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Original article

POWERPIINC (PreOperative Window of Endocrine TheRapy Provides Information to Increase Compliance) trial: Changes in tumor proliferation index and quality of life with 7 days of preoperative tamoxifen

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ABSTRACT

Objectives: A decrease in Ki67 during neoadjuvant therapy predicts response to tamoxifen. Previous trials have shown a decreased Ki67 in breast tumors with as little as two or more weeks of preoperative tamoxifen. Shortening the preoperative treatment time in window of opportunity clinical trials makes these trials more attractive to women. POWERPIINC examined the effect of 7 days of preoperative tamoxifen on breast tumor proliferation and patient symptoms.

Methods: Women with untreated stage I/II, ER-positive, invasive breast cancer with no contraindications to tamoxifen were enrolled. Women received 20 mg of tamoxifen for 7 days up to the day of surgery. Proliferation was assessed by Ki67 immunohistochemistry before and after 7 days of tamoxifen. Symptoms and QOL were assessed by the FACT-ES and MENQOL. Adherence was measured by pill counts.

Results: 52 women were enrolled, and 44 were evaluable for Ki67. The median age was 58.5 years, and the median tumor diameter was 1.2 cm. Most women (73%) were post-menopausal. Most tumors were PR positive (88%) and HER2-negative (92%). The Ki67 decreased by a geometric mean of 40% (95% CI 29% −63%), and 73% (95% CI 57%−85%) of women had tumors with decreased proliferation ($p = 0.0001$ by paired *t*-test). Adherence to taking tamoxifen during the preoperative period was 100%. Women reported minimal bother from psychosocial or physical symptoms at baseline or on the day of surgery.

Conclusion: Seven days of tamoxifen showed a similar relative decrease in Ki67 as that reported for longer courses, was acceptable to women, and could be considered for window of opportunity studies.

1. Introduction

The addition of systemic therapy to the surgical treatment of breast cancer has significantly improved survival of patients. A mainstay of systemic therapy for hormone receptor positive breast cancer is endocrine therapy [1,2]. Despite the known advantages, the adherence with short and long term systemic endocrine therapy is less than ideal [3–5]. As many as 10% of patients per year discontinue their therapy, despite its life saving potential. Even in the setting of randomized trials, which likely overestimate adherence compared to the general population, nearly a quarter of patients don't complete their treatment course [6].

Preoperative trials, also called window-of-opportunity trials, are a rapid way of determining the biological effect of cancer drugs.

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Most trials have utilized time lengths of preoperative treatment of 2 weeks or more. Pre-treatment values of Ki67 have been shown to be prognostic, while the change (decrease) in Ki67 with 2 weeks of hormonal therapy appears to predict recurrence free survival [7,8].

Women in the United States are often fearful of delaying surgery for preoperative trials [9]. In our experience, women are more likely to participate in a one week preoperative trial than a trial lasting two weeks or more [10]. Therefore, this trial was designed to determine if a change in proliferation could be detected with short course (7 days) of treatment.

2. Methods

2.1. Study design

PreOperative Window of Endocrine TheRapy Provides Information to Increase Compliance (POWERPIINC) was a single site, single arm window of opportunity study sponsored by the Huntsman Cancer Institute. The hypothesis was that Ki67 expression would decrease by 40% after 7 days of presurgical tamoxifen therapy. The primary outcome was the reduction in Ki67 expression in tumors after 7 days of preoperative tamoxifen. Key secondary objectives included evaluating tamoxifen adherence and symptom patterns at baseline and day of surgery.

2.1.1. Organization and monitoring

The trial was approved by the Huntsman Cancer Institute protocol review committee as well as the University of Utah Institutional Review Board. The trial was registered at clinicaltrials.gov (#NCT01614210). The trial was overseen by the Huntsman Cancer Institute Data Safety Monitoring Committee (DSMC). Stopping rules were that if the DSMC and/or the PI had concern about unexpected safety issues the study would be stopped.

2.2. Eligibility

Women were eligible for this trial if they were age 18 years or older and had been diagnosed with hormone receptor positive (>1% estrogen or progesterone receptor) invasive breast cancer by core needle biopsy. They had to be clinically stage 1 or 2 by AJCC 7th edition and a candidate for surgical therapy. They were required to have an ECOG performance score of 0–1 and not have received chemotherapy or endocrine therapy for breast cancer in the last 5 years. We required that they have paraffin fixed core needle tissue block or biopsy punch available for analysis for proliferative markers and they could not be pregnant or lactating. Exclusion criteria included pregnancy; lactating; prior personal history of uterine cancer, stroke, deep vein thrombosis or pulmonary embolism; current therapy with strong CYP2D6 inhibitors; prior malignancy except for adequately treated cervical cancer in situ, basal cell or squamous cell skin cancer; concurrent coumarin type anticoagulation therapy; or any other contraindication to tamoxifen therapy.

2.3. Study conduct

2.3.1. Enrollment

Women were approached about the trial after a core needle biopsy diagnosing the hormone positive breast cancer and before surgical intervention. Eligible women who gave informed consent were enrolled. After enrollment, baseline data were collected on the patients including demographics of the patient and the tumor. The women then completed two self-administered quality of life measures specific to breast cancer and menopausal/endocrine symptoms: the FACT-ES and the MENQOL [11,12]. The FACT-ES (Functional Assessment of Cancer Therapy- Breast Cancer plus Endocrine Symptoms) is a 46 item measure that combines the FACT-B, a measure of breast cancer quality of life, with 18 items related to endocrine symptoms. The FACT-B component has 4 subscales that include physical well-being, social/family well-being, emotional well-being and functional well-being. In each subscale, higher numbers indicate better quality of life. The MENQOL (Menopause-Specific Quality of Life questionnaire) is a 29 item measure of health related quality of life and symptoms during menopausal or endocrine therapy and includes 4 subscales: vasomotor, psychosocial, physical, and sexual symptoms. Each subscale has a possible score from 1 to 8 with higher numbers indicating greater symptom burden.

2.3.2. Intervention

After baseline data were collected, enrolled patients were given a drug calendar and the Tamoxifen 20 mg prescription covering the 7 day preoperative period. The FACT-ES and MENQOL were repeated on the day of surgery. Adverse events were recorded using CTCAE Version 4.0. Pill counts were performed on the day of surgery.

Proliferation in the tumor was measured in the pretreatment biopsy and on the surgical specimen using Ki67 (Clone MIB-1, Dako) immunohistochemistry. Percent of invasive cancer cells expressing Ki67 in the pre-tamoxifen and post-tamoxifen samples was performed manually by a certified expert pathologist (RF), who counted at least 500 cells in the most representative portion of the invasive tumor, calculating the ratio of Ki67 positive cells over the total number of cells.

2.4. Statistical analysis

For the primary outcome, change in Ki67 after seven days of tamoxifen therapy, a one sample *t*-test was applied to the log-ratio of Ki67 at resections to pre therapy. Assuming standard deviation of 2 [13] and a correlation of 0.5 between the baseline and resection Ki67 values [14], we estimated 47 evaluable patients would give an 80% power to detect a 40% decrease in Ki67 with a one-sided alpha of 0.05. To account for a 10% dropout rate, we planned to recruit 52 women.

For the primary outcome, change in Ki67 after seven days of tamoxifen therapy, a one sample *t*-test was applied to the log-ratio of Ki67 at resections to pre therapy. We planned that if the ratio was not normally distributed, we would use a non-parametric Wilcoxon test.

For the secondary objectives we used descriptive statistics such as means, standard deviations, ranges, proportions, correlation coefficients and confidence intervals to summarize the outcomes associated with tamoxifen adherence, symptoms and quality of life.

3. Results

3.1. Patient characteristics

Between, August 2013 and October 2015, 64 women were approached, 55 agreed to be screened, 52 were enrolled and started tamoxifen, and 44 were eligible for the primary endpoint because pre and post tamoxifen samples were available for Ki67 analysis. (Fig. 1). Patient demographics are shown in Table 1. The women were representative of the population of women with early stage breast cancer, with primarily small tumors in post-menopausal women. However, the ranges of both patient age and tumor size were large.