Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data

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Summary

Background **Intermediate or surrogate endpoints for survival can shorten time lines for drug approval. We aimed to assess circulating tumour cell (CTC) count as a prognostic factor for survival in patients with progressive, metastatic, castration-resistant prostate cancer receiving first-line chemotherapy.**

Methods **We identified patients with progressive metastatic castration-resistant prostate cancer starting first-line chemotherapy in the IMMC38 trial. CTCs were isolated by immunomagnetic capture from blood samples at baseline and after treatment. Baseline variables, including CTC count, titre of prostate-specific antigen (PSA), and concentration of lactate dehydrogenase (LDH), and post-treatment variables (change in CTCs and PSA) were tested for association with survival with Cox proportional hazards models. Concordance probability estimates were used to gauge discriminatory strength of the informative factors in identifying patients at low-risk and high-risk of survival.**

Findings **Variables associated with high risk of death were high LDH concentration (hazard ratio 6·44, 95% CI 4·24–9·79), high CTC count (1·58, 1·41–1·77), and high PSA titre (1·26, 1·10–1·45), low albumin (0·10, 0·03–0·39), and low haemoglobin (0·72, 0·64–0·81) at baseline. At 4 weeks, 8 weeks, and 12 weeks after treatment, changes in CTC number were strongly associated with risk, whereas changes in PSA titre were weakly or not associated (p>0·04). The most predictive factors for survival were LDH concentration and CTC counts (concordance probability estimate 0·72–0·75).**

Interpretation **CTC number, analysed as a continuous variable, can be used to monitor disease status and might be useful as an intermediate endpoint of survival in clinical trials. Prospective recording of CTC number as an intermediate endpoint of survival in randomised clinical trials is warranted.**

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Introduction

In clinical trials and practice, outcome measures are designed to assess disease activity so that the effects of an intervention can be assessed accurately. In the monitoring of patients with metastatic, castration-resistant prostate cancer, bone scans are insensitive to changes in disease status;[1] and, although change in titre of prostate-specific antigen (PSA) is used to guide treatment decisions, it cannot be used as a surrogate for clinical benefit.[2] Trials in metastatic breast, colorectal, and prostate cancer showed that patients about to start new lines of chemotherapy could be divided into groups with favourable and unfavourable prognosis on the basis of the number of circulating tumour cells (CTCs) measured with the analytically valid CellSearch system (Veridex, Raritan, NJ, USA).[3–5] The US Food and Drug Administration (FDA) cleared the CTC counts to be used in conjunction with other clinical methods as an aid in the monitoring of patients with these diseases.[6]

In the IMMC38 trial, the groups were defined in the protocol as four CTCs or fewer per 7·5 mL blood for the favourable group and five cells or more per 7·5 mL blood for the unfavourable group. This trial enrolled patients with castration-resistant prostate cancer who were about to begin a new first-line, second-line, or third-line chemotherapy regimen.[5] In a separate group of patients with the same disease treated at Memorial Sloan-Kettering Cancer Center, we also showed an association between baseline CTC number and survival, but the association did not have a threshold effect;[7] a third study suggested that a 30% decline in CTC number was most predictive of longer survival.[8] In all three series, the discriminatory power for risk was increased by accounting for known pretreatment prognostic factors.[2,7–13]

Use of discrete cutoff values in clinical practice suggests that a patient with a 90% decline in CTC number from 100 to ten cells is worse off than a patient with a 33% decline from six to four, and that therapy should be discontinued in the patient with a post-treatment value that remains in the unfavourable range, independent of whether or not the value has declined from the pretreatment baseline. We reanalysed the IMMC38 data, taking into account baseline and post-treatment CTC number as a continuous variable. The analysis assessed the contribution of other pretreatment prognostic factors and outcome and addressed the inherent survival difference between patients receiving first-line, second-line, and third-line chemotherapy[14] by only including

patients about to receive first-line therapy. Median follow-up was 6 months longer than that in the original report.[5] We investigated the association of different CTC and PSA progression definitions and survival on the basis of either one or two rising values to further assess its use in both clinical practice and as a potential intermediate endpoint for clinical trials.

Methods

Patients and procedures

Patients in IMMC38 who had histologically confirmed progressive metastatic prostate cancer (as defined in the PSA Working Group criteria)[15] and concentrations of testosterone after medical or surgical castration of less than 1·7 nmol/L (50 ng/dL) and who were starting first-line chemotherapy were screened.[5] Eligibility requirements included an Eastern Cooperative Oncology Group performance status of 0, 1, or 2, a pretreatment PSA titre of 5 ng/mL or more, progression after a trial of antiandrogen withdrawal as appropriate, and no radiation therapy within 30 days of enrolment. Before treatment, all patients had a complete blood count and recording of PSA, alkaline phosphatase, and lactate dehydrogenase (LDH) concentrations; separate samples were taken for CTC count. Patients had radionuclide bone scans, chest radiography or CT, and CT of the abdomen and pelvis. After starting treatment, PSA and CTC number were measured before each chemotherapy cycle until disease progression was noted. Follow-up imaging was at the discretion of the treating physician. The protocol was approved by local institutional review boards; and each patient gave written informed consent.

	Finding (n=164)
Age (years)	70 (49–87)
Gleason score	7 (2–10)
Primary therapy	
Radical prostatectomy	41 (25%)
Radiation therapy to the prostate	49 (30%)
No primary treatment	72 (44%)
Unknown (missing)	2 (1%)
Performance status (ECOG)	
0	75 (46%)
1	72 (44%)
2	11 (7%)
Unknown	6 (3%)
Chemotherapy	
Docetaxel	133 (81%)
Other	29 (18%)
Unknown	2 (1%)
Bone metastases	
Yes	143 (87%)
No	17 (10%)
Unknown	4 (3%)
Visceral metastases	
Yes	62 (38%)
No	101 (61%)
Unknown	1 (1%)
Biochemical markers	
PSA (ng/mL; n=164)	127 (1·9–17 800)
Lactate dehydrogenase (IU/mL; n=154)	223 (103–1092)
Alkaline phosphatase (IU/mL; n=157)	144 (39–2215)
Haemoglobin (g/L; n=160)	126 (8·2–15·7)
Albumin (g/L; n=158)	38 (2·1–4·1)
Circulating tumour cells (n=156)	6 (0–1816)

Data are median (range) or number (%). PSA=prostate-specific antigen.

Table 1: **Baseline characteristics of patients receiving first-line chemotherapy**

CTC counts were done with the CellSearch and CellTracks systems (Veridex, Raritan, NJ, USA).[16,17] Blood samples were drawn into 10 mL evacuated blood-draw tubes (CellSave, Veridex, Raritan, NJ, USA), maintained at room temperature, and processed in a blinded fashion within 96 h of collection in one of four laboratories (Immunicon, Huntingdon Valley, PA, USA; Immunicon, Enschede, Netherlands; IMPATH Predictive Oncology, Los Angeles, CA, USA; and Cleveland Clinic, Cleveland, OH, USA). CTCs were identified as 4′-6-diamidino-2-phenylindole-stained nucleated cells that express cytokeratin and not CD45. Technical details of the assay have been described elsewhere.[16,17]

Statistical analysis

Kaplan-Meier analysis was used to estimate survival. Kruskal-Wallis tests were used to test for equality of CTC numbers between sites (bone or soft tissue). The association between biomarkers and survival time was tested with Cox proportional hazards models. Post-treatment markers were modelled with fold change in CTC (the ratio of the post-treatment value to the baseline value). The hazard ratio associated with each biomarker was derived from the Cox model as an increase in the hazard per unit increase in biomarker. Because of their positively skewed distributions, the concentrations of LDH, albumin, and PSA and CTC counts were log-transformed before modelling. Tests for the association between biomarkers and survival time were based on the score statistic, derived from the Cox proportional hazards model. After the individual tests, the Cox model was used to determine the factors associated with survival time. Factors with p values less than 0·05 in the multiple-variable Cox model were viewed as independently associated with survival time and were included in the final regression models. Concentrations of albumin and haemoglobin and Gleason score did not have independent predictive value in the multivariate models. In addition to adjusting for baseline markers, a landmark analysis was used to explore the prognostic significance of CTC and PSA values recorded 4 weeks, 8 weeks, and 12 weeks after treatment. Landmark analyses were used to avoid