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Cohort Study

Comparison of outcomes in patients with luminal type breast cancer treated with a gonadotropin-releasing hormone analog or bilateral salpingo-oophorectomy: A cohort retrospective study

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ABSTRACT

Introduction: Premenopausal patients with hormone receptor-positive breast cancer require ablation therapy via a pharmacological or surgical approach. Data comparing outcomes between treatment with gonadotropin-releasing hormone (GnRH) analogs and treatment with bilateral salpingo-oophorectomy (BSO) in Indonesia remains limited. Therefore, this study aimed to compare incidence of local recurrence and metastasis, and overall survival (OS) in patients with luminal type breast cancer treated using the two approaches.

Methods: This observational retrospective cohort study examined 100 premenopausal patients diagnosed with luminal type hormone receptor-positive breast cancer who registered at Dr. Wahidin Sudirohusodo Hospital and its networking hospitals in Makassar City from January to December 2017.

Result: Among the 100 study patients, 50 were given GnRH analogs and 50 underwent BSO. Incidence of local recurrence ($P = 0.408$) and metastasis ($P = 0.419$) did not significantly differ between the GnRH analog and BSO groups, although the incidence of local recurrence was higher in the GnRH analog group (68% vs. 58%) and incidence of metastasis was higher in the BSO group (24% vs 19%). The 5-year survival rate did not significantly differ between the GnRH analog and BSO groups.

Conclusion: Incidence of local recurrence and metastasis, and 5-year survival rate did not significantly differ between premenopausal breast cancer patients treated using a GnRH analog and those treated with BSO. Further large-scale studies to compare the efficacy and safety of both approaches are warranted.

1. Introduction

The annual incidence of breast cancer has been increasing 3.1% per year worldwide, from 641,000 cases in 1980 to over 1.6 million cases in 2010 [1,2]. In Indonesia, the reported annual incidence is 42.1 per 100,000 population. The average annual death rate owing to breast cancer is 17 per 100,000 population [3,4].

Hormone receptor (HR)-positive breast cancer has a better prognosis and is treated using adjuvant and endocrine therapy, including surgical ablation [5]. In the last few decades, ovarian function suppression (OFS), a type of extended adjuvant endocrine therapy, has been administered to premenopausal breast cancer patients. Initially, OFS was achieved via bilateral oophorectomy or ovarian irradiation. More recently, gonadotropin-releasing hormone (GnRH) analogs (also known as luteinizing hormone-releasing hormone agonists) have been used [6].

Ovarian ablation has a relatively large positive effect on disease-free survival (DFS) and overall survival (OS) in premenopausal women with breast cancer [7]. Several studies have hypothesized that the hypogonadotropic state elicited by GnRH analogs decreases the number of primordial follicles in the differentiation stage, which is more

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susceptible to chemotherapy [8]. The possibility of administering noninvasive adjuvant treatment that can reduce gonadotoxicity of chemotherapeutic agents is interesting [9].

Although the number of studies comparing GnRH analog administration with bilateral salpingo-oophorectomy (BSO) as OFS in breast cancer treatment is limited and most did not perform a direct comparison, the outcomes appear to be similar [10]. Because of its less invasive nature and lower risk of causing irreversible menopause, the use of pharmacologic ovarian suppression has surpassed BSO over time [11]. Patient preference for nonsurgical treatment may also have played a role. Nonetheless, comparison of the two approaches is important, as each has its own advantages and disadvantages. Therefore, this study aimed to compare incidence of local recurrence and metastasis, and OS in patients with luminal type breast cancer treated using the two approaches.

2. Methods

This was observational retrospective cohort study which examined all patients diagnosed with breast cancer who were registered at Dr. Wahidin Sudirohusodo Hospital and its networking hospitals in Makassar City between January and December 2017. The data was taken from patients' medical record after approval by the Medical Research Ethics Commission of the Medical Faculty of Hasanuddin University (registration number: 739/UN4.6.4.5.31/PP36/2021) and was registered with the Research Registry (no. 7641). This work has been reported in line with the Strengthening the Reporting of Cohort Studies in Surgery criteria [12].

Premenopausal patients diagnosed with invasive luminal type ductal breast cancer who had undergone curative breast cancer surgery and with estrogen-receptor positive or progesterone-receptor positive tumors were eligible for study inclusion. Patients who died from causes other than cancer or who had insufficient medical data were excluded from the study group. A total of 100 patients were selected using the consecutive sampling method: 50 were given a GnRH analog and 50 underwent BSO. Incidence of local recurrence and metastasis which were determined by the patients' clinical manifestation (symptoms and physical examination findings), imaging, tumor markers, and histopathological examination as well as OS were followed up in 5 years and compared between groups.

Statistical analyses were carried out using SPSS software version 25 (IBM Corp., Armonk, NY, USA). Categorical data were compared using the chi-square test or Fisher's exact test. $P < 0.05$ was considered significant. The Kaplan–Meier method was used for univariate survival-rate analysis. The log-rank test was performed to compare differences across groups of variables.

3. Results

The majority of patients in both groups were 35–49 years old. In the SOB group, most patients were in the advanced stage (Stage IV), which was 48%, while in the GnRH group, most respondents were at the locally advanced breast cancer stage (Stage III), which was 46%. The incidence of local recurrence was slightly higher in the GnRH analog group (68% vs. 58%) (Table 1). The incidence of metastasis was slightly lower in the GnRH group (38% vs. 48%) Table 2.

As shown in Table 1, the incidence of local recurrence did not significantly differ between the GnRH analog and BSO groups ($P = 0.408$) (Table 3). The incidence of metastasis also did not significantly differ between the GnRH analog and BSO groups ($P = 0.419$). Survival analysis is shown in Fig. 1. Five-year survival did not significantly differ between the GnRH analog and BSO groups (both curves indicate survival >90%).

Table 1
Sample characteristic.

Variable	SOB (%)	GnRH (%)
Age (years)		
<35	5 (10)	5 (10)
35–49	45 (90)	42 (84)
50–60	0 (0)	3 (6)
>60	0 (0)	0 (0)
Stage		
Early (Stage I-II)	3 (6)	8 (16)
Locally Advanced Breast Cancer (Stage III)	23 (46)	23 (46)
Advance (Stage IV)	24 (48)	19 (38)
Histopathology Grade (WHO)		
Low Grade Malignancy (Grade 1)	2 (4)	4 (8)
Moderate Grade Malignancy (Grade 2)	32 (64)	34 (68)
High Grade Malignancy (Grade 3)	16 (32%)	12 (24)
Recurrency		
Non-recurrence	21 (42)	16 (32)
Local recurrence	29 (58)	34 (68)
Metastasis		
Non-Metastasis	26 (52)	31 (62)
Metastasis	24 (48)	19 (38)
Recurrency Rates (years)		
<1	17 (34)	16 (32)
1–5	27 (54)	31 (62)
>5	6 (12)	3 (6)
Survival Rate (years)		
<1	24 (48)	36 (72)
1–5	22 (44)	12 (24)
>5	4 (8)	2 (4)
Chemotherapy Treatment		
Yes	33 (66)	38 (76)
No	17 (34)	12 (24)

Table 2
Comparison of incidence of local recurrence in patients grouped according to type of ovarian function suppression therapy.

Local Recurrence	Group		p value
	GnRH (%)	BSO (%)	
Non-recurrence	16 (32)	21 (42)	0.408[a]
Local recurrence	34 (68)	29 (58)	

[a] Chi-square test.

Table 3
Comparison of metastasis incidence in patients grouped according to type of ovarian function suppression therapy.

Recurrence (metastasis)	Group		p value
	GnRH (%)	**BSO (%)**	
Metastasis	19 (38)	24 (48)	0.419[a]
Non-Metastasis	31 (62)	26 (52)	

[a] Fisher's exact test.

4. Discussion

Breast cancer is the leading cause cancer in women [13], with a 5-year overall survival rate of only 27% for individuals with metastatic breast cancer (MBC) [14]. A rapidly evolving understanding of cancer biology has led to the development of novel biomarkers and targeted

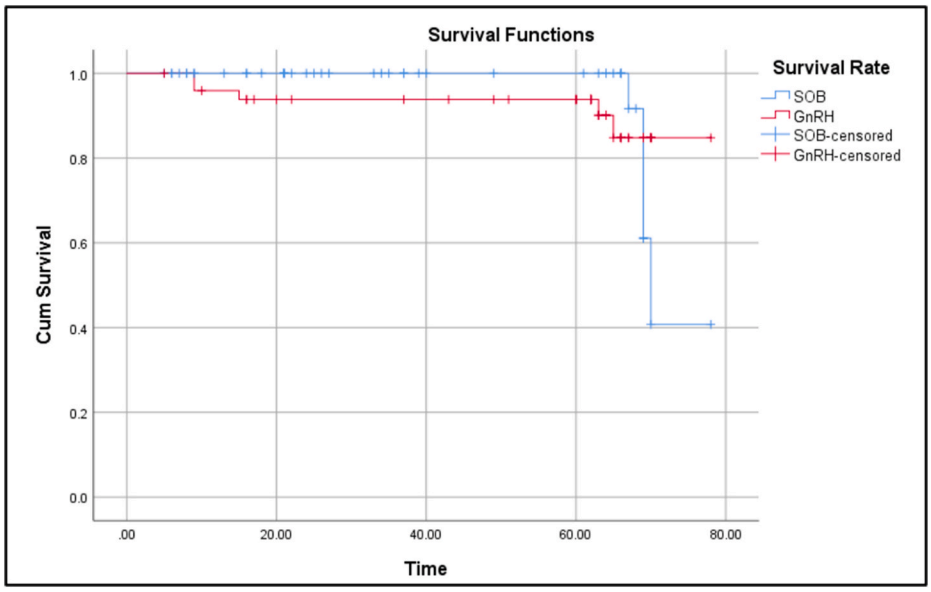

Fig. 1. Kaplan–Meier analysis showed no significant difference in OS between the GnRH analog and BSO groups.

therapy, even though significant improvement on the survival of patients with MBC remains elusive. Patient age, performance status, medical/surgical comorbidities, organ function, histological grade, tumor size and the presence of breast tumor metastasis are contributors to this heterogeneity [15,16].

When treating a premenopausal woman with breast cancer with endocrine therapy, the first decision is whether to treat with ovarian suppression using gonadotropin-releasing hormone agonists, such as leuprolide acetate and goserelin, or oophorectomy to induce menopause [17]. Surgical ablation is usually done as a second- or third-line hormonal therapy after failure of previous lines (as proved by progression or recurrence) [5]. The role of oophorectomy in the treatment of breast cancer is known for over 100 years. The subsequent overview published in 2005 showed that ovarian ablation had a relatively large positive effect on both DFS and OS in premenopausal women when compared to no adjuvant treatment [7].

Few previous studies have directly compared outcomes between breast cancer patients who undergo BSO and those who are treated by a GnRH analog [9]. The American College of Obstetricians and Gynaecologists suggested in 2008 that patients with HR-positive MBC should be treated first with aggressive hormonal therapy using pharmacological or surgical OFS [10].

The majority of patients in both groups were 35–49 years old, the results of this study are in line with the results conducted by, Suh et al. (2017) [9] that found the mean age of patients receiving GnRH was 44 years (n = 42; 64%). Meanwhile, according to Ferrandina et al. (2017) [6], BSO is recommended for the treatment of breast cancer patients aged 40–49 years.

In the GnRH group, the majority of patients were at the stage of Locally Advanced Breast Cancer (Stage III) while in the BSO group, the majority of patients were at an Advanced stage (Stage IV). This report are in line with Huang et al. (2020) [18], about 5–10% of women with breast cancer will be diagnosed with stage IV breast cancer at the time of their initial diagnosis.

In this study, the GnRH analog group experienced a slightly higher rate of local recurrence, lower rate of distant metastasis, and lower 5-year survival rate compared with the BSO group; however, the differences were not significant. Our results are in line with a 2017 study of 66 premenopausal patients with recurrent or MBC conducted by Suh et al. [9]; however, they examined patients with HR-positive and HR-negative tumors who received an aromatase inhibitor (AI) and GnRH agonist (64%) or BSO surgery (36%). Clinical benefit was higher (88%) and DFS was longer in the BSO group (69%). Patients treated with goserelin only (n = 22) had an overall response rate of 27.2% (standard error, 18.6%), whereas those who underwent oophorectomy or ovarian ablation (n = 15) had an overall response rate (proportion of patients who achieved a complete or partial response) of 46.6% (standard error, 25.3%); however, the difference was not significant.

Although Suh et al. [9] and Hsieh et al. [19] reported that both pharmacological and surgical ovarian suppression were effective and resulted in similar OS rates, our findings were slightly different. Guidozzi also reported that hormone suppression with GnRH analogs had the same effectiveness as oophorectomy [11].

In this study, the GnRH analog group experienced a slightly higher rate of local recurrence. This may occur because of the failure of GnRH to induce menopause in the patient, also according to Metwally (2019) [5], because of the potential reversibility of ovarian function with GnRH agonist/antagonist therapy. In addition, our patient's non-adherence to the GnRH injection schedule resulted in failure to reach the post-menopausal levels, this could be due to economic issues with the price of GnRH drugs or in some of our patients who came from rural areas far from the hospital. High cost, treatment adherence, and side effects are disadvantages of GnRH analog therapy, which are significant concerns, particularly in developing countries [20].

Nourmoussavi et al. [20] showed that ovarian ablation combined with AI was more effective but was not considered cost-effective, mainly when OA is controlled with a GnRH agonist or antagonist [20]. BSO blocks estrogen completely, but is a surgical procedure associated with short- and long-term side effects such as vasomotor, urogenital, and psychological sexual effects; osteopenia; osteoporosis; adverse cardiac disorders; and cognitive dysfunction [19].

Today, owing to advances in laparoscopic surgery, BSO can be performed less invasively with a relatively low complication rate that reportedly ranges between zero and 6.1% [11]. Therefore, permanent ovarian suppression via BSO is recommended for patients who wish to avoid monthly GnRH analog injections. In a recent survey of MBC patients receiving pharmacological ovarian suppression, seven out of 13 patients stated that they would opt for oophorectomy if initially offered [21]. Patients and physicians should rationally discuss the choice between BSO and GnRH analog therapy.

Breast cancer ovarian metastasis is uncommon [22,23], with incidence ranging from 3% to 30% in various studies, including preventative or therapeutic oophorectomies, autopsies, and accidental findings in routine surgery. Only 63 patients (2.4%) had histologically

established ovarian metastases in a study of 2648 women that were diagnosed with primary invasive breast cancer (BC) who underwent unilateral/bilateral oophorectomy as a preventative or therapeutic procedure [23,24]. In our study, all ovaries of patients who underwent the BSO procedure were not histopathology examined, so we could not detect ovarian metastases in BC.

The limitations of this study are the retrospective design, the number of cases is relatively small, the schedule for the injection of GNRH in some patients is often not in timely manner because there are some patients who come from rural areas. Routine follow-up of breast cancer patients is very important, especially for patients after mastectomy or with systemic therapy. However, at our centre, follow-up is not routinely performed on each examination item, if the patient is asymptomatic, the diagnosis of progression, recurrence or metastatic case is delayed.

5. Conclusion

Incidence of local recurrence and metastasis, and OS did not significantly differ between premenopausal breast cancer patients treated using a GnRH analog and those treated with BSO. Patients should be informed of the two treatment options and allowed to choose.

Ethical approval

All procedure for human experiment has been approved by Ethics Commission Faculty of Medicine, Hasanuddin University Number: 739/UN4.6.4.5.31/PP36/2021.

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Author contribution

Dwi Ris Andriyanto, Prihantono, Salman Ardi Syamsu, M. Ihwan Kusuma, and Joko Hendarto wrote the manuscript and participated in the study design. Dwi Ris Andriyanto, Prihantono, Salman Ardi Syamsu, M. Ihwan Kusuma, Joko Hendarto, Indra, Nilam Smaradania, Elridho Sampepajung, Asrul Mappiwali, and Muhammad Faruk drafted and revised the manuscript. Dwi Ris Andriyanto, Prihantono, Salman Ardi Syamsu, M. Ihwan Kusuma, Indra, Nilam Smaradania, Elridho Sampepajung, Asrul Mappiwali, and Muhammad Faruk performed treatment and surgery. Dwi Ris Andriyanto, Prihantono, Indra, Nilam Smaradania, Elridho Sampepajung, and Joko Hendarto performed bioinformatics analyses and revised the manuscript. All authors read and approved the final manuscript.

Please state any conflicts of interest

The authors declare that they have no conflict of interests.

Registration of research studies

This study is registered with the Research Registry and the unique identifying number is: research registry 7641.

Guarantor

Prihantono.

Consent

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent on admission to use their prospective data base and files for research work.

Provenance and peer review

Not commissioned, externally peer reviewed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103614.

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