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HER2 Overexpression in Relation to Breast Cancer Histopathological Grading: A Promising Prognostic and Predictive Biomarker for Breast Cancer

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Abstract
Introduction: Many research showed the importance of HER2 as the new biomarker for breast cancer while its overexpression was greatly associated with increased histopathological grading of breast cancer.
Methods: About 90 biopsy were taken from patients with breast cancer from 1 June 2011-1 June 2014. The biopsy samples were then sent to Pathology for HER2 immunohistochemistry. There are three grades of scoring 0 to +3. Score 0/+ 1 as considered negative and score of +3 as considered an HER2 overexpression. Histopathological grading was determined using Nottingham scoring. Statistical analyzes were done with SPSS 16. Categorical Data were analyzed by chi square with a significance limit of 0:05.
Results: Majority of samples had HER2 +1 (55.6%) and histopathological grading mostly found in grade 1 (44,4,2%). Prevalence ratio of HER2/Neu and histopathological grading of breast cancer was 7.667.
Discussion: HER-2 positive are often associated with poor differentiation, metastasis to the lymph nodes, recurrence, and a high mortality rate. In this study, it was shown that ovcerexpression of HER2 increase 8 times risk of having high histopathological grade. These study results have contributed the means of overexpression HER2/neu to being a factor predictive and prognostic factors as well as a breast cancer therapy.
Conclusion: Overexpression of HER2/Neu showed 8 times more likely to have a higher grading breast cancer.

Introduction

Breast cancer is most often diagnosed in women worldwide. In 2012, the world as many as 1.7 million women are diagnosed with breast cancer. It was shown there were estimated 299.673 in Indonesia. Most of the cases are diagnosed at an advanced stage. The high number showed a necessity in the development of prognostic biomarker.[1]

Many research showed the importance of HER2 as the new biomarker. HER2 protein is a glycoprotein or c-erb B2 or neu, which is part of the EGF family.[2-4] HER2 binds to the EGF receptor tyrosine kinase then triggers a complex cascade of Akt/mTOR to support the survival of tumor cells. On the other hand, HER2 binding to its receptor also triggers MAPK, accelerate the G2 to M phase so as activate the proliferation of tumor cells.[5-6] In normal circumstances, HER2 does not bind to many ligand with high affinity, while in amplification, many ligands are binded and leads to cancer.

Overexpression of HER2 was greatly associated with increased histopathological grading of breast cancer.[2-4] The association has been shown in many studies.[7-8] Consistently both biological and clinical histopathological grading describe the behavior of breast cancer.[9-11] Relationship between breast cancer grading and HER2 overexpression has opened up an idea for prognostic biomarkers. While, as predictive biomarker, HER2 can be utilize to monitor response therapy, predict sensitivity, and resistance.

Materials and Methods

This research was conducted in Surgery Oncology Division in Haji Adam Malik Hospital. About 90 biopsy were taken from patients with breast cancer from 1 June 2011-1 June 2014. This study has been approved by Ethical Committee University of Sumatera Utara.

The biopsy samples were then sent to Pathology for HER2 immunohistochemistry analysis. There are three grades of scoring 0 to +3. Score 0/+ 1 as considered negative and score of +3 as considered an HER2 overexpression.[12-14]

Histopathological grading is a representation of the potential aggressiveness of a tumor, where in the low grading tends to be less aggressive than high grading. This study use Nottingham scoring. The assessment is based on gland formation, nucleus description, and mitotic activity with scoring provide in table 1. Each factor has a score of 1-3, and then each of the scores are added to give a total final score ranges between 3-9.[15-16]

Nothingham Scoring

Description	Assessment	Score
Tubule Formation	>75% 10-74% <10%	1 2 3
Nuclear Pleomorphism	Uniform cells (minimal or no nuclear enlargement;minimal or no darkning of chromatin Moderate pleomorphism Marked pleomorphism	1 2 3
Mitotic Count per 10 defined high powered fields	0-9 mitotic figures 10-19 mitotic figures ≥ 20 mitotic figures	1 2 3
Histologic Grade	Grade 1 : Well differentiated Grade 2: Moderatly differentiated Grade 3 : Poorly differentiated	Summary score: 3-5 Summary score: 6-7 Summary score: 8-9

Statistical analyzes were done with SPSS 16. Categorical Data were analyzed by chi square with a significance limit of 0:05.

Results and discussion

Samples in this study had a mean age of 50 years. HER2 immunohistochemical analysis results showed majority has HER2 +1 (55.6%), followed by +2 (14.4%) and +3 (30.0%). Histopathological grading of breast cancer mostly found in grade 1 (44,4,2%), then grade 2 39 (43.3), grade 3 of 11 (12.2%).

Table 1 HER2/neu expression

HER2	**Frekuensi**	**%**
+1	50	55,6
+2	13	14,4
+3	27	30,0
Total	**90**	**100%**

Table 2 Histopathological grading of breast cancer

Histopathological grading	**Frequency**	**%**
1	40	44,4
2	39	43,3
3	11	12,2
Total	**90**	**100**

Statistical analysis showed prevalence ratio of 7.667 of HER2/Neu and histopathological grading of breast cancer**.** It's mean that overexpression of HER2 8-fold risk of having high grading compared with HER2-negative disease.

Tabel 3 Prevalence ratio of HER2/Neu and histopathological grading of breast cancer.

HER2/Neu	Histopathological grading Low Grade	 High Grade	Prevalence ratio (RP)	CI 95 % Lower-upper	P
Negative	36	27			
Positive	4	23	7,667	2.372-24.781	0.000

Discussion

HER2/neu plays role in cell differentiation, adhesion and motility. HER-2 positive are often associated with poor differentiation, metastasis to the lymph nodes, recurrence, and a high mortality rate. Amplification of HER2 itself has been found in 18-30% of breast cancer.[12,17] In this study indicated 27 (30.0%) samples have HER2 overexpression. In literature, it has been showed 10-30% HER2 overexpressioin was found in breast carcinoma. In Surabaya, incidence of HER2 overexpression was 25.6%. In larger study, overexpression of HER2/Neu was obtained in 149 (10.9%) of 1362 respondents.[9]

This study showed no significant association between overexpression of HER2/neu with histopathological grading of breast cancer patients, with prevalence ratio 7,667. Bartlet et al 2007 also reported

a significant association between both.[6] In Indonesia, Octaovianus (2012) also reported a significant relationship with 3.9 prevalence ratio.[18] These study results have contributed the means of overexpression HER2/neu to being a factor predictive and prognostic factors as well as a breast cancer therapy.

Conclusion

Overexpression of HER2/Neu showed 8 times more likely to have a higher grading breast cancer.

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