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ORGANISATION
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News Update: December 2015

Role of GnRH agonists for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy- What does the evidence say?

KEY MESSAGE

Premature ovarian failue (POF) is a central and potentially devastating consequence of chemotherapy. Manifestations include infertility, menopausal symptoms, sexual dysfunction osteoporosis, and infertility.

Temporarily preventing ovarian cycling during chemotherapy with hormone-suppressing drugs such as Goserelin has been investigated as a means to preserve ovarian function
Recent evidence proposes that young women undergoing chemotherapy for breast cancer may be more likely to remain fertile if they receive hormonal treatment as well.

Lately, the 2015 St Gallen International Expert Consensus panel and the National Comprehensive Cancer Network (NCCN) guidelines have been updated to acknowledge the role of GnRHa in preventing chemotherapy-induced POF of hormone receptor-negative breast cancer.

POEMS STUDY (ASCO 2014)

The Prevention of Early Menopause Study (POEMS) was an international, phase 3, randomized study that was performed to evaluate whether administration of the GnRH agonist -Goserelin (Zoladex, AstraZeneca) with chemotherapy would reduce the rate of ovarian failure after adjuvant or neoadjuvant treatment of hormone-receptor–negative early breast cancer.

In this study, 257 premenopausal women, aged 18 to 49, with stage I to IIIA triple negative breast cancer were randomly assigned to treatment with cyclophosphamide-containing chemotherapy alone or chemotherapy plus goserelin.

Goserelin was given as a monthly subcutaneous injection at 3.6 mg beginning 1 week before the initial chemotherapy and was continued to within 2 weeks before or after the final chemotherapy dose.

METHODS

- Randomly assigned 257 premenopausal women
- Operable **hormone-receptor–negative** breast cancer
- Standard chemotherapy with the GnRH agonist goserelin (goserelin group)
    - or
- Standard chemotherapy without goserelin (chemotherapy-alone group).
- The **Primary study end point** was-
    - The rate of ovarian failure at 2 years (ovarian failure defined as the absence of menses in the preceding 6 months and levels of follicle-stimulating hormone (FSH) in the postmenopausal range.)
- **Secondary end points** included-
    - Pregnancy outcomes and
    - Disease-free and overall survival.

RESULTS

218 patients were eligible, 135 with complete primary end-point data

- The ovarian failure rate was
    - 8% in the goserelin group
      vs
    - 22% in the chemotherapy-alone group

(Odds ratio, **0.30**; 95% confidence interval [CI], **0.09 to 0.97**; two-sided **P=0.04**).

- Pregnancy occurred in more women in the goserelin group than in the chemotherapy-alone group **(21% vs. 11%, P=0.03)**
- Women in the goserelin group also had improved disease-free survival **(P=0.04)** and overall survival **(P=0.05)**.

CONCLUSIONS

Administration of Goserelin with Chemotherapy for premenopausal women beginning chemotherapy for early breast cancer appeared to protect against ovarian failure, reducing the risk of early menopause and improving prospects for fertility.

While the benefits and the practice changing nature of this study are clearly elaborated the **caveats of the study** must be pondered upon before embracing it as the new norm

1. There were a lot of missing data points, and only 135 patients were fully evaluable with all data available at two years of follow-up from treatment.
2. The chemotherapy tested was cyclophosphamide based so again the extrapolation of these results for non-cyclophosphamide based chemotherapy cannot be made.
3. The patient group was only Triple negative breast cancer (TNBC) so technically this strategy currently cannot be safely applied to young breast cancer patients who have ER, PR or HER2 receptor positivity, however **recent studies** propose that it **is probably safe in women with hormone-sensitive breast cancer** (PROMISE-GIM6 study and the Triptorelin administered concurrently with chemotherapy in the Tamoxifen and Exemestane Trial).
4. A meta-analysis of all the studies is being undertaken by the same group (CLEVELAND CLINIC) questioning if we should await their results before a blanket adoption.

ANNALS OF ONCOLOGY REVIEW (Lambertini M et al , September 2015)

Recent large meta-analysis to assess the role of temporary ovarian suppression with LHRHa as a strategy to reduce POF and preserve fertility in pre-menopausal breast cancer patients.

METHODS

Literature search was done using PubMed, Embase, and the Cochrane Library, and the proceedings of major conferences, was conducted up to 30 April 2015.

RESULTS

A total of 12 RCTs were eligible including 1231 breast cancer patients. The use of LHRHa was associated with a significant reduced risk of POF (OR 0.55, 95% CI 0.41–0.73, P < 0.001) without heterogeneity. In five studies reporting pregnancies, more patients treated with LHRHa achieved pregnancy (33 versus 19 women; OR 1.83, 95% CI 1.02–3.28, P = 0.041) In three studies reporting Disease Free Survival (DFS), no difference was observed (HR 1.00, 95% CI 0.49–2.04, P = 0.939).

CONCLUSIONS

Temporary ovarian suppression with LHRHa in young breast cancer patients is an effective strategy associated with a reduced risk of chemotherapy-induced POF and seems to increase the pregnancy rate, without an apparent negative consequence on prognosis.

LIMITATIONS of the meta-analysis

- The different definitions of POF used
- Few studies reporting the number of patients attempting and achieving pregnancy
- Limited data on survival outcomes.
- The studies differed in the duration of LHRHa co-treatment and length of follow-up.
- It was not possible to investigate the impact of other important confounders i.e. patients' age, type, dose of chemotherapy, and use of adjuvant tamoxifen on the results of the meta-analysis as the extracted data was not based on individual patient data.

Co-administration of a GnRH agonist with chemotherapy in pre-menopausal breast cancer patients is a new promising option that can be efficiently used in conjunction with traditional fertility-preservation techniques as a means to preserve ovarian function and the likelihood of pregnancy after chemotherapy.

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