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Evaluation of the effect of Letrozol in combination with neoadjuvant chemotherapy on clinical response rate of breast cancer

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ABSTRACT

Introduction: This randomized clinical trial was aimed to assess the efficacy of neoadjuvant Letrozole in combination with standard neoadjuvant chemotherapy regimen on clinical response rate of hormone receptor positive locally advanced breast cancer.

Materials and Methods: In this randomized clinical study, 42 female patients, ≥ 18 years, with clinical stage IIB-IIIC (T1-4, N0-3, M0), pathologically proven hormone receptor positive and HER2 negative, invasive ductal carcinoma of breast, were randomly assigned to receive standard neoadjuvant chemotherapy alone (control group) or letrozole 2.5 mg/d (in association with goserlin in premenopausal patients) concurrent with standard neoadjuvant chemotherapy (study group). Standard neoadjuvant chemotherapy regimen has consisted of 4 cycles of doxorubicin (60 mg/m2) and cyclophodphamide (600 mg/m2), followed by 4 cycles of paclitaxel (175mg/m2) every two weeks.

At the beginning of the study all patients underwent thorough exmination of breast mass and axillary lymph nudes by palpation and ultrasonography. At the end of the study response rates were also evaluated by palpation and ultrasonography and subsequently patients were referred for surgury. Pathologic response rates were also evaluated on surgical specimens. All of the clinical, ultrasonographic and pathologic examinations during the trial were performed by a single specialist. Finally all the data were analyzed statistically.

Results: Overall complete response rates in breast were 95.2%, in both study and control group. Overall complete response rates in axilla were 80.9% and 76.2% in study and control group respectively. Similarly, overall radiologic complete response rates in breast and axilla were 95.2% and 76.2% respectively in both study and control group. Totally, the comparison of overall clinical and radiologic response rates in the breast and axilla, showed no significant difference between control and study group ($p>0.05$).

Conclusion: The addition of Letrozol to standard neoadjuvant chemotherapy regimen was not associated with higher clinical and radiologic response rates in patients with locally advanced hormon receptor positive breast cancer

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Introduction

Breast cancer is a major public health problem. According to WHO, breast cancer is the most common cancer and the second leading cause of cancer related death worldwide (1).

Despite using screening mammography for early detection of breast cancer, locally advanced breast cancers account for a

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remarkable proportion of all breast cancers at the time of diagnosis, particularly in developing countries, which remain a difficult clinical problem, as most of these patients are at risk of treatment failure and will eventually experience local or distant recurrence and have lower chance of long term survival (2).

The term locally advanced breast cancer includesany tumor that is greater than 5 cm or that involves the skin or chest wall, fixed axillary lymph nodes or ipsilateral supraclavicular, infraclavicular, or internal mammary nodal involvement (3).

Neoadjuvant chemotherapy is now considered the standard of care for the treatment of locally advanced breast cancers, in order to downstage the tumor prior to attempting for definitive local therapy, as most of these patients may not be operable at the time of diagnosis and also it can facilitate the breast conserving surgery for those with operable disease amenable to mastectomy (4).

Although, the optimal management for these patients remains a major therapeutic challenge, as breast cancer is biologically a heterogeneous disease and preoperative chemotherapy is less effective for those with hormone receptor positive and human epidermal growth factor receptor 2 (HER2) negative subtypes and it's benefit in terms of pathologic complete response is also limited (5).

So concurrent use of endocrine therapy along with chemotherapy in the neoadjuvant setting, seems to be an attractive idea in theory according to the established efficacy of these agents in the adjuvant setting (5).

To examine this hypothesis, a few trials were designed to compare the efficacy of standard chemotherapy alone or in combination with endocrine therapy. Based on their results, a combination of chemotherapy and endocrine therapy could have synergic effects in hormone receptor positive and HER2 negative breast cancers (5).

Materials and Methods

This prospective randomized clinical study, was conducted in Imam Reza hospital of Mashhad between December 2018 and November 2019. This study was approved by the institutional comitee of medical ethics and all patients signed a written informed consent before participation. It has been registered in IRCT at 2019.02.27 by IRCT ID:20181224042091N1.

Eligible patients were female patients with pathologically confirmed, newly diagnosed, locally advanced, hormone receptor (ER and PR) positive and HER2 negative, invasive ductal carcinoma of breast, with clinical stage IIB-IIIC (T1-4, N0-3, M0), with no history of previous chemotherapy, aged ≥18 years; with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Clinical stages were assigned according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM 2010 staging system (3). ER and PR and HER2 status were assessed by immunohistochemistry (IHC) performed on pretreatment biopsies. ER and PR status were described positive if having ≥ 10% tumor cells. Tumors considered as HER2 negative if they scored 0 to +1 by immunohistochemistry or if the tumor showed less than a twofold amplification of the HER2 gene relative to the centromere of chromosome 17 as assessed by fluorescent in situ hybridization (FISH) (6-8).

Patients were excluded if they were pregnant or breast feeding, had severe cardiovascular, kidney or liver disease, or history of severe allergic drug reactions, and refuse to participate and sign the written informed consent. Patients were also excluded if disease progresion had occured during neoadjuvant therapy.

Forty two eligible patients were randomly divided into two groups. Randomization was performed according to the computer generated list. Patients were assigned to receive standard neoadjuvant chemotherapy alone in the control group. In the study group, post menopusal patients were assigned to receive letrozole 2.5 mg/d concurrent with standard neoadjuvant chemotherapy and premenopausal women also received an LHRH analogue (goserlin 3.6mg SC injection every 28 days), in association with letrozole, beginning with the first chemotherapy cycle and letrozole were initiated within four weeks once the LH and stradiol levels reached post

menopausal values. Standard neoadjuvant chemotherapy regimen had consisted doxorubicin (60 mg/m2) and cyclophodphamide (650mg/m2) for the 4 first cycles, followed by paclitaxel (175mg/m2) every two weeks for the 4 subsequent cycles. Post menopausal status were defined as abcense of spontanous menstrual cycles for at least 12 month, age older than 60 years, history of previous bilateral oophorectomy or FSH and estradiol levels within the post menopausal range for the local laboratory or history of previous bilateral oophorectomy. At the beginning of the study, all eligible patients underwent thorough history and physical examination. Size of breast mass and regional lymph nudes were assessed by palpation and ultrasonography of both breasts and axillary regions. During the treatment, patients in both arms were also visited regularly before each cycle of therapy and clinical size of breast mass and involved lymph nodes were also assessed.

Patients who successfuly completed the full course of protocol specified therapy during the expected time, were evaluated for clinical and radiologic responses by palpation and ultrasonography. Clinical and radiologic tumor responses were assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which is defined as follows: complete response (CR) defined as a complete disappearance of all measurable tumors; partial response (PR) as a 30% or greater decrease in the sum of the longest diameters of all measurable tumors; stable disease (SD) as a less than 30% decrease or a less than 20% increase in the sum of the longest diameters of all measurable tumors; and progressive disease (PD) as 20% or greater increase in the sum of the longest diameters of all measurable tumors or detection of new lesions (9).

Subsequently all the patients were referred for surgury. Either lumpectomy or modified radical mastectomy was performed according to response to neoadjuvant therapy.

All of the clinical and ultrasonographic examinations during the study, were performed by a single oncologist, radiologist and pathologist.

The clinical and radiologic responses of the breast mass and involved lymph nudes were documented and finally all the data were analysed statistically.

The primary end point was overal clinical response rate defined as percentage of complete or partial response determined by physical examination among patients in each treatment arm and secondry end points were assessment of overal radiologic response rates (CR and PR) by ultrasonography.

Statistical analysis

SPSS version 23.0 software was used for all statistical analyzes. Based on the primary end point, a minimum sample size required 19 patients in each arm to insure 80% power at the 5% significance level for detecting improvement in the clinical overall response rate from 50% in chemotherapy group to 90% in concurrent chemotherapy and letrozole group, based on review of data from previous studies (12). T-test and Mann-Whitney tests were used for comparing quantitative variables between two groups and Chi-square and Fisher's exact were used for comparing qualitative variables between two groups. P values < 0.05 were considered statistically significant.

Results

A total of 48 eligible patients were enrolled in the study (24 patients in each arm). In the control group three patients were withdrawn, two patients affected with covid 19 which result in treatment delay and one patients refused to continue therapy due to fear of coronovirus infection. In the study group three patients were also withdrawn, one patient had treatment delay due to COVID19, one patient had stopped Letrozole due to hot flashes and nausea and another patient refused to undergo surgery at the end of neoadjuvant therapy. Finally, 21 patients were left in each treatment arm. Patients and disease charachterestics are represented in table 1.There were no significant difference in patient age, menopausal status, tumor size and clinical T and N and TNM stages between two treatment groups. All of the patients successfully completed the treatment protocol and overall clinical and radiological response rate (complete

reponse and partial reponse), were assessed based on RECIST critria. (Table 2)

Table 1: Baseline charactrestics

	chemo N=21	Chemo+letrozole N=21	p.value
Average age (y)[1]	11.2±53.1	11.2±50.6	0.479
Menopausal status (n%)[2]			
Pre menopause	8 (38.1%)	9 (42.9%)	0.753
Post menopause	13 (61.9%)	12 (57.1%)	
Breat mass size in PE. (cm)[1]	1.63 ± 4.29	1.69 ± 4.31	0.978
Breat mass size in US. (cm)[1]	1.43 ± 4.52	1.82 ± 4.12	0.428
Lymph nude size in PE. (cm)[1]	2.47± 3.48	2.42± 3.14	0.707
Lymph nude size in US. (cm)[1]	2.59± 3.58	2.74 ± 3.57	0.991
Clinical tumor (T) stage (n)[3]			
T0	0	0	
T1	1	2	
T2	9	8	0.453
T3	8	8	
T4	3	3	
Clinical nude (N) stage (n)[3]			
N0	3	3	
N1	7	7	0.104
N2	10	8	
N3	1	3	
Clinical TNM stage (n)[3]			
IIB	2	3	
IIIA	14	12	0.340
IIIB	3	3	
Operability (n%)[3]			
Inoperable	7(33.3%)	7(33.3%)	
Operable	14(66.6%)	14(66.6%)	> 0.99

1. T Test; 2. Chi square Test; 3. Fisher exact Test.

Table 2. Comparison of overall clinical and radiologic response rates after completion of neoadjuvant therapy in both groups.

Response rate*	Breast Mass chemo N=21	Breast Mass Chemo+letrozole N=21	p.value	Axillary lymph nudes chemo N=21	Axillary lymph nudes Chemo+letrozole N=21	p.value
Clinical response rate						
Complete response	0 (0%)	3 (14.2%)		2 (9.5%)	2 (9.5%)	
Partial response	20(95.2%)	17(80.9%)		14(66.6%)	15 (71.4%)	
Stable disease	1(4.7%)	1(4.7%)	0.179	2(9.5%)	1(4.7%)	0.714
Progressive disease	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Overall response	20(95.2%)	20(95.2%)		16(76.2%)	17(80.9%)	
Radiologic response rate						
Complete response	0 (0%)	1(4.7%)		2 (9.5%)	2 (9.5%)	
Partial response	20(95.2%)	19(90.4%)		14(66.6%)	15 (71.4%)	
Stable disease	1(4.7%)	1(4.7%)	0.573	2(9.5%)	1(4.7%)	0.714
Progressive disease	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Overall response	20(95.2%)	20(95.2%)		16(76.2%)	16(76.2%)	

*Mann-Whitney Test

After treatment, the overal clinical response rate of the breast mass in both groups were 95.2% (20/21), although the complete clinical response was 14.2% in the study group and 0% in control group, this difference was not statistically significant (P>0.05) (Table 2). Also the overal clinical response rate in axillary lymph nudes were 80.9% and 76.2% in the study and control group respectively (P>0.05).

Overal radiologic response rate in breast mass were also equal, 95.2%, in both control and study group and overal radiologic response rate in axillary lymph nudes were 80.9% and 76.2 in the study and control group respectively (P>0.05).

Following completion of neoadjuvant therapy, all patients proceeded to surgery. Of those fourteen patients (seven patients in each treatment group), who were considered inoperable at baseline, none of them were inoperable after neoadjuvant treatment. Twenty patients in the control group and eighteen patients in the study group, underwent breast conserving surgery following completion of therapy (P>0.05).

Discussion

Neoadjuvant chemotherapy has become the standard treatment option for locally advanced breast cancer since last 2 decades (10).

Physical examination and sonography are our current armamentarium for evaluating the response to neoadjuvant systemic therapy preoperatively. Pathologic evaluation of surgical specimens is also of exquisite importance in assessing pathologic response to neoadjuvant systemic therapy after surgery (5).

Despite satisfactory clinical and radiologic response rates after neoadjuvant chemotherapy, the expected rate of PCR in patients with hormone receptor positive locally advanced breast cancer is lower than those with hormone receptor negative subtypes, indicating the inadequacy of this treatment option for those patients with positive hormone receptors (5). On the other hand, hormone receptor positive and HER2 negative breast cancer, comprise the most common histologic subtype (4).

So in this study, the role of neoadjuvant chemotherapy combined with concurrent endocrine therapy on the clinical and radiological response rates of locally advanced, hormone receptor positive, breast cancer was investigated.

Few studies have been performed on concurrent administration of neoadjuvant chemotherapy plus endocrine therapy in neoadjuvant setting (5).

Torrisie and colleagues had conducted a study, published in 2008 in breast cancer journal, and investigated the efficacy of endocrine therapy using a GnRH analogue concurrent with chemotherapy on clinical response rate of 36 premenopausal patients with locally advanced hormone receptor positive breast cancer. Overall clinical response rate (complete or partial) was observed in 75% of the patients. They concluded that combination of chemotherapy with GnRH analogue is associated with a high response rate in the treatment of breast cancer (11).

Although this trial was not a case control study, but comparing the overall response rate between the two trials, showed a slightly higher response rates in favor of our study.

One more randomized clinical study performed by Mohammadian Panah and colleagues, published inbreast cancer research and treatment journal in 2012, 101 female patients, 50 to 83 years old, postmenopausal with pathologic locally advanced breast cancer, were randomly assigned to receive neoadjuvant chemotherapy alone or in combination with Letrozole 2.5 mg daily. After completion of neoadjuvant therapy, all patients subsequently underwent modified radical mastectomy. Complete clinical response rates were 27.6% and 10.2% in the study and the control group (P = 0.037) and pathologic complete response rates were 25.5% and 10.2% in the study and the control group, respectively (P = 0.049). The results of this study showed that addition of Letrozole to neoadjuvant chemotherapy provides a higher clinical and pathologic response rates compared with chemotherapy alone in postmenopausal women with locally advanced sensitive

breast cancer. Subgroup analysis of cases with positive hormone receptor, also revealed more prominent complete response rates in study arm compared with control arm (12).

In comparison to our study, only post-menopausal patients were enrolled in Mohammadian Panah study regardless of hormone receptor and HER2 status but their results showed significant difference in complete clinical response rate which was not in agreement with the results of our study.

In another study which was performed by Watanabe and colleagues, published in 2015 in journal of clinical oncology, overall clinical response rate to concurrent chemoendocrine therapy, was evaluated in locally advanced hormone receptor positive breast cancer patients. 28 patients were randomly assigned or receive chemotherapy alone or chemotherapy plus an aromatase inhibitor. The results of this study showed significant decrease in tumor size in chemoendocrine group in comparison with chemotherapy group (p=0.035) (13, 14).

Results of Watanabe study were also not in agreement with the results of our study as our study showed no significant decrease in tumor size between two treatment groups.

One of the reasons why our study did not show a significant benefit for concurrent chemotherapy plus Letrozole compared with chemotherapy alone is the heterogeneity of hormone receptor positive and HER2 negative subtypes of invasive ductal carcinoma of breast, so each patient may need a different treatment strategy based not only on clinical stage but also on tumor characteristics such as hormone receptor expression rate and the proliferation index. The other possibility might came from small sample size. The results of our study showed that concurrent use of chemotherapy plus Letrozole, did not provide significant difference in clinical and radiological response rates between the two treatment arms, although the size of breast mass and involved lymph nodes were decreased significantly in both treatment groups after completion of neoadjuvant therapy, compared to baseline, but the two groups were not different statistically.

Conclusion

In summary, the preoperative implementation of neoadjuvant endocrine therapy combined with concurrent chemotherapy therapy, in patients with locally advanced, hormone receptor positive and HER2 negative breast cancer, did not significantly increased overall clinical and radiologic response rate in comparison to chemotherapy alone.

Although this treatment strategy should not be recommended outside clinical trials based on the results of our present study, but further well-designed randomized clinical trials are still warranted with a larger sample size estimation and more precise selection criteria based on histopathology characteristics of tumors.

Conflicts of interest

The authors have no competing interest.

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