Original Article

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Short-Term Biomarker Modulation Study of Dasatinib for Estrogen Receptor–Negative Breast Cancer Chemoprevention

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ABSTRACT

Objective: Risk-reducing therapy with selective estrogen receptor (ER) modulators and aromatase inhibitors reduce breast cancer risk. However, the effects are limited to ER-positive breast cancer. Therefore, new agents with improved toxicity profiles that reduce the risk in ER-negative breast cancers are urgently needed. The aim of this prospective, short-term, prevention study was to evaluate the effect of dasatinib, an inhibitor of the tyrosine kinase Src, on biomarkers in normal (but increased risk) breast tissue and serum of women at high risk for a second, contralateral primary breast cancer.

Materials and Methods: Women with a history of unilateral stage I, II, or III ER-negative breast cancer, having no active disease, and who completed all adjuvant therapies were eligible. Patients underwent baseline fine-needle aspiration (FNA) of the contralateral breast and serum collection for biomarker analysis and were randomized to receive either no treatment (control) or dasatinib at 40 or 80 mg/day for three months. After three months, serum collection and breast FNA were repeated. Planned biomarker analysis consisted of changes in cytology and Ki-67 on breast FNA, and changes in serum levels of insulin-like growth factor 1 (IGF-1), IGF-binding protein 1, and IGF-binding protein 3. The primary objective was to evaluate changes in Ki-67 and secondary objective included changes in cytology in breast tissue and IGF-related serum biomarkers. Toxicity was also evaluated.

Results: Twenty-three patients started their assigned treatments. Compliance during the study was high, with 86.9% (20/23) of patients completing their assigned doses. Dasatinib was well tolerated and no drug-related grade 3 and 4 adverse events were observed. Since only one patient met the adequacy criteria for the paired FNA sample, we could not evaluate Ki-67 level or cytological changes. No significant change in serum biomarkers was observed among the three groups.

Conclusion: Dasatinib was well tolerated but did not induce any significant changes in serum biomarkers. The study could not fulfill its primary objective due to an inadequate number of paired FNA samples. Further, larger studies are needed to evaluate the effectiveness of Src inhibitors in breast cancer prevention.

Keywords: Chemoprevention; breast cancer risk; Src inhibitors

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Key Points

- Evaluation of agents that can reduce the risk of estrogen receptor-negative breast cancer development is urgently needed.
- Phase 3 breast cancer prevention trials require large numbers of patients and long follow-up durations and are costly.
- Short-term phase 1 and 2 biomarker modulation prevention trials offer a convenient method of studying potential preventative agents for ER-negative breast cancer.

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Introduction

Over the past 30 years, researchers have evaluated selective estrogen receptor (ER) modulators (SERMs) such as tamoxifen and raloxifene and aromatase inhibitors as breast cancer preventive agents in large, prospective phase 3 trials, which showed a reduction in breast cancer risk of 50-65% (1-8). In the United States, tamoxifen and raloxifene have been approved by the US Food and Drug Administration for reduction of breast cancer risk. However, these agents only reduce risk in ER-positive breast cancer. Currently, no agents are available and approved for the prevention of ER-negative breast cancer.

The Src family of kinases (cSrc, Lyn, Fyn, Yes, Lck, Blk, and Hck) is a group of non-receptor tyrosine kinases involved in the regulation of important cellular functions, such as cell proliferation, differentiation, apoptosis, migration, and metabolism (9, 10). Investigators found Src overexpression and activation in more than 80% of ductal carcinoma *in situ* lesions and that they were associated with HER2 expression in such lesions (11, 12). Additionally, Src phosphorylation at Y416 (indicating activation of the Src family of tyrosine kinases) was associated with ER negativity and tamoxifen resistance. The reverse relationship between Src and ER is consistent with previous reports that Src promotes estrogen-dependent ERα degradation in human breast cancers (13). Tamoxifen-resistant breast cancer cells have also exhibited Src activation, and treatment with the Src inhibitor saracatinib suppressed the invasion of tamoxifen-resistant cells (14). Furthermore, a recent study demonstrated that saracatinib administration improved tumor-free and overall survival in two mouse models of ER-negative, Src-activated mammary tumors by delaying the onset and progression of premalignant lesions (15). These results are suggestive of a critical function of Src in ER-negative breast cancer development. Therefore, inhibiting the Src pathway may be an effective strategy for breast cancer prevention.

Large-scale randomized prevention trials are costly, take a long time to produce results, and require large numbers of patients. Short-term, phase 1-2 biomarker modulation prevention trials are practical ways to study potential chemopreventive agents (16) that may show promise for future large-scale trials. Dasatinib, a potent oral tyrosine kinase inhibitor against the Src family kinases, BCR-ABL, platelet-derived growth factor receptor, c-KIT, and ephrin receptor kinases, has displayed anti-proliferative activity against solid tumors and is approved for use in patients with chronic myelogenous leukemia (17) and Philadelphia chromosome-positive acute lymphoblastic leukemia (18).

Several biomarkers associated with breast cancer could be evaluated as potential candidates for short-term phase I and phase II breast cancer prevention trials. The insulin-like growth factor (IGF) signaling pathway plays a vital role in regulating cell proliferation and apoptosis. It is known that IGF-1 and its binding proteins are associated with an increased risk of breast cancer (19). Ki-67, a proliferation index of neoplasm, is well-known as a prognostic and predictive marker for cancer assessment in patients (20). Additionally, cytomorphology has been evaluated as a potential biomarker for breast cancer risk and has been demonstrated to be useful in the context of short-term prevention studies.

In this short-term biomarker modulation prevention study, the aim was to establish the effect of treatment with dasatinib in women who are at increased risk for a second, contralateral, primary breast cancer by evaluating the modulation of a panel of potential biomarkers including IGF-1, IGF-binding protein (IGFBP)-1, IGFBP-3, and Ki-67, as well as cytological findings in normal, but high risk breast tissue and serum samples. Our goal was to understand the pathway involved in ER-negative breast cancer development and progression to inform future studies with agents targeting the Src pathway, ultimately leading to the development of prospective phase 3 studies aimed at ER-negative breast cancer prevention. The toxicity of dasatinib was also assessed in this phase 2 pilot study.

Materials and Methods

Patient Eligibility

Patients diagnosed with ER-negative invasive breast cancer at The University of Texas MD Anderson Center were offered participation in this prospective study. Eligibility criteria included: histologically confirmed stage I, II, or III ER-negative (defined as <10% of tumor cells positively stained for ER expression by immunohistochemistry) breast cancer; completion of all adjuvant therapy, including surgery, chemotherapy, and radiation therapy, if indicated; and an intact contralateral breast. The study was reviewed and approved by the University of Texas MD Anderson Institutional Review Board, and all subjects provided written informed consent.

Study Design

After providing informed consent, eligible patients underwent baseline blood sampling and random, periareolar fine-needle aspiration (FNA) of the contralateral unaffected breast for biomarker evaluation. Patients were randomized in a 1:2:1 fashion to no treatment (control) or treatment with dasatinib at 40 or 80 mg/day for three months (arms A, B, and C, respectively). Patients returned to the clinic at one month for evaluation and received a follow-up telephone call at two months for toxicity assessment. At the end of three months, patients underwent a second blood sampling and repeat FNA and toxicity assessment. Participants were evaluated if they received at least 75% of their assigned treatments.

FNA Samples and Cytological Evaluation

FNA and slide preparations were performed as described previously (21). Briefly, patients underwent FNA of the intact opposite breast. In all patients, eight FNA passes were performed: four at the 3 o'clock position and four at the 9 o'clock position. Following injection of 2 mL of 1% lidocaine, the aspiration needle was moved in multiple directions to ensure sampling of most of the breast tissue, with emphasis on areas of dense breast tissue, where proliferative glandular tissue may often be present. All of the FNA samples were pooled in 5 mL of CytoLyt solution (Hologic Inc. Marlborough, MA, USA).

Cytological samples were prepared using the ThinPrep technique (Cytyc Corporation, Marlborough, MA, USA). One slide per patient was subjected to Papanicolaou staining for cytological diagnosis; the remaining slides were saved in a tissue bank for biomarker studies as per the study protocol. Sample adequacy was defined as having more than 10 epithelial cells on the slide, and sample cellularity was scored based on the number of epithelial cell groups/clusters on the slide as follows: group 1+, one to three groups; group 2+, four to six groups; and group 3+, more than six groups. All slides were assessed by a single expert breast cytopathologist (N.S). Cytological diagnoses were based on previously published criteria (22). The cytological categories used were non-proliferative epithelium (normal), hyperplasia without atypia (benign), atypical hyperplasia, and malignant lesion.

Serum Biomarkers

Blood samples were processed into serum fractions. The serum was frozen at -80°C for analysis of IGF-1, IGFBP-1, and IGFBP-3. IGF-1, IGFBP-1, and IGFBP-3 levels were measured using enzyme-linked immunosorbent assay kits from R&D Systems (Minneapolis, MN, USA) according to the manufacturer's instructions. Baseline and 3-month serum samples were analyzed at the same time.

Statistical Analysis

The primary endpoint was evaluation of Ki-67 changes in pre-treatment and post-treatment FNA samples. We assumed that the change of Ki-67 after the treatment would be positively associated with the dose level. Ki-67 was measured as a continuous variable and assessed by a one-way ANOVA followed by Dunnett's multiple comparison test comparing the change of Ki-67 of each of the two treated groups with control. Secondary endpoints included changes in cytology in high-risk breast tissue and IGF-related serum biomarkers in pre- and post-treatment samples. Enrollment of 66 patients was planned so that attrition would leave at least 60 patients for evaluation with 1:2:1 randomization to the three arms. Patients were evaluated if they had paired pre-and post-treatment serum and/or FNA samples for biomarker analysis. The standard deviation (SD) was about 10% for a single Ki-67 measurement at pre- or post-treatment. The SD of Ki-67 modulation is also 10% based on the conservative assumption that the correlation coefficient of the Ki-67 level before and after treatment is 0.5. As a result, a Ki-67 change of 10% is indicted by an effect size of 1. Assuming an effect size of 1 and a significance level of 0.05, a one-way design with sample sizes of 15 and 30 in the two treatment groups and 15 in the control group can yield an any-pair power of 0.87. The any-pair power is the probability of detecting a significant difference between any treatment groups and the control group. The effect size is the standardized mean difference between a treatment group and the control group, defined as the ratio of detectable difference between the two groups and the common SD within the groups. The difference in the levels of IGF-related serum biomarkers before and after treatment with dasatinib for each patient was summarized and compared between the three study arms using a Kruskal-Wallis test. The McNemar test was used to investigate if there was any difference in cytology before and after treatment.

Results

Patient Characteristics

Twenty-six patients were enrolled in this prospective study, 24 of whom were eligible and randomized. However, 23 patients started their assigned treatments because one patient withdrew consent after randomization within one week and never started treatment.

Characteristics of the 23 patients are shown in Table 1. Their median (range) age was 60.3 (30.7–74.4) years, and all were women. The patients underwent baseline FNA and had blood drawn before starting treatment.

Compliance during the study was high, with 20 patients (87%) completing their assigned treatment. Three patients discontinued dasatinib use early because they withdrew consent (within 2 weeks, 1 month, and 2.5 months, respectively) for reasons unrelated to toxicity. Eighteen patients underwent post-treatment FNA. Two of these patients completed at least 75% of the assigned treatment but did not return for FNA and blood draws. Therefore, they were included in the toxicity assessment but not biomarker assessment.

Toxicity

Toxicity data are reported for all 20 patients who completed study. Dasatinib was well tolerated by the patients as shown in Table 2. We observed no grade 3 or 4 drug-related adverse events. Grade 1–2 adverse effects included fatigue, headache, pruritus, nausea, and other gastrointestinal disorders. In the 40 mg/day arm, one patient experienced a grade 2 fracture that was unrelated to the study treatment. In the 80 mg/day arm, one patient experienced a grade 2 infection that was not related to the study treatment.

Changes in FNA samples

Eighteen patients underwent pre-treatment and post-treatment FNA. The cytological findings are summarized in Table 3. Based on the FNA sample adequacy definition, 14 of 20 patients had non-proliferative benign cellular findings prior to treatment, whereas 7 of 18 had non-proliferative findings after treatment. When we examined the

Table 1. Patient characteristics

	n (%)			
Characteristic	**All randomized patients (n = 23)**	**Arm A: No treatment (n = 5)**	**Arm B: Dasatinib 40 mg/day (n = 12)**	**Arm C; Dasatinib 80 mg/day (n = 6)**
Median (range) age, years	60.3 (30.7–74.4)	53.7 (40.6–63.2)	62.4 (46.1–74.4)	50.8 (30.7–69.6)
Race				
Asian	1 (4)	0	0	1 (17)
Black	4 (17)	2 (40)	1 (8)	1 (17)
Hispanic	4 (17)	1 (20)	2 (17)	1 (17)
White	14 (61)	2 (40)	9 (75)	3 (50)
ER status				
Negative	21 (91)	5 (100)	12 (100)	4 (67)
Low weak	2 (9)	0	0	2 (33)
PR status				
Negative	21 (91)	5 (100)	11 (92)	5 (83)
Positive	2 (9)	0	1 (8)	1 (17)
HER2 status				
Negative	17 (74)	2 (40)	9 (75)	6 (100)
Positive	6 (26)	3 (60)	3 (25)	0
Disease stage				
I	5 (22)	0	4 (33)	1 (17)
II	14 (61)	3 (60)	7 (58)	4 (67)
III	4 (17)	2 (40)	1 (8)	1 (17)

ER: estrogen receptor; PR: progesterone receptor

adequacy of paired pre-treatment and post-treatment FNA samples, we found that only one patient had adequate samples, so we could not assess Ki-67 level or cytological changes. Seventeen of the 18 patients received previous chemotherapy, which may have contributed to the low FNA cellularity yield.

Changes in Serum Biomarker Levels

Of the 20 patients who completed their assigned treatment, 17 underwent both baseline and 3-month measurement of IGF-1, IGFBP-1, and IGFBP-3 in serum: 4 in arm A, 8 in arm B, and 5 in arm C. The differences in serum biomarker levels before and after treatment are shown in Figure 1. We observed no significant differences in the changes in the level of any of these markers in the three arms.

Table 2. Adverse events following treatment with Dasatinib versus no treatment

Adverse event	Two Dasatinib treatment arms			
	Arm B: 40 mg/day (n = 10)		Arm C: 80 mg/day (n = 5)	
	Grade 1 (n)	Grade 2 (n)	Grade 1 (n)	Grade 2 (n)
Alopecia	1	0	1	0
Arthralgia	1	0	0	0
Increased aspartate aminotransferase level	1	0	0	0
Back pain	0	0	1	0
Cough	1	0	1	0
Diarrhea	1	0	1	0
Dizziness	1	0	1	0
Dysgeusia	1	0	0	0
Fatigue	3	0	1	0
Fever	0	0	1	0
Fracture	0	1	0	0
Gastritis	0	0	1	0
Other gastrointestinal disorders	3	0	0	0
Headache	4	0	0	0
Hot flashes	1	0	0	0
Infections and infestations	0	0	0	1
Musculoskeletal and connective tissue disorder	1	0	0	0
Nausea	2	0	2	0
Pain	1	0	0	0
Pain in extremity	0	0	1	0
Peripheral sensory neuropathy	0	0	1	0
Pruritus	2	0	1	0
Rash acneiform	0	0	1	0
Rash maculopapular	1	0	0	0
Renal and urinary disorders	0	0	1	0

Discussion and Conclusion

In this prospective biomarker modulation, breast cancer prevention study of three months of dasatinib-based treatment, we observed no significant differences in serum biomarker levels before and after treatment. Given the very small number of adequate paired samples we could not perform cytological or Ki-67 analysis. Having received previous chemotherapy may have contributed to low cellularity.

Src family kinases are postulated to have roles in insulin and IGF signaling pathways (23, 24). The IGF signaling pathway contains a dynamic network of proteins, including ligands (insulin, IGF-1, and IGF-2), their related receptors (IGF-1R and IGF-2R), and several IGFBPs, that participate in the regulation of human cancer development (25). Many studies have demonstrated a strong positive correlation between circulating IGF-1 levels and breast cancer risk, particularly in premenopausal women (26-30). In light of its mitogenic and anti-apoptotic activity, authors have closely linked IGF-1 with breast cancer progression (31). In this study, no significant differences in serum IGF-1 levels before and after treatment were detected, although the study numbers were small and the duration of treatment was limited to three months.

At least six known IGFBPs bind to IGF-1 and IGF-2 and may regulate their activity. In particular, IGFBP-1, which binds to only a small fraction of circulating IGFs, is thought to be crucial for controlling IGF-1 bioactivity at the cellular level (32). Low LGFBP-1 levels have been linked with increased risk of breast cancer (33). Researchers have studied the IGFBP-1 and IGFBP-3 biomarkers in several chemoprevention trials with different agents, including SERMs and aromatase inhibitors (34-37). We previously reported a significant increase in IGFBP-1 levels in women who received anastrozole-based therapy for six months (37). Likewise, in another study, we observed a significant increase in IGFBP-1 levels in women who received celecoxib-based therapy for six months (38). In this study, we did not see any significant differences in serum IGFBP-1 levels before and after treatment with dasatinib.

Other investigators have reported conflicting data regarding the association between the serum concentration of IGFBP-3, IGF's primary binding protein, and the risk of breast cancer. In some studies, high levels of circulating IGFBP-3 have been linked with decreased risk of breast cancer in premenopausal women (33, 39). In contrast, Renehan et al. (29) found that high concentrations of IGFBP-3 were associated with increased risk of premenopausal breast cancer. Moreover, IGFBP-3 mRNA expression in breast cancer tissue has been associated with poor prognostic factors (hormone receptor negativity, aneuploidy, and high S-phase fractions) (40, 41). Finally, in postmenopausal women with ER-positive breast cancers, Goodwin et al. (42) found that a high level of circulating IGFBP-3 was associated with distant metastasis and recurrence. In this study, we did not see any significant differences in serum IGFBP-3 levels before and after treatment with dasatinib.

Cytomorphology is a potential surrogate endpoint in breast cancer prevention trials. However, several chemoprevention trials failed to detect any changes in cytology after treatment with

Table 3. FNA cytological findings for pretreatment and posttreatment samples

	Cytology			
Cases evaluated	**Acellular**	**Non-proliferative (group 1)**	**Non-proliferative (group 2)**	**Non-proliferative (group 3)**
Pretreatment (n = 20)	6	13	1	0
Post-treatment (n = 18)	11	4	2	1

Sample adequacy was defined as having more than 10 epithelial cells on the slide, and sample cellularity was scored based on the number of epithelial cell groups/clusters on the slide as follows: group 1+, one to three groups; group 2+, four to six groups; and group 3+, more than six groups

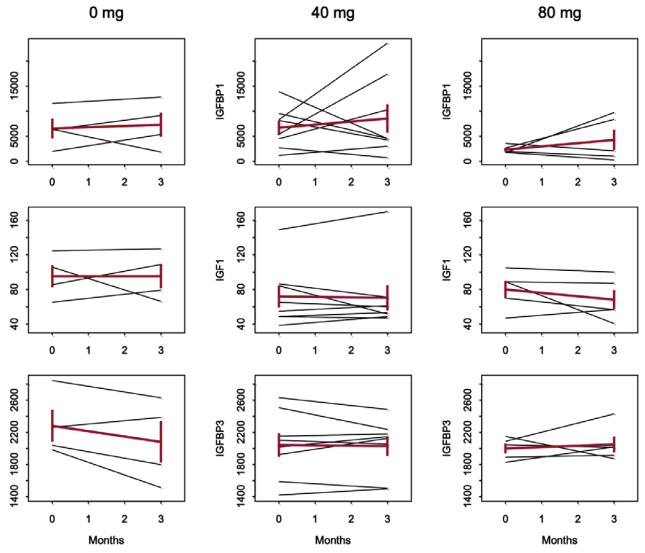

Figure 1. Changes in serum biomarker levels in the three study arms. The red horizontal lines represent the mean levels of each biomarker at each time point. The red vertical lines represent standard deviation. None of the changes differed significantly among the three arms

different agents for prevention (37, 38, 43-45). In this study, given the very small number of adequate paired FNA samples, we could not perform cytological or immunohistochemical marker analysis.

Our study has several limitations and results should only be taken as a starting point for further research. The first limitation is the small study size. However, prospective enrollment in prevention trials requiring analysis of paired breast tissue samples is challenging. Furthermore, it is possible that more tissue can be obtained when breast biopsies are done, but this procedure is likely to be less acceptable for patients compared with FNA. The cost of running biomarker modulation studies using core biopsies would also be higher. The other limitation is that the levels of cytological markers in FNA samples may have been altered as a consequence of previous chemotherapy.

In conclusion, the IGF signaling pathway is known to play a significant role in breast cancer development and progression, based on both epidemiological and molecular studies. Studies targeting this pathway for breast cancer therapy and the development of potential therapeutic agents for breast cancer are ongoing. The research findings concerning Src inhibitors to date highlight the need for further research to better understand the molecular mechanisms by which this signaling pathway drives breast cancer progression. The present study is the first clinical trial designed to determine whether treatment with dasatinib would modulate biomarkers of ER-negative breast cancer development. To date, effective predictive biomarkers for Src inhibition in the clinic have yet to be identified. Detecting phosphorylation of downstream signaling molecules, leading to the initiation of intracellular signaling cascades, such as insulin receptor substrate proteins, may be useful for potential biomarker identification. As a result, further, larger studies are needed to determine the effectiveness of Src inhibitors, ideally new generation agents that are less toxic, for breast cancer prevention.

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Ethics Committee Approval: The study was reviewed and approved by the University of Texas MD Anderson Institutional Review Board 1 on 1/18/2013.

Informed Consent: Written informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.K.A.; Design: B.K.A.; Data Collection and/ or Processing: F.N.A.M., D.D.L., A.M.G., J.E.L.; Analysis and/or Interpretation: D.D.L.; Literature Search: F.N.A.M.; Writing: F.N.A.M., A.M.G., J.E.L., N.K.I., V.V., D.J.B., J.K.L., K.K., D.Y., N.S., B.K.A.

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