Emmanuel van der Schueren Lecture

E1. Challenging tumour aggressiveness – Individualising patient management

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Breast cancer therapy is currently undergoing a major challenge: Effective early detection due to more widespread screening efforts worldwide has resulted in an increasing percentage of small early stage breast cancers at initial diagnosis. The majority of these early cancers will be cured by loco-regional therapy and thus do not require any aggressive adjuvant (chemo-) therapy. In the age of molecular medicine, established clinico-pathological factors are not sufficient to reliably characterise tumour aggressiveness and estimate an individual patient's risk for recurrence. Gene or protein profiling of the primary tumour constitute promising options for gaining clinically meaningful prognostic and predictive information.

The plasminogen activator (PA) system comprises among others the serine protease urokinase-type plasminogen activator u-PA, its cell surface receptor (u-PAR), as well as its type-1 inhibitor PAI-1. This complex system is not only able to catalyse plasminogen into plasmin on the cell surface, leading to degradation of extracellular proteins, but also has multiple interactions between its members as well as with proteins of the extracellular matrix, such as vitronectin and its integrin receptor. Well balanced production and activation of uPA/PAI-1 system components lead to changes in cell adhesion, degradation of the extracellular matrix and consequent stimulation of proliferation, angiogenesis, and tumour cell invasion and metastasis in a variety of solid tumours. [1] Expression of uPA and PAI-1 is higher in tumours than in the surrounding tissue, which thus indicates their key role in tumour invasiveness and metastasis.

With regard to reliable assessment of tumour aggressiveness, uPA and PAI-1 are the only biomarkers whose clinical efficacy has been validated at the highest level of evidence by the prospective clinical Chemo N0 trial [2] and the EORTC Receptor and Biomarker Group (EORTC RBG) pooled analysis comprising more than 8000 primary breast cancer patients. [3] The prognostic impact of uPA and PAI-1 is greatest when both factors are used in combination; [4] it is independent of the HER2 status [5] and currently it is most clinically useful in node-negative disease in order to avoid over-treatment of low-risk patients by adjuvant chemotherapy: Node-negative patients with low levels of uPA and PAI-1 in their primary tumour tissue have an excellent chance of surviving breast cancer with about a 95% 5-year survival even without any adjuvant systemic therapy; node-negative patients with high uPA/PAI-1 are at increased risk of relapse, comparable to patients with axillary lymph node involvement. [2] Tumour biological risk assessment using uPA/PAI-1 provides a more accurate estimate of the future course of disease than epidemiological data-based algorithms such as Adjuvant Online!, which presently rely on clinico-pathological factors. [6]

The uPA/PAI-1 test has been thoroughly quality-assured by collaborative efforts of the EORTC RBG (now: EORTC Pathobiology Group, EORTC PBG). [7] Yet, widespread international acceptance of uPA/PAI-1 has been hampered by the need for fresh frozen tissue for the enzyme-linked immunosorbent assay (ELISA) test, even though the commercially available test can be used on as little tissue as 2–3 core biopsies or a few 90 μm cryostat sections. Nevertheless, in their annually updated, evidence-based guidelines, the Breast Commission of the German AGO (Working Group for Gynaecological Oncology) has accepted uPA/PAI-1 since 2002 as risk-group classification markers for routine clinical decision-making in node-negative breast cancer, complementing established clinical–pathological factors. [8] Recently, based on the high level of evidence for these markers, uPA and PAI-1 have also been recommended for clinical routine use by the ASCO tumour marker panel. [9]

A second confirmatory node-negative breast cancer trial NNBC-3 (AGO/GBG/EORTC/PBG) using uPA/PAI-1 as stratification criteria and evaluating optimised chemotherapy in high-risk node-negative patients is currently open in Germany and France, with more than 2200 patients recruited at present (*www.gbg-crf.com/nnbc3*). In addition to NNBC-3, two other major international trials are currently ongoing, which employ molecular tests to optimise patient selection for adjuvant chemotherapy in early breast cancer: The US Trial Assigning Individualized Options for Treatment Rx (TAILORx) uses the 21-gene recurrence score, [10] which has also been accepted by the ASCO tumour marker panel. [9] Microarray In Node-negative Disease may Avoid Chemotherapy (MINDACT), run by TransBIG, uses the Amsterdam 70-gene signature for risk assessment. [11] Other gene signatures, such as

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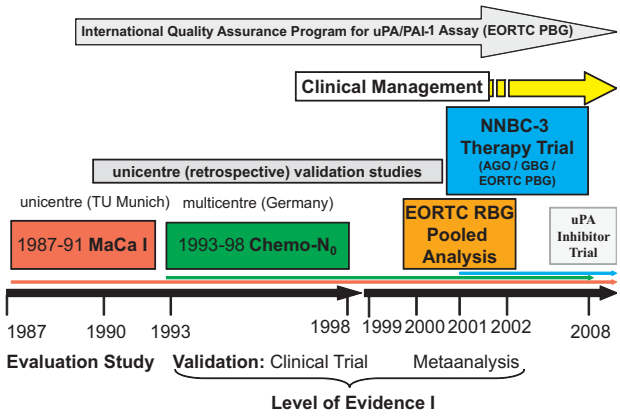

Fig. 1. Implementation time line of uPA and PAI-1 in clinical management of breast cancer (modified after [1]).

the Rotterdam 76-gene signature,[12] have also been thoroughly validated for clinically relevant risk group stratification, though not in a prospective clinical trial.

Next to their prognostic impact, uPA/PAI-1 also have a strong predictive impact regarding response to adjuvant chemo- but not endocrine therapy: Patients with high uPA/PAI-1 in their primary tumour tissue derive an enhanced benefit from adjuvant chemotherapy.[13] High levels of uPA and PAI-1 do thus reflect an aggressive phenotype which may be overcome or suppressed by early systemic therapy as in the adjuvant setting but may be far too advanced for response to palliative therapy at a later stage. Last but not least, their key roles in tumour invasion and metastasis make uPA and PAI-1 interesting therapeutic targets. Commencing in early 2008, an international phase II trial will evaluate an oral uPA inhibitor in metastatic breast cancer.

In conclusion, a more thorough understanding of tumour biology has led to significant advances in management of early breast cancer today. Molecular markers such as uPA/PAI-1, the 21-gene recurrence score, or messenger RNA (mRNA) profiles, such as the 70 or 76 gene profile, are able to select patients with early-stage disease who can be spared the burden of adjuvant chemotherapy due to their excellent prognosis. uPA/PAI-1 as well as other molecular markers also serve as targets for promising novel therapies that affect tumour cells directly or enhance the efficacy of conventional therapeutic approaches such as chemotherapy or endocrine therapy. Validation of uPA/PAI-1 as prognostic and predictive markers as well as development of novel targeted therapeutics against uPA/PAI-1 for clinical application in breast cancer have taken altogether almost 20 years (see Fig. 1). Building on such experience, future biomarker development needs to be substantially faster in the interest of our patients.

Conflict of interest statement

None declared.

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