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Brief Communication

Time to Mammographic Density Decrease After Exposure to Tamoxifen

Magnus Bäcklund[1,*,‡], Mikael Eriksson[1,‡], Mattias Hammarström[1], Linda Thoren[2,3], Jenny Bergqvist[1,4], Sara Margolin[2,3], Roxanna Hellgren[5], Yvonne Wengström[6], Marike Gabrielson[1], Kamila Czene[1], Per Hall[1,2]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[2]Department of Oncology, Södersjukhuset, Stockholm, Sweden
[3]Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
[4]Breast Centre, Department of Surgery, Capio S:t Görans Hospital, Stockholm, Sweden
[5]Department of Radiology, Södersjukhuset, Stockholm, Sweden
[6]Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

*Corresponding author: Magnus Bäcklund, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, SE-171 77 Stockholm, Sweden. Tel: +46 8 524 823 39; Fax: +46-8 524 823 39; Email: magnus.backlund@ki.se
‡Shared first authorship.

Abstract

Mammographic density change has proven to be a reliable proxy for tamoxifen therapy response. The primary aim of this study was to identify time to tamoxifen-induced mammographic density change. We also analyzed side effects and adherence to therapy. In all, 42 women were randomized to 10 or 20 mg of daily oral tamoxifen. Mammograms were taken at baseline, 3, 6, and 9 months. Mammographic density change was measured using the automated STRATUS tool. Adverse events were monitored through a web-based questionnaire based on the FACT-ES tool. Nine out of the 42 (21%) participants discontinued therapy due to adverse events leaving 33 women in the study. A significant decrease in density was seen after 3 months of therapy. Dose did not seem to affect density change, side effects or adherence. Given the size of the study, additional studies are needed to confirm our data.

Key words: breast cancer; clinical trial; primary prevention; breast density; tamoxifen.

Introduction

Randomized tamoxifen prevention trials have shown an approximate 40% decreased incidence of breast cancer using 20 mg, the same dosage as for adjuvant breast cancer treatment.[1] Despite the proven preventive effect, tamoxifen is not an established clinical routine for women at increased risk of breast cancer, one reason being unacceptable side effects.[2] A possible way of reducing side effects and retain the protective effect could be to test lower doses. Using breast cancer incidence as the endpoint in such a dose determination study would demand an extremely large number of participants and many years of follow-up. An alternative is to use mammographic density change as a proxy for therapy response as it has been shown to be a good surrogate marker for the effect of tamoxifen.[3] If time to decrease is shorter than 12 months has however not been studied. To prepare for a larger dose determination study, we therefore estimated time to tamoxifen-induced mammographic density change. We also studied side effects, adherence and a possible difference in effect after exposure to 10 or 20 mg of tamoxifen.

Materials and Methods

The study was designed as a randomized, open-label, feasibility study investigating mammographic density change in healthy women after two different daily doses, 10 and 20 mg, of tamoxifen for 6 months.

The FDA approved software Volpara was used[4] to identify women with a mammographic density corresponding to BI-RADS B-D.[5] Full-field digital mammograms of the mediolateral oblique view were collected. The average percent density (fibroglandular dense tissue area divided by total breast area) of left and right breasts at baseline was calculated and compared with average percent density at the end of the trial period and density change was defined as the difference between these two measures. Before measurements and comparisons were done, images of the same breast were aligned to reduce technical differences between images, a method described previously using the fully automated STRATUS method.[6]

Side effects were reported in a structured questionnaire at baseline and months 3, 6, and 9. Vasomotor, gynecological, sexual, and musculoskeletal symptoms were assessed using a 5-grade Likert severity scale ranging from "no symptom at all" to "very much symptoms". The questionnaire was based on the Functional Assessment of Cancer Therapy - Endocrine Subscale (FACT-ES).[7] A symptom score was calculated as the sum of the last month's symptom severity levels. To ascertain compliance to the follow-up questionnaires, the study personnel contacted participants if questionnaires were not filled out. Adherence to therapy was defined as participants taking

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Table 1. Percent mammographic density and absolute density change at three time points compared with baseline for the 33 women completing at least 6 months of medication, subdivided per dose arm.

Characteristics	Month 0	Month 3	Month 6	Month 9
Number of women having a mammogram	33	33	33	33
All women (N = 33)				
Age at baseline, mean (SD)	62.1 (SD 9.1)			
Postmenopausal, %	82			
Mammography density, mean (95% CI)	17.6 (12.3-22.8)	15.8 (11.0-22.5)	15.3 (10.5-20.1)	14.6 (10.3-19.0)
Absolute density difference, mean (95% CI)	Ref.	−1.8 (−3.3 to −0.2)	−2.2 (−4.2 to −0.3)	−2.9 (−5.0 to −0.9)
Women in the 10 mg arm (N = 19)				
Age at baseline, mean (SD)	60.0 (SD 8.9)			
Postmenopausal, %	68			
Mammography density, mean (95% CI)	15.9 (8.9-22.8)	13.7 (7.4-20.0)	12.7 (6.4-19.0)	12.6 (6.8-18.3)
Absolute density difference, mean (95% CI)	Ref.	−2.1 (−4.2 to −0.1)	−3.1 (−5.7 to −0.5)	−3.3 (−6.1 to- −0.5)
Women in the 20 mg arm (N = 14)				
Age at baseline, mean (SD)	65.1 (SD 5.3)			
Postmenopausal, %	100			
Mammographic density, mean (95% CI)	19.9 (11.8-27.9)	18.5 (11.2-25.9)	18.8 (11.5-26.2)	17.4 (10.7-24.1)
Absolute density difference, mean (95% CI)	Ref.	−1.3 (−3.7 to -1.1)	−1.0 (-4.1-2.0)	−2.5 (−5.7 to 0.8)

Abbreviations: CI, confidence interval; SD, standard deviation.

Table 2. Symptom score and symptom score change at three time points compared with baseline for women completing at least 6 months of medication, subdivided per dose arm.

Characteristics	Month 0	Month 3	Month 6	Month 9
All women				
Number of women reporting side effects	32	31	29	30
Symptom score[a], mean (95% CI[b])	67.9 (65.5-70.4)	68.9 (66.1-71.6)	66.2 (63.0-69.4)	69.8 (66.7-73.0)
Absolute difference in symptom score[c], mean (95% CI[b])	Ref.	1.1 (−1.6-3.8)	−1.4 (−4.4 to 1.5)	2.6 (0.6-4.6)
Women in the 10 mg arm				
Number of women reporting side effects	18	17	17	18
Symptom score[a], mean (95% CI[b])	66.2 (63.0-69.4)	66.3 (62.8-69.8)	64.3 (60.2-68.4)	67.4 (63.5-71.3)
Absolute difference in symptom score[c], mean (95% CI[b])	Ref.	0.4 (−3.3 to 4.1)	−1.6 (−5.5 to 2.4)	1.8 (−0.8 to 4.5)
Women in the 20 mg arm				
Number of women reporting side effects	14	14	12	12
Symptom score[1], mean (95% CI[2])	70.1 (66.5-73.7)	72.0 (68.1-75.8)	68.9 (64.0-73.7)	73.4 (68.7-78.2)
Absolute difference in symptom score[3], mean (95% CI[2])	Ref.	1.8 (−2.1-5.8)	−1.3 (−5.9 to 3.4)	3.7 (0.5-6.8)

[a]Higher symptom score means less symptoms.
[b]95% confidence intervals.
[c]Higher absolute difference means less symptoms.

tamoxifen for at least 6 months. Age and menopausal status at baseline were reported. Average changes of symptom score and mammographic density were calculated at months 3, 6, and 9 with 95% confidence intervals.

Results

A total of 723 participants of the Karma cohort, a prospective screening cohort,[8] were invited when they attended their bi-annual screening mammography. Of these, 56 (7.7%) women were willing to participate and 14 did not meet the exclusion/inclusion criteria (Supplementary Table S1) leaving 42 (5.8%) participants in the study (Supplementary Fig. S1). In all, 33 women completed the 6 months trial period and 9 participants (4 on 10 mg and 5 on 20 mg of tamoxifen) terminated due to intolerable side effects (Supplementary Fig. S1). The mean age of the participants was 62.1 (SD 7.9) and 82% were postmenopausal (Table 1).

The mean mammographic percent density was 17.6 % for all women at baseline. A mean change of −1.8 % (95% CI −3.3, −0.2), −2.2% (95% CI −4.2, −0.3), and −2.9 % (95% CI −5.0, −0.9) were seen after 3, 6, and 9 months of follow-up, respectively (Table 1). If anything, the decrease seemed to be more pronounced in the 10 mg group, with a mean absolute density difference of 1.0 in the 20 mg group, compared with 3.1 in the 10 mg group. A typical decrease over the 6 months' period is depicted in Supplementary Fig. 2.

A total of 911 symptom reports were registered but no serious adverse event was seen. Table 2 shows the calculated symptom scores at baseline, 3, 6, and 9 months of follow up.

No significant side effects were seen for the first 6 months when comparing to baseline. At 9 months, when some of the women had stopped taking tamoxifen, it seemed as if participants randomized to 20 mg had less side effects compared to when entering the study (Table 2).

Discussion

We found a significant mammographic density change within 3 months of tamoxifen exposure. There was no indication of a difference between 10 and 20 mg of tamoxifen when it came to adherence, side effects or density decrease.

Previous studies using mammographic density change as a marker of tamoxifen response have all been observational and the interval between mammograms has been 12 months or more.[3] Our results indicate that the tamoxifen therapy response is visible already at 3 months which lead us to design a larger trial using a 6 month tamoxifen exposure period.[9] Further, the concept of using 20 mg of tamoxifen has recently been challenged. We and others have reported that low dose tamoxifen, in doses of 2.5 or 5 mg, might have a preventive and adjuvant effect similar to 20 mg.[9,10]

One obvious weakness of our trial is the few participants making it difficult to draw firm conclusions. Another weakness was the non-blinded design. However, the measurement of mammographic density and side effects were done blinded to exposure status. A strength was the use of STRATUS for measuring mammographic density change. STRATUS aligns images before density is measured and compared, reducing the technical variability introduced when dissimilar amount of breast tissue is found in the mammogram.[6]

Conclusion

As a conclusion, we have indications that a density reduction after 6 months of tamoxifen treatment could be used as a proxy for therapy response. In our small study we did not find a major difference in mammographic density change, adherence or side effects comparing 10 and 20 mg of tamoxifen. It should be emphasized that we build our assumptions on a very small material and our results should be seen merely as guidance for future studies.

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Conflict of Interest

Mikael Eriksson, **Mattias Hammarström**, **Per Hall**, and **Kamila Czene** disclose a pending patent on compositions and methods for prevention of breast cancer with an option to license to Atossa Therapeutics. The other authors indicated no financial relationships.

Author Contributions

Conception/design: M.E., M.H., M.G., R.H., Y.W., K.C., and P.H. Provision of study material/patients: L.T., S.M., and P.H. Collection and/or assembly of data: M.B., M.E., M.H., J.B., Y.W., and P.H. Data analysis and interpretation: All authors. Manuscript writing: M.B. (drafted the manuscript) and M.E., M.G., M.H., and P.H. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at The *Oncologist* online.

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