

Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer A Randomized Trial

BACKGROUND:

- Premenopausal women receiving systemic treatment with chemotherapy (especially those containing cyclophosphamide), hormone therapy, or both are at high risk of amenorrhea, early ovarian failure.
- Standard treatments for ovarian failure have not been determined and preclinical data has suggested and phase 2 studies have shown that gonadotropin-releasing hormone (GnRH) analogues protect 67-96% of women with breast cancer undergoing chemotherapy.

OBJECTIVE:

- To determine if temporary ovarian suppression by the GnRH analogue, triptorelin, during chemotherapy treatment of breast cancer in premenopausal women reduces the incidence of early menopause.

METHODS

- PROMISE-GIM6 was an experimental, parallel, randomized, open-labeled phase 3 trial conducted at 16 Italian centers and enrolled 281 patients between October 2003 and January 2008.
- **Inclusion criteria** included patients with histologically proven stage I, II, or III breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy, age 18 to 45 years of age, and premenopausal, which was defined as presence of active menstrual cycles or normal menses during the 6 weeks preceding the start of chemotherapy.
- **Exclusion criteria** included those with previous chemotherapy, radiotherapy, for both cancer or non-neoplastic disease; evidence of metastases; other malignancies in the previous 5 years, except basal or squamous cell carcinoma of the skin or adequately treated in situ carcinoma of the cervix; and pregnancy or lactation.
- A 60% rate of early menopause in the group treated with chemotherapy alone was assumed and it was estimated that 280 patients needed to be enrolled to detect a 20% absolute reduction in early menopause in the group treated with chemotherapy plus triptorelin, with a power of 90% and a 2-sided alpha error of 5%.
- 281 patients were enrolled and randomized, 133 patients received chemotherapy alone and 148 patients received chemotherapy plus triptorelin.
 - Triptorelin was given intramuscularly at a dose of 3.75 mg 1 week prior to the start of chemotherapy and then every 4 weeks for the duration of chemotherapy.
- **Primary outcome measures:** monitoring patients for ovarian failure, defined as no resumption of menstrual activity or postmenopausal levels of follicle stimulating hormone and estradiol 1 year after the last cycle of chemotherapy.
- **Data handling** method used was intent-to-treat

RESULTS

- **Reasons for drop out:** refusing intervention (8) and failing to follow up (13)
- **Primary outcome measures:** The rate of early menopause was 25.9% in the chemotherapy alone group and 8.9% in the chemotherapy plus triptorelin group. The absolute difference was -17% and the number needed to treat was 6 (95% CI, -26% to -7.9%; P<0.001).

- **Authors Conclusion:** These results suggest that temporarily suppressing ovarian function by administering triptorelin reduces the incidence of chemotherapy induced early menopause. Therefore, this treatment could be offered to premenopausal patients with breast cancer who wish to decrease the risk of permanent ovarian failure associated with chemotherapy.

STRENGTHS

- The primary outcome measure and secondary analysis were both statistically significant.
- All chemotherapy regimens used in the study include cyclophosphamide, which is highly associated with premature ovarian failure.
- Enough patients were enrolled to achieve a sufficient power and the intent to treat analysis was used to include all patients that began therapy.
- Multivariate logistic regression analysis was done to show that prevention of early menopause was solely due to triptorelin treatment

LIMITATIONS

- Lack of evidence found on the long term maintenance of ovarian function and preservation of fertility
- Unblinded
- No information provided about the treatment centers or if they followed any practice guidelines

CONCLUSIONS

- Triptorelin treatment would be useful due to lack of current treatment for premature ovarian failure due to cyclophosphamide containing chemotherapy regimens for breast cancer.
- Premenopausal ovarian failure is likely due to cyclophosphamide used in chemotherapy regimens; therefore, results should only be extrapolated to premenopausal women receiving chemotherapy with cyclophosphamide.
- More data is needed about long term ovarian function and maintenance of fertility after treatment with triptorelin with chemotherapy.
- The authors' recommendation is valid based on the study with patients receiving cyclophosphamide chemotherapy for breast cancer; however, further phase III studies should be done due to conflicting results from previous studies.

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