Original Study

Associations Between Patient and Anthropometric Characteristics and Aromatase Inhibitor Discontinuation

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Abstract

Adjuvant endocrine therapy is effective but the rates of patients not continuing therapy are high. In the present prospective observational study of 115 postmenopausal women starting endocrine therapy, 40.9% of the patients starting aromatase inhibitor therapy discontinued within the first year because of intolerable side effects. Baseline pain was associated with discontinuation. Future research should focus on proactive treatment of patients at a high risk of not continuing therapy.

Background: Toxicity can lead to noncontinuation of adjuvant endocrine therapy. We hypothesized that endocrine therapy-induced changes in grip strength would predict for early discontinuation of therapy because of musculoskeletal toxicity and would be associated with a patient's body mass index. **Patients and Methods:** Postmenopausal women with breast cancer starting a new adjuvant endocrine therapy were enrolled in the present study. The patients were monitored for 12 months to assess their symptoms, endocrine therapy adherence and change in grip strength and baseline body mass index. The association between the change in grip strength and interval to discontinuation was assessed using a joint longitudinal and survival model. **Results:** Of the 93 aromatase inhibitor (AI)-treated and 22 tamoxifen-treated patients, 40.9% and 9% discontinued endocrine therapy within 12 months because of toxicity, respectively ($P = .019$). A trend was seen toward a greater decrease in grip strength in the AI-treated patients over time ($P = .055$); however, the decrease was not significantly associated with the interval to discontinuation ($P = .96$). Receipt of an AI (hazard ratio, 5.49; $P = .019$) and baseline pain (hazard ratio, 1.19; $P = .004$) significantly decreased the interval to discontinuation. **Conclusion:** In contrast with the findings from previous reports, the change in grip strength in our study was not associated with the interval to discontinuation of AI therapy. Future research should focus on proactive treatment of patients at increased risk of AI intolerance, such as those with high levels of preexisting pain.

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Introduction

Adjuvant aromatase inhibitors (AIs) and tamoxifen reduce the recurrence in, and mortality of, patients with hormone receptor-positive breast cancer.[1] The 3 third-generation AIs in routine clinical use, including 2 nonsteroidal compounds (anastrozole and letrozole) and a steroidal compound (exemestane), have similar benefit and toxicity profiles according to direct and cross-trial comparisons.[2]

Despite the excellent disease outcomes with anti-endocrine therapy, ≤ 20% of patients will not continue with AI therapy, primarily owing to the toxicity of the treatment.[3,4] AI-associated toxicity, which is primarily musculoskeletal, negatively affects the quality of life of breast cancer survivors[5] and can result in worse breast cancer outcomes.[4,6] Despite considerable research, the mechanism that underlies this AI-associated musculoskeletal syndrome remains unknown. In addition, only a few predictors of developing toxicity have been identified, including previous chemotherapy, a shorter interval since menopause, and, possibly, obesity.[3,7-9]

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Tenosynovitis at the wrist and loss of grip strength after the initiation of AI therapy was identified in a small cohort of AI-treated patients.[10] Subsequently, associations between the loss of grip strength and both musculoskeletal symptoms and extremes of body mass index (BMI) were noted in AI-treated patients that were not evident in tamoxifen-treated patients.[11,12]

We conducted a prospective observational study of postmenopausal women starting adjuvant endocrine therapy to validate these findings in a patient population with a greater proportion of obese patients. We hypothesized that patients with decreased grip strength during AI therapy would be more likely to discontinue treatment and would be more likely to have either a low or a high BMI. We also examined the patient-reported symptom experience of patients treated with AIs versus tamoxifen and the endocrine therapy patterns of patients who discontinued initially prescribed AI therapy because of toxicity.

Patients and Methods

Patients

Eligible patients were recruited from a single institution (University of Michigan Medical Center) from September 2009 through July 2013 (ClinicalTrials.gov identifier, NCT01223833). Postmenopausal women with stage 0 to III breast cancer who were scheduled to receive adjuvant endocrine therapy with tamoxifen (Nolvadex) or a third-generation AI (anastrozole, exemestane, letrozole) were eligible. The choice of endocrine therapy was at the discretion of the patient and the treating provider. All surgery, chemotherapy, and radiation therapy were completed before the initiation of adjuvant endocrine therapy. Previous tamoxifen and AI therapy were permitted, although patients were required to have discontinued the medication for $\geq$ 4 weeks before enrollment. No enrolled patients had previously received AI therapy. Patients were ineligible if they had a pre-existing major rheumatologic disorder or concomitant use of sex hormone-containing medications or luteinizing hormone receptor hormone agonist therapy. The University of Michigan institutional review board approved the present study, and all the patients provided written informed consent before participation in any protocol-directed procedures.

Study Design

After enrollment, all the patients underwent a baseline assessment before initiation of adjuvant endocrine therapy. The assessments included measurement of height, weight, hip and waist circumferences, bilateral grip strength, questionnaires, and phlebotomy. The choice of endocrine therapy was at the discretion of the treating physician. Each assessment was repeated at 3, 6, and 12 months after the initiation of adjuvant endocrine therapy. If a patient changed from 1 AI to another during study participation, the assessments were continued and the timing of the assessments was determined from the original treatment start date.

The grip strength was measured using a modified sphygmomanometer (Martin Vigorimeter Measuring Instrument; Albert Waeschle Ltd, Dorset, UK). The patients squeezed the balloon of the instrument 3 times with each hand, and the maximal force from each of the 6 assessments was recorded. The maximum value for either the right or left hand at each measurement point was used.

At each assessment, the patients rated their average pain during the previous 7 days using an 11-point Likert scale. At 3, 6, and 12 months, the patients also completed a questionnaire to more comprehensively assess the musculoskeletal and menopausal symptoms experienced and their perception of the association between the symptoms and the endocrine therapy using a 5-point Likert scale (from "definitely not due to medication" to "definitely due to medication"). Adherence to therapy was also assessed using the Medication Adherence Report Scale-5 questionnaire.[13]

Statistical Analysis

For continuous data, including grip strength, BMI, waist-to-hip ratio, and baseline demographic data, between-group differences were assessed using the Wilcoxon rank sum test. Between-group differences for categorical variables were determined using the χ^2 test or Fisher's exact test. Spearman's correlation was used to assess the association between right and left hand maximum grip strength, the baseline maximum grip strength, and the baseline BMI and waist-to-hip ratio. The Kaplan-Meier method and log-rank test were used to compare the interval to discontinuation of endocrine therapy (defined as the earlier of treatment discontinuation or the end of the study at 1 year) between the AI- and tamoxifen-treated patients. Cox proportional hazards models were used to evaluate the associations between the interval to discontinuation of endocrine therapy and baseline anthropometric factors, controlling for the type of endocrine therapy.

The primary endpoint was the effect of BMI on grip strength after 12 months of therapy based on preliminary data.[12] However, no effect of BMI or its quadratic term was identified when added to a multivariable model in the primary analysis. Therefore, the association among the change in grip strength, the baseline BMI, and the interval to discontinuation of first therapy was examined using a joint longitudinal and survival model that accounted for missing data. The association between the change in grip strength and the development of new or worsening musculoskeletal symptoms (defined as arthralgias or myalgias) was assessed using a generalized linear model (generalized estimating equations). The presence of patient-reported symptoms was compared between treatment groups using the χ^2 test or Fisher's exact test. For all P values reported, no correction for multiple testing was applied.

Results

Patients

Of the 115 patients enrolled in the trial, 93 initiated therapy with an AI and 22 with tamoxifen (Table 1). Of the 93 patients who started AI therapy, 76 (81.7%) received anastrozole, 16 (17.2%) received letrozole, and 1 (1.1%) received exemestane. The median age of all patients was 62 years (range, 41-79 years). The average BMI was 30.1 $\pm$ 7.1 kg/m^2; 42% of the AI-treated patients had a BMI of $\geq$ 30 kg/m^2. Of the AI-treated patients, 64% reported muscle or joint pain in the 3 months before enrollment. The average score for muscle and joint pain for all patients in the week before enrollment was 2.3 $\pm$ 2.1 on an 11-point scale. In this postmenopausal population, all baseline patient characteristics were well-balanced between the 2 groups, with the exception that more AI-treated patients had received adjuvant chemotherapy ($P = .004$)