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ORIGINAL ARTICLE

Retrospective Study

Oncologic efficacy of gonadotropin-releasing hormone agonist in hormone receptor-positive very young breast cancer patients treated with neoadjuvant chemotherapy

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Abstract

BACKGROUND

Breast cancer in young women has been shown to have an aggressive behavior and poor prognosis.

AIM

To evaluate the outcomes of young hormone receptor (HR)-positive patients with breast cancer treated with neoadjuvant chemotherapy (NAC), and the oncologic efficacy of gonadotropin-releasing hormone (GnRH) agonists.

METHODS

This retrospective study involved a prospectively enrolled cohort. We included patients diagnosed with invasive breast cancer who were treated with NAC followed by curative surgery at the Samsung Medical Center and Samsung Changwon Hospital between January 2006 and December 2017. Among patients with HR-positive and human epidermal grow factor 2 (HER2)-negative breast cancer, we analyzed the characteristics and oncology outcomes between the patients equal to or younger than 35 years and the patients older than 35 years.

RESULTS

Among 431 patients with NAC and HR-positive/HER2-negative breast cancer, 78

were 35 years old or younger, and 353 patients were older than 35 years. The median follow-up was 71.0 months. There was no statistically significant difference in disease free survival (DFS, $P = 0.565$) and overall survival ($P = 0.820$) between the patients equal to or younger than 35 years and the patients older than 35 years. The two groups differed in that the GnRH agonist was used more frequently in the group of patients equal to or younger than 35 years than in the other group (52.4% *vs* 11.2%, $P < 0.001$). Interestingly, for the DFS according to the GnRH agonist in the group of patients equal to or younger than 35 years, patients treated with the GnRH agonist had better DFS ($P = 0.037$).

CONCLUSION

Administration of GnRH agonists might improve the DFS rate of HR-positive/HER2-negative breast cancer in the equal to or younger than 35 years group of patients with NAC.

Key Words: Gonadotropin-releasing hormone Agonist; Young; Breast; Cancer

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Core Tip: The treatment of ovarian suppression was effected a better oncology outcome in the group with clinical high risk, hormone receptor (+) breast cancer. However few studies have compared the efficacy of gonadotropin-releasing hormone (GnRH) agonists for 2 years in patients with neoadjuvant chemotherapy. The aim of our study was to evaluate the efficacy of GnRH agonist treatment in young breast cancer patients.

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INTRODUCTION

In Western countries, approximately 4% of the patients with breast cancer are younger than 35 years[1,2]. In Asian countries, approximately 5%-6% of patients with breast cancer are diagnosed at a young age, with the mean age at diagnosis being 10 years younger than that in Western countries[3-5]. According to data from the Korean Breast Cancer Society, 5.3% of patients with breast cancer are aged < 35 years[6].

Previous studies have reported that younger patients diagnosed with breast cancer may have more advanced stages and more aggressive tumor biology. Younger patients had higher-grade tumors that were poorly differentiated, hormone receptor (HR)-negative, and human epidermal growth factor 2 (HER2)-positive, a higher grade[7,8]. Additionally, young patients with breast cancer show a poorer response to treatment than older patients. Therefore, these patients had worse outcomes than older patients[9,10]. Younger patients also exhibited higher rates of recurrence and mortality risk than older patients, and HR-positive/HER2-negative tumors were significantly different in terms of oncological outcomes between the younger and older groups[11,12].

Recently, the suppression of ovarian function trial (SOFT) and the tamoxifen and exemestane trial (TEXT) demonstrated that treatment of ovarian suppression resulted in a better oncology outcome in the clinically high-risk group. Patients who were 35 years or younger exhibited better survival with this treatment than with tamoxifen[13-15]. Treatment efficacy, adherence, and quality of life among women younger than 35 years were evaluated according to the International Breast Cancer Study Group SOFT and TEXT adjuvant endocrine therapy trials[16]. However, few studies have compared the efficacy of gonadotropin-releasing hormone (GnRH) agonists over 2 years in patients receiving neoadjuvant chemotherapy (NAC). The aim of our study was to investigate survival differences in HR-positive/HER2-negative breast cancer patients treated with NAC and to evaluate the efficacy of GnRH agonist treatment in young patients with breast cancer.

MATERIALS AND METHODS

We reviewed the medical records of a prospectively collected cohort. We included patients diagnosed with invasive breast cancer who were treated with NAC followed by curative surgery at the Samsung Medical Center and Samsung Changwon Hospital between January 2006 and December 2017. This study included 431 patients with HR-positive/HER2-negative breast cancer patients. We compared the characteristics and oncological outcomes between the equal-to-or-younger-than-35-years group ($n = 78$) and the older-than-35-years group ($n = 353$) (Figure 1).

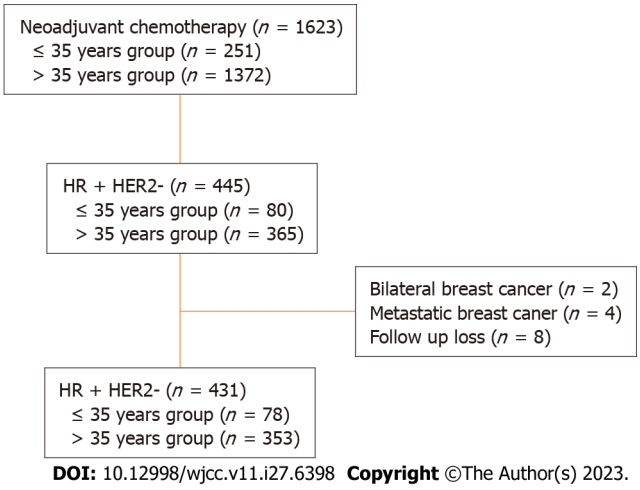

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Figure 1 Algorithm of patient selection with strong hormone receptor-positive/ human epidermal grow factor 2-negative breast cancer.
HR: Hormone receptor; HER2: Human epidermal grow factor 2.

We included patients newly diagnosed with primary invasive breast cancer who were treated with NAC between 2006 and 2017. Patients with metastatic, bilateral, HER2-positive breast cancer, and triple-negative breast cancers were excluded. In HER2-positive breast cancer and triple-negative breast cancers, GnRH agonist treatment is administered before NAC for ovarian protection; however, continuous GnRH agonist treatment is not administered. Therefore, this study included only HR-positive/HER2-negative breast cancer patients who had undergone GnRH treatment for more than two years, excluding HER2-positive breast cancer and triple-negative breast cancer. The two treatment groups were analyzed in this study. One patient received a GnRH agonist concurrent with NAC for fertility preservation and ovarian suppression over the course of two years, and the other received NAC alone during the same period.

We used anti-ER and anti-PgR monoclonal antibodies on 10% formalin-fixed, paraffin-embedded tissues. Only nuclear (non cytoplasmic) staining was performed. A positive test was defined as one having positive staining greater than or equal to 1% of the tumor cells. A negative test result was defined as one having staining of less than 1% of the tumor cells. We also combined our report with the Allred score interpretation system, which includes intensity (0-3) and proportion scores (0-5). We used an anti-HER2 monoclonal antibody in 10% formalin-fixed paraffin-embedded tissues. Incomplete membrane staining that is faint /barely perceptible and in > 10% of tumor cells is "1+". No staining is observed or membrane staining that is incomplete and is faint/barely perceptible and in ≤ 10% of tumor cells is "0". A negative test result was defined as a staining score of 0/1 +.

Most patients were administered anthracycline- and/or taxane-based regimens. These regimens include anthracycline plus cyclophosphamide, followed by a taxane-based regimen. Adjuvant radiotherapy (RT) was performed using tangential fields in all patients after breast conserving surgery.

We used the chi-square test and Spearman's correlation coefficient to compare discrete variables, and conducted survival analysis using the log-rank test. Using the Kaplan-Meier method, we constructed survival curves to determine the statistical significance of survival. Differences were considered significant when the *P* value was less than 0.05. We performed chi-square tests and calculated the logistic regression using SPSS version 22. This study was approved by the Institutional Review Board of 000, Seoul, South Korea (IRB file No. 2017-12-118-002).

RESULTS

Among 431 patients with NAC and HR-positive/HER2-negative breast cancer, 78 patients were equal to or younger than 35 years old, and 353 patients were older than 35 years old. There were no specific differences in the patient characteristics according to age. The pCR of patients equal to or younger than 35 years and patients older than 35 years is both low (4.8% and 3.9%, respectively). However, GnRH agonists were more frequently used in patients younger than 35 years than in patients older than 35 years (52.4% *vs* 11.2%, $P < 0.001$) (Table 1). There were no specific differences in patient characteristics according to GnRH agonist treatment in patients younger than 35 years (Table 2).

The 5 year-disease free survival (DFS) rate of patients equal to or younger than 35 years was 71.8%, and that of patients older than 35 years was 77.6%. There was no statistically significant difference in DFS ($P = 0.565$) and overall survival ($P = 0.820$) rates between the patients equal to or younger than 35 years and those older than 35 years (Figure 2).

Interestingly, among the 78 patients who were 35 years old or younger, 30 were treated with an additional GnRH agonist, and three experienced recurrences. However, 48 patients were not treated with GnRH agonists, and 19 patients experienced recurrence. Among the patients equal to or younger than 35 years, those who were treated with a GnRH agonist had a lower DFS (89.3% *vs* 62.0%, $P = 0.037$) and there was no statistically significant difference in OS ($P = 0.341$) rates (Figure 3).

Table 1 Patient characteristics according to age group

Variable	≤ 35 yr group (*n* = 78), *n* (%)	> 35 yr group (*n* = 353), *n* (%)	*P* value
BMI			0.064
≤ 25	56 (71.8)	211 (59.7)	
> 25	22 (28.2)	142 (40.23	
Clinical tumor stage			0.187
cT1	8 (10.26)	15 (4.25)	
cT2	36 (46.15)	184 (52.12)	
cT3	26 (33.33)	120 (33.99)	
cT4	8 (10.26)	34 (9.63)	
Clinical node stage			0.237
cN1	14 (17.95)	96 (27.20)	
cN2	40 (51.28)	162 (45.89)	
cN3	24 (30.77)	95 (26.91)	
Pathologic tumor stage			0.101
ypT0-is	15 (19.23)	34 (9.63)	
ypT1	23 (29.49)	116 (32.86)	
ypT2	25 (32.05)	111 (31.44)	
ypT3	15 (19.23)	84 (23.80)	
ypT4	0 (0.00)	8 (2.27)	
Pathologic node stage			0.336
ypN0	25 (32.05)	110 (31.16)	
ypN1	30 (38.46)	111 (31.44)	
ypN2	18 (23.08)	86 (24.36)	
ypN3	5 (6.41)	46 (13.03)	
Lymphovascular invasion			0.739
Present	38 (48.72)	168 (47.59)	
Absent	32 (41.03)	157 (44.48)	
Unknown	8 (10.26)	28 (7.93)	
Surgery			0.195
Breast conserving	43 (55.13)	166 (47.03)	
Mastectomy	35 (44.87)	187 (52.97)	
Nuclear grade			0.697
Low	11 (14.10)	37 (10.48)	
Intermediate	32 (41.03)	165 (46.74)	
High	27 (34.62)	121 (34.28)	
Unknown	8 (10.26)	30 (8.50)	
Radiation therapy			0.642
Yes	75 (96.15)	335 (94.90)	
No	3 (3.85)	18 (5.10)	
GnRH agonist			< 0.001
Yes	22 (52.4)	20 (11.2)	
No	20 (47.6)	158 (88.8)	

GnRH: Gonadotropin-releasing hormone; BMI: Body mass index.

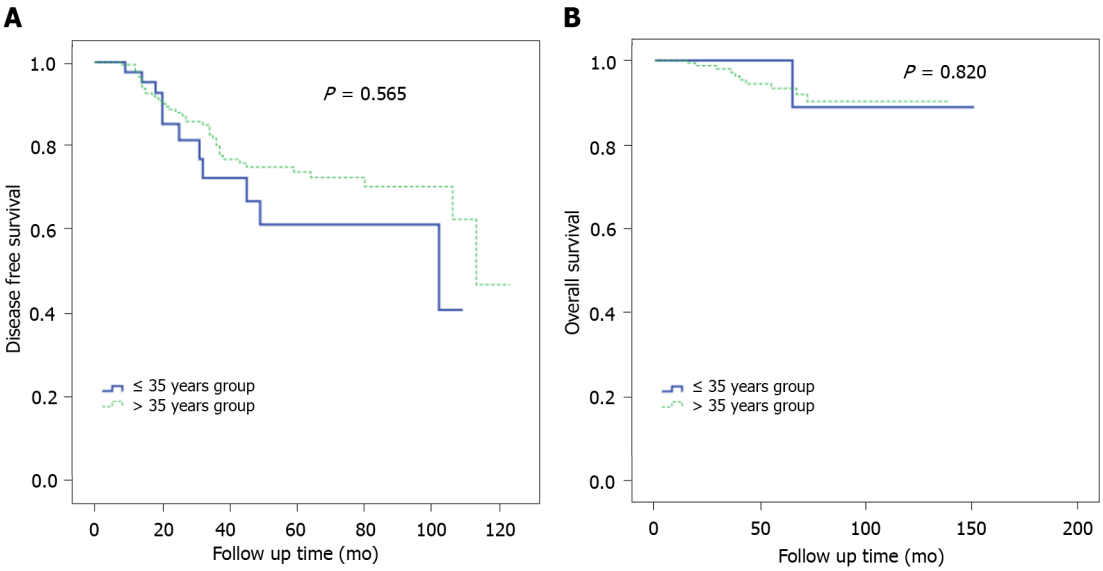

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Figure 2 Kaplan-Meier survival curves for disease free survival rates and overall survival rates between patients equal to or younger than 35 years and patients older than 35 years. A: Disease free survival rates; B: Overall survival rates.

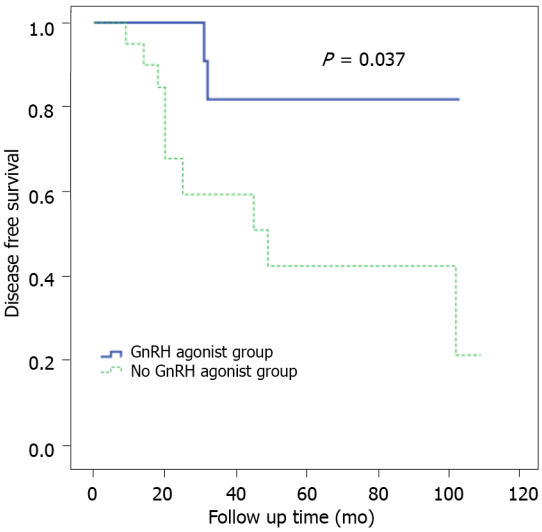

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Figure 3 Kaplan-Meier survival curves for disease free survival according to gonadotropin-releasing hormone agonist among younger than 35 years group. GnRH: Gonadotropin-releasing hormone.

DISCUSSION

Young patients with HR-positive breast cancer were treated with tamoxifen and ovarian suppression with a GnRH agonist after surgery and had a greater advantage in DFS than patients from a previous period[17]. Since the young patients with HR-positive/HER2-negative breast cancer with NAC were treated with tamoxifen and GnRH agonist, our study demonstrates that oncologic outcomes of HR-positive/HER2-negative breast cancer patients equal to or younger than 35 years of age have improved overall with time.

The pCR rate and proliferation index decreased more in HR-positive tumors than in other breast cancer subtypes. For HR-positive tumors, the pCR rate was low and unrelated to survival in a previous neoadjuvant study[18-20]. Therefore, neoadjuvant trials could not determine the oncological efficacy in HR-positive tumors because of the low pCR rate and the absence of any relationship with survival. Understanding the effect on the frequency of recurrence would help clinicians make decisions regarding additional treatment options for patients receiving neoadjuvant treatment for ER-

Table 2 Patient characteristics according to gonadotropin-releasing hormone agonist treatment in equal to or younger than 35 years patients

Variable	GnRH agonist (*n* = 30), *n* (%)	No. of GnRH agonist (*n* = 48), *n* (%)	*P* value
BMI			0.999
≤ 25	25 (83.33)	40 (83.33)	
> 25	5 (16.67)	8 (16.67)	
Clinical tumor stage			0.150
cT1	2 (6.67)	6 (12.50)	
cT2	13 (43.33)	23 (47.92)	
cT3	14 (46.67)	12 (25.00)	
cT4	1 (3.33)	7 (14.58)	
Clinical node stage			0.185
cN1	8 (26.67)	6 (12.50)	
cN2	12 (40.00)	28 (58.33)	
cN3	10 (33.33)	14 (29.17)	
Pathologic tumor stage			0.706
ypT0-is	7 (23.33)	8 (16.67)	
ypT1	8 (26.67)	15 (31.25)	
ypT2	8 (26.67)	17 (35.42)	
ypT3	7 (23.33)	8 (16.67)	
ypT4	0 (0.00)	0 (0.00)	
Pathologic node stage			0.061
ypN0	9 (30.00)	16 (33.33)	
ypN1	10 (33.33)	20 (41.67)	
ypN2	7 (23.33)	11 (22.92)	
ypN3	4 (13.33)	1 (2.08)	
Lymphovascular invasion			0.754
Present	13 (43.33)	25 (52.08)	
Absent	14 (46.67)	18 (37.50)	
Unknown	3 (10.00)	5 (10.42)	
Surgery			0.472
Breast conserving	15 (50.00)	28 (58.33)	
Mastectomy	15 (50.00)	20 (41.67)	
Nuclear grade			0.984
Low	4 (13.33)	7 (14.58)	
Intermediate	13 (43.33)	19 (39.58)	
High	10 (33.33)	17 (35.42)	
Unknown	3 (10.00)	5 (10.42)	
Radiation therapy			0.555
Yes	28 (93.33)	47 (97.92)	
No	2 (6.67)	1 (2.08)	

GnRH: Gonadotropin-releasing hormone; BMI: Body mass index.

positive breast cancer. The persistence of amenorrhea may help prevent relapses. This study demonstrated that young patients with breast cancer treated with GnRH agonists exhibited improved oncological outcomes.

For the SOFT trial, even though there was no statistical significance in treating with an additional GnRH agonist in the first report from this trial, patients aged 35 years or younger exhibited improved survival with this treatment than with tamoxifen. The benefits of tamoxifen combined with a GnRH agonist versus tamoxifen alone were apparent at the highest composite risk. Moreover, the SOFT cohort included more young patients with less lymph node involvement and smaller tumors than the TEXT cohort. Despite these differences, the patients who received chemotherapy exhibited better oncological outcomes than those who received chemotherapy in the SOFT trial. The TEXT subjects were concurrently administered adjuvant ovarian suppression using a GnRH agonist[21]. Early start and persistence of amenorrhea with active endocrine treatment may be important in HR-positive/HER2-negative younger breast cancer patients receiving NAC. Evidence has demonstrated that complete ovarian suppression treatment improves oncological outcomes in younger HR-positive/HER2-negative breast cancer patients.

Advancements in oncological outcomes were found to be statistically significant for HR-positive/HER2-negative patients in the younger age group, which may be related to the greater use of tamoxifen and the introduction of GnRH agonists[17,22]. Administering GnRH agonists to young patients with breast cancer and NAC had the effect of prolongs amenorrhea during chemotherapy[23]. Treating with GnRH agonists can safely be considered in young women with breast cancer in terms of oncological outcomes[24]. The recent initiation of GnRH agonist treatment may be the main reason for the improved survival of younger patients with breast cancer.

This study had several limitations. First, only HR-positive/HER2-negative breast cancer treated with NAC were included. Therefore, a small sample size was used for this study. Second, this retrospective study was limited to two comprehensive cancer institutions. Despite these limitations, this study is valuable, because many young patients with breast cancer have the HR-positive/HER2-negative subtype. This type of NAC is associated with a low pCR rate. In addition, many young women with breast cancer struggle with the competing interests of optimizing personal survival and maintaining ovarian function[25]. GnRH agonists are effective in preserving ovarian function and may have oncologic efficacy against breast cancer.

CONCLUSION

Administration of GnRH agonists might improve the DFS outcome of HR-positive/HER2-negative breast cancer patients who are 35 years or younger with NAC. Therefore, HR-positive/HER2-negative breast cancer patients and those younger than 35 with NAC are encouraged to be treated with GnRH agonist.

ARTICLE HIGHLIGHTS

Research background

There are many younger breast cancer patients in Korea than in the West, and they are known to have a poor prognosis.

Research motivation

To improve the prognosis of hormone receptor (HR) positive young breast cancer patients.

Research objectives

To investigate the efficacy of gonadotropin-releasing hormone (GnRH) agonist treatment in HR positive young breast cancer patients.

Research methods

We analyzed the characteristics and oncology outcomes between the equal-to-or-younger-than-35-years group (n = 78) and the older-than-35-years group (n = 353).

Research results

GnRH agonist was more significantly used in patients younger than 35 years old than in patients older than 35 years (52.4% *vs* 11.2%, $P < 0.001$).

Research conclusions

The GnRH agonists might improve the disease free survival outcome of HR-positive/HER2-negative breast cancer patients.

Research perspectives

Administration of GnRH agonist with anti-hormonenal therapy is helpful in young breast cancer patients.

FOOTNOTES

Author contributions: Choi HJ is the first author, planed and wrote this manuscript; all played a role in the data organization and modulation of this article; Kim HY planed, revised, edited and submitted this article.

Institutional review board statement: This study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (IRB file No. 2017-12-118-002). To protect personal information, patient records and information were anonymized and identities were removed prior to analysis.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: Dataset available from the corresponding author at isepa102@naver.com.

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