with mCRPC expressing AR-V7 might show primary resistance to these drugs. This hypothesis was tested in a prospective study by Antonarakis et al [30], including 62 men with detectable CTCs who were treated with abiraterone or enzalutamide. In this study, the AdnaTest platform was used, which combines immunomagnetic enrichment for epithelial cells with polymerase chain reaction for transcripts specific for prostate cancer. Custom-made AR and AR-V7 primers were used. It was observed that men expressing AR-V7 in CTCs did not respond to treatment with either abiraterone or enzalutamide. PSA response rates for treatment with abiraterone were 0% for AR-V7 positive men versus 68% for AR-V7 negative men (p = 0.004). In men treated with enzalutamide, similar results were obtained (PSA response rate: 0% for AR-V7 positive vs 53% for AR-V7 negative men, p = 0.004).

This study cohort was then extended with men treated with taxane chemotherapy. In men treated with taxanes, PSA response rates were similar in AR-V7 positive versus AR-V7 negative men (41% vs 65%, respectively, p = 0.19) [31]. When comparing outcomes of AR-V7 positive men treated with taxanes versus AR-targeted therapy, PSA response, PSA-PFS, and PFS were significantly in favor of taxane chemotherapy. Concordant with these observations, superior outcome of taxane treatment versus AR-targeted therapy was found in a cohort of 161 men with mCRPC in which AR-V7 status in CTCs was evaluated using the Epic platform [32]. A multivariable model correcting for known prognostic factors showed superior OS with taxanes compared with AR-targeted drugs abiraterone and enzalutamide in men with AR-V7 expression in CTCs (HR: 0.24, 95% confidence interval: 0.10–0.57, p = 0.035). In another cohort of mCRPC men receiving cabazitaxel chemotherapy it was confirmed that AR-V7 status did not affect outcomes of men treated with taxanes [33].
Interestingly, a few men treated with taxanes showed AR conversion from AR-V7 positive to a AR-V7 negative status during treatment with docetaxel or cabazitaxel [34]. The biological rationale behind this phenomenon remains to be elucidated but might reflect a release of selective pressure on the AR during treatment with taxane chemotherapy.

Treated together, AR-V7 expression in CTCs is a promising biomarker that might facilitate future treatment selection in mCRPC. The clinical utility of AR-V7 is now being evaluated in the PRIMACAB study (NCT: 02379390). In this trial, men with mCRPC who develop disease progression within 12 mo after the start of treatment with abiraterone or enzalutamide will be randomized to receive either cabazitaxel or another AR-targeted agent. AR-V7 detection in CTCs will be routinely performed in all patients using the Johns Hopkins assay. In a similar trial called CARD (NCT: 02485691) patients with mCRPC with primary resistance to abiraterone or enzalutamide defined as progression ≤12 mo, before or after docetaxel, will be randomized between the other AR-targeted agent or cabazitaxel. A secondary endpoint is to evaluate the EPIC Science CTC signature of resistance.

3.3.3. Gene fusions: TMPRSS2-ERG

**TMPRSS2-ERG** gene fusion enables AR driven expression of the ERG oncogene, which is a prostate cancer-specific gene alteration. Although, the prognostic implications of **TMPRSS2-ERG** gene fusion detected in CTCs has been investigated in several studies of men with mCRPC, conflicting results have been obtained. In a study of 41 men who were treated with abiraterone postchemotherapy, **TMPRSS2-ERG** fusion was present in 15 of 41 patients [35]. In contrast to CTC enumeration, **TMPRSS2-ERG** status did not predict clinical outcome or PSA response of men treated with abiraterone. However, Attard et al. [36] reported an association between ERG rearrangements and PSA response in men treated with abiraterone in therapy-naive tumors, tumor samples, and CTCs. In this study, 80% of men who had a ≥90% PSA decline showed an **ERG** rearrangement, whereas 32% of men who did not have a ≥90% PSA decline showed **ERG** rearrangement. In addition, an analysis of tumor samples in the COU-AA-302 study of abiraterone in the prechemotherapy setting revealed that men with a **TMPRSS2-ERG** gene fusion secondary to deletion and increased copy number of fusion sequences (2+ Edel) had greater clinical benefit from treatment with abiraterone [37]. In men treated with docetaxel, the presence of **TMPRSS2-ERG** gene fusion determined in whole blood samples was associated with inferior outcomes in terms of PSA response rates, PSA-PFS, and radiological PFS [38]. Future studies will determine what the optimal method for the detection of gene fusions will be and whether they can be used to predict response to therapy in mCRPC.

3.3.4. Genomic aberrations in DNA repair genes

Some men with mCRPC harbor somatic or germline genomic aberrations in DNA repair genes such as **BRCA1**, **BRCA2**, and **ATM** [39]. Poly-(adenosine triphosphate-ribose)-polymerases (PARP) regulate the localization of DNA repair proteins to single strand breaks. When PARP is inhibited, DNA single strand breaks cannot be repaired and eventually become lethal to the cancer cell. This led to the hypothesis that PARP inhibitors might have antitumor activity in men with mCRPC harboring DNA repair defects. The PARP inhibitor olaparib was evaluated in a phase 2 trial of men with mCRPC [40]. The primary endpoint was response rate, defined by Response Evaluation Criteria in Solid Tumors, PSA, or CTC criteria. Defects in DNA repair genes as detected by next-generation sequencing were identified in 16 of 49 evaluable men. Of these 16 men, 14 (88%) demonstrated responses to olaparib, including all seven patients with **BRCA2** loss and 80% with aberrations in the **ATM** gene. These results demonstrate that therapeutic targeting of specific genomic aberrations detected by next-generation sequencing is feasible and can provide an effective personalized treatment approach for a subset of mCRPC patients.

3.3.5. cfDNA

cfDNA consists of small particles of nucleic acids that are not in conjunction with cells. Levels of cfDNA have been used to predict the clinical outcome in several solid tumors. In addition, characterization of cfDNA can be used to analyze genomic alterations associated with resistance to targeted therapies [41].

In a study of 62 men with mCRPC who received amongst others abiraterone or enzalutamide, increased copy numbers of the AR and/or an mutation in exon 8 detected in cfDNA was associated with adverse clinical outcome [42]. In a confirmatory study in 65 men with mCRPC who were treated with enzalutamide, cfDNA samples were obtained and sequenced. In this study, AR amplification, heavily mutated AR (≥2 mutations), and **RB1** loss were associated with worse clinical outcome [43].

In a study including 97 men with mCRPC treated with abiraterone in two institutions, T878A or L702H mutations detected in cfDNA were associated with inferior PSA response rates and shorter OS when treated with abiraterone (HR: 7.33, p = 1.3 × 10−9) [44]. In conclusion, cfDNA is a promising tool for the detection of genomic alterations that might confer resistance to therapy in mCRPC. These studies demonstrate that genomic profiling of cfDNA is feasible in mCRPC patients and is clinically informative in identifying actionable alterations, thereby paving the way to guide the design of future biomarker-driven therapies and trials.

3.3.6. Circulating RNA

Tumor-associated noncoding RNAs (microRNAs) are released into the blood and other biofluids with tumor specific signatures [45]. This way they can be detected with polymerase chain reaction-based assays. With regard to resistance and response to therapy in mCRPC only a few small studies have been published. High miR-21 has been associated with resistance in a small study of 10 men with mCRPC treated with docetaxel [46]. In another study including 97 men with mCRPC treated with docetaxel, miR-200b levels, and postdocetaxel change in miR-20a
levels were associated with OS [47]. In the future, whole-blood mRNA expression arrays might serve to stratify men with mCRPC in risk groups [48] and help to identify transcripts specific for therapy resistance.

4. Conclusions

In summary, there has been major progress in drug development for mCRPC over the past few years. The current challenge is how to deliver these drugs to the patients that will benefit most. Biomarkers for the response to the various treatment options may ultimately facilitate treatment decisions (Table 1). Currently, the determination of AR-V7 in CTCs is a big step towards a more personalized treatment approach for mCRPC. Genomic characterization of liquid biopsies such as CTCs, cfDNA, and circulating RNA are noninvasive tools to further personalize treatment in prostate cancer. Some other clinical parameters are readily available (eg, duration of prior hormonal therapy, NLR), but are derived from retrospective studies and should be interpreted with care. Only by conducting biomarker-drive studies instead of large one-size-fits-all trials will we be able to take prostate cancer treatment further. In the future, this may facilitate treating patients based on their molecular profile, where liquid biopsies may facilitate the selection of a specific targeted therapy, may help to predict treatment response, and to unravel mechanisms of drug resistance.

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**Study concept and design:** van Soest, Tombal.

**Acquisition of data:** van Soest, Efstathiou, Sternberg, Tombal.

**Analysis and interpretation of data:** van Soest.

**Drafting of the manuscript:** van Soest.

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