Clinical Initial Response of Neoadjuvant Chemotheraphy in Triple Negative, HER-2, and Luminal Types of Breast Cancer in Denpasar (A Preliminary Study)

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Objectives: Triple Negative, Luminal, HER-2 subtypes of breast cancer are markers to predict behavior, aggressiveness, and response to chemotherapy. The aim of this study is to understand character and response to standard neoadjuvant chemotherapy in different subtypes of breast cancer.
Method: This is a descriptive study of breast cancer subtypes. From 687 patients (2003-2010) 351 patients have IHC data which divided into 3 groups, Triple negative, Luminal, and HER-2. We used 10% as a cut off point for ER, PR, while 30% & positive 3 for HER-2. We determined initial clinical response after 3 cycles of neoadjuvant chemotherapy although only 77 got standard neoadjuvant chemotherapy and had clinical response data. We used 50% diameters depreciation & no metastasis as cut off point for respond group.
Results: There were 116 (33%) Triple Negative, 60 (17%) HER-2, and 175 (50%) Luminal Subtypes. The mean of age for 351 patients are 48.32 (23-82) years. In this study, it was obtained that no significant difference of means of age (p=0.24) in these 3 groups. Triple negative group significantly more advance in grade if compared with the other two groups (p=0.02). HER-2 group had highest response with standard neoadjuvant chemotherapy (50%), Luminal group had (49%), and Triple negative group had only (15%) response. One pCR in HER-2 group. There were no difference ages in subtypes. Triple negative has more advances in grade. HER-2 group has highest response to standard neoadjuvant chemotherapy and Triple negative has lowest response to standard neoadjuvant chemotherapy.
Keywords: *Triple Negative, Neoadjuvant chemotherapy, breast cancer*.

INTRODUCTION

Recently experts had already developed an instrument to explore breast cancer characteristic and feature according to the expression of some proteins and it can distinguished by immunohistochemistry. This effort intended to determine appropriate therapy for breast cancer patients. This instrument used expression of estrogen receptor (ER), progesterone receptor (PR), Human Epidermal Receptor 2 (HER-2), (Cytokeratin) CK 5/6, Epidermal Growth Factor Receptor (EGFR) as a tool for grouping breast cancer into several subtypes. In worldwide commonly they used 5 subtypes of breast cancer as routine procedure of examination. There are Luminal subtypes that can be divided into A and B, Triple Negative subtype, HER-2 subtype, basal like subtype, and normal breast subtype.[1,2] In our department we used only 4 subtypes to determine the breast cancer characteristic and feature. We used only Luminal A, Luminal B, HER-2, and Triple negative breast cancer (TNBC) subtype due to patient's expense and our laboratories ability. From 1 million cases of breast cancer were diagnosed annually worldwide, approximately 170,000 are Triple-negative subtype. Of these TNBC cases, about 75% are "basal-like".

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The prevalence of TNBC is highest in African American women; a recent report notes that 39% of all African American premenopausal women diagnosed as breast cancer are TNBC subtype. The prevalence of TNBC in this same age group in non–African American women is much less, at approximately 15%. Another report described that Triple negative subtype in African American were 47% compared with 22% in white woman. After adjusting age and stage at diagnosis, African American women were 3 fold likely than white women to have Triple negative tumors.[2-6] From two studies that compared Triple negative with non Triple negative showed that Triple negative have shorter overall survival, local relapse, progression free survival, & have higher risk to visceral metastasis. [7,8] Another some studies compared TNBC with Luminal A subtype and HER-2 Subtypes showed that TNBC had worse disease free survival, overall survival, progression free survival, relapse free survival. [9-12] But this condition is inversed in the clinical response of neoadjuvant chemotherapy. Research increasingly suggests that the molecular subtypes TNBC are associated with chemosensitivity. TNBC subtype has been shown to be more sensitive to neoadjuvant chemotherapy than the Luminal and ER-positive breast cancer. Some studies of anthracycline based neoadjuvant chemotherapy with combination of taxane, fluorouracil, and cyclophospamid in TNBC

with control arm (non TNBC) showed higher pathological complete response (pCR) rate.[13-22] Also neoadjuvant chemotherapy with taxane alone, epirubicin based, capecitabine, carboplatin and cisplatin based in TNBC with non TNBC as control arm showed that TNBC had higher pCR compared with their control arm.[21-24] We began a research to know the characteristic and chemotherapy response of TNBC in Denpasar Bali

METHODS AND PATIENTS

A descriptive analytical study to explore the characteristic of TNBC in Denpasar Bali was conducted in 2010. Subject was collected from government and private hospital, and from 687 data patients between January 2003 and October 2010 were retrospectively analyzed. These data consist of 3% patients in stage I, 28% in stage II, 43% in stage III and 26% in stage IV. For inclusion criteria we included all of breast cancer patients with IHC results, and for exclusion criteria we exclude patients without complete clinical data. After we used consecutive technique to collected samples, so we got 351 patients data samples. Afterward these data were grouped into 3 groups. We grouped our samples into HER-2 group, Luminal group (which consist of Luminal A & Luminal B), and Triple negative group. ER and PR status assessed by scoring the percentage of stained cell using immunohistochemistry staining, 10% or more cells stained without appraise the intensity considered as positive. HER-2 status was assessed by scoring the intensity of membrane staining. Tumors with a score of 3 (strong homogeneous staining) on 30% or more cells were considered HER-2- positive. In case of 2, scores (moderate homogeneous staining) was considered as HER-2 negative. Histopathological grading from these 3 groups was analyzed after we exclude non IDC pathological results. We also analyzed the mean of ages of these all patients also in these 3 groups.

Neoadjuvant Chemotherapy Response

From these data we have 77 patients who have complete medical record and received standard neoadjuvant chemotherapy before surgery. These patients consist of 14 HER-2, 26 Triple negative, and 37 Luminal. In our department we analyzed the response of neoadjuvant chemotherapy according to the comparison tumor diameter before neoadjuvant chemotherapy to tumor diameter after third cycle's neoadjuvant chemotherapy. We used 50% or more diameter depreciation and complete pathological respond as a cutoff point for respond group. And in the opposite group we used less than 50% depreciation or progressive disease as criteria for no respond group. Pathological complete response (pCR) was defined as the absence of invasive carcinoma in both the breast and axilla at microscopic examination of the resection specimen, regardless of the presence of carcinoma in situ. Progressive disease was defined as increased tumor size or emerge new metastasis after third cycle of neoadjuvant chemotherapy.

Tumor diameter size was assessed with a ruler. We used highest diameter of tumor and used the mean of 3 measurements to record every response data. Nodal status prior to neoadjuvant chemotherapy was determined by clinical examination. Metastasis status was assessed with chest x-ray, abdominal USG, CT-scan, bone survey and clinical judgment after third cycle of neoadjuvant chemotherapy. Prior to neoadjuvant treatment, all of patient received open biopsy of the breast tumor to determine the histological subtype, hormone receptor, and HER-2 status.

From patients who participated this study there were some patients in locally advance breast cancer stage and some patients in early operable stage who received neoadjuvant chemotherapy for down staging to improve surgical treatment result. The clinical studies informed consent was obtained from all patients.

Chemotherapy Regimens

Every patients who participated this study received standard neoadjuvant chemotherapy CAF (3 cycles of doxorubicin 50 mg/m2, 5FU 500 mg/m2 and cyclophosphamide 500 mg/m2, every 3 weeks) or CEF (3 cycles of epirubicin 50 mg/m2 5FU 500 mg/m2 and cyclophosphamide 500 mg/m2, every 3 weeks) depend on their insurance. Chemotherapy responses were determined after third cycle's neoadjuvant chemotherapy.[1]

A total of 77 patients were treated in this period were treated according to the standard arm (FAC/FEC). Furthermore, the tumor response was evaluated by clinical examination for tumor size and nodal status, we used x-ray, USG, and CT-scan for metastasis status after third cycle's neoadjuvant chemotherapy. No patient received trastuzumab prior or during adjuvant chemotherapy. Neither received hormonal therapy prior or during adjuvant chemotherapy.

Analysis

Data were analyzed using SPSS version 15.1 (SPSS Inc, Chicago, IL). A multivariate logistic regression model was built to examine the associations between ages, molecular subtype based on tumor receptor status (ER positive vs Triple-negative vs HER-2 positive). The level of significance was set at 0.05.

RESULTS

Table 1 shows the patients and tumors characteristics. Amounts of HER-2 group, Triple negative group and Luminal group were 60 (17%), 116 (33%), and 175 (50%) respectively. The mean age from these 351 patients was 48.23 (range 23–82). We analyzed the means of these 3 subtypes using one way anova after we transformed age data due to abnormal sample distribution.

Table 1
Comparison characteristic of 3 subtypes of breast cancers

	Luminal	HER-2	Triple Negative
Number	175(50%)	60 (17%)	116(33%)
Age (year)	48.5±10.5	49.4±7.6	47.3±10.8
Range of age	(23-82)	(29-64)	(27-81)
IDC Grade low	18(13%)	9(15%)	7(8%)
IDC Grade Med	75(54%)	27(46%)	28(31%)
IDC Grade High	45(33%)	22(39%)	56(61%)
ILC	11	0	6
Other	26	2	19
Respond	18 (49%)	7 (50%)	4 (15%)
No Respond	19 (51%)	7(50%)	22 (85%)

The means ages were Luminal (48.5), HER-2 (49.4), Triple negative (47.3). And we found there was no significantly difference in these 3 groups (P=0.24). From histopathology results there were 82% (288) had IDC, 4% (16) ILC, 14% (47) have other results.
After we divided data into 3 subtypes and exclude non IDC pathologic result, we analyzed grading in these 3 groups as ordinal data using Kruskal-Wallis test. We found there was significantly difference in these 3 groups. Than we did post hoc analysis using Mann-Whitney test to find which one was different with other. We found Triple negative group was significantly different with 2 other groups, and there was no significantly different between HER-2 group and Luminal group. So we concluded that Triple negative had significantly more advance in grading than 2 other groups.

In these 3 groups we assessed the outcome of initial respond to standard neoadjuvant chemotherapy. There were 77 patients who have standard neoadjuvant chemotherapy, 14 in HER-2 group, 26 in Triple negative group, and 37 from Luminal group. Almost all patients had received CAF regimen and only few patient had received CEF regimen. Unfortunately we cannot determine which patient have CEF regimen. We investigated and collect data highest diameter from primary tumor, nodal status and metastasis status. After they received a third cycle's of standard neoadjuvant chemotherapy we analyzed the data. Patient who had partial (tumor shrink more than 50% in diameter) response and complete response grouped in to respond group. Afterward patent with progressive disease and no respond (tumor shrink less than 50% in diameter) grouped into no respond group. We have 48 patients in no respond group and 29 patients in respond group. Luminal group have 49% (18) respond and 51% (19) no respond, HER-2 group have 50% (7) respond and 50% (7) no respond while Triple negative group have 15% (4) respond and 85% (22) no respond.

DISCUSSION

In this study, we assessed the characteristic of 3 different subtypes in these 351 patients and we also assessed the outcome of standard neoadjuvant chemotherapy in different breast cancer subtypes in a consecutive series of 77 patients with locally advance breast cancer (Figure 1).

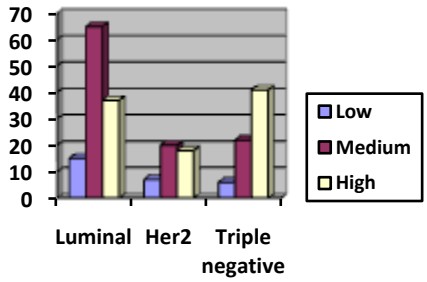

Figure 1
Grade distribution in 3 subtypes

In respond group it had only 4.5% (2) ILC pathologic while in no respond group there was 3.6% (1) patient was ILC (Figure 2).

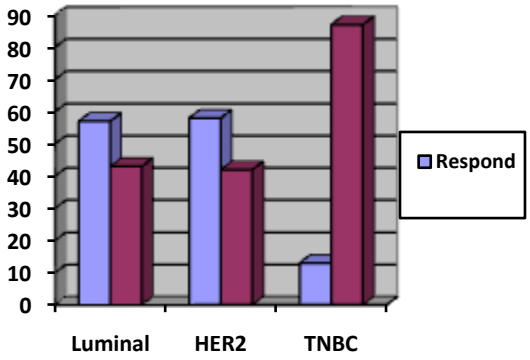

Figure 2
Response distribution in breast cancer subtypes

Total amount Triple negative in Denpasar (32%) was higher than usually declare on western literature, but it similar to the amount of Triple Negative African American women. It is likely that women in

Denpasar have more risk to have Triple negative, and it is similar with African American women. So we can presume that Triple negative in Denpasar will have same characteristic with Triple negative in African women. But we need a large comprehensive study to compare our Triple negative with another human race.

The mean age of our Triple negative women is young, and it is younger than American women [25,27], but they age do not differ with another breast cancer subtype in Denpasar. So breast cancer cases in Denpasar have younger age no matter what subtype is.

From grading data in some subtype, our study showed that Triple negative significantly more advance in grading. They have largest amount of high grade when we compared with other 2 subtype. This data were similar with results from many studies. [25-27] From data of clinical initial respond from standard neo adjuvant chemotherapy showed us that our Triple negative have very poor in initial respond.

Our samples are not large enough to make a conclusion in respond neoadjuvant chemotherapy. But from the calculation our Triple negative have lowest and very different amount respond to neoadjuvant chemotherapy compare with other subtype. A matter of fact from some other study declare that Triple negative have better respond in neoadjuvant chemotherapy and have higher rate of pCR. The outcome in our study showed inappropriate with another studies. [28-30] This condition could be caused by some factors like difference standard immunohistochemical technique between every study. In our study we collected data from 4 different laboratories. Ideally we should have one reference laboratory to confirm the results from every laboratory. Another factor may caused by different cutoff point in our study with another study. In our study, we used only one dimension measurement, largest diameter to measure the clinical response. It is very different with other study which used 3 dimension or measure the volume of tumor used MRI with contras enhancement to determined response. Another factor probably due to different genotype character in our Triple negative this is a matter of fact that we have to investigate furthermore. Some experts explain in their studies that cancer with mutation of gen repair gen will be more respond with chemotherapy. So there are many question arise after finished this study. How many percent basal subtypes present in our Triple negatives? Do our Triple negatives have BRCA mutation or other gene repair gene mutation? What is the difference of our Triple negative compare another Triple negative in different races?

CONCLUSION

There were no difference age but they had significantly difference in grade. Triple negative has more advances in grade. HER-2 group has highest response to standard chemotherapy and Triple negative has lowest response to chemotherapy. Our Triple Negative has difference characteristic in response to neoadjuvant chemotherapy.

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