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Circulating Tumor Cells in a Phase 3 Study of Docetaxel and Prednisone with or without Lenalidomide in Metastatic Castration-resistant Prostate Cancer

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Abstract

Elevated circulating tumor cell (CTC) blood levels (≥5 cells/7.5 ml) convey a negative prognosis in metastatic castration-resistant prostate cancer but their prognostic significance in patients receiving chemotherapy is uncertain. The association between CTC counts (at baseline or after treatment), overall survival (OS), and response to docetaxel with lenalidomide was evaluated in a 208-patient subset from the MAINSAIL trial, which compared docetaxel-prednisone-lenalidomide and docetaxel-prednisone-placebo in metastatic castration-resistant prostate cancer patients. Baseline CTCs were <5 cells/7.5 ml blood in 87 (42%) patients and ≥5 cells/7.5 ml in 121 (58%) patients. Neither tumor response nor prostate-specific antigen response correlated with baseline CTCs. However, CTC count ≥5 cells/7.5 ml was significantly associated with lower OS (hazard ratio: 3.23, $p = 0.0028$). Increases in CTCs from <5 cells/7.5 ml to ≥5 cells/7.5 ml after three cycles were associated with significantly shorter OS (hazard ratio: 5.24, $p = 0.025$), whereas CTC reductions from ≥5 cells/7.5 ml to <5 cells/7.5 ml were associated with the best prognosis ($p = 0.003$).

Patient summary: Our study in metastatic castration-resistant prostate cancer patients treated with docetaxel chemotherapy, with or without lenalidomide, showed that patient survival was best predicted by circulating tumor cell count at the start of treatment. A rising circulating tumor cell count after three cycles of therapy predicted poor survival, while a decline predicted good survival.

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Although treatment of metastatic castration-resistant prostate cancer (mCRPC) has benefited from the introduction of new therapies, docetaxel remains the standard initial chemotherapy [1]. While overall survival (OS) after treatment with docetaxel has been predicted using clinical parameters, accurate quantification of therapeutic response has proven more difficult because of factors such as population heterogeneity and limitations in measurement of bone lesions and associated pain [2,3].

Reliable information on prognostic and predictive biomarkers is lacking in mCRPC, and drug approvals are usually based on OS endpoints in unselected patients [4]. A biomarker that could serve as a robust surrogate endpoint for OS is urgently needed.

Baseline prostate-specific antigen (PSA) levels and PSA decline are not independently or consistently prognostic, or predictive in mCRPC patients [5,6]; the limitations of PSA as a surrogate survival endpoint hinder its use in informing treatment decisions [6,7].

Several studies have demonstrated the relevance of circulating tumor cells (CTCs) as a prognostic marker in mCRPC, including two large prospective phase 3 studies evaluating abiraterone (COU-AA-301) [8] and docetaxel (Southwest Oncology Group; SWOG S0421) [2]. In both studies, CTC count was identified as an accurate and independent indicator of OS.

The present analysis evaluated the association between CTCs (at baseline and after treatment), OS, and response in a subset of patients from the phase 3 MAINSAIL trial (ClinicalTrials.gov Identifier NCT00988208), which investigated the efficacy and safety of lenalidomide in combination with docetaxel and prednisone in 1059 chemotherapy-naïve mCRPC patients.

The design and outcomes of this trial have been previously reported [9]. Patients with mCRPC received intravenous docetaxel 75 mg/m^2 on Day 1 of each 21-d treatment cycle, oral prednisone 5 mg twice daily every day, and either oral lenalidomide 25 mg/d once daily (DPL) or placebo (DP) on Days 1–14 of each 21-d treatment cycle. Dose modifications were allowed if toxicity occurred, per specific protocol guidance. The primary endpoint of the trial was OS, defined as time from randomization to death from any cause. Secondary endpoints were progression-free survival, tumor response, and safety. The trial was terminated early because of futility.

CTC count analyses were based on the biomarker-evaluable population, defined as all randomized patients who received any study treatment and had a baseline CTC measurement. OS, objective response rate, and PSA response were assessed at regular intervals. Tumor response was defined as the best response assessed by the investigator during the study treatment phase. Tumor response assessment was based on the Response Evaluation Criteria in Solid Tumors (version 1.1) [3]. Sampling technique, statistical analysis, and baseline CTC stratification categories are further described in the Supplementary data. The analyses included all North American patients enrolled in the trial with available baseline CTC counts (N = 208; 105 DPL, 103 DP). Baseline characteristics are presented in the Supplementary data and Supplementary Table 1.

Table 1 – Correlation between baseline circulating tumor cell (CTC) count and metastatic castration-resistant prostate cancer disease response

	CTC count at baseline per 7.5 ml blood (no. of cells)	Unconfirmed PSA or RECIST response (%)	p value
30% reduction in	<5	80.0	0.5004
PSA from baseline	≥5	75.6	
50% reduction in	<5	69.4	0.4546
PSA from baseline	≥5	63.9	
RECIST response[a]	<5	44.4	0.8440
	≥5	41.3	

PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.
[a] Only patients with measurable disease.

There was no significant correlation between PSA response (p = 0.50) or tumor response (p = 0.84) and baseline CTC counts (Table 1). Multivariable analysis showed that baseline CTC counts of ≥5 cells/7.5 ml blood (hazard ratio [HR]: 3.23, p = 0.0028) and older age (HR: 1.05, p = 0.0018) were prognostic factors for OS (54 events). Lactate dehydrogenase was not shown to be an independent prognostic factor (Supplementary Table 2). Two-yr OS significantly correlated with baseline CTC counts (Fig. 1). The receiver-operating characteristic curves predicting 2-yr survival rates for baseline CTC count and PSA level showed that the prognostic value of CTC counts was not particularly high and combining baseline PSA level with CTC count did not improve the prognostic value of CTC counts (Supplementary Fig. 1). Median OS was found to correlate with stratified baseline CTC counts (Supplementary Fig. 2).

DPL therapy resulted in a greater mean reduction of CTC count from baseline to minimum post-treatment than DP therapy (−69.7 cells/7.5 ml blood vs −34.1 cells/7.5 ml blood, p = 0.028). Correlative analyses (inclusion criteria in Supplementary data) showed that the response was 61.5% in patients with baseline CTC counts of <5 cells/7.5 ml blood and no CTC count increase at Cycle 4 Day 1; response was 75.0% in those with baseline CTC counts of ≥5 cells/7.5 ml blood and CTC count decrease at Cycle 4 Day 1; response was 25.0% in patients with baseline CTC counts of <5 cells/7.5 ml blood and CTC count increase at Cycle 4 Day 1; response was 0% in patients with baseline counts of ≥5 cells/7.5 ml blood and no CTC count decrease at Cycle 4 Day 1 (p = 0.024). An increase in CTC count from <5 cells/7.5 ml to ≥5 cells/7.5 ml blood after three cycles was associated with significantly shorter OS (HR: 5.24, p = 0.025). A decline in CTC counts from ≥5 cells/7.5 ml blood at baseline to <5 cells/7.5 ml blood was associated with best prognosis (p = 0.003).

Results from these analyses confirm those from the COU-AA-301 and SWOG S0421 trials, which found CTC counts to be prognostic, with increased CTC count after three to four cycles, or 12 wk, predictive of significantly worse OS [8,10].

High baseline CTC counts (≥ 5 cells/7.5 ml blood) were associated with aggressive-disease indices, with very high baseline counts (≥ 54 cells/7.5 ml blood) predictive of poorer outcome, illustrated by a median OS of 14.0 mo

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