VOLUME 34 · NUMBER 22 · AUGUST 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

No Evidence for the Benefit of Gonadotropin-Releasing Hormone Agonist in Preserving Ovarian Function and Fertility in Lymphoma Survivors Treated With Chemotherapy: Final Long-Term Report of a Prospective Randomized Trial

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Published online ahead of print at www.jco.org on May 23, 2016.

Processed as a Rapid Communication manuscript.

Supported by the Fonds National de la Recherche Scientifique (FNRS-Télévie) and by an unconditional grant from the Ipsen Pharmaceutical Group. Triptorelin was provided by the Ipsen Pharmaceutical Group.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/16/3422w-2568w/$20.00

DOI: 10.1200/JCO.2015.65.8864

ABSTRACT

Purpose

We have reported previously that after 1-year follow up, gonadotropin-releasing hormone agonist (GnRHa) did not prevent chemotherapy-induced premature ovarian failure (POF) in patients with lymphoma, but may provide protection of the ovarian reserve. Here, we report the final analysis of the cohort after 5 years of follow up.

Patients and Methods

A total of 129 patients with lymphoma were randomly assigned to receive either triptorelin plus norethisterone (GnRHa group) or norethisterone alone (control group) during chemotherapy. Ovarian function and fertility were reported after 2, 3, 4, and 5 to 7 years of follow up. The primary end point was POF, defined as at least one follicle-stimulating hormone value of > 40 IU/L after 2 years of follow up.

Results

Sixty-seven patients 26.21 $\pm$ 0.64 years of age had available data after a median follow-up time of 5.33 years in the GnRHa group and 5.58 years in the control group ($P = .452$). Multivariate logistic regression analysis showed a significantly increased risk of POF in patients according to age ($P = .047$), the conditioning regimen for hematopoietic stem cell transplant ($P = .002$), and the cumulative dose of cyclophosphamide > 5 g/m^2 ($P = .019$), but not to the coadministration of GnRHa during chemotherapy (odds ratio, 0.702; $P = .651$). The ovarian reserve, evaluated using anti-Müllerian hormone and follicle-stimulating hormone levels, was similar in both groups. Fifty-three percent and 43% achieved pregnancy in the GnRHa and control groups, respectively ($P = .467$).

Conclusion

To the best of our knowledge, this is the first long-term analysis confirming that GnRHa is not efficient in preventing chemotherapy-induced POF in young patients with lymphoma and did not influence future pregnancy rate. These results reopen the debate about the drug's benefit in that it should not be recommended as standard for fertility preservation in patients with lymphoma.

J Clin Oncol 34:2568-2574. © 2016 by American Society of Clinical Oncology

INTRODUCTION

The incidence of Hodgkin lymphoma shows a bimodal age distribution, with an initial peak in young adults, whereas the incidence of non-Hodgkin lymphoma increases with age. However, approximately one in seven (14%) non-Hodgkin lymphomas are diagnosed in the under-50-year age group (UK cancer research statistics).[1] A growing number of hematologic cancer survivors of reproductive age face infertility or permanent amenorrhea resulting from cancer-related therapy. Pharmacologic protection of the ovary during chemotherapy seems to be an attractive option to preserve fertility. Although the administration of gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy has been considered for this indication for at least two decades, their efficiency in preventing premature ovarian failure (POF) is still controversial.[2-5] The majority of the prospective trials evaluating the efficiency of GnRHa in preventing

chemotherapy-induced ovarian damage included few patients or the patients in the trials were not randomly assigned, and results were highly controversial. The largest randomized controlled trials (RCTs) included patients with breast cancer, and the debate was recently relaunched by the publication of the Prevention of Early Menopause Study[6] and long-term outcomes observed in the study Prevention of Chemotherapy-inducing Menopause in Early Breast Cancer Patients (PROMISE),[7,8] which reported significant reduction of ovarian failure rates in patients treated with GnRHa during chemotherapy. A recent meta-analysis of RCT studies suggested a benefit of GnRHa associated with chemotherapy in a population with breast cancer,[15] although clinical evidence remains uncertain for others.[3,9,10]

Because hematologic diseases are often diagnosed in younger patients treated with high gonadotoxic regimen, evidence of GnRHa efficiency in this population is urgently needed to optimize decision making in clinical practice. We previously reported the results of a 1-year follow-up of the largest prospective randomized trial that included 129 patients with lymphoma with a mean age of 26 years.[11] We showed similar rates of POF, defined as a follicle-stimulating hormone (FSH) level $>$ 40 IU/L, in both groups (20% and 19% in the GnRHa and control groups, respectively; $P = 1.000$). The trial did not provide any evidence that GnRHa prevents POF. However, it suggested that the ovarian reserve might be better preserved in the GnRHa group. Hence, the study was prolonged to evaluate the long-term benefit of GnRHa on the ovarian reserve and its impact on fertility. The final analysis presented here reports on the median 5-year follow up of the cohort.

PATIENTS AND METHODS

The study design was as described previously.[11] Participants were enrolled from 15 oncologic centers in France, Belgium, and Italy. Ethical committee approval was obtained for each of the participating centers according to national obligation (ClinicalTrials.gov identifier: NCT01160315). Patients between 18 and 45 years of age who were being treated for Hodgkin or non-Hodgkin lymphoma with alkylating agents were eligible for the trial. The main exclusion criteria were pelvic irradiation; history of amenorrhea ($>$ 3 months); thromboembolic processes; severe hypertension; severe obesity; hepatic or renal insufficiency; contraindication of intramuscular injection; prior chemotherapy treatment; presence of ovarian abnormalities (other than functional cysts); ovarian insufficiency defined as FSH $>$ 15 IU/L at the time of diagnosis; and the receipt of fewer than eight cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine treatment (ABVD; Data Supplement).

Eligible patients were randomly assigned to receive either chemotherapy and an intramuscular injection of 11.25 mg of triptorelin (Decapeptyl LP 11.25 mg; Ipsen Pharma, Merelbeke, Belgium) every 12 weeks in addition to norethisterone acetate at 5 mg once per day (Primolut-Nor 5 mg; Bayer Schering Pharma, Antwerp, Belgium; GnRHa group) or 5 mg of norethisterone acetate alone once per day (control group) during all chemotherapy.[11] According to the protocol, hormonal therapy (contraceptive pill or hormonal substitutive therapy) was interrupted at least 10 days before the blood test. When feasible, a second analysis was required in patients with an FSH level $<$ 40 IU/L. Here, we report hormonal values at random assignment, at the end of the treatment, and during the follow-up (2, 3, 4, and $\geq$ 5 years). Anti-Müllerian hormone (AMH) measurements were performed centrally at the Chemistry Laboratory at Erasme Hospital (Elecsys AMH module; Roche Diagnostics, Vilvoorde, Belgium). The results after 1-year follow-up have been published.[11] In this article, the analysis focuses on the long-term follow-up time points (2 to 4 years and 5 to 7 years).

The primary end point measure of POF was defined as at least one episode of FSH level $\geq$ 40 IU/L during long-term follow up.[12] The secondary end points were the ovarian function recovery rate, defined as FSH $\leq$ 15 IU/L during all the follow up; the ovarian reserve (AMH levels); the fertility rate; and the free-disease survival rate, defined as patients without recurrence or death at the end of the follow up. Adverse events during treatment have been reported previously.[11]

The original study design mandated the accrual of 157 patients to ensure a power of 80% and a type error I probability of 5%, on the basis of an assumed difference of a POF rate of 40%.[13] After the first interim analysis, enrolment was discontinued after the random assignment of 129 patients, because the study was unlikely to meet the primary end point (similar POF rate in both groups).[11]

In this study, categorical variables are represented by proportions and percentages, and they are compared between groups with Pearson's exact χ^2 and Fisher's exact tests. Continuous variables are summed up by their mean $\pm$ SEM. The mean FSH values were compared between groups using *t* tests. The comparisons were performed at each of the time points without using imputation methods (inclusion, end of treatment, and follow-up at 2, 3, 4, and 5 to 7 years).

The evolution of the AMH levels was compared between the start of the treatment and at two follow-up periods (2 to 4 years and 4 to 7 years). When two hormonal levels were available during the period of analysis, the second one was considered. AMH values were compared using paired *t* tests. Logistic regressions were performed using the enter method (explanatory variables are all entered at the same time into the model).

The dependent variable was POF, FSH $\leq$ 15 IU/L, or pregnancy, whereas the explanatory variables were age, conditioning regimen for hematopoietic stem cell transplant (HSCT), coadministration of GnRHa, type of disease (Hodgkin or non-Hodgkin lymphoma), and cumulative dose of cyclophosphamide. This last variable was categorized according to two modalities: patients who had not received cyclophosphamide or had received a cumulative dose $<$ 5 g/m^2, and patients who had received a cumulative dose of cyclophosphamide $\geq$ 5 g/m^2.[14] All tests are two tailed and were considered significant when $P < .05$. Statistical tests were performed using IBM-SPSS for Windows version 22.0 (SPSS, Chicago, IL) and MedCalc statistical software version 14.12.0 (MedCalc, Ostend, Belgium).

RESULTS

Study Population

Between July 2002 and April 2010, 129 patients were randomly assigned to the study. The first triptorelin injection occurred 2 $\pm$ 0.51 days before chemotherapy initiation in the GnRHa group (range, 0 to 19). A total of 67 patients (48.8%) completed at least 2 years of follow up and were eligible for this analysis (Fig 1). The median follow-up time was 5.33 years in the GnRHa group and 5.58 years in the control group ($P = .452$). The basal characteristics of the population according to the study groups and the cumulative doses of the most common alkylating agents are described in Table 1.

Premature Ovarian Failure Rate

As expected, the mean FSH level was significantly lower in the GnRHa group as compared with the control group at the end of chemotherapy, but this difference was no longer observed during the long-term follow up (Fig 2). Here, we identified patients as having POF when at least one episode of FSH value $\geq$ 40 IU/L was reported during the follow-up. A total of 63 out of 67 patients (94%) were included in the analysis of the primary end point. For the remaining four patients, FSH values were unavailable, but spontaneous menstruation and pregnancies were reported during the

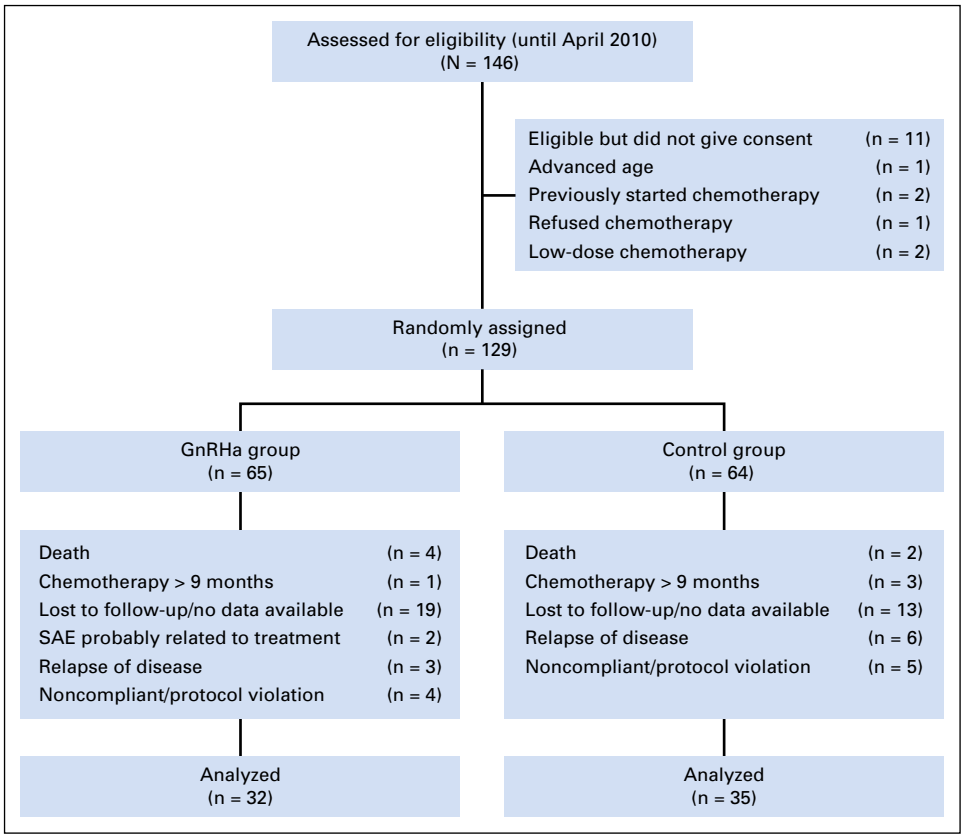

Fig 1. CONSORT diagram. GnRHa, gonadotropin-releasing hormone agonist; SAE, severe adverse event.

follow-up period. Eighty-nine percent of the eligible patients had at least two hormonal values during the long-term follow up. For 46% of the eligible patients, the information about contraceptives was not available at the time of the blood test. For these patients, hormonal values were included in the analysis when they were interpretable (POF values or ovulatory cycle with normal AMH level or pregnancy).

A total of six out of 31 patients (19.4%) in the GnRHa group and eight out of 32 patients (25%) in the control group experienced POF (P = .763). Multivariate logistic regression analysis showed a significantly increased risk of POF in patients who received a conditioning regimen for HSCT (P = .002) or a cumulative dose of cyclophosphamide > 5 g/m^2 (P = .019). An increased risk of POF was also observed according to age (P = .047), but not according to the type of disease (P = .281), nor to the co-administration of GnRHa during chemotherapy (P = .651; Table 2). Six out of 10 patients treated with an HSCT conditioning regimen had postmenopausal FSH values during the follow-up (two of three and four of seven patients in the GnRHa and control groups, respectively). In contrast, by excluding the 12 patients who received less gonadotoxic chemotherapy as ABVD (n = 9), Stanford regimen (n = 2), or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) six cycles or less (n = 1), the POF rates rose to 26% (six of 23) and 26.6% (eight of 30) in the GnRHa and control groups, respectively (P = 1).

Ovarian Reserve

A total of 37 patients had AMH levels available at least once during the follow-up period. Mean AMH values decreased significantly after treatment (3.14 $\pm$ 0.80 ng/mL at inclusion v 1.26 $\pm$ 0.3 ng/mL after 2 to 4 years, P = .039) and remained at a similar level after 5 to 7 years (1.58 $\pm$ 0.38 ng/mL, P = .520; individual values: Fig 3). A higher rate of low AMH (AMH $<$ 0.5 ng/mL) was observed in both groups after 2 to 4 years of follow up (Fig 4).

Thirty-one patients in the GnRHa group and 32 patients in the control group were eligible for analysis of the ovarian function restoration rate (low FSH values: FSH $\leq$ 15 IU/L). A total of 21 out of 31 patients and 16 out of 32 patients had FSH values $\leq$ 15 IU/L throughout the follow-up (P = .202). Multivariate logistic regression analysis showed a significantly decreased risk of low FSH values in patients who received the conditioning regimen for HSCT (P = .043) or a cumulative dose of cyclophosphamide > 5 g/m^2 (P = .004). No difference in the risk of low FSH values was observed according to age (P = .081), type of disease (P = .393), or administration of GnRHa (P = .434).

Pregnancy Outcomes

A total of 17 of 32 patients (53.1%) and 15 of 35 patients (42.8%) achieved pregnancy in the GnRHa and control groups, respectively (P = .467). One additional pregnancy was achieved after egg donation in a patient from the GnRHa group, who was treated with the HSCT conditioning regimen. Surprisingly, five pregnancies (two in the GnRHa group and three in the control group) were reported in patients with protocol-defined POF during the follow-up. These data confirm the possibility of

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Eligible Patients for Primary Objective	
	GnRHa Group (n = 32)	Control Group (n = 35)
Age, years		
Mean ± SEM	25.84 ± 1.00	26.55 ± 0.82
Range	18-38	18-38
BMI, kg/m^2, mean ± SEM	20.39 ± 0.39	21.57 ± 0.40
Race or ethnic group, No. (%)		
White	32 (100.0)	31 (88.6)
North African	0	1 (2.85)
Asian	0	1 (2.85)
Others	0	1 (2.85)
Unknown	0	1 (2.85)
Smoking habits, No. (%)		
No	22 (68.8)	26 (74.3)
Yes	7 (21.9)	6 (17.1)
Unknown	3 (9.3)	3 (8.6)
Fertility history, No. (%)		
Previous infertility	0	0
No conception	19 (59.4)	26 (74.3)
Conception	10 (31.25)	8 (22.8)
Live birth	9 (28.1)	7 (20.0)
Pregnancy lost	1 (3.1)	1 (2.85)
Abortion	3 (9.4)	4 (11.4)
Unknown	3 (9.4)	1 (2.85)
Contraception at random assignment, No. (%)		
None	13 (40.6)	18 (51.4)
Oral contraceptive	16 (50)	15 (42.9)
IUD	2 (6.3)	1 (2.85)
Other	1 (3.1)	1 (2.85)
Diagnosis, No. (%)		
Hodgkin lymphoma	19 (59.4)	23 (65.7)
Non-Hodgkin lymphoma	13 (40.6)	12 (34.3)
Chemotherapy regimen, No. (%)		
HSCT conditioning regimen (BEAM)	3 (9.4)	7 (20)
ACVBP (or modified) ± consolidation	5 (15.6)	5 (14.3)
(Escalated) BEACOPP	4 (12.5)	8 (22.8)
Rituximab with or without cyclophosphamide, doxorubicin, vincristine, and prednisone	7 (21.9)	2 (5.7)
ABVD (≥ 8 cycles)	6 (18.75)	3 (8.6)
CHLVVP/ABVVP	6 (18.75)	9 (25.75)
Stanford V	1 (3.1)	1 (2.85)
Total doses of chemotherapy,* mg/m^2, mean ± SEM (No.)		
Cyclophosphamide	5,088.7 ± 351.5 (19)	5,536.4 ± 477.9 (22)
Ifosfamide	5,250 ± 750 (2)	5,000 ± 689.2 (5)
Dacarbazine	5,475 ± 1,281.7 (9)	3,820 ± 855.8 (5)
Doxorubicin	306.8 ± 27.6 (32)	2,48.5 ± 14.8 (34)
Procarbazine	2,820 ± 510.9 (9)	2,856.2 ± 333.8 (16)
Chlorambucil	207.3 ± 4.1 (6)	220.3 ± 11.9 (10)
Melphalan	140 (3)	140 (7)

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; Consolidation: methotrexate, etoposide, ifosfamide and cytarabine; GnRHa, gonadotropin-releasing hormone agonist; HSCT, hematopoietic stem cell transplant; IUD, intrauterine contraceptive device; Stanford V, doxorubicin, vinblastine, chlormethine, prednisolone, vincristine, bleomycin, etoposide.
*Main gonadotoxic agents are described.

incidental ovarian cycle recovery, leading to fertility restoration several years after treatment in this young population. On the basis of logistic regression analysis, the occurrence of pregnancies was not associated with age (P = .895), type of disease (P = .399), or cotreatment with GnRHa (P = .355).

Overall Survival

There were four and two deaths reported in patients in the GnRHa and control groups, respectively. The overall disease-free survival rates were 87.5% and 82% for patients in the control and GnRHa groups, respectively.

DISCUSSION

This report extends the results of the previously published analysis of a 1-year follow-up.[11] Here, we report hormonal profiles and fertility at longer time points in a randomly assigned cohort of patients with lymphoma, who had either received or did not receive GnRHa during chemotherapy to prevent POF. To the best of our knowledge, this is the first RCT providing accurate information on ovarian function and fertility after a median 5 years of follow up. The trial confirmed our previous data, showing the inefficiency of GnRHa for reducing chemotherapy-induced POF in young patients with lymphoma.

Recently, the Prevention of Early Menopause Study has reopened the debate on the use of GnRHa to counter chemotherapy-induced ovarian damage.[6] After 2 years of follow up, this RCT suggested that the administration of GnRHa during the course of chemotherapy protects ovarian function in patients with breast cancer. In the study, 135 of the 218 randomly assigned patients met the primary end point, defined as amenorrhea for the preceding 6 months and postmenopausal FSH values at 2 years of follow up. The investigators showed that 22% of the patients in the chemotherapy-alone group and 8% of the patients in the GnRHa group had protocol-defined ovarian failure (odds ratio, 0.30; 95% CI, 0.09 to 0.97; P = .04).[6] Updated analysis of the PROMISE-GIM6 trial evaluating the 5-year cumulative incidence of menstrual resumption in patients with breast cancer also reported data in favor of the administration of GnRHa during chemotherapy (age-adjusted hazard ratio, 1.48; P = .006).[8] These recent results led to the updating of the guidelines of the 2015 St Gallen International Expert Consensus Panel and the National Comprehensive Cancer Network to acknowledge GnRHa as a fertility preservation option, whereas ASCO did not change its recommendation.

This study strongly suggests caution with this new recommendation. Most of the studies reported ovarian function or menstruation after short follow-up periods (12 to 36 months). Here, long-term analysis did not show any benefit from GnRHa during high-risk chemotherapy administration in patients with lymphoma. Despite the recent reports of RCTs in patients with breast cancer, the efficiency of GnRHa in reducing ovarian damage during chemotherapy is still controversial. A meta-analysis of 12 RCTs that included 1,231 patients with breast cancer recently confirmed a reduction of POF in patients who

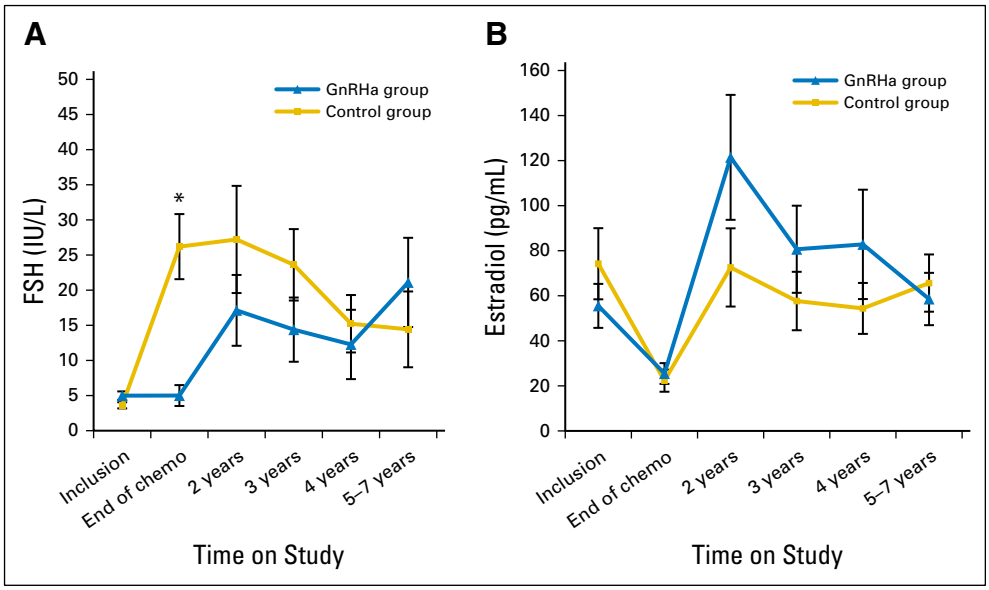

Fig 2. Ovarian function follow-up. Data are presented as mean ± SEM. (A) FSH and (B) estradiol values at the following time points: at inclusion; at the end of chemotherapy; and at 2, 3, 4, and 5 to 7 years of follow-up. *$P < .001$. chemo, chemotherapy; FSH, follicle-stimulating hormone; GnRHa, gonadotropin-releasing hormone agonist.

received GnRHa during chemotherapy (odds ratio, 0.36; 95% CI, 0.23 to 0.57; $P < .001$),[15] whereas another, which included 10 selected RCTs that enrolled patients with breast cancer and lymphoma, did not report any difference in the overall resumption of ovarian function after chemotherapy with GnRH analog cotreatment (risk ratio, 1.12; 95% CI, 0.99 to 1.27; $P = .7$).[9] However, only six studies were selected in common, and the main outcomes also differed. The difference in the conclusions also emphasized the variation in the definition of POF according to the trials, the heterogeneity of the RCTs, and the difference in the follow-up durations and in the median age of the patients.

In a recent paper, Oktay and Turan[3] emphasized that menstruation or amenorrhea should not be considered surrogate markers of evidence of GnRHa efficacy in preserving the ovarian reserve. In the current trial, we showed that patients with POF might occasionally recover temporary ovarian function several years after treatment. Previous pregnancies have been reported in young patients with POF, showing that it could not have been considered as menopause.[16] These results highlight the need for studies with long-term follow-up reporting fertility and FSH levels at different time points before recommending GnRHa as an evidence-based option to preserve fertility. Occurrence of pregnancy is the most accurate hallmark for evaluating the efficiency of fertility preservation therapy. In our cohort, a large proportion of patients conceived, irrespective of GnRHa administration during chemotherapy.

Table 2. Odds Ratio of Age, Type of Disease, Allocation Arm, Total Dose of Cyclophosphamide, and HSCT Conditioning Regimen on Premature Ovarian Failure Risk After Logistic Multiple Regression Entering All Variables Into the Model (N = 63)

Variable	OR (95% CI)	*P*
Patient's age	1.16 (1-1.34)	.047
Type of disease: Non-Hodgkin *v* Hodgkin	0.36 (0.06-2.29)	.281
Protocol: control *v* GnRHa group	0.70 (0.15-3.24)	.651
Cyclophosphamide doses: ≥ 5 *v* < 5 g/m^2	10.18 (1.46-70.97	.019
HSCT conditioning regimen: Yes *v* No	67.68 (4.65-985.70)	.002

Abbreviations: GnRHa, gonadotropin-releasing hormone agonist; HSCT, hematopoietic stem cell transplant; OR, odds ratio.

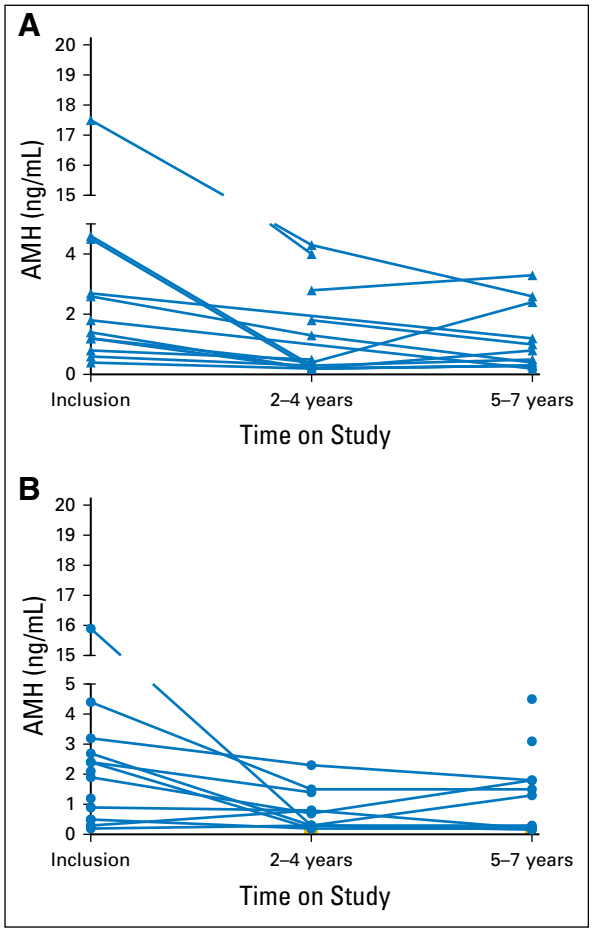

Fig 3. Individual evolution of AMH levels. (A) Control group (n = 19) and (B) GnRHa group (n = 18). AMH, anti-Müllerian hormone; GnRHa, gonadotropin-releasing hormone agonist.

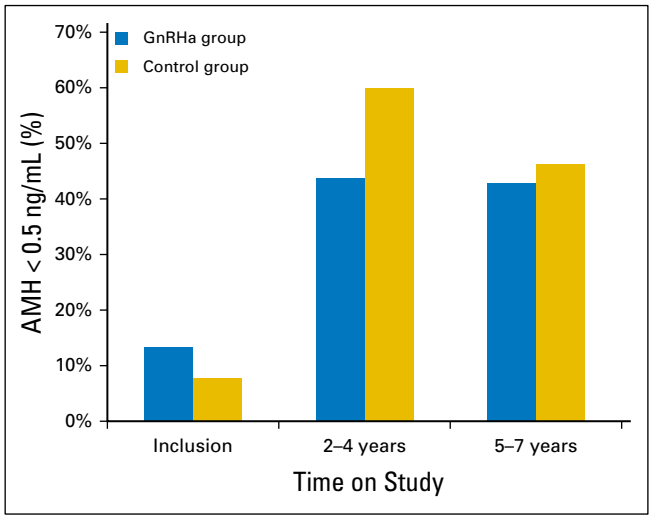

Fig 4. Percentage of women with AMH values of < 0.5 ng/mL in the GnRHa group and the control group at different time points. AMH, anti-Müllerian hormone; GnRHa, gonadotropin-releasing hormone agonist.

Patients treated for advanced-stage lymphoma are younger than those with breast cancer, but are usually treated with more gonadotoxic chemotherapy regimens. Unfortunately, RCTs addressing the potential ovarian-protective effect of GnRHa against chemotherapy in patients with lymphoma are rare, despite the high concern over future fertility issues. First, Waxman et al[17] failed to demonstrate any effect of GnRHa in a small cohort of patients with lymphoma. The German Hodgkin Study Group previously reported no protective effect of GnRHa in this high-risk population after 1-year follow up, leading to the premature closure of the trial.[18] The same group also retrospectively analyzed the ovarian function in patients with Hodgkin lymphoma enrolled onto the HD13 to HD15 trials. They showed that 82% of women with advanced-stage Hodgkin lymphoma who were younger than 30 years old displayed a regular menstrual cycle after a mean follow-up of 43 to 51 months, regardless of whether or not the women had received GnRHa during chemotherapy.[19] However, the administration of GnRHa during chemotherapy positively influenced the subsequent pregnancy rate in patients with favorable-stage diseases.[20] Although these results suggested that GnRHa might be more efficient in preserving fertility in patients treated with a less gonadotoxic regimen, the researchers highlighted that an important bias might be the patient's strong wish to preserve fertility, resulting in more frequent use of GnRHa in nonrandomized trials. In our cohort, POF was not observed in patients who received a low-risk chemotherapy regimen in both groups. Evidence of a benefit of the administration of GnRHa during low-risk chemotherapy is still lacking. Moreover, there is still no proven biologic rationale for the benefit of GnRHa.[21-23]

This study presents some limitations. The drop-out rate reached 50%, and almost 25% was related to loss of follow-up or data unavailability. Others researchers have already emphasized the challenges involved in randomly assigning patients in such a trial and in obtaining valuable data during long-term follow up. In the PROMISE-GIM6 study, almost 30% of the evaluable patients with breast cancer had no hormonal assessment within the first year of follow up.[7,8] To our knowledge, our study is the only RCT reporting the hormonal profile and pregnancy rate during long-term follow up. Moreover, there is no evidence that the missing data would have changed the main finding of the study, because the drop-out population's characteristics were similar to those of the eligible population (data not shown). Finally, logistic regression analyses showed an association between POF risk and age and type of treatment, but there was no association with the GnRHa treatment, and no difference was observed between pregnancy rates.

AMH levels were assessed only in part of the cohort. Therefore, our analysis was not able to provide strong evidence for the effect on the ovarian reserve. However, the trial also failed to demonstrate any effect of GnRHa on low FSH levels (FSH $\leq$ 15 IU/L), whereas the type of treatment (HSCT and high cumulative dose of cyclophosphamide) significantly interacted with this variable. These results suggest that GnRHa does not protect the ovarian function in young patients with lymphoma but the study was not sufficiently powered to reach strong conclusions regarding the effect of GnRHa on the ovarian reserve.

Despite its statistical limitations, this is the largest randomized clinical trial to show that concurrent administration of triptorelin and chemotherapy is not associated with a lower long-term probability of POF in patients with lymphoma. Furthermore, the high pregnancy rate observed in both groups did not suggest that triptorelin is effective in improving fertility. Triptorelin might be administered to prevent menorrhagia induced by thrombocytopenia associated with lymphoma,[11] but alternative fertility preservation options, such as ovarian tissue cryopreservation or oocyte and embryo vitrification, should always be offered to all young patients with a moderate or high risk of chemotherapy-induced ovarian damage.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No Evidence for the Benefit of Gonadotropin-Releasing Hormone Agonist in Preserving Ovarian Function and Fertility in Lymphoma Survivors Treated With Chemotherapy: Final Long-Term Report of a Prospective Randomized Trial

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Research Funding: Genentech (Inst)
Travel, Accommodations, Expenses: Genentech, Takeda Pharmaceuticals, Gilead Sciences

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Dominique Bron
Research Funding: Celgene, Janssen Pharmaceuticals, Gilead Sciences

Yvon Englert
Research Funding: Merck Serono (Inst), Ferring Pharmaceuticals (Inst)
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Acknowledgment

We thank the following investigators, who contributed to the random assignment of the patients: P. Brice (Haematological Department, St Louis Hospital, Paris, France), G. Martinelli, E. Cocorocchio, F.A. Peccatori (Haematological Department, Instituto Europeo di Oncologia, Milano, Italy), F. Walter, A. Kentos (Haematological Department, Erasme Hospital, Brussels, Belgium), D. Bron (Haematological Department, J. Bordet Institute, Brussels, Belgium), I Gaillard, J. Dupuis, C. Haioun, M. Diviné (Haematological Department, Hôpital Henri Mondor, Paris, France), P. Zachee (Haematological Department, Algemeen Ziekenhuis Stuivenberg, Antwerpen, Belgium), O. Casasnovas (Haematological Department, CHU de Dijon, Dijon, France), E. Van Den Neste, A. Ferrant (Haematological Department, St Luc Hospital, Brussels, Belgium), A. Van Hoof (Haematological Department, AZ St Jan, Bruges, Belgium), C. Decanter (Gynaecology and Obstetric Department, CHRU de Lille, Lille, France), F. Morschhauser (Haematological Department, CHRU de Lille, Lille, France), A. Stamatoullas (Haematological Department, Centre Henri Becquerel, Rouen, France), L. Garderet (Haematological Department, CHU St Antoine, Paris, France), P. Lederlin (Haematological Department, CHU de Nancy, Nancy, France), R. Schots (Haematological Department, AZ VUB, Brussels, Belgium), and C. Sebban (Medical Oncology Department, Centre Lyon Berard, Lyon, France).