Editorial Commentary

# Circulating tumor cell-based PSMA and PSA expression as a predictive and prognostic tool in prostate cancer

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Circulating tumor cells (CTCs) play a critical role in advancing the management of prostate cancer. They provide non-invasive insights into the disease's biology, offering predictive and prognostic value, particularly in advanced stages (1). CTCs are cancer cells that detach from the primary tumor or metastases and enter the bloodstream. They are detected and characterized using various techniques, including CellSearch [the only Food and Drug Administration (FDA)-approved system], microfluidic devices, and advanced molecular assays (1,2). While CTC enumeration is a strong independent prognostic factor for worse overall survival (OS) and progression-free survival (PFS) in metastatic castration-resistant prostate cancer (mCRPC) (3), further emphasis has been placed on its predictive value, with high baseline CTC counts predicting poor response to androgen receptor pathway inhibitors (ARPIs) such as abiraterone and enzalutamide (4,5). Molecular profiling of CTCs may provide further insights into the biology of the disease at various stages, particularly when looking at key genes, including prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA) and androgen receptor (AR).

PSA and PSMA are cell-surface protein biomarkers that play a key role in the diagnosis and management of prostate cancer (6,7). Improved use of PSA, combined with age, prostate volume and application of prostate cancer risk calculators, has led to a risk-adapted strategy enabling optimal stratification of men with prostate cancer and avoidance of unnecessary diagnostic procedures (6). In localized prostate cancer, which involves disease confined to the prostate, elevated PSA levels indicate disease presence or/and recurrence after definitive therapy (6). In metastatic hormone-sensitive prostate cancer (mHSPC), which describes the disease that has spread beyond the prostate but is still responsive to hormone therapy, high PSA levels predict worse PFS (7). In mCRPC, which involves the disease that continues to grow despite hormone therapy, PSA levels are critical for monitoring treatment response to life-prolonging therapies as well as an independent prognostic marker (8). PSMA is overexpressed in mCRPC and has been associated with tumor aggressiveness and progression (9). More importantly, PSMA-targeting for diagnostic (PSMA-PET) and therapeutic purposes (PSMA radioligand therapies) has opened new avenues in personalized management of prostate cancer patients, culminating in the approval of $^{177}$Lu-PSMA-617 in 2022 for men with PSMA-PET-positive mCRPC (9,10). However, not all patients respond to PSMA-radioligand therapy, in part owing to inter- and intra-patient heterogeneity of PSMA expression among different sites of metastases.

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Finding a way to directly assess and monitor the expression of these two and other markers related to prostate cancer growth in CTCs opens new avenues in understanding the evolving biology of the disease, its response to different therapies and perhaps a wiser utilization and sequencing of available therapeutic agents. Several studies have investigated the expression of molecular markers on individual CTCs and their predictive potential on patient outcomes. Androgen Receptor Splice Variant-7 (AR-V7) was one of the first markers studied in association with taxane sensitivity over ARPIs (11). PSA responses and clinical outcomes were superior with taxanes compared with enzalutamide or abiraterone therapy in AR-V7-positive men, while they did not differ by treatment type in AR-V7-negative men (11). Overall, CTC+/AR-V7+ patients compared to CTC- or CTC+/AR-V7- were significantly more likely to have Gleason scores ≥8, metastatic disease at diagnosis, higher PSA, prior abiraterone or enzalutamide use, prior taxane use, and Eastern Cooperative Oncology Group ≥1 (12). Interestingly, TP53 inactivation was shown to outperform the predictive and prognostic significance of AR in another study (13). Overall, CTC-based WNT5a and AURKA expression combined with known clinical prognosticators, namely Halabi score (14), or multigene signatures including AR, AR-V7, PSA, PSCA, TSPAN8, NKX3.1, WNT5B and SPINK1 (15) seem to better capture the biology of this heterogeneous disease, predicting clinical outcomes in patients with aggressive and ARPI-resistant prostate cancer. Overall, the transcriptional profile, including AR-Vs, AR targets, and neuroendocrine prostate cancer markers such as RB1, TP53, and PTEN, obtained from CTCs may detect neuroendocrine differentiation and can serve as an independent, prospectively validated prognostic marker (16). Furthermore, expression of the DNA/RNA helicase schlafen family member 11 (SLFN11) may identify patients with CRPC with a better response to platinum chemotherapy independent of histology or other genomic alterations (17).

Cho *et al.* analyzed the relationship between mRNA gene expression of PSMA and PSA in CTC counts, and patient outcomes in prostate cancer patients (18). The aim of their study was to assess whether a CTC-based transcript gene signature, including PSMA mRNA, could help inform prognostication in various stages of prostate cancer, including localized, mHSPC and mCRPC. For this purpose, the authors analyzed a cohort of 247 patients with prostate cancer in total, consisting of 94 subjects with localized prostate cancer, 44 diagnosed with mHSPC, and 109 suffering from mCRPC. They also used 21 healthy individuals as a control group. Six genes, including PSMA, PSA, AR, AR-V7, EpCAM, and KRT 19, were measured for mRNA expression in CTCs of these patients. The impact of CTC-based PSMA and PSA mRNA expression on four distinct clinical outcomes was examined, including biochemical recurrence-free survival in localized disease, mCRPC PFS in mHSPC state, PSA-PFS and radiological-PFS time in mCRPC state (18). From a methodology perspective, the authors first conducted CTC enumeration after isolating them from peripheral blood with use of EpCAM labelling and high-gradient magnetic flux. Then, reverse transcription polymerase chain reaction (PCR) and digital-droplet PCR were performed in CTCs to quantify the mRNA expression of the six genes (PSMA, PSA, AR, AR-V7, EpCAM and KRT-19) in number of copies per μL per CTCs. Finally, using the median values as cut-offs to separate in low and high-expressing subgroups, they evaluated statistical associations between mRNA expression of every separate gene and the afore-mentioned clinical outcomes (18). The study found that high levels of CTC PSMA and PSA mRNA in localized prostate cancer were significantly associated with biochemical recurrence after radical prostatectomy. Specifically, the 2-year biochemical recurrence-free survival was significantly longer in those with low versus high PSMA- and PSA-mRNA levels in their CTCs (P=0.01 and P=0.03, respectively). Additionally, high mRNA expression levels of PSMA and PSA were significantly linked to a 12-month shorter mCRPC-free survival (P=0.01 and P=0.02, respectively). These mHSPC patients had almost 7 times higher measured level of PSMA compared to those who did not progress to mCRPC state. Furthermore, high mRNA levels of PSMA and PSA were associated with a 2- and 3.5-fold higher risk of PSA- and radiographic progression, respectively (P=0.045 and P=0.001, respectively) in patients with mCRPC undergoing treatment with ARPIs (18). Likewise, high PSMA- and PSA-expressors were at least 3 times more likely to experience resistance to docetaxel, evidenced by shorter PSA-PFS and radiographic PFS. Notably, patients unresponsive to ARPIs had 10-times higher numbers of PSMA mRNA copies/μL/CTCs compared to responders (P<0.001).

Similar efforts have been made by other research groups to assess the clinical utility of PSMA, PSA or/and other markers' expression in CTCs with respect to patient outcomes. In the early setting, an increase of positive PSMA and PSA transcripts per blood sample was observed from

 

before to after radiation therapy, while a decrease of positive markers was observed during follow-up (19). Interestingly, CTC PSA and PSMA mRNA pre- and post-radical prostatectomy was reported to improve the accuracy of the Kattan nomogram to predict biochemical recurrence (20). Furthermore, the detection of CTCs was predictive of more positive lymph nodes on salvage lymph node dissection and a shorter biochemical recurrence-free and therapy-free survival (21). In the mCRPC state, a gradient of PSMA CTC detection levels from CTC-negative to CTC positive-PSMA negative to CTC positive-PSMA-positive was an independent adverse prognostic factor (22).

Various platforms for quantifying CTC-based biomarker expression have been developed, for example combining detection of CTCs and plasma exosomes or using immunofluorescence assays (23,24). While a broad consensus on a multi-gene panel for combined testing in CTCs has not yet been reached, it is reassuring to observe that key genes involved in prostate carcinogenesis like HOXB13 are directly associated with these AR-dependent biomarkers (25). Conversely, detection of AR-V7 in CTCs is associated with shorter PFS and OS with abiraterone or enzalutamide, albeit patients with AR-V7-positive disease still benefit from taxane chemotherapy (4,5). In comparison to these prior studies, it is interesting that the results of Cho *et al.* (18) with respect to the prognostic and predictive value of AR- and AR-V7 mRNA expression in CTCs for ARPI or docetaxel response and CRPC-PFS were non-significant or inconclusive. Perhaps the low number of CTCs in several cases with mHSPC and mCRPC may have affected the validity of their findings. It can be postulated that even with fewer CTCs, aggressive prostate cancer may still rapidly progress from mHSPC to mCRPC state or/and manifest unresponsiveness to ARPIs and taxanes. This rapid progression and treatment resistance is better represented by copies of PSMA and PSA in CTCs, according to Cho *et al.* (18).

The study of Cho *et al.* (18) was limited by a relatively limited number of patients per disease stage, which could impact the generalizability of the findings. Thus, future studies should prospectively test a larger sample from each distinct clinical state within the prostate cancer continuum. Additionally, mechanisms leading to tumor recurrence, progression to mCRPC, and drug resistance may not be fully detectable using droplet digital PCR alone. Multiplex PCR, which allows for the evaluation of expression across multiple cancer-related genes or even single-cell RNA profiling, could provide additional insights into tumor heterogeneity, treatment resistance, and potential therapeutic targets. Another important limitation that is inherent to the methodology of PSMA assessment is the lack of special information provided by PSMA imaging. To tackle this, future studies combining CTC-based and nuclear assessment of PSMA expression are needed.

Nevertheless, the novelty of this comprehensive study lies in addressing the role of PSMA and PSA expression in CTCs in various prostate cancer settings within the disease continuum. Overall, there is important clinical relevance in their findings suggesting that CTC-PSMA transcript tests could provide valuable insights into tumor aggressiveness and treatment resistance, thus having broad applications in personalized treatment of prostate cancer patients.

In conclusion, genomic analyses of CTCs, particularly using PSMA, PSA, and other important markers such as AR-V7 are uncovering new therapeutic targets and mechanisms of response or resistance. Incorporating CTC-based PSMA and PSA assessments into clinical practice could enhance personalized treatment strategies and improve patient outcomes in prostate cancer management. First, high levels of PSMA and PSA mRNA in CTCs can indicate resistance to androgen receptor signalling inhibitors (ARSIs) and taxane-based chemotherapy. This information can guide clinicians to consider alternative therapies, such as radioligand therapy (e.g., $^{177}$Lu-PSMA-617) for patients with high PSMA expression. Second, regular assessment of CTC PSMA and PSA levels can help in monitoring treatment efficacy. A lack of significant decrease in these biomarkers may suggest treatment resistance, prompting a change in therapeutic strategy. Third, patients with elevated CTC PSMA and PSA levels may be at higher risk for rapid disease progression and poorer outcomes. This stratification can inform more aggressive treatment approaches or closer monitoring for these high-risk patients. Prospectively testing and developing these biomarkers into robust outcome predictors, with or without use of CTCs as a "vehicle" could offer a powerful tool for comprehensive disease evaluation and informed treatment sequencing at various stages of prostate cancer.

Future research directions and clinical trials focusing on CTC biomarkers in prostate cancer could include large-scale, multicenter clinical trials to validate the prognostic and predictive value of CTC-based PSMA and PSA expression in diverse patient populations. This could help establish standardized thresholds for clinical decision-

 

making. Additionally, implementing trials that assess the pharmacodynamic utility of CTCs could test their value as real-time biomarkers for treatment response. Exploring the potential of advanced molecular profiling of CTCs could be used to identify specific mutations and gene expression patterns that predict treatment responses. This could lead to more personalized therapeutic approaches. Developing and testing new CTC isolation and analysis technologies could improve capture efficiency and purity, enabling better characterization of CTCs and their heterogeneity. Finally, conducting longitudinal studies to monitor CTC dynamics over time could help explore their role in disease progression and treatment resistance, which could inform adaptive treatment strategies.

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