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The Effects of Tamoxifen on Estradiol Levels and Endometrial Thickening in Premenopausal Stage III Breast Cancer

Andreas Rendra[1], J.D.P. Wisnubroto[2]
[1]*General Surgery Department, Brawijaya University, Indonesia*
[2]*Surgical Oncology Department, Brawijaya University, Indonesia*

Abstract:
Introduction: *Breast cancer and cervical cancer are the most common cancer in women in Indonesia. Adjuvant chemotherapy is an adjunctive therapy that is often used after primary treatments, such as surgery. Tamoxifen acts as an antiestrogen on breast tissue but it has an estrogenic effect on the female genital system. The incidence of endometrial thickening in postmenopausal female patients receiving tamoxifen therapy is increasing. This study aims to measure the effectiveness of tamoxifen by measuring estrogen levels and endometrial thickness.*
Method: *This study is experimental research. The treatments were duration of tamoxifen therapy for 3 months and 6 months in patients with post-MRM stage III breast cancer and adjuvant chemotherapy fluorouracil, doxorubicin, cyclophosphamide (FAC) with estrogen receptor (+) (ER+). Samples were taken using the judgment sampling technique.*
Result: *The results found that the average estradiol level at 3 months was 6.25 and at 6 months was 10.75. This result did not show a significant difference (p = 0.057). The mean endometrial thickening at 3 months was 4.5 and at 6 months was 10.75. In the data analysis, it was found that there was a significant difference in the administration of tamoxifen with the endometrial thickness at 3 months and 6 months (p = 0.001).*
Conclusion: *This study found a significant difference in endometrial thickening towards the administration of tamoxifen at 3 months and 6 months.*
Keyword: *Breast Cancer, Endometrial, Estradiol, Tamoxifen*

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I. Introduction

Breast cancer and cervical cancer are the most common cancer in women in Indonesia. According to the 2010 Hospital Information System data, breast cancer patients in the inpatient unit were 12,014 cases (28,7%), cervical cancer was 5,349 cases (12,8%).[1] Adjuvant chemotherapy is an adjunctive therapy that is often used after primary treatments, such as surgery. Tamoxifen is the most widely used hormonal adjuvant. This therapy reduces recurrence by up to 50% and reduces breast cancer mortality by 28%.[2] Tamoxifen acts as an antiestrogen on breast tissue but it has an estrogenic effect on female genital system. The incidence of endometrial thickening in postmenopausal female patients receiving tamoxifen therapy is increasing. The incidence is about 13-20% in patients.[3] Measurement of estradiol levels in tamoxifen therapy was conducted to determine the effectiveness of tamoxifen treatment. The higher the estradiol levels, the greater the occurrence of cell proliferation thus increasing the risk of breast cancer.[4] The objective of the study was to measure the effectiveness of tamoxifen by measuring estrogen levels and endometrial thickness.

II. Material And Methods

This study is experimental research. The patients with post-MRM stage III breast cancer were given treatments in the form of tamoxifen therapy with a duration of 3 months and 6 months and FCA adjuvant chemotherapy with ER (+). The inclusion criteria of this study were patients with post-MRM premenopausal stage III breast cancer and FCA adjuvant chemotherapy with positive estrogen receptors. While the exclusion criteria of this study were patients who received THA-BSO therapy. The collected data were analyzed using an unpaired T-test.

III. Result

The mean age of the research subjects was 44 years with a range of 37 years to 49 years. Based on the determinants of the stages of disease severity were T3N1M0, T2N2M0, T3N2M0 and the highest percentage

was T3N1M0 and T3N2M0 with a total of 7 patients (43,8%). Most of the patients, as many as 9 patients (56,3%) had a breast tumor in the right breast. Based on the duration of treatment, it was obtained a balanced percentage between the groups of patients with a treatment duration (3 months vs 6 months) as many as 8 patients (50%), respectively. Based on the pathological lesions, 10 patients (62,5%) had pathological lesions. The mean values of estradiol levels and endometrial thickness for all patients were 15,4 and 6,57, respectively.

Table no 1 : The Baseline Characteristic .

Characteristic	Mean (SD) Frekuensi (%)
Age (Year)*	44 (3,8)
Stadium	
T3N1M0	7 (43,8%)
T2N2M0	2 (12,5%)
T3N2M0	7 (43,8%)
Tomor location	
Dextra	9 (56,3%)
Sinistra	7 (43,8%)
Duration Therapy (Month)	
3	8 (50%)
6	8 (50%)
Lesion pathologist	
Ya	10 (62,5%)
Tidak	6 (37,5%)
estradiol levels *	15,44 (1,91)
endometrial thickening **	6,57 (0,92)

The measured estradiol level is Estradiol-17β (E2) or a steroid hormone produced primarily in the ovaries which serve to stimulate proliferation of the uterine endometrium, induce the LH surge for ovulation, and inhibit the release of pituitary hormones through negative feedback. The decrease in estradiol levels indicates the effectiveness of adjuvant hormonal therapy given to control micrometastasis so that it will reduce the risk of recurrence and distant metastases. From the results of the analysis that has been conducted based on the duration of administration of tamoxifen hormonal therapy, it was found that the mean of estradiol levels in the group of breast cancer patients who had received therapy for 3 months was 6,25 and 6 months was 10,75, respectively. The mean of estradiol levels based on treatment duration was not statistically significant with a value of p = 0,057 (>0,05).

Endometrial wall thickening refers to the thickening of the endometrium (lining of the uterus) caused by excess estrogen. The administration of tamoxifen therapy which acts as an antiestrogen in breast tissue has an estrogenic effect on the uterus that is associated with uterine abnormalities such as sub-endometrial cysts, hyperplasia, endometrial and endocervical polyps, and endometrial carcinoma.

Based on the analysis, it was found that there was a statistically significant difference in the mean endometrial thickening for cancer patients in each group who had received tamoxifen therapy for 3 months and 6 months with a value of p =0,001 (p<0,05).

IV. Discussion

In this study, it was found that the estradiol levels in the group of patients who received tamoxifen therapy for 6 months had higher estradiol levels with a mean value of 10,75 pg/mL, compared to the group of patients who received tamoxifen therapy for 3 months with a mean value of 6,25 pg/mL, although both are not statistically significant (p = 0,057; p>0,05). These results are different from previous studies, a retrospective study by Lum SS et al., consisting of 47 breast cancer patients who received 10 mg tamoxifen therapy for 2 years, revealed that the estradiol levels of tamoxifen post-treatment patients increased by 239% from 28 pg/mL to 95 pg/mL (p<0.05). This study also found that long-term use of tamoxifen affects the increased serum levels of other hormones, such as dehydroepiandrosterone (DHEA) dan estrone (E1) (p<0.05).[5] This difference in results can be influenced by the differences in the number of samples used, which in the current study only involved 16 patients. Furthermore, the current study only measures the estradiol levels after the patients received tamoxifen for 3 months and 6 months. While in the previous study, estradiol levels were measured before the patients received tamoxifen therapy and 2 years after the patients received tamoxifen therapy.

A study by Baumgart et al., which compared estradiol levels among patients with breast cancer receiving tamoxifen and aromatase inhibitor therapy, revealed that estradiol levels were found to be higher in the tamoxifen therapy group (31.0 pg/mL) than in the aromatase inhibitor therapy group (16.7 pg/mL). Another study by Yamazaki et al., also stated that patients who received tamoxifen therapy for 1 year experienced an increase in estradiol levels with a mean estradiol level of 1015.8 ± 365.5 pg/ mL. This study also compared the estradiol levels in the group of patients who received adjuvant chemotherapy previously and the group of patients who did not receive adjuvant chemotherapy, where there was no significant difference in the estradiol

levels between the two groups. Yamazaki et al., also explained that the mechanism of tamoxifen in increasing estradiol levels is thought to be through the ability of tamoxifen to inhibit negative feedback by estrogen on the hypothalamic-pituitary axis in the follicular phase, causing increased secretion of FSH and LH from the pituitary gland, and inducing follicular growth.[6]

There was a statistically significant difference (p=0,001) in the mean endometrial wall thickness of breast cancer patients who received tamoxifen therapy for 3 months and 6 months, 4,5 mm and 12,5 mm, respectively. These results indicate that clinically significant endometrial wall thickening was only present in the tamoxifen therapy group for 6 months. While in the tamoxifen therapy group for 3 months, it was not considered a pathological endometrial wall thickening because it has a size of <5 mm on ultrasound examination.

These results are in line with the study of Salazar et al., who studied the effect of tamoxifen on endometrial thickening through histological examination in postmenopausal breast cancer patients, where 75% of patients had endometrial thickening, of which 61,5% had endometrial thickening <5 mm and 38,5% had a thickening ≥5 mm. This study also analyzed the effect of treatment duration of tamoxifen between ≥3,5 years and <3,5 years, on endometrial wall thickening, where there was no statistically significant difference. This study also revealed that endometrial thickening in patients receiving tamoxifen therapy is thought to be due to increased estrogen levels in the body caused by tamoxifen, which results in the increased endometrial activity.[7]

A randomized controlled trial conducted by Palva et al. evaluated the effect of preventive tamoxifen therapy for 5 years in people who at risk of breast cancer, also stated that there was endometrial thickening in the group of patients receiving tamoxifen therapy compared to patients receiving placebo therapy which statistically has significant differences (p=0,011), although there was no significant difference between the two groups after discontinuation of tamoxifen therapy for 1 year. Furthermore, this study also found that the tamoxifen group experienced a significantly higher rate of referral to the hospital due to endometrial clinical manifestations and the incidence rate of gynecologic cancers, where the curettage rate in the tamoxifen group increased 4,2 times compared to the placebo groub.[8]

Research by Garrone et al., compared the effect of the use of tamoxifen and the exemestane which belong to the class of antiestrogens known as aromatase inhibitors, stated that there was a statistically significant difference in endometrial thickening between the two groups, where after treatment duration for 6 months, 66,1% of tamoxifen group patients experienced endometrial thickening compared to 12,1% in the exemestane group (p<0,0001), and 64,3% in the tamoxifen group compared to 6,8% in the exemestane group after treatment duration for 12 months (p=0,0001).[9] Research by Donne et al., also shows consistent results, where patients who received tamoxifen therapy had a greater mean endometrial thickening compared to the aromatase inhibitor therapy group and the control group, with a value of p=0,001.[10]

Another study conducted by Lee et al., revealed that the use of tamoxifen based on the number of doses and duration of use is associated with an increased risk of endometrial disorders, such as endometrial proliferation, polyps, hyperplasia, and carcinoma, where clinical manifestation in the form of abnormal uterine bleeding is the most important risk factor for endometrial disorders. However, this study also revealed that the risk of endometrial carcinoma when using tamoxifen was still found inconsistently from various previous studies.[11]

V. Conclusion

It can be concluded that there is a significant difference in endometrial thickening towards the administration of tamoxifen for 3 months and 6 months in patients with post-MRM stage III breast cancer.

References

[1]. Kemenkes RI. Riset Kesehatan Dasar; RISKESDAS. Jakarta: Balitbang Kemenkes RI. 2008
[2]. Suyatno P. Bedah onkologi diagnosis dan terapi edisi ke 2. 2nd ed. Jakarta; 2021. 2014.
[3]. Berliere M, Duhoux F, Dalenc F, Baurain J, Dellevigne L, Galant C et al. Tamoxifen and Ovarian Function. PLoS ONE. 2013;8(6):e66616.
[4]. Ali S, Mondal N, Choudhry H, Rasool M, Pushparaj P, Khan M et al. Current Management Strategies in Breast Cancer by Targeting Key Altered Molecular Players. Frontiers in Oncology. 2016;6.
[5]. Lum S, Woltering E, Fletcher W, Pommier R. Changes in serum estrogen levels in women during tamoxifen therapy. The American Journal of Surgery. 1997;173(5):399-402.
[6]. Yamazaki R, Inokuchi M, Ishikawa S, Myojo S, Iwadare J, Bono Y et al. Tamoxifen-induced ovarian hyperstimulation during premenopausal hormonal therapy for breast cancer in Japanese women. SpringerPlus. 2015;4(1).
[7]. Salazar E, Paredes A, Calzada L. Endometrial thickness of postmenopausal breast cancer patients treatedwith tamoxifen. Gynecological Endocrinology. 2005;21(6):312-316.
[8]. Palva T, Ranta H, Koivisto A, Pylkkänen L, Cuzick J, Holli K. A double-blind placebo-controlled study to evaluate endometrial safety and gynaecological symptoms in women treated for up to 5 years with tamoxifen or placebo – A substudy for IBIS I Breast Cancer Prevention Trial. European Journal of Cancer. 2013;49(1):45-51.
[9]. Garrone O, Bertelli G, Principe E, Lewis PD, Occelli M, Miraglio E, Merlano MC. A prospective randomised study of transvaginal ultrasound effects of tamoxifen and exemestane in postmenopausal women with early breast cancer. *Tumori*. 2014: 100; 620-4.

[10]. LE DONNE M, ALIBRANDI A, CIANCIMINO L, AZZERBONI A, CHIOFALO B, TRIOLO O. Endometrial pathology in breast cancer patients: Effect of different treatments on ultrasonographic, hysteroscopic and histological findings. Oncology Letters. 2013;5(4):1305-1310.
[11]. Lee M, Piao J, Jeon M. Risk Factors Associated with Endometrial Pathology in Premenopausal Breast Cancer Patients Treated with Tamoxifen. Yonsei Medical Journal. 2020;61(4):317.

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