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Original article

Syndecan-1 shedding circulating syndecan-1 is associated with chemotherapy-resistance in castration-resistant prostate cancer

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Abstract

Objectives: Docetaxel chemotherapy is a standard treatment for castration-resistant prostate cancer (CRPC). Rapidly expanding treatment options for CRPC provide reasonable alternatives for those who are resistant to docetaxel. Therefore, prediction of docetaxel resistance has become of great clinical importance. Syndecan-1 (SDC1) has been currently shown to be involved in chemotherapy resistance in various malignancies including prostate cancer. The predicting value of serum SDC1 level has not been evaluated yet.

Patients and methods: We assessed the baseline levels of SDC1 in serum samples of 75 patients with CRPC who received docetaxel therapy until the appearance of therapy resistance. In one patient who was treated with three treatment series, we assessed also 6 additional serum samples collected during a 1-year treatment period. Serum SDC1 levels were correlated with clinical outcomes as well as with serum levels of MMP7.

Results: Pretreatment SDC1 serum levels were not associated with patients' age, the presence of bone or visceral metastases. In univariable analyses, patients' performance status, the presence of bone or visceral metastases, high pretreatment prostate specific antigen and SDC1 levels were significantly associated with cancer-specific survival. In multivariable analysis patients' performance status ($P = 0.005$), presence of bone or visceral metastases ($P = 0.013$) and high SDC1 level ($P = 0.045$) remained independent predictors of patients' survival. In the patient with available follow-up samples serum SDC1 level increased from 50 to 300 ng/ml at radiographic progression. Serum concentrations of SDC1 were correlated with those of MMP7 ($r = 0.420$, $P = 0.006$).

Conclusions: Our present results together with currently published data suggest a role for SDC1 shedding in chemotherapy resistance. Determination of serum SDC1 may contribute to the prediction of docetaxel resistance and therefore may help to facilitate clinical decision-making regarding the type and timing of therapy for patients with CRPC.

Keywords: Prostate cancer; Syndecan-1; SDC1; CD138; Serum; Prognosis; Docetaxel; Chemotherapy; Shedding

1. Introduction

Prostate cancer (PCA) is the second most common cancer in men worldwide, with an estimated 750,000 new cases and over 400,000 deaths annually [1]. Despite advances in diagnostic and therapeutic strategies, PCA remains a leading health burden for men with significant morbidity and mortality.

Although early stages of PCA can often be cured with local therapy, mainstay therapy for metastatic cancer is androgen deprivation therapy. However, PCA

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become resistant to androgen deprivation therapy within 12 to 18 months and develop prostate specific antigen (PSA)-progression or distant metastases despite castrate levels of testosterone [2,3]. This stage is referred to as castration-resistant prostate cancer (CRPC) is a devastating form of PCA unanimously to the patients' demise despite many sequenced therapies. Docetaxel (DOC) chemotherapy has been the standard treatment for CRPC with or without metastatses for more than a decade. In the last few years new therapies such as abiraterone-acetate, alpharadine, cabazitaxel, and enzalutamide with different mechanisms of action have widened the therapeutic armamentarium of CRPC providing potentially effective alternatives to DOC [4]. To choose the right treatment for the right tumor in the right patient at the right time, prediction or early detection of DOC resistance has a direct clinical relevance in terms of timing and sequencing therapy in a personalized fashion in CRPC.

Syndecan-1 (SDC1) is a transmembrane proteoglycan and one of the 4 members of syndecan family. It is predominantly expressed by epithelial cells and critically contributes to cell-cell and cell-extracellular matrix interactions [5,6]. We have currently reported that circulating serum SDC1 levels are elevated in patients with higher Gleason scores as well as with shorter disease-specific survival in patients with clinically localized PCA [8]. In addition, a recent study showed that high pretreatment soluble SDC1 (sSDC1) serum levels were associated with decreased response to chemotherapy in colorectal cancer [9]. The authors demonstrated that SDC1 shedding was induced by matrix metalloproteinase-7 (MMP7) and resulted in reduced chemotherapeutic sensitivity of colorectal cancer cells [9]. Our recent analyses identified serum MMP7 as a predicting factor for DOC therapy in CRPC [10]. Based on these findings, we hypothesized that circulating SDC1 levels may predict response to DOC chemotherapy in CRPC. Therefore, we determined the pretreatment sSDC1 serum concentrations in patients with CRPC who were treated with DOC therapy.

2. Patients and methods

2.1. Patients' characteristics

We assessed the pretreatment serum samples of 75 patients with CRPC who received docetaxel chemotherapy between 2003 and 2010 in a single academic center. Inclusion criteria were castration-resistant stage with or without metastases. Exclusion criteria were ineligibility for docetaxel treatment, presence of a second malignancy as well as treatment with further lines of systemic therapies following docetaxel. Men who completed the first series of docetaxel treatment with a good PSA response and without experiencing radiographic progression underwent a retreatment with docetaxel. After the first retreatment (second series), further retreatments were offered based on the same response criteria. PSA response was defined according to the Prostate Cancer Clinical Trials Working Group Criteria (PCWG) I as at least 50% PSA decline from baseline during the first chemotherapy series [11]. Radiographic progression was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) [12]. The institutional ethics committee approved the study protocol.

All patients received DOC without prednisone using a 3-weekly schedule. 49 of 75 men received one single series of DOC with 5 to 8 cycles, while 26 men were treated with at least two series of DOC. Methods and results are presented according to the REMARK recommendations for biomarker studies [13].

To observe possible changes of sSDC1 levels in response to DOC treatment, we assessed 7 follow-up samples collected during a 1-year of treatment period in 1 patient who received 3 series of DOC.

2.2. Enzyme-linked immunosorbent assay (ELISA) analysis

SDC1 serum levels were quantified by using a sandwich ELISA (Diaclone CD138, Gene-Probe, San Diego, CA; Cat. No.: 950.640.096) according to the manufacturer's instructions. MMP7 levels were measured in a different aliquot of the same sample as SDC1. Details on MMP7 measurements have been published previously [14]. All measurements were performed blinded to the clinical and follow-up data.

2.3. Statistical analysis

For paired comparisons between groups, the nonparametric, 2-sided Wilcoxon rank-sum test was applied. Survival analyses were done using Kaplan-Meier curves, log-rank test and univariable Cox proportional hazards regression analysis. For multivariable analysis, Cox regression models were used. Variables with effect on survival in univariable analysis ($P \leq 0.05$) were considered in the Cox proportional hazards regression models.

Pearson's correlation coefficient was used to assess the relationship between SDC1 and MMP7 serum concentrations. All statistical analyses were 2-sided; $P \leq 0.05$ was considered as statistically significant. All tests were done with the SPSS software package 24.0 (SPSS, Chicago, USA).

3. Results

3.1. Clinical background

The main patients' and follow-up characteristics are given in Table 1. Overall, 259 cycles of docetaxel were administered to the 49 patients who were treated with one single series of DOC; while 354 cycles were administered