Triple Negative Breast Cancer Characteristics Based on Basal-like and Non-Basal-like Subtypes

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Abstract

Objective: To observe triple negative breast cancer (TNBC) characteristics in three hospitals located in Bandung based on basal-like (BL) and non-basal-like (NBL) subtypes.

Methods: This was a cross-sectional study which used descriptive categorical data from medical records and paraffin blocks of TNBC patients treated in Dr. Hasan Sadikin General Hospital, Bandung; Borromeus Hospital; and Santosa Hospital Bandung Central in the period of January 1, 2012–December 31, 2016. The subjects of the study were 57 TNBC patients. The data collected in the study based on medical records were age, tumor size, histopathological images, severity, and immunohistochemical data. The paraffin blocks of the patients based on the completed medicals records were investigated through examinations of immunohistochemichal cytokeratin (CK) 5/6 expressions and epidermal growth factor receptor (EGFR).

Results: Prevalence of TNBC were 82.5% of basal-like subjects and 17.5% of non-basal-like subjects. Among the TNBC subjects, median age of each subtype was 50 years of basal-like subtype and 45 years of non-basal-like subtype. Both subtypes were mostly found in the subjects who aged >40 years. Higher histopathological grade was discovered in both subtypes. The therapy mostly carried out to the subjects was adjuvant chemotherapy. Majority of basal-like subtype subjects were still alive and had longer survival rate and lower incidences of deaths when compared to the non-basal-like subtype.

Conclusions: In TNBC, the basal-like subjects showed greater median age, lower severity stage, and longer survival rate than the non-basal-like subjects. There was no histopathology grade between both subtypes.

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Introduction

Breast cancer (BC) is considered as one of many cancers mostly found in Indonesian people. Incidences of females with BC in Indonesia were approximately 12/100,000 females while in United States 92/100,000 females suffering from BC leading to a large number of mortalities of 27/100.000 or 18% deaths. However, a study stated that in male population there may be 1% of them.[1] Breast cancer is characteristically a heterogenous disease consisting of numerous subtypes with distinctive disease history. It represents large spectrum based on clinical, pathological, and mulecular images and has various prognostic and therapy implications. Recently, central focus related to BC is based on molecular clasification.[2]

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Molecular classification of breast cancer can be distinguished into several groups based on gene expression images by using modest technology of microarray deoxyribonucleic acid (DNA). From gene expression images, BC is classified into 5 subtypes: luminal A, luminal B, triple negative or basal-like, normal like, and excessive human epidermal growth factor receptor 2 (HER2).[3]

The molecular subtypes are commonly associated with survival rate: luminal A tumor has favourable prognosis and normal-like tumor has moderate prognosis. Luminal B, HER2 positive, and basal-like tumors are commonly associated with shorter relapse-free survival (RFS) and overall survival (OS). The molecular subtypes can predict therapy response; HER2 positive and basal-like tumors show greater complete response (CR) after neoadjuvant chemotherapy when compared to luminal and normal-like tumors.[4] Triple negative is also known as breast cancer subtypes with estrogen receptor (ER) negative, progresteron receptor (PR) negative, and lower HER2. The triple negative breast cancer (TNBC) has represented 15–12% of newly BC incidences. It has epidemiological, hispathological, and clinical image which are different from other BC subtypes.[5] It also shows characteristics of more agressive clinical behavior, particular metastasis images, and worse prognosis. The focus is on the TNBC is due to the limitations of the therapy. Until today, the only therapy for TNBC patients is systemic chemotherapy.[6]

In many incidences the TNBC is categorized as basal-like BC. On the contrary, several studies revealed that TNBC and basal-like BC are biologically different tumors. There were many TNBC incidences which could not be identified as basal-like (nearly 80%) and there were basal-like tumors which could not be determined as TNBC.[7] A previous study in 2013 stated that TNBC is a wide subject with various categories so that additional subclassifications is then required.[8]

Gene expression profile (GEP) examination divides TNBC into seven molecular subtypes i.e. basal-like 1, basal-like 2, mesenchymal (M), mesenchymal stem cell like (MSL), immunomodulatory (IM), luminal androgen receptor (AR)-like (LAR), and unknown classification (UNC).[9] The classification based on these subtypes can cause distinctive response during the therapy perceived by each patient.[10] The gene expression profile examination becomes a non-practical medical tool which is regularly conducted in the hospitals due to the expensive costs. Pratt *et al*.[8] suggested that a study on TNBC can be conducted by classifying the subjects based on basal-like tumor versus non-basal-like tumor. Neilsen *et al*.[6] proposed immunohistochemical examination can be used to substitute GEP examination in order to identify BC of basal-like subtype which has the same definition as cDNA microarray examinations such as ER- HER-2- and CK 5/6 or EGFR+. Immunohistochemical examination can illustrate sensitivity (76%) and specifity (100%) in identifying BC of basal-like subtype such as fenotype basal obtained through GEP examination.

The TNBC of basal-like subtype has the same morphological characteristics as the higher histopathology grade. The majority incidences found in TNBC of basal-like subtype were commonly associated with disease history, locoregional disease development, and more agressive metastasis in the first 5 year. This condition can cause shorter survival rate and higher mortalities.

A previous study revealed that TNBC of basal-like subtype becomes an independent marker so that BC can have worse prognosis as commonly found in cancer with or without lymph node metastasis. Tumor with basal-like fenotipe is a worse predictor for the patients such as histopathology grade 3, tumor without lymph node metastasis, and the patients with severe metastasis. The Basal-like tumor determines that metastasis can occur in the brain and lung but metastasis rarely occurs in the bone or liver.[7]

There is another finding of various biological terms from TNBC which is applicable to spread knowledge regarding to effective systemical therapy, provide newly medication including immune checkpoint inhibitor, poly (ADP ribose) polymerase (PARP) inhibitor, cytotoxic therapy including platinum chemoherapy medication, phosphatidylinositol-3 kinase pathway inhibitors, and androgen receptor (AR) inhibitor.[10] Therefore, this study aimed to investigate TNBC characteristics based on basal-like and nonbasal-like subtypes in three hospitals in Bandung.

Methods

Target population in this study was TNBC patients but the population included was carcinoma TNBC patients who had been treated in the three hospitals in Bandung, West Java, Indonesia such as Dr. Hasan Sadikin General Hospital, Bandung, Borromeus Hospital, and

Santosa Hospital Bandung Central, Indonesia in the period of January 1 2012–December 31 2016. The study used cross-sectional method with descriptive categorical design. Samples were the population which met the inclusion criteria.

The inclusion criteria in the study were BC patients who histopathologically and immunohistochemical diagnosed suffering from TNBC carcinoma; slices of paraffin blocks with routine stain of Hematoxylin-eosin, ER-, PR-, dan HER-2- which could be examined; tissue of block paraffin could be evaluated through HE stain or immunohistochemical CK 5/6 and EGFR; the data in the medical records of TNBC patients consisted of age, severity, tumore grading, chemotherapy types, and chemotherapy response; tissue handling was performed based on the standard by using neutral buffer formalin. Exclusion criteria were the patients who had given chemotherapy before histopathological and immunohistochemical examinations while TNBC treatments.

The TNBC patients in the study were treated which were based on histopathological examinations from breast biopsy via immunohistochemical examinations ER(-), PR(-), HER2(-). The immunohistochemical examinations determined that the ER or PR would be negative if the result was <1% while the HER-2 would be negative if the result was ≤+1. The immunoexpressions of CK 5/6 and EGFR were presented in percentage as the cell which expressed CK 5/6 and EGFR from the total tumor cells in representative areas. The CK 5/6 and EGFR assessments were calculated by using histoscore obtained through immunohistochemical examinations consisting of two positive values of qualitative calculations and distribution positive values in several quantitative calculations. Nevertheless, this study could be considered as a semiquantitative study.

The positive values of CK 5/6 and EGFR were obtained from the brown color of BC cytoplasm cells observed by using light microscope which can be classified into 4 levels: 0 (negative) represented color intensity was the same as negative control which is not in brown color; 1 (low positive) was light brown color; 2 (moderate positive) was brown color; 3 (strong positive) was dark color which was the same color intensity as positive control.

The positive values of tumor cells are quantitative values in the form of percentage of brown color intensity distribution per field of view based on the examinations by using light microscope by magnifications of 400 times. The values were categorized into 5 levels: 0 (negative); 1 (<25% if the tumor cells were in brown color); 2 (25–<50% if the tumor cells were brown color); 3 (50–75% if the tumor cells were brown color); 4 (>75% if the tumor cells were brown color).

Both values obtained were distributions of intensity and positivity. Then, the intensity had been timed to positivity due to discover the final value which was regarded as histoscore (HS). This value was determined based on immunoreactive scoring system (IRS) by Remmele W. and Stegner H. E. Negative immunoexpression would be negative if the histoscore was <4 (0–3) and it would be positive if the histoscore was ≥4 (4–12) .[11]

Histoscore= = i x d

There are associations between cancers with the treatments and examinations. The TNBC of basal-like can be diagnosed via immunochemical examination of CK 5/6 (+) and EGFR (+), or CK 5/6 (-) and EGFR (+), or CK 5/6 (+) and EGFR (-). The TNBC non-basal-like can be examined by using examinations of immunochemical CK 5/6 (-) and EGFR (-).

Neoadjuvant is a chemotherapy which is given before surgery.[12] Adjuvant chemotherapy is commonly carried out after surgery. While palliative chemotherapy is given to BC which has been metastased.[12]

Neoadjuvant chemotherapy response are determined as clinical response based on response evaluation criteria in solid tumors (RECIST) with revision version of 1.1 year 2009. The patients may have response if the condition meets complete response (CR) criteria and partial response (PR) but the response does not meet the criteria if the conditions represent progressive disease (PD) and stable disease (SD).[13]

Response of adjuvant chemotherapy in this study was not asssessed based on RECIST because BC mass had been resected. Palliative chemotherapy response was diagnosed by using clinical response based on RECIST. The patients could have response if the condition met the CR, PR, and SD while no response was discovered if the condition met the criteria of PD.[13]

The data in this study were collected by discovering paraffin blocks, recording pathology anatomy, numbers and medica records' numbers from the biopsy specimens of the TNBC patients at the Department of Pathology Anatomy, Dr. Hasan Sadikin General

Hospital, Bandung; Borromeus Hospital; and Santosa Hospital Bandung Central. Afterwards, the data of medical records were synchronized based on the data stored at the three hospitals. If the paraffin blocks were available and still in proper condition, the paraffin blocks would be observed relating to the immunohistochemical expressions of CK 5/6 and EGFR at the laboratory of the Department of Pathology Anatomy, Dr. Hasan Sadikin General Hospital, Bandung.

Results

This study was initiated to investigate the TNBC characteristics based on basal-like and non-basal-like subtypes during March 2017 to November 2017. Population in the study was TNBC patients who were treated in Dr. Hasan Sadikin General Hospital, Bandung; Borromeus Hospital; and Santosa Hospital Bandung Central in the period of January to December 2016.

Among the samples, only 57 samples were included in the study as the subjects. The study could be regarded as the first study which divided TNBC into basal-like and non-basal-like in Bandung, Indonesia.

Among the subjects, fourty seven subjects had TNBC through CK5/6 and EGFR (basal-like subtype) examinations while 10 subjects were observed by using expressions of immunohistochemical CK 5/6 negative and EGFR negative (nonbasal-like subtype) (Table 1).

Adjuvant chemotherapy were mostly given to the subjects in the study (32 out of 57 subjects). The adjuvant chemotherapy commonly given to the subjects combination of were doxorubicin and cyclophosphamide (Table 2).

Neoadjuvant chemotherapy was given to 4 TNBC of basal-like subtype subjects. The results revealed that the response showed partial response (PaR), the tumor shrinked >30% after neoadjuvant chemotherapy. Additionally, all the subjects were given neoadjuvant chemotherapy with surgery and adjuvant chemotherapy.

Neoadjuvant chemotherapy was also given to a subject with non-basal-like with PaR then the subject was given surgery and adjuvant chemotherapy. After six months, metastasis occurred in the lung and brain and the subject died one month later.

Table 1 Basic Characteristics of the Subjects Based on Triple Negative Breast Cancer between Basal-like and Non-basal- like Subtypes

Variables	Basal-like n=47	Non-basal-like n=10
Age (yrs.)		
Mean (SD)	50 ± 11	45 ± 13
Range	30 – 75	23 – 68
Age group (yrs.)		
<40	10 (21.3)	3 (30.0)
>40	37 (78.7)	7 (70.0)
Tumor size (cm)		
≤2	10 (21.3)	2 (20.0)
2.1–5	23 (48.9)	2 (20.0)
>5	14 (29.8)	6 (60.0)
Tumor necrosis		
Existed	14 (29.8)	3 (30.0)
None	30 (63.9)	6 (60.0)
No data	3 (6.3)	1 (10.0)
Lymphocyte infiltration		
Existed	24 (51.1)	2 (20.0)
None	20 (42.6)	7 (70.0)
No data	3(6.3)	1 (10.0)
Lymphovascular invasion		
Existed	26 (55.3)	7 (70.0)
None	21 (44.7)	3(30.0)
Histopathology grade		
Grade 1	2 (4.3)	0 (0.0)
Grade 2	18 (38.3)	3 (30.0)
Grade 3	23 (48.9)	5 (50.0)
No data	4 (8.5)	2(20.0)
Lymp node metastasis		
None	18 (38.3)	5 (50.0)
1–3	15 (31.9)	0 (0.0)
≥4	11 (23.4)	5 (50.0)
No data	3(6.4)	0(0.0)
Tumor stage		
I	4(8.5)	1 (10.0)

II	21 (44.7)	3 (30.0)
III	18 (38.3)	4(40.0)
IV	4 (8.5)	2 (20.0)
Histopathology types		
Invasive ductal carcinoma mammae (IDCM) / invasive carcinoma mammae non specified type	38 (80.9)	8(80.0)
Metaplastic carcinoma mammae	3 (6.4)	0 (0.0)
Invasive lobular carcinoma mammae (ILCM)/ ILCM plemorphic type	3 (6.4)	0 (0.0)
Mucoid carcinoma mammae	0 (0.0)	1 (10.0)
Secretory carcinoma mammae	1 (2.1)	0 (0.0)
Mixed IDCM+ medulary	1 (2.1)	0 (0.0)
Mixed IDCM+ mucoid carcinoma mammae	0 (0.0)	1 (10.0)
Mixed IDCM + Paget Disease	1 (2.1)	0 (0.0)
Type of chemotherapy		
Neoadjuvant	4 (8.5)	1 (10.0)
Adjuvant	29 (63.8)	3 (40.0)
Palliative	2 (8.5)	1 (10.0)
No chemotherapy	5 (6.4)	0 (0.0)
No data	7 (12.8)	5 (40.0)
Ki-67		
<20%	17 (36.2)	8 (80.0)
≥20%	21 (44.7)	0 (0.0)
Without assessment	9 (19.1)	2 (20.0)
P53		
Negative	12 (25.5)	5 (50.0)
Positive	14 (29.8)	4 (40.0)
Without assessment	21 (44.7)	1 (10.0)

Palliative chemotherapy was given to 3 TNBC subjects. Among the 2 subjects with basal-like, 1 subject who was given palliative chemotherapy had lung metastasis and showed response after SD chemotherapy. Palliative chemotherapy was carried out to a TNBC of non-basal-like subject with liver and bone metastases and showed response after SD chemotherapy.

More than a half of TNBC of basal-like subtype subjects were still alive, 20% of non-basal-like subtype subjects were alive, and 30% of the subjects died. However, a half of TNBC of non-basal-like subtype subjects until October 2017 relating to their status were still unknown (Table 3). Mean alive of the TNBC of basal-like subtype subjects had 7 months more of prolonged life when compared to the non-basal-like subtype.

Discussion

Prevalences of TNBC of basal-like subtype in this study were 82.5% (47 out of 57 subjects) while prevalences of TNBC non-basal-like subtype were 17.5% (10 out of 57 subjects). The results were in accordance with a previous study included GEP examination reported that 70–80% TNBC subjects were basal-like subtype and 20–30% subjects were non-basal-like subtype.[9] The GEP examination in BC can distinguish intrinsic subtype which has significant prognostic and predicative value but it is uneasily performed in daily clinical examination. The immunohistochemical is affordable for daily clinical examinations due to identify protein expression as a marker of TNBC of basal-like gene. The immunohistochemical examination is suitable to detect TNBC of basal-like (cytokeratin CK5/6 and or EGFR positive, ER negative, and HER2 negative) which has 76% sensitivity and 100% specifity.[4] The TNBC of basal-like subtype has different molecular lesion (p53 stabilization and more indication of mitosis) and is associated with lower level of survival rate when compared to the non-basal-like subtype.[4,9]

Mean age of TNBC of basal-like subtype in this study was 50 years (ranged 30–75) which lower than the non-basal-like subtype (45 years ranged 23–68). A study by Fadare and Tavassoli revealed that mean age of basal-

Table 2 Characteristic of Chemotherapy Response of Triple Negative Breast Cancer of Basal-like and Non-basal- like Subtypes Based on Chemotherapy Types

Chemotherapy Types	Responses	Basal-like n=36	Non-basal-like n=5
Neoadjuvant	Response (CR, PaR)	4	1
	No respon (SD, PD)	0	0
	Cannot be assessed	0	0
Adjuvant			
	Cannot be assessed	30	3
Palliative	Response (CR, PaR, SD	1	1
	No Response (PD)	1	0
	Cannot be assessed	0	0

like subtype subjects was 47.7–55 while mean age of analyses by using GEP examination was 54.[14] Another previous study stated that tumor with greater basal was mostly found in 40–50 years.[2] There is still unclear finding that TNBC of basal-like subtype subjects are younger than the non-basal-like subtype subjects because many related previous studies have different results.[14] The basal-like subtype have significantly younger mean age when compared to non-basal-like subtype subjects. In contrary, Polish Breast Cancer Study (804 subjects) and Nurses's Health Study (872 subjects) reported that there was no difference age between TNBC of basal-like and non-basal-like subtypes.[14]

The TNBC of basal-like subtype was mostly found in subjects who were in stage II while non-basal-like subtype was mostly found in stage III. The stage IV of TNBC of basal-like subjects in this study had metastases in the lung, bone, and liver while metastases in the liver and bone were found in the non-basal-like subjects. This finding is different from a cohort study in Japan which described that TNBC basal-like subtype had brain and lung metastases. Another study confirmed that TNBC of basal-like subtype and TNBC which has relation to BRCA1 mutation which has metastasis in the brain. The TNBC of basal-like had lower metastases in the bone and liver when compared to ductal carcinoma of stage III non-basal-like subtype.[14]

There is no histopathology different type in both basal-like and non-basal-like subtypes in this study is invasive ductal carcinoma. This is suitable with a study in morphological basal-like subtype with GEP, 21 out 23 patients (91%) was ductal carcinoma. Several studies with immunohistochemical examination also supported that ductal cancer is the mostly histological TNBC of basal-like subtype. If the analyses were focused on the ER- tumor group, the data would show that 80% of both TNBC of nonbasal-like and basal-like subtypes are considered as ductal carcinoma or combination of ductal carcinoma and another hisopathology types.

Beside invasive ductal carcinoma mammae histopathology, other histopathologies can be found in basal-like subtype subjects such as carcinoma metaplastic, invasive lobular carcinoma mammae pleomorphic type, secretory carcinoma mammae, medullary, dan Paget disesase. Among histopathologies, mucoid carcinoma mammae was frequently found in non-basal-like subtype subjects. This finding is similar to a previous study which stated that histopatologies such as medullary carcinoma or combination of ductal carcinoma and medullary carcinoma represents basal-like phenotype.

Table 3 Characteristics of the Last Condition between Triple Negative Breast Cancer of Basal-like and Non-basal-like Subtypes

Last Condition	Basal-like n=47 (%)	Non-basal-like n=10(%)
Alive	25 (53.2)	2 (20.0)
Dead	13 (27.7)	3 (30.0)
Unknown	9 (19.1)	5 (50.0)

The GEP examination from ductal carcinoma and medullary carcinoma with hispathology stage III showed that 95% medullary carcinoma was the ductal basal-like subtype group.[14] In this study, chemotherapy response was assessed in neoadjuvant and palliative chemotherapies. In the neoadjuvant chemotherapy group, the response was found in 3 basal-like subtype subjects and 1 basal-like subtype subject. The subjects who had been given chemotherapies among 57 subjects were 5 subjects (neoadjuvant chemotherapy) and 3 subjects (palliative). Therefore, this study could not clearly describe the response between neoadjuvant and palliative chemotherapies in TNBC of basal-like and non-basal-like subtypes.

In this study, more than 50% subjects (32 out of 57 subjects) were given adjuvant chemotherapy because it is suggested for TNBC and HER2 + subjects in the early up to locally advanced. The TNBC subjects negative who had been given neoadjuvant chemotherapy had pathologic complete response (pCR) approximately 27–45% while the pCR value in BC with HER-2 negative and hormone receptor positive had 10% lower of pCR. In contrary, the TNBC subjects who had been given adjuvant chemotherapy did not show higher risk of pCR leading to early metastasis.[4]

This study determined that among TNBC subjects, non-basal-like subtype had worse condition when compared to the basal-like subtype. This finding is different from the previous study which stated that TNBC of basal-like subtype has worse result than other TNBC subtypes.[10] This condition is caused by different race characteristics between this study and those previous studies. Besides, the samples of TNBC non-basal-like subtype in this study were 10 out of 57 subjects. The results in the study cannot describe precise information relating to the TNBC of non-basal-like subtype so that larger samples are required in order to describe the real condition.

This was a retrospective study which collected the data based on the medical records. Uncompleted data found in the medical records caused problems to obtain sufficient data and information such as carcinoma history of the family, menarche and menopause statuses. The medical records of inpatiens or outpatients at the Department of Oncology Surgery, Department of Internal Medicine, and Department of Pathology Anatomy, of both hospital in Dr. Hasan Sadikin General Hospital, Bandung and Borromeus Hospital did not have integrated access so that the data were collected manually.

In summary, TNBC in the hospitals in Bandung was classified into two subtypes, basal-like and non-basal-like. The prevalences of TNBC of basal-like subtypes were higher than another one. Mean age of TNBC basal-like was higher than non-basal-like. There was no different type and degree of hispathology found in both subtypes. More severe BC was discovered in non-basal-like subtype. The theraphy commonly given to the subjects of both subtypes was adjuvant chemotherapy so that the chemotherapy response was hardly discovered in this study. Among the subjects, deaths in this study were mostly found in TNBC of non-basal subtype when compared to the basal-like subjects.

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