

Evaluation of the effect of GnRH agonist on menstrual reverse in breast cancer cases treated with cyclophosphamide

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Summary

Twenty-five percent of breast cancer cases are detected during premenopausal period and the number of young women suffering from breast cancer is increasing in the world, especially in Iran. Preservation of fertility and ovarian function leads to improved quality of life of these patients. The aim of this study was to evaluate the effect of gonadotropin releasing hormone (GnRH) agonist on menstrual reverse in breast cancer cases treated with cyclophosphamide regimen. *Materials and Methods:* This randomized clinical trial (RCT) was conducted on 42 adenocarcinoma cases. Mean age of patients was 37 ± 5 years (range 25 to 45). Primary stages to Stage II (T2N1M0) whose histology reports were negative ER/PR were enrolled in this study. All the enrolled patients were candidates for cyclophosphamide (600 mg/m²), adriamycin (60 mg/m²), and taxoter (75 mg/m²) chemotherapy regimens. *Results:* Spontaneous menstrual reverse occurred in 90.5% of patients receiving diphereline at three to six months after treatment which occurred in 33.3% of control cases. In control group, 14.3% (three cases) had oligomenorrhea and hypomenorrhea during chemotherapy and 19% (four cases) had spontaneous menstrual reverse at three to six months. It should be noted that there was a significant difference between controls and cases ($p < 0.001$). This difference was insignificant in cases younger than 35 years ($p < 0.594$). In 100% of patients older than 35 years who received diphereline, spontaneous menstrual reverse occurred during six months after chemotherapy, but this occurred in only 20% of controls ($p < 0.001$). Mean serum level of follicle stimulating hormone (FSH) and luteinizing hormone (LH) during and at three months after therapy was significantly lower in cases in comparison with controls, but serum level of estradiol was significantly more in cases three months after chemotherapy ($p < 0.001$). *Conclusion:* GnRH agonists significantly improve ovarian function and fertility. They also lead to spontaneous menstrual reverse in negative ER/PR breast cancer cases.

Key words: Breast cancer; Fertility; Menstrual reverse; Chemotherapy; Cyclophosphamide.

Introduction

Breast cancer is the most prevalent cancer among Iranian women and the second most common cancer in the world following lung cancer. Although less than one percent of breast cancer occurs in women younger than 25 years, however the rate has a significant increase after 30 years. [1]

On the other hand as marrying age has increased, it's not uncommon for a women older than 40 years to become pregnant [2]. Studies performed in Iran reported breast cancer in women ten years younger than the mean age in the world, which can be in correlation with the young population of Iranians [3, 4].

Probably, the most common side-effect of prolonged chemotherapy is gonad dysfunction which can be transient, but the recovery is often unpredictable and in most cases this side-effect is permanent. Therefore fertility preservation and decrease in long-term effect of chemotherapy is very important in improving quality of life of patients. [4, 5]

Most of studies showed positive effect of gonadotropin-releasing hormone (GnRH) agonists on decreasing gonadotoxic side-effect of chemotherapy in breast cancer and Hodgkin's lymphoma. These studies also showed that

GnRH agonists decrease ovarian damage following chemotherapy [5, 6].

Materials and Methods

This clinical trial study was conducted on 42 adenocarcinoma cases visited in Shahid Sadoughi Hospital during 2010-2011 who were in primary Stage to Stage II (T2N/M0) in the age ranging from 25-45 years. Inclusion criteria were negative ER/PR, primary stages of breast cancer, and candidate for cyclophosphamide (600 mg/m²), adriamycin (60 mg/m²), and taxoter (75 mg/m²) chemotherapy regimen.

The patients were randomly divided into two groups. Serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol were checked before chemotherapy through the enzyme-linked immunosorbent assay (ELISA) method.

In one group, 3.75 mg/IM diphereline was prescribed every 28 days for six months simultaneous with chemotherapy and the other group just received chemotherapy.

In both groups, serum levels of ovarian hormones were checked at the end of months three and six and also at three months after chemotherapy. Menstrual reverse status was checked during six months after chemotherapy.

The data were analyzed by SPSS. T-test, Chi-square, S exact and Fisher tests were utilized. Exclusion criteria were advanced stages of the cancer, low complaint cases in receiving diphereline monthly, positive ER/PR, concurrent malignancies, and FSH ≥ 30 at admission.

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Results

Mean age of cases was 37±5 years (range 25-45). In the group received diphereline, spontaneous menstrual reverse occurred in 19 of 21 women (90.5%) during three to six months following chemotherapy and amenorrhea continued in only two women until end of month six. However, menstrual bleeding continued during chemotherapy in only three controls (14.3%). In four controls (19%), spontaneous menstrual reverse occurred during three to six months following chemotherapy and in 14 of them (66.7%) menstrual reverse did not occur. This difference was significant ($p < 0.001$, Table 1).

Dividing patients into two groups younger than 35 and older than 35 years of age showed that menstrual reverse rate difference was not significant in group younger than 35 years (14 cases and 14 controls). In other words, menstruation reversed in six out of eight patients (75%) younger than 35 years who received diphereline and in the other two cases it did not occur until the end of six months follow up.

Table 1 – Comparing menstrual reverse in two groups, six months following treatment (Chi-square test).

p value	Chemotherapy without diphereline	Diphereline + chemo	Parameter
$p < 0.001$	7 (33.3%)	19 (90.5%)	Menstrual reverse
	14 (66.7%)	2 (9.5%)	Amenorrhea

In the other group older than 35 years, all women (n=13) received diphereline had spontaneous menstrual reverse, which was only reported in three out of 15 controls (20%) ($p < 0.001$, Table 2)

Comparing serum levels of LH in two groups showed that mean of LH in the group receiving diphereline was lower than the control group during the study and three months following treatment. Mean serum level of LH three months after chemotherapy was 11.70 ± 6.35 and 22.64 ± 14.98 in patients on diphereline and controls, respectively ($p < 0.001$).

Table 2 – Comparing menstrual reverse in two groups, six months following treatment (Fishers, S. exact test)

Age > 35 years		Age < 35 years		Menstruates
Chemo - diphereline (15)	Chemo + diphereline (13)	Chemo - diphereline (6)	Chemo + diphereline (8)	
3 (20%)	13 (100%)	4 (67.7%)	6 (75%)	Menstrual reverse
12 (80%)	0	2(33.3%)	2 (25%)	Amenorrhea
$p < 0.001$		$p = 0.594$		p value

Table 3 – Comparing FSH, LH, and estradiol levels with ovarian function test (OFT).

p.value	3 months after treatment		6 months during treatment		3 months during treatment		Before chemo		Time OFT
	Chemo-diphereline	Chemo+diphereline	Chemo-diphereline	Chemo+diphereline	Chemo-diphereline	Chemo+diphereline	Chemo-diphereline	Chemo+diphereline	Study group
$p < 0.001$	48.09 (29.67SD)	29.64 (14.11SD)	50.42 (31.98SD)	12.47 (7.11SD)	35.57 (22.20SD)	13.47 (8.68SD)	15.80 (6.12SD)	13.71 (8SD)	FSH
$p < 0.001$	22.64 (14.98SD)	11.70 (6.35SD)	21.61 (13.87SD)	5.87 (3.10SD)	15.11 (8.24SD)	5.95 (3.76SD)	5.70 (3.28SD)	4.95 (2.32SD)	LH
$p < 0.001$	40.14 (37.35SD)	81 (19.35SD)	32.40 (33.62SD)	19.04 (11.10SD)	45.76 (31.65SD)	29.14 (21.11SD)	91.38 (29.59SD)	109.38 (32.58SD)	Estradiol

Table 4 – Ovarian function preservation during chemotherapy in young cases of breast cancer:

Result (reverse of menstruation)	Number of patients	Disease or cancer type	Publication year	Author's name
GnRH a: 89.6%				
No GnRH a: 33.3%	80	Breast cancer	2009	Badawy <i>et al.</i> [5]
Age < 40: 94%				
Age > 40: 42%	29	Breast cancer	2005	Del Mastro <i>et al.</i> [6]
GnRH a: 93%				
No GnRH a: 48%	366	Many of cancers in young women	2007	Clowse <i>et al.</i> [8]
GnRH a: 93.7%				
No GnRH a: 39%	36	Hodgkin's lymphoma	1996	Blumenfeld <i>et al.</i> [9]
GnRH a: 95%				
No GnRH a: 45%	120	Hodgkin's lymphoma	2002	Blumenfeld <i>et al.</i> [10]
GnRH a: 96.9%				
No GnRH a: 63%	150	Hodgkin's lymphoma	2008	Blumenfeld <i>et al.</i> [11]
GnRH a: 90.5%				
No GnRH a: 33.3%	42	Breast cancer in young women	2011-2012	This study

Comparing serum levels of LH in two groups showed that mean of LH in the group receiving diphereline was lower than the control group during the study and three months following treatment. Mean serum level of LH three months after chemotherapy was 11.70 ± 6.35 and 22.64 ± 14.98 in patients on diphereline and controls, respectively ($p < 0.001$, Table 3).

FSH serum level at three and six months during and three months after treatment was significantly lower in patients receiving diphereline (29.64 ± 14.11 vs. 48.09 ± 29.67) (Table 3).

Mean estradiol serum level at the end of month three following chemotherapy was 81 ± 19.35 vs. 40.14 ± 37.35 in diphereline and control groups, respectively ($p < 0.001$, Table 3).

Discussion

The present findings showed that GnRH agonists significantly increase ovarian function and spontaneous menstrual reverse in 90.5% in comparison with 33.3% controls.

This result was similar to the Badawy *et al.* [5] study which was performed on 80 breast cancers (89.6% vs. 33.3% in GnRH agonist and control groups, respectively) (Table 4).

Del Mastro *et al.* [6, 7] conducted a study on 29 cases of breast cancer which showed the menstrual reverse in GnRH agonist group (Table 4). In this study, in 16 out of 17 cases younger than 40 years (94%) and five out of 12 patients older than 40 years (42%), menstruation reversed, but in the present study 100% of 13 cases older than 35 years who received diphereline and three controls (20%) had menstrual reverse. This difference might be due to effect of age and sensitivity of ovarian tissue to chemotherapy. However more similar studies with a higher number of cases are needed to confirm this finding.

A meta-analysis performed by Clowse *et al.* [8] on data collected from nine studies from 1966 to 2000 on 366 different types of breast cancer in young women showed that in 93% of 178 cases who received GnRH agonist and 48% of controls, normal ovarian function was preserved (Table 4).

A study by Blumenfeld *et al.* [9], performed on 36 cases of lymphoma showed that menstrual reverse occurred in 93.7% of women on GnRH agonist during three to six months following treatment. It should be noted that only in 39% of controls in this study did menstruation reverse. The chemotherapy regimen and findings were similar to the present study.

Blumenfeld *et al.* [10] showed spontaneous menstrual reverse in 95% in comparison to 45% control.

Blumenfeld *et al.* [11] performed another survey on 150 cases with Hodgkin's lymphoma which showed menstrual reverse or spontaneous ovulation in 96.9% and 63% of cases receiving GnRH agonist and controls, respectively.

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