Pathology & Oncology Research (2020) 26:1243–1249
https://doi.org/10.1007/s12253-019-00689-y

ORIGINAL ARTICLE

STIP1 Tissue Expression Is Associated with Survival in Chemotherapy-Treated Bladder Cancer Patients

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Received: 18 April 2019 / Accepted: 16 June 2019 / Published online: 27 June 2019

Abstract

To optimize treatment decisions in advanced bladder cancer (BC), we aimed to assess the therapy predictive value of STIP1 with regard to cisplatin therapy. Cisplatin-based chemotherapy represents the standard first-line systemic treatment of advanced bladder cancer. Since novel immunooncologic agents are already available for cisplatin-resistant or ineligible patients, biological markers are needed for the prediction of cisplatin resistance. STIP1 expression was analyzed in paraffin-embedded bladder cancer tissue samples of 98 patients who underwent adjuvant or salvage cisplatin-based chemotherapy by using immunohistochemistry. Furthermore, pre-chemotherapy serum STIP1 concentrations were determined in 48 BC patients by ELISA. Results were correlated with the clinico-pathological and follow-up data. Stronger STIP1 nuclear staining was associated with worse OS in both the whole patient group ($p = 0.034$) and the subgroup of patients who received at least 2 cycles of chemotherapy ($p = 0.043$). These correlations remained significant also in the multivariable analyses ($p = 0.035$ and $p = 0.040$). Stronger STIP1 cytoplasmatic immunostaining correlated with shorter PFS both in the whole cohort ($p = 0.045$) and in the subgroup of patients who received at least 2 cycles of chemotherapy ($p = 0.026$). Elevated STIP1 serum levels were associated with older patient's age, but we found no correlation between STIP1 serum levels and patients' outcome. Our results suggest that tissue STIP1 analysis might be used for the prediction of cisplatin-resistance in BC. In contrast, pretreatment STIP1 serum levels showed no predictive value for chemotherapy response and survival.

Keywords Bladder cancer · STIP1 · Cisplatin · Resistance

Introduction

Bladder cancer (BC) represents the most common malignancy affecting the urinary tract and is worldwide the 7th most commonly diagnosed cancer in men while it drops to 11th position when both genders are considered [1, 2]. The spectrum of the disease ranges from non-muscle-invasive BC (NMIBC) to muscle-invasive BCs (MIBC). Seventy per cent of BCs are non-muscle-invasive at first presentation and exhibit an excellent prognosis with 5 year-survival rates of ~95% after curatively intended transurethral resection. On the other hand, MIBCs are characterized by a poor prognosis with a 5 year-survival ranging from 50% to 60% [3]. In MIBC radical cystectomy with extended pelvic lymph node dissection is the commonly accepted treatment with curative intent. Despite, these patients bear a high risk of metastatic tumor progression and cancer-related death.

Cisplatin-based chemotherapy represents the goldstandard treatment of progressed MIBC. Chemotherapy provides a survival advantage for progressed MIBC patients in both the preoperative (neoadjuvant) and postoperative (adjuvant) setting [4, 5]. In 2017, a novel immunooncological approach became available for the systemic treatment of metastatic BC by the approval of novel anti-PD-L1 and anti-PD-1

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12253-019-00689-y) contains supplementary material, which is available to authorized users.

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checkpoint inhibitor therapies for platinum resistant and/or ineligible a novel therapy approach became available for BC patients. [6]. In addition, a several clinical trials are ongoing investigating the efficacy of various checkpoint inhibitors in the first line setting. Therefore, the prediction of platinum-based therapy became of paramount clinical relevance. Gene expression-based molecular classification of BC has recently been shown to be predictive for cisplatin-based chemotherapy [7]. Unfortunately, because of its complexity, the methodology is not yet suitable for routine clinical use.

While several immunohistochemical biomarkers for instance ERCC1, survivin, emmprin were investigated and found to possess cisplatin-predictive values, no protein markers are used in the current clinical routine [8–12]. A recent meta-analysis found STIP1 to be associated with worse OS and PFS in several human malignancies such as gastric cancer, ovarian cancer, hepatocellular carcinoma, thyroid cancer and colorectal cancer [13]. In BC, Als et al. using a high throughput gene expression profiling previously identified a large set of genes including STIP1 which were associated with patients' survival after cisplatin containing chemotherapy [10]. In this study, we selected STIP1 as a promising prognostic biomarker in several malignancies and analyzed the tissue protein expression in BC patients using immunohistochemistry. Furthermore, we assessed serum STIP1 levels in 48 BC patients who underwent cisplatin-based adjuvant or salvage chemotherapy by using ELISA. Results were correlated with clinicopathological and follow-up data.

Materials and Methods

Patients

Pre-treatment chemo naïve tumor tissues from 98 BC patients who underwent postoperative (adjuvant) chemotherapy samples were collected and divided in three cohorts. The first - "SUSE" – cohort contained 52 formalin-fixed paraffin-embedded (FFPE) tumor samples derived from a Phase II, prospective, multicenter, randomized, double-blinded trial (SUSE, AB 31/05, RUTT 204) comparing the efficacy of gemcitabine-cisplatin (GC) with and without sorafenib [14]. We used the following inclusion criteria: (1) histological confirmed urothelial carcinoma (2) locally advanced or metastatic tumor stage, (3) patients' age > 18 years, (4) ECOG performance status ≤1, (5) at least one measurable lesion on CT or MR. The second ($n = 27$) and third ($n = 19$) single institution cohorts included chemotherapy naïve FFPE tissue samples from patients who received adjuvant cisplatin-based chemotherapy. Patients' characteristics are given in (Table 1). The study protocol was approved by the respective institutional ethic committees (TUKEB 224/2013 and 15–6400-BO).

Pre-treatment serum samples were collected from 48 BC patients who received adjuvant cisplatin-based chemotherapy. All of these patients had histologically confirmed metastatic or locally advanced (T3/T4) urothelial carcinoma and presented with an ECOG performance status of 0 to 2. Written consent from all patients was available. The ELISA cohort consisted of

Table 1 STIP1 immunoreactivity and clinicopathological parameters

	All patients	STIP1		P	STIP1		P
	n	cyt int low n	cyt int high n		nucl neg n	nucl pos n	
Total number of cases	98	49	49		78	20	
Age 64 (37–90)							
≤ 65	52	25	27	0.686	44	8	0.190
> 65	46	24	22		34	12	
Gender							
Male	70	36	34	0.655	56	14	0.874
Female	28	13	15		22	6	
Stage							
T1 - T2	15	11	4	0.096	11	4	0.626
T3 - T4	53	26	27		42	11	
Not available	30						
Performance status							
0	44	20	24	0.417	41	3	**0.003**
1–2	54	29	25		37	17	
Visceral metastasis							
Present	33	16	17	0.831	26	7	0.888
Absent	65	33	32		52	13	

Significant correlations are highlighted by bold type

35 males and 13 females with a median age of 65 ranging from 41 to 81. Age, gender, ECOG, stage, LN status, M status (soft tissue, bone) were noted. In addition, 79 serum samples from further therapy cycles were samples were collected.

Time to progression (PFS) and overall survival (OS) were recorded as time from first chemotherapy to the relevant event or censoring. The study was performed according to the Declaration of Helsinki and the institutional ethics committee approved the study protocol (TUKEB 55/2014). None of the patients received neoadjuvant chemotherapy.

Immunohistochemical Analysis

Hematoxylin and eosin-stained slides were prepared in order to construct from 106 formalin-fixed paraffin-embedded BC-tissue blocks in order to prepare tissue microarray (TMA) construction. Representative tumor regions were marked by a uropathologist (H.R.). Tissue cores were punched with a 2 mm hollow needle from the area of interest on the paraffin embedded tissue block. Cores were then inserted into a recipient paraffin block in an array pattern. Antigen retrieval was routinely performed with Leica bond retrieval solution (Cat. Nr.: M7228) at 96 °C.

A rabbit monoclonal STIP1- antibody (abcam, clone EPR6606) was used to perform IHC staining on 4 μm thick FFPE TMA sections. Automated IHC was conducted using the Dako Autostainer Plus System with the anti- mouse IgG EnVision Plus detection kit (Dako) for secondary and tertiary immunoreactions. Negative controls were included in each run.

STIP1 staining intensity was scored as 0, 1, 2 or 3, corresponding to negative, weak, moderate and strong intensities. In addition a percentage score was defined as follows: 0–10% - 0 Pts., 11–50% - 1 Pts., 51–80% - 2 Pts. and 81–100% - 3 Pts. Finally a histochemical score (H-score) was calculated by multiplying the intensity score by the percentage score. A positive STIP1 nuclear expression was considered when the H-score was higher than 0. In other words, nuclear STIP1 positivity was considered when any staining (intensity >0) was observed in at least 10% of tumor cell nuclei. For dichotomization of cytoplasmic staining, we used a cut-off at the median of cytoplasmic H-score.

Enzyme-Linked Immunosorbent Assay (ELISA)

Patients' STIP1 serum levels were quantified using a STIP1 ELISA kit (Cat.Nr. E-EL-H5592, Elabscience Biotechnology, Huston, TX, USA) according to the manufacturer's instructions.

Statistical Analysis

The Chi-square test was used to evaluate the associations of STIP1 immunostaining and clinicopathological parameters. The lack of normal distribution of serum concentration data (controlled by Shapiro-Wilk test) indicated the use of non-parametric two-sided Wilcoxon rank sum test (Mann-Whitney test) for paired group comparisons. Kaplan–Meier log-rank test and univariable Cox analysis were conducted for univariable survival analyses. For multiple Cox analyses, parameters with a p value less than 0.150 in the univariable analysis were considered. In all tests $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were carried out with the SPSS software package (version 24; SPSS, Chicago, IL).

Results

Clinical Background

Patients' characteristics are demonstrated in Table 1. The median follow-up time in the immunohistochemistry group was 8 months ranging from 1 to 123 months. Seventy-four of 98 patients died within the follow-up period. In 65 patients metastatic progression was detected with a median latency of 5 months range (1–102 months). For the ELISA group the median follow-up time was 17 months ranging from 2 to 101 months. The median number of applied chemotherapy cycles was 6. Twenty-eight of 48 patients died within the follow-up period.

Tissue STIP1 Expressions

STIP1 immunostaining was observed and evaluated separately in the cytoplasm and nuclei of tumor cells and exhibited a finely dispersed immunoreactivity. The cytoplasmic staining was the dominant component in most cases (Fig. 1). Strong cytoplasmic immunostaining of STIP1 (above the median of cytoplasmic H-score) tended to associate with higher tumor stage ($p = 0.096$). A correlation between strong nuclear staining intensity and worse ECOG performance status ($p = 0.003$) was found. We observed no other association with patients' age or sex (Table 1). Presence of STIP1 nuclear staining (at least 10% of positively stained tumor nuclei) was in univariable analysis associated with worse OS considering the whole FFPE cohort ($p = 0.034$) and also in the subgroup of patients who received at least 2 cycles of chemotherapy ($p = 0.043$; Table 2). Stronger STIP1 cytoplasmic immunostaining correlated with shorter PFS both in the whole cohort ($p = 0.045$) and in the subgroup of patients who received at least 2 cycles of chemotherapy ($p = 0.026$) and tended to correlate with shorter OS ($p = 0.076$) (Table 2). Multivariable analysis revealed, that stronger nuclear immunostaining of STIP1 was associated with worse OS in the whole FFPE cohort ($p = 0.035$) and in the subgroup of patients who received at least 2 cycles of chemotherapy ($p = 0.040$). Furthermore, for this subgroup of patients we observed a correlation between a

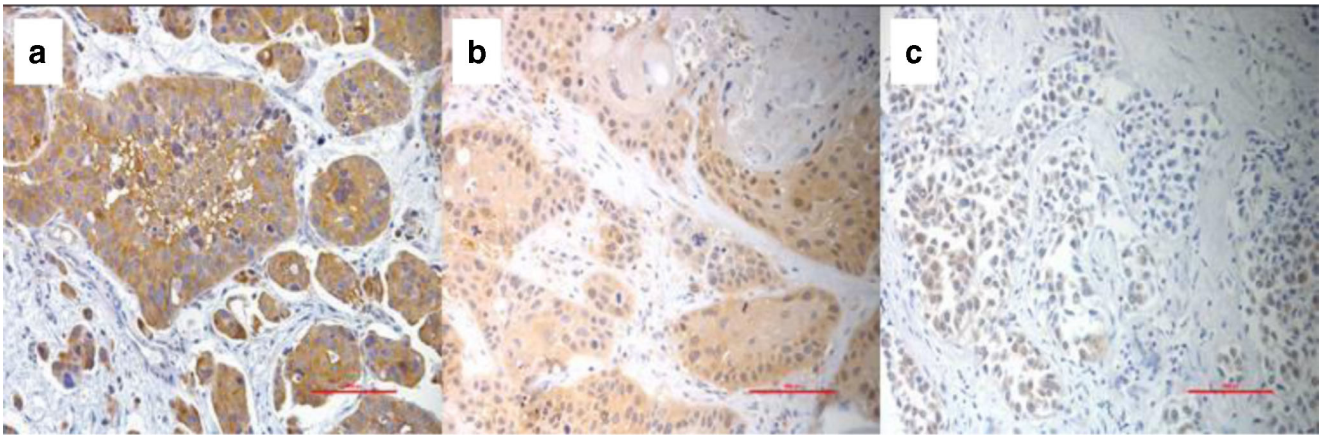

Fig. 1 Immunoreactivity of STIP1 in urothelial carcinoma (UC). **a** In this case of UC with micropapillary features, a strong cytoplasmic staining is observed, while in **b** a case of UC with squamous features and moderate cytoplasmic and focal nuclear staining is displayed. In **c** a case of usual UC with weak and focally absent STIP1 immunostaining is shown. All 200x

strong cytoplasmic immunostaining and a shorter PFS ($p = 0.034$).

Serum STIP1 Levels

The serum values of STIP1 were determined from 48 patients. Forty-eight blood samples were taken before the administration of the first cycle of chemotherapy. Further 79 blood samples were taken during chemotherapy. Elevated STIP1 serum values were solely associated with older patient's age. We could not find any significant correlation between STIP1 serum levels and other clinicopathological or follow-up data (supplementary Table 1). We observed slightly lower risk of death in patients with higher stage tumors. This may be due to the fact, that patients with a stage T1-T2 tumor were only received chemotherapy when they had lymph node or distant metastases which represents a higher risk as locally advanced (T3-T4) tumor stage.

Discussion

Patients with advanced BC represent a clinically heterogeneous group with different response to cisplatin-containing chemotherapy. This remarkable heterogeneity cannot sufficiently be resolved by routine histopathological examination alone. Recent developments in systemic treatment of advanced BC resulted in the approval of novel effective drugs for those patients who are not responsive to cisplatin-based therapy. Therefore, biomarkers are urgently needed for the accurate prediction of cisplatin resistance in order to improve therapy decisions. In the present study, we evaluated STIP1, a formerly identified potential cisplatin therapy-predicting marker and were able to show for the first time the predictive value of STIP1 in cisplatin-treated BC-patients. Stress-induced phosphoprotein 1 (STIP1, also referred as heat shock protein (HSP) 70/90 organizing protein HOP, P60 or STI1), is a 66.2 kDa co-chaperone protein. Stip1 mRNA was first isolated from the yeast *Saccharomyces cerevisiae* [15]. Stip1 contains a nuclear localization signal (NLS) and nine tetratricopeptide repeat (TPR) motifs [16]. The TPR domains of STIP1 stabilizes the connection between HSP70 and HSP90 [17]. The HSP70/90 complex participates in several cellular processes including transcription, protein folding, protein translocation, signal transduction and cell division [18, 19]. The NLS sequence enables STIP1 translocation from cytoplasm to the nucleus under the control of cell-cycle kinases [16]. Research indicates that STIP1 can be secreted out of the cell [20]. Secreted STIP1 interacts with prion proteins on cell surfaces and induces protective signals that rescue the cell from apoptosis [19, 21].

Als et al. formerly performed a gene expression chip analysis on frozen tissue samples taken from BC patients who underwent adjuvant cisplatin-based chemotherapy. They identified a set of 55 genes including STIP1 to be significantly associated with shorter survival under cisplatin-based chemotherapy [10]. However, STIP1 has not yet been tested in an independent patient cohort at the protein level. Therefore, we assessed the correlation between STIP1 protein expression and patients' OS and PFS in adjuvant and salvage chemotherapy treated BC patients. Our present data confirm the findings of Als et al. at the protein level using immunohistochemistry. In addition, strong STIP1 nuclear immunostaining showed a correlation with a poor ECOG performance status ($P = 0.003$) (Table 1). Nuclear immunostaining of STIP1 proved to be strongly associated with OS ($P = 0.034$) and accordingly with OS in the subgroup of patients who received at least 2 cycles of chemotherapy ($P = 0.043$). In the same subgroup, the cytoplasmic staining intensity of STIP1 correlated with PFS ($p = 0.026$) (Table 2). Multivariable analysis showed that positive nuclear

Table 2 Univariable and multivariable analysis of overall and progression-free survival

Univariable analysis												
Variables	Overall survival			Overall survival minimum 2 cycles			Progression-free survival			Progression-free survival minimum 2 cycles		
	$n = 98$			$n = 77$			$n = 98$			$n = 77$		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age												
≤ 65	ref.			ref.			ref.			ref.		
> 65	1.325	0.831–2.114	0.238	1.214	0.707–2.084	0.482	1.363	0.832–2.333	0.219	1.171	0.679–2.018	0.570
Sex												
Male	ref.			ref.			ref.			ref.		
Female	1.695	1.012–2.840	**0.045**	1.680	0.923–3.059	0.089	1.123	0.634–1.989	0.694	1.096	0.583–2.060	0.776
Stage												
T1 - T2	ref.			ref.			ref.			ref.		
T3 - T4	0.934	0.493–1.767	0.833	0.910	0.419–1.978	0.813	1.133	0.545–2.356	0.738	1.376	0.573–3.306	0.475
Performance status												
0	ref.			ref.			ref.			ref.		
1–2	1.382	0.865–2.209	0.176	1.257	0.742–2.128	0.395	1.110	0.677–1.819	0.697	1.048	0.612–1.793	0.865
Visceral metastasis												
Absent	ref.			ref.			ref.			ref.		
Present	1.376	0.853–2.222	0.191	1.628	0.951–2.786	0.076	1.643	0.999–2.700	**0.050**	1.867	1.088–3.205	**0.024**
STIP1 cyt. Int.												
Low	ref.			ref.			ref.			ref.		
High	1.298	0.812–2.075	0.275	1.514	0.903–2.632	0.133	1.680	1.001–2.790	**0.045**	1.861	1.072–3.233	**0.026**
STIP1 nucl.												
Negative	ref.			ref.			ref.			ref.		
Positive	1.844	1.048–3.243	**0.034**	1.955	1.023–3.736	**0.043**	1.220	0.646–2.301	0.540	1.360	0.680–2.719	0.385
Multivariable analysis												
Variables	Overall survival			Overall survival minimum 2 cycles			Progression-free survival			Progression-free survival minimum 2 cycles		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Sex												
Male	ref.			ref.			ref.			ref.		
Female	1.602	0.952–2.695	0.076	1.562	0.852–2.864	0.149	1.091	0.615–1.936	0.765	1.026	0.543–1.938	0.936
Visceral metastasis												
Absent	ref.			ref.			ref.			ref.		
Present	1.384	0.853–2.246	0.188	1.616	0.938–2.787	0.084	1.645	1.000–2.706	**0.050**	1.863	1.082–3.207	**0.025**
STIP1 nucl.												
Negative	ref.			ref.			ref.			ref.		
Positive	1.846	1.045–3.259	**0.035**	1.978	1.031–3.795	**0.040**	1.238	0.655–2.339	0.511	1.355	0.676–2.715	0.936
STIP1 cyt. Int.												
Low	ref.			ref.			ref.			ref.		
High	1.304	0.805–2.113	0.280	1.656	0.965–2.869	0.072	1.526	0.912–2.553	0.108	1.816	1.045–3.156	**0.034**

Significant correlations are highlighted by bold type

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *Ref.* referent

STIP1 immunostaining was independently associated with worse OS in the whole FFPE cohort and in the subgroup of patients who received at least 2 cycles of chemotherapy.

STIP1 is considered to be a secreted glycoprotein and for hepatocellular carcinoma (HCC) Chen et al. found significantly higher STIP1 serum levels in HCC patients compared to healthy controls [22]. As a chaperone molecule mediating cell homeostasis under stress conditions STIP1 appeared to be elevated in patients' sera with metastatic HCC after radiofrequency ablation [23]. Furthermore STIP1 was proposed to play a

critical role in resistance to multiple anti-cancer drugs [24]. Therefore, we assumed STIP1 as a possible serum marker of chemoresistance and collected blood-samples from 48 BC patents before and during cisplatin-containing chemotherapy. Our results revealed no correlation between STIP1 serum values and OS or PFS in BC patients who received cisplatin-containing therapy. The rather small cohort could have distorted these results. In ovarian cancer, STIP1 is secreted by tumor cells in a late stage with a high disease burden. Therefore, the STIP1 autoantibody anti-STIP1 was examined in sera of ovarian cancer patients and healthy controls [25]. Former studies proposed the examination of anti-STIP1 in comparison to STIP1 itself to be more sensitive and specific in ovarian cancer [25]. Possibly this could also apply to bladder cancer. Future research should investigate the value of anti-STIP1 as a serum marker of chemoresistance in BC.

Several limitations of this investigation should be noted. Some limitations are inherent from the retrospective nature of this study. Furthermore, as FFPE samples were collected from several hospitals, different tissue handling methods among institutions could be a confounder. However, we did not find obvious differences when comparing results between larger contributors. We used TMAs for our analyses and tumor heterogeneity is a well-known problem for the analysis of protein markers which affect generalizability of results obtained with this technique.

Conclusions

In summary, we could confirm nuclear STIP1 as a potential tissue marker of cisplatin-resistance in BC at the protein level. In contrast, we could not observe any therapy-predicting value for STIP1 serum concentrations. Further efforts are needed to confirm STIP1 as a marker of cisplatin-resistance in order facilitate therapy decisions and to save patients from the toxicity of ineffective treatments.

Acknowledgements This work was supported by_NKFIH / FK 12443, NVKP 16-1-2016-004 and by the ÙNKP-18-4-SE-66 New National Excellence Program of the Ministry of Human Capacities. Dr. T. Szarvas was supported by a János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

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