Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the Occurrence of Chemotherapy-Induced Early Menopause in Premenopausal Women With Breast Cancer

A Randomized Trial

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Context Premenopausal patients with breast cancer are at high risk of premature ovarian failure induced by systemic treatments, but no standard strategies for preventing this adverse effect are yet available.

Objective To determine the effect of the temporary ovarian suppression obtained by administering the gonadotropin-releasing hormone analogue triptorelin during chemotherapy on the incidence of early menopause in young patients with breast cancer undergoing adjuvant or neoadjuvant chemotherapy.

Design, Setting, and Patients The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients–Gruppo Italiano Mammella 6) study, a parallel, randomized, open-label, phase 3 superiority trial, was conducted at 16 sites in Italy and enrolled 281 patients between October 2003 and January 2008. The patients were premenopausal women with stage I through III breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy. Assuming a 60% rate of early menopause in the group treated with chemotherapy alone, it was estimated that 280 patients had to be enrolled to detect a 20% absolute reduction in early menopause in the group treated with chemotherapy plus triptorelin. The intention-to-treat analysis was performed by including all randomized patients and using imputed values for missing data.

Interventions Before beginning chemotherapy, patients were randomly allocated to receive chemotherapy alone or combined with triptorelin. Triptorelin was administered intramuscularly at a dose of 3.75 mg at least 1 week before the start of chemotherapy and then every 4 weeks for the duration of chemotherapy.

Main Outcome Measure Incidence of early menopause (defined as no resumption of menstrual activity and postmenopausal levels of follicle-stimulating hormone and estradiol 1 year after the last cycle of chemotherapy).

Results The clinical and tumor characteristics of the 133 patients randomized to chemotherapy alone and the 148 patients randomized to chemotherapy plus triptorelin were similar. Twelve months after the last cycle of chemotherapy (last follow-up, August 18, 2009), the rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group, an absolute difference of –17% (95% confidence interval, –26% to –7.9%; $P<.001$). The odds ratio for treatment-related early menopause was 0.28 (95% confidence interval, 0.14 to 0.59; $P<.001$).

Conclusion The use of triptorelin-induced temporary ovarian suppression during chemotherapy in premenopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy-induced early menopause.

Trial Registration clinicaltrials.gov Identifier: NCT00311636

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APPROXIMATELY 6% OF WOMEN with breast cancer are diagnosed before age 40 years,[1] and the probability of developing breast cancer before age 40 years is nearly 1 for every 200 women.[2] Young age is an independent predictor of an adverse outcome,[3-5] and the majority of young patients with breast cancer receive systemic treatment with chemotherapy, hormonal therapy, or both. These patients are at high risk of transient or permanent amenorrhea, and for those women who continue to menstruate or who recover their cycles,

For editorial comment see p 312.

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there is an additional long-term risk of premature ovarian failure.[6] One rough estimate is that each month of chemotherapy translates into 1.5 years of lost reproductive life.[7]

The incidence of premature menopause depends on the type of chemotherapy and the patient's age.[8] Chemotherapy regimens are associated with an incidence of long-term amenorrhea of at least 40%, with a more pronounced effect being associated with the use of regimens containing a high cumulative dose of cyclophosphamide, such as CMF (cyclophospamide, methotrexate, fluorouracil).[8] In women younger than 35 years, the long-term (3 years after diagnosis) incidence of amenorrhea is similar to that of women who do not receive chemotherapy (nearly 10%), but it increases to 50% in women aged 35 to 40 years and to 85% in women older than 40 years.[8] Premature menopause has significant consequences, including vasomotor symptoms, sexual dysfunction, and infertility.[9] This last effect is a major concern for young women with breast cancer and influences treatment decisions in nearly 29% of cases.[10] Young survivors of breast cancer consider premature menopause, sexual dysfunction, and infertility the most distressing aspects of their cancer experience.[11]

No standard strategies for preventing chemotherapy-induced ovarian failure are yet available.[12] Preclinical data have suggested that temporary ovarian suppression with a gonadotropin-releasing hormone (GnRH) analogue during chemotherapy reduces ovarian toxicity,[13,14] and phase 2 studies have shown that GnRH analogues protect the ovaries of 67% to 96% of women with breast cancer undergoing chemotherapy.[15-17]

The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients–Gruppo Italiano Mammella 6) study was a phase 3 trial designed to assess the efficacy of temporary ovarian suppression induced by the GnRH analogue triptorelin in reducing the incidence of early menopause in young patients with breast cancer undergoing adjuvant or neoadjuvant (ie, administered before surgery for breast cancer) chemotherapy.

METHODS

Patient Characteristics

This multicenter, randomized phase 3 trial was approved by the institutional review boards of the participating centers, and all patients provided written informed consent.

Eligible patients had to have histologically proven stage I, II, or III breast cancer and be candidates for adjuvant or neoadjuvant chemotherapy, be of age 18 to 45 years, and be premenopausal. Premenopause was defined as the presence of active menstrual cycles or normal menses during the 6 weeks preceding the start of chemotherapy. The main exclusion criteria were previous chemotherapy, radiotherapy, or for both cancer or nonneoplastic diseases; evidence of distant metastases; other malignancies in the previous 5 years, except basal or squamous cell carcinoma of the skin or adequately treated in situ carcinoma of the cervix; and pregnancy or lactation.

Study Design and Treatment

PROMISE-GIM6 was a parallel, randomized, open-label, phase 3 superiority trial involving women with early-stage breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy and was conducted at 16 Italian centers. The patients were randomly allocated to receive chemotherapy alone or chemotherapy plus triptorelin by faxing the Clinical Trials Unit of the National Cancer Research Institute in Genoa, Italy, where randomization lists, stratified by center, had been prepared with the use of permuted blocks of different sizes and a 1:1 ratio. Data were collected at the Clinical Trials Unit.

Patients received adjuvant or neoadjuvant treatment with anthracycline-based, anthracycline plus taxane–based, or CMF-based (100 mg/m^2 of oral cyclophosphamide on days 1-14 or 600 mg/m^2 of intravenous cyclophosphamide on days 1 and 8; 40 mg/m^2 of methotrexate on days 1 and 8; and 600 mg/m^2 of fluorouracil on days 1 and 8) chemotherapy. The patients allocated to receive triptorelin were given an intramuscular dose of 3.75 mg at least 1 week before starting chemotherapy and then every 4 weeks for the duration of the treatment (the last dose was given before the last cycle of chemotherapy).

All of the patients with hormone-sensitive tumors (estrogen receptor–positive, progesterone receptor–positive, or both) received 20 mg/d of tamoxifen for 5 years starting from the end of chemotherapy. The patients with hormone-sensitive tumors whose ovarian function had returned (as indicated by the occurrence of at least 1 menstrual cycle, premenopausal levels of estradiol [E_2], or both) during the 12-month period of observation after the end of chemotherapy received, in addition to tamoxifen, 3.75 mg of triptorelin every 4 weeks until ovarian function had been suppressed for at least 2 years.

Adverse events were assessed clinically and by means of hematologic and biochemical measurements throughout the period of chemotherapy. Adverse events were recorded and graded in accordance with the National Cancer Institute Common Toxicity Criteria version 2.0,[18] but only those related to the study drug are described here.

Study End Points

The primary study objective was to compare the incidence of chemotherapy-induced early menopause in patients treated with chemotherapy alone or combined with triptorelin. Early menopause was defined as no resumption of menstrual activity and postmenopausal levels of follicle-stimulating hormone (FSH) for 1 year after the end of chemotherapy. Because FSH levels may be affected by the use of tamoxifen (administered for 5 years to the patients with hormone-sensitive tumors starting from the end

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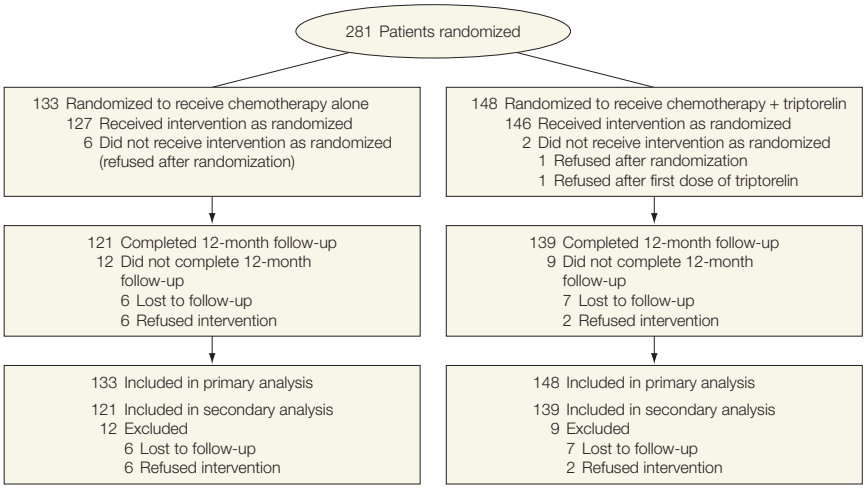
of chemotherapy), the protocol was amended to include E_2 levels in the definition of early menopause. The amended definition of early menopause was no resumption of menstrual activity and postmenopausal levels of both FSH and E_2 for 1 year after the end of chemotherapy. If FSH and E_2 levels were not assessed and menstrual activity did not resume, the patients were considered to be in early menopause. The resumption of menses (regardless of FSH and E_2 levels) within 1 year of the end of chemotherapy, and the occurrence of premenopausal levels of E_2 in the absence of resumed menses were also analyzed. Menstrual activity and FSH and E_2 levels were assessed at 3, 6, 9, and 12 months after the end of chemotherapy. The last follow-up date for the analysis of the primary end point was August 18, 2009, ie, 12 months after chemotherapy was completed for all of the randomized patients. Annual follow-up was planned to record pregnancies, recurrences, and deaths (last annual follow-up, October 28, 2010).

Figure 1. PROMISE-G1M6 Study Flow



No information about the number of patients screened for study eligibility, the number excluded, or the reasons for exclusions is available.

Statistical Analysis

Assuming a 60% rate of early menopause in the group treated with chemotherapy alone,[19] it was estimated that 280 patients had to be enrolled to detect a 20% absolute reduction in early menopause in the group treated with chemotherapy plus triptorelin,[15] with a power of 90% and a 2-sided α error of 5%. Patients were considered evaluable for the primary analysis if they had received at least 1 cycle of chemotherapy and had undergone the 12-month evaluation of menstrual activity. Twelve patients in the chemotherapy-alone group and 9 patients in the chemotherapy plus triptorelin group were considered unevaluable (FIGURE 1). To avoid the exclusion of patients with missing data, an intention-to-treat analysis including all of the randomized patients was performed in which missing values were imputed using the multiple imputation method (10 imputations). Logistic regression and regression methods were used for imputation of categorical and continuous variables, respectively. Missing-at-random assumptions were made.

A secondary analysis was performed with the 260 evaluable patients (92.5% of all of the randomized patients).

The values reported as interquartile ranges (IQRs) correspond to the values of the first and third quartiles of the distribution of continuous variables. Comparisons of proportions were made using the standard χ^2 test for heterogeneity. Median values were compared using the Wilcoxon 2-sample test. The time to the resumption of menstrual activity was calculated as the interval between the end of chemotherapy and the time of resumption; the observation times of the patients who did not resume menstruation during follow-up were censored at the time of the last study visit. The median time to the resumption of menstrual activity was estimated using Kaplan-Meier survival analysis and confidence intervals, according to the methods of Brookmeyer and Crowley.[20] The effects of triptorelin treatment, age, and type of chemotherapy on the development of early menopause were investigated using multivariate logistic regression analysis in which age was categorized by quintiles.

To evaluate the effect of the treatment in the presence and absence of tamoxifen, a post hoc subgroup analysis was performed according to hormone receptor status, using imputed values for missing data.

Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). All reported P values are 2-sided; $P < .05$ was considered statistically significant.

RESULTS

The study enrolled 282 patients between October 24, 2003, and January 14, 2008. One patient allocated to receive chemotherapy alone was mistakenly randomized a second time but considered only once, leaving 281 patients for the analyses. TABLE 1 summarizes their baseline characteristics. Twenty-one patients were considered unevaluable: 12 in the chemotherapy-alone group (6 because they did not receive chemotherapy and 6 because they were lost to follow-up before the planned 12-month evaluation) and 9 in the chemotherapy plus triptorelin group (2 because they did not receive chemotherapy and 7 because they were lost to follow-up). Figure 1 shows the trial profile.

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Table 1. Baseline Patient and Tumor Characteristics by Study Group

Characteristic	No. (%) Chemotherapy Alone (n = 133)	No. (%) Chemotherapy + Triptorelin (n = 148)
Age, median (range), y	39 (25-45)	39 (24-45)
Age ≤40 y	88 (66)	99 (67)
Full-term pregnancies before breast cancer diagnosis		
0	51 (38)	49 (33)
≥1	78 (58)	96 (65)
Unknown	4 (4)	3 (2)
Tumor size		
pT1	75 (56)	90 (61)
pT2	51 (38)	51 (34)
pT3-4	3 (2)	5 (3)
Unknown	4 (3)	2 (1)
Axillary nodes		
pN0	67 (50)	61 (41)
pN1	44 (33)	58 (39)
pN2	18 (14)	27 (18)
Unknown	4 (3)	2 (1)
Tumor grade		
G1	5 (4)	15 (10)
G2	57 (43)	50 (34)
G3	60 (45)	73 (49)
Unknown	11 (8)	10 (7)
Hormone receptor status		
ER-positive, PR-positive, or both	109 (82)	117 (79)
ER-negative and PR-negative	22 (17)	29 (20)
Unknown	2 (1)	2 (1)
Serum FSH, median (IQR), mIU/mL[a]	5.01 (3.66-7.35)	5.45 (3.79-8.08)
Serum estradiol, median (IQR), pg/mL[b]	87 (56-124)	89 (44-156)

Abbreviations: ER, estrogen receptor; FSH, follicle-stimulating hormone; IQR, interquartile range; PR, progesterone receptor.
SI conversion factor: To convert estradiol values to pmol/L, multiply by 3.671.
[a] Evaluated in 112 patients treated with chemotherapy alone and 128 treated with chemotherapy plus triptorelin.
[b] Evaluated in 106 patients treated with chemotherapy alone and 112 treated with chemotherapy plus triptorelin.

Table 2. Multivariate Analysis: Effects of Temporary Ovarian Suppression, Age, and Type of Chemotherapy on Development of Early Menopause (N = 281)[a]

Variable	No.	OR (95% CI)	*P* Value
Random assignment			
Chemotherapy alone	133	1 [Reference]	<.001
Chemotherapy + triptorelin	148	0.28 (0.14-0.59)	
Patient age, y			
≤34	59	1 [Reference]	.47
35-37	56	0.47 (0.16-1.39)	
38-40	72	1.05 (0.41-2.68)	
41-42	44	0.81 (0.28-2.34)	
43-45	50	0.62 (0.20-1.95)	
CMF-containing chemotherapy			
No	269	1 [Reference]	.25
Yes	12	0.28 (0.03-2.38)	
Taxane-containing chemotherapy			
No	130	1 [Reference]	.11
Yes	151	0.57 (0.29-1.13)	

Abbreviations: CI, confidence interval; CMF, cyclophospamide, methotrexate, and fluorouracil; OR, odds ratio.
[a] Early menopause was defined as no resumption of menstrual activity and postmenopausal or unknown levels of follicle-stimulating hormone and estradiol.

The intention-to-treat analysis including all randomized patients and using imputed values for missing data showed a rate of early menopause of 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group, an absolute difference of −17% (95% confidence interval [CI], −26% to −7.9%; $P<.001$). The number needed to treat (ie, the number of patients that need to be treated with triptorelin to prevent early menopause in 1 patient) was 6.

Multivariate analysis showed that only treatment with triptorelin was associated with a significant reduction of the risk of developing early menopause (odds ratio [OR], 0.28; 95% CI, 0.14 to 0.59; $P<.001$); patient age and the type of chemotherapy (taxane-containing or CMF-containing) did not significantly affect the risk (Table 2).

Secondary analyses were performed with 260 evaluable patients (92.5% of the randomized patients), 121 treated with chemotherapy alone and 139 with chemotherapy plus triptorelin. Early menopause occurred in 31 patients (25.6%) in the chemotherapy-alone group and in 11 (7.9%) in the chemotherapy plus triptorelin group, an absolute difference of −18% (95% CI, −27% to −8%; $P<.001$).

Resumption of menses (regardless of the levels of FSH and E_2) was observed in 60 patients in the chemotherapy-alone group (49.6%) and in 88 in the chemotherapy plus triptorelin group (63.3%;), an absolute difference of 13.7% (95% CI, 1.0% to 26.5%; $P=.03$). Premenopausal levels of E_2 without the resumption of menses were observed in 18 patients (14.8%) and 26 patients (18.7%), respectively. A summary of the ovarian function outcomes by treatment group is reported in eTable 1, available at http://www.jama.com.

The median time to the resumption of menstrual activity was 6.7 months in the patients treated with chemotherapy plus triptorelin and was not reached in the patients treated with chemotherapy alone (Figure 2).

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During the 12 months of follow-up, 83 of 121 patients (68%) in the chemotherapy-alone group and 104 of 139 (75%) in the chemotherapy plus triptorelin group underwent at least 1 FSH evaluation (at one of the planned dates of evaluation, ie, 3, 6, 9, or 12 months after the last cycle of chemotherapy): the minimum median FSH values were 5.8 (IQR, 1.8-32.1) mIU/mL and 8.0 (IQR, 3.5-20.7) mIU/mL, respectively (P=.68). Eighty patients in the chemotherapy-alone group (66%) and 98 in the chemotherapy plus triptorelin group (70%) underwent at least 1 evaluation of E_2: the maximum median E_2 values were 27.5 (IQR, 19-109) pg/mL (to convert to pmol/L, multiply by 3.671) and 49 (IQR, 20-129) pg/mL, respectively (P=.08).

In the post hoc subgroup analysis performed according to hormone receptor status, absolute differences in the occurrence of early menopause were –27.9% (95% CI, –47.4% to –8.4%; P=.005) among 51 hormone receptor–negative patients who did not receive tamoxifen (22 treated with chemotherapy alone and 29 treated with chemotherapy plus triptorelin) and –14.9% (95% CI, –25.1% to –4.7%; P=.004) among 226 hormone receptor–positive patients who received tamoxifen (109 treated with chemotherapy alone and 117 treated with chemotherapy plus triptorelin). The resumption of menses was observed in 74% and 93% of hormone receptor–negative patients treated with chemotherapy alone and with chemotherapy plus triptorelin, respectively, and in 44% and 55% of hormone receptor–positive patients treated with chemotherapy alone and chemotherapy plus triptorelin, respectively.

Chemotherapy was never started in 6 patients randomized to receive chemotherapy alone (4.5%) and in 2 randomized to receive chemotherapy plus triptorelin (1.4%). Chemotherapy was administered as adjuvant treatment to 117 patients in the chemotherapy-alone group (88%) and 133 in the chemotherapy plus triptorelin group (90%) and as neoadjuvant treatment to 10 patients (7%) and 13 patients (9%), respectively.

The median duration of chemotherapy was 16.9 (IQR, 15.0-21.3) weeks in the chemotherapy-alone group and 17.8 (IQR, 15.0-21.3) weeks in the chemotherapy plus triptorelin group (TABLE 3).

Anthracycline-based chemotherapy, without CMF or taxanes, was administered to 57 patients receiving chemotherapy alone (42.9%) and 56 receiving chemotherapy plus triptorelin (37.8%); anthracycline and taxane–based chemotherapy was administered to 62 (46.6%) and 86 (58.1%), respectively; and CMF-containing regimens (with or without anthracyclines and taxanes) were administered to 8 (6.0%) and 4 (2.7%), respectively. Details of the chemotherapy regimens are shown in eTable 2.

The median number of administered chemotherapy cycles was 6 (IQR, 6-8) in both groups. The median cumulative doses of cyclophosphamide, anthracyclines, and taxanes were simi-

Figure 2. Time to Resumption of Menstrual Activity

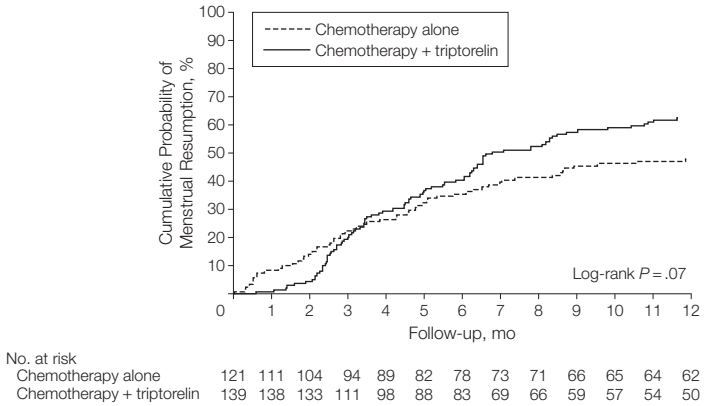

Table 3. Treatment Adherence by Study Group

Treatment	Chemotherapy Alone (n = 133)	Chemotherapy + Triptorelin (n = 148)
Type of chemotherapy, No. (%)		
Not begun	6 (4.5)	2 (1.4)
Anthracycline-based	57 (42.9)	56 (37.8)
Anthracycline and taxane–based	62 (46.6)	86 (58.1)
CMF-based	8 (6.0)	4 (2.7)
Chemotherapy administered, No. (%)		
Adjuvant treatment	117 (88.0)	133 (89.9)
Neoadjuvant treatment	10 (7.5)	13 (8.8)
No. of chemotherapy cycles, median (IQR)	6 (6-8)	6 (6-8)
Duration of chemotherapy, median (IQR), wk	16.9 (15.0-21.3)	17.8 (15.0-21.3)
Cumulative chemotherapy dose, median (IQR), mg/m^2		
Cyclophosphamide	4008 (3624-5550)	4080 (3697-5400)
Anthracyclines	610 (544-762)	600 (540-744)
Paclitaxel	1160 (1048-1440)	1120 (1040-1280)
Docetaxel	565 (435-656)	575 (480-680)
Chemotherapy completed as planned, No. (%)	121 (91.0)	143 (96.6)
No. of triptorelin administrations, median (IQR)	NA	5 (5-6)
Triptorelin treatment completed as planned, No. (%)	NA	142 (95.9)
Tamoxifen at end of chemotherapy, No. (%)	96 (72.2)	100 (67.6)

Abbreviations: CMF, cyclophosphamide, methotrexate, and fluorouracil; IQR, interquartile range; NA, not applicable.

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lar in the 2 groups (Table 3). Table 3 also summarizes treatment adherence. Toxicity was evaluated only in the patients who completed at least 1 cycle of chemotherapy (127 receiving chemotherapy alone and 147 receiving chemotherapy plus triptorelin). There was no difference in the incidence of selected toxicities that may have been partly related to the use of triptorelin (eTable 3).

At the time of the last annual follow-up (October 28, 2010), 1 full-term pregnancy in the chemotherapy-alone group and 3 pregnancies (1 full-term, 1 premature delivery, and 1 voluntary abortion) in the chemotherapy plus triptorelin group were reported. Twenty-seven recurrences (13 in the chemotherapy-alone group, 14 in the chemotherapy plus triptorelin group) and 11 deaths (3 in the chemotherapy-alone group, 8 in the chemotherapy plus triptorelin group) were reported.

COMMENT

The results of the PROMISE-GIM6 study show that the administration of the GnRH analogue triptorelin, before and during chemotherapy, led to a 17% absolute reduction in the occurrence of early menopause in premenopausal patients with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. Early menopause (defined as no resumption of menses and postmenopausal or unknown levels of FSH and E_2, 12 months after the end of chemotherapy) occurred in 25.9% of the patients treated with chemotherapy alone and 8.9% of those treated with chemotherapy plus triptorelin. That the incidence of early menopause in the control group was lower than the expected 60%[19] is probably attributable to the difference between the definition of amenorrhea in previous studies of adjuvant chemotherapy (ie, 3-6 months without menstrual periods) and our definition of early menopause. When a long duration without menses is considered (ie, ≥12 months after the end of chemotherapy), the rate of chemotherapy-induced amenorrhea decreases to 15% in patients younger than 40 years.[21] Moreover, a proportion of patients retain their ovarian function, as indicated by FSH and E_2 premenopausal levels, despite the absence of menstrual activity.[22] In our study, this proportion accounts for 25% of patients treated with chemotherapy alone and for 29% of those treated with chemotherapy plus triptorelin (eTable 1).

The resumption of menses was higher in hormone receptor–negative patients who did not receive tamoxifen (74% and 93% in patients treated with chemotherapy alone and chemotherapy plus triptorelin, respectively) than in hormone receptor–positive patients who received tamoxifen starting from the end of chemotherapy (44% and 55% in patients treated with chemotherapy alone and chemotherapy plus triptorelin, respectively). These data confirmed that the administration of tamoxifen after chemotherapy is associated with an increased incidence of amenorrhea.[23]

The PROMISE-GIM6 study is so far the largest phase 3 study to evaluate the role of a GnRH analogue in preserving ovarian function during chemotherapy for breast cancer, but the results from 4 previous smaller phase 3 studies are available. Badawy et al[24] randomized 78 patients aged 18 to 40 with early-stage breast cancer years to receive chemotherapy alone or in combination with goserelin and found that the rate of premature ovarian failure in the 2 groups was 67% and 11%, respectively. Gerber et al[25] randomized 60 estrogen receptor–negative patients with breast cancer to anthracycline and taxane–containing chemotherapy alone or in combination with goserelin and found that 57% and 70%, respectively, of the patients in the 2 groups satisfied the primary end point of the resumption of normal ovarian function 6 months after the last cycle of chemotherapy, although the difference was not statistically significant. A third phase 3 study[26] found no difference in ovarian protection between patients randomized to chemotherapy alone or combined with goserelin, but the results are still preliminary. Last, Ismail-Khan et al[27] found no difference in menses resumption in 49 patients with breast cancer treated with chemotherapy alone or combined with triptorelin. Furthermore, a systematic review and meta-analysis of 3 randomized and 8 nonrandomized prospective controlled studies, 10 of which involved patients with diseases other than breast cancer, showed that GnRH agonist cotreatment during chemotherapy is associated with a greater likelihood of maintaining ovarian function after treatment (OR, 10.57; 95% CI, 5.22 to 21.39).[28] However, when only the randomized studies were considered, there was no statistically significant difference (OR, 5.76; 95% CI, 0.47 to 71.03), and so the overall result seems to have been influenced by the nonrandomized studies (OR, 13.00; 95% CI, 7.37-22.92).

The World Health Organization defines menopause as no menstrual periods for 12 months.[29] We used this definition and used the last chemotherapy cycle as the start of the 12-month period. Although very young women can resume menstruating (and presumably ovarian function) after more than 1 year of chemotherapy-induced amenorrhea, most who do not resume menstruating in the first year after the end of chemotherapy are likely to lose their ovarian function completely and permanently.[8]

Because menstrual activity is not the best surrogate of ovarian function, FSH and E_2 measurements may be more suitable, but they can be difficult to obtain from all the patients taking part in multicenter clinical trials; in our case, FSH and E_2 levels were not evaluated in nearly 30% of patients. Consequently, early menopause was defined as the absence of menstrual activity for at least 12 months with postmenopausal or unknown levels of FSH and E_2.

The main weakness of studies evaluating the role of GnRH analogues in pre-

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serving ovarian function is the lack of data concerning the long-term maintenance of ovarian function; published data concerning the preservation of fertility are similarly lacking. In our study only 4 pregnancies were recorded so far, 1 in the chemotherapy-alone group and 3 in the chemotherapy plus triptorelin group. Long-term follow-up is necessary to assess these end points.

The mechanisms of action by means of which of GnRH analogues preserve ovarian function are not fully understood but may include the interruption of FSH secretion, a decrease in utero-ovarian perfusion, the activation of GnRH receptors, the up-regulation of intragonadal antiapoptotic molecules such as sphingosine-I-phosphate, or the protection of undifferentiated germline stem cells.[30]

Concerns about the administration of GnRH analogues before and during chemotherapy include potential interactions with chemotherapy and the possible detrimental effect of the lack of chemotherapy-induced amenorrhea on the outcome. However, because data from randomized studies[31-33] do not show any difference in the outcomes of patients undergoing chemotherapy alone or with concurrent ovarian suppression, there does not seem to be a risk of interactions. In relation to the second concern, evidence suggests that chemotherapy-induced amenorrhea is associated with an improved prognosis in patients with early-stage breast cancer,[34,35] and it can be hypothesized that the resumption of ovarian function with consequent estrogen production may adversely affect survival, at least in the case of patients with hormone-sensitive tumors. We addressed this reasonable concern by readministering GnRH analogue at the time ovarian function was resumed and continuing administration for at least 2 years to ensure the usually accepted time of therapeutic suppression.[36] Moreover, standard antiestrogen treatment in hormone receptor–positive patients was guaranteed by the administration of tamoxifen at the end of chemotherapy.

Methods of preserving fertility other than by means of ovarian suppression with GnRH analogues include embryo cryopreservation via in vitro fertilization and oocyte or ovarian tissue cryopreservation. In comparison with cryopreservation strategies, GnRH analogue–induced ovarian suppression has the advantages that it does not require a male partner, is simple to administer, does not require delaying chemotherapy, and is less invasive and less expensive. Moreover, the ovarian suppression induced by GnRH analogues preserves entire ovarian function and not just fertility. For women who have had children by the time they develop breast cancer (which was the case in more than 60% of our patient population), preventing early menopause may be more important than preserving fertility. On the other hand, in women without children, it has been shown that embryo cryopreservation is relatively effective in achieving pregnancy,[12] whereas it has not yet been confirmed that GnRH analogue–induced ovarian suppression is effective in preserving fertility. Last, induced ovarian suppression and cryopreservation are not mutually exclusive but can be used together to increase the probability of preserving fertility, preserving entire ovarian function, or both in young patients with breast cancer who are candidates for chemotherapy.

In conclusion, our results suggest that temporarily suppressing ovarian function by administering triptorelin reduces the incidence of chemotherapy-induced early menopause. This treatment can therefore be offered to premenopausal patients with breast cancer who wish to decrease the risk of permanent ovarian failure associated with chemotherapy.

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