

Correlation of Her-2 Expression with Clinicopathological Characteristics in Invasive Ductal Breast Cancer Patients

Correlación de la expresión de Her-2 con características clínico-patológicas en pacientes con cáncer de mama ductal invasivo

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SUMMARY

Breast cancer is the most common cancer in the world and a leading cause of death in women. This cancer is the major cause of mortality and morbidity in Indonesian women. This study aims to investigate the correlation of Her-2 expression with a clinicopathological profile in invasive ductal breast cancer. This study was retrospective in design. Histopathological diagnosis and immunohistochemical ER, PR, and Her2 from 95 patients with invasive ductal breast cancer were included during the period January 2017 to June 2018. Information of clinical, pathologic, and immunohistochemical examinations was recorded and analyzed. The age of the patients ranged from

25 to 80 years, an average of 48.29 ± 9.686 years. The most common tumor size of patients was 2 – 5 cm, 57 patients (54.3 %) mean 4.327 ± 2.56 cm. Most tumours were grade 3. The Immunohistochemical overexpression of ER, PR, and Her2 was 59 %, 59 %, and 46,7 % respectively. In our study, there was a correlation between overexpression of Her-2 and tumor size and no correlation with histology grade and age. The incidence of invasive breast cancer is highest in premenopausal women. Analysis of tumour size, grade histopathology, lymph vessel invasion characteristic, and immunohistochemical expression is important to therapeutic management in patients with invasive ductal cancer.

Keywords: *Breast cancer, clinicopathological characteristic, Her-2 expression.*

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RESUMEN

El cáncer de mama es el cáncer más común en el mundo y una de las principales causas de muerte en las mujeres. Este cáncer es la principal causa de mortalidad y morbilidad en las mujeres de Indonesia. Este estudio tiene como objetivo investigar la correlación de la expresión de Her-2 con un perfil clínico-patológico en el cáncer de mama ductal invasivo. Este estudio fue de diseño retrospectivo. Se incluyeron diagnósticos histopatológicos e inmunohistoquímicos de ER, PR y Her2 de 95 pacientes con cáncer de mama ductal invasivo durante el período de enero de 2017 a junio de 2018. Se registró y analizó información del examen clínico, patológico e inmunohistoquímico. La edad de los pacientes varió de 25 a 80 años, promedio $48,29 \pm 9,686$ años. El tamaño tumoral más común de los pacientes fue de 2 a 5 cm, 57 pacientes (54,3

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%) con una media de 4,327 ±2,56 cm. La mayoría de los tumores eran de grado 3. La sobreexpresión inmunohistoquímica de ER, PR, Her2 fue del 59 %, 59 % y 46,7 %, respectivamente. En nuestro estudio, hubo una correlación entre la sobreexpresión de Her-2 y el tamaño del tumor y ninguna correlación con el grado histológico y la edad. La incidencia de cáncer de mama invasivo es más alta en mujeres premenopáusicas. El análisis del tamaño del tumor, el grado histopatológico, la característica de invasión de los vasos linfáticos y la expresión inmunohistoquímica son importantes para el manejo terapéutico en pacientes con cáncer ductal invasivo.

Palabras clave: *Cáncer de mama, característica clínico-patológica, expresión Her-2.*

INTRODUCTION

Breast cancer is the most common malignant tumor in a woman with more than a million new cases per year worldwide, representing 22 % of all cancer diagnosed in women. Invasive Ductal Breast Cancer is the commonest type of epithelial breast cancer. There are 1.67 million new cases of breast cancer in the world. The incidence of breast cancer is higher in developing countries. In 2009, the incidence of breast cancer increased from 1.59 % to 2.90 % among American women (1-4). In recent years, the incidence of breast cancer in Indonesian women has also been rising and has shown a younger trend. From the data and information center of the Indonesian Health Ministry 2016, the incidence of breast cancer in Indonesia is 40/per 100 000 people and the mortality rate is 16.6/100 000 people (5). Some of the clinicopathological characteristics have a prognostic significance which includes tumor size, type of tumor, histological grade, and lymph node status (6-8).

Her-2 (gene map to chromosome 17) is a member of the epidermal growth factor receptor (EGFR) family. Activation of the Her-2 could induce tumor cell proliferation. Her-2 overexpression is associated with higher grades of tumor and poor prognosis (9).

Treatment of breast cancer is multidisciplinary and depends on the age of patients, tumor size, lymph node status and histological type, grade of tumour, Estrogen Receptor (ER), Progesterone

Receptor (PR) status, and growth factor (Her-2). This study aims to investigate the correlation between Her-2 expression and clinicopathological characteristics in patients with invasive ductal breast carcinoma. Analysis of clinicopathological characteristics and expression of ER, PR, and Her-2 immunostaining are very useful tools for diagnosing this cancer, important for management protocol therapy and prognosis of the patient (10-12). This study aims to analyze the correlation of Her-2 expression with clinicopathological characteristics in patients with invasive ductal breast cancer.

METHODS

The study was retrospective in design. Data were collected in the pathology department of Murni Teguh Memorial Hospital during the period January 2017 to June 2018. In a total of 95 patients with breast cancer who had undergone surgery without any radiotherapy and chemotherapy before the surgery, pathological and immunohistochemical (as confirmed by Hematoxylin – Eosin stained histopathological examination) were involved. This study was approved by the ethics committee in the Medical Faculty of Universitas Sumatera Utara. The patients with missing data on clinicopathology and immunostaining ER, PR, and Her2/ neu were excluded. The data of age, tumour size (< 2 cm, 2 – 5 cm, > 5 cm), histological type is specified according to the WHO classification of breast cancer, histological tumour grade was performed using the modified criteria of Bloom and Richardson as described by Elston and Ellis, lymph node metastases, lymph vessel angioinvasion was collected as follows. The hormone receptor status (ER, PR) immunohistochemical stain was scored positive at the cell membrane with ≥ 10.0 % as positive and < 10 % as negative. Her2 according to immunohistochemical staining of cells can be divided into 0.1+. 2+ and 3+. Score 0 (negative, no reactivity), 1+ (negative, faint weak reactivity in > 10 % of tumor cells but only a portion of the membrane is positive), 2+ (equivocal, circumferential intense membrane staining in < 30 % of cells). Scores 0 and 1 were considered negative, score 2 was considered

CORRELATION OF HER-2 EXPRESSION

weakly positive and score 3 was considered strongly positive. Only score 3 cases were considered Her-2 overexpressing cases (9,13). The statistical analysis was done using Chi-square with α less than 0.05 to evaluate the between Her2 and clinicopathological characteristics in invasive ductal breast cancer patients such as age, tumor size, histological grade, and lymph vessel invasion.

RESULTS

In our study, 95 of the histopathological tumours and immunohistochemical characteristics in patients with invasive ductal breast cancer were taken. The mean age of patients at the time of surgery was 48.29 ± 9.69 years (median 48 years). The age of patients ranged from 25 – 80 years. The most common age of patients was above 45 years old (60 %), as shown in Table 1. The histological grade of tumor I + II was 26 (27.4 %) patients. Most patients belonged to histological grade III WHO, 69 (72.6 %) patients. The range of tumor size was 1 – 13 cm, mean of 4.33 ± 2.56 cm. Size of tumor ≤ 5 cm was for 62 (65.3 %) patients and tumor size > 5 cm was for 33 (34.7 %). Lymph vessel invasion was present in 52 patients (54.7 %) and absent in 43 (54.3 %). Immunohistochemical ER, PR and Her-2 was positive in 62 (65.3 %), 61 (64.2 %) and 49 (51.6 %) patients respectively. Table 2

showed that Her2 expression was positive in 49 patients (49.6 %). In our study, we found that Her-2 expression is correlated with the size of the tumor ($p: 0.04$) and has no correlation with age, grade of tumor, and lymph-vessel invasion (Table 3).

Table 1

Clinicopathological characteristics of patients with invasive ductal breast cancer

Parameter		N	%
Age (years)	≤ 45	38	40.0
	> 45	57	60.0
Tumor size (cm)	≤ 5	60	63.2
	> 5	35	36.8
Histological grade	I + II	26	27.4
	III	69	72.6
Lymph-vessel invasion	Absent	44	46.4
	Present	51	53.6

Table 2

Immunohistochemical expression (ER, PR, Her-2)

Immunohistochemical expression		n	%
Estrogen Receptor (ER)	Positive	62	65.3
	Negative	33	34.7
Progesteron Receptor (PR)	Positive	61	64.2
	Negative	34	35.8
Her2/neu	Positive	49	51.6
	Negative	46	48.4

Table 3

Correlation between clinicopathology characteristics and immunohistochemical expression Her-2

Clinicopathological Characteristic	Her2 (+)		p-value
	Positive n (%)	Negative n (%)	
Age (years)			0.402
≤ 45	22 (57.9)	16 (42.1)	
> 45	28 (49.1)	29 (50.9)	
Tumor size (cm)			0.004
≤ 5	26 (41.9)	36 (58.1)	
> 5	24 (72.7)	9 (27.3)	
Grade (WHO)			0.216
I + II	11 (42.3)	15 (57.7)	
III	39 (56.5)	30 (43.5)	
Lymph vessel Invasion			0.402
Present	31 (59.6)	21 (40.4)	
Negative	19 (44.2)	24 (55.8)	

DISCUSSION

Breast cancer is the most common malignancy in women. It is a multifactorial disease; the genetic alterations lead to normal cell transformation into the cancer cell. The biology of breast cancer remains poorly understood as the knowledge about individual prognostic factors provides limited information. Recently, most pathologists considered IHC evaluation of estrogen receptor, progesterone receptor, and Her-2 indices as essential parameters in selecting the line of treatment for breast cancer patients. Our study comprised 95 patients with invasive ductal breast cancer. The range of the age of patients was from 25 to 80 years old and the majority age of patients was > 45 years old (60 %).

Tumor size is an important prognostic factor that is directly correlated with the survival of patients. Our study found that the majority of tumor sizes were less than 5 cm. We found a positive correlation between Her2 expression and the size of the tumor among the patients with invasive breast cancer (p-value < 0.05). In our study, the histological grade of the tumor is I + II cm (27.4 %) and grade III (73.4 %) respectively. Many studies have demonstrated a significant association between histological grade, tumor size, and survival of patients in invasive ductal breast cancer (8). The grade is a powerful prognostic factor and should be included as a component of the minimum dataset for histological reporting of breast cancer (14). Mir et al. showed that 72.3 % of patients were in histological grade III and the tumor size ranged from 2 – 5 cm. However, some studies have not demonstrated any correlation between Her-2 positive and high-grade tumors. Tumor size, histopathologic grade, and lymph vessel invasion are the traditional prognostic factor in patients with invasive ductal breast cancer (15).

E Gottfried's study showed that 51.2 % of patients had a 2 – 5 cm size tumor. Five-year survival in breast cancer less than 1 cm is 93 % while it is 63 % for those larger than 5 cm in size (16). Lymph vessel presence was found in 54 (51.4 %) of patients with invasive ductal breast cancer. This is a different result from Schoppmann's study, whereas lymph vessel invasion was present in 36.6 % of cases.

Her2 is a receptor for epithelial growth factor cell proliferation and signal transduction. It plays an important regulatory role in cell physiology. Her2 overexpression is common in the epithelial tumor, whose cell proliferation and metastasis are common.

Three molecular biomarkers, ER, PR and Her2 are used in the routine clinical management of patients with invasive ductal breast cancer. Our study showed that Her-2 expression correlated with tumor size. This shows an inverse relationship with Almunen and Biswal, that Her-2 correlated with grade histopathology (6,9). The overexpression of Her2 in patients with breast cancer is a prognostic and predictive biomarker. Her2 expression is associated with a diminished prognosis (higher risk of recurrence) (16).

CONCLUSION

Our study found that Her-2 overexpression has a significant correlation with the size of the tumor and no correlation with the grade of tumor, age of patient, or lymph vessel invasion.

DISCLOSURE OF POTENTIAL CONFLICT OF INTEREST

The authors have declared no relevant conflict of interest.

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CORRELATION OF HER-2 EXPRESSION

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