Original Investigation

Ovarian Suppression With Triptorelin During Adjuvant Breast Cancer Chemotherapy and Long-term Ovarian Function, Pregnancies, and Disease-Free Survival
A Randomized Clinical Trial

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IMPORTANCE Whether the administration of luteinizing hormone–releasing hormone analogues (LHRHa) during chemotherapy is a reliable strategy to preserve ovarian function is controversial owing to both the lack of data on long-term ovarian function and pregnancies and the safety concerns about the potential negative interactions between endocrine therapy and chemotherapy.

OBJECTIVE To evaluate long-term results of LHRHa-induced ovarian suppression during breast cancer chemotherapy.

DESIGN, SETTING, AND PARTICIPANTS Parallel, randomized, open-label, phase 3 superiority trial conducted at 16 Italian sites. Between October 2003 and January 2008, 281 premenopausal women with stage I to III hormone receptor–positive or hormone receptor–negative breast cancer were enrolled. Last annual follow-up was June 3, 2014.

INTERVENTIONS Patients were randomized to receive adjuvant or neoadjuvant chemotherapy alone (control group) or chemotherapy plus triptorelin (LHRHa group).

MAIN OUTCOMES AND MEASURES The primary planned end point was incidence of chemotherapy-induced early menopause. Post hoc end points were long-term ovarian function (evaluated by yearly assessment of menstrual activity and defined as resumed by the occurrence of at least 1 menstrual cycle), pregnancies, and disease-free survival (DFS).

RESULTS A total of 281 women (median age, 39 [range, 24-45] years) were randomized. Median follow-up was 7.3 years (interquartile range, 6.3-8.2 years). The 5-year cumulative incidence estimate of menstrual resumption was 72.6% (95% CI, 65.7%-80.3%) among the 148 patients in the LHRHa group and 64.0% (95% CI, 56.2%-72.8%) among the 133 patients in the control group (hazard ratio [HR], 1.28 [95% CI, 0.98-1.68]; $P = .07$; age-adjusted HR, 1.48 [95% CI, 1.12-1.95]; $P = .006$). Eight pregnancies (5-year cumulative incidence estimate of pregnancy, 2.1% [95% CI, 0.7%-6.3%]) occurred in the LHRHa group and 3 (5-year cumulative incidence estimate of pregnancy, 1.6% [95% CI, 0.4%-6.2%]) in the control group (HR, 2.56 [95% CI, 0.68-9.60]; $P = .14$; age-adjusted HR, 2.40 [95% CI, 0.62-9.22]; $P = .20$). Five-year DFS was 80.5% (95% CI, 73.1%-86.1%) in the LHRHa group and 83.7% (95% CI, 76.1%-89.1%) in the control group (LHRHa vs control: HR, 1.17 [95% CI, 0.72-1.92]; $P = .52$).

CONCLUSIONS AND RELEVANCE Among premenopausal women with either hormone receptor–positive or hormone receptor–negative breast cancer, concurrent administration of triptorelin and chemotherapy, compared with chemotherapy alone, was associated with higher long-term probability of ovarian function recovery, without a statistically significant difference in pregnancy rate. There was no statistically significant difference in DFS for women assigned to triptorelin and those assigned to chemotherapy alone, although study power was limited.

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The majority of young women with invasive breast cancer are candidates to receive both chemotherapy and endocrine therapy.[1] Ovarian function loss and impaired fertility are possible consequences of anticancer treatments and have a negative impact on global health of young survivors of breast cancer.[2] Moreover, fertility concerns can affect treatment decisions of young patients with breast cancer.[3]

According to the American Society of Clinical Oncology and European Society for Medical Oncology guidelines, embryo or oocyte cryopreservation is the standard procedure for fertility preservation in patients with cancer.[4,5] No proven methods for preservation of ovarian function are yet available. The administration of luteinizing hormone–releasing hormone analogues (LHRHa) during chemotherapy is considered an experimental strategy to preserve ovarian function and fertility, mainly because of the lack of data on long-term ovarian function and pregnancies.[4,5] Moreover, owing to both the possible detrimental effect of the lack of chemotherapy-induced amenorrhea on prognosis[6] and data suggesting potential antagonism with concurrent administration of antiestrogen therapy and chemotherapy,[7-9] there are concerns as to whether the concomitant use of LHRHa and chemotherapy in patients with endocrine-sensitive breast cancer compromises disease-free survival (DFS).[10]

Previous results of the randomized phase 3 PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: a Study in Early Breast Cancer Patients—Gruppo Italiano Mammella 6) study showed that temporary ovarian suppression during chemotherapy induced by the LHRHa triptorelin significantly reduced the occurrence of treatment-related early menopause (defined as no resumption of menstrual activity and postmenopausal levels of follicle-stimulating hormone and estradiol for 1 year after the last cycle of chemotherapy) from 25.9% to 8.9% (odds ratio [OR], 0.28 [95% CI, 0.14-0.59]; $P < .001$) without increasing the incidence of LHRHa-related toxicities, such as hot flushes, headache, sweating, mood modification, and vaginal dryness.[11] In the current analysis, we present long-term outcome results, focusing on long-term ovarian function, pregnancies, and DFS.

Methods

Study Design and Patients

Details of the PROMISE-GIM6 study design and results for primary outcomes have been previously reported.[11] Briefly, the study was a multicenter, randomized, open-label, phase 3 superiority trial aiming to address the effect of temporary ovarian suppression obtained by administering the LHRHa triptorelin before and during chemotherapy as a strategy to reduce the occurrence of early menopause in young women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. The trial protocol is available in Supplement 1.

Eligible patients were women aged 18 to 45 years with stage I to III breast cancer who were premenopausal at the time of diagnosis. Premenopausal status was defined at baseline as presence of active menstrual cycles or normal menses during the 6 weeks before the start of chemotherapy. Patients with either hormone receptor–positive or hormone receptor–negative tumors were eligible. Tumors were defined as hormone receptor–positive by a finding of at least 1% of positive cells for estrogen receptor, progesterone receptor, or both, evaluated by immunohistochemistry analysis.

The study was conducted in 16 Italian centers by the Gruppo Italiano Mammella (GIM) and was approved by ethics committees of all participating institutions. Written informed consent was obtained from all patients before study entry.

Randomization and Blinding

Eligible patients were randomly allocated to receive chemotherapy alone (control group) or chemotherapy plus the LHRHa triptorelin (LHRHa group). Randomization was performed centrally by faxing the Clinical Trials Unit of the National Institute for Cancer Research in Genoa (Italy).[11] Randomization lists were stratified by center and were prepared with the use of permuted blocks of different sizes, with a 1:1 allocation ratio. All data were collected centrally at the clinical trials unit of the National Institute for Cancer Research in Genoa (Italy).

Study Procedures

In patients randomized to receive LHRHa, triptorelin (3.75 mg) was administered intramuscularly at least 1 week before chemotherapy and then every 4 weeks for the duration of chemotherapy. Patients received chemotherapy according to one of the following regimens: anthracycline plus taxane-based, anthracycline-based, or CMF (cyclophosphamide-methotrexate-fluorouracil)-based.[11]

Women with hormone receptor–positive disease received adjuvant endocrine therapy for 5 years starting from the end of chemotherapy. In both study groups, patients who resumed their ovarian function during the 12-month period of observation after the end of chemotherapy or at any time during the following 5 years of follow-up were allowed to receive LHRHa for at least 2 years as part of their endocrine treatment.

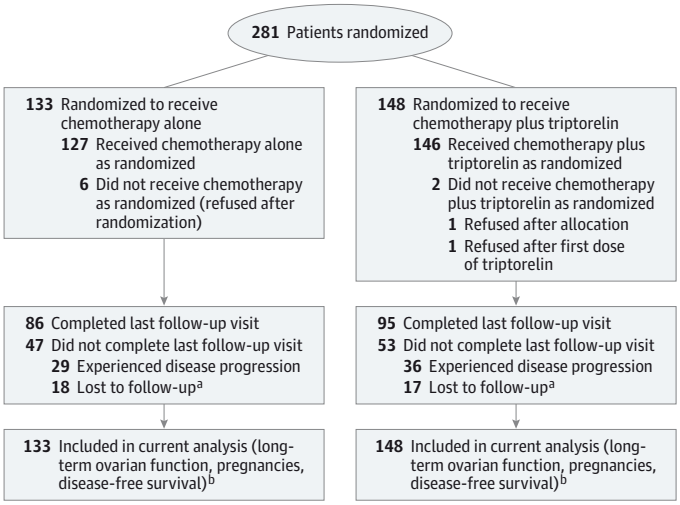
Radiation therapy after completion of chemotherapy was mandatory for patients who underwent a lumpectomy. For patients who underwent a mastectomy, radiation therapy was performed according to the guidelines of each participating institution.

Study Objectives and End Points

Details and results on the primary objectives (ie, chemotherapy-induced early menopause and adverse events) have been previously reported.[11] The aim of the present post hoc extension of the original study design was to investigate the association between treatment groups and long-term outcomes (ie, long-term ovarian function, pregnancies, and DFS).

Long-term ovarian function was evaluated by yearly assessment of menstrual activity at the time of clinic visits. Ovarian function was defined as having resumed based on the occurrence of at least 1 menstrual cycle. Pregnancies were evaluated during annual follow-up visits, and patients reporting no pregnancy were asked about the reasons (eg, pregnancy not desired or failed attempt). Patients who reported at-term or preterm delivery, miscarriage, and/or induced abortion

Figure 1. The PROMISE-GIM6 Trial Profile



The number of patients screened for eligibility, the number of patients excluded, and the reasons for exclusion were not recorded.

[a] Patients without clinical information after December 31, 2012.

[b] Disease-free survival interval was computed from the date of randomization to the date of local recurrence, distant metastases, contralateral or ipsilateral breast tumor, second primary malignancy, or death from any cause, whichever occurred first. Observation times of patients without event were censored on the date of last contact.

were considered as having a pregnancy. DFS events were defined by the occurrence of one of the following: local recurrence, distant metastases, contralateral or ipsilateral breast tumor, second primary malignancy, or death from any cause.

Systematic data collection was based on the annual follow-up visit, including physical examination and mammography, performed by each patient according to clinical practice.

Statistical Analysis

Sample size calculations and statistical assumptions for the primary objective of the study were previously described.[11] Briefly, the trial was designed to detect a 20% absolute reduction (from 60% to 40%) in the incidence of early menopause in the experimental group, with a power of 90% and a 2-sided α error of 5%. Analyses on long-term ovarian function, pregnancies, and DFS were not preplanned in the study protocol, and the power of the statistical analyses for these end points were not prespecified; thus, results are exploratory.

Time to recovery of ovarian function was defined as the interval from the randomization to the occurrence of menstrual resumption. Five-year cumulative incidence of menstrual resumption included patients who resumed menses at any time (ie, within or beyond 12 months after the end of chemotherapy). Time to pregnancy was the interval from randomization to the start of the first pregnancy, independent of its outcome. Only the first pregnancy for each patient was taken into account. DFS interval was computed from the date of randomization to the date of the first occurrence of a DFS event. For each end point, observation times of patients without the event were censored on the date of their last contact. The last annual follow-up visit recorded was performed on June 3, 2014. An administrative censoring at the cut-off date of December 31, 2013, was applied to all time-to-event analyses. No event was observed between the cutoff date and the last annual follow-up visit for each analyzed outcome.

All reported statistical analyses were based on the study intention-to-treat population. The median period of follow-up and its interquartile range were calculated for the entire study cohort according to the reverse Kaplan-Meier method. The cumulative incidence of menstrual resumption and pregnancy were estimated accounting for disease recurrence, second tumor, and death from any cause as competing risk events. DFS probability was computed according to the Kaplan-Meier method. The CIs of survival time probabilities were calculated according to the log-log method. As estimates of treatment effect, unadjusted and adjusted hazard ratios (HRs) with 95% CIs were calculated with the Fine and Gray model in the presence of competing risks and with the Cox proportional hazards model otherwise. An HR greater than 1 indicates that the use of LHRHa increased the probability of developing an event (ie, resumption of menstrual activity, pregnancy, DFS event). In the multivariable model, because of the limited number of analyzed events, only the covariates with known prognostic association (ie, tumor size, nodal status, hormone receptor status) were included. Multivariable analyses were performed after single imputation of missing values in 7 cases. The proportional hazards assumption was checked assessing the Schoenfeld plot.

Subgroup analyses of DFS were performed by means of an interaction test to determine the consistency of the treatment effect on the outcome according to hormone receptor status (positive and negative). The likelihood ratio test was used to test the statistical significance of all coefficients. No adjustment for multiple testing was applied. Because the study was conducted in 16 centers, all the analyses were repeated after adjustment for clustering (eResults in Supplement 2).

All statistical tests were 2-sided, and *P* values of .05 or less were considered statistically significant. Statistical analyses were performed (L. B.) using SAS 9.2 (SAS Institute).

Results

Between October 24, 2003, and January 14, 2008, a total of 281 patients (median age, 39 [range, 24-45] years) were enrolled in the study. **Figure 1** shows the trial profile. At the time

Table 1. Baseline Patient and Tumor Characteristics and Treatments Administered by Study Group

Characteristic	No. (%) Control Group (n = 133)	LHRHa Group (n = 148)
Age, median (range), y	39 (25-45)	39 (24-45)
Age distribution, y		
<30	5 (3.8)	8 (5.4)
30-34	23 (17.3)	23 (15.5)
35-39	45 (33.8)	46 (31.1)
40-44	57 (42.9)	66 (44.6)
45-49	3 (2.3)	5 (3.4)
Full-term pregnancies before breast cancer diagnosis, No.		
0	51 (38.3)	49 (33.1)
≥1	78 (58.6)	96 (64.9)
Unknown	4 (3.0)	3 (2.0)
Tumor size (T)		
pT1	75 (56.4)	90 (60.8)
pT2	51 (38.3)	51 (34.5)
pT3-4	3 (2.3)	5 (3.4)
Unknown	4 (3.0)	2 (1.4)
Axillary nodes (N)		
pN0	67 (50.4)	61 (41.2)
pN1	44 (33.1)	58 (39.2)
pN2	18 (13.5)	27 (18.2)
Unknown	4 (3.0)	2 (1.4)
Tumor grade (G)		
G1	5 (3.8)	15 (10.1)
G2	57 (42.9)	50 (33.8)
G3	60 (45.1)	73 (49.3)
Unknown	11 (8.3)	10 (6.8)
Hormone receptor status		
ER-negative and PR-negative	22 (16.5)	29 (19.6)
ER-positive, PR-positive, or both	109 (82.0)	117 (79.1)
Unknown	2 (1.5)	2 (1.4)
Timing of chemotherapy		
Adjuvant therapy	117 (88.0)	133 (89.9)
Neoadjuvant therapy	10 (7.5)	13 (8.8)
Not begun	6 (4.5)	2 (1.4)
Type of chemotherapy		
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)
Cumulative cyclophosphamide dose, median (IQR), mg/m^2	4008 (3624-5550)	4080 (3697-5400)
Duration of chemotherapy, median (IQR), wk	16.9 (15.0-21.3)	17.8 (15.0-21.3)
Treatment completed as planned		
Chemotherapy	121 (91.0)	143 (96.6)
LHRHa during chemotherapy	NA	142 (95.9)
Type of adjuvant endocrine therapy in hormone receptor–positive patients[a]		
No treatment	6 (5.5)	10 (8.6)
LHRHa alone	3 (2.8)	4 (3.4)
LHRHa + tamoxifen	65 (59.6)	65 (55.6)
LHRHa + aromatase inhibitor	11 (10.1)	10 (8.6)
Tamoxifen	22 (20.2)	28 (23.9)
Tamoxifen followed by aromatase inhibitor	2 (1.8)	0 (0.0)
Duration of endocrine therapy, median (IQR), y	5.00 (4.78-5.03)	5.00 (4.96-5.10)
Duration of adjuvant LHRHa, median (IQR), y	4.10 (2.08-5.04)	4.08 (2.06-4.92)

Abbreviations: CMF, cyclophosphamide, methotrexate, fluorouracil; ER, estrogen receptor; IQR, interquartile range; LHRHa, luteinizing hormone–releasing hormone analogues; NA, not applicable; PR, progesterone receptor.

[a] Percentages calculated on the total number of patients with hormone receptor–positive disease (117 in the LHRHa group and 109 in the control group).

of the current analysis, a total of 35 patients (12.5%) were lost to follow-up, 17 of 148 (11.5%) in the LHRHa group and 18 of 133 (13.5%) in the control group. At the study cutoff date, December 31, 2013, median follow-up time was 7.3 years (interquartile range, 6.3-8.2 years).

Baseline patient and tumor characteristics were similar between treatment groups, as well as chemotherapy adherence (**Table 1**). A total of 226 patients (80.4%) had hormone receptor–positive tumors, and the majority of them (92.9%) received adjuvant endocrine therapy after chemotherapy (Table 1). Among 226 women with hormone receptor–positive disease, 158 (69.9%) received adjuvant LHRHa, 79 of 117 (67.5%) in the LHRHa group and 79 of 109 (72.5%) in the control group (Table 1).

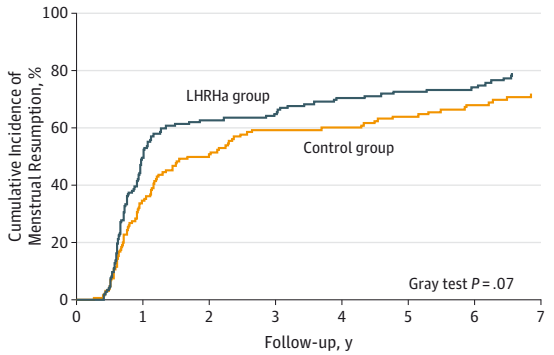
Long-term Ovarian Function

Menstrual resumption at any time occurred in 116 of 148 patients (incidence rate per 100 person-years, 32.4 [95% CI, 26.7-38.8]) in the LHRHa group and in 96 of 133 patients (incidence rate per 100 person-years, 26.0 [95% CI, 21.0-31.7]) in the control group.

The 5-year cumulative incidence estimate of menstrual resumption was 72.6% (95% CI, 65.7%-80.3%) in the LHRHa group and 64.0% (95% CI, 56.2%-72.8%) in the control group (HR, 1.28 [95% CI, 0.98-1.68]) (P = .07) (**Figure 2**). The age-adjusted estimate of HR was 1.48 (95% CI, 1.12-1.95; P = .006).

Among patients with hormone receptor–positive tumors, the 5-year cumulative incidence estimate of menstrual resumption was 69.3% (95% CI, 61.4%-78.2%) in the LHRHa group and 60.7% (95% CI, 52.2%-70.7%) in the control group (HR, 1.25 [95% CI, 0.93-1.68]). Among patients in the hormone receptor–negative subgroup, the 5-year cumulative

Figure 2. Cumulative Incidence Estimate of Menstrual Resumption in the Treatment Groups



No. at risk

Control group	133	82	61	43	42	35	26	16
LHRHa group	148	73	49	46	38	32	28	14

LHRHa indicates luteinizing hormone–releasing hormone analogues.

incidence estimate of menstrual resumption was 86.2% (95% CI, 74.5%-99.7%) in the LHRHa group and 81.0% (95% CI, 65.8%-99.6%) in the control group (HR, 1.41 [95% CI, 0.76-2.65]) (P = .73 for interaction). The age-adjusted estimates of HR were 1.46 (95% CI, 1.07-2.00) among women with hormone receptor-positive tumors and and 1.44 (95% CI, 0.75-2.76) among those with hormone receptor-negative tumors (P = .97 for interaction).

Pregnancies

At the censoring date, 8 pregnancies (incidence rate per 100 person-years, 0.9 [95% CI, 0.4-1.8]) occurred among the 148 patients enrolled in the LHRHa group and 3 pregnancies (incidence rate per 100 person-years, 0.4 [95% CI, 0.1-1.1]) occurred among the 133 women in the control group. The 5-year cumulative incidence estimate of pregnancy was 2.1% (95% CI, 0.7%-6.3%) in the LHRHa group and 1.6% (95% CI, 0.4%-6.2%) in the control group (HR, 2.56 [95% CI, 0.68-9.6]; P = .14). The age-adjusted estimate of HR was 2.40 (95% CI, 0.62-9.22; P = .20).

Among the 5 pregnancies occurring more than 5 years after the end of chemotherapy, 4 occurred in the LHRHa group and 1 in the control group (eFigure 1 in Supplement 2).

Of 11 pregnancies, 4 occurred in women with hormone receptor-positive tumors (4 [3.4%] among the 117 patients in the LHRHa group and 0 [0.0%] among the 109 women in the control group) and 7 in patients with hormone receptor-negative tumors (4 [13.8%] among the 29 patients in the LHRHa group and 3 [13.6%] among the 22 women in the control group).

When the analysis was performed by excluding patients who declared no attempt at pregnancy (43 patients [29.1%] in the LHRHa group and 42 patients [31.6%] in the control group), the HR was 2.48 (95% CI, 0.66-9.29) (P = .18).

None of the 8 offspring were born with congenital abnormalities. One preterm delivery was observed in the LHRHa group. eTable 1 in Supplement 2 shows pregnancy outcomes in the 2 groups.

The interval from randomization to first pregnancy ranged between 1.0 and 6.6 years (6.2-6.6 years among women with hormone receptor-positive tumors and 1.0-6.5 years among those with hormone receptor-negative tumors).

Disease-Free Survival

At the study cutoff date, 65 events were observed in 281 patients (23.1%), 36 of 148 (24.3%) in the LHRHa group and 29 of 133 (21.8%) in the control group (eTable 2 in Supplement 2). Five-year DFS was 80.5% (95% CI, 73.1%-86.1%) in the LHRHa group and 83.7% (95% CI, 76.1%-89.1%) in the control group (**Figure 3**). The crude HR for DFS for the comparison of the LHRHa group vs the control group was 1.17 (95% CI, 0.72-1.92) (P = .52).

In patients with hormone receptor-positive disease, 5-year DFS was 85.1% (95% CI, 77%.2-90.5%) in the LHRHa group and 85.2% (95% CI, 77.0%-90.7%) in the control group (eFigure 2 in Supplement 2). In patients with hormone receptor-negative disease, 5-year DFS was 62.1% (95% CI, 42.1%-76.9%) in the LHRHa group and 76.2% (95% CI, 51.9%-89.3%) in the control group (eFigure 3 in Supplement 2).

Results from the Cox proportional hazard model, adjusting for baseline disease stage and hormone receptor status, showed no statistically significant difference in DFS among treatment groups (HR, 1.10 [95% CI, 0.67-1.79]; P = .72) (**Table 2**). No evidence of proportional hazards assumption violation was detected.

Subgroup analysis of DFS compared patients with hormone receptor-positive tumors with patients with hormone receptor-negative tumors. The HRs were 0.96 (95% CI, 0.55-1.70) for patients with hormone receptor-positive tumors and 2.11 (95% CI, 0.74-5.98) for those with hormone receptor-negative tumors, respectively (P = .19 for interaction).

Discussion

Long-term results from the PROMISE-GIM6 study,[11] after a median follow-up of 7.3 years, show that concurrent administration of triptorelin and chemotherapy, compared with chemotherapy alone, was associated with higher long-term probability of menstrual resumption. Of a total of 11 pregnancies, 8 were reported by women in the LHRHa group and 3 by women in the control group, a nonsignificant difference. There was a higher risk of inferior DFS for women assigned to the LHRHa group that did not reach statistical significance; this increased but statistically nonsignificant risk appeared specific to the patients with hormone receptor-negative tumors.

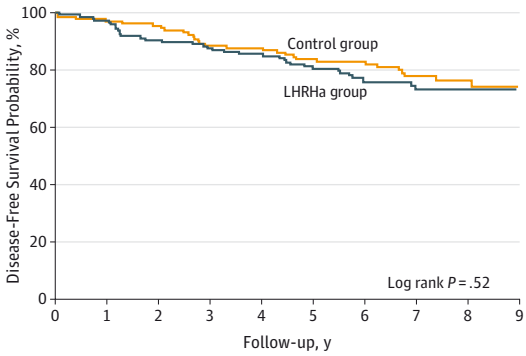
The PROMISE-GIM6 study has longer follow-up than other studies that have evaluated the role of LHRHa as a strategy to preserve ovarian function during chemotherapy in young patients with early breast cancer. Seven other randomized studies have been published on the same issue in breast cancer patients,[12-18] and another trial has been presented at the 2010 ASCO Annual Meeting (eTable 3 in

Supplement 2).[19] Recently, the final results of another large randomized study, the POEMS-SWOG S0230 trial, have been published.[20] The POEMS-SWOG S0230 trial differs from our study in that it included only patients with hormone receptor–negative disease, and thus no adjuvant endocrine therapy was administered; the primary end point of the study, premature ovarian failure, was defined as 6 months of amenorrhea and follicle-stimulating hormone levels in the postmenopausal range at 2 years; and goserelin was the LHRHa used.[20] The most recent systematic review and meta-analysis on this topic showed that ovarian suppression with LHRHa during chemotherapy was associated with a higher rate of ovarian function recovery after 6 months (OR, 2.41; $P = .002$) and at least 12 months (OR, 1.85; $P < .001$) following the last chemotherapy cycle.[21] However, because randomized trials reported conflicting results and the meta-analyses on this issue have the limitation of combining trials with different end points and methods, there is still active debate on the efficacy of this strategy.[22,23] Moreover, concerns persist about the lack of long-term follow-up data supporting the safety of ovarian suppression, especially for women with endocrine-sensitive breast cancer.[6-10] For all these reasons, the 2013 American Society of Clinical Oncology and European Society for Medical Oncology guidelines do not recommend the use of this strategy as a reliable means of preserving ovarian function and fertility in young patients with cancer.[4,5]

The majority of trials evaluating ovarian suppression during breast cancer chemotherapy have reported premature ovarian failure rates at a short follow-up, variable between 6 and 36 months, and there is paucity of data available at longer time points (eTable 3 in Supplement 2). In the current analysis, we showed that LHRHa treatment was associated with an increased probability of menstrual resumption at a long-term follow-up (median follow-up, 7.3 years), although the absolute difference (8.6%) between the 2 groups was modest and lower than that observed 12 months after the end of chemotherapy (13.7%), as described in the primary trial report.[11]

Recently, the POEMS-SWOG S0230 study showed a statistically significant higher number of pregnancies in the LHRHa group as compared with the control group (22 vs 12 pregnancies; OR, 2.45; $P = .03$).[20] Our results are consistent with those of the POEMS-SWOG S0230 study, demonstrating a higher although not statistically significant difference

Figure 3. Disease-Free Survival in the Treatment Groups



LHRHa indicates luteinizing hormone–releasing hormone analogues.

Table 2. Multivariable Cox Proportional Hazards Model: Effect of Temporary Ovarian Suppression, Tumor Size, Axillary Nodes, and Hormone Receptor Status on Disease-Free Survival[a] (N = 281)[b]

Variable	No. Patients	No. Disease-Free Survival Events[c]	HR (95% CI)	*P* Value[d]
Random assignment				
Control	133	29	1 [Reference]	.72
LHRHa	148	36	1.10 (0.67-1.79)	
Tumor size (T)				
pT1	167	33	1 [Reference]	.39
pT2-4	114	32	1.25 (0.76-2.05)	
Axillary nodes (N)				
pN0	133	22	1 [Reference]	.03
pN1-2	148	43	1.80 (1.06-3.05)	
Hormone receptor status				
ER-negative and PR-negative	53	17	1 [Reference]	.05
ER-positive, PR-positive, or both	228	48	0.56 (0.32-0.97)	

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; LHRHa, luteinizing hormone–releasing hormone analogues; PR, progesterone receptor.

[a] Disease-free survival interval was computed from the date of randomization to the date of the occurrence of an event. Observation times of patients without a disease-free survival event were censored on the date of last contact.

[b] After single imputation of missing values on at least 1 covariate in 7 patients.

[c] Disease-free survival event was defined by the occurrence of local recurrence, distant metastases, contralateral or ipsilateral breast tumor, second primary malignancy, or death from any cause, whichever occurred first.

[d] Likelihood-ratio test.

in pregnancy in the LHRHa group. The lower number of pregnancies in our trial compared with the POEMS-SWOG S0230 study could be explained by the fact that the POEMS-SWOG S0230 study enrolled only patients with hormone receptor–negative tumors, whereas the majority of patients in our trial had hormone receptor–positive disease. Most hormone receptor–positive patients received adjuvant endocrine therapy for at least 5 years and delayed pregnancy attempts for at least 6 months after the end of endocrine therapy.

The concerns about the safety of the concurrent administration of LHRHa and chemotherapy rely on both the possible detrimental effect of the lack of chemotherapy-induced amenorrhea on prognosis[6] and the potential negative interaction between the 2 treatments, especially for patients with endocrine-sensitive tumors.[7,8] Because of these concerns, only patients with hormone receptor–negative disease have been included in the majority of the trials.[14,16,19,20] On the first point, data suggest that chemotherapy-induced amenorrhea is associated with improved outcomes in young patients with breast cancer.[6] It can be hypothesized that the resumption of ovarian function, with the subsequent estrogen production, might adversely affect survival. This concern was addressed in our trial by allowing initiation of LHRHa at the time of restoration of ovarian function as part of adjuvant endocrine treatment. A total of 92.9% of patients with endocrine-sensitive tumors received adjuvant hormonal therapy, and 69.9% of them received LHRHa as part of the endocrine treatment. The other concern about the potential detrimental effect of concurrent administration of endocrine therapy and chemotherapy is based on both preclinical data suggesting a potential antagonism between tamoxifen and chemotherapy[7,8] and clinical data from the SWOG 8814 INT-0100 randomized study suggesting a DFS advantage with use of sequential, as compared with concurrent, tamoxifen and chemotherapy in postmenopausal women with breast cancer.[9] However, the mechanism of action of LHRHa is different from that of tamoxifen, and results from randomized trials did not demonstrate any difference in the prognosis of patients undergoing chemotherapy alone or with concurrent ovarian suppression.[24-26] These data are consistent with the recently reported excellent DFS results of the TEXT (Tamoxifen and Exemestane Trial) study with triptorelin administered concurrently with chemotherapy in patients with hormone receptor–positive tumors.[27]

Our secondary analysis of the PROMISE-GIM6 trial has demonstrated that in patients with hormone receptor–positive disease, DFS was not statistically significantly different between the 2 groups (HR, 0.96). However, in those patients who resumed ovarian function after chemotherapy, treatment with LHRHa was advised as part of adjuvant endocrine therapy.[28] In the subgroup of patients with hormone receptor–negative tumors, women randomized to LHRHa had 5-year DFS of 62.1%, whereas those randomized to control had 5-year DFS of 76.2%, with an HR of 2.11. Although this result was not statistically significant, the study included only 53 patients with hormone receptor–negative disease and therefore may have been underpowered to detect outcome differences in this subgroup. Moreover, the lack of statistical significance for the test for interaction (P = .19) also could represent underpowering. This finding is discordant with the results of the POEMS-SWOG S0230 study, which demonstrated superior DFS in 105 women treated with LHRHa in addition to chemotherapy (4-year DFS, 89%) as compared with 113 women treated with chemotherapy alone (4-year DFS, 78%), with an HR of 0.49 (P = .04).[20] Except for the different median follow-up (4.1 years in POEMS-SWOG S0230 and 7.3 years in PROMISE-GIM6), there are no other apparent differences able to explain the observed discrepancy between the 2 trials. The discordance between our finding and that of the POEMS-SWOG S0230 trial, and the potential for breast cancer recurrence beyond 5 years, underscores the importance of obtaining data on long-term recurrence and mortality by hormone receptor status for all participants in trials evaluating preservation of fertility.

The main limitation of this update of the PROMISE-GIM6 study is that the analyses were not prespecified in the study protocol and the decision to collect long-term outcomes was planned at the time of the primary end point analysis, with annual systematic follow-up.[11] In particular, data on patients' intention or desire to become pregnant were available only in a minority of patients. Moreover, the trial was not powered to assess prespecified differences in these end points and to study interactions in the subgroup analyses. Because of these limitations, our results should be considered exploratory. However, they add useful new information about the role of LHRHa for preservation of ovarian function. As compared with the POEMS-SWOG S0230 study, our data suggest that this strategy could be useful and safe not only in women with hormone receptor–negative breast cancer, as recently endorsed by the 2015 St. Gallen International Expert Consensus panel and the National Comprehensive Cancer Network guidelines,[29,30] but also for those with hormone receptor–positive tumors, who account for the majority (ie, more than 65%) of new cases of breast cancer in young women.[31,32]

Our results, together with the findings from the POEMS-SWOG S0230 study, indicate that, in addition to fertility preservation strategies such as embryo and oocyte cryopreservation,[4,5] temporary ovarian suppression with LHRHa is an option to preserve ovarian function in premenopausal women with early stage breast cancer receiving adjuvant chemotherapy.

Conclusions

Among premenopausal women with either hormone receptor–positive or hormone receptor–negative breast cancer, concurrent administration of triptorelin and chemotherapy, compared with chemotherapy alone, was associated with higher long-term probability of ovarian function recovery, without a statistically significant difference in pregnancy rate. There was no statistically significant difference in DFS for women assigned to triptorelin and those assigned to chemotherapy alone, although study power was limited.

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