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

M Lambertini
T Falcone
J Unger
K Phillips
Y Englert

See next page for additional authors

Follow this and additional works at: https://touro scholar.touro.edu/nymc_fac_pubs

Part of the Medicine and Health Sciences Commons

Recommended Citation

This Letter to the Editor is brought to you for free and open access by the Faculty at Touro Scholar. It has been accepted for inclusion in NYMC Faculty Publications by an authorized administrator of Touro Scholar. For more information, please contact touro.scholar@touro.edu.
Authors
M Lambertini, T Falcone, J Unger, K Phillips, Y Englert, Kutluk Oktay, and V Turan
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 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.6 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)7 lends greater specificity. The role of anti-mullerian 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 gonadotropins;9 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Demeestere et al3</th>
<th>POEMS-SWOG S02301</th>
<th>PROMISE-GIM62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-induced POF (CT + GnRHa v CT alone), %</td>
<td>19/25 [OR, 0.72; P = .76]</td>
<td>8/22 [OR, 0.30; P = .04]</td>
<td>8.9/25.9 [OR, 0.28; P &lt; .001]</td>
</tr>
<tr>
<td>Patients with pregnancies (CT + GnRHa v CT alone), %</td>
<td>53/43 [OR, 1.51; P = .47]</td>
<td>21/11 [OR, 2.45; P = .03]</td>
<td>5/2 [HR, 2.40; P = .20]</td>
</tr>
<tr>
<td>Disease-free survival (CT + GnRHa v CT alone), %</td>
<td>82/87.5 (NR)</td>
<td>89/78 [HR, 0.49; P = .04]</td>
<td>80.5/83.7 [HR, 1.17; P = .52]</td>
</tr>
</tbody>
</table>

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, 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 POF; at best, the study showed no evidence that GnRHa reduced the incidence of POF.

Although the study by Demeestere et al 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.

Matteo Lambertini
Breast Adjuvant Study Team Data Centre, Institut Jules Bordet, and Université Libre de Bruxelles, Brussels, Belgium

Tommaso Falcone
Cleveland Clinic Foundation, Taussig Cancer Institute, Cleveland, OH

Joseph M. Unger
Southwest Oncology Group Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA

Kelly-Anne Phillips
Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Victoria, Australia

Lucia Del Mastro
Istituto di Ricovero e Cura a Carattere Scientifico–Azienda Ospedaliera Universitaria San Martino–Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy

Halle C.F. Moore
Cleveland Clinic Foundation, Taussig Cancer Institute, Cleveland, OH

L.D.M. and H.C.F.M. contributed equally to this work.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at jco.org.

REFERENCES

DOI: 10.1200/JCO.2016.69.2582; published at jco.org on November 28, 2016.
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Matteo Lambertini
Other Relationship: European Society for Medical Oncology Translational Research Fellowship

Tommaso Falcone
No relationship to disclose

Joseph M. Unger
No relationship to disclose

Kelly-Anne Phillips
No relationship to disclose

Lucia Del Mastro
Honoraria: Takeda, Roche, AstraZeneca, Novartis
Consulting or Advisory Role: Eli Lilly
Speakers’ Bureau: Takeda, Ipsen
Travel, Accommodations, Expenses: Roche

Halle C.F. Moore
Research Funding: Puma Biotechnology (Inst), Abbvie (Inst), Parexel International (Inst)