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Decline in Circulating Tumor Cell Count and Treatment Outcome in Advanced Prostate Cancer

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Abstract

Background: Treatment response biomarkers are urgently needed for castration-resistant prostate cancer (CRPC). Baseline and post-treatment circulating tumor cell (CTC) counts of ≥5 cells/7.5 ml are associated with poor CRPC outcome.
Objective: To determine the value of a ≥30% CTC decline as a treatment response indicator.
Design, setting, and participants: We identified patients with a baseline CTC count ≥5 cells/7.5 ml and evaluable post-treatment CTC counts in two prospective trials.
Intervention: Patients were treated in the COU-AA-301 (abiraterone after chemotherapy) and IMMC-38 (chemotherapy) trials.
Outcome measures and statistical analysis: The association between a ≥30% CTC decline after treatment and survival was evaluated using univariable and multivariable Cox regression models at three landmark time points (4, 8, and 12 wk). Model performance was evaluated by calculating the area under the receiver operating characteristic curve (AUC) and c-indices.
Results: Overall 486 patients (122 in IMMC-38 and 364 in COU-AA-301) had a CTC count ≥5 cells/7.5 ml at baseline, with 440, 380, and 351 patients evaluable at 4, 8, and 12 wk, respectively. A 30% CTC decline was associated with increased survival at 4 wk (hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.36–0.56; $p < 0.001$), 8 wk (HR 0.41, 95% CI 0.33–0.53; $p < 0.001$), and 12 wk (HR 0.39, 95% CI 0.3–0.5; $p < 0.001$) in univariable and multivariable analyses. Stable CTC count (<30% fall or <30% increase) was not associated with a survival benefit when compared with increased CTC count. The association between a 30% CTC decline after treatment and survival was independent of baseline CTC count. CTC declines significantly improved the AUC at all time-points. Finally, in the COU-AA-301 trial, patients with CTC ≥5 cells/7.5 ml and a 30% CTC decline had similar overall survival in both arms.

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Conclusions: A 30% CTC decline after treatment from an initial count ≥5 cells/7.5 ml is independently associated with CRPC overall survival following abiraterone and chemotherapy, improving the performance of a multivariable model as early as 4 wk after treatment. This potential surrogate must now be prospectively evaluated.
Patient summary: Circulating tumor cells (CTCs) are cancer cells that can be detected in the blood of prostate cancer patients. We analyzed changes in CTCs after treatment with abiraterone and chemotherapy in two large clinical trials, and found that patients who have a decline in CTC count have a better survival outcome.

1. Introduction

Prostate cancer is the second most common malignancy in men, and the fifth leading cause of death from cancer worldwide [1]. Although initially responsive to androgen deprivation, lethal castration-resistant prostate cancer (CRPC) ultimately develops. In recent years, unprecedented advances in drug development for CRPC have been observed with the approval of abiraterone, enzalutamide, cabazitaxel, and radium [2–7].

One of the greatest challenges in the current management of CRPC is adequate assessment of response to treatment. A significant proportion of patients present with disease exclusively in bone, which is not amenable to evaluation by the commonly used Response Evaluation Criteria in Solid Tumors (RECIST). Consensus Prostate Cancer Working Group 2 (PCWG2) criteria [8] rely on bone scintigraphy and changes in prostate-specific antigen (PSA) levels to evaluate response to treatment in these patients. Progression according to bone scintigraphy is not evaluable before 16 wk because of the possibility of spurious flare reactions [9], so a confirmatory scan is required after a first scan indicating progression. Likewise, evaluation of prostate-specific antigen (PSA) values for progression is not recommended before 12 wk of treatment. Most studies evaluating PSA declines as a surrogate of survival have yielded negative results [10–12] and treatment discontinuation based solely on rising PSA values is not recommended [8]. Recent studies have reported a stronger association between radiological progression-free survival (rPFS) and overall survival (OS); however, a definition of progression according to rPFS cannot currently be acquired before at least 12–16 wk of treatment, and is difficult to evaluate in men with widespread bone involvement [13]. Improved biomarkers to identify patients not benefitting from anticancer treatment are urgently needed.

Enumeration of the circulating tumor cell (CTC) count has emerged as a powerful biomarker for evaluating prognosis and treatment response in CRPC. The utility of the CellSearch assay (Janssen Diagnostics, Raritan, NJ, USA) in classifying counts into unfavorable (≥5 cells/7.5 ml) and favorable (≤4 cells/7.5 ml) prognostic groups has been proven in prospective trials including IMMC-38, COU-AA-301, AFFIRM, and SWOG-S0421 [14–19]. Association between post-treatment CTC changes and CRPC survival has been reported in terms of CTC conversion (change from unfavorable at baseline to favorable or vice versa) [14], fold-change in CTC [17], and a 30% CTC decline from baseline [16], and it has been shown that CTC count has superior performance to other circulating biomarkers including PSA. CTCs have also been evaluated as a surrogate endpoint in several prospective trials. In the COU-AA-301 trial, a composite biomarker panel comprising CTC and lactate dehydrogenase (LDH) at 12 wk after treatment satisfied the Prentice criteria for surrogacy at the individual patient level [20]. It is envisaged that validation of these results in further prospective clinical trials could contribute to testing trial-level surrogacy so that CTC counts could become a clinical trial endpoint to accelerate drug approval for advanced CRPC.

We carried out a post hoc analysis of data for patients in the prospective IMMC-38 (chemotherapy) and COU-AA-301 (abiraterone) trials with baseline CTC ≥5 cells/7.5 ml, evaluating the value of a 30% CTC decline from baseline at 4, 8, and 12 wk as a biomarker of response to treatment.

2. Patients and methods

2.1. Study population and procedures

We performed a post hoc analysis of the COU-AA-301 and IMMC-38 trials. COU-AA-301 was a phase 3 trial in which postchemotherapy patients with metastatic CRPC were randomly assigned to abiraterone and prednisone or placebo and prednisone. IMMC-38 was a prospective, open-label study in patients with metastatic CRPC undergoing treatment with chemotherapy. Details of the methodology and the final results for both trials have been published elsewhere [2,14,21]. Both studies were approved by local institutional boards. All patients provided written informed consent before participation. CTC counts were measured at baseline and on day 1 of cycle 2 (weeks 4–5), day 1 of cycle 3 (weeks 8–9), and day 1 of cycle 4 (weeks 12–13) in the COU-AA-301 trial. In the IMMC-38 trial, CTC counts were measured in weeks 2–5 (median 4 wk), weeks 6–8 (median 7 wk), and weeks 9–12 (median 11.9 wk). All CTC counts were measured using the CellSearch assay [22]. Hemoglobin (Hb), alkaline phosphatase (ALP), albumin (ALB), and LDH concentrations were measured at baseline and at each study visit. Eastern Cooperative Oncology Group performance status (ECOG-PS) was recorded at baseline. PSA levels were measured every 4 wk in IMMC-38 and every 12 wk in COU-AA-301.

2.2. Statistical analysis

Kaplan-Meier analysis was used to estimate survival. Univariable and multivariable Cox proportional hazards models were used to test the association between the response biomarker and survival. Logistic regression models were used to calculate odds ratios (ORs). Post-treatment CTC response was defined as a 30% decline from baseline at 4, 8, and 12 wk from treatment initiation. A landmark analysis was used to explore the association between CTC response and survival, and specific 4-, 8- and 12-week populations were defined (Supplementary Fig. 1).

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