ANALYSIS OF MASPIN EXPRESSION IN INVASIVE DUCTAL CARCINOMA OF THE BREAST ON STAGES IIA AND IIIB

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ABSTRACT

Mammary Serine Protease Inhibitor (maspin) is a tumor suppressor gene, a member of the serine protease inhibitor (serpin) family that works by inhibiting motility of cell movement, invasion and metastasis. Maspin expression is expected to be a prognostic factor as well as a predictive factor in mammary tumors. However, in some recent studies, maspin has a variety of expressions. Although it is known that no maspin appears as an indicator of tumor progression and metastasis, recent studies have shown that maspin expression is associated with an aggressive phenotype of breast cancer and with a poor prognosis. Correlations between maspin expression and poor prognosis have also been reported in pancreatic, ovarian, thyroid, bladder and lung cancers. Knowledge of the expression and role of this maspin as well as its relationship with the pathogenesis of breast invasive ductal carcinoma is still small. The aim of this study was to look at differences in maspin expression in breast-invasive ductal carcinoma of stage IIA and stage IIIB groups. This research method used analytic observational research with cross sectional approach. The samples were invasive carcinoma of NST paraffin at the Department of Anatomic Pathology of Dr Soetomo Hospital, Surabaya, from January to December 2015. Thirty samples were divided into two groups, namely stage IIA and stage IIIB groups and immunohistochemical examination with maspin antibody was carried out. The difference of maspin expression in stage IIA and stage IIIB was analyzed using Mann-Whitney statistic test. There were significant differences in maspin expression between stage IIA and stage IIIB groups, where stage IIA has a high maspin expression rather than stage IIIB. (FMI 2018;54:6-9)

Keywords: Invasive breast cancer stages IIA and IIIB; maspin

INTRODUCTION

Mammary Serine Protease Inhibitor (Maspin) is a tumor suppressor gene, a member of the serine protease inhibitor family (serpin) and located on chromosome 18q21.3-q23, a place that often suffers from heterozygous loss (Bodenstine et al., 2012). Maspin has been known as tumor suppressor gene, inhibits motility of cell movement, invasion and metastasis. Maspin can also increase cell sensitivity in apoptotic processes and inhibit angiogenesis processes. (Bodenstine et al 2012, Berrardi et al 2013). Maspin expression is expected to be a prognostic factor as well as a predictive factor in mammmary tumors so that it can be used in therapy (Berardi et al 2013).
However, in some recent studies, maspin has diverse expression (Berardi et al 2013). Although it is known that no maspine appears as an indicator of tumor progression and metastasis, recent research has shown that maspine expression is associated with an aggressive phenotype of breast cancer and with a poor prognosis. Correlations between maspine expression and poor prognosis have also been reported in other organs in pancreatic, ovarian, thyroid, bladder and lung cancers (Berardi et al 2013, Bodenstine et al 2012). There is little knowledge of maspin's expression and role and association with the pathogenesis of breast cancer (Berardi et al 2013). Stark et al (2010) and Mass et al have examined the potential relationship between maspine expression in primary tumors and metastases. They showed that maspine expression decreased in primary tumors and decreased in metastasis (Maass et al 2001, Berardi et al 2013).

The opposite study was reported by Umekita et al (2011) who trace 92 and 192 patients of breast invasive ductal carcinoma. They reported that maspine expression was commonly found in breast invasive ductal carcinoma with aggressive phenotype (high histological grade) and was a poorly prognostic indicator (Berardi et al. 2013, Umekita et al 2002). In addition Umekita and Yoshida (2003) and Lee et al (2006) also reported large tumor size, high histologic grade, positive P53 status as well as negative estrogen and progesterone receptor status and poor prognosis associated with maspine expression (Umekita et al 2011, Berardi et al 2013).

Further research is needed to clarify the true mechanism of excess maspine expression in breast cancer, as well as to use it as a prognostic marker in clinical practice (Berrardi et al. 2013). This study was aimed to determine the potential role of maspin based on tumor stage in breast invasive ductal carcinoma of stage IIA group and stage IIB. In this study will assess maspine expression and its correlation as well as its role as a prognostic factor in breast invasive ductal carcinoma using immunohistochemical methods.

MATERIALS AND METHODS

The study design used was analytic observational with cross sectional approach. The study population was 30 paraffin blocks of patients with invasive breast cancer in the Anatomic Pathology Laboratory of Dr. Soetomo Hospital, Surabaya, from January to December 2015. We obtained the data randomly and divided the samples into two, which were stage IIA and stage IIB groups.

Maspin expression was examined immunohistochemically using the monoclonal mouse anti-human antibody from Santa Cruz Biotechnology using 1:125 dilution. Positively stained tumor cells were counted visually using binocular photon micro-scope at 400x magnification, and grading was made according to percentage and intensity of positively stained cells.

Maspine expressions were considered positive if the cytoplasm was stained. The maspine marking was expressed as a percentage of cells that were positively stained and the intensity of stained cells, then categorized in the following scores: Cell percentage, it had negative value if cell was not stained, one value if positive cells were 1-5%, two if positive cells were 1-5%, three if the positive cells were 6-50% and three if the cells are positive >50%. Cell Intensity, negative if cell is unbound, value one if intensity is weak, two if medium intensity, three if intensity is strong. The final score is the total percentage score and the cell intensity, having a total weak score if the total score is 1-2, while the total score is 3-4 and strong if the total score is 5-6 (Sopel et al 2005).

Data obtained were statistically analyzed. The difference of maspine and VEGF expressions were analysed using the Mann-Whitney and Spearman test (p<0.05).

RESULTS

Thirty subjects in this study had the mean age of 54.70 ± 10.31 years old. The youngest subject was 40 years old and the oldest was 82 years old. In the stage IIA group (15 subjects), the mean age was 56.07 ± 11.25 years old, 41 years old as the youngest subject age and 82 years as the oldest; the stage IIB group (15 subjects) had the mean age of 53.33 ± 9.47 years old, 40 years old as the youngest subject and 71 years as the oldest. In the chi-square test, there was no significant difference on the age distribution between stage IIA and stage IIB groups.

In this study, maspine expression was graded in each sample group based on the cell percentage with score of 0-3 and the cell intensity with score of 0-3 as well as the total score of weak 1-2, moderate 3-4, and strong 5-6. These results were obtained: weak maspine expression in stage IIA group of 7 subjects (43.8%) and stage IIB group of 9 subjects (56.3%); moderate maspine expression in stage IIA group of 7 subjects (43.8%) and stage IIB group of 9 subjects (56.3%); and strong maspine expression in stage IIA group of 0 subject (0%) and stage IIB group of 2 subjects (13.3%). Using Mann-Whitney test, there was significant differences in maspine expressions between stage IIB group compared to stage IIA group (p<0.05).
Table 1. Maspin expression using Mann-Whitney test

<table>
<thead>
<tr>
<th>Maspin expression</th>
<th>Stages</th>
<th>Median</th>
<th>Interquartile deviation</th>
<th>Min</th>
<th>Max</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>IIA</td>
<td>3</td>
<td>0.0</td>
<td>2</td>
<td>3</td>
<td>0.008*</td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>2</td>
<td>0.5</td>
<td>1</td>
<td>3</td>
<td>0.306</td>
</tr>
<tr>
<td>Intensity</td>
<td>IIA</td>
<td>2</td>
<td>0.5</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIIB</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Intensity &amp;</td>
<td>IIA</td>
<td>5</td>
<td>0.5</td>
<td>3</td>
<td>6</td>
<td>0.034*</td>
</tr>
<tr>
<td>Presentation</td>
<td>IIIB</td>
<td>3</td>
<td>1.0</td>
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Fig. 1. Maspin expression using high-intensity microscope in figure A (HE, 40x), medium-intensity in figure B (HE, 100x) and low-intensity in figure C (HE, 100x).

DISCUSSION

Maspin is detected in normal breast and epithelial cells of the prostate, but in tumor cells its expression is lower (Berardi et al 2013). Maspin expression in breast cancer prevents invasion in vitro and metastasis in vivo. Loss of gene expression induces raise of invasion and spread of breast cancer (Bodenstine et al 2012).

There are varied results regarding maspin activity; in some cases it is known to correlate with better prognosis in mammary and prostate tumors. This is shown with the loss of maspin expression in invasive and aggressive mammary tumors. This places maspin in the list of metastasis suppressor genes potentially involved in metastasis (Berardi et al 2013).

According to the spread pattern of maspin expression, in stage IIA group, most of the maspin expression shown were moderate expression, in 8 cases (66.7%), followed by 4 moderate expressions (33.3%) and 2 strong expressions (11.3%). Statistical analysis between maspin and staging status in this study showed that there was significant difference (p=0.034). Stage IIA group had tendency to show stronger maspin expression compared to the stage IIIB group. This result is consistent with previous studies (Berardi et al 2013). The difference of maspin expression between low- and high-expression groups are consistent with role of maspin as the tumor suppressor gene by inhibiting motility, invasion and metastasis of cells, also elevates cell sensitivity against apoptosis process and inhibiting angiogenesis process (Jiang et al 2002, Maass et al 2000, Streuli 2002).

CONCLUSION

There was a difference in maspin expression in breast invasive ductal carcinoma of stage IIA and IIIB groups. Maspin expression was higher in the IIA stage group than that in IIIB stage group. This is in accordance with maspin function as tumor suppressor gene by inhibiting
motility of cell movement, invasion, angiogenesis and metastasis.

REFERENCES


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