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*JNCI J Natl Cancer Inst* (2021) 113(10): djab066

doi: 10.1093/jnci/djab066
First published online April 2, 2021
Editorial

EDITORIAL

# Cyclophosphamide-Free Adjuvant Chemotherapy for the Potential Prevention of Premature Ovarian Insufficiency and Infertility in Young Women With Breast Cancer

Matteo Lambertini, MD, PhD[1,2,*] Ann H. Partridge MD, MPH[3]

[1]Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy; [2]Department of Medical Oncology, UOC Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy and [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

*Correspondence to: Matteo Lambertini, MD, PhD, Medical Oncology Department, UOC Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino—University of Genova, Largo Rosanna Benzi 10, 1632 Genova, Italy (e-mail: matteo.lambertini@unige.it).

Cyclophosphamide is an important component of most adjuvant breast cancer chemotherapy regimens (1,2). However, research has repeatedly demonstrated that it also contributes substantially to the risk of gonadotoxicity in premenopausal women, an issue of great importance for young patients (3,4). The development of chemotherapy-induced premature ovarian insufficiency (POI) is associated with not only attendant infertility but also the additional negative health consequences of an early loss of ovarian function (5). Together with patient age, type, and dose of chemotherapy are the other crucial factors influencing gonadotoxicity risk, with alkylating agents such as cyclophosphamide being associated with the highest negative gonadal impact (3,4,6). Therefore, investigating the possibility of effective novel adjuvant chemotherapy regimens with lower risk of this long-term toxicity is a highly relevant clinical question.

In this issue of the Journal, Yu and colleagues (7) report the results of Substitution of PaclitaxEl for Cyclophosphamide on survival ouTcomes and ResUmption of Menses in young women with ER-positive breast cancer (SPECTRUM), a phase III randomized trial designed to evaluate a cyclophosphamide-free adjuvant chemotherapy regimen to reduce ovarian toxicity in young women with hormone receptor–positive and HER2-negative breast cancer. Through 8 institutions in China, 521 women with a median age of 34 years were randomly assigned to receive adjuvant epirubicin and cyclophosphamidefollowed by weekly paclitaxel (EC-wP) or a cyclophosphamide-free regimen with epirubicin and paclitaxel followed by weekly paclitaxel (EP-wP). At 12 months following chemotherapy completion, a greater proportion of women in the cyclophosphamide-free group resumed ovarian function (63.1% vs 48.3%) and had a posttreatment pregnancy (9.6% vs 2.7%). At a median follow-up of 62 months, the cyclophosphamide-free group experienced better 5-year disease-free survival compared with those in the standard group (84.7% vs 78.3%) (7).

The investigators of the SPECTRUM trial should be applauded for conducting the first prospective trial specifically designed to study a less ovarian toxic regimen in young women with breast cancer receiving adjuvant chemotherapy. They were able to succeed in a challenging setting where prior attempts, including the phase II TRIal evalUating the Menstrual and Ovarian Function of Young Breast Cancer Patients Treated With a cycloPHosphamide-free Regimen (TRIUMPH) study (NCT02053597), have failed. These findings have potential implications for the treatment of young women with breast cancer, providing a new alternative adjuvant chemotherapy regimen. However, these results should be considered in the context of potential study limitations and of other literature addressing this issue.

First, defining chemotherapy-induced POI is challenging (3,4). Although most women who remain premenopausal after treatment will resume menstrual functioning during the first year after chemotherapy, longer-term ovarian function recovery occurs in a nonnegligible proportion of patients between year 1 and 2 or thereafter (8-10). Moreover, the gonadotoxicity of chemotherapy can induce damage to women's ovarian reserve irrespective of the occurrence of perturbation in the menstrual cycle (11). Therefore, empirically defining POI with a composite endpoint including amenorrhea for at least 2 years following chemotherapy completion in conjunction with a postmenopausal hormonal profile and ultrasound evidence of nonfunctioning ovaries has been recommended (12). The antimullerian hormone is currently being investigated as a promising serum marker to more accurately measure the gonadal damage induced by anticancer therapies (3,4).

In the SPECTRUM trial, recovery of ovarian function was defined as 2 consecutive menstrual cycles or 1 menstrual cycle

**Received:** March 26, 2021; **Accepted:** March 31, 2021

and premenopausal hormonal levels (follicle-stimulating hormone and estradiol) within 12 months following chemotherapy completion (7). No information beyond 12 months is available, and the anti-mullerian hormone was not assessed. Moreover, patients with competing events such as loss to follow-up, early intervention of ovarian suppression, relapses, or deaths were considered as non-resumed. Using this definition, approximately half of the patients in the control arm developed chemotherapy-induced POI, an absolute difference of 14.8% compared with the rate observed in the cyclophosphamide-free regimen (7). The rate of chemotherapy-induced POI observed in the SPECTRUM trial appears to be higher than previously reported in trials showing a 1-year POI rate of around 10%-40% (8,9). It is also notable that the absolute benefit in reducing POI rates with the use of a cyclophosphamide-free regimen is similar to the effect demonstrated with the administration of a gonadotropin-releasing hormone agonist during cyclophosphamide-based chemotherapy (absolute difference of 16.8% as compared with chemotherapy alone) (9). The added value of this strategy when combined with cyclophosphamide-free chemotherapy is unknown.

Second, in premenopausal women with hormone receptor–positive/HER2-negative early breast cancer who are candidates to receive chemotherapy, anthracycline- and/or taxane-based chemotherapy regimens including cyclophosphamide are the current standard of care (1,2,12). Prior randomized studies evaluating non-cyclophosphamide-containing regimens (such as the E2197 and National Surgical Adjuvant Breast and Bowel Project (NSABP)-B30 trials) (13,14) have also included postmenopausal women. However, the NSABP-B30 trial prospectively evaluated the role of doxorubicin and docetaxel from an efficacy and ovarian toxicity standpoint and demonstrated inferior disease outcomes in addition to lower ovarian toxicity compared with the cyclophosphamide-containing regimen (6,14). Therefore, caution should be taken in adopting wholesale such regimens. Individual risk of recurrence is crucial to choose between an anthracycline-free regimen or a sequential strategy; in high-risk patients (eg, node-positive and/or luminal B-like disease), dose-dense chemotherapy is associated with additional benefit (15,16), particularly in the setting of premenopausal women (17). Young women with breast cancer are at increased risk of carrying germline pathogenic variants in *BRCA* genes (18,19); genetic testing may have therapeutic implications also in the choice of the optimal chemotherapy backbone considering the important role of DNA-damaging agents (such as platinum agents but also cyclophosphamide) in this setting (20). Moreover, nowadays, in patients deemed at sufficient risk to justify the use of chemotherapy, ovarian function suppression with tamoxifen or an aromatase inhibitor is considered a crucial component of the adjuvant endocrine therapy (21,22).

Notably, in the control arm of the SPECTRUM trial, the dose of epirubicin was 75 mg/m$^2$ given in an every 3-week schedule, and the majority of patients received tamoxifen alone as adjuvant endocrine therapy (ovarian function suppression was given in 20% of the patients, of whom combined with an aromatase inhibitor in only 5% of the cases) (7). No data on *BRCA* status were reported. With these caveats in mind, the experimental arm without the use of cyclophosphamide was more effective than the control arm; a statistically significant interaction was observed between treatment effect and nodal status, with a larger benefit favoring the cyclophosphamide-free regimen in patients with node-positive disease (7). Similar efficacy results were observed in a prior trial investigating a comparable cyclophosphamide-free regimen and that included mostly postmenopausal patients (23).

Although these data are promising, taking also into account the results of the NSABP-B30 trial (6,14), more evidence is needed before supporting the routine use of a cyclophosphamide-free chemotherapy regimen. Further, considering the risk of disease recurrence beyond 5 years in patients with hormone receptor–positive breast cancer (24), longer-term follow-up data from the SPECTRUM trial will be critical to provide more solid efficacy data for the safety of sparing cyclophosphamide in selected patients with early breast cancer who are candidates for (neo)adjuvant chemotherapy.

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## Funding

Matteo Lambertini is supported by the Italian Ministry of Health (5 x 1000 funds 2017; no grant number) and the Italian Association for Cancer Research (AIRC; MFAG 2020 ID 24698) for pursuing his research efforts in the field of oncofertility.

## Notes

**Role of the funders:** The funders had no role in the writing of this editorial or the decision to submit it for publication.

**Disclosures:** Matteo Lambertini acted as consultant for Roche, AstraZeneca, Lilly, and Novartis and received speaker honoraria from Sandoz, Roche, Takeda, Pfizer, Lilly, and Novartis outside the submitted work. Ann H. Partridge declares no conflicts of interest.

**Author contributions:** Writing, original draft—ML, AHP. Writing, editing and revision—ML, AHP.

## Data Availability

Not applicable.

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