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Concordance rates of biomarkers uPA and PAI-1 results in primary breast cancer vs. consecutive tumor board decision and therapy performed in clinical hospital routine: Results of a prospective multi-center study at certified breast centers

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ABSTRACT

Objective: Biomarkers uPA and PAI-1 are guideline recommended by ASCO (USA) and AGO (Germany) in primary breast cancer to avoid unnecessary CTX in patients at medium risk for recurrence. For clinical quality assurance of uPA/PAI-1 testing, analysis of test-therapy concordance was performed.
Methods: Prospective non-interventional multi-center study over 2 years among six Certified Breast Centers in Germany to investigate uPA/PAI-1 results in consecutive decision making for tumor board recommendation and actual therapy in uninfluenced clinical setting. Concordance and discordance rates of uPA/PAI-1 testing were calculated and individual reasons for decision making analyzed.
Results: Among n = 93 uPA/PAI-1 tests evaluated n = 42/93 (45.2%) were uPA + PAI-1 negative and n = 51/93 (54.8%) uPA and/or PAI-1 positive. In uPA + PAI-1 negative test results in n = 35/42 (83.3%) CTX was avoided as recommended. But in n = 7/42 (16.7%) CTX was performed despite, resulting in over treatment. In uPA and/or PAI-1 positive test results in n = 26/51 (51.0%) CTX was performed but in n = 25/51 (49.0%) not despite recommendation for CTX which is under treatment. The conformity of uPA/PAI-1 test result vs. tumor board decision was n = 73/93 (78.5%). The overall concordance of uPA/PAI-1 test result vs. consecutive therapy was n = 61/93 (65.6%). A variety of reasons for individual result-deviating decisions were identified.
Conclusions: Clinical quality assurance of uPA/PAI-1 biomarker testing showed inconsistency of test results with consecutive tumor board decision and/or final therapy performed in up to 1/3 of patients. To close this clinical quality gap in application of uPA/PAI-1 biomarkers, individual analysis of deviations is suggested with process optimization accordingly.

Introduction

Biomarkers uPA and PAI-1 have been established over 20 years in breast cancer diagnostic for the subgroup of G2 being ER/PR positive, Her2neu negative, nodal negative and age >35 years [1,2]. They are validated with level 1 evidence [3] and listed in the Interdisciplinary

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German S3-Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer [4] with LOE 1a. Consecutively they are guideline-recommended by the German AGO and also by the American Society of Clinical Oncology (ASCO) [5]. Prospective 10-year follow up of the NNBC3/ChemoN0 trial showed that the outcome of the uPA and PAI-1-negative group without chemotherapy is comparable to standard treatment [6]. The economic advantages of uPA/PAI-1 testing were demonstrated in a theoretical Markov model [7] as well as in actual savings of chemotherapies and direct medication costs with a return-on-investment rate of at least 8.4 in normal clinical setting [8] and a supra-national cost effectiveness study for three European countries [9].

Scientific publications usually focus on technical aspects of sensitivity and specificity or reliability of test processing when comparing different biomarkers, gene tests or specimen retrieval [10–14]. But in contrast to designed clinical studies with rigid protocols specially focused on biomarkers with mandatory high consistency of its application according to these protocols, the clinical reality of biomarker application and consecutive use of their results varies. Consecutively in normal daily clinical practice not all biomarkers are always used as intended and interference with other aspects from patients or physicians might result in a deviating decision making for breast cancer therapy not exclusively based on biomarker results.

For clinical quality assurance the use of biomarkers uPA and PAI-1 and its influence on decision making for therapy was investigated. This study was performed to identify the clinical concordance rate of individual results of uPA/PAI-1 testing and the consecutive tumor board decision for or against chemotherapy as well as the therapy finally performed in each case within an uninfluenced clinical setting.

Materials and methods

Study design

A prospective, non-interventional multi-center study was performed in six Southeastern German breast centers from 2010 to 2011 to identify chemotherapies spared and direct medication cost savings due to use of uPA and PAI-1 testing [8]. Afterwards a post hoc analysis for quality assurance was performed from this data. This project was funded by AOK Bayern, a Bavarian health care fund. The target was to identify and induce innovative medical care in certified breast cancer centers and promote avoiding unnecessary chemotherapy and thereby increase patients' quality of life.

Study targets

Study targets were identification of concordance rate of uPA/PAI-1 test result and consecutive use in therapy decision for or against adjuvant chemotherapy and actual therapy finally performed. The threshold values for uPA/PAI-1 biomarker are defined with uPA $\leq$ 3 ng/mg protein and PAI-1 $\leq$ 14 ng/mg protein. uPA and PAI-1 are considered low (=low risk group) if both values are below the threshold values; uPA and PAI-1 is considered high (=high risk group) if one or both values are above the threshold values. From guideline recommendations only patients in the uPA/PAI-1 high risk group are suggested to continue therapy with CTX. This analysis was intended primarily for understanding the use of uPA/PAI-1 results on therapy decision making. However, patient data didn't allow judging these results since many decisions in medicine are not based on diagnostic parameter like biomarkers exclusively but rather individual patient and/or physician decisions influenced by external parameter which also can change during a course of disease.

Process of selection of breast centers

To assure and support the highest quality of care level of breast centers only Certified Breast Centers (CBC) with confirmed quality and outcome structure of active certification according to DKG/DGS criteria by German OnkoZert [15] were allowed to participate. For logistic reasons preferred Certified Breast Centers from Southern parts of Bavaria were invited. From n = 15 CBCs approached, n = 6 finally participated representing about 1,500 breast cancers diagnosis per year.

Inclusion and exclusion criteria

Study objects were cases of primary breast cancer. The primary inclusion criteria for uPA/PAI-1-testing were histological grading G2, Her2neu receptor negative, hormone receptor (ER/PR) positive, lymph node negative and patient age of >35 years. A secondary inclusion criterion was physicians' decision to use uPA/PAI-1 biomarkers for therapy decision.

Analysis of patient charts and tumor board decision

For this study all patient charts were analyzed anonymously regarding uPA/PAI-1 test result and compared to each consecutive individual tumor board decision and the final therapy received. All patient charts, tumor board decisions and final therapy decisions were accessible and complete for evaluation.

Ethic Committee approval, data protection and statistics

Due to the aim of this study as non-interventional quality assurance this is covered by the Bavarian law as institutional quality evaluation [16]. Data protection was performed accordingly. Ethic committee decision for this project #5008/11 was performed by Ethic Committee of Technical University of Munich, Germany, confirming that as an organizational study concept for clinical quality assurance no formal EC approval was required.

Results

The concordance rates of uPA/PAI-1 test-therapy decisions and performance for n = 93 breast cancer tumors were identified and

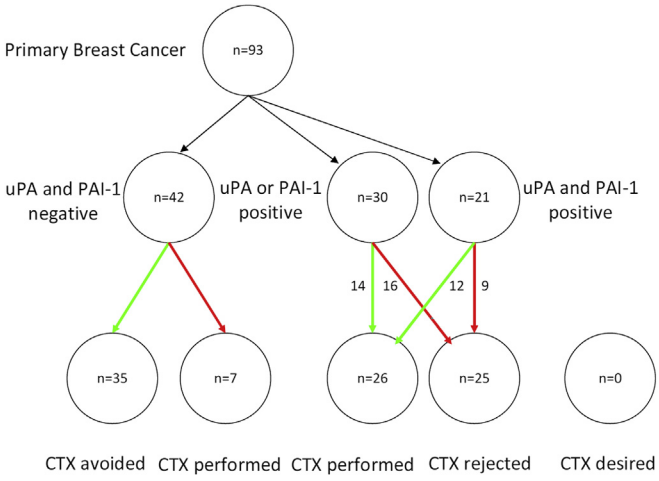

Fig. 1. Study flow diagram of uPA/PAI-1 test result and actual therapy performed. [Fig. expanded from 8]. [green arrow = test-conform decision, red arrow = test-inconsistent decision]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)