Received: 21 February 2019 | Revised: 25 February 2019 | Accepted: 26 February 2019

DOI: 10.1111/tbj.13474

COMMENTARY

The Breast Journal WILEY

Unexpected ovarian activity in premenopausal breast cancer survivors treated with exemestane and GnRH analogues

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Breast cancer is the most common cancer for women in the age range 15-39.[1] The standard adjuvant treatment for premenopausal women affected by hormone receptor-positive (HR+) BC has long been tamoxifen± a gonadotropin-releasing hormone agonist (GnRHa).[2] However, after the publication of the joint analysis of the SOFT and TEXT trials demonstrating that the aromatase inhibitor (AI) exemestane + GnRHa significantly increased disease-free survival compared to tamoxifen + GnRHa,[3,4] the use of exemestane as adjuvant hormone treatment (HT) is growing. A recent substudy of the SOFT trial showed that 17% of patients, mostly <35 years old, had relatively high estradiol levels, suggesting suboptimal ovarian suppression (SOS).[5] This issue is of great concern because appropriate ovarian suppression is mandatory when using AI in premenopausal patients.[2] Apart from estradiol level, nothing has yet been reported about the ultrasonographic (USG) features of the ovaries, circulating levels of gonadotrophins, or the frequency of symptoms (ie, pelvic pain and/or abnormal uterine bleeding) in these women. In addition, a standardized approach to the clinical management of this situation has yet to be established.

We examined the hormonal, USG, and clinical features of women undergoing adjuvant exemestane + GnRHa to determine whether these parameters can help to identify patients with SOS. Premenopausal women treated with tamoxifen + GnRHa were also studied and compared to the exemestane group. Moreover, in the attempt to address the lack of a standardized approach to patients with SOS, we preliminarily evaluated the efficacy of off-label shortening of GnRHa administration from every 28 (q28) to 21 days (q21) in symptomatic women in the exemestane cohort.

We retrospectively evaluated 66 consecutive premenopausal women with regular menses and history of HR + BC. No patient had to be affected by endocrine or immunological disorders. The population was divided into patients treated with exemestane + GnRHa (40 patients) and tamoxifen + GnRHa (26 patients). The two groups received leuprorelin or triptorelin 3.75 mg administered in a single intramuscular injection q28. The following clinical, USG, and endocrinological parameters were collected and compared: age, type of GnRH analogue, previous chemotherapy, diagnosis of polycystic ovarian syndrome, spotting, pelvic pain, hysteroscopy visualization, endometrial thickness (in mm), USG presence of ovarian cysts > 15 mm and ovarian structure (with or without evidence of follicles), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) values, estradiol, estrone, delta-4-androstenedione, and progesterone levels. For the purpose of our study, SOS was defined as the presence of ovarian activity at the ultrasound and/or spotting. As previously reported, an off-label shortening of GnRHa administration was attempted in case of SOS. The above-mentioned parameters were collected in patients undergoing GnRH shortening also

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three months after the start of the new schedule. The chi-square test was used to assess differences between the groups in the distribution of categorical variables. Two-tailed *t* test for independent samples or Mann-Whitney test was used to compare continuous variables. In the exemestane-treated patients with shortened GnRHa schedule, pre- and post-treatment comparisons were performed with a separate Wilcoxon signed-rank and McNemar test. Statistical significance was set at $P < .05$.

The incidence of a clinically defined SOS appeared to be higher than that observed in the SOFT substudy (30% vs 17%).[5] Patient cohorts did not differ for previous chemotherapy ($P = .37$) and GnRHa active principle ($P = .49$). Women in the exemestane group were slightly older ($P = .046$), experienced more frequently pelvic pain ($P = .048$), had higher incidence of ovarian USG cysts ($P = .009$) and higher FSH levels ($P = .013$), and showed a trend to a significantly higher rate of spotting ($P = .08$) compared to the tamoxifen group. No significant differences were observed in USG ovarian structure, endometrial thickness, and hysteroscopy rates ($P = .12$, $P = .14$, $P = .42$, respectively), as well as in estradiol, estrone, delta-4-androstenedione, and LH levels ($P = .85$, $P = .20$, $P = .43$, $P = .1$, respectively). In patients with SOS, the shift to a q21 schedule of GnRHa led to a significant reduction in pelvic pain ($P = .013$), abnormal bleeding ($P = .023$), ovarian follicles ($P = .041$), and estradiol levels ($P = .043$), with a trend for a lower frequency of ovarian cysts ($P = .074$). No other statistically significant differences were observed.

In physiological conditions, the development of follicles is strictly related to FSH levels.[6] Thus, its persistence at relatively high levels in exemestane-treated patients might account for the USG findings in such cohorts and could be explained by the fact that the AI might reduce the estrogen-mediated negative feedback on the hypothalamic-pituitary axis by preventing conversion of androgens to estrogens, resulting in an increased FSH secretion and follicular development.[7] Moreover, AI does not exert a direct anti-estrogenic effect on the endometrium, thus potentially explaining the high number of cases of abnormal uterine bleeding in the exemestane group. However, concomitant administration of GnRHa should lower gonadotropin levels due to continuous pituitary suppression. Therefore, it is possible that monthly administration of GnRHa might not be fully effective in some young BC due to a still unidentified interaction between exemestane and GnRHa. However, it is noteworthy that the shortening of the GnRHa schedule resulted in a significant reduction of symptoms, estradiol levels, and ovarian activity in the exemestane-treated patients.

Overall, it seems that adding USG and clinical gynecological evaluation to the standard follow-up of exemestane-treated premenopausal BC patients might be helpful to better identify SOS. Of note, a shortened GnRHa schedule might represent a possible solution to overcome it. However, further validation in larger and prospective studies is required to draw more definitive conclusions.

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REFERENCES

1. Bleyer A, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B. The distinctive biology of cancer in adolescents and young adults. *Nat Rev Cancer*. 2008;8(4):288-298.
2. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Ann Oncol*. 2017;28:16-33.
3. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014;371:107-118.
4. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372:436-446.
5. Bellet M, Gray KP, Francis PA, et al. Twelve-month estrogen levels in premenopausal women with hormone receptor-positive breast cancer receiving adjuvant triptorelin plus exemestane or tamoxifen in the suppression of ovarian function Trial (SOFT): the SOFT-EST sub-study. *J Clin Oncol*. 2016;34:1584-1593.
6. Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology* (8th ed). Philadelphia, PA: Lippincott, Williams & Wilkins; 2011.
7. Alviggi C, Marci R, Vallone R, et al. High progesterone levels during the luteal phase related to the use of an aromatase inhibitor in breast cancer patients. *Eur Rev Med Pharmacol Sci*. 2017;21:3134-3138.