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Prevention of chemotherapy-induced menopause by temporary ovarian suppression with goserelin in young, early breast cancer patients

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Background: Standard methods to prevent chemotherapy-induced early menopause in young, breast cancer patients are unavailable to date. Preclinical data has suggested that luteinising hormone-releasing hormone (LH-RH) analogs given during treatment can decrease the gonado-toxicity induced by chemotherapy. This phase II study aimed to assess the activity of such a method in young, breast cancer patients undergoing adjuvant chemotherapy.
Patients and methods: Premenopausal patients received the LH-RH analog goserelin 3.6 mg every 4 weeks before and during chemotherapy. According to two-stage optimal phase II Simon design, treatment was considered clinically interesting if it was able to prevent menopause in 19 out of 29 patients of the study population. The resumption of ovarian function was defined by a resumption of menstrual activity or by a follicle-stimulating hormone (FSH) value ≤40 IU/l within 12 months after the last cycle of chemotherapy.
Results: Thirty patients were enrolled and 29 were evaluable. Median age was 38 years (range 29–47). All but one patient received CEF regimen (cyclophosphamide, epirubicin, 5-fluorouracil). Resumption of menstrual activity was observed in 21 patients (72%; 95% CI 52% to 87%) and a FSH value ≤40 IU/l in 24 patients (83%; 95% CI 63% to 93%). Menses resumption was observed in 16 out of 17 patients (94%) with age <40 years and in five out of 12 patients (42%) with age ≥40 years.
Conclusion: Goserelin given before and during chemotherapy may prevent premature menopause in the majority of patients. The different success rate by age, however, indicates the need of a prospective evidence of the efficacy of such a strategy.
Key words: breast cancer, early menopause, fertility preservation

introduction

Nearly 25% of women diagnosed with breast cancer are premenopausal [1] and most are candidates for adjuvant chemotherapy [2]. As a consequence of such a treatment, the majority of these patients develop early menopause. Commonly used chemotherapy regimens, such as CMF (cyclophosphamide, methotrexate, fluorouracil) or CEF (cyclophosphamide, epirubicin, 5-fluorouracil), induce menopause in nearly 60% of patients [3]. Although cumulative dose of chemotherapy has been associated with risk of menopause [3], different CEF regimens seem to be associated with a similar incidence of iatrogenic menopause. CEF regimens based on the intravenous administration on day 1 of all drugs for six cycles (cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2, fluorouracil 600 mg/m^2) induces menopause in 60% of patients [4]. The dose-intensified CEF reported by Levine et al. [5] (cyclophosphamide 75 mg/m^2 orally days 1–14, epirubicin 60 mg/m^2 i.v. days 1 and 8, and fluorouracil 500 mg/m^2 i.v. days 1 and 8) given for six cycles was associated with a 51% rate of menopause. The occurrence of chemotherapy-induced menopause rises with increasing age, ranging from 22% to 61% in women under 40 years of age and from 61% to 97% in those over 40 [6].

Premature menopause has significant consequences, such as hot flushes and night sweats, psychosocial problems, atrophic vaginitis, dyspareunia, skeletal osteoporosis, cardiovascular effects and loss of fertility. This latter effect is a major concern for young women with breast cancer and in nearly 29% of cases it does influence treatment decision [7]. Therefore, preservation of ovarian function and particularly of fertility is an emerging attempt of current clinical research.

No standard treatment to prevent chemotherapy-related premature menopause is available so far. Current attempts to preserve ovarian function are mainly based on invasive

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procedures not easily available in all centers, such as cryopreservation and reimplantation of ovarian tissue [8, 9]. Hormonal methods may offer an important strategy to reduce the gonadotoxicity of chemotherapy. Since cytotoxic drugs mainly affect tissues with a rapid cellular turnover, it has been suggested that a state of induced gonadal inhibition during exposure to chemotherapy may protect the gonads [10, 11]. Chronic administration of luteinising hormone-releasing hormone (LH-RH) analogs decreases follicle-stimulating hormone (FSH) secretion and suppresses gonadal function. This approach has been suggested as a possible protective method against gonadal damage induced by chemotherapy. There is convincing evidence in female rats [12, 13] and rhesus monkeys [14] that treatment with LH-RH analogs can reduce the ovarian toxicity of chemotherapy and preliminary clinical data suggest that this approach works in lymphoma patients [15].

The aim of this phase II study was to evaluate the activity of goserelin, a LH-RH analog, in preventing the development of ovarian failure in premenopausal breast cancer patients undergoing adjuvant chemotherapy.

patients and methods

eligibility criteria

Patients with histologically confirmed breast cancer (stages I–III) who had undergone modified mastectomy or breast-conserving surgery plus full ipsilateral axillary node dissection or sentinel lymph node biopsy were eligible for enrollment in the study if they were premenopausal and candidates for adjuvant chemotherapy. Premenopausal status was defined as the presence of active menstrual cycles within 6 weeks before initiation of chemotherapy. Other eligibility criteria were as follows: age ≥18 years; no evidence of metastases or localized cancer recurrence; no prior chemotherapy for cancer or non-neoplastic diseases; no previous or concomitant other malignancy within the past 5 years except basal or squamous cell carcinoma of the skin or adequately treated *in situ* carcinoma of the cervix; no pregnancy or nursing.

All patients gave their written informed consent before study entry.

study design

This was a single center, prospective, single-arm, phase II study on goserelin activity in preventing chemotherapy-induced menopause. FSH was used as the biochemical marker of menopausal status. FSH was evaluated before treatment and at 3, 6, 9 and 12 months after the last cycle of chemotherapy. A FSH level above 40 IU/l indicated a post-menopausal status. Estradiol (E2) levels were also assessed with a value below 20 pg/ml indicating a post-menopausal status. Menstrual activity was recorded during and after chemotherapy.

The success of the experimental treatment was defined by the resumption of menstrual activity within 12 months after the last cycle of chemotherapy or by the occurrence of a FSH level ≤40 IU/l between 3 and 12 months after the last cycle of chemotherapy.

The Ethical Committee of the National Cancer Research Institute of Genoa, Italy approved the protocol.

treatment regimen

Goserelin (Zoladex, supplied by AstraZeneca, Italy) 3.6 mg was administered subcutaneously at least 1 week before the first cycle of chemotherapy and then every 4 weeks for the duration of chemotherapy. The last administration of goserelin was given before the last cycle of chemotherapy.

Patients with hormone receptor positive tumors received tamoxifen at the end of chemotherapy and if a resumption of menstrual activity was observed during the 12-month follow-up after the last cycle of chemotherapy, they restarted goserelin and continued it for at least 2 years to induce a therapeutic temporary ovarian suppression.

assessment of toxicity

Toxicity was evaluated on the first day of each chemotherapy cycle according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Prespecified side-effects, which were considered related to goserelin administration, were as follows: hot flushes, vaginal dryness, headache, mood swings, breast changes, depression, hypotension, hypertension and decrease of bone mineral density. Bone mineral density was measured using QTC (quantitative computed tomography) measures of the spine.

statistical methods

A two-stage optimal phase II Simon design was used. It was assumed that an experimental drug, in order to warrant further studies, should be associated with a success rate of at least 80%, whereas a drug associated with a proportion of successes ≤50% was of no interest. For a power of 90% against the hypothesis of an 80% rate of success and a 5% false-positive error rate against the hypothesis of a success rate of 50%, nine patients have to be enrolled onto the first stage. If five or fewer successes were observed, then the enrollment had to be terminated. If six or more successes were observed, then an additional 20 patients had to be accrued. The drug was considered sufficiently promising to warrant further studies if 19 or more successes were seen among the total of 29 patients.

Exact 95% binomial confidence intervals (CIs) were computed for rates. The median test was used to verify whether two independent groups differ in central tendencies. To investigate the effect of FSH and E2 on time to resumption of menstrual activity, two Cox proportional hazard models were fit to the data. FSH (≤40 IU/l versus >40 IU/l) and E2 (<20 pg/ml versus ≥20 pg/ml) values, observed during the follow-up, were treated as binary time-dependent variables. Time to resumption of menstrual activity was calculated from the day of the last chemotherapy administration until menstrual resumption. Women who did not resume menstrual activity during the follow-up period were censored at the day of their last follow-up visit. All significance tests were performed at the 0.05 level.

results

Thirty patients were enrolled between October 2001 and June 2003. One patient refused chemotherapy after study entry and was considered not evaluable. The main baseline characteristics of the 29 evaluable patients are reported in Table 1. Median age was 38 years (range 29–47 years). At study entry the median time from last menses was 18 days (range 1–47 days). Median baseline value of FSH was 4.64 IU/l (range 1.68–20.3) and median baseline value of E2 was 114.5 pg/ml (range 26–339).

All but one patient received CEF (cyclophosphamide 600 mg/m^2, epirubicin at doses ranging from 60 to 90 mg/m^2, 5-fluorouracil 600 mg/m^2) chemotherapy administered every 3 weeks for six cycles. Chemotherapy was stopped before the total number of planned cycles in three patients due to toxicity: after five cycles in two patients and after one cycle in one patient. Goserelin was stopped before the completion of the planned treatment in three patients (after two administrations in two patients and after four administrations in one patient) due to chemotherapy interruption (two patients) and refusal to continue goserelin (one patient). All 25 patients (86%) with

receptor-positive tumors received tamoxifen after chemotherapy. Data about treatment compliance are reported in Table 2.

goserelin-related toxicity

The majority of the patients reported side-effects possibly related to the administration of goserelin (Table 3), although a concurrent effect of chemotherapy on such a toxicity cannot be ruled out. These toxicities were of grade 1–2 in all cases. Bone mineral density was assessed at baseline, within 3 months from start of goserelin, in 14 patients and after more than 3 months in 13 patients. Median T-scores were −1.50 (range −2, +2) at baseline and −2.40 (range −4, −2) after more than 3 months of goserelin treatment, indicating a decrease in bone mineral density.

activity

Among the 29 evaluable patients, one patient stopped chemotherapy after one cycle due to severe toxicity. She continued goserelin plus tamoxifen as antitumor treatment and was considered a failure for the purpose of this study. The remaining 28 patients had evaluation of ovarian function during the planned 12-month follow-up period after the last cycle of chemotherapy. Resumption of menstrual activity was observed in 21 patients (72%; 95% CI 52% to 87%). Among the 25 patients in whom the FSH assessment was performed, a value ≤40 IU/l was observed in 24 (83%; 95% CI 63% to 93%). Three patients without FSH assessment experienced resumption of menstrual activity (Table 4). According to our definition of success (FSH ≤40 IU/l and/or resumption of menstrual menses), the overall rate of success was 97% (95% CI 82% to 100%). Median time to menstrual resumption was 5.5 months (range 2.1–12 months). With increasing age a trend to a longer median time to menses resumption was observed: 2.7 months (range 2.4–6.4) in patients ≤35 years old (seven patients); 6.1 months (range 2.1–11.5) in patients 36–38 years old (eight patients); and 7.9 months (range 2.9–12.0) in patients ≥39 years old (six patients). Menstrual activity resumption was observed in 16 out of 17 patients with age <40 years (94%) and in five out of 12 patients with age ≥40 years (42%) (Table 5).

Table 1. Patient characteristics at study entry

	Patients (n = 29)	
	n	%
Age		
<40 years	17	59
≥40 years	12	41
Type of surgery		
Conservative	22	76
Mastectomy	7	24
Tumor size		
pT1	20	69
pT2	6	21
pT3	1	3
pT4	2	7
Nodal status		
pN0	13	45
pN1	14	48
pN2	2	7
Grading		
G1	1	3
G2	20	69
G3	8	28
Hormonal receptor status		
ER positive and/or PgR positive	25	86
ER negative and PgR negative	4	14
Previous pregnancies		
Yes	18	62
Not	11	38

Table 2. Treatment compliance

Patients (n = 29)	
Chemotherapy type [no. patients (%)]	
$C_{600}E_{60–75–90}F_{600}$	28 (97%)
$A_{60}C_{600}$ × 4 cycles followed by T_{175} × 4 cycles	1 (3%)
Median number of chemotherapy cycles	6
Range	1–8
Median number of goserelin administration	5
Range	2–6
Interval (days) between first goserelin administration and the start of chemotherapy	
Median	7
Range	7–15
Tamoxifen administration	25 (86%)
Radiotherapy after surgery	
Yes	26 (90%)
Not	3 (10%)

Table 3. Grade I–II goserelin-related toxicity

Toxicity	Patients (n = 29)	
	n	%
Hot flushes	28	97
Headache	26	90
Sweating	26	90
Mood modification	26	90
Vaginal dryness	17	59

Table 4. Menstrual activity resumption, FSH and E2 values

	Menstrual activity resumption			
	Yes	Not	Unknown	Total
	n = 21 (72%)	n = 7 (24%)	n = 1 (4%)	n = 29 (100%)
FSH ≤40 IU/l	17	7	0	24 (83%)
FSH >40 IU/l	1	0	0	1 (3%)
FSH unknown	3	0	1[a]	4 (14%)
E2 <20 pg/ml	3	3	0	6 (21%)
E2 >20 pg/ml	15	4	0	19 (65%)
E2 unknown	3	0	1[a]	4 (14%)

[a]One patient stopped chemotherapy after one cycle and was considered as a failure.

All 17 patients (59%) with hormone-receptor positive tumors and resumption of menstrual activity restarted goserelin for a planned duration of at least 2 years.

FSH and E2 assessment

Distribution of patients by menstrual activity resumption and FSH and E2 levels is reported in Table 4.

Median values of minimum FSH level observed in each patient between 3 and 12 months after the last cycle of chemotherapy were significantly lower in patients who resumed menstrual activity (6.09 IU/l, range 2.18–59.9) compared with patients who did not (19.20 IU/l, range 9.16–32.3) ($P = 0.02$). Median values of maximum E2 level observed in each patient during the follow-up were significantly higher in patients with menses resumption (181 pg/ml, range <20–766) than in patients without menses resumption (23 pg/ml, range <20–514) ($P = 0.03$). Cox proportional hazard models showed that a value of FSH ≤40 IU/L was not predictive of future menstrual resumption (hazard ratio 1.41, 95% CI 0.47–4.23, $P = 0.53$), whilst E2 level ≥20 pg/ml was a strong predictor of menses resumption (hazard ratio 6.17, 95% CI 2.20–17.19, $P = 0.0005$).

The potential impact of tamoxifen on FSH and E2 levels was evaluated in patients with menses resumption. Minimum FSH values were significantly lower in the 14 patients taking tamoxifen (4.83 IU/l, range 2.18–16.10) compared with the four patients who did not (17.6 IU/l, range 6.48–59.90) ($P = 0.02$). Maximum E2 levels were higher but not significantly different between patients assuming and not assuming tamoxifen (201 pg/ml, range <20–766 versus 151.5 pg/ml, range <20–283) ($P = 0.27$).

discussion

The results of this phase II study suggest that goserelin, given before and continuing every 4 weeks during cytotoxic chemotherapy, may prevent iatrogenic early menopause. On the basis of our 'a priori' criterion for defining the success, the success rate was as high as 97% (95% CI 82% to 100%). Because FSH value alone cannot be considered a reliable marker, a better indicator of ovarian function preservation is menses resumption, which was observed in 72% of patients (95% CI 52% to 87%).

While the resumption of menstrual activity is a clear marker of ovarian function, its absence does not necessarily indicate the lack of such a function [16]. Our study suggests that a level of E2 ≥20 pg/ml after chemotherapy indicates a premenopausal status and that it is predictive of future menstrual activity resumption. FSH value alone cannot be considered a reliable marker of ovarian function. Although median values of FSH were significantly lower in patients who resumed menses compared with those who did not, menstrual activity was observed in one patient despite an FSH value >40 IU/l. In addition a low (<40 IU/l) FSH level was not predictive of future menses resumption. The use of tamoxifen in premenopausal women can affect both FSH and E2 secretion. The effect of tamoxifen on FSH is unclear [17]. An increase in FSH secretion has been seen in some studies, but in other studies this was not found. In our study, lower FSH levels were observed in patients taking tamoxifen. However, due to the low number of patients, such findings should be considered with caution. The previously reported [18] increase in E2 secretion induced by tamoxifen was also observed in our study, although the difference between patients on tamoxifen versus those not taking it was not statistically significant.

Methods other than administration of LH-RH analogs are currently under evaluation to preserve ovarian function. Among them transplantation of cryopreserved ovarian tissue is very promising although little clinical data on its efficacy are available so far. Main limiting factors for this method are: the availability of the procedure, which may be limited to selected centers; the limited life span of ovarian grafts [9], suggesting that transplantation may be useful for fertility restoration but not for the purpose of long-term hormone production; and the risks related to the invasiveness of the procedure and to the potential for ovarian tissue to harbor malignant cells capable of inducing a relapse on reimplantation [19]. Moreover the reported case of live birth after orthotopic transplantation of cryopreserved ovarian tissue [20] has been criticized as the definitive evidence for the feasibility of pregnancy resulting from such procedures [21]. The recently reported strategy of *in vitro* fertilization and embryo cryopreservation after ovarian stimulation with FSH and tamoxifen or letrozole is a promising approach [22] but both its safety and efficacy are still unknown [23].

Concerns about the use of LH-RH analogs before and during chemotherapy are the potential interaction with chemotherapy and the potential detrimental effect on the outcome of the lack of chemotherapy-induced menopause. Data from randomized studies [24, 25, 26] as well as the results of the Early Breast Cancer Trialists' Collaborative Group meta-analysis [27] did not show a different outcome in patients who had received concurrent ovarian suppression and chemotherapy compared with patients treated with chemotherapy alone and thus they did not support the first concern. Regarding the second concern, there is some evidence to suggest that chemotherapy-induced menopause is associated with an improved prognosis in early breast cancer patients [6]. Although reports are not consistent, it cannot be ruled out that resumption of ovarian function and the consequent estrogen production may adversely affect the survival, at least in patients with hormone receptor positive tumors. In our strategy, this reasonable concern was addressed by restarting goserelin administration at the time of ovarian function resumption. LH-RH treatment was continued for at least 2 years, thus assuring a commonly accepted time of therapeutic ovarian function suppression [28]. The activity of

Table 5. Menses resumption and patient age

Age (years)	Total patients	Menses resumption	
		n	%
29–38	15	15	100
39	2	1	50
40	3	1	33
41	3	3	100
42	1	0	0
43	1	0	0
44	3	0	0
47	1	1	100

goserelin in preventing early menopause in patients with receptor positive tumors need to be confirmed after the 2-year period of induced ovarian suppression, when resumption of ovarian function is expected in nearly 80% of patients [27].

Our results corroborate with the findings of other studies in breast cancer patients, showing that the activity of LH-RH analogs in preventing early menopause ranged from 86% to 100% [29–31]. However, our study indicates a different effect according to patient age. Menstrual activity resumption was observed in 94% of patients younger than 40 years and in 42% of those aged 40 or more. Using CEF regimens like that used in our study, the expected rate of menstrual activity resumption is nearly 40% in the overall group of premenopausal patients, 64% in patients younger than 40 years and 30% in those aged 40 or more. Although comparison of these figures with those of the present study suggest an improvement in the preservation of ovarian function by the use of goserelin, it cannot be ruled out that age itself instead of LH-RH analog treatment is the main determinant in ovarian function preservation. Despite LH-RH analog treatment being claimed as an option for menopause prevention [15], definitive evidence of its role needs to be assessed in ongoing phase III studies.

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