Adherence to anti-estrogen therapy in women with hormone receptor-positive breast cancer utilizing bubble packaging: a pilot study

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Abstract

Purpose This pilot study evaluated adherence to anti-estrogen therapy in women with hormone receptor-positive breast cancer utilizing bubble packaging.

Methods This was a single-arm prospective investigational pilot study that enrolled 86 patients between August 2012 and April 2014. Descriptive statistics for patient age, race, insurance, stage, duration of treatment, and comorbidities were computed. All patients received routine prescriptions in a "bubble" pack or daily blister pack dispensed by one pharmacy. Participants were considered adherent if they had taken ≥ 80% of the dispensed drug. Disease-free survival (DFS) and overall survival (OS) data were obtained at 78 months.

Results Fifty patients were included in the analysis. The overall adherence rate was 97%. None of the variables examined (race, age, insurance status, and stage) had an impact on adherence rate. Only duration of endocrine therapy had a marginal effect on adherence (p value = 0.06). The late cohort (duration of therapy 37–60 months) was least likely to be compliant at 89.53%. Our 5-year DFS was 94% and 5-year OS was 96%. There was no statistically significant difference in DFS and OS between patients with adherence rate > 90% and < 90%.

Conclusion Adherence rate to bubble packaging was higher than that in historical studies. Although this is a single-arm pilot study, these data suggest bubble packaging of anti-estrogen may be a reasonable option to improve adherence in hormone receptor-positive breast cancer patients.

Keywords Breast cancer · Anti-estrogen therapy · Bubble packaging · Adherence

Introduction

In the United States, breast cancer is the most frequently diagnosed cancer and the second most common cause of cancer deaths in women [1]. Hormone receptor-positive (i.e., estrogen [ER] and/or progesterone [PR] receptor) breast

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cancer accounts for 73 percent of all cases in the United States [2].

Adjuvant anti-estrogen therapy (Tamoxifen or aromatase inhibitors [AI]) is recommended [3] for all nonmetastatic hormone receptor-positive breast cancers for 5–10 years due to significant reduction in recurrence and mortality [4, 5]. However, for any drug, efficacy ultimately depends on the patient's ability to adhere to the prescribed dosing regimen in the long term.

Adherence to anti-estrogen therapy in breast cancer has been a long-recognized problem and is associated with poor survival [6, 7]. Using a large insurance database, Partridge et al. [8] reported 87% adherence within the first year of therapy which dropped to 50% by the fourth year. Nonadherence to anti-estrogen therapy is multifactorial. Some patients discontinued medication due to side effects or lack of perceived benefit, while others simply forgot to take the medication (18% in one survey) [9, 10]. Several methods have been described to improve adherence including patient information/education, frequent communication between patient and healthcare team, pill counting, and web-based app [11, 12]. Frequent communication with patients is not practical for the average provider, and other methods like web-based app require a patient to own a smartphone, which may be financially limiting for certain patients.

Weekly pill boxes and blister/bubble packs have been previously studied in other chronic diseases and have been shown to significantly improve medication adherence [13]. Monthly blister packaging is familiar to most women as oral contraceptive pills are widely used among women. To our knowledge, there is no report of pill packaging as a means to improve adherence to anti-estrogen therapy within the published literature.

Our pilot study aimed at assessing the feasibility of using monthly bubble packaging to improve adherence rates among women prescribed adjuvant anti-estrogen therapy.

Patients and methods

Study design and recruitment

This was a single-arm prospective investigational study. Participants were all under the care of medical oncologists at the James Graham Brown Cancer Center (JGBCC) at the University of Louisville (Louisville, Kentucky). Patients were enrolled after being prescreened for eligibility during routine oncology clinic visits between August 2012 and April 2014. Written informed consent and Health Insurance Portability and Accountability Act authorization were obtained from all participants. This study was approved by the University of Louisville Institution Review Board.

Eligibility criteria

Women age ≥ 18 years diagnosed with ER/PR-positive Ductal carcinoma in situ (DCIS) or invasive breast cancer (Stage I, II and III) considered for adjuvant anti-estrogen therapy (Tamoxifen and AIs—anastrozole, letrozole, exemestane) were eligible. Patients already on anti-estrogen therapy were also eligible. ER/PR positivity was defined as > 1% estrogen or progesterone expression by immunohistochemistry. Women with metastatic breast cancer were excluded, as were women who were unable to provide informed consent because of moderate or severe dementia.

Study procedure

All participants were divided in three cohorts: (1) new: < 12 months since start of anti-estrogen, (2) intermediate: 12 to 36 months since start of anti-estrogen, and (3) Late: 37–60 months since start of anti-estrogen therapy. All enrolled patients were given a prescription for anti-estrogen to be filled at JGBCC in the form of bubble package. Oncology clinic visits for follow-up were every 4 months.

Bubble packaging of anti-estrogen was prepared by the JGBCC pharmacy as 30-day package with labeled day of the week and dispensed as 1 month or 3 month supply. At each oncology clinic visit, each participant's used and current bubble packages were assessed by either a pharmacist or physician for adherence. This occurred at every oncology clinic visit for 1 year. Participants were considered adherent if they had taken ≥ 80% of the dispensed drug, based on previous studies [12].

Statistical analyses

We performed per-protocol analysis. Participants with < 3 months of data on use of bubble package were excluded from analysis. Descriptive statistics were produced for the study population included in analysis. For continuous variables, means and standard deviations (SDs) were computed. For categorical variables, frequency tables were produced.

Frequencies were compared using a Chi-square test (Fisher's exact test when expected cell frequencies are small). Continuous measures were compared using a two-sample t test or Wilcoxon rank sum test for normally or nonnormally outcome measures, respectively [14]. In addition, linear and logistic regression analyses were used to explore association with different factors. Results were declared significant at significance level of 5% and all analyses are performed using SAS [15].

Results

Patient characteristics

In total, 86 patients were enrolled in the pilot study. From the 86 patients, 50 were included in the analysis (Fig. 1). Patient demographics and clinical characteristics are summarized in Table 1 with a median age of 58 years (Range 27–79 years).

Withdrawal from the study

Forty-eight patients withdrew during the study for various reasons, of which 12 were included in the analysis due to collected data on adherence (Fig. 1). The most common reasons reported for withdrawal were financial or insurance issues with better coverage benefits elsewhere (31%) and inconvenience of prescription pick-up at study pharmacy (20%). Age, race, insurance, stage, and surgery type did not predict for withdrawal.

Adherence to anti-estrogen therapy

The overall adherence rate of this pilot group was 97%. Only 3 (6%) patients had adherence rate of < 90%. None of the variables examined such as race, age, insurance, stage, and treatment history (surgery type, prior chemotherapy or prior radiation) had a significant impact on adherence. There was also no difference in adherence between patients who received 30- versus 90-day supply.

Fig. 1 Flow chart detailing patient enrollment and withdrawal during trial. JGBCC—James Graham Brown Cancer Center, ER—Estrogen Receptor, PR—Progesterone Receptor, Rx—prescription
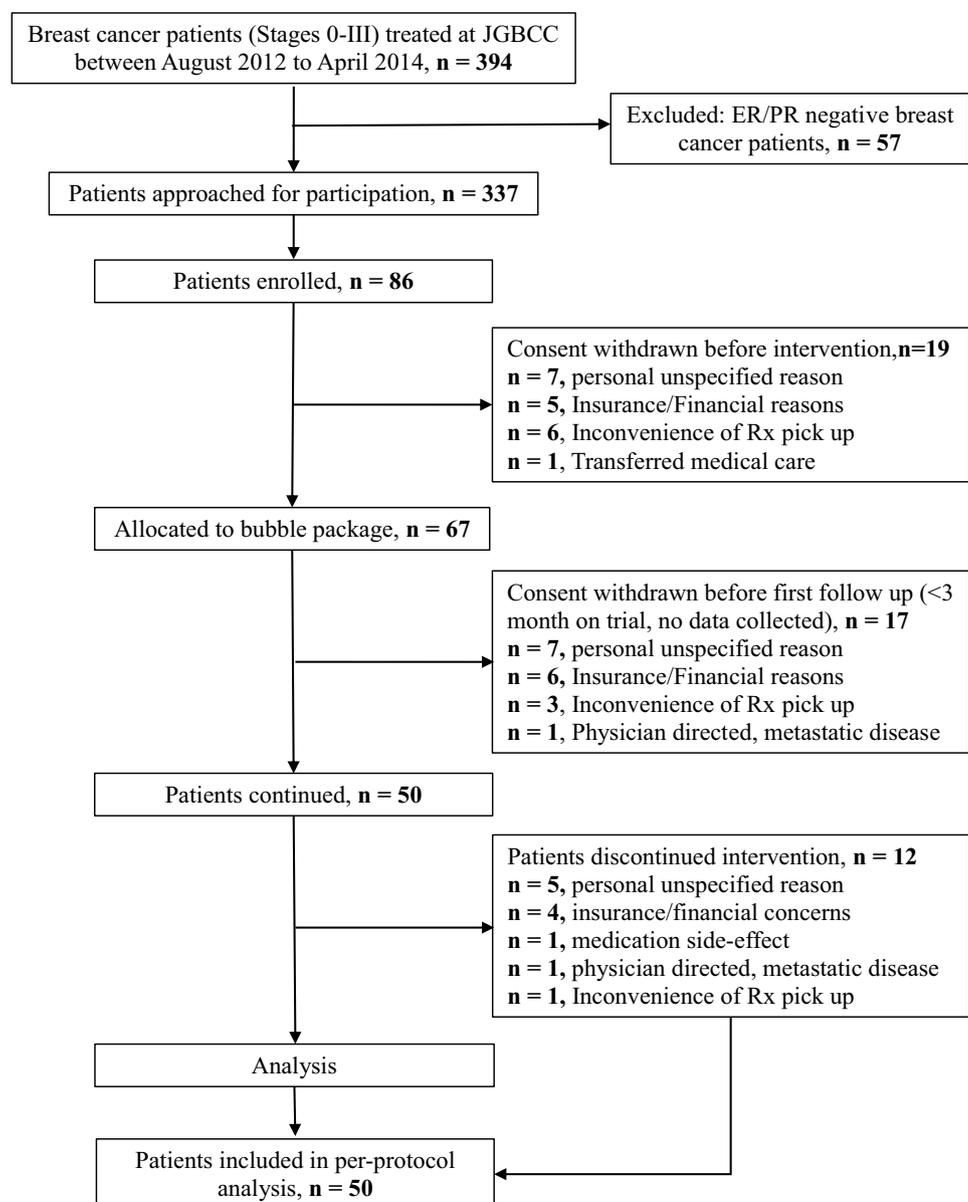
Table 1 Participants' demographics and clinical characteristics

Variable	n (%)
No. of patients	50 (100)
Sex, female	50 (100)
Race	
White	39 (78)
Black	11 (23)
Insurance	
Medicaid/passport	6 (12)
Medicare	9 (18)
Private insurance	35 (70)
Duration of therapy groups	
< 12 months	23 (46)
12–36 months	22 (44)
37–60 months	5 (10)
Anti-estrogen type	
Aromatase inhibitor	28 (56)
Tamoxifen	22 (44)
Stage	
0	6 (12)
I	24 (48)
II	13 (26)
III	7 (14)
Comorbidities	
None (0)	4 (8)
Moderate (1–3)	33 (66)
Significant (> 3)	13 (26)
Surgery type	
Breast conserving	27 (54)
Mastectomy	23 (46)
Prior chemotherapy	
Yes	27 (54)
No	23 (46)
Prescription frequency	
Monthly	33 (66)
Every 3 months	17 (34)
Prescription received	
From pharmacy	29 (58)
Via mail	21 (42)

Duration of therapy had a marginal effect on adherence (p value = 0.06). New and intermediate cohort had similar adherence rate at 97.9%. Late cohort (37–60 months) had the lowest adherence rate at 89.5%, although only represented 10% of the included patients.

Participants had a 5-year disease-free survival (DFS) of 94% and 5-year overall survival (OS) of 96%. There was no statistically significant difference in DFS and OS between patients with compliance > 90% and < 90%.

Discussion

The results of this small pilot study suggest that bubble packaging for anti-estrogen therapy is feasible. With bubble package use (per-protocol analysis), our adherence rate is 97%, which is higher than that previously described in the literature [6, 8, 16]. Although this study suggests improved adherence with bubble packaging, it is limited by the absence of a control arm, small sample size, and high withdrawal rate. Bubble packaging has been shown to improve adherence in other diseases [13] and it is therefore our belief that bubble packaging played a role in higher adherence rate in our study.

Our study had a very high withdrawal rate (55%). It was related to the fact that patient's own insurance was used to fill the prescription and bubble-packaged anti-estrogen could only be provided at study pharmacy. Most of the patient who withdrew were very pleased with the concept of bubble packaging but were limited due to financial or insurance issues with better coverage benefits elsewhere and inconvenience of prescription pick-up at study pharmacy. High trial withdrawal likely altered analysis of adherence rates as it selected for a largely compliant group of patients and may also explain the lack of difference in compliance rate among race, insurance status, and age, which contradicts our current knowledge. Intention-to-treat analysis might have been more appropriate but we did per-protocol analysis as main purpose of this pilot study was feasibility of bubble packaging of anti-estrogen and adherence related to bubble package use.

There was no difference in OS or DFS based on adherence to anti-estrogen therapy. Given the high compliance rate in this small population, the lack of OS and DFS difference is not surprising. Interestingly, there was no difference in adherence rate among age, race, insurance or prescription frequency, which contradicts our current knowledge on high risk groups.

Adherence to anti-estrogen is an area of concern and active research in breast cancer. Many ongoing studies evaluate different methods to improve adherence but may be costly and of limited access to certain disadvantaged patients. Bubble packaging has been shown to improve adherence in other diseases [13] and is now also suggested in breast cancer by this pilot study. Bubble/blister packaging has also reduced the time needed to dispense pills and increased the efficiency of pharmacists' dispensing activities [17]. They may also reduce the number of counting errors. Cost of bubble packaging can be a limiting factor in using them over traditional pill bottles as they are generally more expensive then bulk packaging. Lipowski et al.'s study used 50 types of prescriptions and reported the unit-of-use (bubble/blister) packages cost $6.31 more

[17]. While unit-of-use packages were more expensive, Lipowski et al. showed that the increased cost can be off-set by eliminating the cost of separate prescription vials, decreased counting errors, and the time saved. Another study supports these findings that by using unit-of-use packaging, it can decrease overall inventory costs [18].

There are several limitations to our study. The small sample size, no placebo group, and high withdrawal rate in this pilot study may have affected analysis suggesting better adherence rate with bubble packaging. Therefore, additional more robust study is needed. Bubble package was prepared in-house and were not as small as commercially available bubble-packaged oral contraceptive pills. All participants were treated in an academic hospital, so the adherence rate may not be generalizable to other settings.

Conclusions

Bubble packaging of anti-estrogen therapy is a feasible, reliable, practical, and more familiar method to improve adherence to anti-estrogen therapy in hormone receptor-positive breast cancer. Larger randomized placebo-controlled trials are needed to understand the true impact of bubble packing on adherence and cost analysis of various adherence strategies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

Ethical approval 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.

Informed consent Informed consent was obtained from all individual participants included in the study.

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