Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced premature ovarian failure in premenopausal women with breast cancer

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Abstract: Objective: To test the efficacy of GnRHa administered before and during combination chemotherapy in ovarian function preservation for breast cancer women. **Patient(s):** In this prospective, randomized, study, sixty three patients younger than or equal to 45y old with non metastatic unilateral adenocarcinoma of the breast who had undergone modified radical mastectomy or breast-conserving surgery were included in the study. Patients were assigned randomly to receive combined GnRHa and chemotherapy (anthracycline/ cyclophosphamide/ fluorouracil) or chemotherapy alone. The first GnRHa injection was administered at least 2 weeks before the first chemotherapy cycle, continuing at 3.6 mg subcutaneously every 4 weeks until the end of the last cycle. The primary objective was the reappearance of normal ovarian function, defined as two consecutive menstrual periods within 21 to 35 days at 6 months after end of chemotherapy. **Result(s):** In this study group, 81.2% resumed menses and 71.8% resumed spontaneous ovulation within 3–8 months of termination of the GnRHa/chemotherapy co-treatment; 18.8% experienced hyper-gonadotrophic amenorrhoea and ovarian failure 12 months after treatment. In the control group (chemotherapy without GnRHa), 54.8% resumed menses and 45.1% resumed normal ovarian activity. The mean FSH concentrations, 6 months after completion of the GnRHa/chemotherapy co-treatment group, were significantly less than the control group. During the GnRHa/chemotherapy co-treatment, the concentrations of FSH, LH, and P (progesterone) decreased to almost pre-pubertal levels. However, within 1–3 months after the last GnRHa injection, an increase in LH and FSH concentrations was detected, followed several weeks later in by an increase in progesterone concentrations to within normal levels. The median Time to restoration of menstruation was 178 days with goserelin compared to 220 day without goserelin with statistical significant difference (p<0.00). **Conclusion(s):** GnRHa administration before and during combination chemotherapy for breast cancer may preserve *post-treatment ovarian function in women <45 years. However, Long-term studies are required.*
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1- Introduction

Breast cancer remains one of the most frequently diagnosed malignancies in women. Although the incidence trends of breast cancer decreased from 1998 through 2006, however, the probability of developing breast cancer before age 40 years is 1 for every 206 women.[1] Major advances in treatment of breast cancer have achieved significant benefit from adjuvant systemic chemotherapy in terms of prolonged disease-free and overall survival.[2,3] The increased survival of patients with breast cancer has given rise to fertility problem related to cancer treatment.

In young cancer patients, ovarian toxicity is a major side effect of chemotherapy. Ovarian damage can present with a variety of symptoms, such as transient or permanent amenorrhea, infertility and early menopause. For women who continue to menstruate or who recover their cycles, there is an additional long-term risk of premature ovarian failure (POF) [4].

POF has significant consequences, including vasomotor symptoms, osteoporosis, and increased risk of cardiovascular diseases, sexual dysfunction, and infertility [5]. Temporary ovarian suppression with GnRH agonist (GnRHa) during chemotherapy is a potential strategy to preserve ovarian function. The possible mechanisms by which GnRHa could protect the ovaries during chemotherapy are: the interruption of follicle-stimulating hormone (FSH) secretion, a decrease in utero-ovarian perfusion, the activation of GnRH receptors on the oocytes, the up-regulation of intra-gonadal–anti-apoptotic molecules and/or the protection of undifferentiated germ-line stem cells [6]. Preclinical data confirmed that temporary ovarian suppression with GnRHa during chemotherapy reduces ovarian toxicity [7] and in phase II studies, the large majority (70–100%) of women with breast cancer or lymphoma treated with GnRHa did not

experience ovarian failure [8-11]. However, phase III studies evaluating the effect of GnRHa on chemotherapy-induced POF produced conflicting results. Despite the attempts to summarize the results of the clinical trials by conducting several meta-analyses [12-18], the issue remains still controversial [19].

On the basis of this evidence, we initiated this study to investigate the efficacy of GnRHa administered before and during combination chemotherapy in ovarian function preservation for breast cancer women.

2- Patients and methods

The study included 63 patients who were diagnosed with non metastatic unilateral adenocarcinoma of the breast, with positive or negative lymph node status, that had undergone modified radical mastectomy or breast-conserving therapy. Patients were eligible if they were between the ages of 18 and 45 years and had requested preservation of ovarian function. They had to have regular and spontaneous menstrual periods before study entry, with follicular stimulating hormone (FSH) below 15 mlU/mL in the follicular phase of the menstrual cycle. Patients had to use adequate non hormonal contraceptive measures during study treatment.

Treatment with sex hormones was not allowed. Patients were excluded for known hypersensitivity reaction to the investigational compounds, prior cytotoxic treatment for any reason, and distant metastases Macroscopic metastatic spread of the disease was excluded by the usual investigations. All patients provided written informed consent before inclusion in the study.

Patients were assigned randomly to receive combined GnRHa and chemotherapy or chemotherapy alone by using sealed envelopes. Twenty-four patients in each group were required to give the study a power of 80%. Before the first administration of chemotherapy, ovarian suppression had to be proven (ie, estradiol [E2] level<50 pg/mg and LH level<10m IE/mL). Otherwise, start of chemotherapy was postponed until proven ovarian suppression.

All patients were treated with a FAC regimen (a combination of 5-Fluorouracil 600 mg/m^2 i.v., Doxorubicin 50 mg/m^2 i.v., and Cyclophosphamide 600 mg/m^2 i.v.) on day 1 of therapy to be repeated every 3 weeks for 6 cycles. No patients received radiotherapy as a co-treatment. Two weeks before the initiation of chemotherapy, patients in the study group received goserelin at a dose of 3.6 mg subcutaneously (Zoladex®, ZenekaPharma International, UK) and then every 28-30 days for 6 months. All women had a hormonal profile including: FSH, luteinizing hormone (LH), estradiol (E2), progesterone (P), and prolactin, before starting treatment, and monthly thereafter (for FSH, LH, E2, and P) until resuming spontaneous ovulation and menses up to 12 months after. Serial ultrasound scans were by a trans- vaginal probe (except for non-married patients) at each visit for evaluating the ovary and endometrial thickness.

Objectives

The primary objective was to (verify the role goserelin in accelerating the rate of resuming normal ovarian function within the first year of administration of anthracycline-containing polychemotherapy compared with chemotherapy alone in patients with breast cancer).

Normal ovarian function was defined as two consecutive menstrual periods within 21 to 35 days in a timeframe of 5 to 8 months after last administration of goserelin.

Secondary objectives were time until recovery of regular menstruation; ovarian function (FSH, LH, E2, progesterone) before and at 6, 12 months after end of chemotherapy.

Statistical Analysis

The proportion of menstruation, ovulation, and premature ovarian failure (POF) in each group was compared by using Fisher's exact test. A *P* level of <.05 was considered significant. SPSS version 17 (SSPS, Chicago, IL) was used for analysis.

3- Results

Sixty three patients were randomly assigned and started protocol-defined treatment (32 patients assigned to receive chemotherapy with GnRHa agonist and 31 to chemotherapy without GnRHa agonist).

Patients' baseline characteristics

The baseline characteristics for all patients' were illustrated in Table 1. The baseline characteristics were comparable in the two arms, there were no differences between both groups regarding age, body weight, pretreatment serum LH and serum progesterone level. The serum FSH was significantly less in the chemotherapy GnRHa group, but the mean values were well below 10 mIU/mL (4.7 vs. 5.7). Serum E2 was significantly more in the chemotherapy GnRHa group (296.4 vs. 166.4 pmol/l). The mean total dose of cyclophosphamide, was 5.42 g in the study group and 5.81g in the control group, without significant differences between the two groups.

Treatment efficacy

Of the 32 women in the study group, 26 (81.2%) resumed menses and 23 (71.8%) resumed spontaneous ovulation within 4–10 months of termination of the GnRHa/chemotherapy co-treatment, (Table 2).

In contrast, only 17 of the 31 (54.8%) in the control group (chemotherapy without GnRHa) resumed menses and 13 (41.9%) resumed ovulation (*P*<.01) (Table 2).

Only 6 patients (18.8%) experienced hypergonadotrophic amenorrhoea and ovarian failure 4 months after treatment compared to 14(45.2%) in the control group.(*p*=0.02)

Median time to resume menstruation was statistically different between the two groups (178 days with GnRHa *vs* 220 days without GnRHa; *P*= <0.001); (Fig 1). There was no statistically significant difference between both groups regarding age (*P*<0.30).

Only one case of pregnancy was reported in this study in the GnRHa/chemotherapy Group. Pregnancy occurred 9 months after end of chemotherapy/GnRHa

The median FSH concentrations, 6 months after completion of the GnRHa/chemotherapy co-treatment group, were significantly less than the control group 8.2 vs 11.9 (*P* = 0.03).

During the GnRHa/chemotherapy co-treatment, the concentrations of FSH, LH, and P decreased to almost pre-pubertal levels. However, within 1–3 months after the last GnRHa injection, an increase in LH and FSH concentrations was measured, followed by several weeks later in an increase in P concentrations to within normal levels (Fig. 2).

Twelve months after start of GnRha/chemotherapy co-treatment, the median level of FSH and LH rose from 4.7 to 9.1 mIU/mL and from 4.1 to 7.8 mIU/mL, respectively.

Toxicity

Overall, 337 cycles of chemotherapy were applied, 175 for patients with GnRha and162 for patients without GnRha. Most of our patients received six cycles of chemotherapy.

Six patients in the group with GnRha and 5 patients in the group without GnRha required delays in their chemotherapy dosing, and one patient in the group with GnRha needed chemotherapy dose reduction.

The most commonly reported hematologic adverse events (AEs) were leucopenia, and anemia. The most common non-hematologic AEs were nausea, alopecia, fatigue and hot flashes.. No treatment-related death occurred.

Table (1) patient characteristics

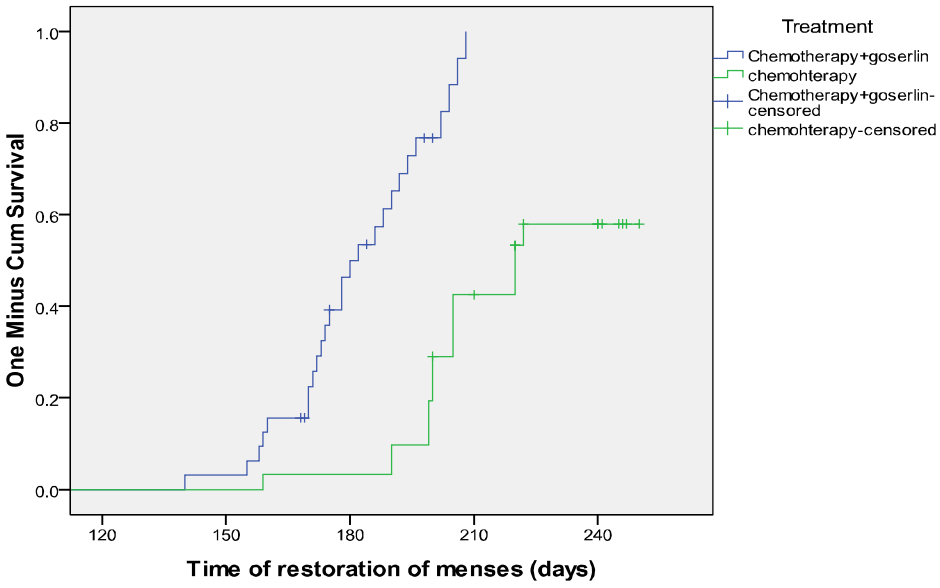
	Cth +GnRha group (NO =32)	Cth alone group (NO=31)	*P* value
Age (years)			
Median	40	39	0.13
range	26-45	25-45	
Body weight (kg)			
Median	74	75	0.97
range	55-115	57-109	
Mean cumulative cyclophosphamide dose (g)	1038	1021	0.72
No of cth cycles	175	162	0.51
Laboratory values			
FSH (iu/l)	4.78	5.79	0.03
LH (iu/l)	4.15	4.33	0.70
Estradiol (pmol/l)	296.43	166.45	0.04
Serum P(ng/ml)	6.87	6.55	0.64
Menopausal status			
Prememopausal	32	32	
Regular menses	32	31	

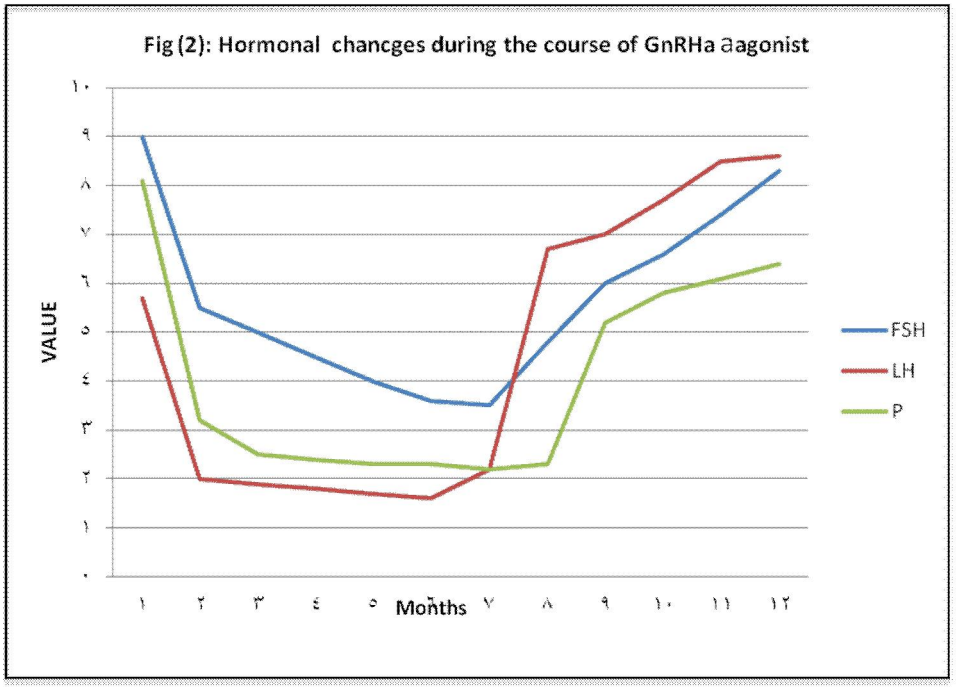
Table (2)Outcome 12 months after therapy

	Cth + GnRha group (NO =32)	Cth alone group (NO=31)	P value
Menstruating	26(81.2%)	17(54.8%)	0.02
Ovulating	23(71.8%)	13(41.9%)	0.01
POF	6(18.8%)	14(45.2%)	0.02
FSH (iu/l)	9.1	13.1	0.02
LH (iu/l)	7.8	13.7	0.08
Estradiol (pmol/l)	334	228	0.00
Serum P(ng/ml)	7.3	4.3	0.01

POF: premature ovarian failure
Pvalue< 0.05 was significant

Fig (1): Time to restoration of menstruation in all patients





4- Discussion

Many drugs used in the treatment of cancer have profound and lasting effects on gonadal function [20]. Both germ cell production and endocrine function may be affected, not infrequently in an irreversible manner. The magnitude of the effect varies with the drug class, the total dose administered, and the age and pubertal status of the patient at the time of therapy.

Drugs most frequently associated with ovarian failure are divided into three classes: (1) those that definitely are associated with gonadal

toxicity: cyclophosphamide, L phenylalanine mustard, busulfan, and nitrogen mustard; (2) those that are unlikely to cause gonadal toxicity: methotrexate, 5-fluorouracyl, and 6-mercaptopurine; and (3) those drugs where the gonadal toxicity is unknown: doxorubicin, bleomycin, vincaalakloids (vincristine and vinblastin), cisplatin, nitrosoureas, and cytosine, arabinoside[20]. It has been reported that 64% of adult female patients undergoing cancer therapy experienced one or more of the symptoms of ovarian failure [21].

There is no unified definition of amenorrhea across studies. A different definition of POF was used in many studies [22–30]: early, permanent cessation of menstruation 6 months after the end of chemotherapy and serum FSH levels >2 mIU/ml [22]; no resumption of spontaneous ovulation 8 months after the end of chemotherapy [23]; absence of menses 36 months after chemotherapy [24]; postmenopausal levels of FSH 12 months after chemotherapy [25]; no resumption of menstrual activity and postmenopausal levels of FSH and estradiol[26]; no reappearance of two consecutive menstrual periods within 21–35 days 6 months after the last administration of goserelin [27]; no maintenance of menses and no resumption of menses 24 months after the end of chemotherapy [28]; FSHP4 U/L 12 months after chemotherapy [29]; no resumption of menstruation 12 months after the end of chemotherapy [30].

Despite extensive research efforts, consisting of 13 randomized trials in 3 different tumor types and seven meta-analyses [12-18], the efficacy of GnRHa in reducing the risk of ovarian failure associated with the use of chemotherapy in premenopausal women, is still considered uncertain [19,31], and temporary ovarian suppression with GnRHa is not considered as a standard strategy to preserve fertility by ASCO and European Society for Medical Oncology (ESMO) guidelines [32,33]. A concern is represented by the conflicting results of the published trials. Our study tries to address this problem.

The present study is a prospective randomized study. The results of the present study are promising; spontaneous ovulation was resumed in 71.8% within 12 months in the GnRHa/chemotherapy group. In contrast, only 41.9 %resumed spontaneous ovulation in the chemotherapy (without GnRHa) group. The outcome measures of the present study included both the changes in menstrual history and hormonal profile, before and after the treatment. Depending on the menstrual history alone have some limitations [34].

About one half (45.2%) of the chemotherapy alone group experienced hypergonadtrophic amenorrhea and POF. A huge variation across studies was observed in the proportion of patients classified as POF, even within the same cancer type. In a recent metanalysis, in the 8 studies of breast cancer patients, the proportion of patients classified as POF varied from 2/21 (9%) to 7/9 (78%) among controls, and from 2/23 (9%) to 7/10 (70%) among treated patients. In the two studies of lymphoma patients the frequency of POF ranged from 18% to 79%, while in the study of ovarian cancer patients 5/15 (33%) of controls and 0/15 of treated patients were classifieed as POF.(35)

The large heterogeneity in the incidence of POF across studies must be underlined. Part of this heterogeneity is due to the trials in women treated for lymphoma, where extremely high frequencies of POF were observed both among women treated with GnRH analogues and in controls. However, the frequency of POF observed in breast cancer studies still ranged from less than 10% to 60–70%. This large heterogeneity cannot be entirely accounted for by chance variation due to the small size of some of these studies, and has two possible explanations: (a) the difference is real, and it is due to the different chemotherapy regimens and age distribution of the study groups and (b) the difference is artifactual, due to differences in the definitions and ascertainment of POF. Probably, both explanations contribute significantly to the variation in the incidence of POF across studies. Yet, the true absolute risk of POF in a premenopausal woman candidate for chemotherapy is possibly the most important determinant of her attitude to undergo treatments aimed at reducing this risk, and in some women, a high risk of POF might even induce them to refuse to receive chemotherapy.

For this reason, the current uncertainty on the true risk of POF as a consequence of chemotherapy should and can be overcomed with adequate research efforts. [35]

In a trial by del Mastro *et al.,*[36] in 271 patients with hormone sensitive and -insensitive breast cancer, the rate of premature menopause measured by E2 and FSH 1 year after end of chemotherapy was 13.5% in those with and 32.3% in those without goserelin, in addition to modern chemotherapy. This is in concordance with our results.

Clinical studies have shown that age represents a significant risk factor for chemotherapy-induced POF.[37].Normal ovarian function itself is age-dependent, with ovarian function declining with age. In our study, age was not a significant risk factor for POF, This may be explained by the older age of the whole group which may increase the rate of POF.

Infertility is another potential complication of adjuvant chemotherapy that is experienced by

some premenopausal women. These women may continue to menstruate or resume their menses after chemotherapy, despite having abnormal fertility. In a recent metaanalysis, three of the RCTs evaluated spontaneous pregnancy rate but no statistically significant increase in spontaneous pregnancies was found for GnRH agonist treatment. However, the follow-up duration was too short to evaluate the real influence on fertility. [38]

Other options for fertility preservation range from the well established techniques such as embryo cryopreservation to experimental ones, such as oocyte or ovarian tissue cryopreservation [39]. Embryo cryopreservation require approximately 2 weeks of ovarian stimulation beginning with the onset of the patient's menstrual cycle. Thus, it is crucial that these patients are referred to appropriate assisted reproductive technology centers as soon as they are diagnosed with breast cancer.

Despite the protective effect of GnRH agonist treatment on preserving ovarian function in premenopausal women treated with chemotherapy, a major concern of both patients and treating physicians is the potential side effects of the GnRH agonists themselves. GnRH agonists suppression of the reproductive axis causes typical symptoms of menopause, such as hot flashes, headaches, mood changes, sweating, and dry skin, as well as decreased bone density and possible predisposition to osteoporosis or bone fracture. However, a recent meta-analysis [38] found no statistically significant differences on adverse effects between those treated with chemotherapy alone (p ¼0.17). Another concern is that GnRH agonists may reduce the effectiveness of the chemotherapy[40].

For this issue, a meta-analysis by Cuzick *et al.,*[41] assessed pooled data of 11,906 premenopausal women with early breast cancer from 16 RCTs and concluded that the administration of GnRH agonists as adjuvant treatment did not reduce the effectiveness of the chemotherapy.

In conclusion, the statistically significant reduction (p = 0.02) in the risk of POF, associated with the use of GnRHa observed in cur study, provides convincing evidence in support of the efficacy of this preventive strategy. Long-term data as well as final results of ongoing study and future research efforts to clarify the mechanisms of action of GnRHa, are needed to further confirm the beneficial effect of GnRHa in reducing the occurrence of chemotherapy-induced POF.

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