

Gonadotropin-Releasing Hormone Agonist for the Prevention of Chemotherapy-Induced Ovarian Failure in Patients With Lymphoma: 1-Year Follow-Up of a Prospective Randomized Trial

Isabelle Demeestere, Pauline Brice, Fedro A. Peccatori, Alain Kentos, Isabelle Gaillard, Pierre Zachee, Rene-Olivier Casanovas, Eric Van Den Neste, Julie Dechene, Vivianne De Maertelaer, Dominique Bron, and Yvon Englert

Isabelle Demeestere, Julie Dechene, Yvon Englert, and Vivianne De Maertelaer, Université Libre de Bruxelles; Alain Kentos and Yvon Englert, Erasme Hospital; Eric Van Den Neste, St Luc Hospital; Dominique Bron, J. Bordet Institute, Brussels; Pierre Zachee, Algemeen Ziekenhuis Stuivenberg, Antwerpen, Belgium; Pauline Brice, St Louis Hospital, Assistance Publique-Hôpitaux de Paris; Isabelle Gaillard, Hôpital Henri Mondor, Paris; Rene-Olivier Casanovas, Centre Hospitalier Universitaire de Dijon, Dijon, France; and Fedro A. Peccatori, Istituto Europeo di Oncologia, Milan, Italy.

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Corresponding author: Isabelle Demeestere, MD, PhD, Research Laboratory on Human Reproduction, Campus Erasme (Bât GE-niv 2), 808 Route de Lennik, 1070 Brussels, Belgium; e-mail: ideemeest@ulb.ac.be.

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ABSTRACT

Purpose

To assess the efficacy of gonadotropin-releasing hormone agonist (GnRHa) in preventing chemotherapy-induced ovarian failure in patients treated for Hodgkin or non-Hodgkin lymphoma within the setting of a multicenter, randomized, prospective trial.

Patients and Methods

Patients age 18 to 45 years were randomly assigned to receive either the GnRHa triptorelin plus norethisterone (GnRHa group) or norethisterone alone (control group) concomitantly with alkylating agents containing chemotherapy. The primary end point was the premature ovarian failure (POF) rate (follicle-stimulating hormone [FSH] ≥ 40 IU/L) after 1 year of follow-up.

Results

Eighty-four of 129 randomly assigned patients completed the 1-year follow-up. The mean FSH values were higher in the control group than in the GnRHa group during chemotherapy; however, this difference was no longer observed after 6 months of follow-up. After 1 year, 20% and 19% of patients in the GnRHa and control groups, respectively, exhibited POF ($P = 1.00$). More than half of patients in each group completely restored their ovarian function (FSH < 10 IU/L), but the anti-Müllerian hormone values were higher in the GnRHa group than in the control group (1.4 ± 0.35 v 0.5 ± 0.15 ng/mL, respectively; $P = .040$). The occurrence of adverse events was similar in both groups with the exception of metrorrhagia, which was more frequently observed in the control group than the GnRHa group (38.4% v 15.6%, respectively; $P = .024$).

Conclusion

Approximately 20% of patients in both groups exhibited POF after 1 year of follow-up. Triptorelin was not associated with a significant decreased risk of POF in young patients treated for lymphoma but may provide protection of the ovarian reserve.

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INTRODUCTION

Over the last few decades, the prognosis of patients with hematologic malignancies has dramatically improved.^{1,2} Because these diseases are highly curable, the long-term consequences of chemotherapy treatment on patients' quality of life have become a major issue. Premature ovarian failure (POF) is an established long-term adverse event of chemotherapy and has a significant impact on quality of life in young patients.³ Different approaches have been developed to preserve fertility in women exposed to chemotherapy, including gametes and ovarian tissue cryopreservation.⁴⁻⁶ The possibility of minimizing gonadal damage by administering protective

drugs during chemotherapy represents another attractive option. Various ovarian protective mechanisms of gonadotropin-releasing hormone agonists (GnRHAs) have been suggested, including the reduction of ovarian perfusion and the inhibition of follicles from entering the growing stage.⁷ However, the understanding of the potential effects of fertility-protective adjuvant treatment during chemotherapy challenges basic research.⁸ At present, scientific evidence for the GnRHa protective mechanisms is still lacking, but animal experiments have suggested that GnRHa is effective in preventing POF induced by alkylating agents.^{9,10} Although this concept is appealing, the potential efficacy of GnRHa treatment in humans is highly debated.¹¹⁻¹⁴

Recent randomized studies including patients with breast cancer showed contradictory results. The Munster et al¹⁵ and Zoladex Rescue of Ovarian Function¹⁶ studies, which included 47 and 60 patients, respectively, observed similar rates of menstruation recovery between patients treated with GnRHa during chemotherapy and the control patients treated with chemotherapy alone. In contrast, the largest study, which enrolled 281 patients, found a significant difference in the rates of early menopause between both groups after 1 year of follow-up (25.9% v 8.9% in the control group and the GnRHa groups, respectively).¹⁷ Because the primary end point was the recovery of menstrual cycling after chemotherapy, however, evidence of the efficacy of GnRHa treatment for the true recovery of ovarian function and ovarian reserves is still lacking.¹⁴ Furthermore, the median age of the cohorts of patients with breast cancer was more than 36 years. The younger patients with lymphoma represent a group that is potentially more concerned with fertility preservation. Thus, we undertook a multicenter, prospective, open, randomized trial in a selected cohort of young patients with Hodgkin and non-Hodgkin lymphoma to test the hypothesis that the GnRHa triptorelin reduces the rate of POF induced by gonadotoxic chemotherapy.

PATIENTS AND METHODS

The trial was conducted in 15 oncologic centers in France, Belgium, and Italy. Institutional review board approval from each of the participating centers was obtained according to national obligations, and written informed consent was obtained from all patients (ClinicalTrials.gov identifier: NCT01160315).

Patients

The trial involved premenopausal women between 18 and 45 years old who were being treated for Hodgkin and non-Hodgkin lymphoma with alkyl-

ating agents. Regimens consisted of three to eight cycles of chemotherapy or high-dose therapy with autologous stem-cell transplantation as the first-line consolidative treatment. Eligible patients had serum follicle-stimulating hormone (FSH) levels less than 15 IU/L at the time of random assignment. The main exclusion criteria were pelvic irradiation, previous history of amenorrhea (> 3 months), thromboembolic processes, severe hypertension, severe obesity, hepatic or renal insufficiency, contraindication of intramuscular injection, prior chemotherapy treatment, and presence of ovarian abnormalities (other than functional cysts). Patients receiving less than eight cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine treatment were also excluded because this regimen manifests low levels of gonadotoxicity.¹⁸

Study Design

Eligible patients were randomly assigned to receive chemotherapy and an intramuscular injection of triptorelin 11.25 mg (Decapeptyl LP 11.25 mg; Ipsen Pharma, Merelbeke Belgium) every 12 weeks in addition to norethisterone acetate 5 mg daily (Primolut-Nor 5 mg; Bayer Schering Pharma, Antwerp, Belgium; GnRHa group) or norethisterone acetate 5 mg daily alone (control group). The treatment was initiated 10 days before the start of chemotherapy if possible. FSH and estradiol levels were measured in each center before the start of treatment, after 10 days, after 3 months, and at the end of the chemotherapy treatment. All local laboratory standards have been collected to validate the POF criteria.

During the follow-up period, FSH and estradiol levels were evaluated at 3, 6, and 12 months. According to the oncologists' recommendations, the patients were allowed to take oral contraception or other hormonal replacement therapy during the follow-up period. However, FSH and estradiol levels were tested at least 10 days after the suspension of the medication. For the remaining patients, the blood tests were preferentially performed at the beginning of the menstrual cycle. When feasible, serum collected at inclusion and at the 1-year follow-up was sent to Erasme Hospital for additional anti-Müllerian hormone (AMH) measurement. Serum AMH level was measured by enzyme immunoassay using commercially available kits (AMH GenII Elisa; Beckman Coulter, Brea, CA).¹⁹ Treatment-related adverse effects were monitored at each visit.

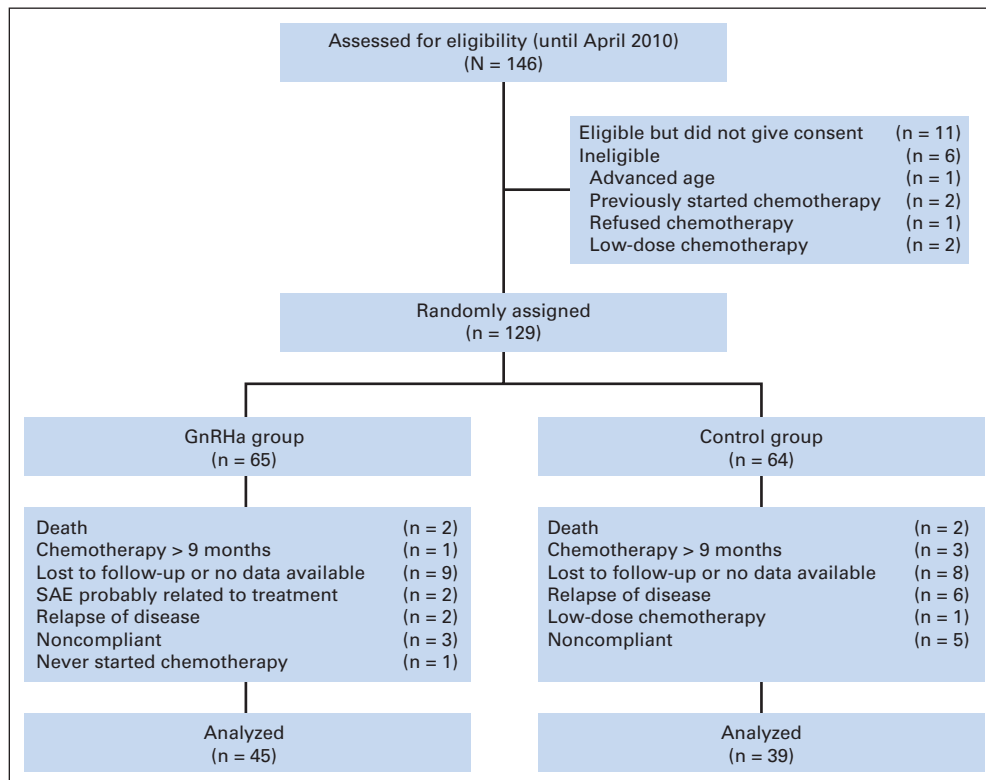


Fig 1. CONSORT diagram. GnRHa, gonadotropin-releasing hormone agonist; SAE, severe adverse event.

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	GnRHa Group (n = 45)		Control Group (n = 39)	
	No.	%	No.	%
Age, years				
Mean	25.57		27.27	
SEM	0.81		0.80	
Range	18-38		18-38	
BMI, kg/m ²				
Mean	20.97		21.73	
SEM	0.41		0.56	
Race or ethnic group				
White	43	95.5	35	89.7
North African	2	4.5	1	2.6
Asian	0		1	2.6
Other	0		1	2.6
Unknown	0		1	2.6
Smoking status				
No	35	77.8	29	74.3
Yes	8	17.8	6	15.4
Unknown	2	4.5	4	10.3
Fertility history				
Previous infertility	0		0	
Conception	12	26.7	10	25.6
Live birth	11	24.4	10	25.6
Abortion	3	6.7	6	15.4
Unknown	3	6.7	0	
Contraception at random assignment				
None	18	40	20	51.3
Oral contraceptive	24	55.3	16	41
IUD	1	2.2	1	2.6
Other	2	4.5	2	5.1
Diagnosis				
Hodgkin lymphoma	24	53.3	26	66.7
Non-Hodgkin lymphoma	21	46.7	13	33.3
Chemotherapy regimen				
Conditioning regimen (BEAM)	3	6.7	6	15.4
ACVBP ± consolidation*	9	20	8	20.5
(Escalated) BEACOPP	8	17.8	9	23.1
(R-)CHOP or R-CHOEP	8	17.8	1	2.6
ABVD (≥ 8 cures)	7	15.5	4	10.2
CHLVVP/ABVVP	6	13.3	9	23
Other	4	8.9	2	5.1
Alkylating agents				
Melphalan	3		7	
Mean cumulative dose, mg/m ²		140		140
SEM		0.0		0.0
Dacarbazine	10		5	
Mean cumulative dose, mg/m ²		4,590.6		3,820
SEM		920.4		850.8
Cyclophosphamide	30		24	
Mean cumulative dose, mg/m ²		5,224.8		5,300
SEM		322.7		431.3
Ifosfamide	4		7	
Mean cumulative dose, mg/m ²		4,875		5,285.7
SEM		718.1		510.1
Chlorambucil	6		9	
Mean cumulative dose, mg/m ²		207.3		214.7
SEM		14.1		11.7

(continued in next column)

Table 1. Patient Demographics and Clinical Characteristics (continued)

Demographic or Clinical Characteristic	GnRHa Group (n = 45)		Control Group (n = 39)	
	No.	%	No.	%
Carmustine	3		7	
Mean cumulative dose, mg/m ²		300		300
SEM		0.0		0.0
Chlormethine	2		1	
Mean cumulative dose, mg/m ²		27		18
SEM		9		0.0
Procarbazine	12		17	
Mean cumulative dose, mg/m ²		3,398.3		3,207
SEM		493.4		331

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ACVBP, doxorubicin, cyclophosphamide, vincristine, bleomycin, prednisolone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; BEAM, carmustine, etoposide, cytarabine, melphalan; BMI, body mass index; CHLVVP/ABVVP, chlorambucil, vinblastine, procarbazine, prednisolone, doxorubicin, bleomycin, vincristine, etoposide; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; GnRHa, gonadotropin-releasing hormone agonist; IUD, intrauterine device; R, rituximab.

*Consolidation consisted of methotrexate, etoposide, ifosfamide, and cytarabine.

End Points

The primary objective was to evaluate the efficacy of triptorelin plus norethisterone versus norethisterone alone in the prevention of chemotherapy-induced POF. In this study, we defined POF as an FSH level ≥ 40 IU/L.

As secondary objectives, we evaluated the complete ovarian function recovery rate, which was defined as FSH ≤ 10 IU/L, and the ovarian reserve (AMH). Correlations between patient age, the doses of chemotherapy, and the FSH values were also analyzed. The incidence of any pregnancies, treatment compliance, and adverse events were recorded during the study.

Statistical Analysis

The sample size was initially calculated accounting for a POF rate of 40% based on the results from the literature and to ensure a power of 80% and a type I error probability of 5%. On the basis of previous studies, the expected difference in the ovarian recovery rates between the two groups was at least 20% to 25%.⁷ For such a difference in the POF rates, a total number of 131 patients were required. With an estimated dropout rate of 20%, 157 patients would need to be randomly assigned in the study. A random allocation sequence was generated using simple random assignment to produce equally sized groups. Allocation concealment was implemented using central telephone or fax systems (Research Laboratory for Human Reproduction).

In 2010, an interim analysis for a first cohort of 99 randomly assigned patients was performed. Considering the low and similar POF rates observed in both groups, the study was unlikely to meet the primary end point, and enrollment was discontinued after the random assignment of 129 patients.

The statistical tests were performed using IBM-SPSS 19.0 for Windows (SPSS, Chicago, IL). Characteristics of the population, expressed in terms of proportions, were compared between groups using Fisher's exact test. The means were compared between groups using the *t* test, in the case of continuous variables, or Welch's *t* test, in case of unequal variances. The longitudinal analysis of the evolution of the groups' mean FSH values with time was performed using an analysis of variance (ANOVA) test with one repeated-measurements factor (time) at four levels (start of treatment and at 3, 6, and 12 months of follow-up) and one between-group factor (groups) at two levels. The mean FSH values were then compared time by time at each of the six different time points between groups using the *t* test or, in case of unequal variances, Welch's *t* test. The evolution of the AMH values between the start of the treatment and 1 year of follow-up was compared between groups using an

Table 2. Adverse Events During Treatment

Adverse Event	GnRHa Group (n = 45)		Control Group (n = 39)		P
	No.	%	No.	%	
Estradiol deficiency symptoms					
Sweating	21	46.6	14	35.9	.377
Hot flushes	11	24.4	12	30.7	.629
Vaginal dryness	7	15.5	5	12.8	.764
Headaches	14	31.1	16	41	.370
Vaginal bleeding	7	15.5	15	38.4	.024

Abbreviation: GnRHa, gonadotropin-releasing hormone agonist.

ANOVA test with one repeated-measurements factor (time) at two levels and one between-group factor (groups) at two levels. Two-tailed tests were performed and considered significant when $P < .05$.

Pearson correlations were used to investigate four relationships between continuous variables. For these multiple analyses, Bonferroni's correction has been applied, leading to stating a significant effect as soon as the P values are less than $.05/4$ (ie, $.0125$).

RESULTS

Study Population

Between July 2002 and April 2010, 146 women with lymphoma age 18 to 45 years were enrolled onto the study. Of the target sample of 146 patients, 129 were randomly assigned into two groups. Twenty (30.7%) of 65 patients in the GnRHa group and 25 (39%) of 64 patients in the control group dropped out during the study ($P = .359$; Fig 1). Forty-five patients in the GnRHa group and 39 patients in the control group completed the 1-year follow-up. The median age of the cohort was 25.6 years (range, 18 to 38 years). There were no significant differences in the baseline characteristics among the groups (Table 1).

There was no significant difference between groups concerning the type of chemotherapy regimens and the cumulative doses of alkyl-

ating agents (Table 1). Cyclophosphamide was the most commonly administered alkylating agent; 66.6% and 61.5% of patients received cyclophosphamide in the GnRHa and control groups, respectively. Treatment with norethisterone or norethisterone plus GnRHa began with a mean time lapse of 1.87 ± 0.4 or 3.82 ± 0.8 days before chemotherapy in the control and GnRHa groups, respectively. Three patients in the GnRHa group received the treatment for longer than 15 days before the start of chemotherapy.

Adverse Events

During treatment, symptoms associated with estrogen deficiency were frequently observed in both groups (Table 2). At least one of these adverse symptoms was observed in 75.5% of the GnRHa patients and 88.5% of the control patients. Vaginal bleeding occurred in 15.5% and 38.4% of patients in the GnRHa and control groups, respectively ($P = .024$). This adverse event prompted the doubling of the norethisterone dose for a few days in four patients in the GnRHa group and nine patients in the control group.

Two patients experienced severe adverse events (SAEs) that were potentially related to the drugs used in the study. These SAEs manifested as a pulmonary thromboembolism in one patient and as erythema nodosum in the other patient. Both patients were observed in the GnRHa group, but a clear link with the study drugs has not been confirmed. No SAEs related to the study were reported in the control group.

Primary Objective

The primary objective of the protocol was to compare the POF rates after 1 year of follow-up among treatment conditions. The mean follow-up duration was 353 ± 14 and 358 ± 10 days in the GnRHa and control groups, respectively ($P = .749$).

Forty-nine patients (25 patients in the GnRHa group and 24 patients in the control group) presented nonmissing FSH values at the start of treatment and at 3, 6, and 12 months of follow-up. The ANOVA for repeated measurements performed on these patients determined a global time effect ($P < .001$), no group effect ($P = .196$),

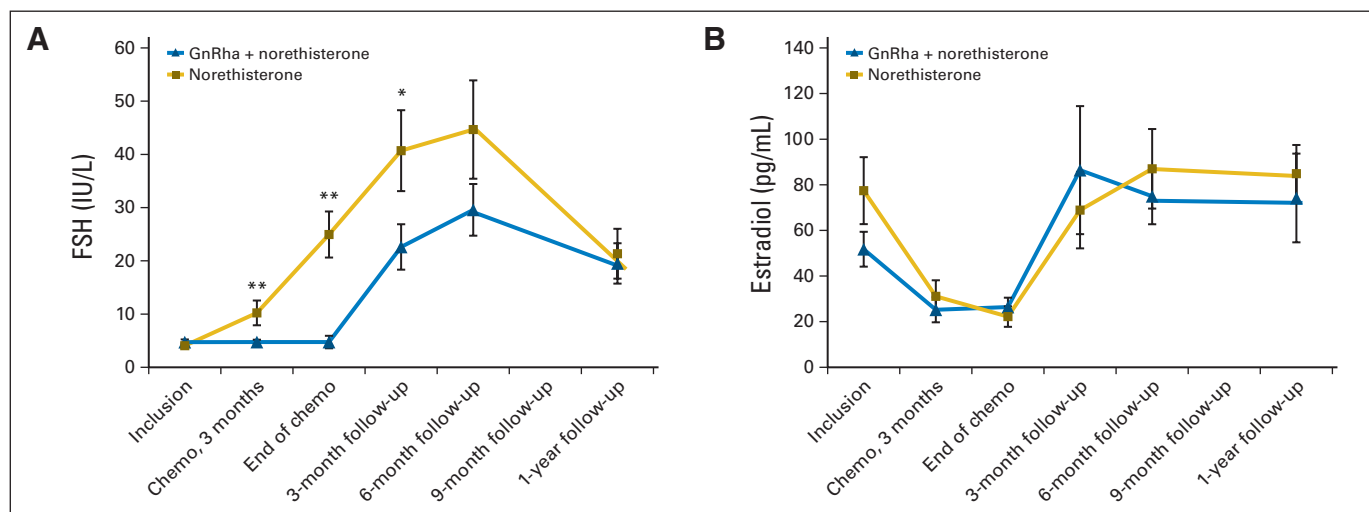


Fig 2. Ovarian function follow-up. Mean (A) follicle-stimulating hormone (FSH) and (B) estradiol values (\pm SEM) at the following time points: at inclusion; after 3 months of chemotherapy (chemo); at completion of chemotherapy; and at 3, 6, and 12 months of follow-up. (*) $P < .05$. (**) $P < .01$. GnRHa, gonadotropin-releasing hormone agonist.

and no interaction between these factors ($P = .109$), meaning that the longitudinal trends are similar in both groups.

A significant global difference in FSH levels between the groups was observed between the start of treatment and the 1-year follow-up ($P = .013$). As expected, patients in the control group had significantly higher FSH values than patients treated with GnRHa during chemotherapy (Fig 2; Appendix Table A1, online only). The mean FSH values were significantly different between groups during treatment ($P = .004$ at 3 months; $P < .001$ at the end of treatment). After chemotherapy, the mean FSH levels increased in both groups (Fig 2). They remained different ($P = .042$) after 3 months of follow-up, but this difference was no longer discernible after 6 months of follow-up ($P = .155$).

After 1 year of follow-up, most of the patients in both groups had recovered ovarian function, with the exception of 20% and 19% of patients in the GnRHa and control groups, respectively, who had POF ($P = 1.000$; Fig 3).

No significant differences were observed between the groups in the estradiol levels sampled during chemotherapy or follow-up (Fig 2). In the cohort of patients who experienced POF, all patients except one had estradiol levels less than 40 pg/mL. For this patient, an additional blood test confirmed the POF.

Secondary Objectives

At the end of chemotherapy, 75% of patients in the GnRHa group had an FSH level ≤ 10 IU/L, whereas only 41% of patients had a low FSH level in the control group ($P = .009$). However, no difference between groups was observed in the rates of patients who completely recovered ovarian function after 1 year of follow-up (FSH ≤ 10 IU/L; Fig 3). AMH levels were measured in 16 and 15 patients in the GnRHa and control groups, respectively. The mean ages of these patients were 25.58 ± 1.60 and 27.55 ± 1.50 years in the GnRHa and control groups, respectively ($P = .378$).

The mean AMH values decreased with time in both groups ($P = .009$). After 1 year of follow-up, the proportion of patients with AMH values greater than 1 ng/mL was higher in the GnRHa

group than in the control group (eight of 16 patients v two of 15 patients, respectively; $P = .023$). The mean AMH values were also higher in the GnRHa group compared with the control group after 1 year of follow-up (1.40 ± 0.35 v 0.56 ± 0.15 ng/mL, respectively; $P = .040$; Fig 4).

No correlation was observed between patient age at random assignment and the FSH values at the start of the study ($r = -0.113$, $P = .308$) or at 1 year of follow-up ($r = 0.094$, $P = .417$). The time interval between the initiation of treatment and the start of chemotherapy also showed no relationship with the patients' FSH values at the end of the follow-up period ($r = -0.117$, $P = .320$). In the population of patients treated with cyclophosphamide, no significant correlation was observed between the cumulative dose of cyclophosphamide and the FSH values at the end of the follow-up period ($r = 0.282$, $P = .051$).

Three and six patients in the GnRHa and control groups, respectively, received high-dose chemotherapy with bone marrow transplantation. Of these patients, two patients in the GnRHa group and four patients in the control group had POF. Two patients in the GnRHa group became pregnant during the follow-up period.

DISCUSSION

Approximately 80% of patients in both groups exhibited a restoration of ovarian function after 1 year of follow-up. Norethisterone was administered continuously in the GnRHa group to reduce the hypoestrogenic adverse effects and in the control group to ensure an amenorrheic condition during chemotherapy. Although a protective effect of norethisterone alone on ovarian function during chemotherapy cannot be excluded,²⁰ this study did not show a significant additional effect of GnRHa on the POF rate after 1 year of follow-up.

There was a significant difference between the mean FSH values of both groups at the end of chemotherapy because of the inhibitory

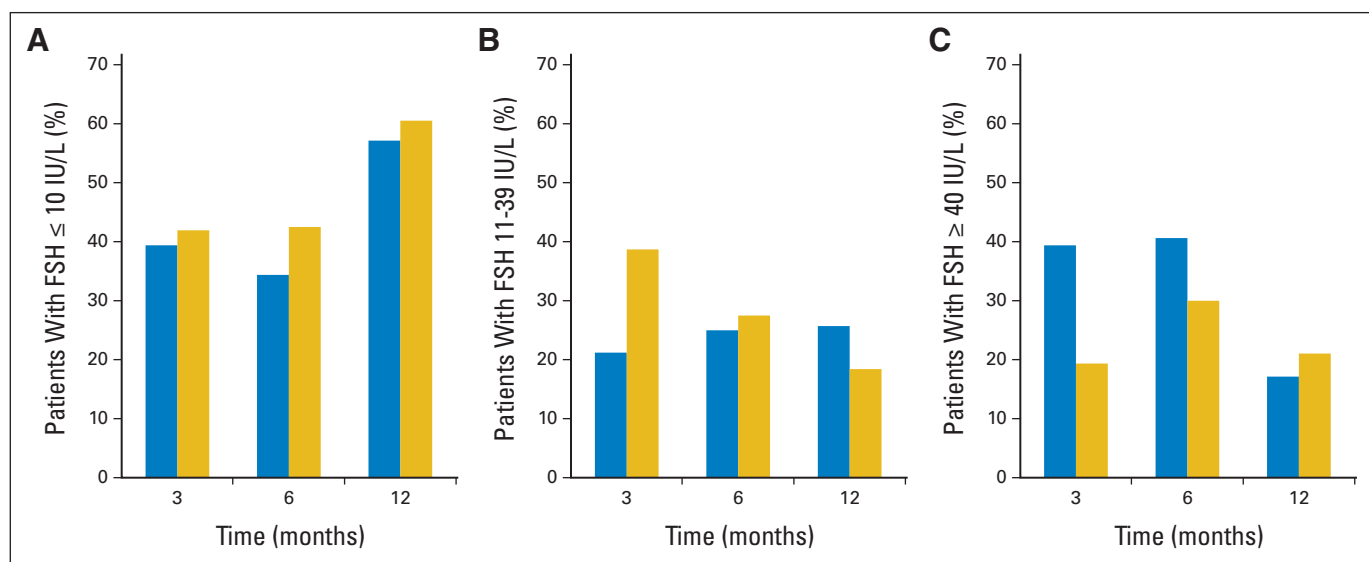


Fig 3. Percentage of women with follicle-stimulating hormone (FSH) values (A) ≤ 10 IU/L, (B) between 11 and 39 IU/L, and (C) ≥ 40 IU/L in the gonadotropin-releasing hormone agonist group (gold) and control group (blue) at different follow-up times (3, 6, and 12 months).

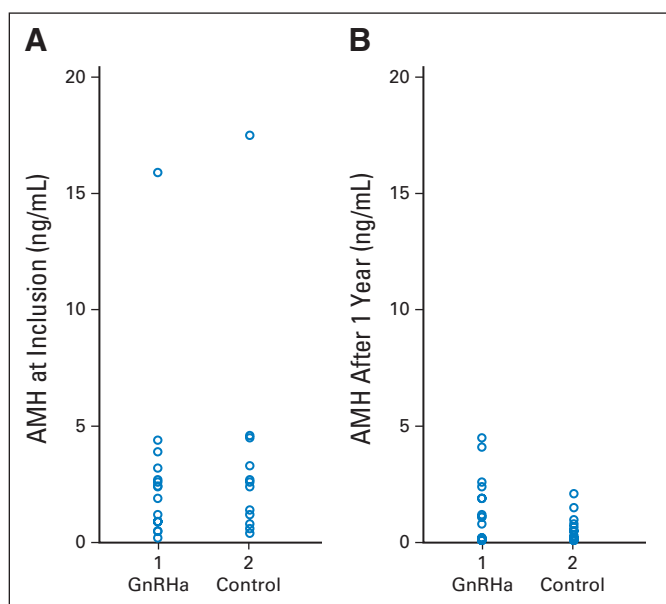


Fig 4. Anti-Müllerian hormone (AMH) values at (A) inclusion and (B) after 1 year of follow-up in the gonadotropin-releasing hormone agonist (GnRHa) and control groups.

effects of GnRHa on gonadotropins secretion. Although this difference was still observed 3 months after the completion of chemotherapy, the mean FSH levels increased in parallel in both groups. After 6 months, the FSH levels decreased as the recruitment of secondary follicles into the growing phase resumed. These results suggest that postchemotherapy acute gonadotoxic effects occurred regardless of whether the patients received GnRHa. Furthermore, conclusions concerning the efficacy of GnRHa treatment should not be drawn before 1 year of follow-up because of the significant variation of FSH values during the first year of follow-up.

We further investigated the potential protective effect of GnRHa treatment during chemotherapy on the ovarian reserve. FSH levels greater than 10 IU/L have been associated with a diminishing ovarian reserve.^{21,22} The AMH level has been reported as a suitable marker of ovarian reserve in women treated for lymphoma, reflecting the gonadotoxicity of the drug regimen.²³ Low FSH levels at the end of follow-up were similarly observed in both groups. Considering the AMH levels, however, the results suggested that the ovarian reserve was better preserved in the GnRHa group. Together, these results suggest that GnRHa does not prevent POF in high-risk patients but may efficiently preserve the ovarian reserve of those who recover ovarian function. However, these results must be confirmed after a longer follow-up.

In addition to the potential protective effects of GnRHa on ovarian reserves, this treatment may reduce the occurrence of hypermenorrhea during chemotherapy.²⁴ Our study showed that vaginal bleeding occurred less frequently in the GnRHa group than in the control group during chemotherapy.

The results from previous observational studies have generated a large debate concerning the efficacy of GnRHa in preventing chemotherapy-induced POF. Blumenfeld et al²⁵ first described the protective effect of GnRHa on ovarian function when administered concomitantly with chemotherapy, and others have con-

firmed these results.²⁶⁻²⁸ In a cohort of 111 patients with lymphoma, age 15 to 40 years, 3.1% and 37% of patients developed POF in the GnRHa and retrospective control groups, respectively ($P < .001$).²⁹

Although these were prospective studies, the control groups of many observational studies included an additional retrospective cohort of patients with differing follow-up times between groups and introduced other possible biases.¹¹ Single-arm studies have also reported a high incidence of resumption of menses after GnRHa treatment.³⁰⁻³² However, without a selected control group, the effect of GnRHa cannot be properly evaluated.

Randomized studies on POF have seldom been performed, mainly because of the difficulty of enrolling young patients, particularly hematologic patients. Waxman et al³³ reported the first prospective, randomized study, but only eight and 10 patients were enrolled onto the study and control groups, respectively. The study failed to demonstrate any significant effect of GnRHa treatment on the ovarian function recovery rate. Similarly, the German Hodgkin study failed to demonstrate any ovarian protective effect of GnRHa after at least 1 year of follow-up in a cohort of 19 randomly assigned patients with lymphoma, and as a result, the study was prematurely closed.³⁴ Other larger randomized studies that enrolled patients with breast cancer have been reported, with contradictory results. Some studies suggested that GnRHa prevents POF,^{35,17} whereas others revealed similar rates of menstruation recovery between patients treated with GnRHa during chemotherapy and patients treated with chemotherapy alone.^{16,36} However, adjuvant therapy may interfere with the evaluation of the true recovery of ovarian function.¹⁴ Despite the difficulty of enrollment and follow-up, the evaluation of the efficacy of GnRHa in a young population with hematologic diseases is crucial for the preservation of their fertility. To the best of our knowledge, this is the largest randomized study reporting the results of a 1-year follow-up in hematologic patients.

In conclusion, this prospective study involving patients with lymphoma did not provide evidence that GnRHa is effective in preventing POF. However, it suggests a long-term benefit of GnRHa on fertility of patients who spontaneously experience restoration of ovarian function. Until long-term results confirm the benefit of GnRHa to improve future fertility, the treatment should not be administered to prevent POF apart from in experimental protocols.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(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.

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AUTHOR CONTRIBUTIONS

Conception and design: Isabelle Demeestere, Dominique Bron, Yvon Englert

Administrative support: Julie Dechene

Provision of study materials or patients: Pauline Brice, Fedro A. Peccatori, Alain Kentos, Isabelle Gaillard, Pierre Zachee, Rene-Olivier Casanovas, Eric Van Den Neste, Dominique Bron

Collection and assembly of data: Isabelle Demeestere, Pauline Brice, Fedro A. Peccatori, Alain Kentos, Isabelle Gaillard, Pierre Zachee, Rene-Olivier Casanovas, Eric Van Den Neste, Julie Dechene, Dominique Bron

Data analysis and interpretation: Isabelle Demeestere, Julie Dechene, Vivianne De Maertelaer, Yvon Englert

Manuscript writing: All authors

Final approval of manuscript: All authors

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