Treatment-Associated Musculoskeletal and Vasomotor Symptoms and Relapse-Free Survival in the NCIC CTG MA.27 Adjuvant Breast Cancer Aromatase Inhibitor Trial

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A B S T R A C T

Purpose

Treatment-emergent symptoms with adjuvant tamoxifen and aromatase inhibitors (AIs) have been associated with superior recurrence-free survival (RFS). We hypothesized that MA.27 anastrozole- or exemestane-treated patients with new or worsening vasomotor and/or joint symptoms would have improved RFS.

Patients and Methods

MA.27 randomly assigned 7,576 postmenopausal women with breast cancer to 5 years of anastrozole or exemestane. Patient-reported symptoms were collected using the Common Terminology Criteria for Adverse Events version 3.0 at protocol-specified baseline and 6- and 12-month clinical visits. Symptoms were considered present with either vasomotor and/or joint complaints. Associations between symptoms and baseline patient characteristics were examined with χ^2 and Fisher's exact tests. Subsequent effects of new or worsening symptoms on RFS were examined with landmark analyses and stratified univariable and multivariable Cox models. We examined the effects of 3-month symptoms arising from unplanned clinic visits as a result of severe toxicity.

Results

Patients were assessable if eligible for the MA.27 trial, received some trial therapy, and had no disease recurrence at the end of a symptom assessment period; 96% of patients ($n = 7,306$ patients) were included at 6 months, and 96% ($n = 7,246$) were included at 12 months. Thirty-four percent of patients had baseline symptoms. For patients without baseline symptoms, 25% and 52% had new symptoms by 6 and 12 months, respectively. Neither treatment-emergent nor baseline symptoms significantly impacted RFS ($P > .10$) in patients with or without baseline symptoms.

Conclusion

In MA.27, anastrozole or exemestane treatment-emergent symptoms were not associated with improved RFS. Women should be supported through treatment and encouraged to remain on their AI regardless of their symptoms.

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INTRODUCTION

An **aromatase inhibitor** (AI) as monotherapy for 5 years or for 3 years after 2 years of tamoxifen is standard adjuvant therapy for postmenopausal women with hormone receptor–positive invasive breast cancer.¹ Approximately one in two women starting an AI will complain of early-onset new vasomotor or joint symptoms, often leading to treatment discontinuation.²⁻⁴

Several investigators have assessed the relationship between endocrine therapy–related symptoms

and survival outcomes; however, results have been mixed. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial investigators reported that new vasomotor or joint symptoms within 3 months of initiating tamoxifen or **anastrozole** were associated with superior recurrence-free survival (RFS).⁵ In the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, women were randomly assigned to exemestane for 5 years or tamoxifen for 2.5 to 3 years followed by exemestane to a total of 5 years. Patients with vasomotor and joint symptoms in the first year of TEAM participation had

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improved survival outcomes.⁶ Likewise, Breast International Group (BIG) 1-98 study investigators reported that patients assigned to monotherapy tamoxifen or letrozole arms with 3-month or 12-month emergent vasomotor or musculoskeletal symptoms had improved outcomes.⁷

The NCIC Clinical Trials Group (CTG) MA.27 trial was the first adjuvant comparison of two third-generation AIs, nonsteroidal anastrozole versus steroidal exemestane. During a median of 4.1 years of follow-up in MA.27, 31.6% of patients discontinued treatment as a result of adverse effects, concomitant disease, or study refusal, with joint pain being the most frequent reason.⁸⁻¹⁰ Neither of the AIs was superior in efficacy, and there were no significant differences in treatment adherence observed.⁸ We hypothesized that new or worsening vasomotor or joint symptoms would be associated with improved RFS. If treatment-emergent symptoms are indeed associated with improved breast cancer outcomes, clinicians and patients can use the information to make important decisions regarding persistence of chronic AI therapy.

PATIENTS AND METHODS

Study Design

NCIC CTG MA.27 (ClinicalTrials.gov identifier: NCT00066573) was an open-label, randomized phase III multinational trial,⁸ approved by health regulatory authorities and the institutional review boards of participating centers; patients provided informed consent. Between June 2003 and July 2008, 7,576 patients were randomly assigned 1:1 to exemestane 25 mg ($n = 3,789$) or anastrozole 1 mg ($n = 3,787$). A factorial design of celecoxib or placebo with concomitant prophylactic aspirin use (< 81 mg/d [yes, no]) was discontinued because of concerns of celecoxib cardiac toxicity after 1,622 patients were randomly assigned.¹¹ Trial stratification factors were use of celecoxib, aspirin, and trastuzumab; lymph node status (negative, positive, or unknown); and prior adjuvant chemotherapy (yes or no). Analyses reported here used the final analysis database, with a median of 4.1 years of follow-up.

MA.27 was funded by the Canadian Cancer Society Research Institute, US National Cancer Institute, and Pfizer. This is a retrospective analysis of treatment-associated symptoms and outcomes. Data were collected, managed, and analyzed by the NCIC CTG. The authors vouch for the integrity of the data and are the sole writers of the article.

Study Population

MA.27 enrolled postmenopausal women with estrogen receptor– and/or progesterone receptor–positive primary invasive breast cancer within 3 to 12 weeks of completing their initial treatment.⁸ Prior hormones or steroids had to be discontinued ≥ 3 weeks before random assignment. Prior treatment with an AI or tamoxifen was not permitted, although raloxifene was allowed for bone health if discontinued ≥ 3 weeks before random assignment. Patients with normal bone mineral density T-scores better than -2.0 enrolled onto the MA.27B (Bone) substudy were not permitted bisphosphonate use.

We included here all eligible MA.27 patients who received at least one dose of protocol therapy, classified by treatment received. Patients randomly assigned to MA.27 included women with and without pre-existing vasomotor and/or joint symptom(s). We investigated symptoms in the following three groups: women without baseline vasomotor or grade 3 or 4 joint symptoms who developed symptoms of any grade of vasomotor or grade 3 or 4 joint symptoms (group 1); women without baseline vasomotor or joint symptoms who developed symptoms of any grade of new vasomotor or joint symptoms (group 2, a subgroup of group 1); and all women, regardless of baseline symptoms, who developed new or worsening vasomotor and/or joint symptoms (group 3, which includes groups 1 and 2).

Adverse Events

Patient-reported symptoms were collected using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Vasomotor symptoms included hot flushes or sweating. Joint symptoms included joint pain, muscle pain, bone pain, arthritis, diminished joint function, or other musculoskeletal problems.⁹

Symptoms were recorded at baseline, at protocol-mandated 6- and 12-month treatment follow-up, annually thereafter, and on treatment case report forms any time after random assignment, when a clinical visit was deemed necessary. Three-month follow-up, 91 days from random assignment, was not mandated, and adverse events (AEs) if noted, were reported on a follow-up form or on an off-treatment report. The 3-month time point corresponded to that of the ATAC investigation and would represent in MA.27 (unacceptable) early toxicity reported before the first scheduled follow-up; early toxicity reports were included in the MA.27 genome-wide association studies of the genetic basis for musculoskeletal events.⁹

Study End Points

The primary end point in MA.27 was event-free survival (EFS), defined as time from random assignment to time of locoregional or distant recurrence, new primary breast cancer, or death. Other studies that looked at the relationship between new or worsening symptoms with outcomes used recurrence or RFS as the end point. Therefore, we used RFS as the end point for this current investigation, defined as time from random assignment to time of locoregional or distant disease recurrence or contralateral breast cancer. Five breast cancer deaths without prior recurrence were excluded. Patients were censored at death or longest follow-up.

Statistical Analyses

MA.27 baseline patient characteristics are listed in Table 1 and are described for each of the three subgroups of women in the analysis. Differences among the three subgroups were examined by χ^2 or Fisher's exact tests.

To examine the effects of new or worsening symptoms on subsequent RFS, we used landmark analyses, which excluded patients who had already experienced a recurrence, and looked at the effect of having or not having symptoms in the initial 3, 6, or 12 months after random assignment on subsequent RFS. We used stratified Cox models for univariable and multivariable assessments, where stratification was by the trial stratification factors. Kaplan-Meier curves were used to illustrate the univariable RFS experience for women who did, or did not, have symptoms. Exploratory multivariable models had forced inclusion of trial therapy and presence of vasomotor/joint symptoms with stepwise addition of multivariable significant ($P \leq .05$) baseline patient characteristics. Hazard ratios (HR) and 95% CIs were reported.

RESULTS

MA.27 randomly assigned 7,576 patients; the median follow-up time was 4.1 years for both the overall study population and the patients included in this analysis. Of the 7,576 patients, 7,344 (97%) were eligible for MA.27, received at least one dose of trial therapy, and were alive without relapse at 3 months, with 2,467 patients (34%) reporting baseline vasomotor and/or joint symptoms. At 6 months, 7,306 patients (96%) were evaluable, with 2,452 (34%) having baseline symptoms. At 12 months, 7,246 patients (96%) were evaluable, with 2,434 (34%) having baseline symptoms (Fig 1).

We evaluated the presence of vasomotor and/or joint symptoms in each the three groups of patients, as described earlier, at landmark time points. The occurrence or worsening of symptoms was similar in each group (reported as group 1, group 2, and group 3) at 6 months (19.2%, 25.4%, and 26.4%, respectively) and 12 months (38.0%, 52.9%, and 52.9%, respectively) and for early severe toxicity clinical visits at 3 months (3.9%, 5.2%, and 5.5%, respectively). At 3-month

Table 1. Baseline Characteristics of Women by Vasomotor and/or Joint Symptoms at Baseline and 12 Months

Variable	No Baseline Symptoms*				P§	With or Without Baseline Symptoms†				P§
	No Vasomotor or Joint Symptom at 12 Months‡ (n = 3,458)		Vasomotor or Joint Symptom at 12 Months‡ (n = 2,115)			No New or Worsening Vasomotor or Joint Symptom at 12 Months (n = 3,412)		New or Worsening Vasomotor or Joint Symptom at 12 Months (n = 3,834)		
	No. of Patients	%	No. of Patients	%		No. of Patients	%	No. of Patients	%	
Age, years					.012					.060
≥ 50 or missing	3,399	98.3	2,058	97.3		3,334	97.7	3,719	97.0	
< 50	59	1.7	57	2.7		78	2.3	115	3.0	
Race					< .001					.008
Nonwhite	238	6.9	95	4.5		217	6.4	189	4.9	
White	3,220	93.1	2,020	95.5		3,195	93.6	3,645	95.1	
Performance status					.006					.021
Other	642	18.6	332	15.7		630	18.5	629	16.4	
Fully	2,816	81.4	1,783	84.3		2,782	81.5	3,205	83.6	
Postmenopausal status					< .001					< .001
Other	3,314	95.8	1,964	92.9		3,228	94.6	3,516	91.7	
≤ 55 years old	54	1.6	80	3.8		79	2.3	168	4.4	
45-59 years old (< 12 months; HRT)	25	0.7	23	1.1		23	0.7	51	1.3	
45-59 years old (< 12 months; hysterectomy)	65	1.9	48	2.3		82	2.4	99	2.6	
Most extensive surgery					.230					
Partial mastectomy or missing	2,327	67.3	1,456	68.8		2,312	67.8	2,634	68.7	.391
Mastectomy NOS	1,131	32.7	659	31.2		1,100	32.2	1,200	31.3	
Axillary dissection					.682					.251
Yes or missing	1,751	50.6	1,059	50.1		1,732	50.8	1,998	52.1	
No	1,707	49.4	1,056	49.9		1,680	49.2	1,836	47.9	
Tumor laterality					.889					
Right	1,679	48.6	1,031	48.7		1,670	48.9	1,835	47.9	.357
Bilateral, left, and missing	1,779	51.4	1,084	51.3		1,742	51.1	1,999	52.1	
T stage					.005					.138
T1	2,425	70.1	1,558	73.7		2,434	71.3	2,795	72.9	
Other	1,033	29.9	557	26.3		978	28.7	1,039	27.1	
N stage					< .001					.995
Other	1,041	30.1	542	25.6		960	28.1	1,079	28.1	
N0	2,417	69.9	1,573	74.4		2,452	71.9	2,755	71.9	
Prior adjuvant chemotherapy					.282					.004
Yes	1,031	29.8	602	28.5		984	28.8	1,226	32.0	
No or missing	2,427	70.2	1,513	71.5		2,428	71.2	2,608	68.0	
Prior raloxifene					.555					.273
Yes	56	1.6	30	1.4		56	1.6	51	1.3	
No, missing, unknown	3,402	98.4	2,085	98.6		3,356	98.4	3,783	98.7	
Prior or concurrent radiotherapy					.415					.152
Yes	2,412	69.8	1,497	70.8		2,396	70.2	2,751	71.8	
No, missing, unknown	1,046	30.2	618	29.2		1,016	29.8	1,083	28.2	
Fractures within 10 years before allocation					.008					.295
Yes	355	10.3	172	8.1		349	10.2	364	9.5	
No, missing, unknown	3,103	89.7	1,943	91.9		3,063	89.8	3,470	90.5	
Cardiovascular history					.014					.006
Yes	1,977	57.2	1,138	53.8		1,893	55.5	2,003	52.2	
No, missing, unknown	1,481	42.8	977	46.2		1,519	44.5	1,831	47.8	

Abbreviations: HRT, hormone replacement therapy; NOS, not otherwise specified.

*Patients had no baseline vasomotor symptoms or grade 3 or 4 joint symptoms (group 1).

†Patients did or did not have any baseline vasomotor and/or joint symptoms (group 3).

‡Patients did or did not have any grade of vasomotor symptoms or grade 3 or 4 joint symptoms (group 1).

§P values from a χ^2 or Fisher's exact test.

||Patients did or did not have any grade of new or worsening vasomotor and/or joint symptoms (group 3).

Fig 1. CONSORT diagram for NCIC Clinical Trials Group MA.27. Group 1 patients are a subgroup of group 3; group 2 patients are a subgroup of group 1; and group 3 patients are all patients assessed for musculoskeletal (MSK) and vasomotor (VM) symptoms.

early clinic visits, 96 (24%) of 403 of patients with vasomotor and/or joint symptoms discontinued treatment. In preplanned visits at 6 and 12 months, the protocol therapy discontinuation rates were 12% and 10%, respectively. We did not observe a difference in adherence by way of time to protocol therapy discontinuation by treatment arm for patients who did not have symptoms by 12 months (HR of exemestane to anastrozole, 1.03; 95% CI, 0.93 to 1.14; $P = .54$; Fig 2). Likewise, we did not observe a difference in time to treatment discontinuation among patients who experienced new or worsening symptoms at 12 months (HR, 1.06; 95% CI, 0.97 to 1.15; $P = .24$; Fig 3).

We compared baseline patient characteristics by subsequent vasomotor and joint symptoms at 12 months (Table 1); 3- and 6-month data are listed in Appendix Tables A1 and A2, respectively (online only). In each table, we report baseline characteristics for patients who had no baseline vasomotor or grade 3 or 4 joint symptoms (group 1) and for patients who did or did not have baseline symptoms (group 3). Notable significant differences ($P < .001$) were seen by age, with proportionately more women ≤ 55 years old having symptoms. For each time period, the exclusion of patients with grade 1 or 2 joint symptoms (group 2) did not lead to significant differences in RFS among patients with or without symptoms (data not shown).

The development of new or worsening vasomotor and joint symptoms did not significantly impact RFS in univariable assessments, at any of the evaluated time points or for any of the three groups. Specifically, for group 1 patients without baseline vasomotor

or grade 3 or 4 symptoms, 3-month HR was 0.62 (95% CI, 0.33 to 1.18; $P = .15$; Appendix Fig A1, online only), 6-month HR was 0.80 (95% CI, 0.59 to 1.07; $P = .13$; Fig 4), and 12 month HR was 0.81 (95% CI, 0.63 to 1.03; $P = .09$; Fig 5). RFS for patients with or without baseline

Fig 2. Time to treatment discontinuation in women without new or worsening symptoms by 12 months. HR, hazard ratio.

Fig 3. Time to treatment discontinuation in women with new or worsening symptoms by 12 months. HR, hazard ratio.

symptoms who subsequently developed new or worsening symptoms (group 3) at 6 and 12 months are depicted in corresponding Appendix Figures A2, A3, and A4 (online only). Likewise, in all patients (group 3), new or worsening symptoms alone did not significantly impact RFS at 3 ($P = .84$), 6 ($P = .10$), or 12 months ($P = .60$).

Multivariable models were stratified by use of celecoxib, aspirin, and trastuzumab and by lymph node status and prior chemotherapy. Neither treatment nor new or worsening vasomotor or joint symptoms significantly impacted RFS ($P > .10$) regardless of presence or absence of baseline symptoms. In all scenarios, RFS was significantly worse ($P < .001$), as expected, for women with T2, T3, or Tx lesions compared with those with T1 lesions and for patients who had no baseline vasomotor or grade 3 or 4 joint symptoms, at 3 months (HR, 2.22; 95% CI, 1.76 to 2.81), 6 months (HR, 2.22; 95% CI, 1.74 to 2.82), and 12 months (HR, 2.24; 95% CI, 1.68 to 2.97).

Fig 4. Recurrence-free survival of group 1 patients without baseline vasomotor (vaso) or grade 3 or 4 joint symptoms who developed vasomotor or grade 3 or 4 joint symptoms at 6 months. HR, hazard ratio.

Fig 5. Recurrence-free survival of group 1 patients without baseline vasomotor (vaso) or grade 3 or 4 joint symptoms who developed vasomotor or grade 3 or 4 joint symptoms at 12 months. HR, hazard ratio.

DISCUSSION

Adjuvant endocrine therapy for 5 to 10 years is recommended for most postmenopausal women with hormone receptor–positive breast cancer. The ability to predict survival outcomes based on baseline or treatment-emergent endocrine symptoms would be clinically important. Retrospective exploratory analyses of the ATAC, TEAM, and BIG 1-98 clinical trials suggested that treatment-emergent symptoms may be associated with superior survival outcomes. In contrast, our analysis of more than 7,000 MA.27 patients demonstrated no relationship between baseline or new or worsening treatment-associated symptoms and RFS ($P > .10$).

Compared with other investigations, a high proportion of evaluable MA.27 participants (34%) experienced baseline CTCAE vasomotor and/or joint symptoms, which may have been in part a result of a required 3-week washout period for hormone replacement therapy (HRT). HRT withdrawal is frequently associated with the appearance of rebound symptoms and improved breast cancer outcomes, which may explain the disparate results between the ATAC analysis and our study.¹² The effects of withdrawal generally occur promptly and would be recorded among baseline symptoms, allowing for independent assessment of the effect of AI therapy on symptoms.¹² In ATAC, which did not require an HRT washout period before random assignment, only 9.5% and 9.3% of patients who started treatment had baseline vasomotor and joint symptoms, respectively. In the TEAM trial, baseline symptom data and prior HRT use were not described.⁶ Approximately 18% of BIG 1-98 patients used HRT within 3 months of initiating study, and 18% of additional patients used HRT more than 3 months before the study.⁷

Only the 3-month symptom data were investigated in ATAC, and 55% of patients receiving either anastrozole or tamoxifen developed symptoms by 3 months. Among these ATAC participants, the emergence of vasomotor symptoms was particularly pronounced in those who had received prior HRT ($P = .003$). In MA.27, patient-perceived severe symptoms led to discontinuation of treatment in

24% of symptomatic participants at 3-month early clinic visits. At the preplanned 6- and 12-month visits, the discontinuation rates for those with symptoms were 12% and 10%, respectively. Prior HRT use up until, or near, the diagnosis of breast cancer could have confounded our results.

Although we did not observe the ATAC differences in cancer outcomes related to treatment-emergent symptoms, there were also important differences in the proportion of trial patients investigated. In MA.27, we investigated the symptoms for 96% of participants. Of the 6,241 ATAC patients randomly assigned to anastrozole or tamoxifen, 3,964 patients (64%) were included in the analysis, with the exclusion of patients who did not start therapy, did not have hormone receptor-positive tumors, and had prior baseline symptoms. Because inclusivity of patients was high for the TEAM (9,325 patients, 95%) and BIG 1-98 (4,798 patients, 97.5%) trials, inclusivity alone is not likely to account for intertrial differences.

An important aspect in interpreting discrepancies between MA.27 and other reports from adjuvant trials could be the method of ascertaining AEs. Patient-reported symptoms were collected for MA.27 in a standardized manner, using CTCAE version 3.0. The ATAC and TEAM trials reported using elicited symptoms or patient responses, respectively, rather than a specific/standard symptom checklist, although in the TEAM trial, the severity of symptoms was determined with National Cancer Institute Common Toxicity Criteria criteria. The BIG 1-98 trial used CTCAE version 2.0 and reported only 38% of patients experiencing symptoms by 12 months. The prospective incorporation not only of standard AE reporting, such as the CTCAE version 3.0, but also of subjective patient-reported outcomes will allow for accurate determination of symptoms both in future trials and in clinical practice.^{13,14}

The effects of arthralgic pain medications may have confounded results. In MA.27, we adjusted for the effects of early random assignment to celecoxib, with concomitant recording of aspirin use (81 mg/d), during the factorial period of MA.27 with stratified analyses. Details of aspirin use and use of other nonsteroidal anti-inflammatory drugs (NSAIDs), which might have been prescribed for symptoms, were not rigorously collected in ATAC; however, 12% of patients reported the use of cyclooxygenase-2 inhibitors. Use of NSAIDs was not reported in the TEAM or BIG 1-98 trials. The use of NSAIDs and cyclooxygenase-2 inhibitors in the ATAC trial could have been directed toward controlling symptoms, which may have improved adherence.

Adherence to endocrine therapy is an important component of efficacy. Overall, 31.6% of MA.27 patients discontinued treatment as a result of AEs, concomitant disease, or study refusal, with joint pain being the most frequent reason.^{9,13} Interestingly, despite a higher proportion of symptomatic patients in ATAC compared with MA.27, ATAC participants had a higher adherence to therapy. Specifically in ATAC, 88% of patients with symptoms and 84% without symptoms adhered to prescribed trial therapy until recurrence, compared with 70% of MA.27 participants. Although the TEAM investigators did not report treatment adherence, they performed a time-dependent Cox regression analysis for time on and off treatment. Early treatment discontinuation did not affect outcomes of patients reporting specific AEs. Moreover, patients who reported specific AEs and discontinued treatment before the designated 5-year stop date still experienced a disease-free survival benefit compared with patients who did not. Adherence to therapy was high in BIG 1-98, approaching 97%.

We recently evaluated the role of emergent symptoms in 672 premenopausal women randomly assigned to tamoxifen or placebo in the MA.12 trial. With a median follow-up time of 9.7 years, we observed only a weak association ($P = .06$) that women older than 50 years had more symptoms on tamoxifen; symptoms did not impact RFS ($P > .90$).¹⁵ Women reporting new hot flashes on tamoxifen in the Women's Healthy Eating and Living Study were more likely to benefit from tamoxifen. The authors of the Women's Healthy Eating and Living Study concluded that anti-estrogen-emergent symptoms were associated with superior therapeutic effects and improved breast cancer outcomes.

The mechanism underlying AI-associated musculoskeletal symptoms remains unknown and may include estrogen suppression and pharmacogenetic or genetic factors.¹⁶⁻¹⁸ Adverse effects may also be influenced by drug adherence or concomitant use of interventions alleviating symptoms.^{17,18} In the MA.27 genome-wide association studies of the genetic basis for musculoskeletal AEs,¹³ we included patients who experienced unacceptable early toxicity before the first scheduled 6-month follow-up and identified four single-nucleotide polymorphisms in the estrogen-dependent gene, T-cell leukemia (*TCL1A*), related to expression of cytokine interleukin-17, associated with musculoskeletal symptoms in women treated with anastrozole or exemestane.⁹ Another study suggested that a variant in the gene encoding for the estrogen receptor may predict AI-associated symptoms.¹⁹ Other factors may include body mass index and prior chemotherapy use, especially taxanes.^{2,4,20} Specific type of adjuvant chemotherapy was not recorded in MA.27; however, different agents should be approximately balanced between the two arms and are not expected to affect outcome.

A limitation of the treatment-emergent analysis of the MA.27 trial is that the original factorial design randomly assigned patients to celecoxib with stratification by aspirin use (81 mg); however, the effects of these factors and the other possible confounders of adjuvant chemotherapy and lymph node involvement were handled with stratified univariable and multivariable results. In addition, approximately 30% of MA.27 patients discontinued trial therapy by final trial follow-up at a median of 4.1 years, which may have impacted our assessment of symptoms. MA.27 collected only severe symptoms during the first 3 months; however, results for this time period were similar to those obtained at protocol-mandated follow-up at 6 and 12 months. In addition, MA.27 patients had high EFS (4-year EFS, 91% on exemestane and 91.2% on anastrozole), which would have made it more difficult to demonstrate a difference in RFS with landmark analyses where events are excluded.

In summary, the majority of studies of patients who received tamoxifen or AI reported a relationship between emergence of vasomotor and musculoskeletal symptoms and survival outcomes. Our study, examining two AIs, failed to show an association between new or worsening symptoms and outcome. Predictive factors are required to determine treatment efficacy and treatment-emergent symptoms. Future prospective analyses of symptoms in AI trials should ensure that symptoms are collected in a similar way to both the positive and negative trials to resolve the issue. Until then, treatment-emergent symptoms should be managed as effectively as possible to support treatment continuation, and it is premature to counsel patients on whether to continue or change their adjuvant AI therapy based on symptoms.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

anastrozole: a third-generation nonsteroidal aromatase inhibitor that prevents the conversion of androgen to estrogen in the peripheral tissues in postmenopausal women. Because hormone-dependent breast cancer progresses with estrogen, anastrozole has been used in the treatment of breast cancer in postmenopausal women. See *aromatase inhibitors*.

aromatase inhibitors: inhibitors used in treating breast cancer in postmenopausal women. Aromatase inhibitors inhibit the conversion of androgens to estrogens by the enzyme aromatase, thus depriving the tumor of estrogenic signals. Because of decreased production of estrogen, estrogen receptors, which are important in the progression of breast cancer, cannot be activated.

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Treatment-Associated Musculoskeletal and Vasomotor Symptoms and Relapse-Free Survival in the NCIC CTG MA.27 Adjuvant Breast Cancer Aromatase Inhibitor Trial

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Appendix

Table A1. Baseline Characteristics of Women by Vasomotor and/or Joint Symptoms at Baseline and 3 Months

Variable	No Baseline Symptoms*					With or Without Baseline Symptoms†				
	No Vasomotor or Joint Symptom at 3 Months‡ (n = 5,424)		Vasomotor or Joint Symptom at 3 Months‡ (n = 221)		P§	No New or Worsening Vasomotor or Joint Symptom at 3 Months (n = 6,931)		New or Worsening Vasomotor or Joint Symptom at 3 Months (n = 403)		P§
	No. of Patients	%	No. of Patients	%		No. of Patients	%	No. of Patients	%	
Age, years					.807					.172
≥ 50 or missing	5,312	97.9	216	97.7		6,751	97.4	388	96.3	
< 50	112	2.1	5	2.3		180	2.6	15	3.7	
Race					.388					.945
Nonwhite	317	5.8	16	7.2		384	5.5	22	5.5	
White	5,107	94.2	205	92.8		6,547	94.5	381	94.5	
Performance status					.049					.121
Other	966	17.8	28	12.7		1,224	17.7	59	14.6	
Fully	4,458	82.2	193	87.3		5,707	82.3	344	85.4	
Postmenopausal status					.002					< .001
Other	5,143	94.8	205	92.8		6,465	93.3	362	89.8	
≤ 55 years old	121	2.2	14	6.3		213	3.1	35	8.7	
45-59 years old (< 12 months; HRT)	47	0.9	1	0.5		73	1.1	2	0.5	
45-59 years old (< 12 months; hysterectomy)	113	2.1	1	0.5		180	2.6	4	1.0	
Most extensive surgery					.253					.054
Partial mastectomy or missing	3,684	67.9	142	64.3		4,739	68.4	257	63.8	
Mastectomy NOS	1,740	32.1	79	35.7		2,192	31.6	146	36.2	
Axillary dissection					.009					< .001
Yes or missing	2,732	50.4	131	59.3		3,545	51.1	248	61.5	
No	2,692	49.6	90	40.7		3,386	48.9	155	38.5	
Tumor laterality					.857					.521
Right	2,635	48.6	106	48.0		3,343	48.2	201	49.9	
Bilateral, left, and missing	2,789	51.4	115	52.0		3,588	51.8	202	50.1	
T stage					.017					.764
T1	3,843	70.9	173	78.3		4,984	71.9	287	71.2	
Other	1,581	29.1	48	21.7		1,947	28.1	116	28.8	
N stage					.700					.231
Other	1,562	28.8	61	27.6		1,958	28.2	125	31.0	
N0	3,862	71.2	160	72.4		4,973	71.8	278	69.0	
Prior adjuvant chemotherapy					.882					.048
Yes	1,596	29.4	64	29.0		2,101	30.3	141	35.0	
No or missing	3,828	70.6	157	71.0		4,830	69.7	262	65.0	
Prior raloxifene					.399					.687
Yes	84	1.5	5	2.3		103	1.5	7	1.7	
No, missing, unknown	5,340	98.5	216	97.7		6,828	98.5	396	98.3	
Prior or concurrent radiotherapy					.294					.138
Yes	3,811	70.3	148	67.0		4,934	71.2	273	67.7	
No, missing, unknown	1,613	29.7	73	33.0		1,997	28.8	130	32.3	
Fractures within 10 years before allocation					.171					.258
Yes	517	9.5	15	6.8		687	9.9	33	8.2	
No, missing, unknown	4,907	90.5	206	93.2		6,244	90.1	370	91.8	
Cardiovascular history					.596					.096
Yes	3,043	56.1	120	54.3		3,752	54.1	201	49.9	
No, missing, unknown	2,381	43.9	101	45.7		3,179	45.9	202	50.1	

Abbreviations: HRT, hormone replacement therapy; NOS, not otherwise specified.

*Patients had no baseline vasomotor symptoms or grade 3 or 4 joint symptoms (group 1).

†Patients did or did not have any baseline vasomotor and/or joint symptoms (group 3).

‡Patients did or did not have any grade of vasomotor symptoms or grade 3 or 4 joint symptoms (group 1).

§P values from a χ^2 or Fisher's exact test.

||Patients did or did not have any grade of new or worsening vasomotor and/or joint symptoms (group 3).

Treatment-Related Joint/Vasomotor Symptoms and Outcomes in MA.27

Table A2. Baseline Characteristics of Women by Vasomotor and/or Joint Symptoms at Baseline and 6 Months

Variable	No Baseline Symptoms*				P§	With or Without Baseline Symptoms†				P§
	No Vasomotor or Joint Symptom at 6 Months‡ (n = 4,539)		Vasomotor or Joint Symptom at 6 Months‡ (n = 1,081)			No New or Worsening Vasomotor or Joint Symptom at 6 Months (n = 5,379)		New or Worsening Vasomotor or Joint Symptom at 6 Months (n = 1,927)		
	No. of Patients	%	No. of Patients	%		No. of Patients	%	No. of Patients	%	
Age, years					.287					.009
≥ 50 or missing	4,449	98.0	1,054	97.5		5,252	97.6	1,860	96.5	
< 50	90	2.0	27	2.5		127	2.4	67	3.5	
Race					.561					.292
Nonwhite	273	6.0	60	5.6		308	5.7	98	5.1	
White	4,266	94.0	1,021	94.4		5,071	94.3	1,829	94.9	
Performance status					.072					.050
Other	819	18.0	170	15.7		969	18.0	309	16.0	
Fully	3,720	82.0	911	84.3		4,410	82.0	1,618	84.0	
Postmenopausal status					< .001					< .001
Other	4,328	95.4	995	92.0		5,061	94.1	1,738	90.2	
≤ 55 years old	75	1.7	60	5.6		128	2.4	120	6.2	
45-59 years old (< 12 months; HRT)	39	0.9	9	0.8		54	1.0	21	1.1	
45-59 years old (< 12 months; hysterectomy)	97	2.1	17	1.6		136	2.5	48	2.5	
Most extensive surgery					.815					.377
Partial mastectomy or missing	3,082	67.9	730	67.5		3,682	68.5	1,298	67.4	
Mastectomy NOS	1,457	32.1	351	32.5		1,697	31.5	629	32.6	
Axillary dissection					.079					< .001
Yes or missing	2,271	50.0	573	53.0		2,702	50.2	1,072	55.6	
No	2,268	50.0	508	47.0		2,677	49.8	855	44.4	
Tumor laterality					.339					.323
Right	2,219	48.9	511	47.3		2,619	51.3	913	47.4	
Bilateral, left, and missing	2,320	51.1	570	52.7		2,760	51.3	1,014	52.6	
T stage					.020					.681
T1	3,202	70.5	801	74.1		3,862	71.8	1,393	72.3	
Other	1,337	29.5	280	25.9		1,517	28.2	534	27.7	
N stage					.036					.791
Other	1,330	29.3	282	26.1		1,521	28.3	551	28.6	
N0	3,209	70.7	799	73.9		3,858	71.7	1,376	71.4	
Prior adjuvant chemotherapy					.885					< .001
Yes	1,337	29.5	316	29.2		1,582	29.4	652	33.8	
No or missing	3,202	70.5	765	70.8		3,797	70.6	1,275	66.2	
Prior raloxifene					.770					.702
Yes	70	1.5	18	1.7		82	1.5	27	1.4	
No, missing, unknown	4,469	98.5	1,063	98.3		5,297	98.5	1,900	98.6	
Prior or concurrent radiotherapy					.846					.730
Yes	3,188	70.2	756	69.9		3,827	71.1	1,363	70.7	
No, missing, unknown	1,351	29.8	325	30.1		1,552	28.9	564	29.3	
Fractures within 10 years before allocation					.106					.511
Yes	442	9.7	88	8.1		536	10.0	182	9.4	
No, missing, unknown	4,097	90.3	993	91.9		4,843	90.0	1,745	90.6	
Cardiovascular history					.004					.009
Yes	2,581	56.9	563	52.1		2,944	54.7	988	51.3	
No, missing, unknown	1,958	43.1	518	47.9		2,435	45.3	939	48.7	

Abbreviations: HRT, hormone replacement therapy; NOS, not otherwise specified.

*Patients had no baseline vasomotor symptoms or grade 3 or 4 joint symptoms (group 1).

†Patients did or did not have any baseline vasomotor and/or joint symptoms (group 3).

‡Patients did or did not have any grade of vasomotor symptoms or grade 3 or 4 joint symptoms (group 1).

§P values from a χ^2 or Fisher's exact test.

||Patients did or did not have any grade of new or worsening vasomotor and/or joint symptoms (group 3).

Fig A1. Recurrence-free survival of group 1 patients without baseline vasomotor (vaso) or grade 3 or 4 joint symptoms who developed vasomotor or grade 3 or 4 joint symptoms at 3 months. HR, hazard ratio.

Fig A2. Recurrence-free survival of group 3 patients with new or worsening vasomotor (vaso) or joint symptoms at 3 months. HR, hazard ratio.

Fig A3. Recurrence-free survival of group 3 patients (women) with new or worsening vasomotor (vaso) or joint symptoms at 6 months. HR, hazard ratio.

Fig A4. Recurrence-free survival of group 3 patients (women) with new or worsening vasomotor (vaso) or joint symptoms at 12 months. HR, hazard ratio.