The Breast 31 (2017) 219–223

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

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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ARTICLE INFO

Article history:
Received 26 September 2016
Received in revised form
31 October 2016
Accepted 18 November 2016
Available online 6 December 2016

Keywords:
Tamoxifen
Ki-67 antigen
Neoadjuvant therapy
Breast neoplasms

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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http://dx.doi.org/10.1016/j.breast.2016.11.016

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.

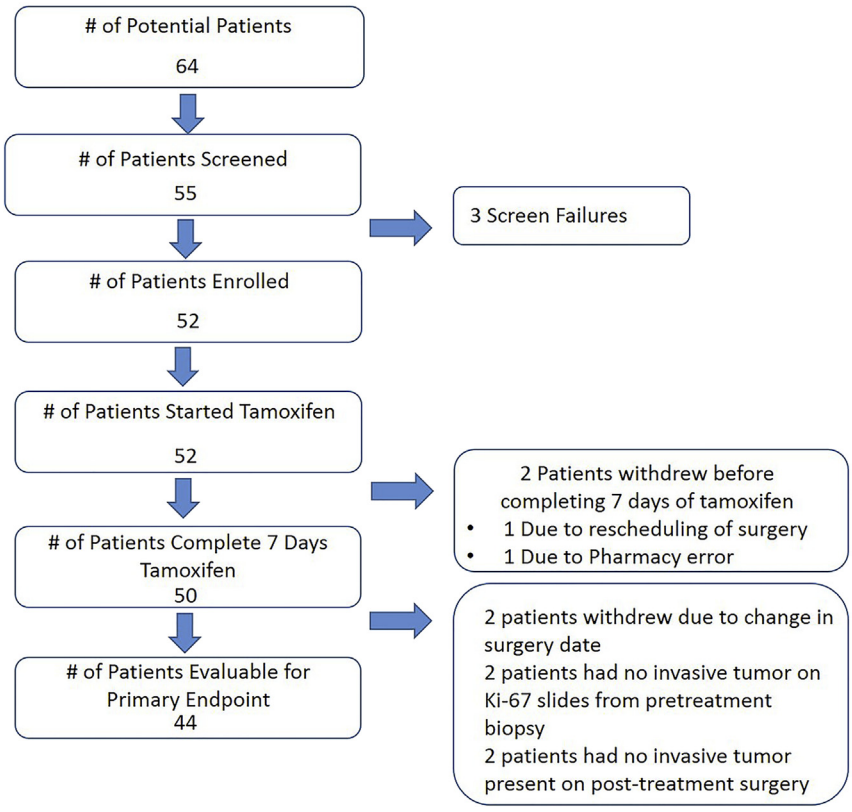

Fig. 1. CONSORT diagram of patient flow through the study.

Table 1
Patient demographic characteristics.

	Median (range) or number (percent)	
	All subjects, N = 52	Primary endpoint, N = 44
Tumor diameter at baseline by US, cm	1.2 (0.1–10)	1.2 (0.1–10)
Age, years	58.5 (38–79)	58.0 (38–79)
Menopausal status		
Pre-menopausal	8 (15)	8 (18)
Peri-menopausal	6 (13)	6 (14)
Post-menopausal	38 (73)	30 (68)
Receptor status		
ER+	52 (100)	44 (100)
PR+	46 (88)	38 (86)
HER2+	4 (8)[a]	3 (7)
Functional status		
Independent	50 (96)	42 (95)
Partially dependent	2 (4)	2 (5)

[a] One subject had missing HER2 status.

3.2. Proliferation

Thirty-two (73%, 95% CI 57%–85%) women had a decrease in Ki67 after 7 days of tamoxifen(Fig. 2). The geometric mean decrease in Ki67 was 40% (95% CI, 29–63%) after seven days of preoperative tamoxifen. The Lillefour's test confirmed normality of the data, so a *t*-test could be used to assess the change in Ki67, showing a statistically significant decrease in Ki67 with seven days of tamoxifen ($p = 0.0001$) (Table 2).

3.3. Patient reported outcomes

Compliance with taking tamoxifen in the 7 day preoperative period was excellent. All women (52 out of 52, 100%) took all of their pills as prescribed. Two women did not take 7 days of tamoxifen, one because the pharmacy incorrectly dispensed 6 pills instead of 7 and one because she went off study after 6 days when her surgery was rescheduled for unrelated reasons. Baseline scores on the FACT-ES, and MENQOL are shown in Tables 3 and 4. There was no significant change in quality of life or in menopausal symptom burden measured on the FACT-ES or MENQOL. There were several small changes seen in psychosocial function, physical QOL and well-being, social well-being, and emotional well-being from baseline to the day of surgery. Changes in FACT-ES (rho = −0.02, p = 0.9), or its subscores, and MENQOL subscores (rho ranged −0.21 to 0.068, p ranged 0.19 to 0.68), did not correlate with changes in Ki-67.

4. Discussion

POWERPIINC successfully demonstrated the feasibility of conducting a perioperative study of tamoxifen with 7 days given

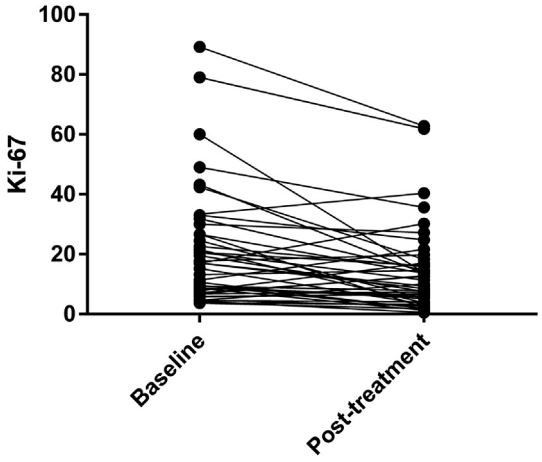

Fig. 2. Before and after graph of the Ki67 for the 44 women evaluable for the primary endpoint.

preoperatively. There was a high acceptance rate (86%) in women willing to participate in the study and take tamoxifen preoperatively. The decrease in proliferation seen with seven days was similar to that seen in other studies using two weeks of preoperative endocrine therapy [15]. It is also similar to what is seen with 10 days of anastrozole in a small study [16]. Our study can thus lay the foundation and provide important background data for planning future perioperative studies of endocrine therapy.

In the European IMPACT trial, decreases in the proliferative marker Ki67 were seen in 84–93% of patients with hormone positive breast cancer after 2 weeks of neoadjuvant endocrine therapy [7,15]. In the P024 trial, after 4 months of neoadjuvant endocrine therapy with either letrozole or tamoxifen, Ki67, pathological tumor size, node status and ER status were each independently associated with recurrence-free and overall survival [17]. Based on these results, several randomized trials are examining the effect short course preoperative endocrine therapy [8]. Results from POWERPIINC reported here suggest that the duration of preoperative therapy can be shortened to 7 days for

Table 2
Before treatment and after treatment Ki67 for all evaluable women.

Variable	N	Median (interquartile range)	Range	P-value (95% CI)
Pre Ki67 (%)	45	17.0 (7.8–26.6)	3.70–89.20	
Post Ki67 (%)	46	9.0 (4.4–16.1)	0.50–62.80	
Log10(Post Ki67/Pre Ki67)	44	−0.15 (−0.38–0.04)	−1.08–0.34	0.0001335 (−0.33–−0.12)

Table 3
Descriptive and comparative statistics for the FACT-ES at baseline and on the day of surgery after 7 days of tamoxifen treatment. Higher numbers indicated higher quality of life.

FACT-ES subscale		Possible range	Mean	Median (range)	P-value (95% CI)
Physical well-being	Baseline (N = 50)	0–28	24.9	26 (15–28)	
	Day of surgery (N = 47)		25.7	26 (15–28)	
	Surgery vs baseline (N = 46)			0 (−3.5–13)	0.24 (−0.49–2.00)
Social/family well- being	Baseline (N = 50)	0–28	23.9	24 (11–28)	
	Day of surgery (N = 47)		24.6	25 (0–28)	
	Surgery vs baseline (N = 46)			1 (-28–10)	0.0141 (0.50–2.83)
Emotional well-being	Baseline (N = 50)	0–24	17.8	18 (7–24)	
	Day of surgery (N = 47)		18.1	19 (7–24)	
	Surgery vs baseline (N = 46)			0 (−6–10)	0.21 (−0.50–2.00)
Functional well-being	Baseline (N = 50)	0–28	21.5	21 (11–28)	
	Day of surgery (N = 47)		21.5	22 (0–28)	
	Surgery vs baseline (N = 46)			1 (−28–10)	0.16 (−0.50–2.00)
Endocrine symptoms	Baseline (N = 45)	0–72	8.1	7 (0–34)	
	Day of surgery (N = 41)		10.7	9 (0–49)	
	Surgery vs baseline (N = 37)			0 (−9–16)	0.21 (−1.0–4.50)
Total scale	Baseline (N = 50)	0–180	151.3	152 (117–180)	
	Day of surgery (N = 47)		151.8	153 (108–176)	
	Surgery vs baseline (N = 46)			1.5 (−54–21)	0.0956 (−0.52–6.67)

Table 4
Descriptive and comparative statistics for the MENQOL at baseline and on the day of surgery after 7 days of tamoxifen treatment. Higher numbers indicate greater symptom burden.

MENQOL subscale		Mean	Median (range)	P-value (95% CI)
Vasomotor	Baseline (N = 50)	1.79	1.33 (1–5)	
	Day of surgery (N = 47)	1.96	1.33 (1–7)	
	Surgery vs baseline (N = 46)		0.0 (−2.33–3.00)	0.61 (−0.33–0.83)
Psychosocial	Baseline (N = 50)	1.88	1.71 (1–4.14)	
	Day of surgery (N = 47)	1.67	1.57 (1–3.71)	
	Surgery vs baseline (N = 44)		−0.143 (−2.29–1.14)	0.033 (−0.57–−0.00045)
Physical	Baseline (N = 48)	1.79	1.58 (1–4)	
	Day of surgery (N = 46)	1.61	1.45 (1–3.21)	
	Surgery vs baseline (N = 43)		−0.11 (−1.90–1.05)	0.020 (−0.32–−0.026)
Sexual	Baseline (N = 48)	1.54	1 (1–6.33)	
	Day of surgery (N = 44)	1.61	1 (1–6.67)	
	Surgery vs baseline (N = 43)		0 (−1.67–2.00)	0.92 (−0.67–0.67)

future trials. Whether the changes in Ki67 after 7 days of tamoxifen correlate with clinical outcomes or adherence is being evaluated as part of the long term follow up of this study and will be reported in the future.

Interestingly, we saw little change in symptom scores in the preoperative tamoxifen therapy period. This was true across both FACT ES and MENQOL scales. Statistically significant small changes in symptoms reported from baseline to the day of surgery may not be clinically significant and actually indicated a slight lessening of symptoms. Thus, taking the 7 days of tamoxifen did not increase symptom burden in the preoperative period. It is possible that the lack of increased symptoms was due to tamoxifen not reaching steady state in 7 days. We plan long term follow up with our quality of life measures and this should help clarify whether any of these factors are related to a woman's willingness to comply with therapy in the long term.

Our study does have a few weaknesses. To maximize the efficiency of the study, we did not collect data on some variables, such as strength of ER-positivity, type of surgery, or CYP450 genotypes. Although these would not impact the primary outcome, they may impact on adherence with endocrine therapy long term. This trial was not randomized, so regression to the mean or retesting effects are possible, but the variation in Ki-67 with repeat biopsies is well described in other studies with placebos or no treatment, which showed no change in mean or median Ki-67 [18,19]. We did not look at other potential markers of tamoxifen sensitivity, such as ER-β or plasma estradiol [20,21]. Ki-67 is known to vary between labs, so all of our samples were analyzed in the same laboratory by the same pathologist [22].

Several open questions remain for future research. Despite the correlation between decrease in Ki67 and freedom from breast cancer recurrence, it is not known whether telling women the amount of Ki67 decrease could increase adherence and/or tolerance to endocrine therapy. It is also unknown if there is a relationship between symptom burden from tamoxifen and either tumoral changes seen with short course preoperative therapy or symptoms experienced during perioperative therapy.

In conclusion, 7 days of tamoxifen decreases proliferation in breast cancer by an average of 40%, which is similar to what is seen with longer courses. Women were willing to participate and take tamoxifen the week prior to surgery without undue symptom burden. Short preoperative trials are feasible and can be used to both explore the biologic effects of novel therapies or to examine the attitudes of and symptoms experienced by women with breast cancer.

Funding source

This work was supported by the National Institutes of Health (P30CA042014 awarded to the Huntsman Cancer Institute).

Conflicts of interest

The authors declare they have no conflicts of interest related to this research.

Acknowledgements

We thank all of the participants in the POWERPIINC trial.

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