**Original Article**
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# Rate and Time of Ovarian Function Restoration in Menopausal Breast Cancer Patients Who Received Letrozole Following Chemotherapy

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## Abstract

**Background:** The present study aimed to investigate the rate and time of ovarian function restoration in breast cancer patients between 40 and 60 years of age who were in menopause (biochemically documented) and received letrozole after chemotherapy. We intended to further clarify the management strategy for breast cancer patients with different menopausal status.

**Methods:** We prospectively measured the effects of replacing tamoxifen with letrozole on ovarian function recovery in 90 women from two age groups (40-50 and 51-60 years). All had breast cancer and were treated by chemotherapy. Patients had laboratory documentation of menopause (FSH >40 mIU/ml and estradiol <20 pg/mL). Patients did not have menstruation for at least one year. Study patients received letrozole. At three month intervals, we checked their FSH and estradiol levels.

**Results:** At three months after beginning letrozole, 12 patients in the younger age group had laboratory ovarian function restoration, among which three had vaginal bleeding. In the older group, 8 patients had increased estradiol levels; however, there was no evidence of vaginal bleeding in this group. At 6, 9 and 12 months, no ovarian function restoration was seen in the older group. However in younger patients, 4 had laboratory evidence of ovarian function restoration at 6 months, 2 at 9 months and 1 patient showed laboratory ovarian function restoration at 12 months of follow-up. Totally, there was a significant difference in the occurrence of ovarian function restoration between the two groups ($P$=0.03).

**Conclusion:** A remarkable portion of women with chemotherapy-induced amenorrhea may develop ovarian function restoration. Therefore, endocrine therapy using aromatase inhibitors in patients with chemotherapy-induced amenorrhea should be followed by a regular hormonal study.

***Keywords:*** Breast cancer, Menstruation restoration, Chemotherapy-induced amenorrhea, Letrozole

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## Introduction

Breast cancer is the most common malignancy and leading cause of cancer-related deaths in women.[1] In recent years, breast cancer screening has resulted in a larger number of breast cancer patients diagnosed at lower ages and earlier stages.[2] In previous decades, tamoxifen has been considered the standard adjuvant endocrine therapy for those with positive hormone receptor breast cancer. Approximately 22% of breast cancer patients are between 45 and 54 years of age. Considering the menopausal age to be around 51 years, a substantial number of breast cancer patients are perimenopausal.[3,4]

Menopause does not occur at a definite point in time; rather, it is a continuous period of hormonal and clinical change. Menopause is the permanent termination of menstruation due to loss of ovarian function. It is diagnosed retrospectively 12 months after amenorrhea. Perimenopausal period starts several years before menopause and continues until the first year after discontinuation of menses.[4,5] Overall, 80% of women who are older than 40 and have received chemotherapy develop amenorrhea. However, the amenorrhea may not always be permanent.[6,7] An important therapeutic challenge in these patients is when chemotherapy-induced amenorrhea leads to menopause and how they can be treated, especially in hormone positive cases. Adjuvant endocrine therapy in chemotherapy-induced menopausal women is similar to the postmenopausal ones. Nevertheless, change in endocrine treatment is more frequently required in chemotherapy-induced amenorrhic patients. Patients who develop amenorrhea have better survival compared to those without amenorrhea.[3,8] Tamoxifen significantly reduces breast cancer recurrence and mortality.[9] Recently, aromatase inhibitors (AIs) have been introduced as more effective than tamoxifen in postmenopausal women.[10,11]

When AIs are used in patients who have recently stopped menstruation, ovulation resumption should be kept in mind. Aromatase inhibitors inhibit estrogen synthesis, resulting in increased blood FSH levels. FSH induces ovulation in the ovaries; therefore, AIs are widely under study for ovulation induction. In these studies, 2.5-5 mg per day of letrozole has been prescribed. Various doses (0.1-10 mg/day) have been tested in different studies on adjuvant endocrine therapy in patients with breast cancer. According to research findings, 2.5 mg letrozole once per day is effective and does not affect adrenal or other steroidal hormones.[12,13]

Nonetheless, careless utilization of AI may not only be ineffective, but it may also lead to ovarian stimulation or even pregnancy.[6,14] The present study has sought to investigate the rate and time of ovarian function restoration (OFR) in biochemically documented menopausal patients between 40 and 60 years of age who received letrozole following chemotherapy. We intended to further clarify the management strategy for breast cancer patients of different menopausal status.

## Materials and Methods

This prospective study aimed to determine the patients who needed to change adjuvant endocrine therapy according to serum FSH and estradiol (E2) levels in two age groups (40-50 and 51-60 years). This study was carried out at Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran from January 2011 to December 2012. We randomly choose patients who referred to our clinic after surgery and received chemotherapy. Study inclusion criteria included: newly diagnosed breast cancer, positive receptors for estrogen and/or progesterone, between 40 and 60 years of age, no history of endocrine or menstruation disorders, FSH >40 mIU/ml, E2 <20 pg/ml, and no menstruation for at least one year. The patients with more than 1% positive cells for estrogen or progesterone receptors according to an immunohistochemical study were considered hormone positive.

Exclusion criteria included: previous history of breast cancer or chemotherapy, negative or undetermined receptor status, presence of endocrine or menstruation disorders, contraindication to AIs, and having undergone bilateral

**Table 1.** Patients' characteristics and treatment of the study population.

| Variables | Group A | Group B | Total |
|---|---|---|---|
| Mean age (years) | 46.71 | 54.3 | 50.53 |
| Abortion | 10 | 21 | 31 |
| Menarche | 12.83 | 12.94 | 12.89 |
| Pregnancies | 3.26 | 4.31 | 3.79 |
| Chemotherapy | | | |
| TAC | 6 | 6 | 12 |
| AC×4 → T×4 | 13 | 17 | 30 |
| CAF | 26 | 22 | 48 |

TAC: Docetaxel, Doxorubicin, Cyclophosphamide; AC: Doxorubicin, Cyclophosphamide; T: Docetaxel; CAF: Cyclophosphamide, Doxorubicin, 5-fluorouracil.

oophorectomy or hysterectomy. Patients with serum FSH or E2 levels in the premenopausal range were also excluded. Because of the need for continuation of chemotherapy and probable short survival, metastatic patients were excluded from the study. All patients were informed about the importance of the menopausal status on choosing adjuvant endocrine therapy and signed written informed consents for study participation. Patients who were reluctant to have their blood drawn were excluded from the study. Study patients were divided into younger (40-50 years) and older (51-60 years) age groups.

According to the previous study, the rate of OFR following chemotherapy-induced amenorrhea was 25% in premenopausal women.[15] Therefore, based on the sample size formulation for estimating a ratio, with $\alpha$=0.05 and absolute error of 15%, we determined the sample size to be at least 33 cases for each group. To decrease the error rate, we included 45 cases in each group.

Before starting chemotherapy, all patients were asked about their age at menarche, date of last menstruation, age at marriage, regularity or irregularity of the menstruation status, number of pregnancies, age of first and last pregnancies, and abortion (if any). The presence of any systemic and gynecological diseases was also recorded. A general physical examination was performed for every patient prior to starting chemotherapy and before each injection. After completion of adjuvant chemotherapy, serum levels of FSH and E2 were checked for the study patients in our hospital laboratory; those patients who met all of the previously mentioned criteria were entered into the study. Subsequently, adjuvant endocrine therapy was started as follows. Patients who were amenorrhic, and whose FSH and E2 levels were at the menopausal level received 2.5 mg/day of letrozole. All patients were asked regarding their menstruation status each month when visiting the physician or through phone contact. Serum FSH and E2 levels were also checked before starting letrozole and at each visit (3, 6, 9, and 12 months). FSH and E2 levels were measured by the radioimmunoassay technique with a minimal detection range of 5 pg/mL. FSH was measured by IRMA technique which had an ability to detect the minimum detectable concentration of 0.09 mIU/mL. FSH and E2 levels were measured with commercially available immunoassay (Immunotech/ Beckman Coulter, Czech Republic) and with ELISA (DRG, Germany) kits, respectively. Hormonal rebound was defined as FSH <40 mIU/ml or E2 >20 pg/ml. Letrozole was changed to tamoxifen in those patients who developed bleeding or hormonal rebound.

Analysis was performed with SPSS software version 18.0. Chi-square or Fisher's exact tests for qualitative and the student's t-test for quantitative clinical and pathological factors were used to assess differences. A *P*-value less than 0.05 was considered statistically significant.

## Results

During the 12-month study period, we checked serum FSH and E2 levels every three months. All patients had regular follow-up visits and well-tolerated letrozole. Patients were divided into two groups; younger patients who were between 40 and 50 years of age were allocated to group A, while those who were between 51 and 60 years of

**Table 2.** Ovarian function restoration (OFR) according to parameter and group.

| Follow-up | Group A | | | | Group B | | |
|---|---|---|---|---|---|---|---|
| | E2 | FSH | Clinical | Total OFR | E2 | FSH | Clinical |
| 3rd | 6 | 9 | 3 | 12 | 8 | 0 | 0 |
| 6th | 3 | 1 | 1 | 4 | 0 | 0 | 0 |
| 9th | 1 | 1 | 1 | 1 | 0 | 0 | 0 |
| 12th | 1 | 1 | 0 | 1 | 0 | 0 | 0 |

E2: Estradiol

age were assigned to group B for a total of 45 patients per group. The mean age of the patients in group A was 46.7 years and for group B, it was 54.3 years. There was no statistically significant difference regarding age at menarche, which was 12.48 years for group A patients and 12.95 years for group B patients ($P$=0.9). The mean number of pregnancies in group B (4.31) was significantly higher than group A (3.26; $P$=0.008). The history of abortion was also higher among older patients; 22% of the younger patients and 46.7% of the older ones underwent abortions ($P$=0.02). The demographic characteristics of the study patients are presented in Table 1.

In group A, at three months following onset of letrozole, 3 patients developed vaginal bleeding and 12 patients had hormonal rebound (Table 2). Three patients had both elevated E2 and decreased FSH levels. Three patients had elevated E2 levels and 6 other patients had decreased FSH levels. In group B, 3 months following the onset of letrozole, only 8 patients had premenopausal E2 levels. However, none of the patients had decreased FSH levels or vaginal bleeding. Six months after treatment with letrozole in group A patients, 1 case developed both decreased FSH and increased E2. Two other patients had only an increase in E2 levels. None of these patients had vaginal bleeding. However one patient had vaginal bleeding with postmenopausal hormonal levels.

None of the patients in group B (51-60 years) developed hormonal rebound at the 2nd, 3rd, and 4th visits. There was no vaginal bleeding reported at the clinic visits or during monthly telephone follow-ups. At the 3rd visit (9 months after treatment), the group A patient who had vaginal bleeding at the 2nd visit developed hormonal rebound. Another patient in this group had vaginal bleeding at the 3rd visit, however her hormonal markers were at the postmenopausal level. In the 4th visit, another patient had hormonal rebound. Overall, 18 patients (40%) in group A had clinical and/or laboratory hormonal rebound and their adjuvant endocrine therapy was changed to tamoxifen. However, 13 patients had only laboratory evidence of pre-menopausal status. A total of 4 patients had both laboratory and clinical evidence; 1 patient only had vaginal bleeding and no hormonal rebound. The mean age of clinical and biochemical rebound in this group was 46.2 years. In group B, 8 patients had only increased E2 levels and FSH was at the post-menopausal level. None of these patients had vaginal bleeding. The mean age of clinical and biochemical rebound in this group was 54.6 years. The results of the chi-square test showed that the difference between the two groups was statistically significant ($P$=0.03; Table 2).

## Discussion

In the present study we investigated the rate and time of OFR in breast cancer patients who were in menopause following adjuvant chemotherapy and received letrozole. Of 90 patients, 26 (29%) developed clinical and/or biochemical OFR. However, the ORF was significantly higher (40% vs. 18%, $P$=0.03) for patients ≤50 years compared with those who were >50 years of age.

Estrogens are produced in ovaries as well as the peripheral tissues. Tamoxifen directly blocks the estrogen receptors at the body organs, while AIs inhibit estrogen production from androgen precursors in the peripheral tissues. After menopause, the only source of estrogen in the

**Table 3.** Studies for the measurement of ovarian function restoration (OFR).

| | Patients (N) | Menopause definition | Biochemical restoration only | Clinical restoration only | Clinical and lab | Total OFR | Pregnancy | Mean age (years) | Mean age at OFR (years) |
|---|---|---|---|---|---|---|---|---|---|
| Smith[15] | 45 | Clinical or biochemical | 8 | 10 | | | 1 | 47 (39-52) | 44 (40-50) |
| Nagao[28] | 66 | Both clinical and biochemical | 6 | - | - | 6 | | - | - |
| Guerrero[6] | 53 | Both clinical and biochemical | 5 | 7 | 5 | 17 | 0 | 48 | 46 |
| Present study: Group A (40-50 years) | 45 | Both clinical and biochemical | 12 | 1 | 5 | 18 | 0 | 46.7 | 46.1 |
| Present study: Group B (51-60 years) | 45 | Both clinical and biochemical | 8 | 0 | 0 | 8 | 0 | 54.35 | 54.6 |

body is androgen conversion to estrogen in the peripheral tissues.[16] In postmenopausal women, serum estrogen levels are almost totally suppressed by AIs. These agents should be used when ovaries are not functional or have been removed. Letrozole is one of the most potent AIs among other similar agents, such as anastrozole and exemestane.[17]

Adjuvant and neoadjuvant endocrine therapy using AIs has been approved in the treatment of postmenopausal women who are hormone receptor positive and have locally advanced breast cancer.[18,19] Aromatase inhibitors not only reduce blood E2, estrone (E1), and estrone sulfates (E1S), but they also reduce these hormones in the tumor tissue.[20] In one study, Geisler et al. found a significant decrease in the tumor tissue and serum levels of estrogen after 15 weeks of neoadjuvant AI treatment. In their study, 1 mg anastrozole was administered to 12 postmenopausal patients. According to the results, both tumor and serum levels of E1, E2, and E1S were reduced in both responders and no responders. Other studies also showed serum and tumor decreases in estrogens using AIs.[21]

In general, patients with 12 months chemotherapy-induced amenorrhea will be permanently amenorrhic and considered postmenopausal; although, there are exceptions.[3] Goodwin et al. in a prospective study have analyzed the effective factors in menopausal occurrence in premenopausal women with breast cancer. Among the 183 patients with regular menstruation, 108 cases were treated by chemotherapy [cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or cyclophosphamide, epirubicin, and 5-fluorouracil (CEF)] and 75 patients did not receive chemotherapy.[2] Totally, 102 patients became menopausal. They defined menopause as at least one year of disrupted menstrual bleeding. In that study, chemotherapy regimen and age were the only significant factors.[22]

Hargis has reported the case of a woman who consumed tamoxifen for five years. After biochemical and clinically documented menopause, she took letrozole and her menstruation restarted two weeks later.[17,23,24] Although several markers can be helpful in the diagnosis of menopause, the best is FSH. FSH levels of more than 40 IU/l represent menopausal status.[8] According to the National Comprehensive Cancer Network (NCCN) guideline, FSH and E2 in postmenopausal levels in women less than 60 years old is considered as menopause.[25]

Considering the menopausal process and individual differences among patients, it is difficult to treat patients similarly.[23,24] Smith et al. conducted a study on 45 patients with a mean age of 47 (range: 39-52) years who received AI and found that 12 (27%) had ovarian function recovery. Their patients were evaluated at different treatment steps after chemotherapy. Sixteen cases received letrozole or anastrozole as the first adjuvant endocrine therapy, while 29 were treated with tamoxifen (1-5 years). Among these, 10 resumed menstruation and 1 became pregnant

without vaginal bleeding. In their study, before starting AI therapy, biochemical confirmation for menopause was performed for only 33 patients, 8 of whom had restored ovarian function. On the other hand, after clinical evidence of ovarian function resumption, only 8 patients had biochemical confirmation. The mean age of patients with OFR was 44 (40-50) years. They concluded that more accurate laboratory tests should be applied for monitoring the E2 level during the course of therapy and AIs should be employed with caution.[15] Finally, considering such a high rate of OFR (more than one quarter) and 2% pregnancy rate,[26,27] we checked our patients biochemically and clinically. In the current study, we observed a 28% OFR rate.

Nagao et al. in a study on 66 patients measured FSH, LH, and E2 levels every 3 months for 1 year while their cases received anastrozole. According to their results, 4 patients had elevated E2 levels in the 6th month and 2 had elevated E2 levels in the 9th month. In their study, 27% of the patients showed OFR among whom, 19 (21%) had elevated E2 levels. Most (14 or 16%) had OFR in the 3rd month and 1 patient had elevated E2 levels at the 12th visit. However, the current study in addition to the study performed by Nagao were not large enough.[28]

Guerrero et al. conducted a study on 53 patients who had two years of chemotherapy-induced amenorrhea and postmenopausal E2 levels. They reported 30%-32% OFR. In their study, patients were treated with tamoxifen which was switched to exemestane after menopause. E2 and FSH levels were checked at 1, 3, and 6 months. According to the results, menstruation restarted in 12 patients and 5 had biochemical evidence of OFR. The mean age at time of starting exemestane was 48 (41-55) years and all were amenorrhic for 2.5 (2-4.5) years; however, in approximately one third of the patients, there was restoration of ovarian function. The researchers proposed that patients under the age of 48 years should not switch to AI.[6] We took into consideration the results of the two above-mentioned studies and followed our patients carefully in order to change endocrine treatment as soon as was necessary.

In our study, a larger number of patients had biochemical OFR; the two other similar studies had more clinical OFR (Table 3). This might be due to the technical differences in our measurements. In the current study, total OFR was 29%, but younger patients had 40% OFR and a significant difference regarding the resumption of ovarian function was found between the two age groups. None of the older patients had clinical OFR, while in the younger group, 4 patients had both vaginal bleeding and hormonal elevation, and 1 patient only had bleeding.

However, larger studies should be conducted in order to reach to a more reliable conclusion.

The two age groups and larger sample size compared to previous studies were the strengths of the current study. The limitation of this study was the restriction of AI to letrozole.

## Conclusion

A remarkable number of women with chemotherapy-induced amenorrhea may develop ORF. Endocrine therapy using AIs in patients who develop chemotherapy-induced amenorrhea may potentiate the risk of OFR. Therefore, these patients should be followed by a regular hormonal study for early detection of ORF. However, further investigation is warranted with large numbers of cases and longer-term follow-up periods.

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## Conflict of interest

No conflict of interest is declared.

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