



The Effect of Chemotherapy on Estradiol Levels in Patients with HER 2-Overexpression Breast Cancer in Dr Moewardi General Hospital, Surakarta, Indonesia

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Abstract

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AIM: This study aims to evaluate the effect of adjuvant chemotherapy on estradiol levels in patients with HER 2-overexpression breast cancer in a developing country.

METHODS: This comparative study with pre- and post-design model observation approach, involving patients with HER 2-overexpression breast cancer who had undergone surgery and had never received chemotherapy or hormonal therapy before, who were then given adjuvant chemotherapy. Estradiol levels were measured before and after chemotherapy. The study was carried out in the surgical oncology division of RSUD Dr. Moewardi (RSDM) Surakarta from January 2020-December 2020. Descriptive data are presented in a frequency table based on age, menstrual status, parity status, breastfeeding status, contraception, contraception duration, family history, stage, and histological grade. Before and after chemotherapy in patients with breast cancer, the estradiol levels employed the paired sample t-test of the Wilcoxon rank test because the data did not meet the normality assumption.

RESULTS: From the total data of 21 patients, 15 patients experienced a decrease in estradiol levels after chemotherapy, while six patients underwent an increase. The mean estradiol level before chemotherapy was 89.41 pg/ml, whereas the mean estradiol level after chemotherapy was 55.90 pg/ml. It indicates a difference in the decrease in estradiol levels of 33.51 pg/ml. The statistical test results also obtained a p-value of = 0.033 ($p < 0.05$), which signifies a significant difference between estradiol levels before and after chemotherapy. Thus, chemotherapy is effective in lowering estradiol levels in patients with breast cancer.

CONCLUSION: Chemotherapy affects decreasing estradiol levels in patients with HER2 overexpression breast cancer.

Introduction

Breast cancer is the second leading cause of death after lung cancer. The incidence rate is the highest type of cancer diagnosed in women in the ASEAN region and globally [1]. Indonesia is one of the countries with a high incidence of breast cancer, followed by Japan, Malaysia, the Philippines, Singapore, Sri Lanka, and Taiwan [2].

The presence of estrogen and its metabolites and estrogen receptors in breast tissue may play a role in the emergence of breast cancer tissue. Estrogen and estrogen receptor complex will stimulate the growth of breast epithelial tissue and have a local effect. Polymorphisms in one gene encoding enzyme or the estrogen receptor will result in changes in the miliary breast and potentially cause malignancy [3]. Estrogen in the catechol pathway (estradiol) which produces equine estrogen metabolites is a carcinogenic metabolite in several tissues, such as the liver, kidneys, uterus,

and breast glands. Then, it may have contributing to breast cancer through protective inhibition of Phase II enzymes [4].

Human Epidermal Growth Factor Receptor (HER) is oncogenic receptor that managed in growth, defense, proliferation and cell differentiation. HER2+ overexpression has prognostic and predictive values. Patients with HER2+ tumors also have a higher risk of recurrence. HER2+ gene amplify and overexpression of its products leads to cell transformation [5]. HER2+ patient that may have higher estradiol lead to poor prognostic value.

In this study, we want to see the correlation of chemotherapy only in respond to estradiol level, the lower estradiol level – the better prognostic for HER2+ patient. However, chemotherapy with targeted therapy in patients with HER2 overexpression of breast cancer is still the primary choice. However, in developing countries, targeted therapy cannot be given to all patients because it is not covered by government insurance.

Materials and Methods

This comparative study with pre- and post-design model added into account patients with HER2 overexpression breast cancer who had undergone surgery and had not received chemotherapy or prior hormonal therapy. The research was carried out at the surgical oncology division, RSDM Surakarta, from January to December 2020.

Data were obtained from patients with triple-negative breast cancer. Patients were checked for serum estradiol levels twice before starting adjuvant chemotherapy and after completing six cycles of chemotherapy. Both estradiol values were recorded by including the study subjects' characteristics, comprising age, menopausal status, parity status, breastfeeding status, hormonal contraception, hormonal contraception duration, stage, histological grade, and family history.

The data were then analyzed statistically to determine the effect of chemotherapy on serum estradiol levels. Descriptive data are presented in the frequency table. Differences in changes in serum estradiol before and after chemotherapy were reported in terms of mean and standard deviation (mean \pm SD). Data analysis utilized SPSS version 25.0.

Results

Characteristics of research subjects

From January 2020 to December 2020, 25 new patients had HER 1 overexpression breast cancer (never received therapy, chemotherapy, or hormonal therapy before). However, 21 patients followed this study, with four patients losing follow-up (not coming back for treatment or not continuing chemotherapy).

The research subjects' characteristics are presented in the frequency distribution value (%). Table 1 shows that by age, most patients with age >40 years were 18 patients (85.7%). The grading was mainly in Grade 3 in 11 patients (52.4%). Furthermore, the staging was primarily the LABC category, with 17 patients (81.0%). Most menopausal categories of patients were postmenopausal categories in 14 patients (66.7%). In this study, the parity of most patients with children < 2 children was 11 patients (52.4%). For the breastfeeding duration in this study, most patients with duration > 2 years were 18 patients (85.7%). Meanwhile, most patients used contraception in 15 patients (71.4%), and the contraception duration in most patients was <5 years in 18 patients (85.7%). At last, there were three patients (14.3%) with a family history of cancer in the study.

Table 1: Analysis of research subjects' basic characteristics and changes in estradiol levels before and after chemotherapy

Characteristics	N	%	Estradiol increase %	Estradiol decrease %	The difference in estradiol change (mean \pm sd)
Age					
<40 years old	3	14.3	2 (67)	1 (33)	0.81 \pm 11.94
>40 years old	18	85.7	4 (22)	14 (78)	1.9439.23 \pm 76.86
Grade					
Grade I	1	4.8	1 (100)	0 (0)	24.30 \pm -
Grade II	9	42.9	2 (22)	7 (78)	1.9429.41 \pm 68.72
Grade III	11	52.4	3 (27)	8 (73)	1.9442.12 \pm 79.20
Stage					
EBC	1	4.8	1 (100)	0 (0)	11.94 \pm
LABC	17	81.0	4 (23)	13 (76)	-41.34 \pm 78.68
MBC	3	14.3	1 (33)	2 (67)	-4.31 \pm 7.02
Menopause					
Pre menopause	7	33.3	2 (28)	5 (72)	-9.91 \pm 17.46
Post Menopause	14	66.7	4 (28)	10 (72)	-45.31 \pm 86.45
Parity					
<2 children	11	52.4	5 (45)	6 (55)	-22.61 \pm 65.14
>2 children	10	47.6	1 (10)	9 (90)	-45.50 \pm 81.41
Breastfeeding duration					
<2 years	3	14.3	2 (66)	1 (33)	0.81 \pm 11.94
>2 years	18	85.7	4 (22)	14 (88)	-39.23 \pm 76.86
Contraception					
Yes	15	71.4	6 (40)	9 (60)	-44.44 \pm 83.65
No	6	28.6	0 (0)	6 (100)	-6.18 \pm 10.77
Contraception duration					
<5 years	18	85.7	4 (22)	14 (78)	-37.75 \pm 77.61
> 5 years	3	14.3	2 (67)	1 (33)	-8.07 \pm 9.08
Family history					
Exist	3	14.3	2 (67)	1 (33)	1.79 \pm 21.20
Not exist	18	85.7	4 (22)	14 (78)	-39.39 \pm 76.53

Statistic analysis

Differences in estradiol levels before and after chemotherapy in patients with breast cancer employed a paired sample t-test of the Wilcoxon rank test because the data did not meet the normality assumption. The results of differences in estradiol levels before and after chemotherapy in patients with breast cancer are shown in Table 2.

Table 2: Differences in estradiol levels before and after chemotherapy in patients with HER-2 overexpression breast cancer

Variable	Pre	Post	p-value	Difference
Estradiol	89.41 \pm 72.60	55.90 \pm 20.31	0.033*	-33.51 \pm 72.40
Negative rank	15			
Positive rank	6			
Ties	0			

Numerical data do not meet the normality assumption two paired samples t-test of the Wilcoxon rank test; *Significant at = 5%.

Based on Table 2, it is shown that before chemotherapy, the mean estradiol level was 89.41 \pm 72.60. After chemotherapy, the mean estradiol level was 55.90 \pm 20.31. It denotes that there was a difference in the decrease in estradiol levels of -33.51 \pm 72.40. In other words, after chemotherapy, there was a mean decrease in estradiol levels of 37.5%. In this study, 15 negative ranks were also known, or 15 patients experienced decreased estradiol levels after chemotherapy. Then, the number of positive ranks was six, or six patients experienced an increase in estradiol levels after chemotherapy.

The statistical test result obtained p-value of = 0.033 ($p < 0.05$). It means that there was a significant difference in estradiol levels before and after chemotherapy. Thus, chemotherapy is effective in lowering estradiol levels in patients with breast cancer.

Discussion

Breast cancer risk factors are classified into two: modifiable and non-modifiable risk factors. Modifiable factors include physical activity, obesity, hyperlipidemia, diet, alcohol consumption, contraception, smoking, and hormonal use. Meanwhile, factors that cannot be modified encompass family history, menopausal status, parity, age, and breastfeeding [6].

Age is one of the most important risk factors for breast cancer. In America, the incidence of breast cancer increases at an older age. Approximately 71.2% of breast cancer in America occurs in the age range of 40-60 years. Therefore, screening mammography is needed at the age above 40 years [7], [8].

Moreover, early menarche and late menopause increase the risk of breast cancer. It is related to the duration of exposure to endogenous estrogen produced by the ovaries during the menstrual cycle [9], [10], [11], [12], [13].

In this study, three patients (14.3%) had a history of breastfeeding for ≤ 2 years, and 18 patients (85.7%) with a history of breastfeeding for more than 2 years. Breastfeeding is associated with a 4% reduction in breast cancer risk associated with every 12 months of breastfeeding, which is independent of and in addition to a 7% reduction in risk with each live birth [14], [15].

Based on the use of hormonal contraception, there were 15 patients with a history of contraceptive use, with six patients (40%) experiencing an increase and nine patients (60%) experiencing a decrease. In six patients without a history of using hormonal contraception, all experienced a decrease. Based on the duration of hormonal contraception use, 18 patients had a duration of use <5 years, with four patients (22%) experiencing an increase and 14 patients (78%) experiencing a decrease, and three patients with a history of contraceptive use [16].

In this study, three patients (14.3%) had a family history of breast cancer, while 18 patients (85.7%) had no family history of cancer. The risk of developing breast cancer with a family history has been assessed in studies reporting that the risk of breast cancer is increased in a woman's first-degree relative [17].

In addition, there were six patients in this study with increased estradiol levels, consisting of two patients with premenopausal and with a history of hormonal contraception, two patients with a history of hormonal contraception, and two patients with a family history. It is because, in premenopausal patients, the endogenous estrogen produced by the ovaries is more significant following the menstrual cycle. The use of hormonal contraceptives containing estrogen also increases serum estrogen levels [18].

This study also revealed that before chemotherapy, the mean estradiol level was 89.41 ± 72.60 , while after chemotherapy, the mean estradiol level was 55.90 ± 20.31 . It signifies the difference in the decrease in estradiol levels by -33.51 ± 72.40 , or after chemotherapy, there was a mean decrease in estradiol levels of 37.5%. In this study, 15 negative ranks were found, or 15 patients experienced decreased estradiol levels after chemotherapy. Meanwhile, the number of positive ranks was six, or six patients experienced an increase in estradiol levels after chemotherapy. In addition, the statistical test results obtained a $p = 0.033$ ($p < 0.05$), meaning that there was a significant difference in estradiol levels before and after chemotherapy. Hence, chemotherapy is effective in reducing estradiol levels in patients with breast cancer.

Chemotherapy uses anti-cancer drugs that can be given intravenously or orally. In some cases, chemotherapy can be given directly into the spinal cord [19]. In this study, only first-line chemotherapy was used without using trastuzumab as targeted therapy. It is because, since April 1, 2018, the Social Security Agency (BPJS) no longer guarantees trastuzumab even though this drug has gone through stages of four large-scale adjuvant clinical trials and has been shown to have a positive impact, namely increasing the survival of patients with HER2-positive breast cancer in several countries.

This chemotherapy helps block the estrogen receptor so that estrogen production is expected to be stopped, and the growth of cancer cells can be inhibited. Giving free anthracite base chemotherapy can reduce E1, E2, and FSH levels. These hormones initiate the proliferation and invasion of cancer cells by activating the oncogene enzyme protein, thereby increasing cancer growth [20], [21], [22], [23].

Recent studies have exposed that administration of taxane (docetaxel) and platinum salt base (carboplatin) for chemotherapy in hormonally receptor-negative breast cancer can reduce the risk of recurrence and have a lower risk of heart complications compared to anthracite base [24]. Hans Christian *et al.* also studied 78 patients with HER-2 overexpression who were given anthracycline base and free-anthracycline base chemotherapy. The results showed that 48.5 months of tumor-free anthracycline base free was better than anthracycline base [25], [26].

These two chemotherapy drugs help block the estrogen receptor so that estrogen production is expected to be stopped, and the growth of cancer cells can be inhibited. Giving free anthracite base chemotherapy can reduce E1, E2, and FSH levels. These hormones initiate the proliferation and invasion of cancer cells by activating the oncogene enzyme protein, thereby increasing cancer growth [14]. These drugs can also suppress the function of the ovaries so that they can reduce the production of endogenous estrogen [26]. Chemotherapy can also cause menopause in 50% of women under 40 years and 86% over 86 years in patients with HER positive due to suppressing the

Ovarian Leutenizing Hormone-Release Hormone (LH-RH) [27]. Research carried out by Stephan Pam (2019) reported the suppression of estradiol in patients with combination chemotherapy and post-chemotherapy treatment; estradiol levels also showed a decrease. It is also in accordance with previous research by Berry *et al.* (2006), who mentioned a decrease in estradiol levels in patients with HER-2 overexpression breast cancer.

Several studies have also uncovered that the expression of estrogen and progesterone receptors is decreased after chemotherapy. In a pooled meta-analysis of 14 eligible studies, Zhang *et al.* (2012) have shown that estrogen and progesterone status can decrease significantly with the use of chemotherapy [28]. More importantly, these hormonal changes are of prognostic significance as they correlate significantly with disease-free survival over 10 years [29].

Considerations for hormonal therapy after chemotherapy in patients with HR-negative breast cancer

Of the 21 samples studied, 20 patients had high estradiol levels. Of the seven patients with premenopausal status with high serum estradiol levels before chemotherapy, two patients had increased estradiol levels, and five patients decreased after chemotherapy. Despite the decline, four patients still had high estradiol levels, and one patient had normal estradiol levels. Meanwhile, in 14 postmenopausal patients with high pre-operative estradiol levels, four patients experienced an increase, and ten patients experienced a decrease after chemotherapy, but all of them still had high estradiol levels.

Serum estradiol values that decreased after chemotherapy but were still in the high range can be considered in administering anti-estrogen drugs after chemotherapy, such as tamoxifen, including in cases of HR-negative breast cancer tumors.

ER-negative breast cancer is not absolute without ER expression. ER-negative status is assigned based on the low expression of the ER α isoform. Several studies have focused on the importance of ER β expression as a prognostic marker and/or predictive marker and its role in regulating breast cancer proliferation and apoptosis [30].

Moreover, normal breast glands in mice and humans express more ER β than ER α , and breast epithelial cells in mice with deactivated ER β are hyperproliferative, indicating a tumor-suppressive role of ER. A study stated that a group of ER-negative patients with moderate expression of ER β showed increased recurrence-free breast cancer survival (RFS) after adjuvant tamoxifen therapy. Another study on premenopausal women with early-stage breast cancer revealed better RFS in tamoxifen-treated patients with ER-negative status (high ER β 1 and SRAP levels) [30].

Conclusion

Chemotherapy affects reducing estradiol levels in patients with HER2 overexpression breast cancer. In addition, there are patients with high estradiol levels after chemotherapy, which can be a consideration for giving anti-estrogens in patients with HER2 overexpression breast cancer. Targeted therapy after chemotherapy still primary recommendation, however; in many cases chemotherapy only, with intensive monitoring, could be the alternative management.

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