Effects of GnRHa on Ovarian Function Against Chemotherapy-induced-gonadotoxicity in Women With Breast Cancer in China (EGOFACT)

NCT02518191

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Trial Oversight

The trial was an investigator-initiated, two-center, randomized, phase 3, open-label, superiority, controlled trial involving premenopausal female breast cancer patients needed neoadjuvant or adjuvant chemotherapy in two parallel groups: chemotherapy with or without GnRHa treatment. The trial was funded by the Science and Technology Commission of Shanghai Municipality and Zhejiang Medical Society, and conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

The trial was conducted at the Shanghai Jiao Tong University Affiliated Shanghai Sixth People's Hospital in Shanghai, China and Zhejiang Cancer Hospital in Hangzhou, China. The practitioners in these two hospitals treat approximately 3000 breast cancer patients annually. The trial protocol and all amendments were approved by an independent ethics committee or the institutional review board at each site.

Safety data were assessed by an independent data monitoring committee. Written informed consent was provided by all the patients. Representatives of the sponsor designed the trial and confirmed the accuracy of and compiled the data for analysis. All the authors had access to the data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All the authors contributed to the writing and review of all manuscript drafts and were involved in the interpretation of the data.

The trial protocol has not been published previously. The manufacturers of the GnRHa (goserelin & leuprorelin), did not provide support for the trial and were not involved its design or conduct or in the writing of the manuscript. There were no agreements concerning confidentiality of the data between the sponsors and the authors or their institutions.

Participants

Inclusion Criteria: 1. Premenopausal women 18 to 49 years of age were eligible for enrollment. 2. Patients had operable stage I to III breast cancer for which treatment with adjuvant or neoadjuvant cyclophosphamide-containing chemotherapy was planned. 3. Eligible participants had taken no estrogens, antiestrogens, selective estrogen-receptor modulators, aromatase inhibitors, or hormonal contraceptives within the month before enrollment. 4. Human chorionic gonadotropin negative by urine test before entering the group. 5. Informed consent, understanding and compliance with the requirements of the study. 6. No significant chronic disease and any organ dysfunction.

Exclusion Criteria: 1. Exceptions were made for the use of hormonal contraception in women younger than 35 years of age that was discontinued before randomization. 2. Use of hormonal treatment for up to 2 months for the purposes of in vitro fertilization and cryopreservation of embryos or oocytes before randomization. 3. Patients with metastatic lesions or history of bilateral ovariectomy, ovarian radiation were excluded. 4. Patients received previous adjuvant endocrine therapy for breast cancer were not suitable to this trial. 5. Patients with uterine and/or adnexal diseases needing medical or surgical treatment were not suitable. 6. Allergic to active or inactive excipients of GnRHa was an exclusion criterion.

Trial Procedures and Interventions

Considering ethical issues related to randomization of patients with fertility desire, all patients enrolled in our study were comprehensively informed and volunteered to this trial. Crossover between the two groups was permitted. The randomization procedure was prepared by an independent statistician. The

assignments remained concealed in opaque, sealed envelopes, with a 1:1 allocation ratio. All the patients as well as all investigators who administered treatment, assessed outcomes, and analyzed data were unaware of the trial-group assignments. However, after randomization, all patients and all researchers involved in the treatment and evaluation of the results were aware of the allocation of the trial group, except the investigators who analyzed the data.

In eligible patients who were randomized to receive GnRHa, 3.6mg goserelin or 3.75mg leuprorelin was injected subcutaneously once every 28 days, from 1-2 weeks before the first cycle of chemotherapy to 4 weeks after the last cycle of chemotherapy. Eligible patients with breast cancer were treated without GnRHa while receiving chemotherapy in the controlled group.

Patients received chemotherapy according to one of the following cyclophosphamide-based regimens: TEC (docetaxel 75mg/m^2 + epirubicin 60mg/m^2 + cyclophosphamide 500mg/m^2), EC-T(H) (epirubicin 90mg/m^2 + cyclophosphamide 600mg/m^2 for 4 cycles followed with 4 additional cycles of docetaxel 100mg/m^2 $\pm$ trastuzumab), TC(H) (docetaxel 75mg/m^2 + cyclophosphamide 500mg/m^2 $\pm$ trastuzumab), FEC (5-fluorouracil 500mg/m^2 + epirubicin 90mg/m^2 + cyclophosphamide 500mg/m^2). All of the patients with human epidermal growth factor receptor 2 (HER2) positive tumors received trastuzumab (8mg/kg with first dose, followed by 6mg/kg for 1 year). Women with hormone receptor–positive disease received adjuvant endocrine therapy for 5 years starting from the end of chemotherapy. In both study groups, patients who resumed their ovarian function during the 12-month period of observation after the end of chemotherapy or at any time during the following 5 years of follow-up were allowed to receive GnRHa for at least 2 years as part of their endocrine treatment.

Radiation therapy after completion of chemotherapy was mandatory for patients who underwent a lumpectomy or breast conserving surgery. For patients who underwent a mastectomy, radiation therapy was performed according to the guidelines of each participating institution.

End points

The primary objective was to compare the rate of chemotherapy-induced premature ovarian insufficiency (POI) between the GnRHa group and the Controlled group. POI was defined as AMH＜0.5ng/mL in this study. The serum levels of AMH were measured using human AMH ELISA kit (11351, Biofine)), and the AFC (antral follicle with 2–10mm in mean diameter) observed with transvaginal or endoanal ultrasonography was not calculated and analyzed due to low compliance. The levels of AMH were evaluated before treatment, at 6 months and 1 year after last cycle of chemotherapy. Ovarian function recovery was defined as an AMH concentration ⩾0.5 ng/ml (Cohen et al., 2015). Patients who became pregnant were considered not to have had ovarian failure.

The secondary outcomes were survival rates. Events in the analysis of overall survival (OS) included deaths due to any cause; Tumor free survival (TFS) events were defined by the occurrence of one of the following: local recurrence, distant metastases, contralateral or ipsilateral breast tumor, or death from breast cancer. Only adverse events related to hormonal effects and serious adverse events that occurred during chemotherapy with or without goserelin were routinely assessed, with assessment according to the Common Terminology Criteria for Adverse Events, version 4.03. Annual follow-up was planned to record recurrences, and deaths (last annual follow-up, December 31, 2020).

Statistical Analysis

A sample size of 368 was required for a 90% chance of detecting an absolute difference of 14 percentage points in the rate of POI between the GnRHa group and the Controlled group at a two-sided significance level of 5%. The allowable withdrawing rate is 10%, thus the max sample size estimated was 409. The incidence of POI refers to the results of POEMS/S0230: At year 1, data were available for 153 patients (70%). Ovarian dysfunction was present in 28 of 75 patients (37%) in the chemotherapy-alone group and in 18 of 78 patients (23%) in the goserelin group (odds ratio, 0.64; 95% CI, 0.30 to 1.37; P = 0.25).

OS interval was computed from the date of randomization to the date of death. TFS interval was computed from the date of randomization to the date of the first occurrence of a TFS event. For each end point, observation times of patients without the event were censored on the date of their last contact. Median TFS was estimated with the use of the Kaplan–Meier method, and hypothesis testing was carried out with the use of a stratified log-rank test. Hazard ratios, 95% confidence intervals, and P values for differences in TFS were derived with the use of multivariable Cox regression, with adjustment for stratification factors.

Categorical data were recorded as frequency and percentage. Continuous data were recorded as mean ± standard deviation. The statistical analysis included both unadjusted and adjusted analyses. Outcome measures were compared between the groups with the use of the chi-square test or Fisher's exact test (unadjusted analysis). Effect sizes were reported as relative risk with 95% confidence interval. There was no data loss in 330 cases that finally included in the analysis; hence, the main analysis was based on cases with complete data. All tests were two-sided, and a *P* value of less than 0.05 was considered to indicate statistical significance. Data were analyzed with the use of SPSS software, version 19.0.