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

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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 compared a 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 who were diagnosed with HR-positive HER2-negative BC (stage I – III) at Dr. Sardjito General Hospital from January to December 2019. All patients had undergone surgery and chemotherapy or radiation therapy. Moreover, study participants received anastrozole, letrozole, or exemestane for at least one year. Kaplan Meier estimation survival curve was used to analyze the 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 (Figure. 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 characteristics

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)

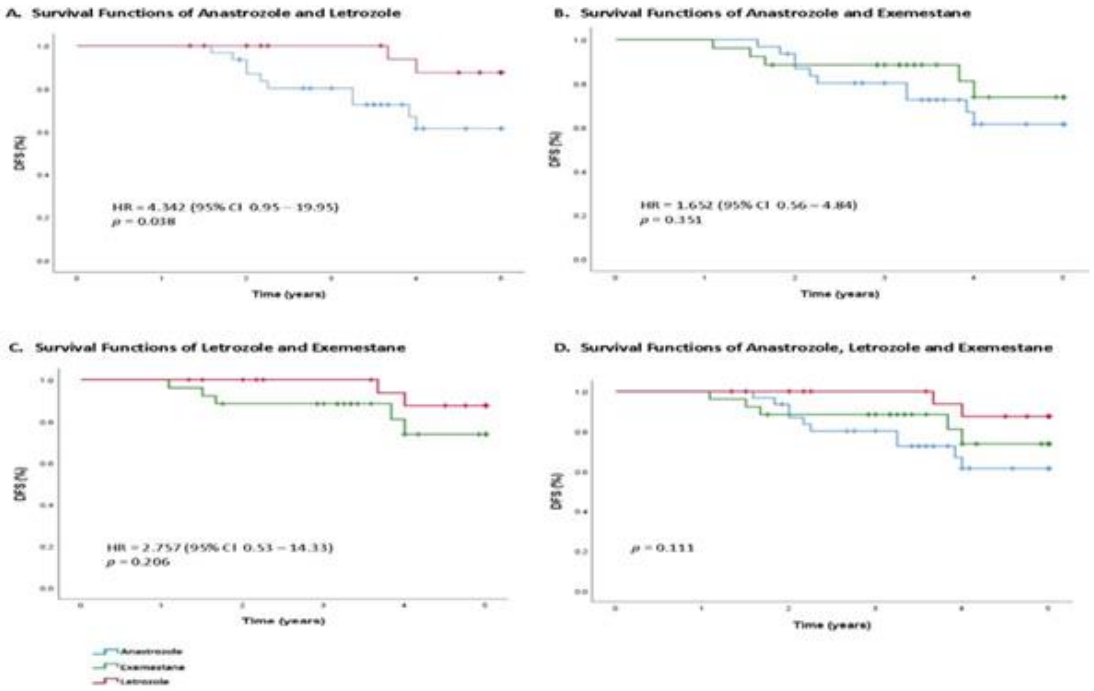

Figure 1. Kaplan-Meier 5-year curve of disease-free survival of aromatase inhibitor

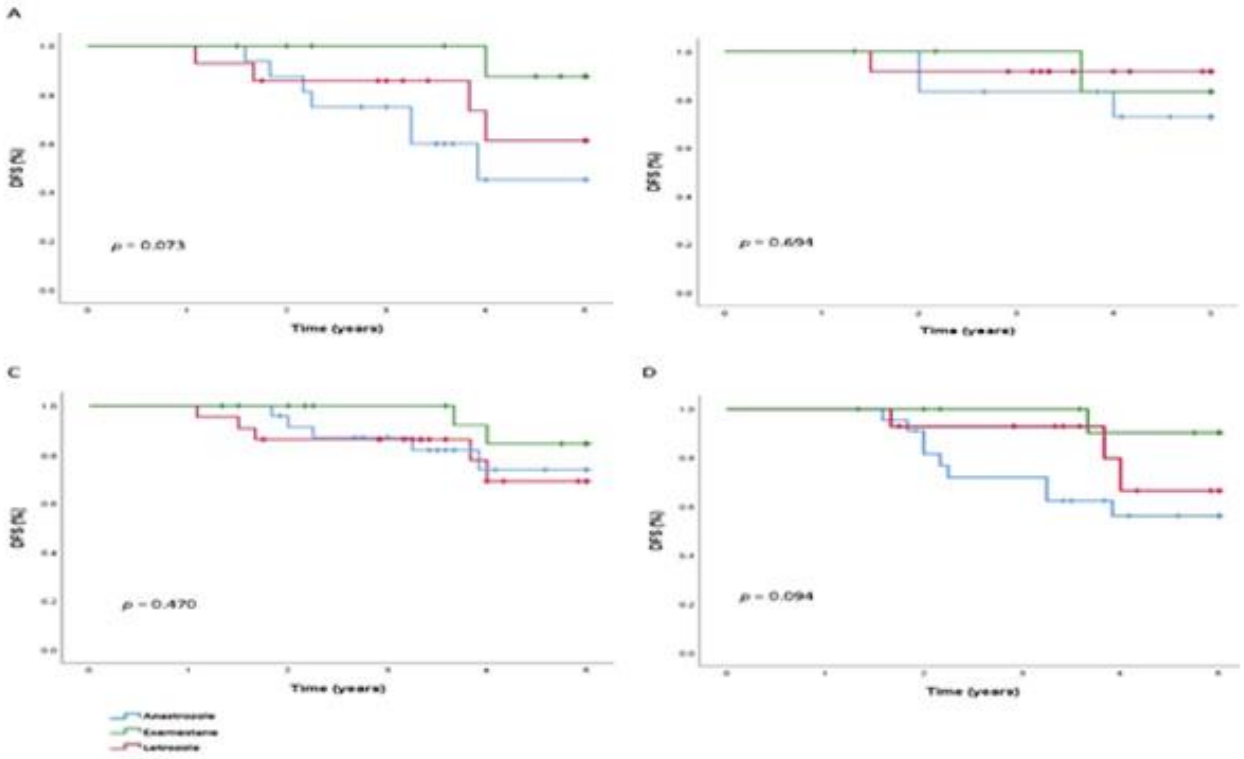

Figure 2. DFS rate for cluster 55-65 years (A), >65 years (B), IDC (C), and stage III (D)

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 efficacy20.

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 Japan24.

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.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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