

Effect of Luteinizing Hormone–Releasing Hormone Agonist on Ovarian Function After Modern Adjuvant Breast Cancer Chemotherapy: The GBG 37 ZORO Study

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Submitted September 7, 2010; accepted February 17, 2011; published online ahead of print at www.jco.org on May 2, 2011.

Written on behalf of the German Breast Group Investigators.

Presented in part in poster format at the 45th Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 29–June 2, 2009, and as an oral discussion at the European Cancer Organisation/European Society for Medical Oncology Multidisciplinary Congress, Berlin, Germany, September 20–24, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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0732-183X/11/2917-2334/\$20.00

DOI: 10.1200/JCO.2010.32.5704

ABSTRACT

Purpose

Observational studies suggested that luteinizing hormone–releasing hormone agonists (LHRHa) might prevent premature ovarian failure resulting from adjuvant chemotherapy in premenopausal patients. We aimed to test the efficacy of ovarian function preservation with the LHRHa goserelin in patients with breast cancer.

Patients and Methods

In a prospective, randomized, open-label, controlled multicenter study, 60 patients younger than age 46 years with hormone-insensitive breast cancer were allocated to receive anthracycline/cyclophosphamide (with or without taxane) –based neoadjuvant chemotherapy with or without goserelin. The first goserelin 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.

Results

Fifty-three patients (88.3%) experienced temporary amenorrhea (93.3% with v 83.3% without goserelin). No significant difference was observed regarding the reappearance of menstruation at 6 months after chemotherapy (70.0% with v 56.7% without goserelin; difference of 13.3%; 95% CI, –10.85 to 37.45; $P = .284$). All but one evaluable patient reported regular menses at 2 years after chemotherapy. Time to restoration of menstruation was 6.8 months (95% CI, 5.2 to 8.4) with goserelin and 6.1 months (95% CI, 5.3 to 6.8) without goserelin ($P = .304$). Chemotherapy resulted in a decreased ovarian reserve measured by inhibin B and anti-Müllerian hormone during follow-up, supporting the other findings.

Conclusion

Premenopausal patients with breast cancer receiving goserelin simultaneously with modern neoadjuvant chemotherapy did not experience statistically significantly less amenorrhea 6 months after end of chemotherapy compared with those receiving chemotherapy alone.

J Clin Oncol 29:2334–2341. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Currently, 1.9% and 10.5% of all newly diagnosed breast cancers are detected in those between the ages of 20 and 34 years and 35 and 44 years, respectively.¹ Breast cancer in young patients represents a unique biologic entity driven by specific oncogenic signaling pathways and is characterized by a higher incidence of hormone-insensitive, undifferentiated, and human epidermal growth factor receptor 2–overexpressing tumors.² Patients younger than 50 years, especially those with hormone-insensitive breast cancer, achieve significant benefit

from adjuvant systemic chemotherapy in terms of prolonged disease-free and overall survival.^{3,4} However, a considerable number of these young patients will suffer from premature ovarian failure (POF) thereafter, depending on age at diagnosis and type of chemotherapy used.⁵ Apart from the loss of fertility, POF leads to subjective (hot flashes, sweats, sleep disturbance, loss of libido) and objective (osteoporosis, cardiovascular incidents, genital atrophy, loss of mental efficiency, cognitive dysfunction, mood swings, dyspareunia, loss of vitality) menopausal symptoms, which can negatively affect short- and long-term quality of life.⁶

There are no proven methods or recommendations for effective preservation of ovarian function in these young patients.^{7,8} Cytotoxic agents, especially anthracyclines and alkylating agents such as cyclophosphamide, induce POF, probably by causing apoptotic oocyte death in primordial follicles and thus damaging ovarian reserve.⁹ Observational studies¹⁰⁻¹² and one recent single-institution randomized study¹³ have shown that luteinizing hormone–releasing hormone agonists (LHRHa) might prevent POF in premenopausal patients with breast cancer. However, there is currently no biologic explanation for how LHRHa can affect ovarian reserve.¹⁴ Therefore, results from prospective, randomized, multicenter studies are needed to clarify whether LHRHa can possibly be used as an effective prevention of chemotherapy-induced POF. The GBG-37 (German Breast Group) ZORO (Zoladex Rescue of Ovarian function) study was designed to investigate using a randomized controlled design the preventive effect of the LHRHa goserelin on chemotherapy-induced ovarian failure in young patients with hormone-insensitive breast cancer treated with anthracycline/cyclophosphamide (with or without taxane) –based neoadjuvant chemotherapy.

PATIENTS AND METHODS

Study Design and Patients

This was a prospective, randomized, open-label, controlled, multicenter phase II study in premenopausal patients with primary hormone-insensitive breast cancer undergoing anthracycline/cyclophosphamide (with or without taxane) –based neoadjuvant chemotherapy. 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 had regular and spontaneous menstrual periods before study entry, with follicular stimulating hormone (FSH) below 15 mIU/mL in the follicular phase of the menstrual cycle. Patients had to use adequate nonhormonal 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 and if (primary or secondary) ovarian insufficiency was suspected.

Treatment

Patients were randomly assigned in a ratio of one to one to receive chemotherapy either with or without goserelin. Patients randomly assigned to the goserelin group received their first injection of 3.6 mg at least 2 weeks before start of chemotherapy independently from the day of menstrual cycle and then every 4 weeks (28 ± 3 days) until the end of the last chemotherapy cycle. Before the first administration of chemotherapy, ovarian suppression had to be proven (ie, estradiol [lsbq]E₂) level < 50 pg/mg and LH level < 10 mIU/mL). Otherwise, start of chemotherapy was postponed until proven ovarian suppression. It was planned that patients would receive modern a chemotherapy regimen including at least an anthracycline and cyclophosphamide with more than 500 mg/m² per cycle and more than 2,400 mg/m² in total per regimen, administered every 3 weeks for six or eight cycles.

Objectives

The primary objective was to show that ovarian protection with goserelin increases the rate of normal ovarian function at 6 months after administration of neoadjuvant, anthracycline-containing polychemotherapy compared with chemotherapy alone in patients with hormone receptor–negative 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, sexual hormone–binding globulin) before and at 6, 12, 18, and 24 months after end of chemotherapy; long-term ovarian function reserve and fertility by anti-Müllerian hormone (AMH), inhibin B, E₂, FSH, and follicle count by trans-

vaginal ultrasound; pregnancy rate; treatment compliance; and toxicity using National Cancer Institute Common Toxicity Criteria version 2.0. A qualified gynecologist checked all menstruation logs.

Statistics

Sample size was determined based on the assumption that the number of patients with intact ovarian function 6 months after anthracycline-based chemotherapy could be improved by 30%, from 50% without goserelin to 80% with goserelin. The error rate for a false positive (α) was set at 5% using a one-sided test. The false negative rate (β) was set at 20% (ie, power of trial was 80% for difference of clinical interest). A total of 62 patients (31 in control arm and 31 with proven ovarian suppression in goserelin arm) were required, as calculated using nQuery Advisor (Saugus, MA).

Descriptive statistics are given for patient data collected at baseline, throughout therapy, and at end of study. If applicable, a 95% CI was calculated. Age, weight, and height at baseline were compared by *t*-test, whereas other baseline characteristics were analyzed by using χ^2 test. The number of patients with normal ovarian function (as defined under Objectives) for efficacy was compared using Fisher's exact test. Primary efficacy analysis included all patients who started treatment according to the intent-to-treat principle. SPSS version 14 (SSPS, Chicago, IL) was used for analysis.

The study was approved by the ethics committees. All patients gave written informed consent. This study is registered with EudraCT No. 2004 to 003980-62 and ClinicalTrials.gov.

RESULTS

Between March 2005 and December 2007 in 16 centers, 60 patients were randomly assigned and started protocol-defined treatment (30 patients assigned to receive chemotherapy with goserelin and 30 to chemotherapy without goserelin). Three additional patients withdrew consent, two before random assignment and one after but before treatment started. In each arm, 28 patients finished chemotherapy as planned (Fig 1). No major protocol deviation was reported in this study.

The baseline characteristics were comparable between the two arms (Table 1). Patients in the group with goserelin tended to be younger than those in the group without goserelin (35 v 38.5 years; $P = .092$).

Overall, 63.3% of patients had regular menses 6 months after end of chemotherapy (70.0% [95% CI, 53.6% to 86.4%] in group with goserelin v 56.7% [95% CI, 39% to 74.4%] in group without [difference, 13.3%; 95% CI, –10.85 to 37.45]; one-sided $P = .142$; two-sided $P = .284$). In a logistic regression analysis with age as covariate, age predicted independently the odds of menstruating at month 6 (odds ratio, 1.15; 95% CI, 1.01 to 1.29; $P = .028$), but treatment group did not (odds ratio, 1.24; 95% CI, 0.39 to 3.9; $P = .717$). After adjusting for age, 70.4% in the group with goserelin versus 65.9% ($P = .708$) in the group without menstruated. Neoadjuvant chemotherapy–induced amenorrhea (CIA) was clinically reversible in all but one patient in the observation arm 24 months after end of chemotherapy (Table 2). Median time to resume menstruation was not statistically different between the two groups (6.1 months [95% CI, 5.3 to 6.8] with goserelin v 6.8 months [95% CI, 5.2 to 8.4] without; $P = .304$; Fig 2). Seven patients with a median age of 31 years never stopped menstruation; two were in the group with goserelin, and five were in the group without.

Two cases of pregnancy were reported in this study, one in each group. Pregnancies occurred 8 and 12 months after end of chemotherapy/LHRHa. The woman in the group without goserelin had an abortion during the first trimester, while receiving trastuzumab.

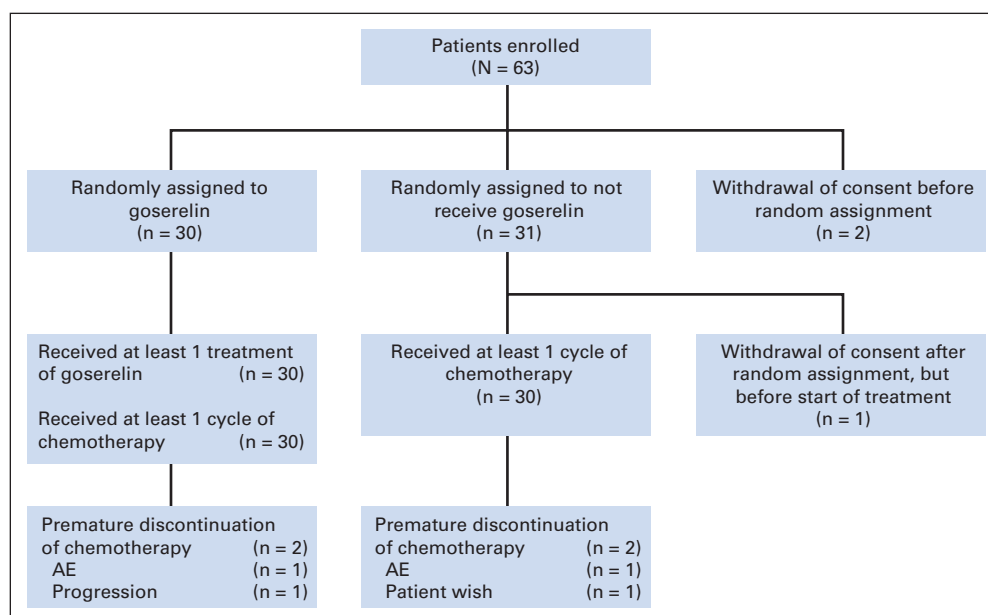


Fig 1. CONSORT diagram. AE, adverse event.

E₂ levels decreased, but no significant differences were seen between the groups at the different time points. It seems that the hormones secreted by the pituitary gland (LH, FSH) increased over time (Fig 3). At month 12 after end of chemotherapy, there was a significant difference ($P = .015$) between the LH level in the group with goserelin compared with that in the group without goserelin. The sexual hormone-binding globulin and progesterone levels were similar in the two groups.

Seventeen of 60 patients were accessible for hormone measurement (inhibin B, AMH, E₂, FSH) and follicle count by ultrasound

during follow-up to estimate ovarian function. Median time from random assignment to measurement of AMH and inhibin B values was 4 years. Eight of these 17 patients received goserelin, and nine were treated without goserelin. All patients had inhibin B levels less than 10 ng/L; seven patients had AMH levels greater than 0.2 µg/L (range, 0.44 to 2.7 µg/L), and 10 patients had AMH levels less than 0.2 µg/L. AMH correlated strongly with age, with lower AMH levels in older patients (Fig 4). Three (33.3%) of nine patients in the group without goserelin had an AMH level greater than 0.2 µg/L, whereas in the group with goserelin, four (50%) of eight had an AMH level greater than 0.2 µg/L.

Table 1. Baseline Patient Characteristics

Characteristic	Chemotherapy With Goserelin (n = 30)		Chemotherapy Without Goserelin (n = 30)		Total	
	No.	%	No.	%	No.	%
Age, years						
Median	35.0		38.5*		36.5	
Range	26-44		29-47*		26-47	
Weight, kg						
Median	67.5		64.5			
Range	47-112		50-100			
Premenopausal status, %	100		100		100	
Regular menstruation, %	100		100		100	
Mean cumulative cyclophosphamide dose, g	4,716		4,526		4,621	
No. of chemotherapy cycles	154		183		347	
Laboratory values						
Estradiol, pmol/L	224		162			
FSH, IU/L	5.6		5.7			
LH, IU/L	4		5			
Menopausal status						
Premenopausal	30	100	30	100	60	100
Regular menses	30	100	30	100	60	100
ER/PgR negative	30	100	30	100	60	100

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; ER, estrogen receptor; PgR, progesterone receptor.

* $P = .092$.

Table 2. Patients With Regular Menses After End of Chemotherapy in ITT Population

Characteristic	Patients With Regular Menses				P
	Chemotherapy With Goserelin (n = 30)		Chemotherapy Without Goserelin (n = 30)		
	No.	%	No.	%	
Time after end of chemotherapy, months					.142 (one sided); .284 (two sided)
6 (range, 5-8; primary endpoint)	21	70.0	17	56.7	
95% CI, %		53.6-86.4		39-74.4	
12		25		24	
18		27		26	
24		28		28	
≥ 24		28		29	
Total	28	93.3	29	96.7	
Missing		2		1	

These differences might have resulted from the different ages at the time of sample collection.

Follicle count was measured in 10 of the 17 patients (three in group with goserelin and seven in group without). In four patients, no follicles were seen; one or two follicles were counted in four patients; four and seven follicles were seen in one patient each. Both of these patients had an AMH level greater than 0.2 µg/L.

Overall, 347 cycles of chemotherapy were applied, 154 with and 183 without goserelin. Most patients (n = 49; 81.7%) received six cycles of chemotherapy. The most frequently used chemotherapy was six cycles of fluorouracil plus epirubicin plus cyclophosphamide and fluorouracil plus doxorubicin plus cyclophosphamide (Table 3). The mean cumulative dose of cyclophosphamide per patient was comparable in both groups (4,716 g in the group with goserelin and 4,526 g in group without).

Eight patients in the group with goserelin and 11 patients in the group without goserelin required delays in their chemotherapy dosing, and one patient in the group with goserelin and two pa-

tients in the group without needed chemotherapy dose reduction. All but two patients in the group with goserelin received goserelin throughout chemotherapy.

The most commonly reported hematologic adverse events (AEs) were leucopenia, neutropenia, and anemia. The most common non-hematologic AEs were nausea, alopecia, and fatigue. None of the AEs were considered to be related to goserelin. No treatment-related death occurred. Hot flashes were reported in 16 versus 10 patients, mood swings in two versus two, insomnia in five versus one, and urogenital symptoms in six versus one in the group with goserelin compared with the group without, respectively.

DISCUSSION

The ZORO study demonstrated that the rate of regular menstruation is not statistically significantly different in the group with the LHRHa goserelin during standard anthracycline-based chemotherapy for hormone-insensitive breast cancer. The menstruation rates in the goserelin and observation arms 6 months after end of chemotherapy were 70.0% and 56.7%, respectively, which is in the range of the reported data.⁵ CIA was clinically reversible in almost all patients in groups with and without goserelin within 2 years after the end of chemotherapy. There was no significant difference of earlier resumption of menstruation in the group with goserelin compared with the group without.

There are two clinically relevant confounding factors in our trial. First, the patients in the goserelin group tended to be younger than those in the group without goserelin, because we did not stratify for age, and second, the number of applied chemotherapy cycles was lower in the group with goserelin compared with that in the group without. Therefore, it can be hypothesized that the menstruation rate in the goserelin group could be even lower.

It is known that after the age of 35 years, ovarian function and fertility rate decrease.¹⁵ The rate of CIA depends strongly on a patient's age; dosage, schedule, and duration of therapy; type of cytotoxic agents used; and use of endocrine treatment.^{5,16} Alkylating agents like cyclophosphamide are known to be gonadotoxic.¹⁷ There is no unified definition of amenorrhea across studies. Moreover, the resumption of

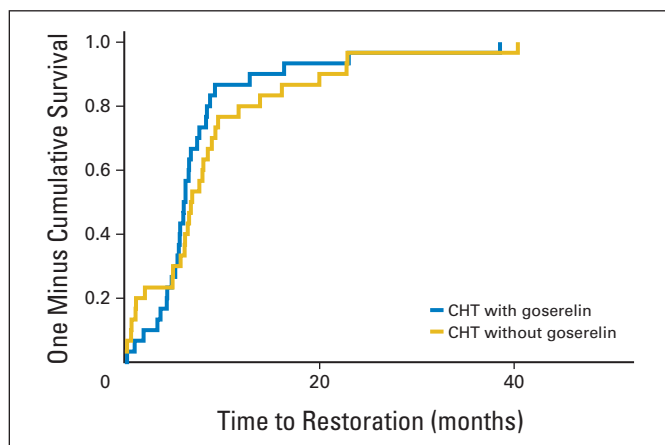


Fig 2. Time to restoration of menstruation in all patients, regardless of whether menses stopped during chemotherapy (CHT). Seven patients never stopped menstruating (median age, 31 years; two in group with goserelin and five in group without). Median time was not different between the two groups (6.1 months [95% CI, 5.3 to 6.8] with goserelin v 6.8 months [95% CI, 5.2 to 8.4] without; two-sided *P* = .304).

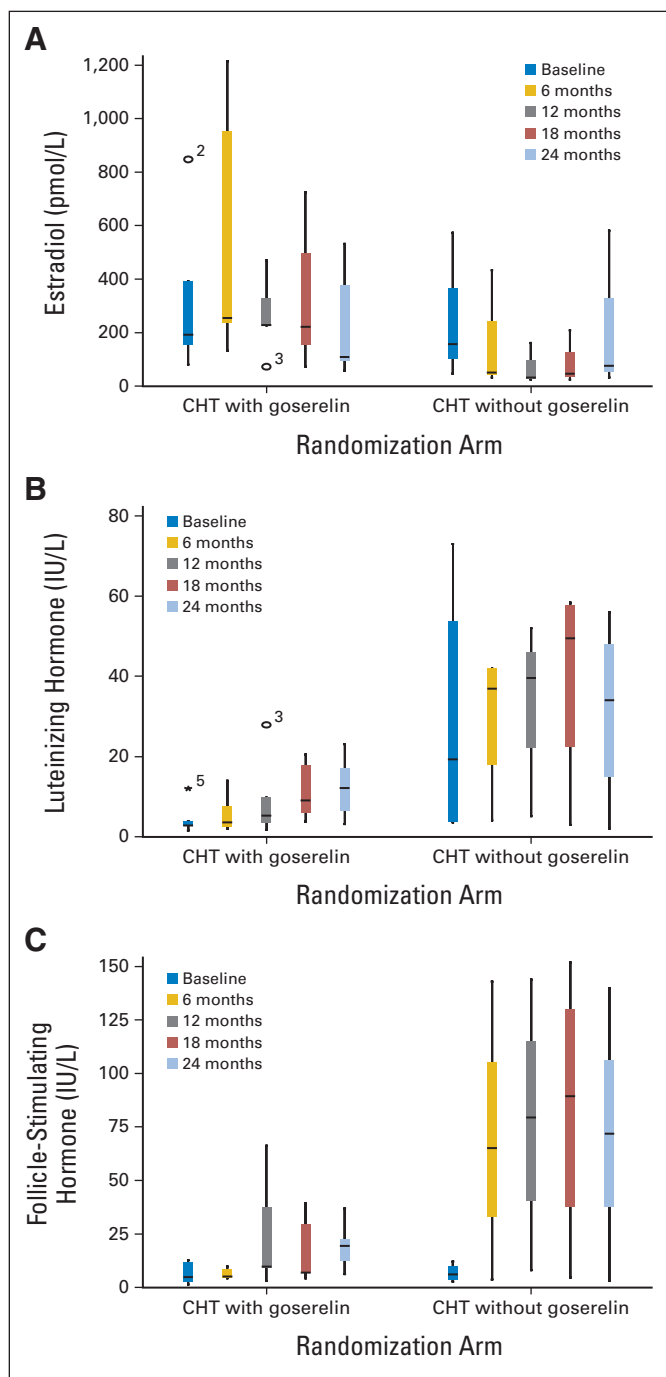


Fig 3. Laboratory values at the different time points before start of chemotherapy (CHT) and at 6, 12, 18, and 24 months after end of chemotherapy for (A) estradiol, (B) luteinizing hormone, and (C) follicle-stimulating hormone in the groups with and without goserelin.

ovarian function increases with time from the end of anthracycline-and/or taxane-containing chemotherapy but not after cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy.¹⁶

Other randomized trials must be interpreted with this in mind. In a single-center study from Egypt, 78 patients with a median age of 30 years were randomly assigned to receive nonstandard chemotherapy with fluorouracil plus doxorubicin plus cyclophosphamide, with or

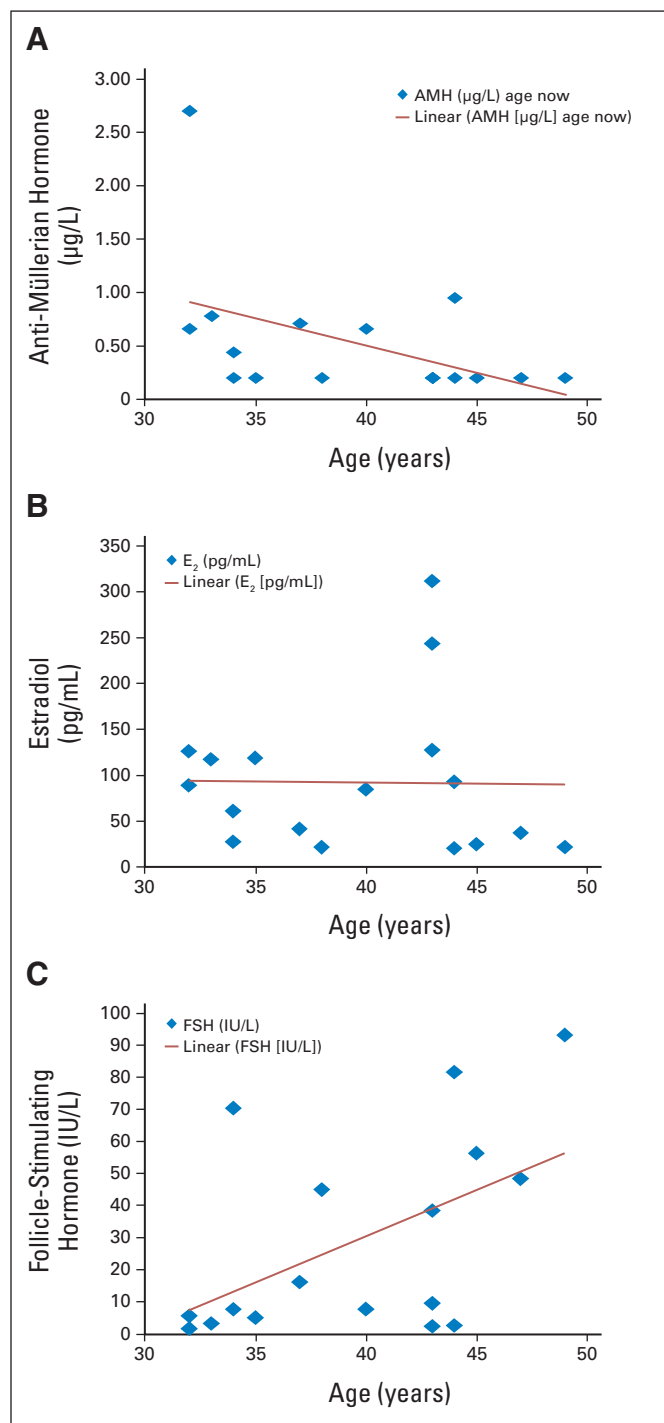


Fig 4. Laboratory values indicating ovarian function during follow-up beyond 2 years: (A) anti-Müllerian hormone (AMH), (B) estradiol (E_2), and (C) follicle-stimulating hormone (FSH) levels by age in patients during follow-up after treatment with chemotherapy with or without goserelin. Median follow-up time from start of chemotherapy was 4 years. Median age at the time of hormone measurement was 40 years (range, 32 to 49 years). AMH correlated significantly with age; the older the patient, the lower the AMH value ($P = .031$; $\rho = -0.53$). E_2 did not correlate with age ($P = .336$; $\rho = 0.25$). FSH correlated significantly with age; the older the patient, the higher the FSH value ($P = .026$; $\rho = 0.54$). The values indicated a loss of fertility.

Table 3. Chemotherapy Regimen and Cycles Administered to Patients With or Without Goserelin

Treatment	No. of Cycles	Regimen	No. of Patients	
			Chemotherapy With Goserelin (n = 30)	Chemotherapy Without Goserelin (n = 30)
FEC → Doc	6	3× FEC + 3× Doc	5	3
	6	3× FEC + 3× Doc/H	0	1
	8	4× FEC + 4× Doc	1	0
EC → Doc	7	4× EC + 3× Doc	2	0
	8	4× EC + 4× Doc	0	3
	8	4× EC/H + 4× Doc/X/H	0	1
	12	4× EC + 4× Doc + 4× X	0	1
FEC/FAC	5	5× FEC/FAC	0	1
	6	6× FEC/FAC	14	13
TAC	5	5× TAC	0	1
	6	6× TAC	7	5
Other	7	3× EC/AC + 4× Doc	0	1
	6	3× FEC + 3× G	1	0

Abbreviations: FEC, fluorouracil 500 mg/m², epirubicin 90-100 mg/m², cyclophosphamide 600 mg/m²; Doc, docetaxel 100 mg/m²; H, trastuzumab; EC, epirubicin 90 mg/m², cyclophosphamide 600 mg/m²; X, capecitabine 1800 mg/m² days 1-14; FAC, fluorouracil 500 mg/m², doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²; TAC, docetaxel 75 mg/m², doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²; AC, doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²; G, gemcitabine 1,250 mg/m² weekly.

without goserelin.¹³ The authors reported a resumed menstruation rate up to 8 months after end of chemotherapy of 89.6% in the group with goserelin and 33.3% ($P < .001$) in the group without. But this study had several limitations, which were pointed out in detail (eg, different baseline hormone levels between groups, no report on use of tamoxifen, general high incidence of amenorrhea, follow-up too short).¹⁸ The Swedish ZIPP (Zoladex In Premenopausal Patients) study in hormone-sensitive premenopausal patients reported menses 1 year after completion of CMF and endocrine therapy in 36% of patients with goserelin, 13% with tamoxifen, 7% with goserelin and tamoxifen, and 10% with chemotherapy alone (overall $P = .006$).¹⁹ Tamoxifen use was an independent factor for persistent CIA.²⁰ None of our patients received CMF or tamoxifen.

In a trial by del Mastro et al,²¹ 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. The general higher menstruation rate might have been the result of the lower cyclophosphamide dose or the later time point of assessing ovarian function. In the ZORO study, the group with goserelin was younger and received fewer chemotherapy cycles, which supporting our results. An explanation for the positive results might be the larger sample size and the focus on laboratory values. However, final publication is awaited to draw firm conclusions. In a randomized US trial investigating triptorelin with 49 patients, menstruation rates at 6, 12, and 18 months after end of chemotherapy in the respective groups are comparable to ours, as was time of menses restoration.²² The Ovarian Protection Trial In Premenopausal Breast Cancer Patients (OPTION) from the United Kingdom also reported no difference with regard to premature menopause: 42.3% with and 36% without goserelin, which is also in the range of ZORO results.²³ The Southwest Oncology Group is currently investigating the effect of LHRHa on the rate of premature ovarian failure at 2 years. Keeping our results in mind, 2 years might be too late to detect any effect even with a larger sample size (ClinicalTrials.gov No.

NCT00068601). In addition, the Predictors of Ovarian Insufficiency in Young Breast Cancer Patients (POISE) trial will look at biomarkers related to risk of ovarian insufficiency. Intertrial comparisons are difficult, because all trials have different end points (amenorrhea v menstruation v laboratory values), different time points when effect is assessed, different populations, different cyclophosphamide doses, and different methodologies.

There are several strengths and limitations of the ZORO study. Its multicenter randomized design included only hormone receptor-negative patients with an application of modern anthracycline/cyclophosphamide (with or without taxane) –based chemotherapy. Goserelin was started at least 2 weeks before chemotherapy, which is important for downregulation of ovarian function. All patients had at least a 2-year follow-up. The trial was designed to detect a large (30%) but clinically relevant difference between treatment groups. We cannot rule out a 37% absolute increase in menstruation rate at 6 months in the group with goserelin compared with that in the group without. However, after adjusting for age, the difference became smaller. The rate of regular menstruation was taken as surrogate for intact ovarian function. FSH, LH, and E₂ were measured in parallel.

The cellular mechanisms of cytotoxic action of chemotherapy on ovarian follicles have not yet been investigated. Because the development from the primordial follicle to the small preantral follicle is a gonadotropine-independent process, it is not likely that suppression of LH and FSH secretion by LHRHa reduces the cytotoxic effects of chemotherapy.¹³

Speculative mechanisms have been suggested as to how LHRHa may protect ovarian reserve against chemotherapy, especially because primordial follicles do not express FSH receptors.^{24,25} However, these mechanisms have never been proven to be functional in human oocytes, and hence, the biologic plausibility for LHRHa preservation of ovarian reserve is lacking.¹³

Preservation of ovarian function in patients with breast cancer is different from other tumor entities.²⁶ First, the resumption of ovarian function could stimulate clinically occult tumor cells, especially in

hormone-sensitive tumors. Therefore, we included only hormone-insensitive tumors. A meta-analysis investigating the influence of CIA on prognosis demonstrated a significant survival advantage for amenorrhoic patients in 15 of 23 included studies.⁶ However, it is still unknown whether amenorrhea is an independent prognostic factor or may just indicate that patients with amenorrhea are more chemotherapy sensitive compared with those resuming ovarian function after chemotherapy.²⁷ Second, a negative interaction of LHRHa administered concomitantly as fertility preservation and adjuvant chemotherapy in hormone-sensitive tumors cannot be ruled out.²⁸ Therefore, this trial was undertaken only in patients with hormone-insensitive tumors. Third, the risk of *BRCA* mutations in young patients with breast cancer is high. The potential for the development of ovarian cancer makes transplantation of cryo-conserved ovarian tissue a poor option in this population.²⁹ Newer techniques of human reproduction, like cryopreservation of embryos and oocytes, are promising.

The determination of AMH, inhibin B, and follicle number counted by ultrasound correlate with ovarian reserve in young women with breast cancer.³⁰⁻³² Because of the limited patient number and the age difference in both groups, these data are merely hypothesis generating, and no definite conclusion can be drawn. Similar to recent publications, our data suggest decreased ovarian function at 4 years, despite restoration of menstruation in almost all patients at 2 years after chemotherapy.³³ However, a marked reduction of AMH was observed 1 year after chemotherapy, which was not predictive for subsequent menstrual function.³⁴

In conclusion, the ZORO trial did not provide evidence that use of goserelin for ovarian suppression was associated with a large clinically and statistically significant protective effect on ovarian function in patients with hormone-insensitive breast cancer. The resumption rate of regular menstruation within 2 years after modern chemotherapy was highly independent of goserelin. Other randomized trials must be awaited to clarify finally the role of LHRHa in protecting ovarian function in young chemotherapy-treated patients with breast cancer. Until these results are available, the uncritical use of LHRHa for ovarian protection should be stopped, and patients should be enrolled onto clinical trials. Other fertility preservation strategies such as oocyte or embryo freezing might be preferred.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Bernd Gerber, AstraZeneca, Roche, sanofi-aventis, Novartis, GlaxoSmithKline; Olaf Ortmann, Novartis, Pfizer, AstraZeneca; Tanja Fehm, Roche, Novartis **Research Funding:** Bernd Gerber, Novartis; Gunter von Minckwitz, AstraZeneca; Tanja Fehm, Novartis **Expert Testimony:** None **Other Remuneration:** None

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Final approval of manuscript: All authors

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