Original Article

Patient-Reported Symptoms and Discontinuation of Adjuvant Aromatase Inhibitor Therapy

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BACKGROUND: Aromatase inhibitor (AI) therapy results in substantial survival benefits for patients with hormone receptor-positive breast cancer. The rates of poor adherence and discontinuation of AI therapy are high, primarily because of treatment-related toxicities like musculoskeletal pain. Although pain-related symptoms may worsen during AI therapy, the authors hypothesized that nonpersistence with AI therapy was associated with symptoms that were present before treatment initiation. **METHODS:** Postmenopausal women initiating AI therapy who were enrolled in a prospective clinical trial completed questionnaires at baseline to assess sleep, fatigue, mood, and pain. Reasons for treatment discontinuation during the first year of treatment were recorded. Associations between baseline patient-reported symptoms and treatment discontinuation because of toxicity were identified using logistic regression. **RESULTS:** Four hundred forty-nine patients were evaluable. The odds of treatment discontinuation were higher in patients who reported a greater number of symptoms before AI initiation. Baseline poor sleep quality was associated with early treatment discontinuation, with an odds ratio (OR) of 1.91 (95% confidence interval [CI], 1.26-2.89; $P = .002$). Baseline presence of tired feeling and forgetfulness had similar ORs for discontinuation (tired feeling: OR, 1.76; 95% CI, 1.15-2.67; $P = .009$; forgetfulness: OR, 1.66; 95% CI, 1.11-2.48; $P = .015$). An increasing total number of baseline symptoms was associated with an increased likelihood of treatment discontinuation, with an OR of 1.89 (95% CI, 1.20-2.96; $P = .006$) for 3 to 5 symptoms versus 0 to 2 symptoms. **CONCLUSIONS:** Symptom clusters in breast cancer survivors that are present before the initiation of adjuvant AI therapy may have a negative impact on a patient's persistence with therapy. Interventions to manage these symptoms may improve breast cancer outcomes and quality of life. ***Cancer* 2014;120:2403-11**. © *2014 American Cancer Society.*

KEYWORDS: breast cancer, aromatase inhibitor, patient-reported outcomes, nonpersistence, symptoms.

INTRODUCTION

Aromatase inhibitors (AIs) are routinely used for adjuvant therapy of postmenopausal women with estrogen receptor (ER)-positive, early stage breast cancer. Randomized controlled trials have demonstrated improvements in disease-free survival (DFS) and overall survival (OS) with AI therapy compared with tamoxifen.[1,2] Early discontinuation of AI therapy, however, has been observed in >25% of patients, primarily caused by the toxicity of therapy.[3,4] Nonadherence to AI therapy has been associated with increases in mortality.[5]

The most common toxicities reported by AI-treated patients are musculoskeletal symptoms, including arthralgias and myalgias.[3] Attempts to identify the cause of these side effects have focused on clinical and treatment factors, such as time since menopause, body mass index (BMI), prior tamoxifen therapy, and prior taxane chemotherapy.[3,6-8] Despite those studies, the etiology of AI toxicity remains undefined, although it is believed to be caused, at least in part, by estrogen depletion.[9,10] Vitamin D deficiency may also play a role in the development of toxicity.[11]

Studies of breast cancer survivors have demonstrated high rates of patient-reported symptoms, including pain, insomnia, fatigue, cognitive dysfunction, and mood disorders, which can be present during all phases of treatment and can persist into the survivorship period.[12,13] A similar constellation of symptoms is commonly reported by patients with

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DOI: 10.1002/cncr.28756, **Received:** January 9, 2014; **Revised:** February 24, 2014; **Accepted:** March 3, 2014, **Published online** May 6, 2014 in Wiley Online Library (wileyonlinelibrary.com)

other chronic pain conditions, including fibromyalgia and temporomandibular joint disorder.[14] In patients with breast cancer, these symptoms may partly arise from the multiple treatment modalities used for disease management, including surgery, chemotherapy, radiation therapy, and/or endocrine therapy. In addition, these symptoms may be related to the stress of the diagnosis itself.[15]

By using data from the 503-patient Exemestane and Letrozole Pharmacogenetics (ELPh) trial, we previously reported associations between clinical and treatment factors and early discontinuation of therapy because of toxicity.[3] In that study, >75% of patients reported musculoskeletal pain at the time of discontinuation. On the basis of the literature from other chronic pain disorders, we hypothesized that some breast cancer patients who develop musculoskeletal pain might also have other symptoms that are observed in response to stressors, such as sleep disturbances, fatigue, mood disorders, and cognitive dysfunction.[16] If this were the case, then it is possible that some individuals would discontinue AI therapy because of their total symptom burden at baseline, not solely because of the emergence of their musculoskeletal pain.[17,18] In this article, we report associations between the presence of patient-reported symptoms before the initiation of an AI and treatment discontinuation within 1 year of starting the drug in the ELPh trial.

MATERIALS AND METHODS

Study Participants

Postmenopausal women with stage 0 through III hormone receptor-positive breast cancer who were initiating treatment with an AI were eligible for enrollment on the ELPh trial (clinicaltrials.gov identifier NCT00228956). Details of the ELPh trial have been reported elsewhere.[19] In brief, all indicated surgery, chemotherapy, and radiation therapy were completed before enrollment, and patients who previously received tamoxifen therapy were permitted to enroll. The clinical trial was approved by the institutional review boards at all 3 participating sites, and patients were required to provide written informed consent before undergoing study-related procedures.

Study Procedures

Patients were randomized 1:1 to treatment with oral exemestane (Aromasin; Pfizer, New York, NY) 25 mg daily or oral letrozole (Femara; Novartis, Basel, Switzerland) 2.5 mg daily. Before AI initiation, enrolled patients completed a battery of questionnaires and underwent phlebotomy. Patients then initiated treatment and returned to the clinic for follow-up assessments, including phlebotomy and questionnaire completion, after 1 month, 3 months, 6 months, 12 months, and 24 months of AI therapy.

Questionnaires

At each time point, patients completed the following questionnaires: depression (Center for Epidemiologic Studies–Depression [CESD])[20]; anxiety (Hospital Anxiety and Depression Scale-Anxiety [HADS-A])[21]; sleep quality (Pittsburgh Sleep Quality Index [PSQI])[22]; and general symptoms, including joint pain, fatigue, difficulty concentrating, forgetfulness, and vaginal dryness (the Breast Cancer Prevention Trial [BCPT] Symptom Checklist).[23]

Laboratory Studies

Serum samples obtained at the baseline and 3-month time points were assayed for estradiol (E2), estrone-1-sulfate (E1S), and estrone (E1) using an ultrasensitive gas chromatography tandem mass spectroscopy assay, as previously described.[24] The lower limits of quantification were 0.625 pg/mL for E2, 2.88 pg/mL for E1S, and 1.56 pg/mL for E1.

Statistical Plan

The primary objective of the ELPh trial was to determine the genetic predictors of change in breast density after 24 months of either an azole (letrozole) or a steroidal (exemestane) AI medication; those results are being published separately.[25] The primary objective of the exploratory analysis reported in this article was to investigate associations between patient-reported symptoms before AI initiation and discontinuation of AI therapy because of toxicity during the initial 12 months of therapy.

Validated questionnaires to evaluate fatigue or cognitive dysfunction were not included in this trial. Therefore, to investigate these symptoms, the following individual items on the BCPT questionnaire[23] were analyzed: "joint pain" (pain), "forgetfulness" and "difficulty concentrating" (cognitive dysfunction), and "tired feeling" (fatigue). "Vaginal dryness" was also analyzed as a common AI-related symptom, which is believed to be predominantly peripherally mediated rather than centrally mediated. The presence of each symptom was defined as the patient reporting any degree of severity of the symptom (ie, slightly, moderately, quite a bit, or extremely).

Descriptive analyses were conducted of all baseline characteristics for the entire sample and by discontinuation status. Odds ratios (ORs) and their significance comparing the characteristics of women who discontinued AI

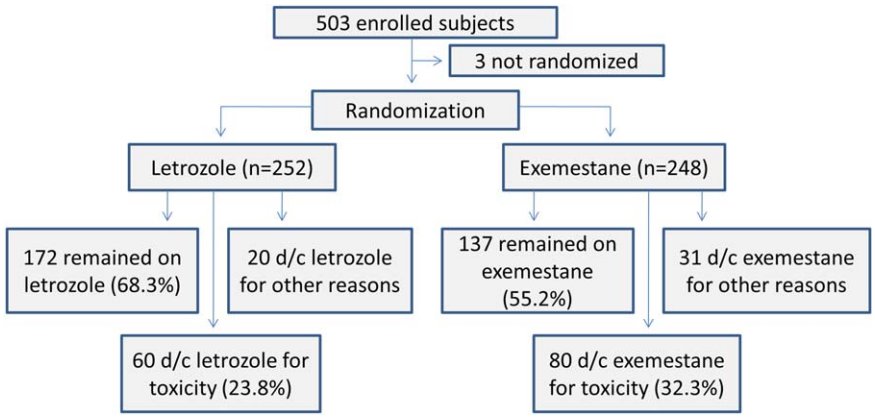

Figure 1. This is a Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow in the Exemestane and Letrozole Pharmacogenetics trial (d/c indicates discontinued).

therapy because of symptoms by the end of 1 year with the characteristics of women who remained on treatment at 1 year were calculated using logistic regression. Baseline characteristics that were associated with AI discontinuation because of symptoms by the end of the first year by a P value $< .20$ were included in a multivariable model in which a stepwise procedure was used to identify those variables that were associated significantly with AI discontinuation because of toxicity. Estrogen measurements were natural log-transformed in all models.

In addition, symptoms were combined to account for the total number of symptoms each patient experienced at baseline. Symptoms that were included in this variable were sleep quality (poor [PSQI >5] vs good [PSQI ≤ 5]), concentration (any severity vs none or no severity), tired feeling (any severity vs none or no severity), anxiety (none or no: HADS-A ≤ 7 vs borderline or definite: HADS-A >7), and depression (none [CESD <16] vs possible or probable [CESD ≥ 16]). If the baseline characteristic score was missing, then it was conservatively coded as a 0, and the total number of symptoms was summed for each patient for a final number of symptoms ranging from 0 to 5. The total number of symptoms was dichotomized as either from 0 to 2 or from 3 to 5, and the association between this variable and AI discontinuation was assessed in the univariate and multivariable setting. All analyses were performed in SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Patient Characteristics and Treatment Discontinuation Caused by Toxicity

The ELPh trial included 503 patients, of whom 500 were randomly assigned to letrozole or exemestane for 24 months (Fig. 1). Enrolled patients who discontinued therapy within 1 year of treatment initiation because of toxicity were compared with those who continued study participation beyond the 1-year time point (Table 1). During the 24-month study, in total, 51 patients discontinued therapy for reasons other than treatment-emergent toxicity, including inability to undergo phlebotomy and recovery of ovarian function, as previously reported.[3]

Of the 449 patients who were eligible for the analysis, 140 (31.2%) discontinued AI therapy because of symptoms by the end of the first year of treatment (Table 1). Patients who discontinued therapy were significantly younger than those who continued therapy (median age, 56 years vs 60 years; OR, 0.97; 95% confidence interval [CI], 0.95-1.00; $P = .035$). As previously reported,[3] no univariate statistically significant association (at the $P = .05$ level) was identified between treatment discontinuation and BMI ($P = .76$), baseline serum estrogen concentration (E2, $P = .50$; E1S, $P = .18$; and E1, $P = .73$), race ($P = .33$), previous receipt of chemotherapy ($P = .51$), taxane-based chemotherapy ($P = .18$), radiation therapy ($P = .51$), prior tamoxifen ($P = .18$), or prior hormone-replacement therapy ($P = .18$). Similarly, there was no statistically significant association between stage of breast cancer at diagnosis and the likelihood of treatment discontinuation ($P = .99$). Treatment with exemestane was associated significantly with an increased risk of treatment discontinuation compared with letrozole treatment (OR, 1.67; 95% CI, 1.12-2.51; $P = .012$).

Although half of the analyzed patients started AI therapy within 6 months of undergoing definitive surgery, the time interval ranged from 0 to 109 months. The time from surgery to the initiation of AI therapy was not

TABLE 1. Baseline Patient Characteristics by Aromatase Inhibitor Treatment Discontinuation Status[a]

Characteristic	Total, n = 449		Discontinued Because of Symptoms, n = 140		All Others, n = 309		OR [95% CI]	*P*
	No.	%[b]	No.	%[b]	No.	%[b]		
Age (median value)	449	(59)	140	(56)	309	(60)	0.97 [0.95-1.00]	.035
BMI, kg/m^2[b]	448	(29.1)	140	(28.7)	308	(29.3)	1.00 [0.96-1.03]	.76
Estradiol, pg/mL[c]	436	(4.7)	132	(4.1)	304	(4.9)	0.91 [0.71-1.18]	.50
Estrone sulfate, pg/mL[c]	432	(243.5)	128	(275)	304	(228)	1.20 [0.92-1.56]	.18
Estrone, pg/mL[c]	437	(23)	133	(21.7)	304	(23.8)	0.95 [0.68-1.31]	.73
Race								
White	401	89.3	128	91.4	273	88.3	1.00 [—]	.33
Black/other	48	10.7	12	8.6	36	11.7	0.71 [0.36-1.41]	
Breast cancer stage								
DCIS	27	6	8	5.8	19	6.2	1.00 [—]	.99
I	234	52.3	73	52.5	161	52.3	1.08 [0.45-2.57]	
II	143	32	45	32.4	98	31.8	1.09 [0.44-2.68]	
III	43	9.6	13	9.4	30	9.7	1.03 [0.36-2.95]	
Chemotherapy								
Yes	200	44.5	64	45.7	136	44	1.07 [0.72-1.60]	.51
No	249	55.5	76	54.3	173	56	1.00 [—]	
Taxane								
Yes	144	32.1	51	36.4	93	30.1	1.33 [0.87-2.03]	.18
No	305	67.9	89	63.6	216	69.9	1.00 [—]	
Radiation therapy								
Yes	355	79.4	113	81.3	242	78.6	1.19 [0.72-1.97]	.51
No	92	20.6	26	18.7	66	21.4	1.00 [—]	
Tamoxifen								
Yes	163	36.5	57	41	106	34.4	1.33 [0.88-2.00]	.18
No	284	63.5	82	59	202	65.6	1.00 [—]	
Hormone-replacement therapy								
Yes	231	51.8	65	47.1	166	53.9	0.76 [0.51-1.14]	.18
No	215	48.2	73	52.9	142	46.1	1.00 [—]	
Drug assignment								
Exemestane	217	48.3	80	57.1	137	44.3	1.67 [1.12-2.51]	.012
Letrozole	232	51.7	60	42.9	172	55.7	1.00 [—]	
Depression: CESD								
Normal	381	85	113	81.3	268	86.7	1.00 [—]	.14
Possible/probable: CESD >16	67	15	26	18.7	41	13.3	1.50 [0.88-2.58]	
Anxiety: HADS-A								
Noncase	383	85.7	118	84.9	265	86	1.00 [—]	.75
Borderline or case	64	14.3	21	15.1	43	14	1.10 [0.62-1.93]	
Sleep quality: PQSI								
Good: PQSI ≤5	224	52.1	55	41	169	57.1	1.00 [—]	.002
Poor	206	47.9	79	59	127	42.9	1.91 [1.26-2.89]	
Joint pain severity								
None or not at all	184	41.4	50	36.2	134	43.8	1.00 [—]	.14
Slight to extreme	260	58.6	88	63.8	172	56.2	1.37 [0.91-2.08]	
Forgetfulness								
None or not at all	239	53.6	62	44.9	177	57.5	1.00 [—]	.015
Slight to extreme	207	46.4	76	55.1	131	42.5	1.66 [1.11-2.48]	
Tired feeling								
None or not at all	186	41.8	45	32.6	141	45.9	1.00 [—]	.009
Slight to extreme	259	58.2	93	67.4	166	54.1	1.76 [1.15-2.67]	
Concentration								
None or not at all	342	76.7	100	71.9	242	78.8	1.00 [—]	.11
Slight to extreme	104	23.3	39	28.1	65	21.2	1.45 [0.92-2.30]	
Vaginal dryness								
None or not at all	301	68.1	87	63	214	70.4	1.00 [—]	.13
Slight to extreme	141	31.9	51	37	90	29.6	1.39 [0.91-2.13]	

Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies-Depression; CI, confidence interval; DCIS, ductal carcinoma in situ; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; OR, odds ratio; PSQI: Pittsburgh Sleep Quality Index.

[a] Listed are baseline dichotomous characteristics of patients enrolled in the Exemestane and Letrozole Pharmacogenetics trial who discontinued aromatase inhibitor therapy because of any symptom by or at 12 months versus all others. Comparison of the cohort that discontinued versus all others was performed using logistic regression.

[b] Mean values are indicated in parenthesis.

[c] Logged values were used in logistic regression.

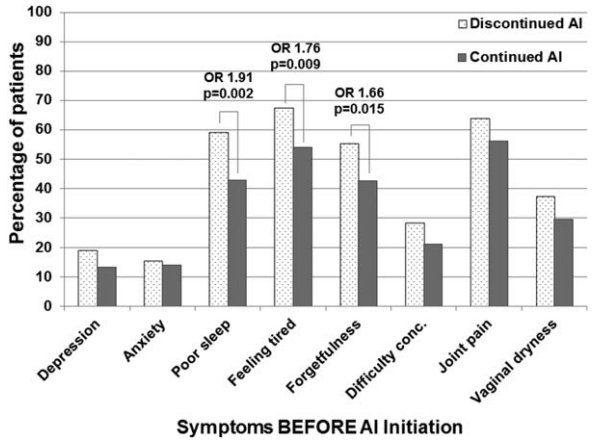

Figure 2. The percentage of evaluable patients who continued or discontinued aromatase inhibitor (AI) therapy within the first year of treatment is illustrated according to baseline symptoms that were present before AI initiation. Light bars represent the percentage of total evaluable patients who discontinued AI therapy within 1 year, and dark bars represent the percentage of total evaluable patients who continued AI therapy beyond 1 year. Odds ratios (OR) and p values are given for those comparisons that were statistically significant. Conc indicates concentrating.

associated significantly with AI discontinuation because of symptoms. Those who discontinued therapy had a median time since surgery of 8 months (range, 1-108 months), whereas those who remained on AI therapy beyond 12 months had a median time since surgery of 6 months (range, 0-109 months; $P = .11$).

Patient-Reported Symptoms Before AI Therapy Initiation and Treatment Discontinuation

In the ELPh trial, 67 patients (15%) reported being possibly or probably depressed at the time of AI initiation (using the CESD), and 64 patients (14.3%) reported being borderline or definitely anxious (using the HADS-A questionnaire) (Table 1, Fig. 2). An analysis of depressive symptomatology scores as a dichotomous variable (possibly or probably depressed vs not depressed) using the CESD questionnaire did not demonstrate a statistically significant association between depression before AI initiation and an increased risk of treatment discontinuation within the first year (OR, 1.50; 95% CI, 0.88-2.58; $P = .14$). Similarly, no significant association was identified between pre-existing anxiety assessed using the HADS-A questionnaire and discontinuation of AI therapy (OR, 1.10; 95% CI, 0.62-1.93; $P = .75$).

In the ELPh trial, 206 patients (47.9%) reported poor sleep quality on the PSQI questionnaire before the initiation of AI therapy (Table 1, Fig. 2). A larger percentage of patients who had poor sleep quality before AI initiation discontinued therapy because of toxicity by 1 year compared with those who had good sleep quality (59% vs 42.9%; OR, 1.91; 95% CI, 1.26-2.89; $P = .002$). Of the 206 patients who reported poor sleep quality before AI initiation, 139 (67.5%) reported poor sleep quality at $\geq$75% of their subsequent visits during AI therapy, and 7 who reported sleep problems at the initial assessment discontinued therapy before the next time point. Fifty-seven of those 139 patients (41%) patients discontinued AI treatment by the end of 1 year.

Other patient-reported symptoms were collected using a general symptom questionnaire (Table 1, Fig. 2). No statistically significant association was identified between patient-reported presence of joint pain at baseline and treatment discontinuation because of toxicity (63.8% vs 56.2%, respectively; OR, 1.37; 95% CI, 0.91-2.08; $P = .14$). Patients who reported forgetfulness or feeling tired before AI initiation were more likely to discontinue therapy because of toxicity compared with those who did not report having the symptom (forgetfulness: 55.1% vs 42.5%; OR, 1.66; 95% CI, 1.11-2.48; $P = .015$; tired feeling: 67.4% vs 54.1%; OR, 1.76; 95% CI, 1.15-2.67; $P = .009$). In addition, there was no statistically significant univariate association between difficulty concentrating before starting AI therapy and treatment discontinuation (28.1% vs 21.2%, respectively; OR, 1.45; 95% CI, 0.92-2.13; $P = .11$) or vaginal dryness and treatment discontinuation (37% vs 29.6%, respectively; OR, 1.39; 95% CI, 0.91-2.13; $P = .13$).

The following 5 symptoms were combined to assess whether having more symptoms at baseline was associated with treatment discontinuation: poor sleep quality (PSQI score, >5), depression (CESD score, ≥ 16), anxiety (HADS-A score, ≥ 7), any degree of tired feeling, and any degree of difficulty concentrating. Patients who reported a greater number of symptoms before treatment initiation were more likely to discontinue therapy because of toxicity (Fig. 3). There was a statistically significant difference in the treatment discontinuation rate among those who reported the presence of 0 symptoms, 1 or 2 symptoms, and 3 to 5 symptoms before AI initiation ($P = .007$). Of the 117 patients who did not report any of these symptoms at baseline, 26 (22%) discontinued AI therapy within 1 year because of side effects. Of the 225 patients who reported 1 or 2 symptoms before AI initiation, 69 (31%) discontinued AI therapy. In contrast, of the 107 patients who had ≥ 3 of these symptoms, 45 (42%) discontinued AI therapy. Compared with those patients who reported none of the symptoms at baseline, those patients with 1 or 2 symptoms at baseline had an increased

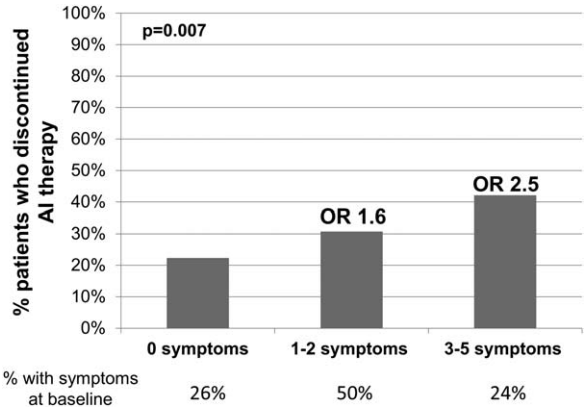

Figure 3. The percentage of patients who discontinued aromatase inhibitor (AI) therapy is illustrated according to the number of symptoms present before the initiation of AI therapy. The total percentage of patients in each group is provided below the x-axis. OR indicates odds ratio.

TABLE 2. Multivariable Logistic Regression Analysis of Predictors of Aromatase Inhibitor Treatment Discontinuation, Including Individual Symptoms[a]

Variable	OR (95%CI)	*P*
Age	0.97 (0.95-1.00)	.028
Drug: Exemestane vs letrozole	1.63 (1.07-2.49)	.024
Sleep quality: PSQI >5 vs ≤5	1.79 (1.15-2.79)	.010
Concentration vs none		.017
Not at all or slight	0.75 (0.42-1.33)	
Moderate to extreme	2.62 (1.22-5.65)	

Abbreviations: CI, confidence interval; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index.
[a] These are multivariable logistic regression results from a step-down analysis of treatment discontinuation during the first year of aromatase inhibitor (AI) therapy according to baseline sleep and concentration difficulties before AI initiation and patient characteristics (n = 428; area under the curve = 0.65).

likelihood of AI discontinuation during the first year (OR, 1.55; 95% CI, 0.92-2.60), and those with 3 to 5 symptoms had an even greater increased likelihood of discontinuing during the first year (OR, 2.54; 95% CI, 1.42-4.54; $P = .007$). Furthermore, we observed that, on average, individuals who discontinued AI therapy within 1 year because of toxicity reported having ≥3 symptoms at 37% of their subsequent visits, compared with 22% of those who did not discontinue therapy ($P = .0009$).

Multivariable Analysis of Predictors of Treatment Discontinuation Caused by Toxicity

Multivariable logistic regression was used to evaluate predictors of treatment discontinuation because of toxicity. By including all variables in Table 1 that were related in the univariate analysis to discontinuation, we sought a more parsimonious model using a stepwise approach. Thus, we evaluated a model that included age, AI medication, sleep quality, and concentration (Table 2). E1S at baseline ($P = .14$) and pain score ($P = .12$) were the last variables to be removed from the model. With all 5 variables included, the area under the curve (a measure of predictive power in logistic regression) was 0.68. In either the full model or the reduced model (which excluded E1S and pain score), both poor sleep quality and difficulty concentrating remained statistically significant. In the reduced model detailed in Table 2, those with poor sleep quality had 1.79 times the odds of discontinuing AI medication by the end of the first year of treatment, holding age, AI medication, and concentration severity constant ($P = .01$). Those with moderate-to-extreme difficulty concentrating had 2.62 times the odds of discontinuing treatment, holding all other variables constant ($P = .017$). The area under the curve of this reduced model was 0.65.

TABLE 3. Multivariable Logistic Regression Analysis of Predictors of Aromatase Inhibitor Treatment Discontinuation, Including Symptom Clusters[a]

Variable	OR (95% CI)	*P*
Age	0.97 (0.95-1.00)	.025
Drug: Exemestane vs letrozole	1.66 (1.10-2.50)	.016
VAS pain score	1.09 (0.99-1.20)	.067
Total no. of symptoms ≥3 vs ≤2	1.68 (1.05-2.70)	.031

Abbreviations: CI, confidence interval; OR, odds ratio; VAS, visual analog scale.
[a] These are multivariable logistic regression results from a step-down analysis of treatment discontinuation during the first year of aromatase inhibitor (AI) therapy according to the number of symptoms present before AI initiation and patient characteristics (n = 447; area under the curve = 0.64).

A second model was evaluated to specifically analyze the effect of total number of symptoms at baseline (3-5 symptoms vs 0-2 symptoms) (Table 3). In this model, age (OR, 0.97; $P = .03$), AI medication (OR, 1.66; $P = .02$), and ≥3 symptoms (OR, 1.68; $P = .03$) had statistically significant associations with treatment discontinuation caused by to toxicity. This model also included a pain score (measured on a visual analog scale) in which each 1-point increase in pain increased the odds of discontinuation by 1.09 ($P = .07$). This model had an area under the curve of 0.64. When baseline E1S ($P = .17$) was also included in this base model, the area under the curve increased slightly to 0.65.

DISCUSSION

Early discontinuation of AI therapy, which is associated with worse breast cancer outcomes, is frequently caused

by the development of side effects, especially musculoskeletal toxicity.[3,5] Numerous previous studies of AI therapy have reported an increased risk of developing musculoskeletal symptoms during AI treatment for factors such as age, body mass index, pre-existing pain or arthritis, prior chemotherapy, and prior tamoxifen.[3,6-8] For the current analysis, instead, we focused on associations between patient-reported nonpain symptoms that were present before the initiation of AI therapy, such as poor sleep quality, fatigue, depression, and anxiety, and increased rates of premature treatment discontinuation because of toxicity. In the relatively large ELPh trial, we observed that pre-existing poor sleep quality and difficulty concentrating were strongly associated with early treatment discontinuation because of toxicity. In addition, increased symptom burden before AI therapy initiation was associated with both increased symptom burden during AI treatment and increased likelihood of treatment discontinuation within 1 year.

Our findings are consistent with those reported in the MA.27 trial of exemestane versus anastrozole.[26] In that study, the hazard ratio of early treatment discontinuation because of bother from side effects from previous treatment that were present at the time of AI initiation was 1.29 (95% CI, 1.08-1.55; $P = .006$). The contributions of specific side effects were not described.

The symptom cluster of mood disorders, fatigue, and difficulty sleeping is frequently identified in patients across diseases, including cancer and chronic pain syndromes.[27] Many of the published reports evaluating symptom clusters in breast cancer patients have focused on patients undergoing therapy with short-term treatment modalities, including chemotherapy and/or radiation therapy. For example, in 1 study, patients who reported a greater number of symptoms before the start of chemotherapy were more likely to report worse symptoms during the treatment.[27] Other studies have identified specific patterns of change in symptoms over time during chemotherapy and radiation. These patterns ultimately impact functional status and quality of life, and they may influence patient management.[17,28] In contrast, few published reports have focused on patterns of specific symptoms that occur during long-term adjuvant endocrine therapy. Analogous to what has been observed previously with chemotherapy, in the ELPh trial, we identified an association between a greater number of symptoms before treatment and decreased persistence with AI therapy because of toxicity. The symptoms of poor sleep and difficulty concentrating stood out as clinically important contributors to this symptom cluster.

Knowledge of these associations is clinically relevant, because these symptoms are not frequently recognized as problematic and are not typically carefully assessed or aggressively managed by oncologists. Indeed, because difficulty sleeping and complaints of fatigue are common among patients with breast cancer[29] and often are believed to be self-limited side effects of prior therapies, including chemotherapy and radiation therapy, oncologists may not appreciate that the presence of these symptoms could compromise future treatments. These results raise the possibility that asking patients about these symptoms and addressing them at the time of AI initiation, or even prophylactically, could identify patients at risk and allow the implementation of measures to improve adherence/persistence with subsequent adjuvant endocrine therapy.

Although the management of these symptoms is essential for improving quality of life, the current data suggest that it may also have an impact on breast cancer outcomes if improvement in symptoms leads to increased adherence to and persistence with therapy. There is a paucity of effective treatment options for poor sleep, cognitive problems, and fatigue among cancer survivors. Numerous clinical trials have been conducted to test various pharmacologic therapies for fatigue, although few studies of pharmacologic treatments have been conducted specifically for sleep disturbance in cancer patients.[18] Meta-analyses have demonstrated a statistically significant benefit from methylphenidate compared with placebo for cancer-related fatigue, although the clinical benefit is modest.[30] There are also considerable data supporting the use of cognitive behavioral therapy for treatment of both insomnia and fatigue in cancer patients.[30-32] The use of cognitive behavioral therapy is recommended in the National Comprehensive Cancer Network guidelines for the management of cancer-related fatigue,[33] although it is unknown how often these behavioral techniques are actually used in clinical practice. Improvements in fatigue have also been noted in patients with cancer who received other nonpharmacologic interventions, including physical activity.[30] Although several treatment options are listed in the currently available national guidelines, no individual modality is preferred.[33]

Our study has multiple strengths. The findings were derived from a large, prospective clinical trial in which reasons for discontinuation were prospectively recorded. Validated questionnaires were used to assess patient-reported sleep, pain, and mood disorders, although fatigue and cognitive function data elements had to be obtained from a more general symptom questionnaire. The study medication was provided to the patients by the

study, so cost of the medication was not a factor in persistence with therapy.

In this analysis, we identified a numerically greater but not statistically significant increased risk of treatment discontinuation within 1 year among patients who received a taxane-based chemotherapy regimen, which we and others have previously reported. One important difference between the prior analysis of the ELPh trial and the current report is the focus on discontinuation specifically within the first year of AI therapy. This 1-year limitation was intended to restrict analyses to the symptoms likely caused by the AI medication and less likely caused by changes that can occur over time with the natural aging process, such as worsening osteoarthritis. Our findings suggest that pre-existing symptoms are more strongly associated with AI discontinuation because of toxicity than clinical factors, such as prior chemotherapy. However, it remains possible that prior treatments like chemotherapy contributed to the symptoms reported by patients at the time of their baseline study visit.

Our findings demonstrate the importance of symptom clusters that include poor sleep and difficulty concentrating in patients with breast cancer and the potential detrimental effects of these symptoms not just on quality of life but also on AI treatment adherence and breast cancer outcomes. Therapies to improve the constellation of symptoms rather than those that target individual symptoms should be considered to allow optimal patient care. Clinical trials are warranted to evaluate the impact of the management of symptom clusters on adherence to potentially life-saving adjuvant endocrine therapies.

FUNDING SUPPORT

N.L.H. is a Damon Runyon-Lilly Clinical Investigator supported (in part) by the Damon Runyon Cancer Research Foundation (grant CI-53-10). This study was also supported in part by Pharmacogenetics Research Network grant U01-GM61373 (to D.A.F.) and Clinical Pharmacology training grant 5T32-GM08425 (to D.A.F.) from the National Institute of General Medical Sciences (National Institutes of Health [NIH], Bethesda, Md) and by grants M01-RR00042 (to the University of Michigan), M01-RR00750 (to Indiana University), and M01-RR00052 (to Johns Hopkins University) from the National Center for Research Resources, a component of the NIH. In addition, these studies were supported by grants from Pfizer, Inc (to D.F.H.), Novartis Pharma AG (to D.F.H.), and the Fashion Footwear Association of New York/QVC Presents Shoes on Sale (to D.F.H.). Study medication was provided by Pfizer (exemestane) and Novartis (letrozole).

CONFLICT OF INTEREST DISCLOSURES

Dr. Harte has served as a consultant to Analgesic Solutions and Pfizer and has received research funding from Forest and Cerephex. Dr. Hayes has received research funding from AstraZeneca, Novartis, and Pfizer. Dr. Storniolo has received research funding from Novartis and Pfizer. Dr. Flockhart has received research funding from Novartis and Pfizer and serves on the Scientific Advisory Board for Quest Diagnostics and as a consultant to Boehringer-Ingelheim. Dr. Stearns has received research grants from Abbott, Celgene, Medimmune, Merck, Novartis, and Pfizer. Dr. Clauw has served as a consultant to/received honoraria from Pfizer, Cerephex, Lilly, Merck, Nuvo, Forest, Tonix, Theravance, Johnson & Johnson, Pierre Fabre, Cypress Biosciences, Wyeth, UCB, AstraZeneca, Jazz, Abbott, Perdue, and Iroko and has received research funding from Pfizer, Cerephex, Eli Lilly, Merck, Nuvo, Forest, and Cypress Biosciences. Dr. Williams has served as a consultant to Pfizer and Health Focus Inc. and has received research support from Pfizer. Dr. Henry has received research funding from AstraZeneca, Eli Lilly, BioMarin Pharmaceuticals, and Sanofi Aventis.

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