Pre-menopausal triple-negative breast cancer at HAM hospital medan

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Abstract. Triple-negative breast cancers (TNBC) are a type of breast cancer that does not have any or lack expression of the three receptors of estrogen (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER-2). This cross-sectional study was performed on patients TNBC in HAM hospital Medan from 2013 to 2016 by immunohistochemistry stained. A total 60 invasive breast cancer samples with TNBC. The more frequent in TNBC group were 51-60 years (19 cases, 31.66%) and pre-menopause (34 cases, 57%). Tumor size T3 and T4 with *staging* IIIA and IIIB, histology sub-type IC-NOS and ILC with grade 2 and grade 3 of histologic was more common in TNBC.

1. Introduction

Triple-negative breast cancer (TNBC) is different from the other types of breast cancer because it does not have any expression of the receptors commonly found on breast cancer cells Estrogen(ER), and progesterone (PR), as well as lack or no expression receptor of human epidermal growth factor receptor 2 (HER-2).[1] TNBCs distinct entities as compared with estrogen receptor (ER)+ tumors strongly support by epidemiology studies. TNBC still a problem in breast cancer therapy due to ineffective of hormonal and Her-2 therapy. Lack of ERs is an equivocally crucial indicator of poor prognosis and fatal outcome in breast cancer.The etiologic factors, clinical characteristics, and therapeutic possibilities may vary by molecular subtypes.[2-4] TNBC represents approximately 15%-20% of invasive breast cancers, and clinically TNBCs fairly aggressive local growth, rapid progression and a high rate of early metastases.[5,6]

In worldwide breast cancer is the second most common cancer in women with about 1.68 millions cases (3%) of all cancer in women, and is the second cause of mortality.[7] Data from Indonesian Ministry of Health in 2013, the incidence of breast cancer in Indonesia has the second most common cancer after cervical cancer. Data from Department of Oncology in RSUP Haji Adam Malik Medan in 2011-2015 were about 600 new cases per year.[8]

Several reproductive and hormonal factors also endogenous sex hormonal are thought to influence therisk of breast cancer. Sufficient data from studies of hormones and risk breast cancer in postmenopausal women now exist [9], but data for pre-menopausal women are fewer.

Histologically, TNBC is a heterogeneous tumor consisting of several subtypes of low grade and high-grade tumor. TNBC has a more aggressive compared with other cancer types, and to date, there

is still argument about its therapy because TNBC is ineffective with hormonal therapy such as tamoxifen, or targeted anti-HER2 such as Herceptin.[10-12]

2. Material and Method

2.1 Research location
This research took place in RSUP Haji Adam Malik/Department of Anatomical Pathology Medical Faculty USU Medan and Department of Surgical Oncology RSUP Haji Adam Malik Medan.

2.2 Method
We enrolled 60 cases TNBC who had undergone surgery for primary breast cancer HAM hospital/ Department of Anatomical Pathology Medical Faculty of USU Medanfrom January 2013 to December 2016. This is adescriptive study with across-sectional design. All patients were diagnosed withinvasive breast cancer underwent mastectomy orradical mastectomy. None had received chemotherapy or radiotherapy. Clinicopathological information was obtained by reviewing medical records (including from Department of Surgical Oncology RSUP HAM Medan) and pathology reports. We obtained the following variables such as age, clinical stage (tumor size, lymph node status), sub-type histology, and Bloom-Richardson method histological grade that had been modified by Elston Ellis.

Furthermore, paraffin block samples fulfilling inclusion and exclusion criteria were immunohistochemically stained with ER (clone 6F11, Dako, dilution 1: 100), PR (clone PgR 636, polyclonal Ab, Dako, dilution 1: 200), and Her-2 (clone A0435, polyclonal Ab, Dako, dilution 1: 200). Based on ASCO/CAP guidelines, breast cancer was considered positive for hormone receptor (ER and PR) if at least 1% of tumor cells stained positive in nuclei (Hammond et al., 2010). Breast cancer was considered positive for Her-2 if strongly and homogenous stained in membrane cell/ chicken wire pattern (score 3+). If it was not stained/ weakly stained, the tumor would be scored as 0 or 1+, but if the membrane cells of atumor incomplete homogenous stained (borderline/ moderate), the tumor would be scored as 2.

This study was carried out after getting permission from Ethical Committee of Medical Faculty USU Medan.

3. Result
In total 60 cases TNBC in this study and summarizes the patient and tumor characteristics (Table 1), all the patients were all female, the median age was 46 years (range 27-73 years), the mean age was 47.18 ± 47.18 years. The most common age was in the range of 51- 60 years old (19 cases, 31.66%), while the least was in ≤ 30 years old (3 cases, 5%).

Table 1. Clinical characteristics of TNBC.

TNBC		Total (n)	Percentage (%)	Information
Sample size		60		
Age (years)	≤ 30	3	5	Median 46 years old,
	31-40	16	26.67	Mean 47.18 ± 11.23 years old
	41-50	16	26.67	
	51-60	19	31.66	
	≥ 60	6	10	
Menstrual status	Pre-menopause	34	57	
	Post-menopause	26	43	

Premenopausal cases (34 cases, 57%) was found much more than post-menopausal (26 cases, 43%).

Table 2. Clinical characteristics and pathology of pre-menopausal and post-menopausal in TNBC.

TNBC		Pre-menopause		Post-menopause		
		Total (n)	Percentage (%)	Total (n)	Percentage (%)	
Menstrual status		34	57	26	43	
Tumor size	Tx	1	3	2	8	3 (5%)
	T1	0	0	1	4	1 (2%)
	T2	0	0	0	0	0
	T3	15	44	11	42	26 (43%)
	T4	18	53	12	46	30 (50%)
Lymph node status	- No	8	24	8	31	16 (27%)
	- Nx	2	6	2	7	4 (7%)
	- N1	22	65	15	58	37 (61%)
	- N2	2	6	1	4	3 (5%)
Tumor staging	IIIA	8	23.5	7	27	15 (25%)
	IIIB	26	76.5	19	73	45 (75%)
Histopathology subtype	*IC-NOS*	30	88	18	69	48 (80%)
	ILC	4	12	8	31	12 (20%)
	Others	0	0	0	0	0
Grading histology	Grade 1	8	24	1	4	9 (15%)
	Grade 2	11	32	15	57	26 (43%)
	Grade 3	15	44	10	39	25 (42%)

Tx = undetermined of tumour size, T2 = tumour size < 2 cm, T3 = tumour size more than 5 cm, T4 = tumour size expanding to chest wall and/ or to skin. IC-NOS =invasive carcinoma no special type, ILC = Invasive lobular carcinoma.

Pre-menopausal in TNBC (Table 2) had 15 cases (44%) with tumor size > 5 cm (T3), 18 cases (53%) of T4, and 1 case (3%) of undetermined tumor size (Tx) and no case with tumor size < 1 cm (T1) and < 2 cm (T2). Lymph node status in pre-menopausal TNBC, there were 24 (72%) cases had positive with N1 and N2, but only 8 cases (24%) were negative (To). Based on staging, there were 26 cases (75%) of stage IIIB pre-menopausal TNBC had expanding to chest wall and/ or to skin (T4) with or without metastasis to ipsilateral axillary lymph node (N0, N1, N2), and 15 cases (25%) of stage IIIA with tumor size < 5 cm (T0, T1, T2) accompanied with metastasis to ipsilateral axillary lymph node level I and II clinically involving ipsilateral internal lymph node (N2), or with tumor size > 5 cm with or without metastasis to ipsilateral axillary lymph node or clinically involving ipsilateral internal lymph node (N1, N2).

Based on histopathology sub-type, there were 30 cases (88%) of IC-NOS and 4 cases (12%) of ILC. Other sub-types (such as tubular carcinoma, medullary carcinoma) were not found. The grading of TNBC with pre-menopausal found in this study were grade 1 (8 cases, 24%), grade 2 (11 cases, 32%), and grade 3 (15 cases, 44%).

4. Discussion

As we study TNBC in the present study, despite TNBCscan found in all ages, but pre-menopausal have a higher rate than post-menopausal women. Pre-menopause TNBC in this study is relatively has large size, high grade, and high rate of node positivity at diagnosis. Literary data support that young age is associated with equivocally higher incidence rate TNBCs as compared with older female cases.[13] In spite of the various age grouping, hormonally mediated risk factors are regarded as being

essential in the apparently higher TNBC incidence rate among young cases. Great hormonal changes occurring during a woman's life might strongly define the inclination to initiate any type of breast cancer, including TNBC.The stronger hormonal imbalance, characterized mainly by hyperinsulinism, hyperandrogenism, and low estrogen exposure, the higher breast cancer risk, particularly for poorly differentiated TNBC type.[14]

The three main phases particularly dangerous for breast cancer initiation in women's life, such as: (1). Adolescence (14-18 years), (2). Peri-menopausal phase (45-55 year), and (3). Older age (over 60 year). Two of adolescence and peri-menopausal are crucial periods present risks if the biologic processes in the background become pathologic. Pubertal changes, since the abrupt somatic and sexual development presents real danger for development of insulin resistance and imbalance of male-to-female sexual hormone ratio. Inherits genetic or acquired somatic anomaly, such as glucose intolerance or obesity, overproduction of androgen will develop, at the expense of defective estrogen synthesis.[15] Especially risky phase older age when the hormonal and metabolic imbalance become stronger and the defense mechanisms against cancer are debilitated. Perimenopausal is the second risky period for breast cancer initiation, when there is a slow or steep decline in ovarian female sexual steroid synthesis.[16] Similar data from previous researchers supported that young age has higher incidence of TNBC than old age.[17,18] Boyle's stating that the risk of having TNBC in pre-menopause women are three times higher than post-menopause and have aworse prognosis than other breast cancers.[19] However, Yuan suggested that there are no significant differences among agroup of age and status of menopause in the incidence of TNBC in China.[20]

Pre-menopausal TNBC had most of thetumor size expanding to thechest wall and/ or spreading to the skin (T4) with size more than 5 cm (T3), and also outspreading to lymph node with stage tumor of IIIB and IIIA. Recent studies about tumor size and metastasis to lymph node found diverse results. Yuan found that TNBC has a tendency to metastasis to lymph node compared with other breast cancers.[20] However, this results were in contrast to the study by Rakha [21] and Tschkowitz [22], that there were no differences in the frequency of metastasis TNBC to lymph node with other breast cancers. The size of primary tumor (tumor/T), involvement of lymph node (nodes/N), and the presence of absence of spreading/ distant metastasis (metastasis/M) based on AJCC (American Joint Committee on Cancer)/ UICC (Union for International Cancer Control) give important information for determining disease control locally or assessing systematically.[23]

From this research, we found pre-menopausal TNBC with invasive carcinoma no special type (IC-NOS) and invasive lobular carcinoma (ILC) as histopathology subtype. IC-NOS subtype was found more than ILC. Other sub-types such as tubular carcinoma, cribriform carcinoma, mucinous carcinoma, and etc. were not found in this study. Most common grading histology of TNBC in this research was grade 2 and grade 3, but grade 1 only 8 cases (24%). This study was in accordance with Abdollahi and Etemadi [18]and Boyle [19] who found that most TNBC was diagnosed with high-grade histology. TNBC with various tumor sizes and stages would have a worse prognosis if the histology grading were higher.[18]

5. Conclusion

TNBC can be found in all ages;premenopausal have a higher rate of *TNBC* than postmenopausal women.Most of them with tumor size > 5cm, and had already metastasized to the lymph node, and has a histopathology diversity with high-grade histology.

TNBC needs special attention so that clinicians can predict the prognosis and can help in further more optimal handling. Furthermore, we need to give counseling to the community of several socioeconomic levels in order to recognize and to early prevent breast cancer.

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