IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

The 5-Year Disease-Free Survival of Third Generation Aromatase Inhibitor for Postmenopausal Women with HR-positive HER2-negative Non-Metastatic Breast Cancer

Ria Etikasari[1], Tri Murti Andayani[2], Dwi Endarti[2], Kartika Widayati Taroeno-Hariadi[3]

[1]Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[3]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Corresponding Author: Ria Etikasari, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
E-mail: riaetikasari@gmail.com

Received: 15, Jan, 2021
Accepted: 07, .Feb, 2021

ABSTRACT

Background: Several studies showed the superiority of aromatase inhibitor (AI) as first-line therapy for patients with hormone-receptor (HR)-positive breast cancer (BC). For the clinician, studies in the real world are warranted to determine treatment based on the efficacy of each drug. We conducted a comparison of 5-y disease-free survival (DFS) of each AI in terms of survival benefit.

Materials and Methods: We evaluated 450 medical records of postmenopausal women at Dr. Sardjito General Hospital who were diagnosed with HR-positive HER2-negative BC (stage I – III) from January to December 2019 and had undergone surgery, received chemotherapy or radiation therapy, and at least one year of anastrozole, letrozole, or exemestane administration. Kaplan Meier estimation survival curve was used to analyse of survival rate.

Result: Of 79 patients meeting inclusion criteria, there were 21.52% distant metastases documented. Time to disease progression of anastrozole, letrozole and exemestane was 49 months, 58 months, and 53 months, respectively. Letrozole was found better than anastrozole (hazard ratio (HR)=4.342, 95% CI 0.95-19.95; p=0.038). Letrozole versus exemestane (HR=2.757, 95% CI 0.53-14.33; p=0,206) and anastrozole versus exemestane (HR=1.652, 95% CI 0.56-4.84; p=0.351) were found not significantly different. 5-y DFS rate of letrozole was better found (87.5%) than exemestane (73.7%) and anastrozole (61,4%).

Conclusion: 5-year letrozole administration could be proposed as first-line therapy for postmenopausal women with HR-positive HER2-negative BC. A considerable subject and long-term follow-up are needed for validation.

Keywords: Aromatase inhibitor; Breast cancer; Disease-free survival; HR-positive; Postmenopause

INTRODUCTION

Breast cancer (BC) is the most common type of cancer diagnosed in women worldwide, with an incidence of 24.2%. In Indonesia, there were 52.256 new cases in 2018[1]. Hormone-receptor (HR)-positive BC contributed to 75% in all cases and 91% of the 5-y survival rate in all stages[2]. Some molecular abnormalities are associated with more aggressive

proliferation such as the human epidermal growth factor receptor 2 (HER2-negative), Ki67, BRCA1, and BRCA2 gene mutations. Based on immunohistochemical tests, there are four molecular subtypes of BC: luminal A, luminal B, HER2-enriched, and triple-negative BC[3].

Therapeutic guidelines recommend a variety of health technologies for BC treatments. Those modalities are surgery, chemotherapy, radiation therapy, and hormonal therapy. Various treatments are used dependent upon the type of histology cell, stage of cancer, and molecular subtype [4]. Hormonal treatments are prescribed based on hormone receptor expression and menopausal status. Patients with HR-positive will receive hormonal therapy for a period of 5-10 years[5]. Hormone treatments have different mechanisms of action on the targeted molecular cell. Aromatase inhibitor (AI) works by blocking the enzyme involving the synthesis of oestrogen from androgen, while the selective oestrogen receptor modulator (SERM) and selective oestrogen receptor degrader (SERD) groups inhibit the action of oestrogen by binding and changing the conformational of oestrogen receptor. Hence, the oestrogen synthesized could not be bound with the receptor[6]. A guideline to choose appropriate anti-oestrogen is needed for optimizing treatment in hormone-sensitive patients.

AI has been recommended for the treatment of BC with HR-positive and HER2-negative. Since its development in the early 1990s, AI has been widely used in various clinical studies comparing it with other hormonal therapies or between AIs themselves. Studies comparing AI with tamoxifen showed that AI has an advantage in terms of efficacy in postmenopausal women[7,8]. Several studies comparing AIs also found that the descriptions of differences in response rates, event-free survival (EFS) rate, or disease-free survival (DFS) rate were not significant. Meta-analysis studies reported that letrozole has higher efficacy than anastrozole and exemestane [9].

The safety of AI has been published in many studies. The adverse events of AI are cardiac failure, joint pain, muscle pain, bone pain and neutropenia occurred on a 2-4 scale. Studies comparing the safety of anastrozole and letrozole conclude that there was no significant difference between them. On contrary, the incidence of exemestane adverse events was found higher than anastrozole [10–12].

The Indonesian National Formulary Standard Treatment Guideline recommends anastrozole, letrozole, and exemestane as first-line therapy in postmenopausal women diagnosed with HR-positive BC. During guideline implementation, no studies were conducted to compare the clinical outcomes of the drugs directly. A study of AI in postmenopausal women diagnosed with HR-positive BC has been carried out in several countries. In Indonesia, research on DFS in AI was conducted, but no remarkable difference was observed among anastrozole, letrozole, or exemestane. As the study population consist of premenopausal and postmenopausal women[13]; therefore, guidance to choose anastrozole, letrozole, or exemestane as the first-line adjuvant hormonal treatment for postmenopausal women is needed. The study aimed to compare the 5-y DFS rate amongst AI and to report the common adverse event found in daily practice.

MTERIALS AND METHODS

This observational retrospective cohort study was conducted at Dr. Sardjito General Hospital from January to December 2019. Inclusion criteria included postmenopausal women diagnosed with HR-positive HER2-negative BC (stage I – III), having undergone a mastectomy or breast-conserving therapy (BCT), *receiving or not receiving* chemotherapy or radiation therapy, and using hormonal therapy (anastrozole, letrozole, or exemestane) for at least one year as the first-line adjuvant hormonal therapy. Patients were excluded if medical record data were incomplete, and there was switching to other AI or SERM before one year. Data completeness included the availability of histology examination, immunohistochemistry testing, complete blood count and imaging studies (breast sonography, abdominal sonography, chest sonography, bone sonography), fine-needle aspiration during follow-up at certain points to document progression.

Seventy-nine out of 450 BC patients met the inclusion criteria: 31 received anastrozole, 22 used letrozole, and 26 received exemestane. The data collected were demographic and clinical outcomes data of patients. All data were verified by the clinician. One-way ANOVA and Chi-square tests were conducted to observe the statistical differences in patient characteristics. Descriptive analysis was performed on chemotherapy regimens and adverse events. The estimates of DFS differences were analysed using the log-rank test method and presented in the Kaplan Meier estimation survival curve. The log-rank test was used to see the significance of differences in DFS between groups. DFS was defined as the time interval from the first time AI was administered until the patients experienced distant metastases. Ethical Clearance was obtained from the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada (number KE/FK1197/EC/2018).

RESULTS

The mean (SD) for age was 62.7 (6.24) years (Table 1). The One-way ANOVA and Chi-square test results showed insignificant difference in the groups for age, histology, progesterone receptor hormone status, and stage of BC (p> 0.05). The most common histology was invasive ductal carcinoma (IDC) (82.28%), and mostly stage III (63.29%). All patients underwent mastectomy or BCT. There were 17 (21.52%) patients who experienced distant metastases in which the major metastases were bone (nine patients), and the others were lungs (four patients), liver (three patients), and skin (one patient).

Estimates of survival were analyzed using the log-rank test method and presented in the Kaplan-Meier curve (Figure. 1). Time to disease progression of anastrozole was 49 (95% CI, 44-55), letrozole was 58 (95% CI, 55-60), and exemestane was 53 months (95% CI, 47-58). The 5-y DFS letrozole was superior to anastrozole (Figure 1A). The 5-y DFS exemestane was found better than anastrozole (Figure 1B), but it did not suggest that the superior of exemestane improves DFS significantly than anastrozole. The 5-y DFS letrozole versus exemestane (Fig. 1C) also indicated that the difference in DFS between the two groups was not significant even though letrozole appeared to be higher than exemestane.

Comparing three groups of AIs, the 5-y DFS rate of letrozole was superior to anastrozole or exemestane (Figure 1D). It was 87.5% for letrozole, 73.7% for exemestane, and 61.4% for anastrozole. Median survival for the three groups was not achieved, which means that for 5 years, over 50% of the sample had not experienced distant metastases, and patients had high survival. Since the comparison of DFS for the three groups had p=0.111, there was no significant difference between the groups in increasing DFS.

The 5-y DFS rate for the cluster aged 55-65 years old revealed that letrozole (87.5%) was better than exemestane (61.2%) or anastrozole (45%) (Figure 2A). The superior of letrozole was also experienced at cluster IDC (Figure 2C) and stage III (Figure 2D), but not for the age of >65 years old in which exemestane had a higher DFS rate than anastrozole or letrozole. The estimation of the 5-y DFS rate in the comparison of the steroid (exemestane) and non-steroidal (anastrozole and letrozole) groups showed an insignificant difference in the choice of therapy between steroid or non-steroidal AI group in DFS outcome (hazard ratio (HR)=1.069, 95% CI 0.53-14.33; p=0.899).

Table 1: Patient characteristic

Characteristic		Anastrozole N = 31(%)	Letrozole N = 22(%)	Exemestane N = 26(%)	p-values
Age (year)		62.29 ± 6,36	61.77 ± 5,42	64.12 ± 6,73	0.382
Age distribution	<55	3 (9.68)	2 (9.09)	0	0.533
	55 – 65	16 (51.61)	12 (54.55)	14 (53.85)	
	>65	12 (38.71)	8 (36.36)	12 (46.15)	
Histology	IDC	24 (77.42)	19 (86.36)	22 (84.62)	0.702
	ILC	5 (16.13)	1 (4.55)	3 (11.54)	
	Others	2 (6.45)	2 (9.09)	1 (3.85)	
PgR status	PgR+	21 (67.74)	15 (68.18)	20 (76.92)	0.710
	PgR-	10 (32.26)	7 (31.82)	6 (23.08)	
Stage	I	0	1 (4.55)	3 (11.54)	0.339
	II	9 (29.03)	7 (31.82)	9 (34.62)	
	III	22 (70.97)	14 (63.64)	14 (53.85)	
Surgery		31 (100)	22 (100)	26 (100)	
Chemotherapy	**Yes**	28 (90.32)	21 (95.45)	23 (88.46)	0.683
	No	3 (9.68)	1 (4.55)	3 (11.54)	
Radiation therapy	**Yes**	18 (58.06)	9 (40.91)	13 (50.00)	0.467
	No	13 (41.94)	13 (59.09)	13 (50.00)	
Events of metastases		10 (32.26)	2 (18.18)	5 (19.23)	

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; PGR: Progesterone receptor

Table 2: Adjuvant chemotherapy

Regimen		N=72(%)
FEC→T	5-Fluorouracil-Epirubicin-Cyclophosphamide, Docetaxel	22 (30.56)
AC→Pacli	Doxorubicin-Cyclophosphamide, Paclitaxel	12 (16.67)
T Carbo	Docetaxel-Carboplatin	6 (8.33)
AT	Doxorubicin-Docetaxel	5 (6.94)
TAC	Doxorubicin-Cyclophosphamide-Docetaxel	5 (6.94)
AET	Doxorubicin-Epirubicin-Docetaxel	3 (4.17)
E-Pacli	Epirubicin-Paclitaxel	3 (4.17)
ET-Carbo	Epirubicin-Docetaxel-Carboplatin	3 (4.17)
Others	FAC, EC-Pacli, A-Pacli, TC, TE, FEC, CMF, AT-Carbo	13 (18.06)

Table 3: Adverse event

Adverse event	Anastrozole (N=31)	Letrozole (N=22)	Exemestane (N=26)	Total (N=79)
Dry skin	2 (6.45)	1 (4.55)	4 (15.38)	7 (8.86)
Fatigue	2 (6.45)	5 (22.73)	7 (26.92)	14 (17.72)
Dizziness	5 (16.13)	4 (18.18)	7 (26.92)	16 (20.25)
Arthralgia	11 (35.48)	9 (40.91)	15 (57.69)	35 (44.30)

Insomnia	1 (3.23)	1 (4.55)	0	2 (2.53)

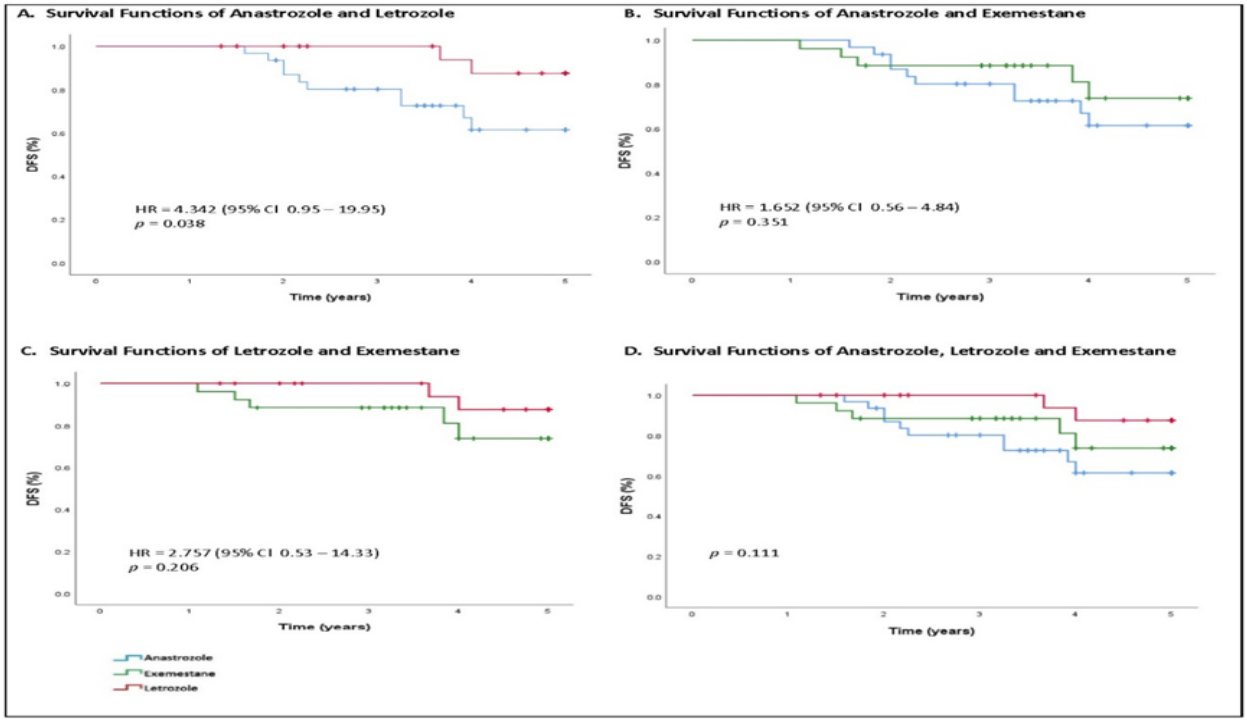

Figure 1. Kaplan Meier 5-year curve of disease-free survival of Aromatase Inhibitor

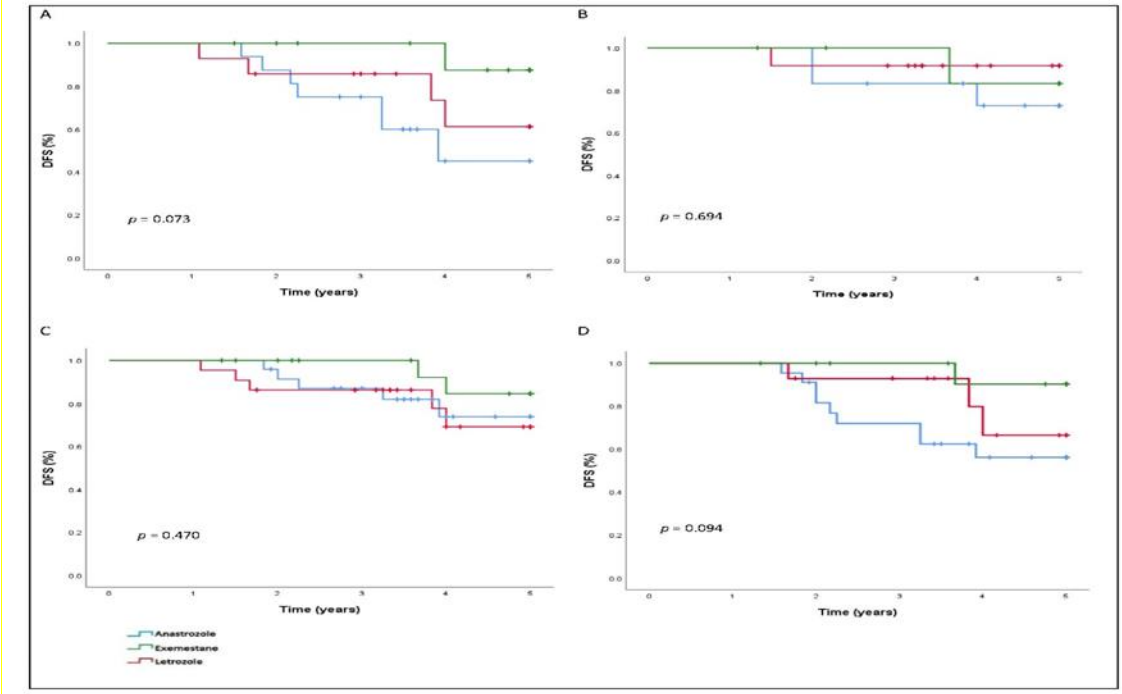

Figure 2. DFS rate for cluster 55-65 years (A), >65 years (B), IDC (C), and stage III (D)

DISCUSSION

The previous study showed that metastases could exist in about 20-30% of the whole BC patients [14], and our study found 21.52% of patients developed metastases. Our data were the same as another study showing bone metastases as the most frequent site [15,16].

Our study supported that letrozole provides better benefits in increasing DFS than anastrozole. These are similar to the previous study in that 5-y letrozole (84.9%) was slightly superior to anastrozole (82.9%) but it was not significantly different [11]. It was also similar to the previous study that the administration of exemestane or anastrozole resulted in insignificant differences in EFS (p=0.85) [17]. A study comparing oestrogen concentration between letrozole and exemestane concluded that letrozole statistically was significantly different from exemestane on suppression estrone (E1) and estrone sulfate (E1S) but not for oestradiol (E2) [18]. While a study directly comparing DFS letrozole and exemestane as first-line therapy for BC patients with HR-positive HER2-negative is not conducted yet so far. Previous studies comparing the clinical response outcomes of the three drugs found that the three drugs were not significantly different [19]. Studies that directly compare anastrozole, letrozole, and exemestane with the clinical outcome of DFS have not yet been found.

We found that the DFS rate steroid versus non-steroid AI was insignificantly different. Steroid and non-steroid AI had the same worksite to inhibit oestrogen synthesis from androgen but have different character mechanisms. Non-steroid AI was bound to aromatase protein reversibly, whereas steroid was bound irreversibly, which might be responsible for the difference in their clinical efficacy[20].

IDC is the most common breast carcinoma histologic subtype worldwide and drives the higher mortality of cancer in women [21]. The result of this study is similar to the one conducted at Sanglah General Hospital [22], M. Djamil General Hospital [23], and the study conducted in Japan[24].

Based on a previous study, the use of docetaxel could increase DFS by 4% [25] and 4.4% [26] compared to the one without using docetaxel. Various chemotherapy regimens and small sample size of patients were the main limitations to this study, which limited us to assess the effect of chemotherapy regimens on DFS. The adverse event that occurred in this study was also existed in previous AI studies, so new adverse event was found. This study did not document any adverse event associated with cardiac failure, vaginal bleeding, and hair loss like previous studies. RCT studies comparing the safety of anastrozole and letrozole concluded that there was no difference between the two groups. For instance, on discontinuation of therapy, anastrozole and letrozole were experienced by 14.3% and 15.1% of patients, respectively. Similarly, in comparison between anastrozole and exemestane, treatment discontinuation occurred in 29.4% and 33.8% of patients, respectively [11, 12, 27–30].

The DFS rate in BC patients is influenced by prognostic factors (stage, histology, or hormone receptor) and predictive factors (related to therapeutic responses)[31,32]. In other studies, prognostic factors (clinical-stage, neoadjuvant or adjuvant therapy, and age) were the significant determinants of DFS [17]. The small sample size, the little number of patients having distant metastasis, and the time of follow-up were not adequate to achieve the median DFS. Additionally, stage III of BC was seen more in patients on anastrozole than letrozole or exemestane, hence it influenced the DFS rate. Further research with a large sample size and long-term follow-up to achieve better results is recommended.

CONCLUSION

Five years of the administration of letrozole significantly increased dfs compared to anastrozole. There was no difference in dfs between exemestane and anastrozole, as well as exemestane and letrozole. Clinicians are recommended to choose based on patient tolerability. Moreover, there was no significant difference in terms of choosing steroidal or non-steroidal ai as the first-line adjuvant hormone therapy in BC. The most common adverse events were arthralgia and dizziness.

ACKNOWLEDGMENT

The authors would like thank the cancer registry Dr. Sardjito Hospital/Faculty of Medicine, public health and UGM nurses for their assistance in data collection.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Fitzmaurice Ch, Abate D, Abbasi N, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2019;5(12):1749-1768.

2. Lin PL, Hao Y, Xie J, et al. Real-world effectiveness of everolimus-based therapy versus endocrine monotherapy and chemotherapy in patients of HR+/HER2- breast cancer with liver metastasis in the USA. Expert Opin. Pharmacother.2015; 16(14): 2101–2111.

3. Anderson WF, Rosenberg RS, Prat A, et al. How many etiological subtypes of breast cancer: two, three, four, or more?.J Natl Cancer Inst. 2014; 106(8): dju165.

4. Panigoro S, Hernowo BS, Purwanto H, et al. Panduan Penatalaksanaan Kanker Payudara. Kementerian Kesehatan Republik Indonesia. Komite Penanggulangan Kanker Nasional, 2015.

5. Moo TA, Sanford R, Dang CH, et al. Overview of Breast Cancer Therapy. PET Clin.2018; 13(3): 339–354.

6. Abdulkareem IH, Zurmi IB. Review of hormonal treatment of breast cancer. Niger J Clin Pract. 2012; 15(1): 9–14.

7. Coates AS, Keshaviah A, Thürlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol Off J Am Soc Clin Oncol. 2007; 25(5): 486–492.

8. Forbes JF, Cuzick J, Buzdar A, et al."Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol. 2008; 9(1): 45–53.

9. Zhang J, Huang Y, Wang C, et al. Efficacy and safety of endocrine monotherapy as first-line treatment for hormone-sensitive advanced breast cancer. Medicine (Baltimore); 96(33): e7846.

10. Diéras V, Harbeck N, Joy AA, et al. Palbociclib with Letrozole in Postmenopausal Women with ER+/HER2- Advanced Breast Cancer: Hematologic Safety Analysis of the Randomized PALOMA-2 Trial. Oncologist. 2019; 24(12): 1514–1525.

11. Smith I, Yardley D, Burris H, et al. Comparative Efficacy and Safety of Adjuvant Letrozole Versus Anastrozole in Postmenopausal Patients With Hormone Receptor-Positive, Node-Positive Early Breast Cancer: Final Results of the Randomized Phase III Femara Versus Anastrozole Clinical Evaluation (FACE) Trial. J Clin Oncol. 2017; 35(10): 1041–1048.

12. Pritchard KI, Burris 3rd HA, Ito Y, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. Clin Breast Cancer. 2013;13(6):421-432.e8.

13. Wahyuni FS, Windrasari W, Khambri DD, et al .Evaluasi Terapi Adjuvant Hormonal Dan Hubungannya Terhadap Outcome Klinis Pasien Kanker Payudara Stadium Dini Di Kota Padang. J Sains Farm Klin. 2019; 5(3): 176–184.

14. Pulido C, Vendrell I, Ferreira AR, et al. Bone metastasis risk factors in breast cancer. Ecancermedicalscience. 2017; 11:715.

15. Bighin C, Dozin B, Poggio F, et al. Hormonal therapy followed by chemotherapy or the reverse sequence as first-line treatment of hormone-responsive, human epidermal growth factor receptor-2 negative metastatic breast cancer patients: results of an observational study. Oncotarget. 2017: 8(27): 44800–44810.

16. Beck JT, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane as first-line therapy in HR^+, $HER2^-$ advanced breast cancer in BOLERO-2. Breast Cancer Res. Treat. 2014; 143(3): 459–67.

17. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. J Clin Oncol. 2013; 31(11): 1398–404.

18. Robarge JD, Desta Z, Nguyen AT, et al. Effects of exemestane and letrozole therapy on plasma concentrations of estrogens in a randomized trial of postmenopausal women with breast cancer. Breast Cancer Res Treat. 2017; 161(3): 453–461.

19. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol. 2011; 29(17): 2342–9.

20. Miller WR, Bartlett J, Brodie AMH, et al. Aromatase inhibitors: are there differences between steroidal and nonsteroidal aromatase inhibitors and do they matter?. Oncologist. 2008; 13(8) 829–837.

21. Zangouri VM, Akrami MM, Tahmasebi SM, et al. Medullary Breast Carcinoma and Invasive Ductal

Carcinoma: A Review Study. Iran J Med Sci. 2018; 43(4): 365–371.

22. Wangsa I, Wayan N, Adiputra P, et al. Gambaran stadium dan jenis histopatologi kanker payudara di Subbagian Bedah Onkologi RSUP Sanglah Denpasar tahun 2015-2016. Intisari Sains Medis. 2018; 9(1):80-84.

23. Irwan I, Azamris A, Bachtiar H. Perbandingan Prognosis Subtipe Molekuler Kanker Payudara Antara Pasien Kanker Payudara Wanita Usia Muda dan Tua di RSUP DR. M. DJAMIL PADANG. Maj Kedokt Andalas. 2016; 38(3): 208–217.

24. Hasegawa Y, Tanino H, Horiguchi J, et al. Randomized Controlled Trial of Zoledronic Acid plus Chemotherapy versus Chemotherapy Alone as Neoadjuvant Treatment of HER2-Negative Primary Breast Cancer (JONIE Study). PloS One. 2015; 10(12): e0143643.

25. Sakr H, Hamed RH, Anter AH, et al. Sequential docetaxel as adjuvant chemotherapy for node-positive or/and T3 or T4 breast cancer: clinical outcome (Mansoura University). Med Oncol.2013;30(1): 457.

26. Coudert B, Asselain B, Campone M, et al. Extended benefit from sequential administration of docetaxel after standard fluorouracil, epirubicin, and cyclophosphamide regimen for node-positive breast cancer: the 8-year follow-up results of the UNICANCER-PACS01 trial. Oncologist. 17(7): 900–909.

27. Sagara Y, Kosha SH, Baba SH, et al. Adverse events and bone health during anastrozole therapy in postmenopausal Japanese breast cancer patients. Breast Cancer. 2010; 17(3): 212–217.

28. Im SA, Mukai H, Park IH, et al. Palbociclib Plus Letrozole as First-Line Therapy in Postmenopausal Asian Women With Metastatic Breast Cancer: Results From the Phase III, Randomized PALOMA-2 Study. J Glob Oncol. 2019; 5:1-19.

29. Sonke GS, Hart LL, Campone M, et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 2018; 167(3): 659–669.

30. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. J Clin Oncol.2013; 31(11): 1398–1404.

31. Yazdani A, Yaseri M, Haghighat SH, et al. Investigation of Prognostic Factors of Survival in Breast Cancer Using a Frailty Model: A Multicenter Study. Breast Cancer (Auckl). 2019;13:1178223419879112.

32. Corbeau I, Jacot W, Guiu S. Neutrophil to Lymphocyte Ratio as Prognostic and Predictive Factor in Breast Cancer Patients: A Systematic Review. Cancers (Basel). 2020;12(4):958.