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Debated Role of Ovarian Protection With Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Women With Cancer

TO THE EDITOR: In 2015, two large randomized controlled trials (RCTs) in patients with breast cancer (ie, Prevention of Early Menopause Study–Southwest Oncology Group [POEMS-SWOG] S0230 and Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients–Gruppo Italiano Mammella 6 [PROMISE-GIM6]) demonstrated improvement in both ovarian function and fertility with gonadotropin-releasing hormone agonist (GnRHa) administration during chemotherapy.^{1,2} The consistent absolute and relative results support the reliability of these findings (Table 1).¹⁻³ The largest meta-analysis including all RCTs in patients with breast cancer confirmed a reduced risk of premature ovarian failure (POF; odds ratio [OR], 0.36; $P < .001$) and an increased chance of achieving pregnancy (OR, 1.83; $P = .04$) with GnRHa during chemotherapy.⁴ On the basis of these findings, current guidelines recommend use of GnRHa as a strategy to offer patients with breast cancer who are interested in fertility and/or ovarian function preservation.⁵

Demeestere et al³ have recently reported follow-up data from their RCT investigating use of GnRHa during chemotherapy for preservation of ovarian function and fertility in patients with lymphoma. The authors concluded that after more than 5 years of follow-up, GnRHa administration did not significantly reduce POF or increase pregnancy rate.³ However, several issues should be considered in interpreting the results.

Although there is no standard definition of chemotherapy-induced POF, a composite end point using both clinical and laboratory measures (eg, irregular periods or amenorrhea with follicle-stimulating hormone [FSH] levels > 40 mIU/mL)⁶ lends greater specificity. The role of anti-müllerian hormone (AMH),

a marker of ovarian reserve commonly used in fertility clinics, is controversial in predicting chemotherapy-induced gonadal damage and subsequent fertility loss.⁷ Demeestere et al³ relied only on FSH or AMH levels, which might have increased false-positive results that incorrectly identified patients as having POF who did not in fact develop the event, as confirmed by the observation of five pregnancies in women with protocol-defined POF.

Although pregnancy represents the best marker of fertility, prevention of POF has other advantages in preserving quality of life. None of the RCTs of ovarian protection with GnRHa required interest in future pregnancy for eligibility, and only a minority reported pregnancies. The POEMS-SWOG S0230 trial, the only study to include pregnancy as a predefined secondary end point, showed a significantly higher pregnancy rate with use of GnRHa.^{1,8}

In the study by Demeestere et al,³ the use of the hormone norethisterone acetate in both study arms during chemotherapy may have diminished the observed protective effect of GnRHa. Norethisterone acetate directly affects the hypothalamic-pituitary axis, slowing gonadotropin-releasing hormone pulse frequency and lowering gonadotropins⁹; this effect would only be seen in the control arm, because the pituitary gonadotropin-releasing hormone receptors would be downregulated by the GnRHa in the experimental arm.

Furthermore, 46% of patients had no information on the use of hormonal contraceptives at the time of ovarian function assessment.³ Hormonal contraceptives can suppress FSH, which may have further confounded the results, especially if use was unbalanced between the two treatment arms.

According to the original analysis plan, 157 patients were required; however, only 129 women were randomly assigned, with 84 patients (65%) completing 1 year of follow-up and included in the primary analysis.¹⁰ Long-term analyses were not preplanned; hence, the time points for ovarian function evaluation were not prespecified or mandatory. Only 63 patients (49%) and 37 patients (29%) had information on FSH and AMH, respectively.³ Although reported as a negative study, the ORs for POF and pregnancy seen in the trial by Demeestere et al³ are consistent with the protective effect of GnRHa seen in other studies (Table 1) and may not have achieved statistical significance only because of lack of power.

Table 1. Main Results of the Largest Randomized Controlled Trials Investigating the Role of GnRHa During Chemotherapy in Preservation of Ovarian Function and Fertility in Women With Cancer

| Outcome | Demeestere et al ³ | POEMS-SWOG S0230 ¹ | PROMISE-GIM6 ² |
|--|--------------------------------|--------------------------------|------------------------------------|
| Treatment-induced POF (CT + GnRHa v CT alone), % | 19 v 25 (OR, 0.72; $P = .76$) | 8 v 22 (OR, 0.30; $P = .04$) | 8.9 v 25.9 (OR, 0.28; $P < .001$) |
| Patients with pregnancies (CT + GnRHa v CT alone), % | 53 v 43 (OR, 1.51; $P = .47$) | 21 v 11 (OR, 2.45; $P = .03$) | 5 v 2 (HR, 2.40; $P = .20$) |
| Disease-free survival (CT + GnRHa v CT alone), % | 82 v 87.5 (NR) | 89 v 78 (HR, 0.49; $P = .04$) | 80.5 v 83.7 (HR, 1.17; $P = .52$) |

Abbreviations: CT, chemotherapy; GnRHa, gonadotropin-releasing hormone agonist; HR, hazard ratio; NR, not reported; OR, odds ratio; POEMS-SWOG, Prevention of Early Menopause Study–Southwest Oncology Group; POF, premature ovarian failure; PROMISE-GIM6, Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients–Gruppo Italiano Mammella 6.

Regarding the assessment of missing data, although characteristics between patients who did versus did not drop out were similar,³ this is not relevant to the assessment of whether missing data bias the treatment effect. It is more important to know whether there was differential dropout between patients who did versus did not drop out by arm using interaction tests. Finally, because their study was not designed to test the equivalency of the two regimens, the absence of a beneficial effect with GnRHa cannot be claimed to confirm that GnRHa is not efficient in preventing POF³; at best, the study showed no evidence that GnRHa reduced the incidence of POF.

Although the study by Demeestere et al³ was unable to demonstrate ovarian protection with GnRHa during chemotherapy in patients with lymphoma, this was an underpowered and exploratory analysis of a study in which both control and experimental arm patients received hormonal treatment and in which the end point was flawed. Hence, these results should be considered as exploratory and do not refute findings from well-designed large RCTs on this topic.

Although embryo or oocyte cryopreservation is the first choice for fertility preservation, GnRHa during chemotherapy remains an option for women interested in preserving ovarian function and fertility.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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