RESEARCH ARTICLE

Molecular Subtypes of Indonesian Breast Carcinomas - Lack of Association with Patient Age and Tumor Size

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Abstract

Objective: Breast carcinoma (BC) is a heterogeneous disease that exhibits variation in biological behaviour, prognosis and response to therapy. Molecular classification is generally into Luminal A, Luminal B, HER2+ and triple negative/basal-like, depending on receptor characteristics. Clinical factors that determined the BC prognosis are age and tumor size. Since information on molecular subtypes of Indonesian BCs is limited, the present study was conducted, with attention to subtypes in relation to age and tumor size. **Methods:** A retrospective cross-sectional study of 247 paraffin-embedded samples of invasive BC from Dr. Sardjito General Hospital Yogyakarta in the year 2012- 2015 was performed. Immunohistochemical staining using anti- ER, PR, HER2, Ki-67 and CK 5/6 antibodies was applied to classify molecular subtypes. Associations with age and tumor size were analyzed using the Chi Square Test. **Results:** The Luminal A was the most common subtype of Indonesian BC (41.3%), followed by triple negative (25.5%), HER2 (19.4%) and luminal B (13.8%). Among the triple negative lesions, the basal-like subtype was more frequent than the non basal-like (58.8 % vs 41.2%). Luminal B accounted for the highest percentage of younger age cases (< 40 years old) while HER2+ was most common in older age (> 50 years old) patients. Triple negative/basal-like were commonly large in size. Age ($p = 0.080$) and tumor size ($p = 0.462$) were not significantly associated with molecular subtypes of BC. **Conclusion:** The most common molecular subtype of Indonesian BC is luminal A, followed by triple-negative, HER2+ and luminal B. The majority of triple-negative lesions are basal-like. There are no association between age and tumor size with molecular subtypes of Indonesian BCs.

Keywords: Molecular subtypes- breast carcinoma- age- tumor size

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Introduction

Breast carcinoma is the most common malignancy among woman in Asia-pacific population (Youlden et al., 2014). It is a heterogeneous disease. There is a high biological complexicity, distinctness of prognosis and therapy response (Polyak, 2011; Zardavas et al., 2015). Tumors with similar clinical and pathological appearance may have different biological behaviours. It is believed that these complexity of breast carcinoma are due to molecular differences (Verigos and Magklara, 2015).

Molecular subtypes of breast carcinoma is classified into luminal A (ER + and / or PR +, HER2-, Ki-67 <14%), luminal B (ER + and / or PR +, HER2-, or ER + and / or PR +, HER2-, Ki-67 ≥ 14%), HER2 + (ER-, PR-, HER2 +) and triple negative (ER-, PR- and HER2-) (Goldhirsch et al., 2011). Triple negative subtype which expressed CK 5/6+ called basal-like (Rakha et al., 2009). Each subtype represents different prognosis and response to therapy.

Luminal A has smaller size of tumor, best prognosis and lowest recurrence rate than the other subtypes (Carey, 2010; Goldhirsch et al., 2013). It is characterized higher level of ER and lower level of proliferation related genes. Recommendations for these subtype is mainly based on endocrine therapy (Goldhirsch et al., 2011; Gnant et al., 2015). Luminal B subtype has a more aggressive phenotype and worse prognosis compared to luminal A subtype. There is an increased of proliferation rate and higher expression of growth receptor signaling such as EGFR and HER2 (Tran and Bedard, 2011). Luminal B respons better to neoadjuvant chemotherapy (Gnant et al., 2015). HER2+ subtype has highly proliferation rate, and poor prognosis. HER2+ subtype can be treated with antiHER2 therapy such as Trastuzumab/ Herceptin. (Gnant et al., 2015). Triple negative subtypes have most aggressive behavior with worst outcome (Bosch et al., 2010; Widodo et al., 2017). This subtype is reported to not respond well to adjuvant anthracycline based chemotherapy and need to specific targeted therapy (Naidoo and Pinder, 2016).

Clinical factors that determine breast carcinoma prognosis are patient's age and tumor size. Younger age tend to have aggresive phenotype, advance stage

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and worse prognosis (Aryandono et al., 2006; Ng et al., 2011). Tumor size has conventionally been thought as a fundamental and critical determinant of clinical outcome. Saadatmand et al (2015) revealed that mortality increased with progressing tumor size. Nevertheless, the association between tumor size and molecular subtypes of breast carcinoma was still inconsistent (Hashmi et al., 2014; Liu et al., 2015; Park et al., 2012; Tiwari et al., 2015; Widodo et al., 2014).

The first report about distribution molecular subtypes of Indonesian carcinoma was done by Widodo et al., (2014). The study used ER, PR, HER2 and Ki-67 markers. The association between clinical factors with molecular subtypes of breast carcinoma remains unclear and several studies revealed controversial results. Further study involving larger number of sample and more biomarkers are needed to clarify the distribution, as well as the association of molecular subtypes with their clinical factors. This study was performed to analyse the distribution of molecular subtypes of Indonesian breast carcinoma and their association with patient's age and tumor size.

Materials and Methods

Patients and Methods

A cross-sectional retrospective study was performed at Sardjito General Hospital, Yogyakarta Indonesia involving patients from 2012 until 2015. Approval from ethical review committee (KE/FK/636/EC/2016) was taken antecedent to conducting the study. Clinical information was retrieved from the medical records. There were 816 cases during this study period but only 266 cases have Formalin-Fixed Paraffin-Embedded (FFPE) blocks available. After Immunohistochemical staining, 19 cases were excluded due to small focus on the tumor or non-invasive carcinoma. Age was grouped into < 40, 40-50 and > 50 years old. Tumor size was categorized into < 2cm, 2-5 cm and > 5 cm.

Paraffin blocks and immunohistochemical staining

Immunohistochemical staining was performed using FFPE blocks. Briefly, thick section of 3 μm were stained against five primary antibodies : ER (CRM 301 A,B,C Biocare, dilution 1:100), PR (CRM 302 A,B,C Biocare, dilution 1:200), HER2 (CRM 342 A,B dilution 1:100), Ki-67 (CRM 325 A,B Biocare, dilution 1:200) and CK 5/6 (ACR 105 A,B,C Biocare, dilution 1:100). Immunodetection was performed using biotinylated antimouse/rabbit immunoglobulin, diaminobenzidine chromogen and counter stained Hematoxylin Mayer.

The positive control slides were prepared from tissues of breast carcinoma (ER, PR, HER2), normal tonsil (Ki-67) and normal skin (CK 5/6). Negative control was obtained by omitting the primary antibodies. Interpretation of IHC expression was determinded by two independent observers.

Tumors with ≥ 1% positively nuclear-stained cells were considered positive for ER and PR expression (Hammond et al., 2010). Tumor contains ≥ 14% of nuclear Ki-67 expression was considered as high Ki-67 rate (Cheang et al., 2009). HER2 staining was scored by counting the number of cells positively stained on the membrane and expressed as a percentage of total tumor cells according to the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guidelines. HER2 positive was scored 3+ if circumferential membrane staining that is complete, intense, and within > 10% of tumor cells (Wolff et al., 2013). A positive score for CK 5/6 was recorded if any cytoplasmic and/or membrane staining of tumor cells (Potemski et al., 2006).

Definition of molecular subtypes

Based on the expression of ER, PR, HER2, Ki-67 and CK 5/6, samples were divided into four subtypes: Luminal A (ER+ and/or PR+, HER2- and Ki-67 < 14%); luminal B (ER+ and/or PR+, HER2+/- and Ki-67 ≥ 14%); HER2+ (ER-, PR- and HER2+) and Triple Negative (ER-, PR-, HER2- and CK 5/6+). Triple-negative subtype expressed positive CK 5/6 was classify further into basal-like.

Statistical analysis

Chi square test was employed to examine the association of molecular breast carcinoma subtypes with age and tumor size groups. The value of $p < 0,05$ was considered as significant.

Results

Profile molecular subtypes of Indonesian breast carcinoma

A total of 247 cases of breast carcinoma were included in this study. Median of patient's age was 52 years old (range from 24 – 92 years old). The majority of patient's age was > 50 years old (53,4%). Median of tumor size was 4 cm (range from 0.5 – 21 cm). The molecular subtypes as determined by the expression of ER, PR, HER2, Ki-67 and CK5/6 are shown in Figure 1. Luminal A comprised the most common subtype among the population (41,3%), followed by triple negative subtype (25,5%), HER2+ (19,4%) and luminal B was least common (13,8%). Among 63 cases of triple-negative cases, 58,8% exhibited basal-like phenotype (CK 5/6+) . The characteristics of these breast carcinoma molecular subtypes in Indonesia were presented in Table 1.

Association between age specific groups with molecular subtypes of Indonesian breast carcinoma

All subtype were dominated by older patients (> 50 years old). Patients with younger age (below 40 years old) were more frequently seen in luminal B, triple negative and HER2+ compared to luminal A. HER2+ cases had the highest percentage of older age (> 50 years old). However, there was no significant association between patient's age with molecular subtypes (p= 0,080) (Table 1). Among triple-negative, basal-like had higher frequency in older age (> 50 years old) than non basal-like. Chi-square test showed there was no correlation between patient's age and triple negative/basal-like (Table 2).

Association between tumor size with molecular subtypes of Indonesian breast carcinoma

Thirty eight percent cases had tumor size more than

Table 1. Profile Molecular Subtypes of Indonesian Breast Carcinoma Based on Five Molecular Markers and Their Clinical Factors Characteristics (N = 247 Cases)

Variable	All cases n (%)	Luminal A n (%)	Luminal B n (%)	HER2+. n (%)	Triple-Negative n (%)	p- value
	247 (100)	102 (41.3)	34 (13.8)	48 (19.4)	63 (25.5)	
Age at diagnosis						
mean ± SD (years)	51.89 ± 11.44	52.35 ± 11.63	49.70 ± 11.25	52.52 ± 10.13	51.84 ± 12.26	
Median (min-max years)	52.00 (24-92)	50.00 (24-92)	49.50 (26-72)	53.00 (31-77)	52.00 (27-81)	
Age group						0.080
< 40 years old	32 (13.0)	8 (7.8)	8 (23.5)	6 (12.5)	10 (15.9)	
40 - 50 years old	83 (33.6)	43 (42.2)	10 (29.4)	11 (22.9)	19 (30.1)	
> 50 years old	132 (53.4)	51 (50.0)	16 (47.1)	31 (64.6)	34 (54.0)	
Tumor size group mean ± SD (cm)	5.34±3.98	5.01 ± 3.71	4.89 ± 3.30	5.31 ± 4.08	6.13 ± 4.60	
Median (min-max) cm	4.00 (0.5-21)	4.00 (1-21)	4.50 (1-12)	4.25 (0.6-17)	5.00 (0.5-20)	
Tumor size group						0.462
< 2 cm	42 (17.0)	16 (15.7)	9 (26.5)	10 (20.8)	7 (11.1)	
2– 5 cm	110 (44.5)	50 (49.0)	12 (35.3)	20 (41.7)	28 (44.4)	
> 5 cm	95 (38.5)	36 (35.3)	13 (38.2)	18 (37.5)	28 (44.4)	

Tabel 2. Comparison of Basal-Like and Non Basal-Like in Triple-Negative Subtype of Indonesian Breast Carcinoma and Their Association with Age and Tumor Size, (N = 63 Cases)

Variable	Triple-Negative n (%)		p- value
	Basal-like	Non basal-like	
	37 (58.8)	26 (41.2)	
Age group			0.295
< 40 years old	5 (13.5)	5 (19.2)	
40 - 50 years old	9 (24.3)	10 (38.5)	
> 50 years old	23 (62.2)	11 (42.3)	
Tumor size group			0.715
< 2 cm	4 (10.8)	3 (11.5)	
2– 5 cm	15 (40.6)	13(50.0)	
> 5 cm	18 (48.6)	10 (38.5)	

5 cm, 44,5 % had tumor size 2 to 5 cm and only 17 % cases had tumor size under 2 cm. Luminal B had the highest percentage of small tumor size group (< 2 cm), while triple-negative has the highest percentage of larger size group (> 5 cm) compared to other subtypes. The association between tumor size and molecular subtypes was not significant (Table 1). Among of triple negative, basal-like had higher percentage of larger (> 5 cm) tumor size (48,6 %). However, there was no correlation between tumor size and basal-like subset (p=0,715) (Table 2).

Discussion

We evaluated the distribution of molecular subtypes of breast carcinoma using immunohistochemistry markers and studied their association with patient's age and tumor size. Sample of this study was 247 patients, represented the larger sample size of the similar study in Indonesia. The median age in this study was 52 years old, similar to study conducted in the University Malaya Medical Centre (Ng et al., 2011). Studies in China, Morocco and Northern Iraq showed lower age of diagnosis (46-48 years old) (Elidrissi Errahhali et al., 2017; Runnak et al., 2012; Wei et al., 2014). Higher of median patients age was showed in the United States study (61 years old) (Howlader et al., 2017).

Luminal A was the most common breast carcinoma subtype in this study. The results was similar with others studies (Hashmi et al., 2014; Munirah et al., 2011; Park et al., 2012; Tiwari et al., 2015; Widodo et al., 2014; Widodo et al., 2017; Wong et al., 2011). Different results was reported in African breast carcinoma study in which the highest frequency was triple negative subtype (Huo et al., 2009; Ly et al., 2012). High frequency of luminal A subtypes were influenced by many factors such as early menarche and nullipara (Li et al., 2017), advance age at first birth (Turkoz et al., 2013) and western lifestyle (Devi et al., 2012).

Luminal B subtype was the lowest frequency of breast carcinoma subtypes. This result was similar to previous studies in Japan (Tamaki et al., 2013), Malaysia (Munirah et al., 2011), Thailand (Chuthapisith et al., 2012) and India (Munjal et al., 2009). Studies in China and Korea found that the lowest carcinoma was HER2+ subtype (Jia et al., 2014; Lee et al., 2015; Liu et al., 2015; Park et al., 2012).

BC cases in Indonesia showed higher frequency of triple-negative (25,5%) compared to HER2+ subtype (19,4%). This result similar to studies in Pakistan (Hashmi et al., 2014), Japan (Shibuta et al., 2011; Tamaki et al., 2013), China (Jia et al., 2014; Liu et al., 2015), Korea (Lee et al., 2015; Park et al., 2012) and Malaysia (Munirah et al., 2011). Different profile of molecular subtypes among worldwide population may be caused by different allele frequencies of breast carcinoma-associated genes (Shibuta et al., 2011), different etnicity/ race and risk factors in the population (Devi et al., 2012). Frequency of triple-negative in this study relatively higher than

other populations in Asia (Lee et al., 2015; Munirah et al., 2011; Park et al., 2012; Wong et al., 2011). This may be due to family history of breast carcinoma, obesity in younger age (Turkoz et al., 2013) and no-breastfeeding (Gaudet et al., 2011).

We observed a higher percentage of young age below 40 years old in luminal B, triple negative and HER2+ subtypes carcinoma as compared to luminal A. This indicated that younger patients tend to have worst prognosis. Among those three subtypes, Luminal B has the highest precentage of the younger age group. The same result was seen in population-based studies in Tianjin and Shanghai China (Tang et al., 2015; Wang et al., 2011). However, it different from previous report in Pakistan and Indonesia in which triple negative was the most frequent subtype of younger age group (Hashmi et al., 2014; Widodo et al., 2014).

On the other hand, older age group mostly found in of HER2+ carcinoma (64,6%). This result was similar to Brazilian study (de Macêdo Andrade et al., 2014). Somehow this was different from previous study performed by Widodo et al (2014) that older age group was mostly found in luminal A.

Nevertheless they were different distribution of the molecular subtypes, statistical analysis showed no significant association between patient's age and molecular subytpes. The same results were observed in Malaysia (Munirah et al., 2011), India (Tiwari et al., 2015), Japan (Tamaki et al., 2013) and China (Liu et al., 2015), but not in previous study by Widodo et al (2014).

The average of tumor size was 5,34 ± 3,98 cm with median of 4 cm (0.5- 21 cm). The results were similar with previous study in Indonesian population as most Indonesian breast tumor had large size (Widodo et al., 2014). Among breast carcinoma subtypes, triple-negative had the highest percentage of larger tumor size (> 5 cm) than the other subtypes. In triple-negative subset, basal like subtype was mostly found in larger tumor size (> 5 cm). It may be due to a higher expression of laminin, p-Chaderin, caveolin, basal cytokeratin (Rakha et al., 2009) and MMP 9 (Liu et al., 2013) in basal-like subtype that play crucial roles in several aspect of tumor growth, invasion and metastasis (Goubran et al., 2014; Liu et al., 2013).

There were several limitations of this study, i.e criteria for HER2+ only based on IHC result and not with FISH. Hence 2+ HER2 classified as negative. Other factor such as genetic background, ethnic and risk factors were not consistently evaluated. Further investigation of molecular heterogeneity is necessary.

In conclusion, the frequency of molecular breast carcinoma subtypes vary among different human populations. This study confirmed that the most common molecular subtypes of breast carcinoma in Indonesia was luminal A, followed by triple-negative/basal-like, HER2+ and luminal B. There were no association between different molecular subtypes with patient's age and tumor size.

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Statement conflict of Interest

All authors declare no conflict of interest.

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