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Hot Topic

The use of circulating tumor cells in guiding treatment decisions for patients with metastatic castration-resistant prostate cancer

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ABSTRACT

The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has drastically changed over the past decade with the advent of several new anti-tumor agents. Oncologists increasingly face dilemmas concerning the best treatment sequence for individual patients since most of the novel compounds have been investigated and subsequently positioned either pre- or post-docetaxel. A currently unmet need exists for biomarkers able to guide treatment decisions and to capture treatment resistance at an early stage thereby allowing for an early change to an alternative strategy. Circulating tumor cells (CTCs) have in this context intensively been investigated over the last years. The CTC count, as determined by the CellSearch System (Janssen Diagnostics LLC, Raritan, NJ), is a strong, independent prognostic factor for overall survival in patients with mCRPC at various time points during treatment and, as an early response marker, outperforms traditional response evaluations using serum prostate specific antigen (PSA) levels, scintigraphy as well as radiography. The focus of research is now shifting toward the predictive value of CTCs and the use of the characterization of CTCs to guide the selection of treatments with the highest chance of success for individual patients. Recently, the presence of the androgen receptor splice variant 7 (*AR-V7*) has been shown to be a promising predictive factor. In this review, we have explored the clinical value of the enumeration and characterization of CTCs for the treatment of mCRPC and have put the results obtained from recent studies investigating the prognostic and predictive value of CTCs into clinical perspective.

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Introduction

Over the past decade, the advent of new drugs have led to a substantial improvement in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). After the approval of docetaxel in 2004, six more agents have been registered, among which the next-generation taxane cabazitaxel, the androgen receptor (AR) antagonist enzalutamide, and the CYP17A1 inhibitor abiraterone [1,2]. In view of the preclinical and clinical evidence for the emergence of cross-resistance between docetaxel, abiraterone, and enzalutamide [2–6], the optimal treatment sequence yet remains to be determined. Importantly, optimal treatment sequencing may be patient-dependent, requiring deliberate (tailored) choices of specific agents for specific patients at specific times.

The options for a personalized treatment approach for patients with mCRPC are currently limited given the only few prognostic and predictive markers that are available for treatment selection and early evaluation of treatment efficacy. An initial Gleason score $\geqslant 7$ and/or a short interval between the start of initial androgen deprivation therapy (ADT) and the development of mCRPC may select for patients who will likely benefit most from first-line docetaxel instead of AR-targeted treatment [7,8]. Monitoring of treatment response is mostly done through the dynamics of serum levels of prostate-specific antigen (PSA) and changes in bone scintigraphy and/or computed tomography (CT). However, these modalities are at most modestly useful and the read-out of efficacy

Abbreviations: aCGH, array comparative genomic hybridization; ADT, androgen deprivation therapy; AR, androgen receptor; AR-V7, androgen receptor splice variant 7; CI, confidence interval; CK, cytokeratin; CT, computed tomography; CTC, circulating tumor cell; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; FDA, Food and Drug-administration; FISH, Fluorescence *in situ* Hybridization; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IF, immunofluorescence; IM, immunomagnetical; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; mRNA, messenger ribonucleic acid; OS, overall survival; PCR, polymerase chain reaction; PCWG2, Prostate Cancer Working Group 2; PD, progressive disease; PFS, progression-free survival; PSA, prostate specific antigen; PSMA, prostate specific membrane antigen; RECIST, response evaluation criteria in solid tumors; RR, response rate; RT-qPCR, reverse transcription quantitative polymerase chain reaction; sd, standard deviation.

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needs at least three months after treatment start due to the long half-life and release from apoptotic cells of PSA, flare-up phenomena on bone scans, and slow changes in combination with inter-observer variability in tumor size on CT scans [2].

Circulating tumor cells (CTCs) are tumor cells present in the peripheral circulation of patients with different solid malignancies including mCRPC, which have detached from tumor sites. Although occurring at very low frequencies in the peripheral blood, CTC countsbefore and during treatment have proven to be an accurate early response marker with a strong independent prognostic value at all time-points during treatment [9,10]. Also, CTCs have generally been considered as surrogates for metastatic cells and the characterization of CTCs may in this respect function as a "*liquid biopsy*" to aid in the tailoring of treatments [11,12]. In this review, we discuss the progress that has been made regarding the use of CTCs as a prognostic and predictive marker for patients with mCRPC, thereby focusing on the clinical relevance of CTCs and to what extent they may guide treatment decision-making and optimal treatment sequencing in mCRPC.

Enumeration of CTCs

In 2008, a landmark paper was published showing the strong, independent prognostic value of a CTC count from peripheral blood in patients with mCRPC when taken before the start of a new treatment line [10]. The enumeration of CTCs was done from 7.5 mL of blood by the CellSearch System (Janssen Diagnostics, Raritan, NJ). This semi-automated system immunomagnetically enriches epithelial cells from peripheral blood using anti-epithelial cell adhesion molecule (EpCAM)-antibodies bound to ferrofluid nanoparticles. Enriched cells, consisting of CTCs and still a thousand-fold of contaminating leukocytes, are immunofluorescently stained and manually counted after digital microscopy; nucleated (4′,6-diamidino-2-phenylindole (DAPI)^{pos}), cytokeratin (CK)^{pos}, and CD45^{neg} cells with a diameter $\geqslant 4 \times 4$ μm and a round to oval morphology are thereby considered CTCs. This way, patients can be stratified as having a favorable CTC count – defined as <5 CTC/7.5 mL – or an unfavorable CTC count of $\geqslant 5$ CTC/7.5 mL. It was shown in 231 patients that having a favorable CTC count predicted for a significantly improved progression-free survival (PFS) and overall survival (OS) compared to an unfavorable count of $\geqslant 5$ CTCs at all time-points before and during treatment [10]. Conversions of the CTC count, from unfavorable to favorable or *vice versa*, during treatment were shown to be associated with an improvement or deterioration of the prognosis, respectively, already 2–5 weeks after the start of treatment. By contrast, a 30% or 50% decline in PSA only started to be of prognostic significance after 6–8 weeks with maximum hazard ratio (HR) after 13–20 weeks. At all times, the HR of the favorable versus unfavorable

Table 1
Overview of the studies investigating the prognostic value of the CTC count as assessed by the CellSearch System before and during treatment in patients with mCRPC.

Reference	*N*	Treatment	Patients with $\geqslant 5$ CTCs	Prognostic value
Danila et al. (2007) [68]	120	Any chemotherapy; first/s-line	57%	Baseline CTC count strongly associated with OS in univariate analysis ($P < 0.001$)
De Bono et al. (2008) [10]	231	Any chemotherapy; first/s/third-line	57%	Baseline HR for OS: 3.3 (95% CI 2.2-5.1, $P < 0.0001$) HR after 2-5 weeks: 4.5 (95% CI 3.0–6.7, $P < 0.0001$) CTCs were more strongly prognostic than PSA at all time points
Goodman et al. (2009) [69]	100	Any chemotherapy; any line (1-7th)	Not reported	LDH and CTC both independent prognostic factors for OS Baseline HR of the CTC count $\geqslant 4$ for OS: 3.65, $P < 0.001$
Olmos et al. (2009) [70]	119	Any chemotherapy; any line (1-5th)	50%	Baseline HR for OS: 3.25 (95% CI 1.4–7.4, $P = 0.005$) Changes in CTC counts during treatment predict a change in prognosis, $P < 0.0001$)
Scher et al. (2009) [65]	156	Docetaxel monotherapy or combination; first-line	54%	Baseline HR for OS: 1.58 ($P < 0.0001$) Changes in CTC counts were strongly associated with OS at all times, whereas changes in PSA were only modestly associated with OS after 12 weeks
Danila et al. (2011) [56]	48	Abiraterone; second- or third-line	73%	Unfavorable CTC count after 4 weeks of abiraterone was association with worse OS (49 versus 122 weeks; $P < 0.001$)
Scher et al. (2013) [71]	144	Cabozantinib; second-line or more	71%	A CTC conversion from unfavorable to favorable was associated with improved OS: HR 0.42 (95% CI 0.19–0.92; $P = 0.03$)
Thalgott et al. (2013) [72]	55	First-line docetaxel or second-line treatment	57%	Unfavorable baseline CTC counts were associated with worse OS ($P = 0.003$)
Vogelzang et al. (2013) [73]	208	Docetaxel ± lenalidomide; first-line	58%	Baseline HR for 2-year OS: 3.5 ($P < 0.05$) HR for an increase in CTCs between baseline and cycle 4 for OS: 5.2 ($P = 0.03$)
Goldkorn et al. (2014) [74]	263	Docetaxel ± atrasentan; first-line	51%	A decrease of CTCs to < 5 during treatment was correlated to PSA response (63% versus 44%; $P = 0.01$) and RECIST response (31% versus 14%; $P = 0.05$) Baseline HR of the CTC conversion for 2-year OS: 2.74 (95% CI 1.72–4.37; $P < 0.001$); HR of $\geqslant$ 50% decrease if baseline CTCs $\geqslant 5$ for OS: 0.53 (95% CI 0.27–1.06; $P = 0.07$); HR of the conversion favorable to unfavorable CTC count: 6.47 (95% CI 1.96–21.4; $P = 0.002$)
Okegawa et al. (2014) [75]	57	Docetaxel; first-line	58%	Baseline unfavorable CTC count predicted for worse OS (11 vs 25 months; $P < 0.001$). Conversions in the CTC count during treatment were associated with OS
Chang et al. (2015) [76]	70	Docetaxel or ketokonazol; first-line	43%	Baseline HR for OS: 2.73 (95% CI 1.21–6.13; $P = 0.02$)
Fleisher et al. (2015) [77]	258	Enzalutamide; second- or third-line	49%	Conversions from unfavorable to favorable were observed in 48% of the patients and were associated with an OS benefit
Lorente et al. (2015) [78]	439	Abiraterone or chemotherapy; first-/second-/third-line	Not reported	The baseline CTC count as continuous variable and a 30% decrease in CTC count after 4 and 12 weeks of treatment were both independently associated with OS ($P = 0.001$)
Scher et al. (2015) [79]	711	Abiraterone or prednisone; second- or third-line	48%	CTC count after 12 weeks strongest prognostic factor for OS; biomarker panel of CTC counts and LDH after 12 weeks of treatment fulfilled all four Prentice criteria of individual patient-level surrogacy for OS
Thalgott et al. (2015) [80]	33	Docetaxel; first-line	61%	CTCs were strongly prognostic for OS at all time points before and during treatment with HR 3.8–5.8; $P < 0.01$ CTC conversions were more strongly predictive for OS than radiology and PSA evaluations

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