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Breast Cancer

Measuring Ovarian Escape in Premenopausal Estrogen Receptor-Positive Breast Cancer Patients on Ovarian Suppression Therapy

Ethan Burns,[a] Emre Koca,[b] Jiaqiong Xu,[c] Edward McLean,[d] Rosetta Lee,[d] Tejal Patel,[b] Jenny Chang,[b] Polly Niravath[b]

[a]Department of Medicine, Houston Methodist Hospital, Houston, Texas, USA; [b]Department of Hematology and Medical Oncology, Houston Methodist Cancer Center, Houston, Texas, USA; [c]Center for Outcomes Research, Houston Methodist DeBakey Heart & Vascular Center, Houston Methodist Research Institute, Houston, Texas, USA; [d]Houston Methodist Department of Pharmacy, Houston, Texas

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Ovarian suppression • Ovarian escape • ER-positive breast cancer • Premenopausal

Abstract

Purpose. This study evaluated the proportion of premenopausal women who experience persistent ovarian escape (OE) while receiving ovarian suppression (OS) therapy for estrogen receptor-positive (ER+) breast cancer treatment. The study also examined clinical factors that may predispose to higher risk of persistent OE.

Materials and Methods. This was a retrospective, "real-world" study to evaluate premenopausal women receiving adjuvant endocrine OS therapy. The primary objective was to measure the percentage of persistent OE within the first 3 months of OS injections (using either leuprolide or goserelin). The secondary objective was to associate baseline clinical data (age, body mass index [BMI], and previous chemotherapy) with the probability of OE.

Results. Of the 46 patients included in this analysis, 11 (23.9%) women did not achieve OS within 3 months. Three women (6.5%) remained in OE at 12 months. Older age (odds ratio, 0.86; confidence interval, 0.76–0.98, p = .024) was associated with lower chance of developing OE. BMI, previous chemotherapy, and drug used (tamoxifen versus aromatase inhibitor) did not correlate with the likelihood of OE in this patient cohort.

Conclusion. Among the premenopausal women who did not attain complete ovarian suppression, young age was a significant risk factor for likelihood of OE. Although the clinical relevance of this finding is not yet known, it should prompt further studies to determine whether inadequate OS is associated with higher recurrence risk for patients with ER+ breast cancer. ***The Oncologist*** 2021;26:e936–e942

Implications for Practice: Because up to a quarter of premenopausal women do not attain adequate ovarian suppression within the first 3 months of gonadotropin-releasing hormone (GnRH) agonist therapy, bloodwork should be checked to ascertain hormone levels prior to starting aromatase inhibitor therapy, and at regular intervals, for these women.

Introduction

Breast cancer is the most common malignancy in women globally, with 276,480 estimated cases in the U.S. in 2020 [1]. Approximately 70% of these cases are hormone receptor-positive (HR+) [2]. Patients younger than 45 years contributed to 8.4% of new cases from 2012 to 2016 in the U.S. SEER database, whereas patients younger than 35 years made up 1.9% of new breast cancer cases [1]. Although the premenopausal cohort composes a small proportion of total annual breast cancer incidence, it must be given special consideration because of a higher likelihood of advanced disease at presentation [3]. Although systemic chemotherapy has a proven benefit with an absolute reduction in recurrence among women younger than 50 years [4], Aebi et al. reported that women younger than 35 years with HR+ breast cancer who did not achieve chemotherapy-induced amenorrhea had a higher rate of disease relapse and death at 10 years compared with women older than 35 years, who also did not achieve amenorrhea with

Correspondence: Polly Niravath, M.D., Department of Hematology and Medical Oncology, Houston, Methodist Cancer Center, 6445 Main Street, Floor 24, Suite 326, Houston, Texas 77030, USA. Telephone: 713-441-9948; e-mail: paniravath@houstonmethodist.org Received July 10, 2020; accepted for publication February 5, 2021; published Online First on March 11, 2021. http://dx.doi.org/10.1002/onco.13722

chemotherapy [5]. These findings suggest that younger women may have differing host factors and/or disease biology that distinguish them from older women, and lower estrogen levels may play an even more important role in younger women with HR+ breast cancer than in older women.

In 2007, a meta-analysis involving 11,906 premenopausal patients with HR+ breast cancer indicated that luteinizing hormone-releasing hormone (LHRH) agonists were more effective in reducing disease recurrence in women younger than 40 years, as compared with those over 40 years. Furthermore, when an LHRH agonist was used in conjunction with tamoxifen, chemotherapy, or both, there was a significant reduction in disease recurrence and death after recurrence [6]. In 2013, two randomized trials were initiated by the International Breast Cancer Study Group: The Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT). The results of the SOFT and TEXT trials created a paradigm shift in the management of high risk premenopausal women with estrogen receptor-positive (ER+) and/or progesterone receptor-positive breast cancer. At 8 years, the disease-free survival was superior for women who received either tamoxifen or aromatase inhibitor (AI) with ovarian suppression (OS), as compared with the women who received tamoxifen alone [7]. With a proven benefit in disease-free survival, the American Society of Clinical Oncology recommended in 2016 that premenopausal women with high risk of disease recurrence should receive OS with adjuvant endocrine therapy [8].

Despite these promising findings, ancillary analysis of the SOFT trial subpopulation (SOFT-EST) noted that one-quarter of the patients did not achieve adequate OS at 3 months while on exemestane and triptorelin. Even at 12 months, 17% still did not attain adequate OS [9]. The clinical significance of this remains unknown, but failure to achieve maximally suppressed estradiol levels could theoretically contribute to poorer outcomes for ER+ breast cancer survivors. The aim of this study was to assess premenopausal patients with ER+ breast cancer in a "real world" clinical setting who did not achieve maximal estradiol (E2) suppression within 3 months and to evaluate potential contributing risk factors.

Materials and Methods

Study Design

This was an institutional review board-approved, single institution, retrospective study that evaluated ovarian escape (OE) in premenopausal women receiving adjuvant endocrine therapy with pharmacologic OS (either leuprolide or goserelin) over a 95-month period from February 1, 2010, to January 9, 2018. Patient information was initially found by the use of the Vigilanz system (a clinical surveillance platform). All patients receiving either leuprolide or goserelin were isolated, and then screened for medication indications. Patients who did not have ER+ breast cancer were excluded. The rest of patient data was collected through the electronic medical record EPIC and securely stored in Microsoft Excel 2013 data files. Patients were included if they were over 18 years of age; had stage I–III ER+ breast cancer; were receiving OS with goserelin or leuprolide in conjunction with either tamoxifen or an AI including exemestane, letrozole, or anastrozole; and were determined to be premenopausal by their treating oncologist, by appropriate laboratory or clinical parameters. Patients were excluded from the analysis if they had metastatic disease. For adjuvant endocrine therapy, patients were prescribed either subcutaneous goserelin (3.6 mg every 1 month or 10.8 mg every 3 months) or leuprolide (3.6–7.5 mg every month or 11.25 mg every 3 months) with dosing and administration frequency determined by the prescribing clinician. E2 values, body mass index (BMI), age, and receipt of previous chemotherapy were collected. For all patients, estradiol level was measured via an ultrasensitive assay, using quantitative high performance liquid chromatography–tandem mass spectrometry, with a lower limit of detection of 2.0 pg/mL. All testing was sent out to Associated Regional and University Pathologists (ARUP) laboratories in Salt Lake City, Utah. OE was defined as an E2 level >2.7 pg/mL if on AI therapy. This definition was based on the recommended guidelines by Smith et al., which were also employed in the SOFT-EST analysis [9, 10]. Although there is no guideline or universally accepted standard for determining adequate ovarian suppression while on OS + tamoxifen, we defined this as having an estradiol level <21 pg/mL because this is the cutoff used by ARUP laboratories, and accepted by our institution, for pre- versus postmenopausal estradiol level. When receiving adjuvant endocrine suppression with an LHRH agonist, circulating levels of E2 are equivalent to values seen in postmenopausal women and women with surgical oophorectomy [11]. The primary objective of this analysis was to determine the proportion of patients that failed to achieve adequate OS in a "real-world" clinical setting within 3 months of initiation of adjuvant endocrine therapy. E2 levels were measured to delineate between OS and OE. E2 levels were monitored for up 12 months in patients that continued to receive OS after 3 months. If OE was documented within the initial 3 months, a secondary analysis was conducted to determine the proportion of these patients who had sustained OE at 6 months and 12 months. Sustained OE was defined as not having any estradiol values lower than the cutoff by the end of that particular time period in question. If patients did not have any estradiol values measured during that time period, they would not be included in the "sustained OE" group. The major secondary aim was to assess baseline data that may potentially impact ovarian reserve, which included age, receipt of previous chemotherapy, and BMI.

Statistical Analysis

OE was defined as achieving an E2 level >2.7 pg/mL if on AI or >21 pg/mL if on tamoxifen, as explained above. The primary endpoint was women who developed OE within 3 months after the initiation of leuprolide or goserelin. Baseline characteristics were presented by OE or OS as mean ± SD for continuous variables and number (percentage) for categorical variables. The comparison between OE and OS was assessed with Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables.

Table 1. Baseline characteristics by OE or OS

Characteristics	Total (*n* = 46)	OE (*n* = 11)	OS (*n* = 35)	*p* value
Age, mean ± SD, yr	41.9 ± 6.8	38.5 ± 6.7	43.0 ± 6.6	.037
BMI, mean ± SD	27.9 ± 6.7	29.0 ± 7.6	27.5 ± 6.5	.677
Previous chemotherapy, *n* (%)	27 (58.7)	6 (54.6)	21 (60.0)	.999
Oral endocrine drug, *n* (%)				.768
Anastrozole	14 (30.4)	3 (27.3)	11 (31.4)	
Exemestane	4 (8.7)	0 (0)	4 (11.4)	
Letrozole	8 (17.4)	3 (27.3)	5 (14.3)	
Tamoxifen	20 (43.5)	5 (45.5)	15 (42.3)	
Ovarian suppression, *n* (%)				.655
Monthly goserelin	28 (60.9)	5 (45.5)	23 (65.7)	
Q3 month goserelin	5 (10.9)	2 (18.2)	3 (8.6)	
Monthly leuprolide	10 (21.7)	3 (27.3)	7 (20)	
Q3 month leuprolide	3 (6.5)	1 (9.1)	2 (5.7)	

Data were presented as mean ± SD for continuous variables and *n* (%) for categorical variables. Fisher's exact test (categorical variables) and Mann-Whitney test (continuous variables) were used to compare subjects between OE and OS.
Abbreviations: BMI, body mass index (kg/m^2); OE, ovarian escape; OS, ovarian suppression; Q3, every 3.

Univariable and multivariable logistic regression models were applied to examine the association between age, BMI, or previous chemotherapy with OE. All analyses were performed with STATA version 16 (StataCorp 2019 Stata Statistical Software: Release 16. College Station, TX) Statistical significance was defined as two-tailed $p < .05$ for all tests.

Results

Between February 1, 2010, and January 9, 2018, a total of 46 women met inclusion criteria to be included in our retrospective analysis. The mean age of the total population was 41.9 ± 6.8 years. The mean age of the 8 women less than 35 years was 30.9 ± 3.1 years, and the mean age for the 38 women older than 35 years was 44.2 ± 4.8 years. The mean BMI for the entire cohort was 27.9 ± 6.7, with 58.7% of the women overweight or obese. Baseline characteristics of the entire group, as well as those who developed ovarian suppression versus ovarian escape, are summarized in Table 1.

There were 11 (24.0%) patients with OE within the first 3 months. On average, the women who achieved ovarian suppression were significantly older than the ones who experienced ovarian escape. The mean age of women with OE compared with OS was 38.5 years versus and 43.0 years, respectively ($p = .037$; Table 1). The mean time from first injection of goserelin or leuprolide to collection of E2 labs was 2.5 ± 1.45 months.

Of the 11 women with OE at 3 months, 10 continued adjuvant endocrine therapy beyond 3 months. At 6 months, 4 of these 10 women had sustained OE. At 12 months, three of three women who had not yet achieved ovarian suppression remained in OE (Fig. 1; Table 2). Ultimately, of the 46 women in our analysis, 11 (24%) did not attain OS at 3 months, and 3 women (6.5%) still had not attained OS after 12 months of LHRH agonist therapy. Those with persistent ovarian escape tended to be younger and overweight. For those with ovarian escape at 3, 6 and 12 months, their median age was 38.5, 35.9, and 36.9 years, respectively (Fig. 2). Mean BMI for these women ranged from 28.5–30 (Fig. 3).

On multivariable analysis of age, BMI, and receipt of previous chemotherapy, age was the only variable with retained statistical significance (odds ratio, 0.86; 95% confidence interval, 0.76–0.98; $p = .024$; Table 3) for achieving OE.

Although our study was not powered to look at the various dosing frequencies of gonadotropin-releasing hormone (GnRH) agonists, it is interesting to note that 38% (3/8) of women who received every 3 months (q3 month) injections (median age 43.4 years) experienced ovarian escape, compared with only 21% (8/38) of those who received monthly injections (median age 41.6 years). However, there was a smaller difference for ovarian escape between those who received goserelin versus leuprolide (21% vs. 30.8%). Rates of ovarian escape were similar in women who were receiving aromatase inhibitor versus tamoxifen (23% vs. 25%).

Discussion

In this single institution, real-world evaluation of premenopausal patients with ER+ breast cancer, 24% of women in the first 3 months were not adequately suppressed as defined by E2 parameters. Of those with OE within the first 3 months, one-quarter of patients had persistent inadequate OS as defined by E2 levels in the first year. Younger age (38.5 ± 6.7) was the only statistically significant risk factor associated with higher likelihood of OE.

The use of adjuvant endocrine therapy to achieve OS has become rather common in high risk premenopausal women. As its use in conjunction with AI therapy or tamoxifen becomes a mainstay of therapy in this patient population, it is prudent to define potential associations or risk factors that may predict or contribute to inadequate OS. The proportion of women with OE at 3 months in the present study and in the SOFT-EST trial were both

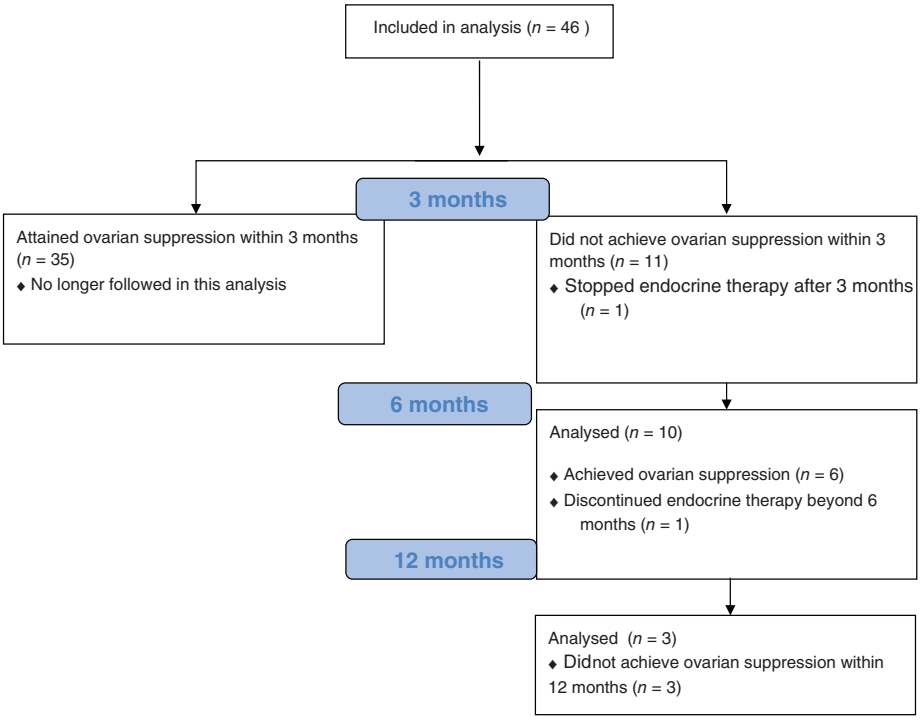

Figure 1. CONSORT diagram.

approximately 25%, suggesting a consistent and significant ratio of early OE [9]. In the final SOFT-EST 4-year prospective analysis presented at the 2018 San Antonio Breast Cancer Symposium, Bellet et al. noted that up to 25% of women monitored with triptorelin and exemestane had suboptimal E2 suppression in two or more readings, and early suboptimal suppression within the first year predicted additional OE over the 4 years these patients were followed [12]. In the current study, only women who continued to experience OE were monitored for a longer period of time. Those who developed OS were no longer followed, although some of them may have developed later OE, especially if they received chemotherapy prior to OS therapy.

Results from this study suggest one in four younger women are more likely to have suboptimal suppression during the first 3 months of GnRH agonist therapy, and some women will continue to produce extra estrogen, especially those who are younger. Although the clinical implications of OE in this cohort can only be theorized, it is possible that women with either persistent OE or recurrent episodes of suboptimal suppression are at a greater risk for disease recurrence. In the meta-analysis conducted by Key et al. of nine prospective trials, there was a statistically significant twofold increased risk of breast cancer with increasing concentrations of sex hormones, including E2 in postmenopausal women [13]. However, it is uncertain if this risk can be extrapolated to premenopausal patients with regard to breast cancer recurrence. Furthermore, it is unknown if premenopausal patients with OE despite OS therapy have an inherently higher risk of breast cancer

Table 2. Characteristics of patients with persistent OE at 3, 6, and 12 months

Characteristits	3 mo, *n* (%)	6 mo, *n* (%)	12 mo, *n* (%)
Patients on adjuvant endocrine therapy	46	10	3
Patients with sustained OE	11 (23.9)	4 (40.0)	3 (100)
Age, yr	38.5 ± 6.7	35.9 ± 4.5	36.9 ± 2.4
BMI	29.0 ± 7.6	28.5 ± 7.9	30.6 ± 8.3
Previous chemotherapy	6 (54.5)	3 (75.0)	2 (66.7)
Number on leuprolide	4 (36.4)	3 (75.0)	2 (66.7)
Number on goserelin	7 (63.6)	1 (25.0)	1 (33.3)
Tamoxifen	3 (27.3)	1 (10.0)	1 (33.3)
Anastrozole	3 (27.3)	0	0
Exemestane	2 (18.2)	0	0
Letrozole	3 (27.3)	3 (75.0)	2 (66.7)

Abbreviations: BMI, body mass index (kg/m^2); OE, ovarian escape.

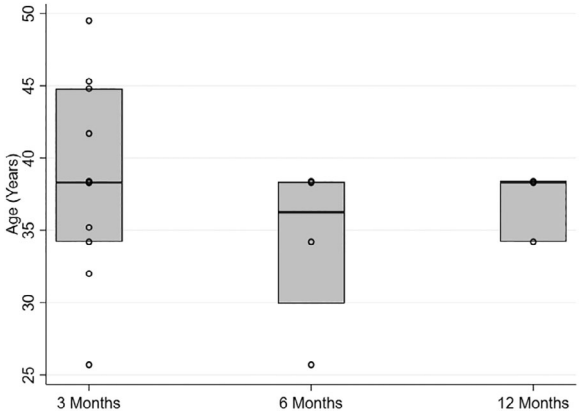

Figure 2. Association between age and ovarian escape at various time points during GnRH agonist therapy.

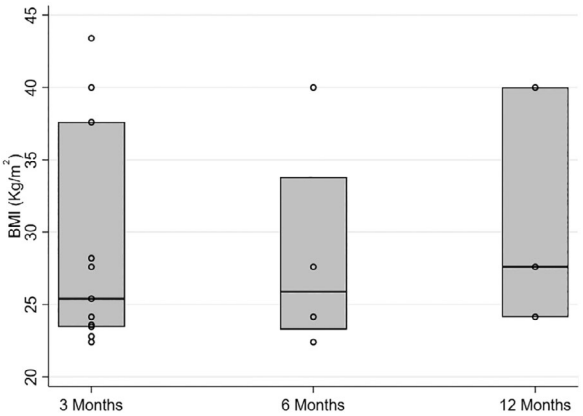

Figure 3. Association between Body Mass Index and ovarian escape at various time points during GnRH agonist therapy. Abbreviation: BMI, body mass index.

recurrence due to greater ovarian reserve. Therefore, an understanding of additional contributory risk factors is necessary. Pertinent factors reported in the initial SOFT-EST analysis that predicted the odds of OE included a lower follicle-stimulating hormone (FSH) and LH ($p < .01$), higher BMI ($p = .05$), and patients who were chemotherapy naive ($p = .06$) [9]. In the final analysis reported, baseline high E2 and lower FSH and LH were associated with higher risk of escape [12]. These were not found to be statistically significant factors in the present study, which is likely related to the smaller sample size and overall younger age of patients in our analysis. It also should be noted that we did not analyze FSH and LH because of lack of consistently available data in this regard. However, it is important to note that in women with sustained OE at 6 months and 12 months, a higher proportion of women had a receipt of previous chemotherapy (a similarity shared with the SOFT-EST study) and were overweight (Fig. 1). Although underpowered for statistical assessment in the current study, these factors should be assessed in future studies.

Although baseline younger age (38.5 years) was determined to be a significant risk factor for initial OE in our patient cohort, it was not in the SOFT-EST trial [9]. The median overall age of the women studied in the SOFT-EST trial was 45 years, and the median age of having at least one lab value signifying OE was 44 years [9]. By comparison, the women in the present study had an average age of 42 years, and the mean age of the OE group in our study was 38.5 years. When examining OE in younger women, who tend to have stronger ovarian reserve, it should be considered that their likelihood of achieving OS may not be as affected by other factors such as BMI, as compared with slightly older premenopausal women.

Although the clinical ramifications of age on OE in patients with ER+ breast cancer remain unknown, clinicians should be aware of potential ovarian escape when administering ovarian suppression to young women. Use of an AI in the SOFT/TEXT trials demonstrated better disease-free survival compared with tamoxifen [7], and both the SOFT-EST and single institution phase III HOBOE trials studies have demonstrated AI therapy to have a greater degree of sustained E2 suppression compared with tamoxifen [9, 14]. However, a total of 34% of patients on AI in the SOFT-EST trial had OE documented during at least one point in time, and 46% of these patients were chemotherapy naive [9]. In addition, there have been prospective and retrospective studies that indicate patients with chemotherapy-induced OS and concomitant AI therapy may be at risk of OE over time, including women who were switched from tamoxifen to an AI [10, 15, 16]. As with the present study demonstrating greater risk of OE with younger age (38 years), these trials suggest patients at a younger age ranging from a median of 43–49 years may be at risk of recovery of ovarian function over the course of their treatment [10, 15, 16]. Age appears to have a significant impact on ovarian function via a greater degree of ovarian resistance leading to difficulty with initial and sustained OS in a subgroup of women with ER+ breast cancer. Although the pivotal trials have demonstrated improved outcomes of AI therapy over

Table 3. Odds ratio for achieving ovarian escape within 3 months from univariable and multivariable logistic regression models

	Univariable		Multivariable	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
Age	0.90 (0.81–1.01)	.063	0.86 (0.76–0.98)	.024
BMI	1.03 (0.94–1.14)	.533	1.08 (0.97–1.22)	.17
Previous chemotherapy	0.8 (0.20–3.14)	.749	0.61 (0.13–2.78)	.523

Abbreviations: BMI, body mass index (kg/m^2); CI, confidence interval; OR, odds ratio.

tamoxifen with concomitant OS, it may be reasonable to consider tamoxifen as the initial therapy in younger women who are chemotherapy naive on OS, until true ovarian suppression is achieved and confirmed through laboratory testing.

There are several limitations in the present study. First, this is a retrospective, real-world review. As a result, and because of the limited population of premenopausal women that meet inclusion criteria at a single institution, standardizing the patient population in a uniform pattern is a significant challenge, as it is with many retrospective real world experiences. For example, this analysis included all patients who were receiving ovarian suppression, but it only continued to follow those patients who did not achieve ovarian suppression. Because of the variability in which E2 levels were collected in the "real world" setting, there was no uniform or regularly scheduled monitoring of estradiol levels. Although the order sets did have an estradiol lab "built in" to the orders every time a patient received a GnRH agonist shot, these values were not necessarily available every month for every single patient. Second, the definition for adequate ovarian suppression while on a GnRH agonist and tamoxifen is not clearly delineated. In the absence of a widely accepted definition, we chose to use the estradiol cutoff levels used for naturally postmenopausal women. Additionally, our sample size was rather small and, thus, underpowered to adequately examine other factors thata may contribute to OE, such as dosing frequency of leuprolide and goserelin, BMI, and receipt of previous chemotherapy. Another limitation of this study was patients were not followed if OS was achieved within 3 months. It is possible that some patients that initially achieved OS had OE as the length of time from their chemotherapy increased, or for those switched from tamoxifen to an AI which is a documented risk in younger patients [10, 15, 16]. The goal of this study was to assess persistence of inadequate suppression rather than assess OE after suppression has been documented.

Furthermore, because of the "real world," retrospective nature of this study, some of the women who did not attain complete ovarian suppression initially were changed from q3 month to monthly GnRH agonists, but this was not done routinely. Any changes to the treatment plan were executed per the discretion of each treating patient's oncologist. Specifically, of the 11 women who did not achieve OS in the first 3 months, three of them were on q3 month GnRH agonist injections. Two of these patients switched to monthly injections, and one of them achieved OS within 2 months of starting the monthly injections. The other patient who was switched to monthly injections remained unsuppressed throughout the trial. The third patient, who remained on q3 month injections, achieved ovarian suppression within 6 months. In the same vein, a handful of patients stayed on OS + AI therapy despite not achieving ovarian suppression immediately, whereas others changed to tamoxifen. This decision was also left to the treating oncologist. At this point, as there is no level I evidence recommending that estrogen levels need to be followed closely, or that clinical outcomes differ based on degree of ovarian suppression, it is not the current standard of care to immediately change from AI to tamoxifen or stop AI in the case of incomplete ovarian suppression.

Conclusion

In premenopausal patients with ER+ breast cancer, approximately 25% of women were not maximally suppressed within the first 3 months of OS therapy. Of these women who did not attain initial ovarian suppression, one in four women had persistent OE over 12 months. Young age (median, 38 years) was the only significant risk factor for likelihood of persistent inadequate suppression. Given the frequency of this phenomenon, future studies should evaluate whether OE in young, premenopausal women may be associated with higher recurrence risk and whether frequency, dose, and choices of adjuvant endocrine therapy has a role in women who have persistent OE over time.

Acknowledgments

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This was a retrospective, institutional review board-approved study. All patient information was anonymized prior to study initiation, so informed consent was not required.

Author Contributions

Conception/design: Polly Niravath, Ethan Burns, Emre Koca
Provision of study material or patients: Edward McLean, Rosetta Lee, Tejal Patel, Jenny Chang, Polly Niravath
Collection and/or assembly of data: Emre Koca, Ethan Burns, Rosetta Lee, Edward McLean
Data analysis and interpretation: Jiaqiong Xu, Edward McLean, Rosetta Lee, Tejal Patel, Jenny Chang, Polly Niravath
Manuscript writing: Emre Koca, Ethan Burns, Tejal Patel, Jenny Chang, Polly Niravath
Final approval of manuscript: Emre Koca, Ethan Burns, Jiaqiong Xu, Edward McLean, Rosetta Lee, Tejal Patel, Jenny Chang, Polly Niravath

Disclosures

The authors indicated no financial relationships

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