Prognostic Significance of Matrix Metalloproteinase-1 and Tissue Inhibitor of Metalloproteinase-1 in Voided Urine Samples from Patients with Transitional Cell Carcinoma of the Bladder

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ABSTRACT

Purpose: To study the role of urinary matrix metalloproteinase-1 (MMP-1) and tissue inhibitor of metalloproteinase-1 (TIMP-1) in bladder cancer and their relationship to tumor progression.

Experimental design: MMP-1 and TIMP-1 were measured by ELISA in urine samples from 131 patients with bladder tumors (7 cis, 74 Ta, 29 T1, and 21 T2-T4; 46 G1, 41 G2, and 37 G3), 5 patients with prostate cancer, 33 patients with benign lower urinary tract disorders, and 36 healthy volunteers. Complete clinical data were available for 100 patients with bladder cancer with a median follow-up time of 24 months (range: 4–39 months).

Results: MMP-1 was detected in urine samples from 21 of 131 (16%) patients with bladder cancer but was undetectable in samples from all other groups (P < 0.0001). Urinary MMP-1 was detected in a higher percentage of patients with T2-T4 tumors and G3 tumors than patients with cis/Ta/T1 or G1/G2 tumors (P = 0.04 and P = 0.0074, respectively). Patients with detectable concentrations of urinary MMP-1 had higher rates of disease progression (P = 0.04) and death from bladder cancer (P = 0.02) than patients with undetectable urinary MMP-1. All patient groups had higher urinary TIMP-1 concentrations than healthy volunteers (P = 0.02). Patients with muscle-invasive tumors had higher concentrations of urinary TIMP-1 than patients with cis/Ta/T1 tumors (P = 0.037), but there was no association between TIMP-1 and tumor grade. Urinary TIMP-1 levels strongly correlated with tumor size (P = 0.0002). Progression-free survival rates were lower for patients with urinary TIMP-1 concentrations above the median (1.8 ng/ml, P = 0.04), but urinary TIMP-1 levels were not related to disease-specific survival. Patients with T2-T4 tumors and G3 tumors had significantly lower urinary MMP-1/TIMP-1 ratios than patients with Ta/T1 bladder tumors (P = 0.039) or G1/G2 tumors (P = 0.0415).

Conclusions: Where urinary MMP-1 is detectable, the patient is more likely to have a bladder tumor of advanced stage or grade and may be at increased risk of disease progression and death of bladder cancer. The relationship between urinary TIMP-1, muscle-invasion, and disease progression in bladder cancer is at variance with its role as an inhibitor of MMPs and warrants additional evaluation.

INTRODUCTION

The extracellular matrix presents a formidable barrier to tumor cell invasion. A unique class of matrix degrading enzymes, the MMPs, possess the ability to degrade the various components of the extracellular matrix and basement membrane, thereby facilitating tumor cell dissemination (1). The MMPs are broadly classified into four different subgroups: (a) the collagenases (MMP-1, -8, and -13); (b) the gelatinases (MMP-2 and -9); (c) the stromelysins (MMP-3, -7, -10, and -11); and (d) membrane-type MMPs (MT 1–4 MMP). Many studies, both in experimental models and human tumors, have shown a significant association between tumor progression and increased expression of certain MMPs (2, 3). More recently, it has emerged that, in addition to degrading extracellular matrix, the MMPs play a key role in maintaining a supportive local environment that promotes tumor cell growth both at the primary and metastatic site (4). Because of their potentially destructive nature, the activities of the MMPs are tightly regulated at different levels, including transcriptional control, secretion from the cell as inactive precursors, and inhibition of function by a family of specific molecules, the TIMPs, of which four members have been identified to date (TIMP-1, -2, -3, and -4; Refs. 5–8).

TCC of the bladder is the fourth commonest malignancy in males and remains a significant cause of morbidity and mortality. Most bladder cancers (70–80%) present as nonmuscle-invasive papillary tumors, which frequently recur (50–80%) but less frequently (5–30%) progress to invade bladder wall muscle.

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3 The abbreviations used are: MMP, matrix metalloproteinase; TCC, transitional cell carcinoma; TIMP, tissue inhibitor of metalloproteinase; CI, confidence interval.
In contrast, the remaining 20–30% of bladder cancers are aggressive, muscle-invasive tumors, which have a much higher risk of metastasis, often despite radical treatment. Although tumor stage and grade are key determinants of prognosis, currently, there are no reliable methods of predicting which tumors will progress to muscle-invasion or metastasis.

One of the principal components of the extracellular matrix is fibrillar collagen, the major substrate of MMP-1 (interstitial collagenase). Immunohistochemical studies in colorectal and esophageal cancer have shown that MMP-1 expression can identify patient subgroups at higher risk of death (9, 10). In bladder cancer, it has been shown that muscle-invasive tumors display significantly higher collagenase activity than their non-invasive counterparts (11). Recently, we reported that MMP-1 was detectable in the urine of patients with bladder cancer and that concentrations of MMP-1 were significantly increased in samples from patients with tumors of high stage and grade (12). It has also been reported that increased concentrations of the active form of MMP-1, measured by ELISA in fresh-frozen tumor tissue homogenates, are associated with decreased survival of patients with bladder cancer (13).

In cancer, disruption of the balance between the expression of MMPs and TIMPs is thought to facilitate tumor progression and metastasis (14). TIMP-1 is a glycoprotein of Mr 30,000 that binds MMPs tightly with 1:1 stoichiometry (15). The i.p. injection of recombinant TIMP-1 was found to inhibit the formation of pulmonary metastases by the mouse melanoma B-16 F10 cell line (16). Also, decreased expression of TIMP-1 was shown to correlate with increased collagenase activity and metastatic potential in murine mammary carcinoma cell lines (17). These studies suggest that TIMP-1 plays an important role in the prevention of tumor cell invasion, and reduced TIMP-1 expression favors tumor progression and metastasis. However, other studies have shown that the relationship between MMP and TIMP expression in patients with cancer is more complex. In urothelial cancer, of patients who had undergone complete surgical resection, those with a higher preoperative serum MMP-2:TIMP-2 ratio had significantly poorer disease-free survival than patients with lower ratios (18), although high levels of immunoreactivity for TIMP-2 in tumors have been associated with poor prognosis in patients with invasive bladder cancer (19). Increased expression of TIMP-1 mRNA has been associated with poor outcome in patients with cancers of the breast, stomach, lung, and colon (20–23). Others have shown that high concentrations of TIMP-1 in tumor tissue homogenates, measured by ELISA, were predictive of poor outcome in patients with breast cancer (24).

An alteration in circulating levels of TIMP-1 may be useful in monitoring patients with urological malignancy. In prostate cancer, patients with metastatic disease were noted to have higher levels of plasma TIMP-1 when compared with healthy controls, patients with benign prostatic hyperplasia, or patients with localized prostate cancer (25). Patients with bladder cancer were also found to have high circulating levels of serum TIMP-1 compared with healthy volunteers, and positive correlations between higher TIMP-1 levels and tumor invasion and metastasis were also observed (26).

Because MMP-1 is detectable in urine samples from patients with bladder cancer (12), its inhibitor, TIMP-1, might also be present. In this study, MMP-1 and TIMP-1 were measured in voided urine samples from patients with bladder cancer, and their relationships with established prognostic factors, such as tumor stage, grade, size, multifocality, and recurrence rate, as well as tumor progression and disease-specific survival, were investigated. The ratio of urinary MMP-1:TIMP-1 was also calculated, as the significance of this relationship has not been reported previously. Evidence is presented in support of roles for urinary MMP-1 and TIMP-1 as potential prognostic markers for patients with bladder cancer.

**MATERIALS AND METHODS**

**Patients.** Freshly voided urine samples were collected prospectively from patients with suspected carcinoma of the bladder attending a hematuria clinic or from patients with a known or previously treated bladder tumor before check cystoscopy, transurethral resection of bladder tumor, or cystectomy. Urine samples were obtained from 131 patients with bladder cancer [106 males and 25 females; mean age: 70 ± 12 years (range: 35–90 years)], 5 patients with carcinoma of the prostate [mean age: 81 ± 4 years (range: 78–87 years)], 33 patients with benign urological conditions [29 males and 4 females; benign prostatic hyperplasia: n = 19, cystitis: n = 14, mean age: 68 ± 11 years (range: 34–80 years)], and 36 healthy volunteers [16 males and 20 females; mean age: 39 ± 14 years (range: 21–78 years)] with no previous history of any urological disorder.

Bladder tumors were staged using the Tumor-Node-Metastasis classification (UICC 1997; Ref. 27). Seven patients had primary carcinoma *in situ*, 74 had Ta tumors, 29 had T1 tumors, and 21 patients had muscle-invasive (T2-T4) tumors. Tumors were graded using the WHO system (28). There were 46 G1, 41 G2, and 37 G3 tumors. Complete clinical data were available on 100 patients (5 *cis*, 63 Ta, 21 T1, and 11 T2-T4; 37 G1, 37 G2, and 21 G3). The number of tumors within the bladder at the time the voided urine sample was obtained was recorded, and for patients with Ta/T1 tumors, the presence or absence of tumor recurrence at subsequent follow-up cystoscopy was noted. Maximum tumor size was recorded for all patients. The median duration of follow-up was 24 months (range: 4–39 months). Stage progression for patients with Ta/T1 tumors or development of metastasis for patients with muscle-invasive disease was also noted. The presence of metastases was determined by computerized tomography scanning, bone scintigraphy, or chest radiography.

**Preparation of Urine Samples.** Immediately after collection, urine samples were centrifuged at 1200 × g for 5 min, and the supernatant was stored at −20°C until analyzed. Before analysis, samples were thawed, gently mixed, and concentrated 8-fold using Centriprep-10 and Centricon-10 concentrators (Amicon, Beverly, MA). The final results were adjusted for the concentration factor of each sample.

**ELISA.** Concentrations of both urinary TIMP-1 and MMP-1 were determined using separate two-step sandwich immunoassays. Urinary TIMP-1 was measured using a commercially available ELISA kit [Biotrak TIMP-1 (human) ELISA system (RPN 2611); Amersham Life Science, Little Chalfont, Buckinghamshire, United Kingdom]. The assay measures both free TIMP-1 and TIMP-1 complexed with MMPs. The assay is...
Urinary MMP-1 and TIMP-1 in Bladder Cancer

Specific for human TIMP-1 and does not cross-react with other members of the TIMP family or with TIMP-1 from other species. The sensitivity of the assay is stated as 1.25 ng/ml. Urinary MMP-1 was measured using the method described by Clark et al. (29). The assay measures total MMP-1 (both pro- and active forms), as well as MMP-1 complexed with TIMPs. For MMP-1, the primary antibody used was a mouse monoclonal antihuman antibody designated RRU-CL1 (Rheumatology Research Unit, University of Newcastle upon Tyne, United Kingdom). The secondary antibody was a biotinylated polyclonal anti-MMP-1 antibody designated β-anti-CL1 (Rheumatology Research Unit).

Statistical Analysis. Statistical analyses were performed using Graph Pad Prism, version 2.01 (Graph Pad Software, Inc.). All tests of significance were two sided. Data were presented as medians with 95% CI, and distributions were compared using nonparametric analyses. Proportions were compared using contingency tables, and correlations were determined using Spearman’s rank test. Follow-up time and time to recurrence were calculated from the date of surgery to the date of the relevant event. Progression-free survival was defined as the interval between the date of surgery and the date of diagnosis of disease progression. Disease-specific survival was calculated as the interval between the date of surgery and the date of death from bladder cancer. Assessments of recurrence-free, progression-free, and disease-specific survival rates were performed by Log-rank analysis. P < 0.05 was considered significant.

RESULTS

Urinary MMP-1 and TIMP-1 in Patients with Bladder Cancer Versus Other Patient Groups/Normal Volunteers. MMP-1 was detected in urine samples from 21 of 131 (16%) patients with bladder cancer but was undetectable in samples from patients with other urological disorders and normal volunteers (P < 0.0001, Fisher’s exact test). In patients with detectable MMP-1, the median urinary MMP-1 concentration was 0.26 ng/ml (CI: 0.093–0.5622 ng/ml). In contrast, TIMP-1 was detectable in the majority (92%) of urine samples analyzed. There was no significant difference in median urinary TIMP-1 concentrations between patients with bladder cancer [1.816 ng/ml (CI: 1.041–3.173 ng/ml)], patients with prostate cancer [3.787 ng/ml (CI: 2.71–25.23 ng/ml)], or patients with benign urological disorders [1.79 ng/ml (CI: 0.876–3.42 ng/ml)]. However, as shown in Fig. 1, all patient groups had significantly higher urinary TIMP-1 concentrations than normal volunteers [0.685 ng/ml (CI: 0.399–1.48 ng/ml); P = 0.02, Kruskal-Wallis].

Tumor Stage. For patients with muscle-invasive (T2-T4) tumors, urinary MMP-1 was detectable in 7 of 21 (33%) samples compared with 14 of 110 (13%) samples from patients with cis/Ta/T1 tumors (P = 0.04, Fisher’s exact test). However, no significant difference in urinary MMP-1 concentration was found between patients with T2-T4 tumors [0.265 ng/ml (CI: 0.093 to 0.624 ng/ml)] and cis/Ta/T1 tumors [0.08 ng/ml (CI: 0.005–0.153 ng/ml); P = 0.15, Mann-Whitney U test]. Concentrations of urinary TIMP-1 were significantly higher in samples from patients with T2-T4 tumors than patients with cis/Ta/T1 tumors [4.92 ng/ml (CI: 2.012–7.81 ng/ml) versus 1.61 ng/ml (CI: 0.803–2.823 ng/ml), P = 0.037, Fig. 2].

Tumor Grade. Urinary MMP-1 was detectable in a higher percentage of samples from patients with poorly differentiated (G3) tumors [12 of 37 (32%)] compared with tumors of low (G1) grade [5 of 46 (11%)] or intermediate (G2) grade [4 of 41 (10%), P = 0.0074, χ²]. In addition, patients with G3 tumors had significantly higher concentrations of urinary MMP-1 [0.166 ng/ml (CI: −0.04 to 0.371 ng/ml)] than patients with either G1 [0.109 ng/ml (CI: −0.0507 to 0.276 ng/ml)] or G2 [0.078 ng/ml (CI: −0.003 to 0.161 ng/ml)] tumors (P = 0.0185, Kruskal-Wallis). No significant variation in urinary TIMP-1 concentrations with tumor grade was found [G1 (1.43 ng/ml; CI: 0.677–3.375 ng/ml) versus G2 (2.51 ng/ml; CI: 1.102–5.779 ng/ml) versus G3 (2.8 ng/ml; CI: 0.846–5.531 ng/ml); P = 0.39].

Ratio of Urinary MMP-1:TIMP-1. Patients with muscle-invasive tumors with detectable levels of urinary MMP-1 had a significantly lower urinary MMP-1:TIMP-1 ratio than...
patients with Ta/T1 tumors \[0.029 \text{ (CI: 0.002–0.1844) versus 0.0017 \text{ (CI: 0.0011–0.0578); } P = 0.039, \text{ Mann-Whitney U test}}.\]

Similarly, patients with high-grade tumors had a significantly lower urinary MMP-1:TIMP-1 ratio than patients with tumors of low or intermediate grade \[G_1 \text{ (0.143; CI: 0.0496–0.4624) versus } G_2 \text{ (0.0372; CI: 0.0226–0.7724) versus } G_3 \text{ (0.0136; CI: 0.0016–0.0286); } P = 0.0415, \text{ Kruskal-Wallis}}.\] There was no association found between the urinary MMP-1:TIMP-1 ratio and tumor size, multifocality, recurrence, progression, or survival.

**Tumor Burden: Number of Tumors, Tumor Size.**

Thirty-eight of 95 patients (40%) had multifocal tumors (31 Ta, 4 T1, and 3 T2), whereas 57 (60%) had solitary tumors. There was no correlation between the number of tumors and urinary MMP-1 concentration (Spearman’s rank correlation coefficient, \[r = 0.006, P = 0.95\]), nor was there a correlation between tumor multifocality and urinary TIMP-1 levels \(r = 0.085, P = 0.41\). Tumors ranged from 0.2 cm to 10 cm in diameter [median: 1 cm (CI: 0.74–2 cm)]. No correlation was found between urinary MMP-1 and tumor size \[r = 0.18, P = 0.088\], but higher urinary TIMP-1 levels correlated strongly with tumors of increasing diameter \(r = 0.39, P = 0.0002\); Fig. 3).

**Recurrence.** Of 100 patients with available follow-up data, 89 had cis/Ta/T1 tumors, whereas 11 had muscle-invasive disease. Forty-three patients (48%) with cis/Ta/T1 tumors had a recurrence during the period of follow-up, and of these, 24 (28%) had a positive 3-month check cystoscopy. There was no association between urinary MMP-1 or TIMP-1 concentrations and tumor recurrence at the time of the 3-month check cystoscopy, nor was any association found between urinary MMP-1 or TIMP-1 concentrations and overall recurrence-free survival or tumor recurrence rate.

**Progression-free and Disease-specific Survival.** During follow-up, 12 patients (12%) had tumors that underwent disease progression. Five patients with muscle-invasive tumors developed metastatic disease, whereas 7 patients with Ta/T1 tumors progressed (Ta \(\rightarrow\) T1, Ta \(\rightarrow\) T1 + cis, Ta \(\rightarrow\) upper tract T3 tumor, and 4 T1 \(\rightarrow\) T2). Ten patients died, 3 from causes other than bladder cancer, 2 from cardiovascular disease, and 1 from bronchopneumonia. The 7 patients that died of bladder cancer had high-grade muscle-invasive tumors at presentation.

Patients with detectable concentrations of urinary MMP-1 had higher rates of disease progression and poorer disease-specific survival compared with patients in whom urinary MMP-1 was undetectable (Log-rank test, \(P = 0.04\) and \(P = 0.02\), respectively; Figs. 4 and 5). Those patients with tumors that progressed had significantly higher urinary TIMP-1 concentrations than patients with tumors that did not progress \[6.143 \text{ ng/ml (CI: 0.85–32.27 ng/ml) versus 1.48 ng/ml (CI: 0.807–2.801 ng/ml), } P = 0.044, \text{ Mann-Whitney U test}}.\] Patients with urinary TIMP-1 levels greater than or equal to the median (1.8 ng/ml) had significantly lower rates of progression-free survival than patients with urinary TIMP-1 levels <1.8 ng/ml (Log-rank test, \(P = 0.04\); Fig. 6). Urinary TIMP-1 levels were not associated with disease-specific survival \(P = 0.53\).

**DISCUSSION**

Where previously it was thought that tumor progression resulted from overexpression of MMPs in conjunction with down-regulation of the TIMPs (14), evidence is now accumulating that this represents an oversimplification of this complex process. We have noted that patients with bladder tumors of
advanced stage/grade have significantly lower urinary MMP-1:TIMP-1 ratios than patients with tumors of low stage/grade, indicating a significant excess of TIMP-1 over MMP-1 in these individuals. The presence of detectable urinary MMP-1 is very specific for bladder cancer and indicates that the patient is more likely to have an aggressive tumor of advanced stage or grade, which complements the findings of our previous study (12). Also, patients with detectable urinary MMP-1 had higher rates of disease progression and poorer disease-specific survival than patients with undetectable urinary MMP-1. One possible explanation for these observations is that patients with muscle-invasive bladder tumors remain at high risk, both of progression to metastatic disease and of death, often despite radical treatment. Ultimately, the presence of detectable levels of urinary MMP-1 may identify a subset of patients at high risk of disease progression, who would benefit from early and aggressive adjuvant therapy after radical cystectomy or radiotherapy for muscle-invasive disease.

In contrast to MMP-1, TIMP-1 was detectable in the majority of urine samples analyzed from patients with bladder tumors. TIMP-1 is a ubiquitous protein detectable in the majority of human bodily fluids (15). The only previous report of urinary TIMP-1 in bladder cancer found that it was undetectable in 16 healthy volunteers but detectable in 18 of 33 (55%) of patients with bladder tumors (30). No relationship was found between urinary TIMP-1 and stage or grade. Interestingly, the ratio between urinary MMP-9:TIMP-1 in patients with bladder cancer in that study remained unchanged, particularly in patients with Ta/T1 tumors (30). In contrast, we detected urinary TIMP-1 in samples from healthy volunteers but without MSSs resulting in up-regulation in all individuals, which may be additionally up-regulated under pathological conditions. Possible explanations for the discrepancies between our findings and those of the previous study include differences in sample processing and the use of a different ELISA method.

Cytokines, such as interleukin-1β and interleukin-6, can stimulate the expression of TIMP-1 (31, 32), which may account for the observation that patients with benign inflammatory lower urinary tract disorders show similar levels of urinary TIMP-1 as patients with bladder or prostate cancer. The majority of urinary TIMP-1 is likely to be actively secreted into the urine from adjacent urothelium or tumor tissue, although a certain amount may be derived from circulating serum TIMP-1, as a direct consequence of hematuria, or may be filtered by the kidney. Additional studies measuring urinary TIMP-1 levels in patients with nonurological malignancies or inflammatory conditions, such as rheumatoid arthritis, would give some indication of what proportion of urinary TIMP-1 is derived from that present in the circulation.

In contrast with previous in vitro studies showing an inverse relationship between TIMP-1 levels and tumor progression (33, 34), we have noted that increased urinary TIMP-1 levels are associated with tumors of higher stage and larger diameter, as well as being associated with tumor progression. It is now well recognized that TIMP-1 is a multifunctional protein with a variety of activities that are independent of MMP inhibition (35). It has been shown that TIMP-1 can stimulate growth in a wide range of cell lines, including fibroblasts, epithelial cells, and K562 cells (36). TIMP-1 is also known as erythroid potentiating activity, a growth factor for early erythrocyte precursors (37). Erythroid potentiating activity mediates autocrine growth stimulation by binding to a Mₘ 38,000 cell surface receptor (38), which is now known to be identical to the TIMP-1 receptor on K562 cells (36). It has recently been shown that TIMP-1 can increase the proliferative rate of a highly tumorigenic breast cancer clonal cell line (BC-61) in a dose-dependent manner, mediated in this instance via a Mₘ 80,000 transmembrane receptor protein, suggesting cell type-specific TIMP-1 receptor expression (39). Interestingly, TIMP-1 stimulation of BC-61 cells in this study resulted in the induction of tyrosine kinase activity analogous to that resulting from growth factor stimulation (39). TIMP-1-mediated growth of transitional carcinoma cells, however, has not yet been described.

Maximal growth of TIMP-1-stimulated cells is seen at concentrations between 10 and 200 ng/ml (15), whereas in vitro inhibition of proteolytic degradation of extracellular matrix by MMPs requires TIMP-1 levels >1 μg/ml (40). Because urinary TIMP-1 concentrations in patients with bladder tumors were in the range 0–137.5 ng/ml, it is possible that TIMP-1 may be acting to promote tumor cell growth and progression rather than inhibiting matrix degradation. Alternatively, higher urinary TIMP-1 levels may represent a cellular response to the presence of protease in a protective attempt to limit aggressive tumor growth. Invasive carcinoma cells often induce an inflammatory response, and the release of cytokines from recruited macrophages resulting in up-regulation of TIMP-1 expression (41, 42) is another possible explanation for our observations. Currently, this issue remains unresolved, although it is clear that in vitro models do not accurately reflect the complex interactions between MMPs and TIMPs in the patient with cancer.

Our results are consistent with the findings of others, indicating that increased levels of TIMP-1 are associated with adverse outcomes in certain human malignancies (22, 23). Up-regulation of TIMP-1 expression by the primary tumor may represent an important mechanism for reimplantation of circulating tumor cells to secondary sites to facilitate inhibition of MMP-mediated degradation of extracellular matrix during the
formation of new stroma (20). From a number of clinical studies in different human cancers, TIMP-1 has emerged as a potentially new marker of progression to metastasis and decreased survival. Additional studies of its prognostic significance in patients with TCC of the bladder are warranted.

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