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Relationship Between E-Cadherin Expression and Response to Anthracycline-Based Neoadjuvant Chemotherapy in Stage IIIB Luminal Subtype Breast Cancer Patients

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Abstract:
Background*: Breast cancer is the most common cancer affecting women worldwide. Breast cancer is a malignant tumor that attacks breast tissue originating from the glands, gland ducts and breast supporting tissues. It is caused by disruption of genes that regulate growth and differentiation therefore these cells grow and reproduce uncontrollably. In Indonesia, based on data in 2008, breast cancer ranks first as the most frequent cause of hospitalization in all hospitals and almost 75% of patients suffer from advanced breast cancer. Along with the development of medical science, currently there are various types of breast cancer therapy and surgery remains as the main therapeutic modality. Surgery can be combined with radiotherapy, chemotherapy, and hormonal therapy to increase the success of treatment. In patients with stage III breast cancer, it is an inoperable condition that requires neoadjuvant chemotherapy to reduce both the size and spread of the nodule (tumor free margin resection). E-cadherin is a calcium-dependent epithelial cell adhesion molecule expressed at adherens junctions. In the EMT process, an increased expression of E-cadherin indicates an increased response to chemotherapy. Increased expression of E-cadherin can increase the induction of cancer cell apoptosis. Cancer cell apoptosis indicates that the sensitivity to neoadjuvant chemotherapy treatment is also high, thus preventing the metastatic state. On the clinical picture, it will appear that the tumor size is reduced which indicates decreased progression. These factors make E-cadherin has the potential as a predictor of chemotherapy response in breast cancer.*
Materials and Methods*: In this observational analytical study, 30 patients of stage IIIB luminal subtype breast cancer with the age of max. 65years were proceeded to have taken biopsy surgery for tumor tissue samples. The variables measured in this study were epithelial to mesenchymal transition (EMT) markers and the size of the base tumor before and after chemotherapy. The marker measured was E-cadherin in primary tumor tissue. Subjects then proceeded to receive neoadjuvant chemotherapy. IHK (immunohistochemistry) which has been marketed using monoclonal antibodies against the identified proteins was used to examine e-cadherine. Relationship between E-cadherin expression and chemotherapy response was observed and analyzed after chemotherapy was given.*
Results*: The e-cadherin expression before chemotherapy has significance, which in this case means that it can be a predictor of how the patient responds to chemotherapy (significance value of $p<0.05$). The E-cadherin sensitivity and specificity values before chemotherapy and chemotherapy response have the cut off value of 1.5. As a variable that is considered to be a predictor of an independent variable, namely the response to chemotherapy.*
Conclusion: *There was a significant relationship between e-chaderin expression after chemotherapy and chemotherapy response. E-chaderin expression before chemotherapy has the potential to be the chemotherapy predictor in stage IIIB luminal subtype breast cancer patients. Further research is needed to analyze the expression of e-cadherin as a predictor of chemotherapy response with a larger sample.*
Key Word*: Breast Cancer, E-cadherin, Neoadjuvant Chemotherapy, Stage IIIB Luminal Subtype.*

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I. Introduction

Breast cancer is the most common cancer affecting women worldwide. Breast cancer is a malignant tumor that attacks breast tissue originating from the glands, gland ducts and breast supporting tissues. It is caused by disruption of genes that regulate growth and differentiation therefore these cells grow and reproduce uncontrollably. [1]

In Indonesia, based on data in 2008, breast cancer ranks first as the most frequent cause of hospitalization in all hospitals and almost 75% of patients suffer from advanced breast cancer. This will affect the patient's prognosis and recovery. If the patient is diagnosed in an early stage, the recovery rate will be better. In patients with localized tumor cells in breast tissue, the survival rate is close to 97%. However, it is drastically reduced to 23% when the tumor cells have spread to other organs (metastasis).[2]

Along with the development of medical science, currently there are various types of breast cancer therapy and surgery remains as the main therapeutic modality. Surgery can be combined with radiotherapy, chemotherapy, and hormonal therapy to increase the success of treatment. Chemotherapy agents that are most often given as neoadjuvant are anthracyclines and taxanes.

In patients with stage III breast cancer, it is an inoperable condition that requires neoadjuvant chemotherapy to reduce both the size and spread of the nodule (tumor free margin resection).

Immunohistochemical examination is used to understand the molecular pathogenesis of the breast which is divided into several subtypes. These molecular subtypes have various risk factors, tumor progression, chemotherapy response, and tumor prognosis. The most common subtypes were Luminal A (66%), TNBC (22%), HER2 type (7%) Luminal B (5%).[3] The prognostic effect of ER was assessed in the absence of adjuvant tamoxifen therapy. In ER positive, the tumor had a 5-year survival rate of 74% and an overall survival of 92%, while ER negative patients had a 5-year survival rate of 66% and an overall survival of 82%. Positive ER or PR are a strong predictors of chemotherapy response.[4]

E-cadherin is a calcium-dependent epithelial cell adhesion molecule expressed at adherens junctions. In the EMT process, an increased expression of E-cadherin indicates an increased response to chemotherapy. Increased expression of E-cadherin can increase the induction of cancer cell apoptosis. Cancer cell apoptosis indicates that the sensitivity to neoadjuvant chemotherapy treatment is also high, thus preventing the metastatic state. On the clinical picture, it will appear that the tumor size is reduced which indicates decreased progression. These factors make E-cadherin has the potential as a predictor of chemotherapy response in breast cancer.[5]

Based on several studies of breast gland carcinoma, until now there has been no satisfactory tumor marker to assess the response to neoadjuvant chemotherapy in advanced breast cancer. Therefore, in this study, we will investigate the use of E-cadherin as a tumor marker in advanced breast cancer to provide more precise and better therapeutic success.

II. Material And Methods

This study was observational analytic and carried out on breast cancer patients in Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia with the duration of 24 weeks from February 2020 to February 2021. A total 30 adult subjects of aged maximum of 65 years were included in the samples.

Study Design: Observational analytical study

Study Location: Department of Surgery and PA Laboratorium, at Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia

Study Duration: February 2020 to February 2021.

Sample size: 30 patients.

Sample size calculation: The sample size was calculated using formula referring to the quota sampling. The sample size obtained for this study was 30 patients for each group.

Subjects & selection method: The study population was drawn from breast cancer patients in Dr. Saiful Anwar General Hospital with advanced local stage with Luminal subtype (A and B) of stage IIIB diagnosed with PA and immunohistochemistry examination, within the inclusion and exclusion criterias.

Inclusion criteria:

1. Breast cancer patients (advanced local stage with Luminal subtype (A and B) of stage IIIB diagnosed with PA and immunohistochemistry examination)
2. Aged max. 65 years,
3. Karnofsky scale > 70%
4. Subject approved and signed the information of consent to do biopsy and 3-serial neoadjuvant combination chemotherapy, after given explaination about the chemotherapy procedure.

Exclusion criteria:

1. Patients had chemotherapy contraindications, such as congestive heart failure, history of acute myocardial infarction, chronic liver disease, chronic renal disease
2. Patients who had undergone tumor removal surgery, other kinds of chemotherapy or hormonal therapy.

Procedure methodology

After written informed consent was obtained, medical records of patients who met the criterias were documented. Tissue samples were obtained from the PA laboratorium, in which the stage IIIB luminal subtype samples were collected. The variables measured in this study were epithelial to mesenchymal transition (EMT) markers and the size of the base tumor before and after chemotherapy. The marker measured was E-cadherin in primary tumor tissue. The examination of E-cadherin is by using IHK (immunohistochemistry) which has been marketed using monoclonal antibodies against the identified proteins.

E-chaderins were assessed from the intensity and quantity of immunostaining. To do the immunostaining procedure, it takes breast tumor tissue that has been fixed with 10% formalin buffer no later than 30 minutes after the specimen is taken and no later than 48 hours the specimen has been processed in the form of paraffin blocks.

Prior to IHC examination or staining, the tissue specimens to be examined must be fixed in order to prevent autolysis, maintain tissue antigenicity, strengthen the refractive index of tissue sections, and strengthen cell elements against the tissue staining process. Subsequent processes include tissue dehydration, removal or cleaning of tissue from dehydrating agents, infiltration by embedding media/material, and cutting/slicing of tissue for antibody staining. The fixation used is 10% buffered formalin. Painting depends on each product of the monoclonal antibody kit. This antibody kit product, before use, must be stored at room temperature between 20-250 and must always be calibrated. Room temperature must also be maintained during the painting process is carried out. Likewise, the glass object remains in a wet condition and must not dry during the painting process. Drought can lead to increased nonspecific staining, and may lead to different interpretations.

The intensity of immunotaining was grouped based on the staining reaction as follows:

1 = weak cytoplasmic staining intensity;

2 = moderate cytoplasmic staining intensity;

3 = strong cytoplasmic staining intensity;

4 = very strong cytoplasmic staining intensity.

The clinical response research process was evaluated based on WHO (World Health Organization) by comparing tumor size before and after neoadjuvant chemotherapy was given.

Ways to measure tumor diameter/tumor volume:

- The location of the breast tumor is determined and drawn on the surface of the skin of the breast, then ascertained the longest size of the tumor and the shortest size. Diameter is measured from the longest size, volume is determined from the longest size times the shortest size.
- Tumor size after the third series of neoadjuvant chemotherapy will be used as the final measure to determine the level of tumor response.
- The tumor response rate was measured by comparing the initial size of the tumor, categorized into positive (complete response, partial response) and negative (no response, progressive) which actually had a positive and negative limit of 50%.

Table no 1: Chemotherapy response

Type of response	Tumor decreasement	Objective	Limit value
A. Positive			
Complete response	Died down	Died down	
Partial response	Decrease > 50%	< 50% left	The percentage 50%
B. Negative			draws the line between
			(+) and (-) response
No response	Decresae < 50%	> 50% left	
Progressive	Increase	Increase	

Statistical analysis

Data was analyzed using SPSS version 20. Wilcoxon test was used to determine the significance of E-chaderin expression before and after chemotherapy. Chi-square test was then used to learn the relationship between E-chaderin expression and chemotherapy response. This study used the logistic regression analysis to understand further about the E-cadherin expression and chemotherapy response. The level $P < 0.05$ was considered as the cutoff value or significance.

III. Result

After 24 weeks of follow up, it was found that prior to therapy, most of the intensity of E-chaderin breast cancer samples were weak and moderate. After chemotherapy, most of the intensity of E-chaderin was strong. These results indicate that there is an increase in the intensity of E-chaderin from before chemotherapy and after chemotherapy. Wilcoxon statistical test results showed that there was a significant difference between the intensity of E-chaderin before and after chemotherapy ($p<0.05$). This shows that changes in E-cadherin levels before and after chemotherapy are statistically significant, where a positive response to chemotherapy is described by an increase in E-cadherin. These are shown on Table 2.

Table no 2: Difference of E-chaderin expression between before and after chemotherapy

Expression	Pre-chemotherapy	Post chemotherapy	*p-value*
Weak	12	1	0,000
Moderate	12	4	
Strong	6	15	
Very strong	0	10	

Table no 3: Shows the positive response to chemotherapy mostly have strong and very strong E-cadherin intensity. The negative response to chemotherapy has intensity, weak, moderate, and strong. The results of the chi-square statistical test showed that $p<0.05$, which means that there is a relationship between the intensity of E-chaderin and the response to chemotherapy. The relationship is shown in the statistics that each positive response has a tendency for the intensity of E-cadherin to be stronger than the intensity of E-cadherin in the negative response to chemotherapy. From these results, further research is needed, which is regression analysis to analyze the ability of E-chaderin expression as a predictor of chemotherapy response.

Table no 3: Relationship between E-chaderin expression and chemotherapy response

Expression	Chemotherapy response		*p-value*
	Positive	Negative	
Weak	0	1	0,002
Moderate	0	4	
Strong	8	7	
Very strong	10	0	

Table no 4**:** Shows the expression of E-chaderin before chemotherapy as a response predictor. This shows that most of the expressions were weak and moderate expression. The fraction of e-cadherin expression before chemotherapy was strong. There was no very strong expression of e-cadherin before chemotherapy. This is similar to the results of the chemotherapy response, so it is necessary to carry out logistic regression analysis to determine the ability of e-cadherin before chemotherapy in predicting chemotherapy response.

Table no 4: Expression of E-chaderin before chemotherapy as a response predictor.

Expression of e-cadherin pre-chemotherapy	Total
Weak	12
Moderate	12
Strong	6
Very strong	0

Table no 5 Shows the logistic regression analysis between E-chaderin expression and chemotherapy response. E-cadherin measurement before chemotherapy affects chemotherapy response. Data analysis used logistic regression because E-Cadherin Expression was in the form of qualitative and non-pametric data. This table shows a variable, in this case E-cadherin whether it is able to be a good predictor of an independent variable, which was chemotherapy. From these data it is evident that the E-cadherin data before chemotherapy has significance, which in this case means that it can be a predictor of how the patient responds to chemotherapy. This is proven by the significance value of $p<0.05$. The opposite was seen in the expression of e-cadherin after chemotherapy which did not affect the response to chemotherapy ($p>0.05$).

Table no 5: The logistic regression analysis between E-chaderin expression and chemotherapy response.

Variables	*p-value*
E-cadherin expression post chemoterapy	0,998
E-cadherin expression pre chemoterapy	0,017

ROC curve of E-cadherin expression before chemotherapy and chemotherapy response

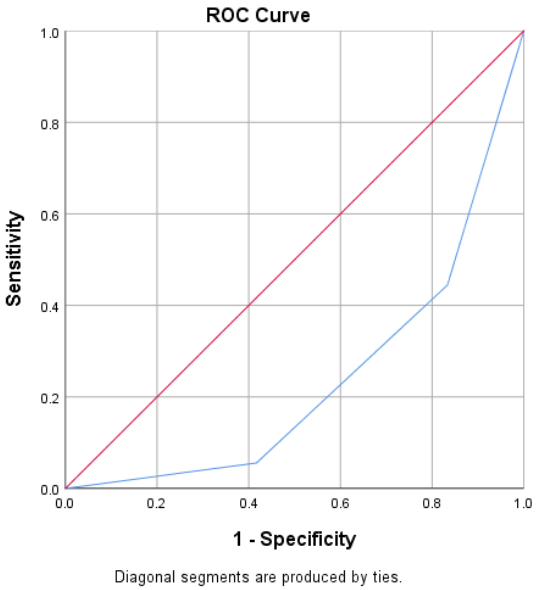

Table no 6 Shows E-cadherin sensitivity and specificity values before chemotherapy and chemotherapy response. The cut off value of E-cadherin before chemotherapy was 1.5. As a variable that is considered to be a predictor of an independent variable, namely the response to chemotherapy, it is necessary to find out at which point E-cadherin has the best accuracy value. The use of the ROC (Receiver Operating Characteristic) table can see at which point the value of E-cadherin pre-chemotherapy has the best sensitivity and 1-specificity. From the graph formed, the best cut off value is 1.5 because it has higher sensitivity and specificity compared to other cut offs.

Table no 6: E-cadherin sensitivity and specificity values before chemotherapy and chemotherapy response.

Variable	Cut off	Sensitivitity	1-Specificity
E-cadherin pre-chemotherapy	0,00	1,000	1,000
	1,50	**0,444**	**0,833**
	2,50	0,056	0,417
	4,00	0,000	0,000

Table no 7 AUC value of E-cadherin expression before chemotherapy based on chemotherapy response. The AUC of E-cadherin before chemotherapy was 76.4%. AUC (Area Under Curve) is an area under the curve that describes the probability with sensitivity and specificity variables with a limit value of 1 to 0. The higher the AUC number, the better accuracy. With an AUC number of 0.764, it shows the level of accuracy of E-cadherin was medium.

Table no 7: AUC value of E-cadherin expression before chemotherapy based on chemotherapy response**.**

Variable	AUC	Asymp. Sig	IK 95%		Cut off point
			Lower	Upper	
E-cadherin pre-chemotherapy (E1)	0,764	0,136	0,584	0,944	1,50

Table no 8 shows the diagnostic value. The sensitivity of E-cadherin before chemotherapy was 44.44% and specificity was 16.67%. Which means, the ability of E-cadherin to predict patients who do respond positively to chemotherapy is 44.44% and the ability to predict patients who do not respond to chemotherapy is 16.67%. With these two values, the accuracy of E-cadherin pre chemotherapy as a predictor is 33.33%. While the Odd ratio value of E-cadherin before chemotherapy is 0.1, which indicates that if the E-cadherin value is above the cut off (1.5), the probability of a positive chemotherapy response is 0.1 or 10%.

Table no 8: Diagnostic value.

Variable	Cut off	Response (+)	Response (-)	Sensitivity (%)	Specificity (%)	PP (%)	PN (%)	Acc (%)	Odd Ratio
E1	>1,5	8	10	44,44	16,67	44,44	16,67	33,33	0,1
	<1,5	10	2						

IV. Discussion

Differences in E-cadherin Expression Before and After Chemotherapy

In this study, the expression of E-cadherin increased after chemotherapy. E-cadherin is a cell adhesion molecule expressed by normal breast tissue, and a phenotypic marker in breast cancer. If the amount of expression of these cells is lost or reduced, it usually indicates a lobular type of breast tumor.[6] A decrease in the amount of E-cadherin expression or even loss also indicates a poor tumor prognosis[7] which is characterized by a larger size, more malignant histopathological grade, estimated stage of metastasis, and the presence of negative ER tumor receptors.[6]

The aim of this study was to analyze the expression of E-cadherin as a predictor of response to anthracycline-based neoadjuvant chemotherapy in stage IIIB luminal subtype breast cancer. In this study, samples of patients with stage IIIB breast cancer were used. Patients were then measured histopathologically E-cadherin expression before and after chemotherapy. There are 30 research samples with the average age of the sample is 47.67 years with a standard deviation of 6.43 years.

Based on the data, it was found that the expression of E-cadherin before neoadjuvant therapy was quite low, indicating that histopathologically this breast cancer was quite invasive. Invasive breast cancer has a tendency to spread to surrounding organs more quickly and progressively. Decreased or missing expression of E-cadherin activates the Wnt signaling pathway. Activation of this pathway contributes to an increase in the level of -catenin both in the cytoplasm and in the nucleus and will increase the interaction of cell growth and activation of EMT (epithelial mesenchymal transition).[8,9] Impaired signaling of Wnt activation can be said to initiate the oncogene cell proliferation process. It is proven that in breast cancer patients used is an advanced stage, namely IIIB where the tumor is > 5 cm in size, there is an infiltration of cancer cells on the skin or in the chest muscle. Infiltration of cancer cells in the skin can form clinical features such as ulcers, satellite nodules or peau d'orange (breast skin like orange peel) even if it reaches the chest muscle can cause skin dumpling. In the luminal subtype, it is very important to see the expression of hormones ER (estrogen receptor), PR (progesterone receptor) or HER-2 (Human epidermal growth factor receptor 2).[10]

The results of this study were supported by Skalova's study in 2019 who proved that there was an increase in the intensity of e-cadherin after chemotherapy was given. In this study, samples of patients with invasive breast cancer were used.[11]

Relationship between E-cadherin Expression and Chemotherapy Response

After given neoadjuvant chemotherapy the expression of e-cadherin increased. This increase in the intensity of e-cadherin is also associated with the response to therapy. This shows that E-cadherin has the potential as a marker of positive response to treatment so that it is capable of surgical removal of tumors.[12] Under these circumstances miRNAs in the form of pre-miR-200b or pre-miR-200c can be recognized and become MDA-MB-231 cells thereby upregulating E-cadherin expression by reducing ZEB1 transcriptional levels and increasing CDH1 transcription levels.[13,14] Increased expression of CDH1 will decrease the activation of EMT to MET (mesenchymal-epithelial-transition), increase the sensitivity of neoadjuvant chemotherapy drugs by inducing gene regulation of the p53 apoptotic pathway.[7,13] Increased expression of E-cadherin can increase the induction of cancer cell apoptosis. The binding of the ligand and the E-cadherin/β-catenin receptor will initiate the signaling of the eccentric apoptotic pathway. In addition, E-cadherin will support the DR4/DR5 pathway towards the DISC (death-inducing silencing complex) through the actin cytoskeleton linkage, and amplify the apoptotic effect on cancer cells by coupling the TRAIL receptor ligand. E-cadherin is a cancer cell biomarker with potential sensitivity to proapoptotic receptor agonists (PARA) developed against TRAIL receptors.[8,15] Cancer cell apoptosis indicates that the sensitivity to neoadjuvant chemotherapy treatment is also high, thereby preventing further metastases. The clinical picture also shows that the tumor size is reduced which indicates decreased progression.

The results of this study are in line with previous studies showing a relationship between e-cadherin and chemotherapy response.[11] Another study also aims to determine the expression of e-cadherin as a prognostic biomarker in breast cancer patients. The results of this study indicate that e-cahderin has the potential as a biomarker to determine the prognostic value of breast cancer. In this study, it was explained that increasing e-cadherin showed a good prognosis in breast cancer patients. In addition, in this study the expression of e-cadherin can also be used as a biomarker of metastases from breast cancer.[16]

In this study, the number of samples tested was not representative enough so further multi-center research is needed to increase the research sample. In addition, all samples were not determined by the type of

breast cancer metastases so that it was not possible to analyze the relationship between the intensity of e-cadherin and the incidence of breast cancer metastases.

E-cadherin Expression as a Predictor of Chemotherapy Response

In this study, the variable that proved significant as a predictor of chemotherapy response was E-cadherin expression before chemotherapy. Based on the ROC curve of E-cadherin expression before chemotherapy, the AUC value was 76.4% with a cut-off point of 1.5. Based on the cut-off points, the sensitivity, specificity, and accuracy were 44,44%, 16.67% and 33.3%, respectively. Sensitivity is the ability of a diagnostic tool to show which individuals are sick out of the entire population who are really sick. Specificity is the ability of a diagnostic tool to classify people who are not sick as true people who do not have the disease. Accuracy is a measure of the measurement result with the target value.

High E-cadherin expression indicates a positive chemotherapy response prediction, which means that cancer cells have undergone necrosis or apoptosis. The low expression of e-cadherin indicates a negative chemotherapeutic response prediction, which means that the cancer cells have not undergone necrosis or apoptosis so that further chemotherapy is needed. This is consistent with the initial theory, that E-cadherin plays an important role in epithelial cell adhesion and loss of function of E-cadherin is a major contributor to tumor development because the majority of solid tumors are malignancies of epithelial cell origin.[17-19] The recommendation is that further research is needed to analyze the expression of e-cadherin as a predictor of chemotherapy response with a larger sample.

V. Conclusion

There was a significant relationship between e-chaderin expression after chemotherapy and chemotherapy response. E-chaderin expression before chemotherapy has the potential to be the chemotherapy predictor in stage IIIB luminal subtype breast cancer patients. Further research is needed to analyze the expression of e-cadherin as a predictor of chemotherapy response with a larger sample.

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