External Validation of Association of Baseline Circulating Tumor Cell Counts with Survival Outcomes in Men with Metastatic Castration-Sensitive Prostate Cancer

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ABSTRACT

Approximately 20% of men with metastatic castration-sensitive prostate cancer (mCSPC) progress within 1 year of treatment, and biomarkers to identify them up front are lacking. In a randomized phase III trial in men with mCSPC (SWOG S1216), higher baseline circulating tumor cells (CTCs) were prognostic of inferior outcomes. We aimed to validate these findings and interrogate corresponding tumor genomic profiles. Consecutively seen men with newly diagnosed mCSPC undergoing systemic therapy and baseline CTC enumeration by CellSearch assay were included. Gene alterations were determined by comprehensive genomic profiling of tumor tissue by Clinical Laboratory Improvement Amendments—certified lab. The relationship between categorized CTC counts and both progression-free survival (PFS) and overall survival (OS) was assessed in the context of Cox proportional hazards models, both unadjusted and adjusted for age, Gleason score, PSA at androgen-deprivation therapy initiation, disease volume, *de novo* status, treatment intensification, and number of altered genes. Overall, 103 patients were included in the analysis. On multivariate analysis high CTCs (≥ 5 vs. 0) were associated with poorer PFS [HR, 4.52; 95% confidence interval (CI), 1.84–11.11; $P = 0.001$) and OS (HR, 3.59; 95% CI, 0.95–13.57; $P = 0.060$). Patients with higher CTC counts had a greater number of altered genes and total number of alterations (all $P < 0.02$). In this article, for the first time, we externally validate the association of higher CTC counts with inferior survival outcomes in men with mCSPC and show a distinct associated tumor genomic landscape. These findings may improve prognostication, patient counseling, and treatment selection in men with mCSPC.

Introduction

Intensification of androgen-deprivation therapy (ADT) with novel hormonal therapies (NHTs; abiraterone, apalutamide, or enzalutamide) or docetaxel has shown to improve survival outcomes for patients with newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC) in randomized controlled trials and is considered standard of care (1–5). However, recent studies show an alarming underutilization of intensified ADT in the real world, with < 30% of patients receiving intensified ADT in three distinct and large cohorts of patients in the United States (6–9). Furthermore, even with intensified ADT ∼20% of patients with mCSPC experience disease progression within a year of starting treatment, and experience inferior outcomes (1–5). Up front identification of these men at the highest risk of progression and/or death will not only improve patient counseling and prognostication, but also drive clinicians to offer intensified ADT to the patients or preferentially enroll them in clinical trials.

Yet, there is no biomarker available in clinic use to identify these patients with a new diagnosis of mCSPC. Genomic alterations such as in *AR* and cell-cycle genes have been associated with poor overall survival (OS), while alterations in *SPOP* and *WNT* pathway have been associated with better OS (10, 11). However, comprehensive genomic profiling (CGP) of the tumor tissue may not be possible in up to one-third of patients in the real world, needs a few weeks to obtain the results, and is expensive (12).

Circulating tumor cells (CTCs) have been established as a reliable predictive and prognostic marker in the setting of metastatic castration-resistant prostate cancer (mCRPC; ref. 13, 14). CellSearch is the only FDA-approved method for CTC enumeration and is readily available in the clinic (13, 14). Recently, in a prospective randomized phase III trial of ADT combined with orteronel or bicalutamide in patients with mCSPC (SWOG S1216), higher baseline CTCs (≥ 5 vs. 0/7.5 mL) predicted a lower likelihood of 7-month PSA responses [≤ 0.2 ng/mL; an intermediate endpoint for OS and inferior 2-year progression-free survival (PFS); ref. 15].

Herein, we aimed to validate these findings in men with mCSPC in the real world and interrogate tumor genomic profiles with respect to the CTC level.

Materials and Methods

After institutional review board approval, we identified consecutive patients who received ADT with or without intensification with docetaxel or NHTs for a new diagnosis of mCSPC and had enumeration of baseline CTCs by FDA cleared CellSearch CTC assay at

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Table 1. Baseline patient characteristics overall and within ADT intensification vs. no ADT intensification subgroup, as well as comparisons of characteristics between ADT intensification subgroups.

Characteristic[a]		Overall ($N = 103$)	ADT intensification therapy ($N = 44$)	No ADT intensification therapy ($N = 59$)	P[b]
Age		67 (60–73) years	66 (61–70)	67 (60–73)	0.535
Gleason score		9 (8–9)	9 (8–9)	9 (7–9)	0.631
PSA at ADT initiation		41.0 (12.2–102.0) ng/mL	39.6 (14.4–104.0) ng/mL	42.6 (11.8–102.1) ng/mL	0.957
De novo metastatic disease		67 (65.0%)	29 (65.9%)	38 (64.4%)	1.000
Volume of disease	Low	44 (46.3%)	16 (37.2%)	28 (53.8%)	0.158
	High	51 (53.7%)	27 (62.8%)	24 (46.2%)	
CTC counts at ADT initiation	0	48 (46.6%)	17 (38.6%)	31 (52.5%)	0.025
	1–4	27 (26.2%)	9 (20.5%)	18 (30.5%)	
	≥5	28 (27.2%)	18 (40.9%)	10 (16.9%)	

Abbreviations: ADT, androgen-deprivation therapy; CTC, circulating tumor cell; PSA, prostate-specific antigen.
[a]Quantitative characteristics summarized as median (interquartile range), categorical characteristics summarized as number (percent).
[b]Quantitative characteristics compared via Wilcoxon rank-sum tests, categorical characteristics compared via χ^2 test.

metastatic diagnosis before treatment initiation (13, 14). CTC counts were categorized as 0, 1–4, and ≥ 5/7.5 mL. Gene alterations were determined by CGP of baseline primary or metastatic tumor tissue (Foundation Medicine, Cambridge, MA; Clinical Laboratory Improvement Amendments—certified), which interrogates all exons from 324 cancer-related genes and has been described previously (16). All variant types were analyzed, including small mutations, copy-number alterations, and gene rearrangements. Variants of unknown significance were excluded (16). The primary endpoint was to investigate the PFS and OS by CTC enumeration using the same cutoffs described in the *post hoc* analysis of the SWOG 1216 trial. The secondary endpoints included assessing the correlation between number of genes altered, number of mutations per patient, or proportion of specific altered genes with the separate CTC enumeration brackets.

OS was defined from the time of ADT initiation to the time of death from any cause or loss to follow-up. PFS was defined from the time of ADT initiation to the time of either PSA, radiographic, or clinical progression (per Prostate Cancer Working Group 2 criteria), whichever occurred first, or death from any cause. The relationships between CTC counts and both PFS and OS were assessed by Cox proportional hazards models, both unadjusted and adjusted for age, Gleason score, PSA at ADT initiation, *de novo* versus non–*de novo* metastatic disease at diagnosis, presence or absence of ADT intensification therapy, volume of disease (high or low per CHAARTED criteria; ref. 5), number of genes altered, and categorized CTC counts (0, 1–4, and ≥ 5/7.5 mL). Relationships between CTC counts, and the number of genes altered and individual gene alterations (after excluding variants of unknown significance) were assessed via Kruskal–Wallis and χ^2 tests, respectively. Throughout, results are only presented for individual genes where they show suggestive evidence ($P < 0.10$) of an association with either CTC counts, PFS, or OS as appropriate.

Data availability

The data generated in this study are not publicly available as they could compromise patient privacy but are available upon reasonable request from the corresponding author.

Results

Patient demographics and disease characteristics

Overall, 103 patients were eligible. Baseline patient characteristics and subgroup comparisons are summarized in **Table 1**. There was no evidence of differences in age, Gleason score, PSA at ADT initiation, percentage of patients with *de novo* metastatic disease, or volume of disease between patient subgroups who received or did not receive ADT intensification therapy (all $P \geq 0.158$). Median time between tumor biopsy and CTC enumeration was between 1.3 months prior to, and 0.6 months after CTC enumeration. Patients who underwent ADT

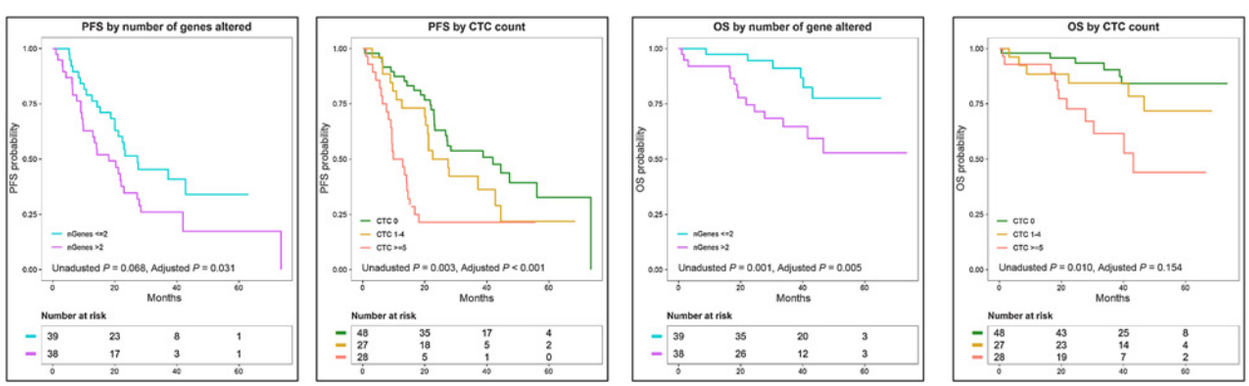

Figure 1.
Kaplan–Meier survival curve estimates for PFS and OS by number of genes altered and CTC count at first-line initiation. Unadjusted *P* value refers to the univariate analysis while adjusted *P* value refers to the multivariate analysis.

Table 2. Univariate and multivariate analysis results for PFS and OS.

Characteristic[a]		PFS		OS	
		Univariate analyses	Multivariate analyses	Univariate analyses	Multivariate analyses
Age (per 10 years)		0.93 (95% CI, 0.69–1.24; $P = 0.623$)	0.59 (95% CI, 0.36–0.97; $P = 0.038$)	1.21 (95% CI, 0.76–1.91; $P = 0.419$)	0.92 (95% CI, 0.47–1.81; $P = 0.804$)
Gleason score		1.24 (95% CI, 0.93–1.65; $P = 0.143$)	1.51 (95% CI, 1.00–2.29; $P = 0.052$)	1.53 (95% CI, 0.91–2.58; $P = 0.108$)	1.69 (95% CI, 0.86–3.31; $P = 0.129$)
PSA at ADT initiation (per doubling)		1.14 (95% CI, 1.03–1.27; $P = 0.016$)	1.23 (95% CI, 1.04–1.46; $P = 0.014$)	0.99 (95% CI, 0.83–1.18; $P = 0.926$)	1.06 (95% CI, 0.82–1.35; $P = 0.672$)
De novo metastatic disease		1.22 (95% CI, 0.74–2.02; $P = 0.435$)	0.66 (95% CI, 0.27–1.59; $P = 0.353$)	1.41 (95% CI, 0.58–3.43; $P = 0.452$)	0.79 (95% CI, 0.20–3.15; $P = 0.737$)
ADT intensification therapy (yes vs. no)		0.65 (95% CI, 0.39–1.08; $P = 0.100$)	0.54 (95% CI, 0.27–1.07; $P = 0.078$)	1.86 (95% CI, 0.82–4.25; $P = 0.140$)	2.17 (95% CI, 0.72–6.58; $P = 0.171$)
Volume (high vs. low)		1.67 (95% CI, 1.00–2.79; $P = 0.052$)	1.58 (95% CI, 0.79–3.17; $P = 0.199$)	1.68 (95% CI, 0.70–4.01; $P = 0.242$)	0.97 (95% CI, 0.32–2.93; $P = 0.951$)
Number of genes altered		1.17 (95% CI, 0.99–1.38; $P = 0.068$)	1.33 (95% CI, 1.03–1.71; $P = 0.031$)	1.55 (95% CI, 1.21–1.99; $P = 0.001$)	1.65 (95% CI, 1.16–2.35; $P = 0.005$)
CTC counts at ADT initiation (0 reference)	1–4	1.50 (95% CI, 0.82–2.74; $P = 0.189$)	2.43 (95% CI, 1.03–5.72; $P = 0.043$)	1.87 (95% CI, 0.60–5.79; $P = 0.280$)	1.79 (95% CI, 0.44–7.30; $P = 0.414$)
	≥5	3.53 (95% CI, 1.95–6.38; $P < 0.001$)	4.52 (95% CI, 1.84–11.11; $P = 0.001$)	4.55 (95% CI, 1.67–12.40; $P = 0.003$)	3.59 (95% CI, 0.95–13.57; $P = 0.060$)

Abbreviations: ADT, androgen-deprivation therapy; CTC, circulating tumor cell; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
[a]Estimates provided as HR (95% CI, *P* value); multivariate analyses include all characteristics listed in the Table.

intensification therapy tended to have higher CTC counts at ADT initiation than patients who did not (40.9% vs. 16.9% with CTC counts ≥ 5, $P = 0.025$). The 2-year PFS of the cohort was 48% [95% confidence interval (CI), 39%–59%], and 2-year OS was 87% (95% CI, 80%–94%). Median PFS was 23 (95% CI, 20–39) months and median OS was not reached.

Baseline CTC number altered genes and prognosis

Kaplan–Meier survival estimates stratified by ADT intensification therapy, number of genes altered, and CTC counts at ADT initiation for both OS and PFS are presented in **Fig. 1**.

In univariate and multivariate analyses, CTC counts, and the number of genes altered were strongly associated with both PFS and OS (**Table 2**). The unadjusted HR for CTC ≥ 5 versus 0 with regard to PFS was 3.53 (95% CI, 1.95–6.38; $P < 0.001$), and for OS, it was 4.55 (95% CI, 1.67–12.40; $P = 0.003$). The unadjusted HR per gene altered with regards to PFS was 1.17 (95% CI, 0.99–1.38; $P = 0.068$), and for OS, it was 1.55 (95% CI, 1.21–1.99; $P = 0.001$).

In multivariate analyses, adjusted for age, Gleason, PSA (log) at ADT initiation, *de novo* status, volume of disease, number of genes altered, and presence or absence of ADT intensification therapy, the PFS HR for CTC ≥ 5 versus 0 was 4.52 (95% CI, 1.84–11.11; $P = 0.001$), and the OS HR was 3.59 (95% CI, 0.95–13.57; $P = 0.060$). Similarly, in multivariate analyses, the PFS HR per gene altered was 1.33 (95% CI, 1.03–1.71; $P = 0.031$), and OS HR per gene altered was 1.65 (95% CI, 1.16–2.35; $P = 0.005$). Univariate associations of PFS and OS with different genomic alterations are summarized in Supplementary Table S1.

Patients with greater CTC counts had a greater number of altered genes ($P = 0.017$) and a greater number of total alterations ($P = 0.017$; **Fig. 2**). Among patients harboring *TP53* alterations, the proportion of patients with CTC ≥ 5 was significantly higher than

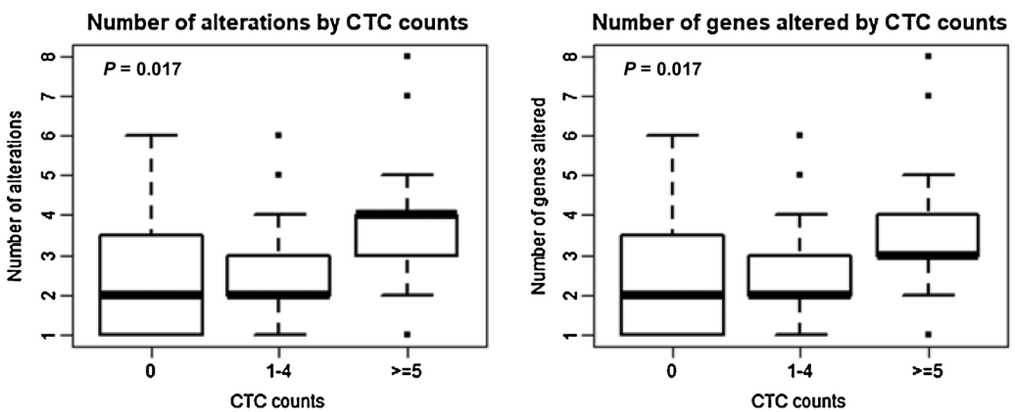

Figure 2.
Relationships between CTC counts and genomic landscape (excluding variant of unknown significance) in terms of the number of genes altered and the total number of alterations.

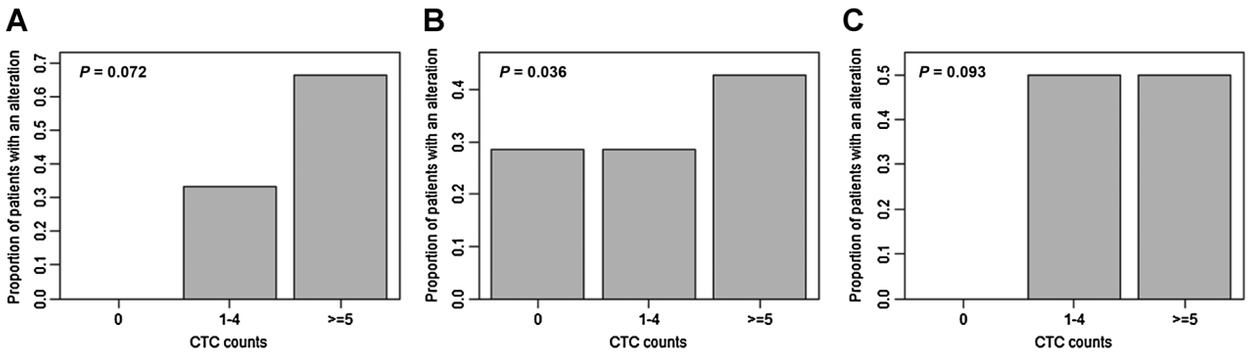

Figure 3.
CTC count rates among patients with metastatic prostate cancer harboring *MYC* (**A**), *TP53* (**B**), and *ATM* (**C**) mutations (only differences with $P < 0.10$ were included).

those with a CTC count of 0 ($P = 0.036$), whereas with *MYC* ($P = 0.072$) and *ATM* ($P = 0.093$), alterations were marginal (**Fig. 3A–C**). No other individual genes showed suggestive or stronger evidence of a relationship to CTC counts (all $P \geq 0.10$). Alterations categorized by CTC counts along with individual patient characteristics such as age, Gleason score, PSA levels, *de novo* status and volume of disease are summarized in Supplementary Fig. S1.

Discussion

CTCs were first reported in 2008 as the most accurate and independent predictor of OS in patients with mCRPC leading to the assay approval by the FDA for evaluation in this disease setting (14). A meta-analysis of five prospective randomized phase III trials enrolling a total of 6,081 patients (COU-AA-301, AFFIRM, ELM-PC-5, ELM-PC-4, and COMET-1) showed that CTC0 (change from detectable to undetectable CTCs) and CTC conversion had a higher discriminatory power for OS as compared with PSA change supporting its use as a better response biomarker (16). Moreover, the prognostic biomarker status of CTCs is independent and complementary to androgen receptor activity/signaling pathways (17, 18).

SWOG S1216 recently reported CTCs as a prognostic biomarker in mCSPC (15). Herein, we, for the first time, externally validate the previous findings from a prospective trial (15) of the association of higher CTC counts with inferior survival outcomes in an independent cohort of patients with mCSPC through CellSearch assay. We show that the prognostic nature of CTCs is independent of baseline characteristics and not a surrogate for disease volume. We also show that a higher CTC continues to be associated with a worse prognosis with both ADT and ADT with treatment intensification.

Our study also reveals that patients with mCSPC who had higher CTC counts had a significantly higher number of altered genes and total alterations. The rate of patients with CTC counts ≥ 5 was significantly higher among patients harboring *TP53* alterations (**Fig. 3**). Alterations in *TP53* have already been reported to be associated with worse prognosis in patients with mCSPC (10). Therefore, patients with higher CTC counts may have a tumor genomic landscape, which indicates aggressive disease. Limitations include a single-institution retrospective cohort and a small number of patients compared with the prospective study reported by Goldkorn and colleagues (15). In addition, the significance level of *ATM* and *MYC* were marginal and did not account for other confounding factors such as tumor purity.

To summarize, we show that a high baseline CTC count (≥5/7.5 mL) is associated with a worse prognosis in patients with mCSPC regardless of ADT intensification and is associated with a distinct tumor genomic landscape. These findings may improve prognostication and patient counseling, help identifying men at the highest risk of disease progression or death at the time of diagnosis, which may affect treatment selection such as preferential use of intensified ADT or enrollment on a clinical trial, and design of future trials in this setting.

Authors' Disclosures

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Note

Supplementary data for this article are available at Molecular Cancer Therapeutics Online (http://mct.aacrjournals.org/).

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