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Original article

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

Table 1
Patients' characteristics

Variables	*n*
Total number of patients	75
Age at baseline median (range)	71 (47–86)
ECOG PS at enrollment	
0	51
1	19
2	5
Bone metastasis	58
Lymph node metastasis (>2 cm)	17
Soft tissue lesions (lung/liver)	7
Docetaxel therapy	
First line	56
Second line	19
Doc only	65
EMP/Doc	10
Number of Doc series median (range)	1 (1–6)
Number of Doc cycles median (range)	6 (2–28)
Single (only one series)	49
Retreatment (at least 2 series)	26
Number of patients died	69
PC-specific deaths	67
Follow-up time in weeks median (range)	56 (5–221)

EMP = estramustine phosphate; pretreated with EMP or vinorelbine.

to those 26 patients who were retreated with DOC. The total number of rechallenges was 47 (36 × 2 series, 4 × 3, 5 × 4, 1 × 5, 1 × 6). Nineteen patients received DOC as second-line treatment and in 10 men DOC was administered in combination with estramustine phosphate (Table 1).

Out of 75, 65 patients with CRPC had metastases, whereas 10 patients were treated after failure of androgen deprivation therapy with rising PSA but without known metastasis on conventional imaging. Of the 65 patients with metastatic PCA, 58 had bone metastases, 17 had lymph node, and 7 had visceral metastases. The median patients' age was 71 years (range: 47–86). The distribution of ECOG performance status (PS) among CRPC patients was as follows; 51 × PS 0, 19 × PS 1, and 5 × PS 2 (Table 1).

3.2. Associations of clinicopathological and therapy parameters with serum levels of SDC1 and PSA at baseline

Associations of baseline serum levels of SDC1 with clinicopathological parameters are shown in Table 2. Patients' age, ECOG PS, presence of lymph node, bone or visceral metastasis had no significant effect on sSDC1 levels. SDC1 levels were not significantly different between single treatment and retreatment patients. Similarly, pretreatment with other first-line therapy or with estramustine phosphate did not correlate with sSDC1 levels. In contrast, PSA was higher in patients with bone metastases ($P = 0.029$).

Median MMP7 levels were significantly higher ($P = 0.004$) in single treatment patients (who received only one series of DOC) 7.00 ng/ml (range: 4.1–16.1) compared to patients who received DOC rechallenges; 4.3 ng/ml (range: 1.1–34.3).

Table 2
Correlations of baseline sSDC1 levels with clinicopathological parameters

	n	SDC1 Serum concentration (ng/ml) Median (range)	*P*
Age, y			
≤71	40	99 (34–422)	0.181
>71	35	129 (39–416)	
Docetaxel therapy			
First line	56	102 (34–422)	0.724
Second line	19	96 (34–421)	
Docetaxel therapy			
Doc only	65	114 (43–416)	0.791
EMP/Doc	10	101 (34–422)	
Number of Doc series			
Single treatment	49	102 (34–122)	0.628
Retreatment	26	99 (39–416)	
ECOG PS			
0	51	102 (34–422)	0.510
1–2	24	97 (34–421)	
Any mets.			
No	10	92 (43–295)	0.289
Yes	65	103 (34–422)	
Lyph node status			
N−	58	97 (34–422)	0.990
N+	17	114 (34–211)	
Bone mets.			
No	17	97 (34–295)	0.346
Yes	58	103 (34–422)	
Visceral mets.			
No	68	99 (34–422)	0.122
Yes	7	124 (71–416)	

RPE = radical prostatectomy; EMP = estramustine phosphate.

3.3. Associations of patients' survival with serum levels of SDC1 and PSA at baseline

Univariable Cox analysis found presence of any metastasis, bone metastasis or visceral metastasis as well as SDC1 levels (above the median) to be significantly associated with poor overall and disease-specific survival (Table 3 and Fig. 1). Pretreatment PSA levels were associated with shorter disease-specific survival ($P = 0.041$) and showed a trend to be associated with shorter overall survival ($P = 0.075$) (Fig. 1). In addition, ECOG PS > 0 proved to be a significant prognostic factor for overall survival ($P = 0.041$) and tended to be associated with disease-specific survival ($P = 0.057$).

In the multivariable models only factors with effect on survival in the univariable analyses were included. These analyses revealed ECOG PS > 0, presence of any metastases and high SDC1 serum levels as independent and unfavorable prognostic factors for both overall and disease-specific survival (Table 4).

3.4. SDC1 levels in response to docetaxel treatment

We analyzed the sSDC1 levels in samples taken during the chemotherapy treatment from a patient who received

Table 3
Univariable Cox analysis

Variables	Overall survival			Disease-specific survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, y						
≤71	ref.			ref.		
>71	0.700	0.564–1.469	0.910	0.911	0.561–1.481	0.707
Docetaxel therapy						
First line	ref.			ref.		
Second line	0.934	0.544–1.602	0.803	0.901	0.519–1.564	0.710
Docetaxel therapy						
EMP/Doc	ref.			ref.		
Doc only	1.846	0.935–3.643	0.077	1.779	0.899–3.519	0.098
ECOG PS						
0	ref.			ref.		
1–2	1.735	1.024–2.939	0.041	1.686	0.985–2.888	0.057
Any mets.						
No	ref.			ref.		
Yes	3.050	1.436–6.481	0.004	3.426	1.540–7.624	0.003
Lyph node status						
N−	ref.			ref.		
N+	1.341	0.758–2.373	0.313	1.390	0.783–2.467	0.261
Bone mets.						
No	ref.			ref.		
Yes	2.154	1.201–3.861	0.010	2.257	1.237–4.116	0.008
Visceral mets.						
No	ref.			ref.		
Yes	4.055	1.744–9.430	0.001	4.005	1.744–9.430	0.001
SDC1 serum concentration						
≤101 ng/ml	ref.			ref.		
>101 ng/ml	2.498	1.439–4.337	0.001	2.313	1.324–4.040	0.003
PSA serum, concentration						
≤55 ng/ml	ref.			ref.		
>55 ng/ml	1.585	0.954–2.634	0.075	1.726	1.023–2.914	0.041

RPE = radical prostatectomy; EMP = estramustine phosphate.

3 series of DOC in a time period of 337 days (Fig. 2.). The third series of treatment was terminated because of radiographic progression on DOC treatment. The patient has died of PCA shortly after the detection of radiographic progression. Changes in sSDC1 and PSA levels in treatment series and treatment holidays are shown in Fig. 2.

3.5. Correlations between SDC1 and MMP7 levels

Pearson's correlation analyses revealed a significant and linear correlation between SDC1 and MMP7 serum concentrations ($r = 0.420$, $P = 0.006$) (Supplementary Fig. 1).

4. Discussion

In the present study, we determined the pretreatment sSDC1 levels in serum samples of 75 patients with CRPC who underwent DOC chemotherapy. Our results revealed circulating serum SDC1 to be independently associated with disease-specific survival suggesting, for the first time, sSDC1 as a potential predictive factor for DOC treatment in CRPC.

SDC1 is a transmembrane adhesion molecule that plays an essential role in the maintenance of epithelial cell morphology and is involved in the interactions between cells and their microenvironment. Dysregulated expression of SDC1 has been observed in several tumors [7]. Loss of SDC1 expression in tumor cells is associated with reduced cell adhesion, increased cell motility and invasion [15,16]. In addition, SDC1 as a co-receptor for growth factors such as TGFB, bFGF, VEGF, and HGF and facilitates their binding to cognate receptors enhancing the proliferation of fibroblasts, endothelial and cancer cells [17–19]. The extracellular domain of SDC1 can be released through proteolytic shedding driven by MMP7, MMP9 and heparanase [20]. Cells constitutively release small amounts of SDC1 ectodomain in the environment which can be measured in the blood stream. Enhanced SDC1 shedding was observed in various pathological processes including tumor cell proliferation and invasion. In accordance, while sSDC1 levels are relatively low in healthy individuals, significantly elevated serum SDC1 levels have been demonstrated in patients with various hematological malignancies and colorectal cancer [7].

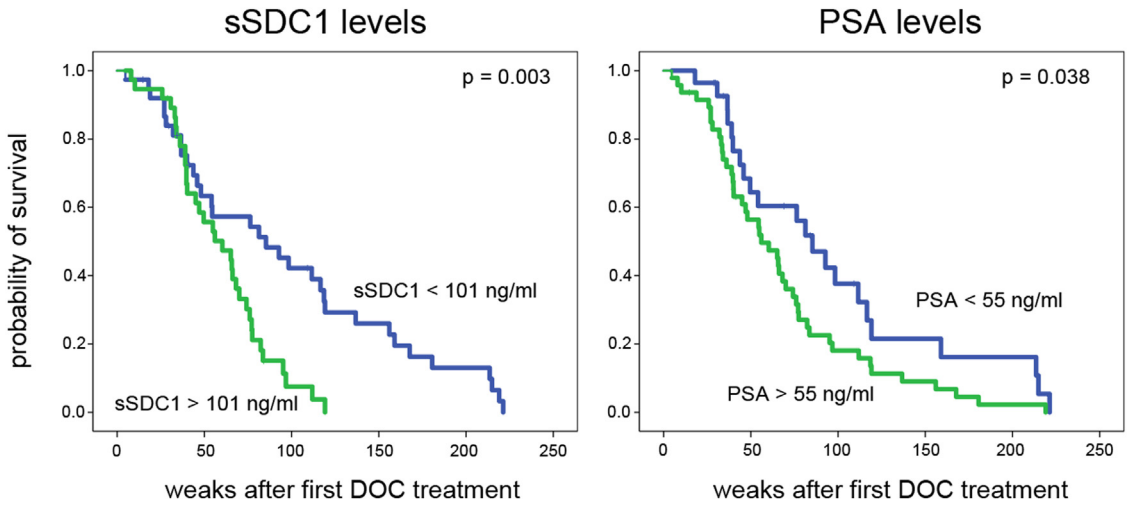

Fig. 1. Kaplan-Meier curves of cancer-specific survival according to sSDC1 and PSA pretreatment (baseline) levels.

Serum SDC1 levels have also been found to be associated with response to chemotherapy. Three independent studies in multiple myeloma consequently found high serum baseline levels of SDC1 in patients who did not respond to chemotherapy [21–23]. In colorectal cancer sSDC1 levels significantly decreased after surgery and patients with high preoperative sSDC1 levels were less responsive to chemotherapy [9]. The authors suggested that shedded SDC1 ectodomain is causally involved in chemotherapy resistance by activating EGFR phosphorylation and downstream signaling pathways [9]. Furthermore, addition of MMP7 decreased cell surface SDC1 and increased SDC1 shedding and enhanced EGFR phosphorylation [9]. In line with these data, the authors found that chemotherapy induces the shedding of SDC1 and shedded SDC1 actively contributes to the establishment of a more aggressive phenotype and cancer relapse [24]. Similar results have been reported in PCA. Shimada et al. assessed tumor initiating (or stem-like) cells in PCA which are known to be resistant to chemo- and radiotherapy and are supposed to be a source of tumor recurrence. They demonstrated that SDC1 gene silencing inhibits the proliferation of stem-like cells and enhances their sensitivity to DOC. These data suggest that SDC1 is necessary for the maintenance of chemoresistance of tumor initiating cells in PCA [25]. Furthermore, using an in vivo mouse model they showed that both knock-down of SDC1 and pharmaceutical inhibition of its shedding strongly increased DOC-treatment efficacy [25]. Interestingly, a recent immunohistochemical study identified a dedifferentiated/stem-like cell population with strong SDC1 expression in PCA. These SDC1 expressing cells were characterized by high migratory activity and their increased numbers were associated with high Gleason scores [26]. In addition, Fujii et al. [27] demonstrated that SDC1 expression contributes to epithelial-to-mesenchymal transition (EMT) of PCA cells due to the regulation miR-331-3p and EMT was found to be strongly correlated with DOC resistance of PCA in various functional studies [28,29].

Table 4
Multivariable Cox analysis

Variables	Overall survival			Disease-specific survival		
	HR	95% CI	*P*	HR	95% CI	*P*
ECOG PS						
0	ref.			ref.		
1–2	2.342	1.317–4.167	0.004	2.337	1.296–4.212	0.005
Any mets.						
No	ref.			ref.		
Yes	2.559	1.145–5.722	0.022	2.925	1.255–6.820	0.013
SDC1 serum concentration						
≤101 ng/ml	ref.			ref.		
>101 ng/ml	2.188	1.178–4.062	0.013	1.880	1.008–3.505	0.047
PSA serum concentration						
≤55 ng/ml	ref.			ref.		
>55 ng/ml	1.126	0.620–2.045	0.698	1.269	0.689–2.339	0.445

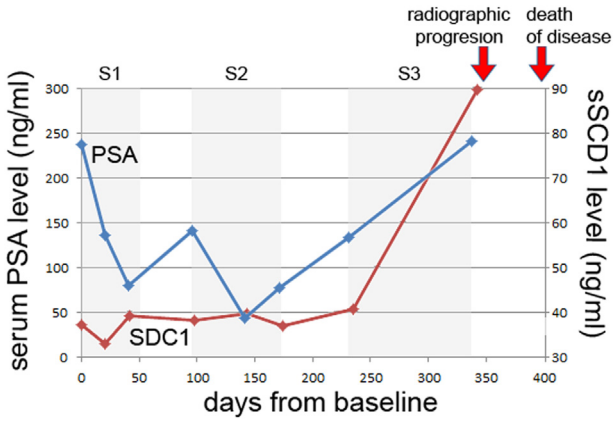

Fig. 2. Changes in serum levels of sSDC1 (red line) and PSA (blue line) during docetaxel treatments and treatment holidays in case of one patient. S—series (treatment periods). The assessed samples were as follows: (1) baseline sample—first day of first cycle of first[t] series (day 1), (2) first day of second cycle of first series (day 21), (3) first day of third cycle of first series (day 42), (4) first day of first cycle of second series (day 97), (5) first day of third cycle of second series (day 142), (6) last day of second series (day 172), (7) first day of first cycle of third series, (8) last day of third series (day 337). PSA level decreased during the first and second series of DOC treatment, while it increased in both treatment holidays. The sSDC1 levels were unchanged during the first two treatment series. In the third series the tumor acquired therapy resistance and progressed despite DOC treatment. This was accompanied by the markedly increase of both sSDC1 (from 40–300 ng/ml) and PSA (from 134–241).

The association between serum sSDC1 levels and DOC resistance, however, has not been assessed in patients with CRPC yet. Our results demonstrated an independent correlation between sSDC1 and both overall and disease-specific survival in DOC-treated patients with CRPC and are therefore in line with the results of Shimada. These data together, may suggest the involvement of SDC1 shedding in DOC resistance of PCA. Our present data also demonstrate a significant correlation between serum MMP7 and sSDC1 levels suggesting that MMP7 may play a role in SDC1 shedding in PCA [10]. Despite the fact that the immunoassay used in this study recognizes the extracellular domain of SDC1, we cannot be sure that the measured serum SDC1 signals originate exclusively from ectodomain shedding and not from disintegrated tumor cells.

Our results revealed constantly low-sSDC1 concentrations in the first and second series of DOC treatment. In contrast, sSDC1 concentration has 7.5-fold increased during the third treatment series when the tumor acquired therapy resistance as evidenced by radiographic progression suggesting sSDC1 as a promising marker for therapy monitoring in CRPC. Correlative studies embedded in clinical trials are necessary to validate these results for clinical decision-making. Furthermore, whether SDC1 is predictive only for DOC treatment or also for other CRPC treatments such as abiraterone and enzalutamide remains to be elucidated in subsequent analyses.

The involvement of SDC1 shedding in chemoresistance in various malignancies suggests SDC1 as a potential target for therapy. In this context, it is interesting that pharmacological inhibition of heparanase—one of the potent sheddases of SDC1—recently was found to be effective in overcoming chemoresistance in myeloma [30]. Moreover, the use of the heparanase inhibitor Roneparstat either during or after chemotherapy diminished regrowth of myeloma tumors in vivo following therapy [30]. Similarly, another anti-heparanase, PG545 was shown to synergistically inhibit the growth and migration of ovarian cancer cells when administered in combination with paclitaxel and cisplatin [31].

Our study has some limitations due to its retrospective nature. In addition as we did not assess a cohort with similar characteristics but untreated with DOC, we cannot firmly answer the question whether sSDC1 serum levels are predictive or only prognostic. Finally, as we measured monitoring samples (collected during DOC treatment) in one single patient, the value of SDC1 in monitoring DOC treatment has to be confirmed in subsequent studies with available posttreatment samples.

5. Conclusions

Our data suggest a potential role for sSDC1 in the prediction of DOC treatment in CRPC. Therefore, sSDC1 may help to identify non-responsive patients to DOC therapy and thus may help to optimize treatment decisions in CRPC. Further research is needed to assess the functional involvement of SDC1 in DOC resistance in order to establish SDC1 shedding as a target for anticancer therapy.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.urolonc.2018.03.010.

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