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New onset vasomotor symptoms but not musculoskeletal symptoms associate with clinical outcomes on extended adjuvant letrozole – Analyses from NCIC CTG MA.17☆

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ABSTRACT

Purpose: New onset symptoms on adjuvant aromatase inhibitors for hormone receptor positive early breast cancer may associate with clinical outcomes. We performed this exploratory analysis of the association of new onset musculoskeletal (MSK) and vasomotor (VM) symptoms with clinical outcomes in the NCIC CTG MA.17 trial 5 years of extended adjuvant endocrine therapy with letrozole after tamoxifen.
Methods: Symptoms were collected at baseline, 1, 6, and every 12 months on study. Multivariate Cox Models adjusting for age, nodal status, duration of tamoxifen and prior chemotherapy were used to compare disease-free survival (DFS), distant disease-free survival (DDFS), and overall survival (OS) based on data collected before, and after, the unblinding between women with VM or MSK symptoms and those without.
Results: Data post-unblinding showed new VM symptoms on extended letrozole significantly improved DFS and DDFS when occurring 1 month (DFS HR 0.52, 95% CI, 0.28–0.96; p = 0.04; DDFS HR 0.49, 95% CI, 0.24–0.99; p = 0.046) and 6 months (DFS HR 0.43, 95% CI, 0.24–0.78; p = 0.006; DDFS HR 0.44, 95% CI, 0.22–0.85; p = 0.02) after treatment initiation. Those with new VM symptoms at 12 months also had a significantly better DFS (HR 0.47, 95% CI 0.26, 0.84; P = 0.01) and a trend in improved DDFS. Only a trend to improved OS was found for those with VM symptoms 6 month after treatment. No significant improvement was found for those with new MSK symptoms at any time point or for any endpoint.
Conclusions: New onset VM symptoms with extended letrozole may be useful in predicting treatment benefit.

Key message

Vasomotor and musculoskeletal symptoms from aromatase inhibitors (AI) are common and bothersome. On the other hand, these symptoms might be markers of clinical efficacy of AI use. We have performed an exploratory analysis of new onset symptoms on extended adjuvant letrozole in the MA 17 study and their correlation with clinical outcomes. Our results suggest that new onset vasomotor symptoms up to 12 months after initiation of extended letrozole use might be useful in predicting treatment benefit.

Introduction

Musculoskeletal (MSK) and vasomotor (VM) symptoms are frequent side effects of endocrine therapy for breast cancer. These

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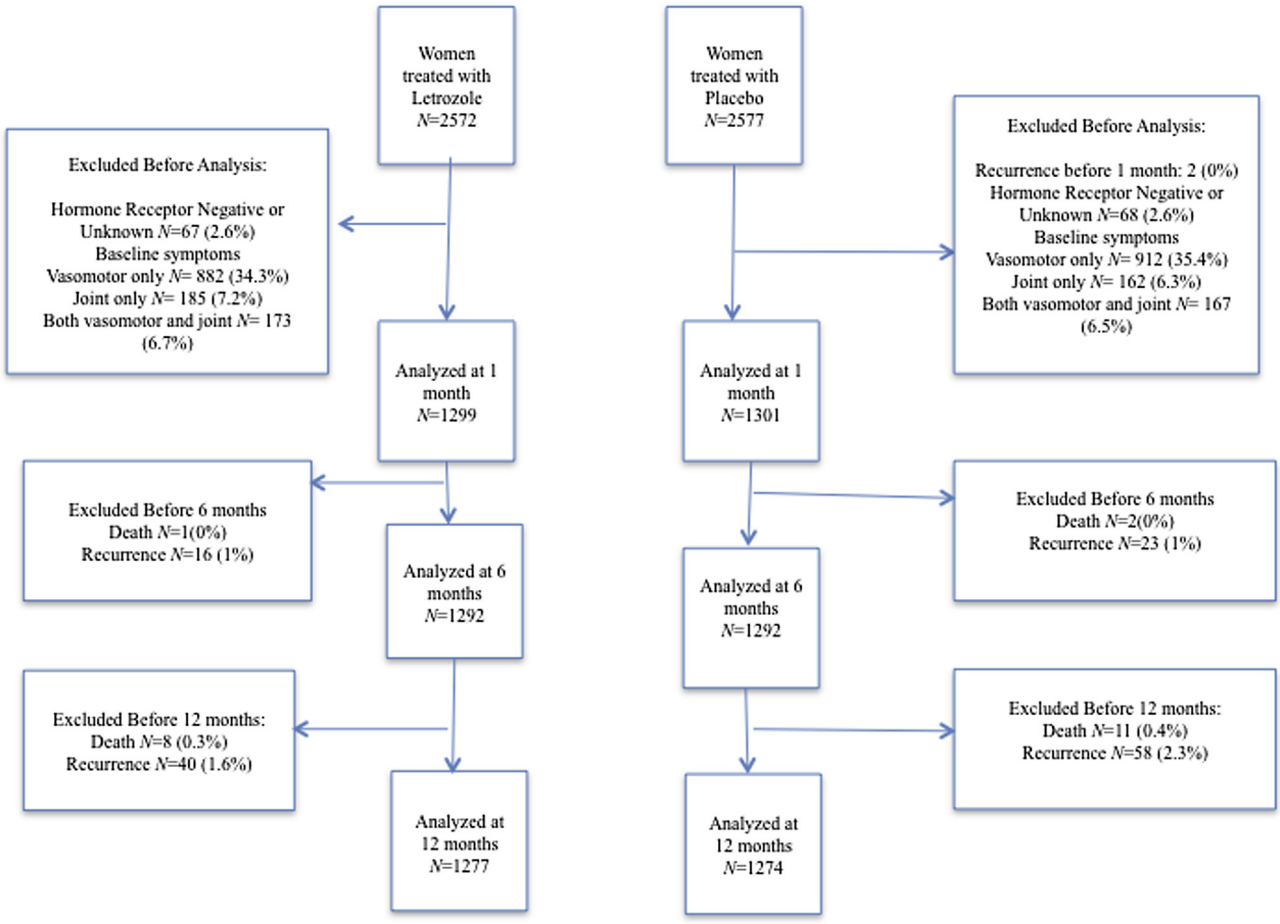

Fig. 1. Consort diagram.

symptoms are frequently bothersome for women and have been identified as an important factor for poor adherence and treatment abandonment [1]. The reason for the occurrence of MSK symptoms is not clear, but recent pharmacogenetic association studies linked symptom occurrence to single nucleotide host DNA polymorphisms in women receiving adjuvant aromatase inhibitor (AI) therapy [2,3].

New onset symptoms on AI therapy for hormone receptor positive early breast cancer (EBC) has been investigated as a marker

Table 1
Patient baseline characteristics.

Characteristic	One month after randomization			Six months after randomization			12 months After randomization		
	Either VM or MSK symptom ($N = 649$)	Neither VM nor MSK symptom ($N = 1951$)	*P*-value	Either VM or MSK symptom ($N = 1010$)	Neither VM nor MSK symptom ($N = 1574$)	*P*-value	Either VM or MSK symptom ($N = 907$)	Neither VM nor MSK symptom ($N = 1332$)	*P*-value
Age									
<60 years	273 (42.1)	632 (32.4)	<0.0001	407 (40.3)	493 (31.3)	<0.0001	379 (41.8)	411 (30.9)	<0.0001
≥ 60 years	376 (57.9)	1318 (67.6)		603 (59.7)	1080 (68.7)		528 (58.2)	920 (69.2)	
Nodal status									
Negative	315 (48.7)	971 (49.9)	0.17	499 (45.6)	786 (50.1)	0.34	440 (48.6)	674 (50.8)	0.17
Positive	309 (47.8)	874 (44.9)		467 (46.4)	701 (44.7)		427 (47.2)	581 (43.8)	
Unknown	23 (3.6)	100 (5.1)		41 (4.1)	82 (5.2)		38 (4.2)	72 (5.4)	
Duration of Prior Tamoxifen									
≤ 5 years	288 (44.4)	850 (43.7)	0.73	448 (44.4)	679 (43.3)	0.55	407 (45.0)	589 (44.3)	0.76
>5 years	360 (55.6)	1096 (56.3)		560 (55.6)	891 (56.7)		498 (55.0)	740 (55.7)	
Prior chemotherapy									
Yes	316 (48.8)	832 (42.7)	0.007	466 (46.2)	674 (42.9)	0.10	442 (48.8)	567 (42.6)	0.004
No	332 (51.2)	1117 (57.3)		543 (53.8)	898 (57.1)		464 (51.2)	763 (57.4)	
Randomized Treatment									
Letrozole	342 (52.7)	957 (49.1)	0.11	535 (53.0)	757 (48.1)	0.02	488 (53.8)	624 (46.9)	0.001
Placebo	307 (47.3)	994 (50.9)		475 (47.0)	817 (51.9)		419 (46.2)	708 (53.1)	

VM: Vasomotor; MSK: musculoskeletal.