Reviewer’s report

Title: Genomic alterations identified by array comparative genomic hybridization as prognostic markers in tamoxifen-treated estrogen receptor-positive breast cancer

Version: 1 Date: 28 November 2005

Reviewer: A. Dellas

Reviewer’s report:

Category:
Major Compulsory Revisions - The author must respond to these before a decision on publication can be reached.

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Review Text

“Genomic alterations identified by array comparative genomic hybridization as prognostic markers in tamoxifen-treated estrogen receptor-positive breast cancer”

Wonshik Han, et al.

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1. Is the question posed by the authors new and well defined?

Are the data sound and well controlled?

The authors applied high-resolution array CGH with 1,440 human BAC clones to assess copy number changes in 28 fresh-frozen ER-positive breast cancer tissues. All patients received at least one year of tamoxifen treatment. In addition, most patients (96%) received adjuvant chemotherapy and those with breast conserving surgery (14%) underwent adjuvant radiotherapy.

Among the clinico-pathological characteristics the authors found 85.7% of tumors of T2 stages. Further, more than 70% of all patients had axillary lymph node metastasis during the time of their primary surgery. Of 28 ER-positive invasive ductal carcinomas 46% were characterized as «high combined histologic grade» (Nottingham combined histological grade G3, unfavorable). Within the course of 5 years 32% of the patients had distant metastasis.

The authors divided their patients in a Recurrence group and in a Non-Recurrence group.

By doing so, the patient selection and their separation show a mixed risk of tumor progression based on the mix of favorable and unfavorable clinico-pathological prognostic factors within their respective groups (Table 1). In analyzing copy number changes between recurring and non-recurring breast cancers the authors expose themselves to biased results in the survival and Cox regression analysis due to mixed risk factors and mixed adjuvant therapies which the patients underwent.

It would have been much more appropriate to divide the patients into axillary lymph node negative and lymph node positive invasive ductal carcinomas, because the axillary lymph node status has been shown to be the single most important prognostic factor for disease-free survival and overall survival in breast cancer patients. This would avoid the confusion created by the Cox regression
analysis, showing a single copy number aberration at 11p15.5 as the most significant prognostic factor and none of the other known, such as tumor size, histological grade, lymph node status and vascular invasion.

Nevertheless and before re-submitting their manuscript, I recommend that the authors re-group their patients into those with and without axillary lymph node metastasis. They should analyze the genomic alterations separately within the group of lymph node negative and lymph node positive breast cancers. This would allow them to compare CGH results between the different risk groups.

Despite the aforementioned remarks, the aim of the study is well defined.

There are relatively few reports about the analysis of copy number changes in tamoxifen treated invasive ductal carcinomas.

The question posed by the authors is interesting, because their results would allow comparing them with study results reported by others before introducing the adjuvant tamoxifen therapy (1990) as standard treatment in estrogen receptor-positive breast carcinomas.

References:


2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

The applied methods are appropriate and they are sufficiently described. They are standard techniques, thus enabling others to replicate the work with a different sampling.

3. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Yes.

4. Are the discussion and conclusions well balanced and adequately supported by the data?

The discussion and conclusions should be re-written according to the new data collection following the re-grouping, as recommended in the first part of the review.

5. Do the title and abstract accurately convey what has been found?

Yes.

6. Is the writing acceptable?

I would like to suggest some improvements.
Throughout the manuscript, the authors use two terms to describe the histological type of the investigated invasive breast cancer samples:

- infiltrating duct carcinoma, page 4 and line 21, page 21 and line 3
- invasive ductal carcinoma, page 13 and line 6.

To my knowledge, the term «infiltrating duct carcinoma» does not exist.

The term «infiltrating ductal carcinoma» is used by the Armed Forces Institute of Pathology and was the nomenclature adopted in the previous WHO classification. Today, the term «invasive ductal carcinoma» is the preferred terminology.

Therefore, I recommend using the term «invasive ductal carcinoma» within the manuscript.

Further recommendations:

- Page 4, line 9: Please change the sentence. Tissue samples do not have a prognosis, patients have.
- Page 14, line 14: Please change the last sentence as follows: «An analytical tool that can identify the clones between two subject groups has not yet been established for array CGH». Please delete the following phrase «this was the most challenging issue in our study».
- Page 14, line 18-21: Please create short and concise sentences like: «In conclusion, using array CGH analysis with BAC clones, we were able to detect various genomic alterations in ER-positive breast cancers. Patients in the Recurrence group showed a significantly different pattern of chromosomal gain and loss than patients in the Non-recurrence group».

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory 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.

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