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Relationship of Grade, Intrinsic Subtype and Clinical Response to Neoadjuvant Chemotherapy in Breast Cancer

Adliah Purnawaty[a*], William Hamdani[b], Idham Djaya Ganda[c]

[a,b]*Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[c]*Department of pediatric, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[a]*Email: adelia28cawidu@gmail.com*

[b]*Email: williamhamdani_mks@yahoo.co.id*

[c]*Email: idhamjaya_spa@yahoo.co.id*

Abstract

Neoadjuvant chemotherapy has become the standard treatment strategy for locally advanced breast cancer. Currently, neoadjuvant chemotherapy was applied empirically; there are no conventional biomarkers that allow for predicting clinical response and benefit from a particular chemotherapy regimen. Studies mention that grade and intrinsic subtypes are predictors for clinical response to chemotherapy. Purpose of this study were to know the relationship of grade, intrinsic subtype, and clinical response to neoadjuvant chemotherapy in breast cancer. Cross-sectional studies by examining breast cancer patients who underwent chemotherapy in Wahidin Sudirohusodo, a top referral hospital with 913 bed in Makassar Indonesia, from January 2015 to December 2016. Results: During the periods, neoadjuvant chemotherapy have been conducted to 119 breast cancer patients. In the bivariate analysis, we found that grade significantly associated with chemotherapy response obtained p-value = 0.002 ($p < 0.005$). Clinical response to neoadjuvant chemotherapy based on subtypes was Luminal A 55.2%, Luminal B 61.2 %, Her2 80%, Triple Negative 87.5%. Association of subtype and chemotherapy response was also significant with p-value = 0.056. Conclusion: histopathological grading and Intrinsic subtype were associated with anthracycline-based neoadjuvant chemotherapy response on breast cancer.

Keywords: Breast Cancer; Chemotherapy; Clinical Response; Grade; Subtype.

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* Corresponding author.

1. Introduction

Breast cancer is one of the most common cancers suffered by women across the globe. It accounts for about 23% of all malignancy in women, and every year 1.1 million women are diagnosed with breast cancer [1].

In the USA, it is estimated that 192.370 new invasive breast cancer cases and 62.280 in situ breast cancer cases are diagnosed each year.

Mean breast cancer patients age is 61 year with incidence rate 124 per 100.000 women per year [2]. In Indonesia, breast cancer is the most common cancer found, followed by cervical cancer. On 2012 breast cancer incidence rate in Indonesia was estimated about 48.998 [3].

According to Jakarta cancer registry, breast cancer has the highest incidence rate in Indonesia with 18.6 per 100.000 population per year [4]. In 2013, the death rate due to breast cancer in Indonesia was approximately 19.750 [3].

Breast cancer treatment consists of surgery, radiotherapy, chemotherapy, and hormonal therapy[5, 6]. Chemotherapy is a type of treatment which uses drug combination to destroy or slow down cancer cell growth[7, 8]. Today chemotherapy is the most critical component in breast cancer treatment[9, 10].

Neoadjuvant chemotherapy has become the standard for local breast cancer treatment, and treatment of choice for early stage operable breast cancer. Neoadjuvant chemotherapy has much profits for breast cancer treatment, which can give the better operative option and better chemotherapy response[11].

2. Materials and Method

2.1. Collection of Samples

This is an observational study using the longitudinal method to assess the relationship between ER, PR, HER2, and the Ki-67 expression on women who suffered locally advanced breast cancer.

This research was conducted in Dr. Wahidin Sudirohusodo General Hospital, Makassar, South Sulawesi. The study period was from December 2015 until December 2016.

The study subject was all women suffered from locally advanced breast cancer (III-B) who underwent treatment in Dr. Wahidin Sudirohusodo General Hospital.

2.2. Expression DUSP4 by Immunohistochemistry

ER, PR, HER2, and Ki-67 expression examination were conducted in Pathological Anatomy Laboratory, Medical Faculty of Hasanuddin University, Makassar.

2.3. Classification of clinical response to chemotherapy

Chemotherapy response is classified as nonresponsive, if tumor size is reduced ≤ 30%, no change or increased in tumor size, or if found a new tumor; while responsive, if tumor is disappear, or there is a reduction >30% and no new tumor found.

2.4. Data Analysis

Data analysis using the SPSS (Statistical Package for Social Science) version 22. Analysis of patient's characteristics and clinical response using chi square.

2.5. Ethical Clearence

Ethical approval for this study was obtained from Research Ethics Committee, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.

3. Results

During the study period from December 2015 until December 2016, we collect breast cancer patient's data who had undergone neoadjuvant chemotherapy in Oncology Surgery Division, dr. Wahidin Sudirohusodo General Hospital.

Makassar, and we found 119 sample who met the inclusion criteria, in which 80 patients (67.2 %) responsive to neoadjuvant chemotherapy, and 39 (32.8 %) nonresponsive patients.

3.1. Characteristics

In this study we found 119 patient who had breast cancer, the youngest being 29 years old, and the oldest is 75 years old, 74 (62.2%) of them aged < 50 years old. From histopathological grading, we found 10 cases (8.4%) low grade, 76 cases (63.9%) average grade, and 33 (27.7%) high grade.

From immunohistochemical panel, we found 74 (62.2%) ER+, 60 (50.4%) PR+, 59 (49.6%) Her2+, and 57(47.9%) Ki-67+. From that immunohistochemical panel result, we also found 29 (24.4%) luminal A subtype, 49 (41.2%) luminal B subtype, 25 (21%) Her2, and 16 (13.4%) triple negative.

Eighty patients (67.2%) were responsive to the neoadjuvant chemotherapy given. Characteristics of the breast cancer patients can be seen in Table 1 below.

3.2. Relationship between age and neoadjuvant chemotherapy response on breast cancer

In this study, we analyze the effect of various clinicopathologic factors toward neoadjuvant chemotherapy response on breast cancer because some of those clinicopathologic factors are also confounding factors which influence dependent and independent variable.

Table 1: Characteristics of breast cancer patients who underwent neoadjuvant chemotherapy

Characteristics	Total (%)
AGE	
≤ 50	74 (62,2%)
> 50	45 (37,8%)
GRADE	
Low Grade	10 (8,4%)
Moderate Grade	76 (63,9%)
High Grade	33 (27,7%)
STADIUM	
I	0 (0%)
II	0 (0%)
III A	11 (9,3%)
III B	108 (90,7%)
IV	0 (0%)
HISTOPATHOLOGY	
IDC	109 (91,5%)
ILC	7 (5,8%)
Adenoca musinosum	1 (0,8%)
Adenoca papiler	1 (0,8%)
Adenoca meduler	1 (0,8%)
IMMUNOHISTOCHEMICAL	
ER	74 (62,2%)
PR	60 (50,4%)
HER2	59 (49,6%)
Ki-67	57 (47,9%)
SUBTYPE	
Luminal A	29 (24,4%)
Luminal B	49 (41,2%)
Her2	25 (21%)
Triple Negative	16 (13,4%)
REGIMENT (NEO & ADJUVANT)	
CAF/CEF	89 (74,7%)
TAC	22 (18,4%)
TA/TE	9 (7,5%)
CHEMOTHERAPY RESPONSE	
Responsive	80 (67,2%)
Nonresponsive	39 (32,8%)

Table 2: Relationship between Age and Chemotherapy Response on Breast Cancer

AGE	Chemotherapy Response		Total
	Responsive	Nonresponsive	
≤ 50	48 (64,9%)	26 (35,1%)	74 (100%)
> 50	32 (71,1%)	13 (28,9%)	45 (100%)
Total	80 (67,2%)	39 (32,8%)	119 (100%)

4. Relationship between grading and neoadjuvant chemotherapy response on breast cancer

To assess whether grading has correlation with anthracycline-based neoadjuvant chemotherapy response on breast cancer, we use bivariate analysis as can be seen in table 3.

Table 3: Relationship between Grading and Chemotherapy Response On Breast Cancer

Grading	Chemotherapy Response		Total
	Responsive	Nonresponsive	
Low Grade	2 (20%)	8 (80%)	10 (100%)
Moderate Grade	51 (67,1%)	25(32,9%)	76 (100%)
High Grade	27 (81,8%)	6 (18,2%)	33 (100%)
Total	80 (67,2%)	39 (32,8%)	119 (100%)

chi-square X^2 = 10,619 df = 1 p = 0,001 (p > 0,05)

Grading analysis, we found that there's chemotherapy response difference between each grade: 10 (8.4%) on low grade, 76 (63.9%) moderate grade, and 33 (27.7%) high grade on breast cancer patients who show responsiveness for anthracycline-based neoadjuvant chemotherapy, with p-value = 0.001 (p > 0.05). So it can be said that grading is a predictive factor for anthracycline-based neoadjuvant chemotherapy response.

5. Intrinsic Subtype Profile and Neoadjuvant Chemotherapy Response on Breast Cancer

To find out whether intrinsic subtype has correlation with anthracycline-based neoadjuvant chemotherapy response on breast cancer, we used bivariate analysis as can be seen in table 4.

Table 4: Relationship between Subtype and Chemotherapy Response on Breast Cancer

Subtype	Chemotherapy Response		Total
	Responsive	Nonresponsive	
Luminal A	16 (55,2%)	13 (44,8%)	29 (100%)
Luminal B	30 (61,2%)	19 (38,8%)	49 (100%)
Her2	20 (80%)	5 (20%)	25 (100%)
Triple Negative	14 (87,5%)	2 (12,5%)	16 (100%)
Total	80 (67,2%)	39 (32,8%)	119 (100%)

chi-square X^2 = 7,014 df = 1 p = 0,008 (p > 0,05)

Subtype have a great impact on chemotherapy responsiveness on breast cancer. From that data we found 16 (55.2%) luminal A responsive, 30 (61.2%) luminal B responsive, 20 (80%) HER2 responsive, and 14 (87.5%) triple negative. Statistically, there has been a significant difference between each subtype on breast cancer chemotherapy response with p-value = 0.008 (p > 0.05).

4. Discussion

Studies about biomarkers in relation to chemotherapy response in breast cancer are the primary concern in our center as mostly the patients came in advanced stages. The previous research found expression of Ki-67 were related to neoadjuvant chemotherapy response [12]. While expression of BCL-2, ER and PgP have an insignificant correlation with chemotherapy response in breast cancer [13] [14]. Overexpression of DUSP4 tends to responsive to neoadjuvant chemotherapy but statistically insignificant [15].

From this study we found different age, the youngest being 29 years old, the oldest being 75 years old, median 46 years old, and 74 (62.2%) aged < 50 years old. Globally, 33% breast cancer patient was aged < 50 years, 42% in the Asia Pacific, 47% South East Asian, and 21% Australia. SEER data from the USA shows that most of the breast cancer patients were aged 55 – 64 years old with median 61 years old [2].

In this study we found; 8.4% low grade, 63.9 % moderate grade, and 27.7% high grade. From chi-square analysis we found p-value = 0.001 ($p > 0.05$), it means that grading is a predictive factor for anthracycline-based neoadjuvant chemotherapy response.

Histopathological grading is an already well known prognostic factor. Various new research has confirmed histopathological grading importance as a prognostic and predictive factor on breast cancer. Engstrøm and his colleagues found that during the first five years, grade 2 and grade 3 breast cancer have a worse prognosis compared with grade 1 breast cancer [16].

Grading is also an independent factor to predict pCR for luminal tumor, clinical tumor staging for HER2 like-tumor, and age for triple-negative tumor. Grading can give independent information about the clinical response for triple negative tumor group. Grading and age can identify subtype on luminal and triple-negative patients who will have benefit from NACT [17].

From 119 samples which underwent immunohistochemical examination, we found 24.4 % luminal A, 41.2 % luminal B, 21% HER2, and 13.4% triple negative. Minhao and his colleagues (2010) research found 19.6% luminal A, 22.5% luminal B, 17.6% HER2, and 40.2% triple negative. Cong Xue and his colleagues (2012) who assessed 5806 breast cancer patients in China, described the distribution of 31.1% luminal A, 30.4% luminal B, 13.1 % HER2+, 9% HER2, and 5% triple negative. Carol Parise (2014) research data from 143.333 breast cancer patients consist of 71.778 (50%) luminal A cases, 19.011 (13.3%) luminal B / HER2- cases, 19.017 (13.3%) luminal B / HER2+ cases, 9.792 (6.8%) HER2+ cases, and 18.724 (13%) triple negative cases. Reina Haque (2011) research described that the most common breast cancer subtype is luminal A (66%), followed by basal-like (22%), HER2 (7%), and luminal B (5%).

Subtype plays a critical role in chemotherapy response. From our research data, we found 55.2% responsive luminal A subtype, 61.2% luminal B responsive subtype, 80% HER2 responsive subtype, and 87.5% triple negative responsive subtype. From statistical analysis, we found a significant difference between various subtype with neoadjuvant chemotherapy response on breast cancer with p-value = 0.008 ($p > 0.05$).

A previous report in Wahidin Sudirohusodo hospital in 2014, conducted in 247 breast cancer patients, Chemotherapy response by subtype were in Luminal subtype responsive 67%, Her2 responsive 70%, Triple Negative responsive 88% [18].

Neoadjuvant chemotherapy for breast cancer allows tumor response assessment on various intrinsic subtype. ER, PR and HER2 status on breast cancer are important markers for choosing the best chemotherapy drug[19-21].

Rouzier research found that complete pathologic response (pCR) on basal-like subtype about 45%, HER2 45%, while luminal only have 6% pCR rate. There's no pCR for the normal-like subtype. Basal-like and HER2 breast cancer subtype are more sensitive to adjuvant chemotherapy containing paclitaxel and doxorubicin compared with luminal and normal-like subtype [21].

5. Conclusion

This study found that histopathological grading and Intrinsic subtype were significantly associated with anthracycline-based neoadjuvant chemotherapy response on breast cancer. Thus, histopathological grading and intrinsic subtype are predictive factors for chemotherapy response on breast cancer.

6. Recommendation

Histopathological grade and intrinsik subtype to be considered for choosing chemotherapy regimen in breast cancer.

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7. Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare

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