

Reducing the Long-term Effects of Chemotherapy in Young Women With Early-Stage Breast Cancer

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ALTHOUGH THE MEDIAN AGE OF WOMEN DIAGNOSED with breast cancer is 61 years, about 35% of women newly diagnosed with breast cancer are 54 years or younger, and 12%—almost 25 000—are younger than 45 years.¹ The majority of women with breast cancer will receive adjuvant therapy including chemotherapy, hormone therapy, or both, which has been documented to improve disease-free and overall survival. Treatment has a number of adverse effects that directly affect short-term and, in some cases, long-term quality of life. For young women of childbearing age, one of the most devastating adverse effects involves the prospect of loss of fertility, and this concern may influence choice of therapy and adherence to a prescribed treatment plan.² For some women, concern about early menopause is paramount.

Chemotherapy agents exert toxicity in the ovary by causing apoptotic oocyte death in primordial follicles, damaging ovarian reserve and interrupting follicle recruitment and maturation.³ Almost all women develop at least temporary chemotherapy-induced amenorrhea. Reports have suggested a wide range of permanent amenorrhea rates following adjuvant chemotherapy, with important variables including age, treatment regimen, and use of tamoxifen. Historically, the risk of permanent amenorrhea in women younger than 40 years with early-stage breast cancer following adjuvant chemotherapy was reported to be about 40%, compared with 76% in older women.⁴ Alkylating agents, particularly the combination regimen of oral CMF (cyclophosphamide, methotrexate, and fluorouracil), are associated with the highest risk of ovarian failure, reaching 90% in women older than 40 years.⁴

Current chemotherapy regimens generally have less ovarian toxicity, with significantly lower rates of perma-

nent amenorrhea. Although recovery of menses is still closely related to the variables listed above, in one report 85% of women aged 40 years or younger treated with adjuvant anthracycline and taxane-based chemotherapy recovered menses within 1 year,⁵ with docetaxel regimens resulting in higher rates of prolonged amenorrhea.⁶ In addition, although menses generally returns within 6 months following the end of chemotherapy, recovery may be delayed for up to 2 years. Although the effects of tamoxifen on ovarian function remain unclear, the majority of studies suggest delayed recovery of menses. Ongoing research will help to clarify this effect.

In general, resumption of menses is used as a surrogate marker for fertility, with recent studies including additional measures such as levels of follicle-stimulating hormone (FSH) and estradiol. However, resumption of menses is not the same as ovarian reserve—an end point that clearly affects reproductive potential but is more difficult to measure.⁷ A variety of tests have been used to try to provide a better estimate of this reserve, with the best data provided from anti-Mullerian hormone levels, ultrasound-derived antral follicle count, and family history.⁷ Indeed, data from the California Cancer Registry suggest that, even with recovery of menses, a history of chemotherapy use predicts a higher than expected rate of infertility⁸ and lower ovarian reserve.⁹

Gonadotropin-releasing hormone (GnRH) agonists have been postulated to provide protection against chemotherapy-induced premature ovarian failure, although the mechanism of this action is unclear. It has been hypothesized that reduction in levels of gonadotropins functions to place the ovaries in a quiescent or prepubertal state, although the potential protective value of this effect remains controversial.¹⁰ Initial data from observational trials have suggested that suppression of ovarian

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function during chemotherapy for early-stage breast cancer resulted in at least some degree of protection against permanent ovarian failure compared with historical reports of permanent amenorrhea induced by chemotherapy, as measured by recovery of regular menses.¹⁰ However, these trials were limited by lack of controls using the same chemotherapy regimens.

The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients—Gruppo Italiano Mammella 6) trial reported by Del Mastro and colleagues in this issue of *JAMA*¹¹ is the largest of 5 randomized trials evaluating the ability of ovarian suppression with a GnRH agonist to preserve ovarian function after adjuvant or neoadjuvant chemotherapy for early-stage breast cancer.¹²⁻¹⁵ In this phase 3 study, 281 premenopausal women aged up to 45 years with early-stage (stages I-III) breast cancer were randomized to receive chemotherapy with or without the GnRH agonist triptorelin. Chemotherapy included anthracyclines with or without taxanes or CMF with oral cyclophosphamide (6% no triptorelin vs 2.7% triptorelin); women with hormone receptor–positive disease (about 80% of the trial population) also received tamoxifen for 5 years.

Recovery in the intention-to-treat population, defined either as resumption of menses within 1 year of the end of chemotherapy or as premenopausal levels of estradiol without menses, was significantly higher in women receiving triptorelin (91.1%) vs those receiving chemotherapy alone (74.1%, $P < .001$). In multivariate analysis, only treatment with triptorelin was associated with a reduction in early menopause, with an odds ratio of 0.28 (95% confidence interval, 0.14-0.59). Recovery of menses was less common in women receiving tamoxifen, and the protection with triptorelin from early menopause was greater in women with hormone receptor–negative disease compared with those with hormone receptor–positive disease. Patients with hormone receptor–positive disease who met the criteria for recovery received triptorelin to suppress their menses for 2 years in addition to 5 years of tamoxifen to avoid adverse effects of ovarian production of estrogen on disease outcome.

In 2 of the 5 studies on this topic, including the GBG 37 (German Breast Group) ZORO (Zoladex Rescue of Ovarian Function) trial, use of a GnRH agonist had no effect on ovarian function recovery. In addition, the ZORO trial enrolled only patients with hormone receptor–negative disease, to avoid the potential adverse effect of preserved estradiol production on disease outcome and of tamoxifen on evaluation of the end point.¹⁴ Sixty patients were randomized, with no difference in recovery based on use of the GnRH agonist and a 63% overall rate of recovery at 6 months following chemotherapy. All but 1 patient resumed regular menses within 2 years. The second trial, which ended accrual because of

futility after enrolling 49 patients, reported recovery of menses in 90% of patients in both treatment groups within the same period.¹⁵

Two other randomized trials found significant reductions in the rate of early menopause in patients receiving GnRH agonists with a variety of chemotherapy regimens, including CMF. However, the rate of recovery of menses in the control groups was markedly higher in the 2 negative trials compared with that seen in trials showing benefit from the GnRH agonist, despite use of similar chemotherapy regimens. In the ZIPP (Zoladex in Premenopausal Patients) trial, treatment with CMF and 2 years of goserelin appeared to result in less permanent amenorrhea at 3 years compared with CMF and tamoxifen or with CMF and both goserelin and tamoxifen (recovery of menses in 36%, 13%, and 7%, respectively).¹³ An Egyptian trial reported that 89.6% of women recovered menses within 8 months of completing chemotherapy with a GnRH agonist, compared with 33% of those who received chemotherapy alone.¹² One potential difference between these trials is that the rates of tamoxifen use differed widely. In addition, the definition for recovery of menses as well as ovarian failure varied among the trials.

Recovery of a single menstrual cycle or premenopausal levels of estradiol are not definitive measures of recovery of ovarian function. In addition, the use of 2 years of ovarian suppression in patients with hormone receptor–positive disease who had a single menses or elevated estradiol level in the study by Del Mastro et al¹¹ means that it is impossible to evaluate the effects of ovarian suppression on true recovery of ovarian function or on ovarian reserve. Indeed, recent data have confirmed that amenorrhea 12 months after start of therapy had an important effect on outcome, with an almost 50% relative improvement in risk of recurrence or death in women with hormone receptor–positive disease and amenorrhea, compared with those with persistent menstrual function.⁶ In addition, the effect of estradiol suppression on efficacy of chemotherapy in hormone-sensitive disease is unknown.

The current data reported by Del Mastro et al¹¹ are intriguing and represent an important and encouraging addition to the study of ovarian preservation for women in this difficult situation. The Southwest Oncology Group 0230 randomized phase 3 trial (NCT00068601) sought to evaluate the ability of ovarian suppression during adjuvant chemotherapy in women with hormone receptor–negative disease to preserve ovarian function. Because of issues with drug supply and funding, that trial was closed after slightly more than half of the intended 420 patients were enrolled; those patients will undergo follow-up for study end points. The OPTION (Ovarian Protection Trial in Premenopausal Breast Cancer Patients) study, which enrolled 227 patients, has presented only preliminary data on a subset of enrolled patients to date.¹⁶ Given that patients with hormone receptor–positive disease in the current

study who had evidence of ovarian recovery were immediately suppressed without data on long-term recovery and that breast cancer outcome data are not available, and given as well the potential adverse effects on disease outcome, the use of GnRH agonists concomitant with chemotherapy cannot be recommended as a standard treatment and should be approached with caution in women with hormone-sensitive disease.

The most effective option for fertility preservation is assisted reproductive technology with embryo or oocyte cryopreservation, and this option should be discussed with young women facing chemotherapy for breast cancer and other curable malignancies.¹⁷ International guidelines recommend discussion of fertility options before starting chemotherapy, and when possible before surgery, to allow optimal timing for consultation and oocyte harvesting. When feasible, and for patients with hormone-insensitive disease, GnRH agonist therapy to suppress ovarian function during chemotherapy is an additional treatment that can potentially expand fertility possibilities. Although recovering menses is not the same as fertility preservation, it is one step in the right direction.

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