

Phase II Study of Propranolol Feasibility With Neoadjuvant Chemotherapy in Patients With Newly Diagnosed Breast Cancer

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Abstract

Purpose: Propranolol regulates angiogenesis in pre-clinical models and reduces distant breast cancer (BC) metastases in observational studies. We assessed the feasibility of combining propranolol with neoadjuvant chemotherapy (NAC) in patients with BC.

Methods: Women with clinical stage II-III BC undergoing NAC [weekly paclitaxel x 12, followed by dose-dense adriamycin/cyclophosphamide (AC) x 4] started propranolol 20 mg PO BID with paclitaxel #1, and increased to 80 mg extended release (ER) PO daily, as tolerated. The primary endpoint was to assess feasibility, defined as at least 75% of patients having at least 80% adherence to propranolol as prescribed. Secondary endpoints included identifying safety, rate of dose holds and modification, and rate of reaching 80 mg ER daily. The proposed sample size was 20 patients.

Results: From November 2012 to September 2015, ten patients were enrolled. Median age was 50.5 years (range, 44-67). All patients had hormone receptor-positive/HER2-negative breast cancer. Three women had grade I bradycardia that resulted in a 1-week delay in increasing the propranolol dose. Ninety percent of women reached the target propranolol dosing of 80 mg ER daily, and 70% took the target propranolol dose until the night before surgery. Of the 4 women who dose reduced propranolol, 1 increased to the target propranolol dose. Mean adherence to propranolol dosing was 96% (range: 91-100%). All patients went to surgery.

Conclusion: Our results support the feasibility of combining propranolol (up to 80 mg ER) with neoadjuvant taxane/anthracycline-based chemotherapy.

Introduction

Angiogenesis is essential in the metastatic potential of breast cancer cells [1,2]. Bevacizumab, the humanized recombinant monoclonal antibody that inhibits angiogenesis by blocking the binding of vascular endothelial growth factor (VEGF) to high-affinity receptors, was initially FDA-approved after demonstrating an improvement in progression-free survival and response rate when administered in combination with chemotherapy in HER2-negative metastatic breast cancer [3]. However, it was revoked by the FDA in 2011 for significant side effects with minimal clinical benefit [4,5]. Thus, there remains a need to identify well-tolerated and inexpensive anti-angiogenic agents for the treatment of breast cancer.

Propranolol, a non-selective beta-adrenergic blocker with non-oncologic treatment indications including cardiovascular disease, has also been shown to regulate angiogenesis in primary breast tumors and reduce distant breast cancer metastases in observational studies [6,7,8,9,10,11]. For example, beta blocker use independently predicted reduced metastatic risk [hazard ratio (HR)=0.43], lower breast cancer-specific mortality at 10 years (HR=0.29), and reduced breast cancer recurrence ($p<0.05$) [12]. In another study, breast cancer-specific mortality was significantly lower for propranolol users (median, 80 mg daily) as

compared to non-users (HR=0.19; 95% CI, 0.06 to 0.60); however, this effect was not seen with the beta-1 blocker atenolol, suggesting the beta-2 adrenergic receptor was the likely mediator [13].

In accordance, there are pre-clinical data demonstrating that beta blockers offer this advantage by impacting the primary breast cancer environment. In the absence of a beta blocker, norepinephrine activates cellular beta-adrenergic receptors, triggering transcription factors to regulate tumor cell proliferation and apoptosis inhibition and stimulating the migration and chemotaxis of triple negative (TN) breast cancer cells [14,15]. This effect is completely inhibited by beta-2 blockers and only partially reduced by beta-1 blockers. It is also seen in estrogen receptor positive cells [16]. These findings support evaluating propranolol as an angiogenic modulator in breast cancer. Thus, we conducted a phase II trial to evaluate whether combining propranolol with neoadjuvant taxane/anthracycline-based chemotherapy was feasible and to assess associated safety and tolerability.

Methods

Participants

Patients were women diagnosed with breast cancer being treated at Columbia University Irving Medical Center (CUIMC) who were administered neoadjuvant propranolol along with 12 cycles of weekly paclitaxel followed by 4 cycles of dose-dense adriamycin and cyclophosphamide (AC) biweekly. Patients with any subtype of breast cancer were eligible, and if a patient had HER2-positive breast cancer, trastuzumab and pertuzumab would be given along with paclitaxel. Inclusion criteria included the following: a) English or Spanish speaking women at least 18 years old, b) any stage invasive breast cancer with a tumor size > 1 cm, c) heart rate (HR) > 60 beats per minute (bpm), d) systolic blood pressure (SBP) >100 mmHg, and e) echocardiogram with ejection fraction (EF) > 50%. Exclusion criteria included: a) QTc prolongation defined by > 470 ms on electrocardiogram (ECG), b) first degree atrioventricular (AV) block on ECG as indicated by PR interval lengthening > 200 ms; second-degree heart block; or third-degree heart block, c) current or recent (within 3 months) beta blocker treatment, or d) history of asthma, given concern for beta-blockade. Patients provided written informed consent. This study was approved by the Institutional Review Board at CUIMC and was listed on clinicaltrials.gov (NCT01847001).

Study Procedure and Treatment

All trial participants completed a baseline physical exam, echocardiogram, and ECG. Once enrolled, patients started propranolol 20 mg PO BID (40 mg daily) the same week that they initiated paclitaxel. Patients received paclitaxel every week for 12 weeks and continued taking propranolol daily, with up-titration to a maximum dose of 80 mg extended release (ER) by mouth (PO) as tolerated. The propranolol dose level was increased every 2 weeks depending on the patient's AEs and vital signs (Table 1). Every other week, patients returned for a physical exam, an assessment of AEs, and a pill count check. At the completion of the 12 weeks of paclitaxel, patients underwent a second ECG and echocardiogram. Subsequently, they began a 4-cycle treatment of AC every 2 weeks, while continuing to take propranolol

daily. A third ECG and echocardiogram were performed upon completion of AC. Patients took daily propranolol until the night before surgery.

Clinico-Pathologic Characteristics

Clinical and pathologic staging were determined based on the American Joint Committee on Cancer (AJCC) TNM Staging Manual, 7th edition. Hormone receptor positivity was defined as estrogen or progesterone receptor positivity of $\geq 1\%$ expression on any biopsy in accordance with the American Society of Clinical Oncology/College of American Pathologist (ASCO/CAP) guidelines.¹⁷ Tumors were considered HER2-positive if they were 3+ by immunohistochemistry (IHC), demonstrated gene amplification with a ratio of HER2/CEP17 ≥ 2.2 by *in situ* hybridization, or had HER2 average copies/cell ≥ 6 on either the core biopsy or surgical pathology specimen [¹⁸]. Race/ethnicity was self-reported as Asian, Black, Hispanic, or non-Hispanic white.

Adverse Events

All AEs were documented and graded per CTCAE v. 4.0. AEs were categorized into cardiac and non-cardiac toxicities. Grade I cardiac toxicities resulted in propranolol being held at the same dose level for 2 weeks, at which point toxicity was re-assessed; if the toxicity had resolved, the propranolol dose could be up-titrated one level (Table 1). Grade II or higher cardiac toxicities would result in the patient being removed from the study. For non-cardiac toxicities, grade I and II AEs resulted in continuing up-titration of propranolol every 2 weeks until 80 mg ER PO daily, per physician discretion. Grade III or IV non-cardiac toxicities related to propranolol resulted in propranolol dose reduction by 1 level, and re-assessment at 2 weeks, until the toxicity was deemed to be \leq grade II.

Chemotherapy doses were delayed or dose-reduced if any of the following toxicities occurred: 1) grade III or IV febrile neutropenia, as defined by temperature $> 38.5^{\circ}\text{C}$ and absolute neutrophil count (ANC) $< 1,000/\text{mm}^3$, 2) platelet nadir $< 50,000$, 3) grade III or IV neuropathy, or 4) grade III or IV non-hematologic toxicities, excluding neuropathy and cardiac toxicities. AEs were categorized based on their relationship to propranolol, chemotherapy, both, or neither. The study was monitored by the Herbert Irving Comprehensive Cancer Center Data and Safety Monitoring Board.

Statistical Analysis

The primary endpoint was to assess the feasibility of giving neoadjuvant propranolol in combination with cytotoxic chemotherapy. The combination was deemed feasible if at least 75% of patients were adherent with taking $>80\%$ of propranolol as prescribed (nonadherence/medication possession ratio of $<20\%$) [^{19,20}]. Patient adherence was determined by the proportion of pills taken to the expected number of pills at biweekly pill checks. Dose holds and discontinuations were not considered as patient non-adherence. Pills that were not returned were assumed to be taken. The proposed sample size was 20 patients, based on an accrual rate of 2 patients per month over a 12-month period. Secondary endpoints were the

following: a) safety and tolerability of neoadjuvant propranolol with chemotherapy, b) dose modifications and holds, and c) ability to achieve the 80 mg ER PO dose any time during the study.

Results

Baseline characteristics

Between November 2012 to September 2015, 10 women consented to the study. The trial was stopped early due to slow accrual. The demographic characteristics are described in Table 2. At baseline, the median age was 50.5 years (range, 44-67) and the median body mass index (BMI) was 26.2 kg/m² (range, 18.9-36.4 kg/m²). Of the 10 patients, 1 patient self-identified as Asian, 1 as black, 5 as Hispanic, and 3 as non-Hispanic white. Six patients were premenopausal and 4 were postmenopausal. The majority of tumors were invasive ductal cancer (90%), stage II (70%), and poorly differentiated (60%). All 10 patients had hormone receptor-positive/HER2-negative breast tumors.

The median baseline heart rate (HR) was 77.5 bpm (range, 61-94 bpm), the median baseline SBP was 125 mmHg (range, 107-138 mmHg), and the median baseline diastolic blood pressure (DBP) was 72 mmHg (range, 63-78 mmHg).

Feasibility, Safety, and Adherence

All 10 patients had greater than 90% adherence rate to propranolol dosing as prescribed over the entire study period. The mean patient adherence was 96% (range: 91-100%). Of the 10 women, 9 (90%) reached the target propranolol dosing of 80 mg ER daily in a median of 28 days (range, 25-49 days). Six of these 9 women (66%) took 80 mg ER until the night before surgery without any AEs necessitating a decrease in dose. The other 3 required a dose reduction due to grade II fatigue after AC #2, grade II QTc prolongation, or grade II intermittent fevers after AC #4. Thus, 40% of women required a dose reduction due to AEs. Of the 3 patients who dose-reduced from 80 mg ER daily, 1 patient returned to taking 80 mg ER daily and continued that dose until the night prior to surgery. One woman had continuation of grade II fatigue, stopped propranolol after AC #3, and did not proceed with AC #4. The other patient completed the study period at 30 mg PO BID. Of the 10 women, only 1 woman did not reach the target propranolol dosing and completed the study at 20 mg BID, which was dose reduced from 30 mg BID because of grade I dizziness. Overall, 70% of patients were able to take the target dose of propranolol 80 mg ER daily until the night before surgery.

All women completed 12 weeks of paclitaxel, except for one woman who was switched to nab-paclitaxel at week 3 due to a transfusion-related, non-anaphylactic reaction and another woman had her fourth dose of paclitaxel postponed one week due to a grade III decreased absolute neutrophil count (ANC) (Table 3). Three of the 10 patients (30%) postponed, but completed, one cycle of AC for 1-2 weeks due to colitis, fatigue, or a central line infection. One of the three women omitted AC #4 due to grade II tremor, weakness, and dyspnea. All reasons for delay were related to chemotherapy, except for fatigue which was

deemed possibly related to propranolol for 1 patient. Overall, 90% of women were able to complete weekly taxane x 12, followed by dose-dense AC.

The median pre-surgical HR was 76.5 bpm (range, 60-117), the median pre-surgical SBP was 111 mmHg (range, 99-134), and the median surgical DBP was 66.5 mmHg (range, 63-82). The median change in HR from baseline to pre-surgery was +2.5 bpm (range, -11 to +23), the median change in SBP from baseline to pre-surgery was -13 mmHg (range, -26 to +7), and the median change in DBP from baseline to pre-surgery was -1.5 mmHg (range, -9 to +6).

Cardiac Adverse Events

Of the reported toxicities, the only cardiac AE related to propranolol use was bradycardia. Three women had a one-time measurement of grade I bradycardia that resulted in 2 women delaying increasing the dose of propranolol by 1 week. The third patient's bradycardia had resolved after initial measurement so no changes were made to propranolol dosing. The bradycardia occurred at the doses of 20 mg BID, 30 mg BID, and 80 mg daily, and all women were able to up-titrate to or remain at 80 mg daily. Other reported cardiac AEs included chest tightness, palpitations, and a right atrial thrombus, but all were deemed not related to propranolol.

Pathologic Response

All patients in the trial had operable breast cancer. At the time of surgery, 1 patient (10%) had a pathologic complete response (pT0pN0), 1 (10%) had residual tumor in the lymph nodes, 4 (40%) had residual tumor in the breast, and 4 (40%) had residual tumor in both the breast and lymph nodes. The patient with the pathologic complete response had invasive ductal carcinoma, T1N1, and completed the course of 80 mg daily of propranolol without a dose reduction.

Discussion

The primary goal of this study was to evaluate the feasibility of combining propranolol with taxane/anthracycline-based neoadjuvant chemotherapy in women with operable breast cancer. Our results demonstrate that the use of propranolol (up to 80 mg ER daily) in this population is safe and tolerable. The majority of women were able to take propranolol at the target dose without significant symptoms and with acceptable adherence. Women who had to dose reduce because of propranolol-related symptoms were mostly able to resume the target dose and did not have prolonged symptoms. Additionally, the majority of the women who were not able to tolerate 80 mg ER of propranolol were able to do so at a lower dose. One patient experienced grade II fatigue and weakness possibly related to propranolol or chemotherapy after AC #3, discontinuing both early. All patients proceeded to surgery. Pathologic response was descriptive.

Recently, propranolol has been studied as pre-operative therapy for many types of cancers, including breast, melanoma, prostate, liver, gastric, and thyroid [21,22,23,24,25]. In a window of opportunity trial for

patients with operable breast cancer, propranolol was associated with a reduction in intra-tumoral mesenchymal proliferation and promotion of immune cell infiltration. These findings are concordant with other recent studies which suggest that concurrent use of propranolol improves tumor response to immunotherapy [26,27]. Additional anti-metastatic properties of propranolol are thought to be through reduction of catecholamine-associated rates of cancer cell proliferation, migration, invasion, and angiogenesis and lymphangiogenesis; induction of apoptosis of cancer cell lines; and inhibition of the catecholamine-induced immunosuppression by inflammatory molecules such as PGE2 [28]. In metastatic breast cancer, propranolol use was shown to decrease biomarkers of metastasis and increase pro-apoptotic epigenetic expression [29,30]. While our study supports the safety of combining propranolol with chemotherapy, there are other potential therapeutic partners that may potentially lead to benefit in combination with propranolol, such as checkpoint inhibitors.

Studying the feasibility and efficacy of utilizing repurposed drugs is beneficial due to lower cost, potentially decreased risk, and more rapid transition into clinical practice than the development of new cancer drugs [31]. Currently, other medications with non-cancer indications that are being tested in the adjuvant setting for breast cancer include metformin and aspirin due to a strong pre-clinical and observational rationale [32,33,34,35,36]. Both are being evaluated in large adjuvant trials to determine their potential benefit in reducing the rates of breast cancer recurrence.

One strength of this study was that frequent pill and symptom checks allowed for close monitoring of propranolol adherence and associated symptoms. While there were a limited number of patients in this study, the study enrolled a racially and ethnically diverse patient population, highlighting its generalizability. This study was stopped early due to slow accrual. Given our small sample size, we were unable to draw conclusions related to changes in HR, SBP, and DBP from baseline and outcomes related to propranolol efficacy.

In conclusion, our study suggests that neoadjuvant administration of propranolol on a daily basis over several months in combination with taxane/anthracycline-based chemotherapy is feasible and tolerable for operable breast cancer. Propranolol use should be considered safe to evaluate in larger studies to determine whether it improves clinical outcomes, including disease-free survival, as well as predictive biomarkers of response.

Declarations

Funding:

No funding to report

Conflicts of interest:

MBH owns stock in Viking Therapeutics, Karyopharm Therapeutics, Regeneron, Eli Lilly, and Amgen. MM is employed by Bristol-Myers Squibb. KK has served an advisory/consulting role for Eli-Lilly, Pfizer,

Novartis, Eisai, AstraZeneca, Immunomedics, Merck, Seattle Genetics, and Cyclocel, owns stock in Grail, Array BioPharma, and Pfizer, and his spouse was previously employed by Array Biopharma and Pfizer.

Availability of data and material:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability:

Not applicable

Authors' contributions:

All authors contributed to the study conception and design. Material preparation and analysis were performed by MBH, SL, and KK. The first draft of the manuscript was written by MBH and KK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval:

This study was approved by the Columbia University Irving Medical Center Institutional Review Board.

Consent to participate:

Informed consent was obtained from all individual participants included in the study.

Consent for publication:

Not applicable

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Tables

Table 1
Neoadjuvant Propranolol Dosing

Dose Level	Propranolol Dose	Reduced Dose if not tolerating
4 (Maximum dose)	80 mg ER po daily	60 mg po daily (in divided dosing)
3	60 mg po daily (in divided dosing)	40 mg po daily (in divided dosing)
2 (starting dose)	40 mg po daily (in divided dosing)	20 mg po daily (in divided dosing)
1	20 mg po daily (in divided dosing)	Off-study
Abbreviation: ER: extended release, PO: by mouth		

Table 2
Baseline demographic and clinical characteristics (N = 10)

Mean age, years (SD)	52.6 (8.0)
Mean weight, kg (SD)	70.2 (17.0)
Mean body mass index, kg/m ² (SD)	26.7 (5.7)
Race/ethnicity	
Asian	1
Black	1
Hispanic	5
Non-Hispanic white	3
Menopause status	
Pre-menopausal	6
Post-menopausal	4
Breast cancer type	
Invasive ductal	9
Mixed ductal and lobular	1
Breast cancer stage, N	
Stage II	7
Stage III	3
Breast cancer grade, N	
1 (well differentiated)	0
2 (moderately differentiated)	4
3 (poorly differentiated)	6
Tumor Subtype	
Hormone Receptor-positive/HER2-negative	10
Mean baseline heart rate (SD)	76.8 (9.0)
Mean baseline systolic blood pressure, mmHg (SD)	121.7 (10.6)
Mean baseline diastolic blood pressure, mmHg (SD)	70.7 (4.9)
Smoking status	
Never smoker	5
Former smoker	3
Current smoker	2
SD: standard deviation	

Table 3 not available with this version.