Reviewers report

Title: Prognostic significance of urokinase Plasminogen Activator and Plasminogen Activator Inhibitor-1 mRNA expression in advanced breast cancer

Version: 1 Date: 1 May 2006

Reviewer: Tanja Cufer

Reviewers report:

General
This paper addresses an important topic of measuring uPA and PAI-1 expression in primary tumor by RT-PCR, which seems to be much more practical and clinically useful method than already validated biochemical measurements are. Although it is an retrospective observation, the result of this work offer the additional information on the prognostic value of uPA and PAI-1 levels determined by RT-PCR, hypothesis that deserves to be tested in a prospective fashion.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Information on whether all the patients were free of metastases at the time of diagnosis and data on primary surgery (radical or not) should be added.
2. Introduction: Among references related to the predictive value of uPA and PAI-1 for response to HT reference 10 should be added; in addition my suggestion is to add the reference on the paper published by P Manders et al in Cancer Research in 2004, which yields additional data on this topic.
3. Referring to ref 22, when discussing flaws and weaknesses of IHC determination of uPA and PAI-1, is not appropriate. In this paper shortages with regard to the reproducibility and interpretation of IHC staining of uPA and PAI-1 are not presented at all.
4. Menopausal status classification should be explained. Usually, if clinical data on menopause are missing, age of 50 years is taken as a cut off (also in EBCTG overview); dividing line of 55 years needs some explanation.
5. It should be clarified whether in MFS definition a death without a prior cancer event was taken as an event or not.
6. Instead of overall survival the authors should refer to breast cancer specific survival.
7. More appropriate terms are: distant relapse instead of metastasis relapse and histologic type instead of tumor type.
8. In Fig 2 and Fig 3 number of pts and number of events in each arm should be added. In y axis probability of survival is presented and not survival as such.

Discretionary Revisions (which the author can choose to ignore)

1. When discussing results in the last paragraph of the article it would be nice to explain to the readers the authors’ view on what could be the reasons that grade (one of the most important prognostic factors in HR+ disease) did not emerge as an independent important factor in their analysis.
2. The conclusion they are driving from their results that the identification of prognostically bad HR+ patients (based on uPA and PAI-1 levels) could help clinicians to identify patients that need more aggressive ChT does not seem in line with current knowledge on biology driven response to ChT, HT and to targeted agents in breast cancer. Some thoughts in direction of possible improvement in HT (OS in younger patients, AIs in pomenopausal pts) and information that uPA and PAI-1 may serve as a target for targeted therapy (with references on anti-PAI-1 phase II studies) would add a lot.
What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.