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Brief Communication

Topical Endoxifen for Mammographic Density Reduction—A Randomized Controlled Trial

Magnus Bäcklund[1,*,‡], Mikael Eriksson[1,‡], Marike Gabrielson[1], Mattias Hammarström[1], Steve Quay[2], Jenny Bergqvist[1,3], Roxanna Hellgren[4], Kamila Czene[1], Per Hall[1,5]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[2]Atossa Therapeutics, Inc., Seattle, WA, USA
[3]Department of Surgery, Breast Centre, Capio S:t Görans Hospital, Stockholm, Sweden
[4]Department of Radiology, Södersjukhuset, Stockholm, Sweden
[5]Department of Oncology, Södersjukhuset, Stockholm, Sweden

*Corresponding author: Magnus Bäcklund, MD, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, SE-171 65 Stockholm, Sweden. Tel: +46-8-524-823-39; Email: magnus.backlund@ki.se
‡Shared first authorship.

Abstract

Although breast cancer incidence is increasing, there are few primary preventive initiatives. Tamoxifen can reduce breast cancer incidence but is rarely used for primary prevention due to adverse events and tolerance issues. We tested if endoxifen, a tamoxifen metabolite, applied directly to the skin of the breast, could reduce mammographic density, a proxy for therapy response. Ninety women were randomized to placebo, 10 and 20 mg of topical Z-endoxifen for 6 months. Mammographic density and symptoms were measured at baseline and study exit. Despite a high discontinuation rate, driven by skin rashes, we found a significant mammographic density decrease, a dose-dependent increase in the concentration of plasma Z-endoxifen but no systemic side effects. Topical application of tamoxifen metabolites has the potential to decrease breast cancer incidence without major systemic side effects. However, endoxifen may not be suitable for topical administration and is unlikely to be used for breast cancer prevention.

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

Introduction

Breast cancer prevention trials have shown that tamoxifen reduces breast cancer incidence,[1] but acceptance among women at high risk is low because of systemic side effects.[2]

Only the breast tissue has to be exposed to a drug when preventing breast cancer. A transdermal delivery has the potential to reach a high local concentration in the breast tissue and a low systemic exposure. Of the tamoxifen metabolites, the (Z)-form of endoxifen has the highest binding affinity to the estrogen receptor.[3] Tamoxifen reduces mammographic density, and a reduction in mammographic density has been shown to be a proxy for therapy response.[4,5]

In this randomized double-blind controlled trial, we tested if a topical application of endoxifen to the skin of the breasts resulted in a mammographic density reduction, measurable plasma endoxifen levels, and systemic side effects. The study aimed to give guidance to the design of a larger dose-optimizing study.

Materials and Methods

We performed a double-blinded, randomized, three-armed (placebo, 10 and 20 mg of topical Z-endoxifen for 6 months) feasibility study including 30 women in each arm. The endpoints were mammographic density change, measures of plasma endoxifen, and side effects. The formulated product was dispensed into single-dose "sachets" containing 0, 5, or 10 mg of Z-endoxifen. The liquid content of one sachet was applied to each breast, thus women in the active arms were daily exposed to 10 and 20 mg, respectively.

At study entry, each participant performed a baseline mammogram, answered questions on background factors, and preexisting symptoms also related to tamoxifen exposure; hot flashes, cold sweats, night sweats, vaginal discharge, itching, bleeding, or dryness, discomfort at intercourse, and lost interest in sex. The answers were scored "not at all," "a little bit," "somewhat," "quite a bit," and "very much." The same questions were reported spontaneously and/or during the scheduled reports at 1, 3, and 6 months.

The FDA-approved software Volpara was used[6] to identify women with a mammographic density corresponding to BI-RADS B-D.[7] Full-field digital mammograms of the mediolateral oblique view were collected. The average percentage dense area (cm^2) of left and right breasts at baseline was calculated and compared with average percentage dense area at the end of the trial period. Density change was defined as the absolute 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.[8]

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Intention-to-treat analysis was performed. Outcome measures after endoxifen exposure were compared with corresponding baseline measures stratified by endoxifen dose. Mammograms were taken at study entry, at study exit, or after 6 months for those fulfilling the entire study period. Mammographic density and side effects were analyzed using mixed-effects linear and log-binomial regression models. The full data including missing outcome measures were analyzed using maximum likelihood. Z-endoxifen levels were reported using median and 95% confidence levels. All statistical tests were two-sided using alpha = 0.05.

Adherence to the study protocol was monitored according to Good Clinical Practice by an independent monitor. Participants signed an Informed Consent Form and the study was performed in accordance with the requirements of the Swedish Medical Products Agency, Regional Ethical Board, and Radiation Board at Södersjukhuset.

Results

A total of 9199 consecutive women attending the Swedish National Mammography Screening Program were invited to participate (Supplementary Figure 1). Of these, 137 (1.5%) women were willing to participate, and 47 women did not meet the exclusion/inclusion criteria leaving 90 (1.0%) women in the trial (Supplementary Table 1).

In all, 7, 28, and 30 women discontinued the study (Supplementary Figure 1), and the mean time to study exit was 4.9, 2.5, and 1.6 months in the placebo, 10 and 20 mg group, respectively (Table 1). The major reason for discontinuation was skin rashes, and approximately 50% of the participants in the active arms reported skin rashes to be severe (Table 1).

Topical endoxifen gave dose-dependent concentrations of endoxifen (Table 2), and the increase per month of exposure was significantly different when comparing 10 mg (0.10 ng/mL; 95% CI, 0.03-0.17) and 20 mg (0.43 ng/mL; 95% CI, 0.21-0.76) (Supplementary Figure 2). Women showed similar mammographic density measures at baseline in the three arms (Table 2). The absolute reduction in mammographic density during follow-up compared with baseline was 0.3% (P = .12), 0.9% (P = .04), and 1.9% (P = .03) per month, in the placebo, 10 and 20 mg arms, respectively (Supplementary Figure 3). No significant difference in reporting of systemic side effects was noted when comparing a number of women answering "quite a bit" and "very much" at baseline and study exit (Supplementary Figure 4).

Discussion

After less than 3 months of exposure to Z-endoxifen, we saw a significant mammographic density decrease in the 20 mg arm compared with placebo. We also found a dose-dependent increase in concentrations of Z-endoxifen in plasma per month, no systemic side effects but severe skin reactions in both the active arms. Clearly, no therapeutic window was identified. In fact, 10 mg caused intolerable side effects without evidence of effect compared with placebo.

All except 2 participants of the active arms discontinued treatment because of skin rashes that appeared after 3-4 weeks. The explanation could be the abundantly expressed estrogen receptors in the endothelium that trigger vasodilation.[9,10]

Given that >10% of the women in the Western world are diagnosed with breast cancer, preventive measures are warranted. Tamoxifen substantially reduces breast cancer incidence in high-risk women when 20 mg is used,[1] and FDA approved the expanded indication more than 20 years ago. Despite that, tamoxifen is rarely used for primary prevention and there is a low acceptance for providing healthy individuals a drug that is potentially harmful.[2]

Table 1. Age, BMI, severe skin rashes, number of women discontinuing, and months to study exit, in relation to dose of topical endoxifen.

Characteristic	Dose group			
	Doses combined	0 mg	10 mg	20 mg
No. of women randomized	90	30	30	30
Assessment at baseline				
Age, mean (SD[a])	56.5 (7.5)	54.9 (6.0)	56.9 (8.0)	57.7 (8.4)
BMI[b], mean (SD[a])	25.2 (3.1)	24.9 (2.8)	25.6 (3.6)	25.2 (3.1)
Severe skin rashes[c], %	1.1	3.3	0.0	0.0
Assessment at study exit				
No. of women discontinuing (%)	65 (72)	7 (23)	28 (93)	30 (100)
Months to study exit, mean (SD[a])	3.0 (2.1)	4.9 (2.1)	2.5 (1.5)	1.6 (0.8)
Severe skin rashes[c], %	34.5	3.3	46.7	55.6
Difference between study exit and baseline				
Months to study exit[d], mean (95% CI[e])	−3.0 (−3.4 to −2.5)	−1.1 (−1.7 to −0.5)	−3.5 (−4.0 to −2.9)	−4.5 (−4.9 to −3.8)
Severe skin rashes[c], % (95% CI[e])	33.3 (22.8 to 43.8)	0.0 (−13.6 to 13.6)	46.7 (26.5 to 63.9)	55.6 (33.5 to 72.4)

[a]Standard deviation.
[b]Body mass index.
[c]Skin rashes reported as "quite a lot" or "very much."
[d]Month at study exit minus the study defined 6-month follow-up time.
[e]95% confidence interval.

Table 2. Number of women assessed, Z-endoxifen level at study exit, and mammographic density at baseline, exit and, absolute difference in relation to dose of topical endoxifen.

Characteristic	Dose group			
	Doses combined	0 mg	10 mg	20 mg
Plasma Z-endoxifen level, at exit				
No. of women assessed	71	25	20	26
Exit Z-endoxifen level (ng/mL), median (95% CI[a])		<0.05	0.24 (0.10 to 0.49)	0.75 (0.38 to 1.11)
Mammographic density, at baseline and exit				
No. of women assessed at baseline/exit	90/74	30/26	30/23	30/27
Baseline mammographic density, mean (SD[b])	24.5 (16.0)	23.6 (17.2)	23.9 (12.9)	26.2 (18.0)
Exit mammographic density, mean (SD[b])	22.4 (16.5)	22.0 (17.8)	22.4 (14.0)	22.8 (18.0)
Absolute difference[c], mean (95% CI[a])	−2.2 (−3.4 to −0.9)	−1.6 (−3.6 to 0.3)	−1.5 (−3.5 to 0.6)	−3.4 (−6.7 to −0.6)

[a]95% confidence interval.
[b]Standard deviation.
[c]Absolute differences were calculated for women with available baseline and exit measures.

Conclusion

Our results indicate that targeting the breast directly with Z-endoxifen has the potential to reduce breast cancer incidence, but that the skin toxicity prohibits its use. Future studies should test alternative approaches of topical applications.

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Conflict of Interest

Mikael Eriksson, Per Hall, Kamila Czene, and **Mattias Hammarström:** pending patent on compositions and methods for prevention of breast cancer with an option to license to Atossa Therapeutics, Inc. (IP); **Steve Quay:** Atossa Therapeutics, Inc. (RF, IP). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

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

Ethics and Regulatory Approval and Consent to Participate

The study was performed complying with ethical standards according to International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and to current laws in Sweden, where the study was performed. Informed consent was obtained from all individual participants included in the study. The Stockholm Ethical Review Board approved the study on March 14, 2020 (dnr 2018/402-31). The study gained full regulatory approval from the Swedish Medical Products Agency on April 21, 2020 and was issued with the EudraCT number 2018-000573-72. Registration number on clinicaltrials.gov is NCT04616430 (retroactively registered, November 5, 2020).

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author. The datasets generated and analyzed during the current study are not publicly available due to traceability but are available from the corresponding author on reasonable request.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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