Risk of Ovarian Function Recovery Should Be Considered When Switching From Treatment With Adjuvant Tamoxifen to Aromatase Inhibitor Therapy in Women With Chemotherapy-Induced Amenorrhea

The results of this study indicate that clinicians need to be very aware of the risk of ovarian function recovery after switching from tamoxifen to aromatase inhibitor therapy in patients with breast cancer who are aged younger than 50 years at the time of breast cancer diagnosis, even if these women have been amenorrheic for over 1 year while receiving tamoxifen and have postmenopausal estradiol levels at the time of switching to an aromatase inhibitor.

A recent study has highlighted the frequency of ovarian function recovery (OFR) during treatment with aromatase inhibitors (AIs) among women with early breast cancer (J Natl Cancer Inst. 2017;109:djx074).

AIs are an evidence-based adjuvant endocrine therapy for postmenopausal women with early-stage breast cancer, including those with chemotherapy-induced ovarian function failure. However, therapy with AIs is not effective for women with functioning ovaries. To add to the information in the medical literature regarding the frequency of OFR during a switch to AIs after tamoxifen therapy in patients with early breast cancer, Vivianne C.G. Tjan-Heijnen, MD, PhD, head of the department of medical oncology at Maastricht University Medical Center in Maastricht, the Netherlands, performed a subanalysis of the DATA trial to address this question.

The DATA trial is a phase 3 randomized study assessing the efficacy of 3 years versus 6 years of adjuvant anastrozole in postmenopausal women who had previously received 2 to 3 years of adjuvant therapy with tamoxifen for hormone receptor–positive breast cancer. Patients with chemotherapy-induced amenorrhea were selected. Women who were aged 45 to 57 years at the time of randomization with a history of chemotherapy-induced ovarian function failure and documented estradiol levels in the postmenopausal range prior to the switch to anastrozole were the subject of the current analysis. Approximately 83% of the patients had received anthracycline-based chemotherapy without taxanes for a median of 5 cycles. Women who underwent bilateral ovariectomy or those who were treated with luteinizing hormone-releasing hormone agonists before random assignment were excluded. Plasma levels of estradiol and follicle-stimulating hormone (FSH) were monitored at 6-month intervals after the initiation of treatment with anastrozole. The primary endpoint was OFR within 30 months, defined as a return to premenopausal estradiol/FSH levels with or without the return of menstrual bleeding.

Of the 329 eligible patients, a total of 39 (11.9%) developed OFR within 30 months of initiating treatment with anastrozole; 15.2% of those were aged younger than 50 years at the time of breast cancer diagnosis, and 1.2% were aged 50 to 54 at the time of diagnosis of breast cancer.
Only approximately one-half of the women experiencing biochemical OFR reported menstrual bleeding.

Clinical Implications
“Though most practicing oncologists are aware that ovarian function may recur in patients with chemotherapy-induced amenorrhea after a switch from tamoxifen to an AI...[they] may not be aware of the frequency with which this occurs... and this article is a good reminder,” says Gini Fleming, MD, professor of medicine and medical oncology director at the University of Chicago.

“In the population who were under 50 at diagnosis, the risk of return of premenopausal status needs to be discussed with patients (for continued birth control use as well as breast cancer issues), and in very young women at highest risk of OFR, ovarian function suppression may be reasonable for those with chemotherapy-induced amenorrhea if a switch to AI therapy is contemplated,” explains Dr. Fleming. “Regular monitoring with FSH and estradiol as suggested by the authors is a potentially mitigating strategy. However, how long true ovarian function recovery would persist in most women on an AI with no menstrual bleeding (and hence how much ‘lead time’ is obtained with monitoring) is not known. In addition, as discussed in the article, caution should be used in interpreting isolated slight elevations in estradiol levels, as the effect of these on breast cancer survival is unknown, and the performance of most estradiol assays at low levels is poor. Moreover, there may be cross-reactivity between metabolites of the steroidal AI exemestane and estradiol in many assays.”

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