Prognostic Impact of Proteolytic Factors (Urokinase-Type Plasminogen Activator, Plasminogen Activator Inhibitor 1, and Cathepsins B, D, and L) in Primary Breast Cancer Reflects Effects of Adjuvant Systemic Therapy

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ABSTRACT

Purpose: Prognostic and predictive impact of five proteolytic factors associated with tumor invasion and metastasis in primary breast cancer were evaluated after long-term follow-up.

Experimental Design: Antigen levels of urokinase-type plasminogen activator, plasminogen activator inhibitor-1 (PAI-1), Cathepsins B, D, and L were determined using immunochemical assays in primary tumor tissue of 276 patients.

Results: During follow-up (median 109 months), 119 (43%) patients relapsed, and 117 (42%) died. In the whole collective, lymph node status (P < 0.001; RR 3.8), Cathepsin L (P < 0.001; RR 2.6), and PAI-1 (P = 0.027; RR 1.7) were the only independent significant factors in multivariate analysis for disease-free survival (DFS). For overall survival (OS), lymph node status (P < 0.001; RR 2.9), Cathepsin L (P = 0.017; RR 1.9), PAI-1 (P = 0.01; RR 1.9), and grading (P = 0.026; RR 1.7) were significant. In the node-negative subgroup, PAI-1 was the only significant factor for DFS (P = 0.004; RR 3.7) and the strongest factor (P = 0.004; RR 3.7) for OS next to grading (P = 0.017; RR 3.1). In node-positive patients, Cathepsin L was the only significant factor for both DFS (P < 0.001; RR 3.2) and OS (P = 0.003; RR 2.5). For all proteolytic factors but Cathepsin L, the univariate prognostic impact on DFS was substantial in patients without adjuvant systemic therapy but was diminished if adjuvant therapy had been administered. Cathepsin L maintained its strong prognostic impact on DFS even in patients with adjuvant endocrine therapy (P = 0.01; RR 2.8).

Conclusions: The observed effect of adjuvant systemic therapy on their prognostic strength suggests that the assessed proteolytic factors supply predictive information on therapy response.

INTRODUCTION

Invasion of a malignant tumor into the surrounding extracellular matrix and the basement membrane is a prerequisite for subsequent systemic spread and metastasis. In breast cancer, distant metastasis is of great clinical relevance because patients presenting with distant disease recurrence cannot be cured by currently available therapies. Tumor-associated proteolytic factors enable tumor cells to disintegrate the stroma in their immediate vicinity, intravasate into lymphatic or blood vessels, and then spread systemically. Among the key players in the proteolytic cascade leading to tumor invasion and metastasis are factors of the plasminogen activation system, such as the serine protease uPA and its type-1 inhibitor PAI-1, or the aspartyl protease Cathepsin D and the cysteine proteases Cathepsins B and L.

In the late 1980s, the first reports on the clinical relevance of proteolytic factors in human cancer were published. In 1988, Duffy et al. (4) reported that in breast cancer, an increased enzymatic activity level of uPA in the tumor tissue is associated with poor prognosis. In 1989, two groups independently found that an increased tumor tissue content of Cathepsin D is also linked to shorter patient survival in breast cancer (5, 6). Since then, numerous reports have discussed the clinical impact of proteases in primary breast cancer. In the early 1990s, our group was the first to report that not only the protease uPA but also its inhibitor PAI-1 display significant prognostic strength in node-positive and node-negative breast cancer (7, 8). Convincing confirmatory data by many international research groups have since been put forward associating high levels of uPA and/or PAI-1 with shorter DFS and OS in primary breast cancer (9–11).
In addition, a prospective randomized multicenter therapy trial (“Chemo N_0”) validated the independent and significant prognostic impact of uPA and PAI-1 in node-negative breast cancer patients (18).

Next to uPA and PAI-1, the aspartyl protease Cathepsin D is the proteolytic factor that has most frequently been implicated as a prognostic factor in primary breast cancer. A significant impact of high Cathepsin D antigen levels in the primary tumor on patient prognosis has emerged in the literature over the last decade (5, 6, 19–22). First data on the prognostic impact of the cysteine proteases Cathepsins B and L in human breast cancer were put forward by our group in 1995, when we reported that high levels of both proteases were associated with poor patient survival (23). Confirming this initial finding, Foekens et al. (24) showed in a large collective of 1500 breast cancer patients that high levels of both Cathepsin B and L in primary tumor cytosols were correlated with poor prognosis.

Although efficient tumor-associated proteolysis requires complex interactions between various extra and intracellular proteases and their inhibitors (25), up to now, a relatively few authors have looked at the prognostic impact of factors from different proteolytic systems within the same patient collective in breast cancer or other solid tumors (15, 26–28). Even more important, data on the predictive value of proteolytic factors, such as uPA, PAI-1, or Cathepsins B, D, and L, are still scarce. We have therefore evaluated the influence of adjuvant systemic therapy on the prognostic impact of these five different proteolytic factors within the same collective of primary breast cancer patients after a long-term median follow-up of >9 years.

**MATERIALS AND METHODS**

Patients. In a collective of 276 patients with primary breast cancer, the clinical relevance of uPA and PAI-1, as well as Cathepsins B, D, and L, was evaluated. Informed consent for determination of tumor-biological factors was obtained before primary surgery. Patients either had a modified radical mastectomy (n = 214) or underwent breast-conserving surgery with subsequent irradiation of the breast (n = 62) at the Department of Obstetrics and Gynecology of the Technische Universität München, Germany, between 1987 and 1991. Treatment decisions were based solely on consensus recommendations at the time of recruitment. Of the total 276 patients, information about adjuvant systemic therapy was missing from 1 patient; 52 patients received adjuvant chemotherapy, 95 patients received adjuvant endocrine therapy, 9 patients received combined chemo-endocrine therapy, and 119 patients did not receive any adjuvant systemic therapy after primary surgery. Of the 130 node-negative patients, 110 (85%) did not receive any adjuvant endocrine therapy, and 119 patients did not receive any adjuvant endocrine therapy, 9 patients received combined chemo-endocrine therapy, and 117 patients (42%) died.

**Table 1 Patient collective (n = 276)**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Patientsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node status</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>130 (47%)</td>
</tr>
<tr>
<td>Positive</td>
<td>146 (53%)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>89 (32%)</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>186 (68%)</td>
</tr>
<tr>
<td>Grading</td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>172 (63%)</td>
</tr>
<tr>
<td>3/4</td>
<td>103 (37%)</td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>59 (21%)</td>
</tr>
<tr>
<td>Positive</td>
<td>217 (79%)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
</tr>
<tr>
<td>Pre/perimenopausal</td>
<td>105 (38%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>171 (62%)</td>
</tr>
</tbody>
</table>

a For some patients, not all information was available.

**Laboratory Assays.** Tissue extraction for determination of proteolytic factors was performed as follows: deep frozen tumor tissue was pulverized, and the resulting powder was dispersed in buffer [1 ml of Tris-buffered saline, 0.02 M Tris-HCl, and 0.125 M NaCl (pH 8.5)] containing 0.1% (volume for volume) of nonionic detergent Triton X-100. Cytosol fractions were prepared accordingly but without detergent. uPA and PAI-1 antigen have been measured in detergent extracts by ELISA (uPA; Imubind # 894, PAI-1; Imubind # 821; American Diagnostica, Greenwich, CT) since 1987 in a prospective fashion in all breast cancer patients who had their primary surgery performed at our institution (8). Antigen levels ranged for uPA from 0.07 to 15.17 ng/mg protein (median 2.17) and for PAI-1 from 0.06 to 167.29 ng/mg protein (median 7.69). Antigen levels of Cathepsins B, D, and L were determined in breast cancer cytosol fractions obtained from the same tissue specimens. Cathepsin D was measured by a radiometric immunoassay (ELSA-CATH-D, CIS Bioindustries, Gif-sur-Yvette, France); Cathepsins B and L were measured by ELISA (Diagnostic International, Karlsruhe, Germany; Ref. 23). Levels ranged for Cathepsin B from 46 to 5934 ng/mg protein (median 855), for Cathepsin D from 5.22 to 217.93 pmol/mg protein (median 43.39), and for Cathepsin L from 51 to 4619 ng/mg protein (median 429.5).

Steroid hormone receptor status (ER and progesterone receptor) was determined and classified as “positive” or “negative” as described (29).

**Statistical Analysis.** Correlations between continuous variables were analyzed using the Spearman rank test. Associations between continuous and/or categorical variables were analyzed using the Mann-Whitney U test. Continuous variables were coded as binary variables by using Log-rank statistics to determine optimal cutoffs discriminating low- and high-risk patients (8, 30). For univariate analysis of DFS and OS, Kaplan-Meier curves (31) were plotted and then compared using Log-rank statistics. Multivariate analyses were performed in a stepwise forward fashion by applying the Cox proportional hazards model (32) using the SPSS software package (SPSS, Inc., Chicago, IL) and by CART analysis (33). The cutoffs determining binary variable coding were maintained during CART analysis. All test decisions were performed at a significance level of a = 0.05. Estimated values are provided with a 95% confidence interval.

To test for a possible time variation of the prognostic
Correlations and Associations between Proteolytic Factors and Established Factors

In general, similar to the correlations among proteolytic factors, no strong correlations were observed between proteolytic and established factors (Table 2b).

Univariate and Multivariate Survival Analysis. In univariate analysis of the whole collective, uPA, PAI-1, and Cathepsin D and L were statistically significant for both DFS and OS. Cathepsin B was not significant, neither for DFS nor OS. Of the traditional prognostic factors, lymph node status, grading, and hormone receptor-status was significant only for OS. Menopausal status failed univariate statistical significance for both DFS and OS. In multivariate analysis (Cox model) for DFS, lymph node status (P < 0.001; RR 3.8), Cathepsin L (P < 0.001; RR 2.6), and PAI-1 (P = 0.027; RR 1.7) were significant factors in all patients; Cathepsin D and uPA were not. For OS, lymph node status (P < 0.001; RR 2.9), Cathepsin L (P = 0.017; RR 1.9), and PAI-1 (P < 0.01; RR 1.9) were again statistically significant next to grading (P = 0.026; RR 1.7).

Multivariate Cox analysis in node-negative patients (n = 130) showed that PAI-1 was the only significant factor for DFS (P = 0.004; RR 3.7) and the strongest significant factor (P = 0.004; RR 3.7) for OS next to grading (P = 0.017; RR 3.1). In node-positive patients (n = 146), Cathepsin L was the only significant factor both for DFS (P < 0.001; RR 3.2) and OS (P = 0.003; RR 2.5). All of the other factors failed statistical significance in this subgroup. The qualitative weighting of the factors in our subgroup analyses for DFS using the Cox model was consistent with the picture obtained by another multivariate model, CART analysis. In the CART model, lymph node status was the strongest discriminator between high-risk and low-risk patients (P < 0.001). Among node-negative patients, PAI-1 was...
the strongest prognostic factor for DFS ($P < 0.001$). Node-negative breast cancer patients whose tumors had low levels of both PAI-1 and Cathepsin D had a 5-year relapse rate of 9.3% compared with 31.2% in patients with either or both factors high. Among the node-positive patients, Cathepsin L was the strongest prognostic factor ($P = 0.001$).

**Time Varying Analysis.** No significant time variation of the prognostic impact on DFS was found for either lymph node status, uPA, or for any of the cathepsins using the univariate test of Grambsch and Therneau (34). In contrast, for PAI-1, the previously described (29) time variation in its effect on DFS ($P = 0.025$ for linear time dependency) was confirmed even after prolonged time of follow-up. Modeling the univariate relative risk of PAI-1 by smoothing splines, one finds that in the first 2.5 years after surgery, its prognostic impact is higher ($RR_{\text{var}} = 3.4$) than that determined by a proportional hazards model ($RR_{\text{pha}} = 2.30$) but that it declines steadily over time. The main contribution to the relative risk associated with PAI-1 is attributed to the first 5 years of follow-up. Hence, we recalculated a multivariate survival model for DFS, including those covariates already selected in the proportional hazards model (lymph node status, Cathepsin L, and PAI-1), but also taking into account time variation for PAI-1. This multivariate model resulted in a better fit, whereas the (constant) impact of lymph node status and Cathepsin L rendered comparable results ($RR_{\text{LNMstatus}} = 3.32$, $RR_{\text{CatL}} = 2.46$). As for traditional prognostic factors, the time-dependent effect of hormone receptor status (29) was confirmed ($P < 0.001$ for logarithmic time dependency). In addition, a time-varying impact was noted for grading ($P = 0.034$ for logarithmic time dependency).

**Effect of Adjuvant Systemic Therapy on Prognostic Impact of Proteolytic Factors.** The prognostic impact of the proteolytic factors on DFS and, in particular, that of PAI-1 and Cathepsin L differed rather substantially between node-negative and node-positive patients. These patient subgroups differed substantially with regard to the frequency of adjuvant systemic therapy. We therefore looked at the influence of adjuvant systemic therapy on prognostic impact (DFS) of proteolytic factors using univariate Cox analysis (Table 3). In patients who did not receive any adjuvant systemic therapy, uPA, PAI-1, and Cathepsins D and L had a significant and Cathepsin B a borderline significant prognostic impact. In patients who received adjuvant systemic therapy, the prognostic significance disappeared for all factors except Cathepsin L, which retained a significant prognostic impact on DFS even in patients who received adjuvant hormone therapy. This impact was just as strong as in the patients who did not receive adjuvant therapy. Fig. 1 shows the Kaplan-Meier curves for DFS of the two strongest proteolytic factors, PAI-1 and Cathepsin L, in patient subgroups defined by administration of adjuvant systemic therapy.

After merging the two therapy groups (chemotherapy and endocrine therapy) to increase the patient number in the “treatment category,” only Cathepsin L ($P = 0.001$; $RR = 2.7$), but none of the other proteolytic factors, was significant in univariate Cox analysis for DFS in patients who received adjuvant systemic therapy.

**DISCUSSION**

To date, once breast cancer has recurred after primary therapy, it cannot be cured by currently available therapy regimens. Thus, identification of patients at high risk for recurrence after primary surgery is a prerequisite for individualizing concepts for adjuvant systemic therapy in primary breast cancer. Proteolytic factors are essential for a tumor’s invasive and metastatic capacity and have thus been implicated as clinically relevant prognostic factors in a variety of solid tumors, including breast cancer. To assess and rank their clinical usefulness, we have studied the prognostic and predictive impact of five different proteolytic factors, uPA, PAI-1, and Cathepsins D, B, and L, in a single collective of primary breast cancer patients after long-term follow-up of >9 years.

All five proteolytic factors were determined in primary tumor tissue extracts using immunochemical assays. For uPA and PAI-1 (36), as well as for the cathepsins (1, 2, 37), the assay procedures are standardized, and international quality control data are available. In the present investigation, clinically validated cutoffs for uPA and PAI-1 were used (17, 18), whereas cutoff values for the cathepsins were reevaluated. The cutoffs for Cathepsins D and L have remained remarkably stable after prolonged follow-up, whereas no optimized cutoff was found for Cathepsin B. For Cathepsin D, our optimized cutoff corresponded well to that found by other researchers using the same immunochemical assay (17, 22, 38). For Cathepsin L, we confirmed our previously optimized cutoff of 360 ng/mg protein (26). The observed significant correlations between tumor tissue levels of the different proteolytic factors are consistent with the known complex interactions between various extra and intracellular proteases and their inhibitors (25).

After a long-term follow-up, the tumor-associated proteolytic factors uPA and PAI-1, as well as Cathepsins D and L, still provided significant prognostic information in primary breast cancer patients, whereas Cathepsin B did not retain its previously reported prognostic impact on DFS (23, 24, 38). In our

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>No adjuvant therapy ($n = 119$)</th>
<th>Adjuvant chemotherapy ($n = 52$)</th>
<th>Adjuvant hormone therapy ($n = 95$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>uPA</td>
<td>$P = 0.008$</td>
<td>$RR_{\text{uPA}} = 2.4 (1.3-4.7)$</td>
<td>$P = 0.060$</td>
</tr>
<tr>
<td>PAI-1</td>
<td>$P &lt; 0.001$</td>
<td>$RR_{\text{PAI-1}} = 4.3 (2.1-8.4)$</td>
<td>$P = \text{n.s.}$</td>
</tr>
<tr>
<td>Cathepsin B</td>
<td>$P = 0.085$</td>
<td>$RR_{\text{CatB}} = 2.7 (0.9-8.4)$</td>
<td>$P = \text{n.s.}$</td>
</tr>
<tr>
<td>Cathepsin D</td>
<td>$P = 0.001$</td>
<td>$RR_{\text{CatD}} = 4.0 (1.8-9.2)$</td>
<td>$P = \text{n.s.}$</td>
</tr>
<tr>
<td>Cathepsin L</td>
<td>$P = 0.030$</td>
<td>$RR_{\text{CatL}} = 3.0 (1.1-8.0)$</td>
<td>$P = 0.068$</td>
</tr>
</tbody>
</table>

**n.s.** = not significant.
whole patient collective, PAI-1 outperformed uPA and Cathepsin D in multivariate analysis for DFS in primary breast cancer, although all three factors were significant in univariate analysis. This finding is in concordance with other retrospective studies (9, 10). The strong prognostic impact of the individual factors is enhanced by a combination of factors, thus allowing clinically relevant risk group assessment, in particular with regard to identification of low-risk node-negative patients. Our findings after long-term follow-up are in agreement with data by Kute et al. (15) that the combination of PAI-1 and Cathepsin D is well suited for identifying node-negative breast cancer patients at low risk of recurrence. In a cohort of node-negative breast cancer patients, we found that the combination of PAI-1 and Cathepsin D is superior to the individual factors in predicting DFS.

Fig. 1  
A, effect of adjuvant systemic therapy on prognostic impact of PAI-1 on DFS in primary breast cancer. With regard to DFS, events are relapses (all sites). 
B, effect of adjuvant systemic therapy on prognostic impact of Cathepsin L on DFS in primary breast cancer. With regard to DFS, events are relapses (all sites).
cancer patients without any adjuvant systemic therapy, we had demonstrated previously that with regard to selection of low-risk patients, another combination of proteolytic factors, i.e., uPA and PAI-1, is superior to either factor taken alone as well as to established prognostic or other tumor-biological factors (30). The clinical relevance of this combination, uPA and PAI-1, for risk group stratification in node-negative breast cancer has already been validated by the German “Chemo N₀” trial in a prospective randomized multicenter fashion (18).

In our subgroup of node-negative breast cancer patients, PAI-1 maintained its role as the strongest prognostic factor for DFS, whereas in node-positive patients, Cathepsin L was the strongest. Interestingly, these nodal subgroups also differed substantially with regard to the frequency of adjuvant systemic therapy. After general recommendations at the time of recruitment, the majority (85%) of our node-negative patients did not receive any adjuvant systemic therapy, whereas in node-positive patients, only 6% remained untreated after primary locoregional therapy. For all of the proteolytic factors assessed, the univariate prognostic impact on DFS was substantial in patients without adjuvant systemic therapy (Table 3). This underlines the strong association of the proteolytic factors uPA, PAI-1, and Cathepsins D, B, and L with an aggressive tumor phenotype leading to invasion and metastasis (2, 3). However, except for Cathepsin L, the prognostic strength of the proteolytic factors is diminished in patients who received adjuvant systemic therapy. This diminished univariate significance in patients with adjuvant systemic therapy might be attributed to their node-negative status. However, in a different patient collective in which about half of the node-negative patients did not receive any adjuvant systemic therapy, uPA and PAI-1 had a strong, significant prognostic impact that was similar for node-negative and node-positive patients (39). Hence, at least with regard to uPA and PAI-1, the apparent dichotomy in prognostic impact of proteolytic factors with respect to nodal status is best explained by the effect of adjuvant systemic therapy. This explanation is also consistent with the well-established evidence that the relative risk reduction achieved by adjuvant therapy is independent of nodal status (40, 41). In addition, there was no significant association between tissue levels of proteolytic factors and nodal involvement in our study, except for Cathepsin B.

For uPA and PAI-1, the apparent benefit of adjuvant systemic therapy in our retrospective study agrees with data from the prospective randomized multicenter “Chemo N₀” therapy trial demonstrating benefits from adjuvant CMF chemotherapy in node-negative patients with high uPA and/or PAI-1 levels in their primary tumors (18). A European follow-up study will now compare different chemotherapy regimens for these high-risk patients. In another prospective study, no correlation was found between PAI-1 levels in core biopsies of the primary tumor and local response to anthracycline containing neo-adjuvant chemotherapy (42). In that study, PAI-1 tumor levels were not altered by chemotherapy; however, the authors did not present any data on correlation of PAI-1 levels with patient outcome. Retrospective data from metastatic breast cancer, that high PAI-1 in the primary tumor is associated with poor response to palliative endocrine therapy (43, 44), cannot be directly compared with data derived from the adjuvant setting and additionally underlines the need for prospective studies.

A beneficial effect of adjuvant tamoxifen in patients with elevated Cathepsin D tumor levels has also been observed in other retrospective analyses (20, 45). It also agrees well with the fact that estrogens do induce Cathepsin D overexpression in ER-positive cell lines (1).

Our data support the conclusion that high-risk primary breast cancer patients as identified by high levels of uPA, PAI-1, and Cathepsins B and D do benefit from adjuvant systemic therapy with regard to DFS. Whether this benefit extends to OS needs to be evaluated prospectively considering that systemic treatment after first relapse is quite heterogeneous, thus hampering retrospective analysis.

Concerning Cathepsin L, our data and the above discussion indicate that the strong prognostic impact of Cathepsin L in node-positive patients is in fact attributable to its particular prognostic strength in patients treated by adjuvant systemic therapy. This finding suggests that high-risk patients as identified by Cathepsin L do not necessarily benefit from adjuvant systemic treatment. This statement holds in particular for the patient group treated by tamoxifen.

Different tumor-biological properties of the proteolytic factors studied here may well be responsible for their different prognostic and predictive impact, although in vitro data do not necessarily reflect the in vivo situation. Whereas lysosomal cathepsins are predominantly involved in degradation of the extracellular matrix (2), proteolytic factors uPA and PAI-1 are also associated with tumor cell migration or angiogenesis (3). Yet, how these biological differences translate into differential therapy response has not been studied up to now and is an interesting subject for additional experimental research.

In conclusion, the present study clearly demonstrates a substantial influence of adjuvant systemic therapy on the prognostic impact of proteolytic factors. Thus, the apparent dichotomy in their prognostic strength within node-negative or node-positive patient subgroups may merely reflect effects of adjuvant systemic therapy and hence indicate a predictive potential for therapy response. Consequently, the influence of adjuvant systemic therapy needs to be accounted for in any prognostic factor study to put the results into a clinically valid perspective. Prospective studies addressing the predictive impact of proteolytic factors in primary breast cancer are still scarce. However, in view of the convincing data on significant and clinically relevant risk group selection based on proteolytic factors, such as uPA, PAI-1, or Cathepsin D or L, such prospective data are urgently needed to individualize adjuvant therapy accordingly. The evidence in this paper suggests that there could be a group of patients that are not at all, or only temporarily, benefiting from standard adjuvant therapy regimens. These patients would either be candidates for “more aggressive” chemo or endocrine regimens or for therapies specifically targeted toward the invasive phenotype of their tumor (3).

REFERENCES


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