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Patient preferences and adherence to adjuvant GnRH analogs among premenopausal women with hormone receptor positive breast cancer

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Abstract

Purpose—Adjuvant ovarian function suppression (OFS) in premenopausal hormone receptor (HR) positive breast cancer (BC) improves survival. Adherence to adjuvant gonadotropin-releasing hormone analogs (GnRHa) remains a challenge and is associated with toxicities and inconvenient parenteral administration. The goal of this study was to describe real-world adherence patterns and patient preferences surrounding adjuvant GnRHa.

Methods—We analyzed the medical records of premenopausal women with non-metastatic HR positive BC from January 2000 to December 2017; participants received adjuvant monthly goserelin or leuprolide at The Ohio State University. Data collected included demographics, clinicopathologic characteristics, and OFS adherence/side effects. We defined non-adherence as discontinuation of GnRHa within 3 years for a reason other than switching to an alternate OFS, delay > 7 days from a dose, or a missed dose. Chi-square tests assessed associations between clinical characteristics and outcomes.

Results—A total of 325 patients met eligibility. Of these, 119 (37%) patients were non-adherent to GnRHa; 137 (42%) underwent elective bilateral salpingo-oophorectomy after initial GnRHa.

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Those opting for surgery reported significantly more hot flashes (74% vs 48%, $p < 0.001$), arthralgias (46% vs 30%, $p = 0.003$), and vaginal dryness (37% vs 21%, $p = 0.001$) compared with patients remaining on GnRHa.

Conclusion—Non-adherence to adjuvant GnRHa occurred in over a third of patients and almost half the patients initiating GnRHa underwent subsequent surgical ablation. These high frequencies highlight real-world patterns of OFS. Additionally, treatment toxicities may impact personal preference of OFS modality. Personalized practices to target predictors of adjuvant GnRHa non-adherence are critical to optimize symptoms, adherence, and survivorship.

Keywords

Ovarian suppression; GnRH; Endocrine therapy; Premenopausal; Ovarian ablation; Breast cancer

Background

The addition of ovarian function suppression (OFS) to adjuvant endocrine therapy (ET) among premenopausal women with hormone receptor (HR) positive early breast cancer has shown to reduce the risk of relapse and improve overall survival in large randomized trials [1–5]. In particular, the Suppression of Ovarian Function (SOFT) trial randomized 3066 patients to one of three arms to complete 5 years of adjuvant ET; this included tamoxifen, tamoxifen plus OFS, or exemestane plus OFS. Compared to tamoxifen alone, the absolute gain in 8-year invasive disease-free survival (iDFS) with tamoxifen plus OFS ($p = 0.009$) or exemestane plus OFS was 4.3% and 7%, respectively. Tamoxifen plus OFS also demonstrated improved overall survival (OS) in the intent to treat population (91.5% with tamoxifen vs 93.3% with tamoxifen plus OFS, $p = 0.01$). Younger age (≤ 35 years of age) at diagnosis or receipt of chemotherapy was associated with greater clinical benefit from the addition of OFS to adjuvant ET [1].

Ovarian suppression in premenopausal women can be accomplished using (a) periodic parenteral administration of gonadotropin-releasing hormone agonists/analogs (GnRHa), (b) radiation-induced ovarian ablation, or (c) surgery (bilateral salpingo-oophorectomy). GnRHa suppress ovarian steroidogenesis via a negative feedback mechanism in the hypothalamic-pituitary-ovarian axis. Exposing the pituitary gonadotrophs to a continuous concentration of GnRH (in contrast to endogenous pulsatile secretion) leads to a decrease in gonadotropic hormones, thereby suppressing ovarian estrogen production. Patient preferences most commonly guide the choice of OFS [6]. Among women enrolled in SOFT, a vast majority of participants (81%) received OFS entirely through monthly GnRHa injections. However, approximately a quarter experienced treatment interruption or early discontinuation of adjuvant ET secondary to adverse events [1, 5]. GnRHa use is associated with a higher incidence of menopausal symptoms (hot flashes, mood disturbances, sexual dysfunction, and weight gain) which negatively impact quality of life [7]. Accelerated loss of bone mineral density resulting in osteoporosis/osteoporotic fractures is also a potential toxicity [8]. In the real world, non-adherence to adjuvant ET poses a significant challenge, potentially affecting cancer-specific outcomes. In addition, the need for frequent, long-term parenteral injections may lead to an increase in the number of patients who miss, defer, or experience early discontinuation of adjuvant GnRHa. Some women may prefer to opt instead for

alternative methods of OFS such as bilateral salpingo-oophorectomy. Herein, we describe one of the first reported real-world experiences in patient preferences and adherence patterns surrounding adjuvant OFS in premenopausal women with HR positive breast cancer.

Patients and methods

The primary aim of this study was to evaluate adherence to adjuvant GnRHa in premenopausal women with HR positive breast cancer treated at The Ohio State University Comprehensive Cancer Center (OSUCCC-James). This study was an IRB-approved (OSU 2019C0117) single institution retrospective chart review of the clinical and histopathologic data of pre-menopausal women diagnosed with non-metastatic HR positive invasive breast cancer. Participants must have received adjuvant GnRHa therapy with goserelin acetate or leuprolide acetate. Patients were seen at OSUCCC-James between January 1, 2000 and December 31, 2017. Patients with incomplete clinical data, those who had stage IV disease, received medical OFS solely for fertility preservation, and who received adjuvant breast cancer treatment at other institutions were excluded. Patients were deemed non-adherent if they: (1) missed a dose, (2) delayed their prescribed dose by greater than seven days, or (3) discontinued therapy within three years of initiation for any reason other than undergoing alternate forms of ovarian ablation. Secondary endpoints included summarizing (i) treatment-related adverse events with GnRHa therapy, (ii) resumption of menstruation after treatment discontinuation, and (iii) patterns of switching to alternate OFS in patients initiating GnRHa. Broad data were obtained from The Ohio State University James Cancer Registry via the Honest Broker Committee and uploaded into the REDCap database [9]. Data were manually entered based on a review of each patient's electronic medical record, and patients that did not meet the eligibility criteria outlined in the study design were not considered in the analysis. Data collected included patient's demographic profile, clinical characteristics, cancer diagnosis/stage, treatment modalities (surgery, chemotherapy, ET), OFS type (medical, surgical, or radiotherapy), other specific OFS information (duration, side effects, adherence, obstetric referrals after initiating OFS), and presence of disease recurrence.

Statistical analyses

Demographics, clinical characteristics, treatment modalities, and adverse events were summarized using descriptive statistics. Comparisons of these characteristics and adverse events were made between GnRHa treatment non-adherence and adherence groups as well as between patients who underwent oophorectomy or maintained GnRHa therapy. Categorical variables were compared between adherence and treatment groups using Chi-square tests, and continuous variables were compared with a two-sample t test. All data analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 361 consecutive charts were reviewed, of which 325 patients met eligibility for this study. Table 1 describes the demographic, clinical, and treatment characteristics of the cohort. The mean age at diagnosis was 43 years (range 22–62). The majority of patients were white (284, 87%) with lymph node positive (194, 60%) and HER-2 negative (270,

83%) early breast cancer. The mean Body Mass Index (BMI) was 28.5 kg/m^2 (range 11–61). A total of 213 (66%) patients received chemotherapy; neoadjuvant chemotherapy accounted for 83 (39%) of these patients. Almost all patients received adjuvant goserelin acetate (315, 97%), with the remainder receiving leuprolide acetate (10, 3%). A total of 299 (92%) patients initiated concurrent adjuvant aromatase inhibitor or tamoxifen (aromatase inhibitor: 52% vs. tamoxifen: 41% as initial adjuvant endocrine agent).

Non-adherence to GnRHa use was reported in 119 (37%) patients, a majority from early discontinuation (73, 61%). Other causes included delayed administration (36, 30%) or missed doses (8, 7%) during adjuvant treatment. There was no association detected between treatment non-adherence and age at diagnosis (mean years: 43 vs 42, $p = 0.105$) or BMI (mean: 29 vs 28, $p = 0.721$) in this population; however, mood disturbances during treatment was associated with treatment interruption (23% vs 11%, $p = 0.004$).

A total of 137 (42%) patients underwent elective bilateral salpingo-oophorectomy after initial GnRHa therapy. The mean age at diagnoses in this cohort was 43 years (range 25–54) with a mean treatment duration of 16 months (range 1–77 months) with adjuvant GnRHa therapy. This cohort also reported significantly higher rates of hot flashes (74% vs 48%, $p < 0.001$), arthralgias (46% vs 30%, $p = 0.003$), and vaginal dryness (37% vs 21%, $p = 0.001$) compared with those who continued to remain on periodic GnRHa (Table 2). Overall, the frequency of treatment-related AEs in this study population was consistent with previous studies evaluating adjuvant OFS with ET. Among patients who did not undergo oophorectomy, 32 (17%) resumed menstruation and 2 (1%) reported pregnancies after completing planned ET. Receipt of chemotherapy was inversely associated with resumption of menses (65% vs 47%, $p = 0.050$).

Discussion

In this contemporary study of premenopausal women undergoing GnRHa for OFS with adjuvant ET, treatment non-adherence was more frequent compared to controlled randomized trials in this population [10, 11]. For example, in SOFT and the Tamoxifen and Exemestane Trial (TEXT), the rate of non-adherence with OFS in women younger than 35 years of age was 17% [11]. On the other hand, we observed non-adherence to GnRHa in more than a third of patients (119, 37%). Notably, a vast majority of patients in this study were over 40 years of age (234, 74%) at diagnoses. Early discontinuation (HR 1.26) and non-adherence (HR 1.49) to adjuvant ET is associated with poor prognosis, underscoring the importance of strategies required to address this challenge in the real world [10]. This is key in the era of genomics and personalized therapy where de-escalation of adjuvant systemic therapy with increased use of adjuvant OFS is considered in lieu of chemotherapy for those with operable HR positive breast cancer and intermediate recurrence scores found on Oncotype Dx testing [12, 13].

Although several aspects of GnRHa make adherence challenging, evidence suggests a large proportion of premenopausal women with HR positive breast cancer opt for periodic GnRHa injections for achieving OFS. We found almost half of all patients at our institution who were administered adjuvant GnRHa ultimately chose to undergo surgical OFS. This

occurred at a substantially higher rate than SOFT and TEXT trials, where 16–18% of patients switched from reversible OFS to a permanent option of either irradiation or surgery [5, 14]. Many patients may choose surgical OFS given the inconvenience associated with monthly GnRHa injections. For instance, in a small survey of women with early stage or metastatic disease receiving goserelin, participants were offered the option to switch to a non-pharmacological OFS method. Over half of the subjects indicated a preference for a switch to oophorectomy, citing inconvenience issues as the main influencing factor [15]. The findings in our study substantiate these results and emphasize the high rate of change from medical OFS to a non-pharmacologic option in the real world. Financial toxicity from long-term monthly GnRHa may also influence decision in favor of surgery [16]. In addition, bilateral salpingo-oophorectomy is often considered in younger women with known pathogenic germline variants in *BRCA1* or *BRCA2*. This study also demonstrates that certain toxicities may also influence this decision. Our findings suggest the cohort of patients undergoing BSO were more likely to experience treatment-related adverse effects such as hot flashes, arthralgias, and vaginal dryness from adjuvant ET. A plausible explanation could be more frequent occurrences of missed/deferred doses in patients experiencing certain side effects, thereby raising concern of inadequate ovarian suppression and need for definitive surgical ablation. Additionally, patients attributing toxicities to monthly goserelin may be less likely to continue with therapy and instead undergo alternate forms of OFS. While this study is limited in ability to address the cause-effect relation in patient preferences, our findings bring to light that treatment-related toxicities with monthly GnRHa may be a contributing factor in influencing some patients to undergo bilateral oophorectomy.

Based on our institutional practice, patients at our breast center receive GnRHa on a monthly schedule consistent with evidence from large randomized trials. Dosing GnRHa at an alternative schedule of every three months has been proposed to improve patient convenience and treatment adherence. However, there is only limited data to support the use of this approach in breast cancer [17, 18]. There remains a theoretical concern that every three month treatment frequency may result in a greater risk of inadequate ovarian suppression. This is particularly problematic in patients receiving a concurrent aromatase inhibitor.

In the SOFT Estrogen Substudy, blood samples for serum estradiol were checked at various time points within a 12-month period in a subset of patients who were on monthly GnRHa. Notably, at least 17% had estradiol levels greater than the postmenopausal threshold [19]. Estradiol levels which are not appropriately suppressed could present either subclinically or clinically as vaginal bleeding during therapy. Our study found vaginal bleeding during medical OFS to be a rare occurrence ($n = 6$). We also found resumption of menstruation following discontinuation of GnRHa to be an uncommon event. This is in contrast to results from The International Breast Cancer Study Group trial VIII, in which women less than 40 years ($n = 53$) returned to their premenopausal state 6 months after the termination of adjuvant GnRHa [20]. Our finding of infrequent resumption of menstruation following medical OFS may be related to the older mean age of patients in our population [21]. Additionally, greater than half the patients (66%) in this cohort received chemotherapy, which can result in gonadotoxicity.

Based on the high rate of non-adherence with adjuvant OFS, future studies should focus on novel interventions to improve patient adherence. One strategy is to target known predictors of ET discontinuation. In a retrospective study of 3395 patients, a higher risk of adjuvant ET discontinuation was associated with multiple risk factors including a higher baseline comorbidity index, age less than 40 years, and use of certain medications including analgesics, sedatives, and antidepressants [22]. Depression prior to the start of adjuvant ET has also been associated with non-adherence [23]. Additionally, adherence to ET can be impacted by socioeconomic and demographic factors. These health disparities were found to be barriers to ET adherence in the Carolina Breast Cancer Study [24]. Moreover, sexual side effects can be a predictor of non-adherence [7]. In a single arm pilot study of a personalized psychosocial intervention (entailing rehabilitation, exercises, mindfulness, and telephone check-ins) to target sexual dysfunction related to OFS in young breast cancer survivors, there was a significant improvement in sexual function following the intervention [25]. Behavioral interventions to improve ET adherence are additionally an active area of investigation [26]. Personalized practices such as these to target predictors of nonadherence and improve symptom management are critical to promote continuation of OFS therapy and improve breast cancer survival in premenopausal women.

This retrospective study is not without limitations. It is a single institution study with a limited number of events. Moreover, there may be possible confounding and/or selection bias, which are known limitations of retrospective review. For example, the decision for medical OFS and choice of oral endocrine partner was based on the discretion of the provider and patient. While we have detailed the side effects related to ET, it was not possible to determine which toxicities may be related to OFS compared with oral ET, as the majority of patients were on both treatments concurrently. Nevertheless, multiple studies have demonstrated that the addition of OFS compared with oral ET alone is associated with worse vasomotor symptoms and increased sexual dysfunction [7, 11, 27]. Furthermore, it was difficult to ascertain differences in recurrence, toxicity, or adherence patterns with aromatase inhibitors compared to tamoxifen, given that many patients had a change in their oral endocrine agent through the course of their adjuvant treatment. Our study also lacks adequate power to address the impact of non-compliance (missed dose, delayed dose) or early discontinuation on cancer prognosis. Additionally, the number of missed or delayed doses for those that were non-adherent was challenging to collect with accuracy due to the retrospective nature of chart review. Lastly, while our study provides insight into patient preferences and impact of toxicities on OFS treatment patterns, it cannot determine causality.

Conclusion

Non-adherence to adjuvant GnRHa poses a significant challenge in the real world with over a third of patients reporting treatment interruptions or early discontinuation of OFS; improved strategies are critical for optimized survivorship. This study also provides insight into patient preferences surrounding choice of OFS. Almost half of the patients ultimately opted to change from GnRHa to oophorectomy and treatment-related toxicities impacted choice of OFS. Future studies targeting unique challenges in survivorship for this younger premenopausal population are required to enhance care delivery.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the article and/or the tables. Raw data were generated at The Ohio State University. Derived data supporting the findings of this study are available from the corresponding author SS on request.

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Table 1

Demographic, clinical, and treatment characteristics

Variable	Level	Total (n = 325)
Age at diagnosis	Mean (SD)	43.1 (6.4)
	(min, max)	(22.4, 62.4)
Gender	Female	325 (100%)
BMI	Mean (SD)	28.5 (7.81)
	(min, max)	(10.8, 61.1)
Race	Asian	10 (3.1%)
	Black or African American	21 (6.5%)
	More than one race	10 (3.1%)
	White	284 (87.4%)
Ethnicity	Hispanic or Latino	1 (0.3%)
	Not Hispanic or Latino	324 (99.7%)
Stage (clinical)	0	12 (3.7%)
	I	126 (38.8%)
	II	141 (43.4%)
	III	32 (9.8%)
ER positive	Positive (IHC 1–100%)	325 (100%)
PR positive	Positive (IHC 1–100%)	324 (99.7%)
HER2 status	Negative	283 (87.1%)
	Positive	42 (12.9%)
Breast cancer recurrence		33 (10.2%)
Receipt of chemotherapy		213 (65.5%)
	Total	83 (39.0%)
	Neoadjuvant Adjuvant	130 (61.0%)
Type of GnRHa	Goserelin	315 (96.9%)
	Leuprolide	10 (3.1%)
Non-adherence to GnRHa	Total	119 (36.6%)
Cause of Non-adherence	Discontinued within 3 years 73 (61.3%)	73 (61.3%)
	Missed dose	8 (6.7%)
	Delay > 7 days	36 (30.3%)
	Unknown	2 (1.7%)
Initial	Aromatase inhibitor	169 (52.0%)
Oral endocrine	Tamoxifen	132 (40.6%)
Agent	Unknown	24 (7.4%)

Table 2

Adverse event comparisons between patients that remained on gonadotropin-releasing hormone analogs compared with those who opted for surgical ablation

Symptom	Medical suppression (*n* = 188)	Surgical ablation (*n* = 137)	*P* value
Hot flashes	91 (48.4%)	101 (73.7%)	< 0.001
Arthralgia	56 (29.8%)	63 (46%)	0.003
Mood disorder worsening	27 (14.4%)	22 (16.1%)	0.673
Weight gain	14 (7.4%)	15 (10.9%)	0.274
Osteoporosis	12 (6.4%)	12 (8.8%)	0.419
Vaginal atrophy/dryness	39 (20.7%)	51 (37.2%)	0.001