Comparison of Anastrozole versus Tamoxifen as Preoperative Therapy in Postmenopausal Women with Hormone Receptor-Positive Breast Cancer

The Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) Trial

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BACKGROUND. The Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) study was a randomized, multicenter study comparing anastrozole with tamoxifen as a preoperative treatment of postmenopausal women with large, operable (T2/3, N0-2, M0), or potentially operable (T4b, N0-2, M0) breast cancer. The effect of preoperative endocrine therapy in patients scheduled for mastectomy or with inoperable tumors at baseline was also investigated.

METHODS. Patients with hormone receptor-positive breast cancer received anastrozole ($n = 228$) or tamoxifen ($n = 223$) with or without chemotherapy for 12 weeks before primary surgery.

RESULTS. Objective responses for anastrozole and tamoxifen occurred in 39.5% and 35.4% of patients, respectively (ultrasound measurements), and 50.0% and 46.2% of patients, respectively (caliper measurements). In hormonal therapy-only patients ($n = 314$), feasible surgery at baseline improved after 3 months in 43.0% of patients receiving anastrozole and 30.8% receiving tamoxifen ($P = .04$). In the intent-to-treat population, improvement in feasible surgery at baseline to actual surgery at 3 months was found to be numerically higher in the anastrozole group compared with the tamoxifen group, although this difference did not reach significance. Drug-related adverse events were reported in 20.2% and 18.1% of patients, respectively, in the anastrozole and tamoxifen groups.

CONCLUSIONS. Anastrozole is an effective and well-tolerated preoperative therapy, producing clinically beneficial tumor downstaging and reductions in tumor volume. These effects enable more minimal surgical interventions in patients scheduled for mastectomy, and mastectomy in patients with previously inoperable tumors. Anastrozole appears to be at least as effective as tamoxifen in this setting, and more effective than tamoxifen in certain clinically relevant subgroups. ***Cancer* 2006;106:2095–103.** © *2006 American Cancer Society.*

KEYWORDS: anastrozole, tamoxifen, preoperative, neoadjuvant, hormone receptor, estrogen receptor, breast cancer, tumor reduction, postmenopausal.

In the 1970s and 1980s, treatment with tamoxifen alone was investigated as an alternative to surgery for older patients with breast cancer.[1–4] Such long-term therapy was used in those old, frail, and infirm patients who could not tolerate surgery. Since that time, the concept of using a medical treatment before surgery has developed. Clinical studies have shown that preoperative cytotoxic chemotherapy offers advantages in the short term, although to our knowledge, no additional effect on disease-free and overall survival has been reported in a comparative study of preoperative versus postoperative chemotherapy.[5–12]

Using a medical treatment before surgery, so-called neoadjuvant

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or preoperative treatment, in patients with breast cancer may result in tumor downstaging. Downstaging may mean that, in some patients, a tumor previously considered inoperable may become operable, or conservative surgery may be performed where previously only mastectomy was possible. Studies reporting the benefits of tamoxifen and, more recently, aromatase inhibitors as neoadjuvant treatment have been published, although to our knowledge there have been no studies comparing the use of neoadjuvant plus adjuvant therapy with adjuvant therapy alone.[4,13–19]

Aromatase inhibitors prevent estrogen biosynthesis by inhibiting the enzyme aromatase, which catalyzes the conversion of adrenal androgens (androstenedione and testosterone) to estrogens (estrone and estradiol). The triazole derivatives (e.g., anastrozole [Arimidex, AstraZeneca, Wilmington, DE]) are a new group of aromatase inhibitors, with combined potency and high selectivity for aromatase and have no discernible effects on adrenal function at the maximally effective aromatase inhibiting doses. The triazoles have been shown to be active at low dose for maximally effective aromatase inhibition. The triazoles have also been shown to reduce circulating estradiol levels in postmenopausal women to the limits of detection of the most sensitive assays.[20–22]

The efficacy and tolerability advantages of anastrozole over existing endocrine treatments have been confirmed in randomized studies in patients with both advanced and early breast cancer. In the early disease setting, anastrozole demonstrated superior efficacy and tolerability compared with tamoxifen. Some noncomparative studies have reported the benefit of anastrozole in the neoadjuvant setting.[13,23]

The main objective of the current study was to investigate the use of preoperative treatment with anastrozole in postmenopausal women with hormone-sensitive breast cancer. The effect of ethnicity on treatment response was also investigated. To this end, Japanese centers were included in this study to provide a cohort of non-white patients. In the longer term, the study also aimed to investigate the effect of anastrozole and tamoxifen treatment on both disease-free and overall survival. The results of the neoadjuvant part of the study are reported herein.

MATERIALS AND METHODS

Patients

Postmenopausal women with large, operable, or potentially operable (i.e., inoperable at baseline, but in the investigator's judgment would be operable after preoperative treatment), locally advanced estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PgR+) breast cancer were recruited from 81 breast cancer clinics in the U.S. (12 centers), Japan (25 centers), and Europe/rest of the world (44 centers).

All patients had to satisfy the following criteria: have proven ER+ and/or PgR+ invasive breast cancer; have operable or potentially operable, locally advanced measurable breast cancer (≥3 cm in greatest dimension); and be postmenopausal. Women were considered postmenopausal if they were age ≥60 years; had undergone a bilateral oophorectomy; were age <60 years with a uterus, and had been amenorrheic for at least 12 months; or were age <60 years with amenorrhea for <12 months and with follicle-stimulating hormone levels within the postmenopausal range. Written, informed consent had to be obtained from each patient and documented.

Patients were ineligible if they had any severe coincident medical disease that would prevent them from receiving surgery, place them at unusual risk, or confound the study results; were unwilling or unable to stop drugs affecting sex hormones (including hormone replacement therapy); had suffered from any invasive malignancy within the previous 10 years (other than carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied); had the human immunodeficiency virus (HIV) or hepatitis B; had received any previous breast cancer treatment or tamoxifen as part of a breast cancer prevention study; or had received treatment with nonapproved drugs during the 3 months before randomization.

Criteria for withdrawal from the study included patients who had completed the study treatment (after 5 years); did not begin randomized therapy; withdrew informed consent; had confirmed disease progression before surgery or confirmed recurrence after surgery; were lost to follow-up; had an adverse event; or were withdrawn at the investigator's discretion.

Study Design

This was a randomized, double-blind, double-dummy, multicenter study. Eligible patients were to be randomized 1:1 to receive a daily dose of either anastrozole at a dose of 1 mg plus tamoxifen placebo or tamoxifen at a dose of 20 mg plus anastrozole placebo (Fig. 1). Concomitant chemotherapy was permitted and patients could receive both chemotherapy and radiotherapy after surgery if appropriate. Eligible patients were to receive surgery at 3 months, then continue receiving study medication as adjuvant therapy for up to 5 years or until recurrence, intolerable toxicity, or withdrawal of patient consent. Patients were to be followed for 30 days after surgery to record any adverse events that were considered an immediate complication of surgery, then every 6 months for assessment of disease-free and overall survival.

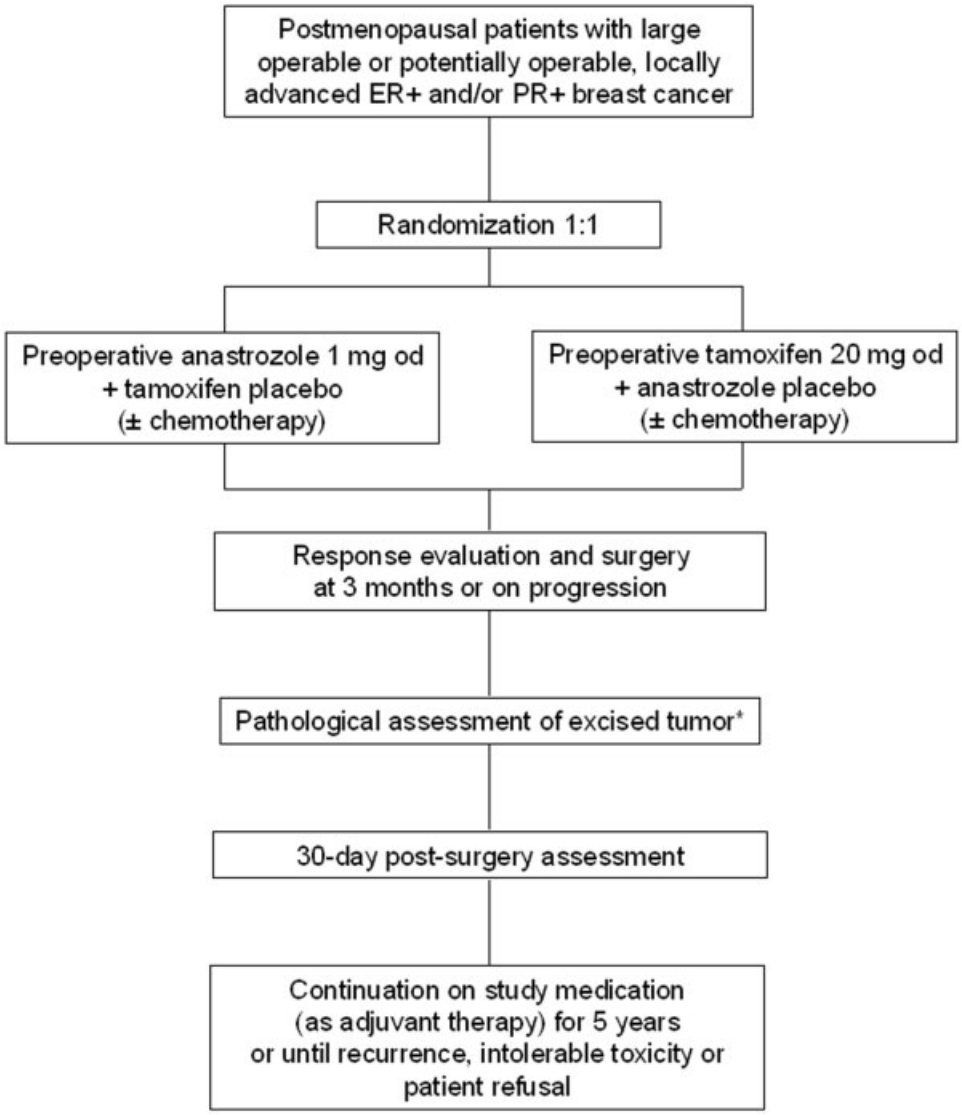

FIGURE 1. The Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial design. ER+: estrogen receptor-positive; PR+: progesterone receptor-positive; od: once daily. *Pathology specimen and unstained slides were stored for possible retrospective assessment of tumor characteristics.

The trial was conducted in accordance with the principles specified in the Declaration of Helsinki and was consistent with International Conference on Harmonization/Good Clinical Practice requirements. All patients provided written, informed consent.

Clinical Assessments

The primary study objective was to compare the differences between anastrozole and tamoxifen in terms of objective response (OR) after 3 months of preoperative therapy, based on ultrasound measurements of tumor size (although response based on caliper measurements was also obtained).

The OR (the primary endpoint) was calculated at 3 months as the percentage of patients with a complete response (disappearance of the tumor), or partial response (≥30% decrease from baseline in the largest dimension of the tumor), according to the World Health Organization Response Evaluation Criteria in Solid Tumors.[24] The largest diameters of the tumors were measured by ultrasound and caliper at baseline and at 3 months, although the response based on ultrasound measurements was the predefined primary endpoint.

Secondary objectives included changes in feasible and actual surgery performed at 3 months compared with baseline assessment, evaluations of correlations between clinical (ultrasound) and pathologic and caliper responses, evaluation of percentage tumor shrinkage at 3 months, comparison of axillary lymph node downstaging from baseline to 3 months, and tolerability assessment. The sample size calculation was based on the primary endpoint, OR, during the preoperative phase of the study. At baseline and im-

mediately before surgery, the investigator recorded the extent of the least invasive feasible breast surgery option at that particular time: whether breast-conserving surgery or mastectomy was needed, or whether the tumor was inoperable. The percentage of tumor shrinkage was calculated as 100 × [(largest dimension at baseline) − (largest dimension at 3 months)]/(largest dimension at baseline), using ultrasound and caliper measurements taken at baseline and immediately before surgery.

Statistical Analysis

Assuming a response rate of 60% with tamoxifen, 220 patients per treatment arm were needed to detect an increase in response with anastrozole to 73% with 80% power using the Fisher exact test and a 2-sided 5% significance level.

Analysis was on an intent-to-treat (ITT) basis. A comparison of OR rates between treatment groups was made using logistic regression, adjusting for treatment and chemotherapy use in the preoperative part of the trial. The treatment effect was tested at the 5% significance level, with the treatment difference expressed as the odds ratio (anastrozole:tamoxifen), with the corresponding 2-sided 95% confidence intervals (95% CI) and *P* value. The logistic regression analyses were repeated with the additional prognostic covariates of age (<65 years vs. ≥65 years) and stage of disease (operable vs. locally advanced), because these were considered important prognostic factors. A comparison of tumor shrinkage between treatment groups was made using an analysis of covariance model adjusting for treatment and chemotherapy use, the treatment effect being tested at the 5% level; the least-squares mean treatment difference and corresponding 95% CI and *P* value were calculated.

A logistic regression model with preoperative chemotherapy as a covariate was fitted to test the between-treatment difference in the improvement rate for extent of surgery at the 2-sided 5% significance level. Odds ratios (anastrozole/tamoxifen) with 95%, 2-sided CI and *P* values were calculated. Only patients with tumors considered inoperable or those requiring mastectomy at baseline were included. Disease-free and overall survival data from the 2 treatment arms will be reported when available.

Since the inception of this study, it has become evident that patients scheduled for mastectomy or inoperable at baseline may benefit from preoperative endocrine therapy.[14] Therefore, these patients were analyzed as a subgroup to assess the effect of preoperative endocrine therapy in enabling surgery and breast-conserving surgery in patients previously considered inoperable or scheduled for mastectomy, respectively. The level of axillary lymph node downstaging was monitored for each treatment group, with axillary lymph node downstaging defined as the lymph node status of the patient decreasing between baseline and 3 months from N1 to N0 or from N2 to N1 or N0. The effect of ethnicity on outcome was also investigated, with outcomes for Japanese patients (patients living in Japan) compared with outcomes for the rest of the population.

RESULTS

Patients

Between August 2000 and September 2002, 451 women from 81 oncology centers in the U.S., Japan, and Europe/rest of the world were randomized to receive treatment with anastrozole ($n = 228$ women) or tamoxifen ($n = 223$ women) (Fig. 2). The groups appeared to be well balanced with regard to patient characteristics and demographics (Table 1). The duration of treatment was similar for the 2 treatment groups, with the majority of patients (163 of 228 [71.5%] for anastrozole, and 155 of 221 [70.1%] for tamoxifen) receiving treatment between 10 weeks and 14 weeks before their presurgical assessment.

Objective Response Rates

The OR rates for the overall population, for those patients who received anastrozole or tamoxifen alone, and the subset of patients who received anastrozole or tamoxifen alone and were scheduled for mastectomy or were inoperable at baseline are shown in Table 2. Although the OR rates observed in this study were lower than those used in the sample size and power calculations, the relative treatment effect, expressed via the odds ratio anastrozole:tamoxifen, is comparable. Therefore, the power of the statistical analysis remained at approximately 80%.

The OR was numerically higher after 3 months' treatment with anastrozole at a dose of 1 mg once daily ($n = 228$) compared with tamoxifen at a dose of 20 mg once daily ($n = 223$), assessed using both ultrasound and caliper, for the overall population and for those patients receiving anastrozole or tamoxifen alone (Table 2). In patients eligible for mastectomy or inoperable at baseline ($n = 262$), the OR rate was significantly greater as assessed both by ultrasound ($P = .03$), and caliper ($P = .04$).

In the overall ITT population, treatment comparisons of OR rate between Japanese patients and the rest of the population revealed no significant treatment ethnicity interaction. Furthermore, the OR rate of Japanese patients, whether based on ultrasound (odds ratio, 0.92; 95% CI, 0.56-1.49) or caliper measurements (odds ratio, 1.11; 95% CI, 0.70-1.76), was

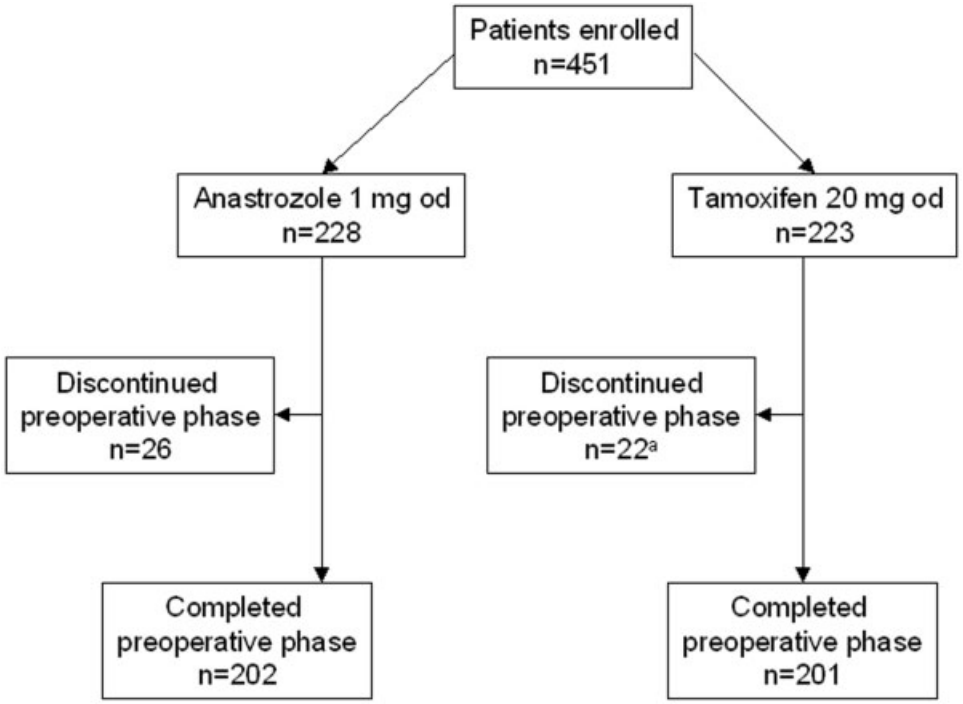

FIGURE 2. The Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial profile. od: once daily. [a]Includes 2 patients who did not receive treatment.

not found to be statistically significantly different from that of patients of other ethnicity ($P = .73$ and $P = .65$, respectively, for ultrasound and caliper measurements).

Improvement in Surgery

Of the 451 randomized patients, 386 would have either required a mastectomy or were considered inoperable at baseline (202 in the anastrozole group and 184 in the tamoxifen group). More patients in the anastrozole group showed an improvement between feasible surgery at baseline and actual surgery at 3 months compared with those in the tamoxifen group (Table 3). In patients assessed at baseline as being eligible for mastectomy or inoperable, there was a relatively higher benefit for anastrozole in both feasible and actual surgery at 3 months. Surgery became feasible in 83 of 202 patients receiving anastrozole (41.1%) compared with 66 of 184 patients receiving tamoxifen (35.9%) (odds ratio, 1.22; 95% CI, 0.80-1.84 [$P = .36$]). Actual surgery improved in 77 of 202 patients receiving anastrozole (38.1%) compared with 55 of 184 patients receiving tamoxifen (29.9%) (odds ratio, 1.42; 95% CI, 0.93-2.17 [$P = .11$]).

In endocrine treatment-only patients, the majority of patients (314 of 451), improvement in feasible and actual surgery at 3 months was also greater with anastrozole. Feasible surgery improved in 67 of 142 patients receiving anastrozole (47.2%) compared with 46 of 120 patients receiving tamoxifen (38.3%) (odds ratio, 1.44; 95% CI, 0.88-2.36 [$P = .15$]). Actual surgery improved in 61 of 142 patients receiving anastrozole (43.0%) compared with 37 of 120 patients receiving tamoxifen (30.8%) (odds ratio, 1.69; 95% CI, 1.01-2.81), a difference that was statistically significant ($P = .04$).

Reduction in Tumor Size and Stage

In the overall ITT population, whether derived via ultrasound or caliper measurements, tumor shrinkage was found to be similar between treatment groups ($P = .54$ and $P = .38$, respectively, for ultrasound and caliper measurements) (Table 4). In patients who received anastrozole or tamoxifen alone and who were eligible for mastectomy or were inoperable at baseline, caliper-measured mean tumor shrinkage was statistically significantly greater in the anastrozole group than in the tamoxifen group (30.7 cm vs. 23.9 cm, respectively; $P = .03$) (Table 4). Ultrasound-measured mean tumor shrinkage demonstrated a similar trend (26.1 cm and 21.1 cm for the anastrozole and tamoxifen groups, respectively); however, this difference did not reach statistical significance ($P = .12$).

Axillary Lymph Node Downstaging

The percentage of patients with N1 or N2 disease at baseline ($n = 208$) exhibiting axillary lymph node downstaging was slightly higher in the anastrozole group (43.4%; $n = 99$) compared with the tamoxifen group (38.5%; $n = 109$). The odds ratio for axillary

TABLE 1
Patient Demographics and Baseline Characteristics in the PROACT Trial

Demographic characteristics	Anastrozole (No. of Patients)	Tamoxifen (No. of Patients)
Age, y	(*n* = 228)	(*n* = 223)
Mean (SD)	67.3 (9.6)	66.7 (9.8)
Range	48.7–91.5	44.1–95.9
Race, no. (%)	(*n* = 228)	(*n* = 223)
White	156 (68.4)	153 (68.6)
Japanese*	48 (21.1)	49 (22.0)
Hispanic	8 (3.5)	7 (3.1)
Afro-Caribbean	4 (1.8)	10 (4.5)
Other	12 (5.3)	4 (1.8)
Baseline characteristics		
Height, cm	(*n* = 226)	(*n* = 219)
Mean (SD)	157.2 (6.8)	156.4 (7.1)
Range	140.0–178.0	137.0–173.0
Weight, kg	(*n* = 225)	(*n* = 217)
Mean (SD)	67.3 (15.0)	67.3 (13.8)
Range	35.0–144.0	38.0–118.0
Disease characteristics		
Feasible surgery, no. (%)	(*n* = 228)	(*n* = 223)
Breast conserving	26 (11.4)	38 (17.0)
Mastectomy	185 (81.1)	168 (75.3)
Inoperable	17 (7.5)	16 (7.2)
Not recorded	0	1 (0.4)
Tumor dimension, cm		
By ultrasound	(*n* = 223)	(*n* = 215)
Mean (SD)	3.6 (1.5)	3.6 (1.4)
Range	1.1–9.5	0.4–8.9
By caliper	(*n* = 228)	(*n* = 222)
Mean (SD)	5.3 (2.1)	5.1 (1.8)
Range	2.1–15.0	2.7–14.0
Receptor status, no. (%)	(*n* = 228)	(*n* = 223)
ER+ and PgR+	159 (69.7)	152 (68.2)
ER+ and PgR-	56 (24.6)	59 (26.5)
ER- and PgR+	3 (1.3)	2 (0.9)
ER+ and PgR unknown	9 (3.9)	9 (4.0)
ER unknown and PgR+	1 (0.4)	0 (0.0)

PROACT: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) Trial; SD: standard deviation; ER: estrogen receptor; PgR: progesterone receptor.
* Patients living in Japan.

lymph node downstaging in the anastrozole group compared with the tamoxifen group was 1.257 (95% CI, 0.718-2.202; $P = .4239$).

Tolerability

Both anastrozole and tamoxifen were well tolerated. Adverse events considered to be study related were reported in 20.2% of patients (46 of 228 patients) in the anastrozole group and 18.1% of patients (40 of 221 patients) in the tamoxifen group. Those events occurring in ≥3% of patients in either group are shown in Table 5. Nearly all the reports of neutropenia were noted in patients who received concomitant chemotherapy. Overall, the safety profiles of the 2 study drugs were consistent with existing tolerability data.

There were 2 deaths in the neoadjuvant + 30 days phase (1 patient in each treatment group). Only 8.5% of patients (38 of 449 patients) overall reported a serious adverse event in the neoadjuvant + 30 days phase and a similar percentage of serious adverse events were reported in the 2 treatment groups (9.6% and 7.2%, respectively, for the anastrozole and tamoxifen groups). Only 1 patient from each treatment group was removed from the study because of a serious adverse event during the neoadjuvant + 30 days phase (for colon cancer not otherwise specified in the tamoxifen group and for respiratory failure in the anastrozole group). The percentage of patients discontinuing from the study in the neoadjuvant + 30 days phase was similar in each treatment group (12.7% and 11.8%,respectively, for the anastrozole and tamoxifen groups). A similar pattern of adverse events and adverse events leading to discontinuation was observed in the neoadjuvant-only phase. No deaths were reported during this time period.

DISCUSSION

Preoperative chemotherapy can downstage large primary breast tumors and render previously inoperable tumors operable, or render operable tumors that require mastectomy suitable for breast-conserving surgery. Although endocrine therapy has fewer side effects than chemotherapy, to our knowledge, few studies to date have evaluated preoperative endocrine therapy in hormone-sensitive breast tumors.

The results of the current study suggest that preoperative therapy with anastrozole is at least as effective as tamoxifen in all patients. The OR rate for the overall population at 3 months was numerically higher for patients receiving anastrozole compared with tamoxifen, although the difference was not statistically significant. Significant benefits for anastrozole over tamoxifen were noted in common clinical scenarios: in patients receiving endocrine therapy only, whose tumors were inoperable or required mastectomy at baseline, anastrozole resulted in a better OR rate and a greater improvement in actual surgery compared with feasible surgery at baseline. Both anastrozole and tamoxifen were well tolerated. The current study results indicate that anastrozole is more effective than tamoxifen at improving surgical outcome in patients who have not received any prior or concomitant chemotherapy. These data support the use of anastrozole alone as a neoadjuvant treatment option for postmenopausal women

TABLE 2
Objective Tumor Responses in the ITT Population at 3 Months According to WHO RECIST Criteria

	Objective response, No. (%)		Anastrozole versus Tamoxifen	
	Anastrozole (No. of Patients)	Tamoxifen (No. of Patients)	Odds Ratio (95% CI)	*P*
All patients	(*n* = 228)	(*n* = 223)		
Ultrasound	90 (39.5)	79 (35.4)	1.24 (0.84–1.83)	.29
Caliper	114 (50.0)	103 (46.2)	1.19 (0.82–1.72)	.37
Endocrine therapy-only patients	(*n* = 163)	(*n* = 151)		
Ultrasound	59 (36.2)	40 (26.5)	1.57 (0.97–2.55)	.07
Caliper	81 (49.7)	60 (39.7)	1.50 (0.96–2.34)	.08
Endocrine therapy-only, mastectomy/inoperable at baseline patients	(*n* = 142)	(*n* = 120)		
Ultrasound	52 (36.6)	29 (24.2)	1.81 (1.06–3.11)	.03
Caliper	69 (48.6)	43 (35.8)	1.69 (1.03–2.78)	.04

ITT: intent-to-treat; WHO RECIST: World Health Organization Response Evaluation Criteria In Solid Tumors; 95% CI: 95% confidence interval.

TABLE 3
Improvements in Feasible Surgery at Baseline to Actual Surgery at 3 Months

	Improved, No. (%)	Odds Ratio (95% CI)	*P*
All patients			
Anastrozole (*n* = 202*)	77 (38.1)†	1.42 (0.93–2.17)	.11
Tamoxifen (*n* = 184*)	55 (29.9)		
Endocrine therapy-only patients			
Anastrozole (*n* = 142*)	61 (43.0)	1.69 (1.01–2.81)	.04‡
Tamoxifen (*n* = 120*)	37 (30.8)		

95% CI: 95% confidence interval.
* Patients who were inoperable or eligible for mastectomy at baseline.
† Five patients responded well to anastrozole and did not undergo surgery.
‡ Statistically significant at the 5% significance level.

with large or locally advanced breast tumors. No significant difference in OR rate was detected for Japanese patients compared with the rest of the study population, indicating that ethnicity does not significantly affect the efficacy of preoperative endocrine therapy.

The current study has similarities to a previous randomized study in which 4 months of neoadjuvant letrozole treatment was compared with tamoxifen in 337 postmenopausal women with hormone receptor-positive breast cancer.[14] In this study, none of the patients were eligible for breast-conserving surgery or were receiving chemotherapy, and so are comparable with the subgroup of patients in our study receiving endocrine therapy only, and whose tumors were inoperable or required mastectomy at baseline. Letrozole was associated with a statistically significantly better OR rate than tamoxifen (55% vs. 36% by clinical palpation [$P<.001$]; and 35% vs. 25% by ultrasound [$P = .042$]), and enabled more patients to undergo breast-conserving surgery (45% vs. 35%; $P = .022$).[22] These results are similar to those for the comparable population in the current study: OR rates were 49% and 36% (caliper-measured; $P = .040$), respectively, and 37% versus 24% (ultrasound-measured; $P = .03$), respectively, and improvement in actual surgery occurred in 43% and 31%, respectively, of patients ($P = .04$) for anastrozole and tamoxifen, respectively. Whether there will be any differences noted in long-term tolerability between patients treated with neoadjuvant letrozole or anastrozole remains to be determined, because there are several differences between anastrozole and letrozole in terms of pharmacokinetics and effects on lipid profiles and steroidogenesis.[25]

To our knowledge to date, there has been some speculation about the effect of tamoxifen therapy on tumor radiosensitivity. However, a recently published exploratory analysis of data with a median follow-up of over 10 years suggests that tamoxifen therapy has no adverse effect on local or systemic control with respect to radiotherapy for node-negative breast cancer. The authors, however, encourage a randomized trial to validate this finding.[26]

Anastrozole is at least as effective as tamoxifen as preoperative therapy for postmenopausal women with breast cancer, and is more effective than tamoxifen in certain clinically relevant subgroups. Anastrozole represents an effective preoperative endocrine treatment option for postmenopausal patients with hormone-responsive breast cancer.

TABLE 4
Percentage Reductions in Baseline Tumor Area at 3 Months

	Mean Percentage Reduction (SD) (No. of Patients)			
	Anastrozole	Tamoxifen	LSM*† (95% CI)	P*
All patients				
Ultrasound	−27.3 (26.0) (n = 200)	−26.2 (32.1) (n = 191)	1.76 (−3.92 to 7.43)	.54
Caliper	−34.3 (26.3) (n = 207)	−32.6 (27.4) (n = 203)	2.29 (−2.82 to 7.40)	.38
Endocrine therapy-only patients				
Ultrasound	−25.2 (25.5) (n = 145)	−19.9 (32.1) (n = 129)	5.22 (−1.64 to 12.1)	.14
Caliper	−33.1 (26.5) (n = 150)	−26.6 (25.2) (n = 138)	6.45 (0.45–12.46)	.04
Endocrine therapy-only. mastectomy/inoperable at baseline patients				
Ultrasound	−26.1 (24.8) (n = 127)	−21.1 (22.8) (n = 102)	4.97 (−1.29 to 11.24)	.12
Caliper	−30.7 (24.0) (n = 131)	−23.9 (23.9) (n = 109)	6.82 (0.70–12.95)	.03

SD: standard deviation; LSM: least square mean; 95% CI: 95% confidence interval.

* Anastrozole versus tamoxifen.

† A LSM difference >0 indicates greater tumor shrinkage for patients receiving anastrozole versus tamoxifen.

TABLE 5
Adverse Events that Occurred at a Rate of ≥3% During the Preoperative Phase of the PROACT Trial

	No. of Patients (%)	
Adverse Event	Anastrozole (n = 228)	Tamoxifen (n = 221)
Nausea	47 (20.6)	38 (17.2)
Alopecia	35 (15.4)	44 (19.9)
Hot flashes	19 (8.3)	16 (7.2)
Emesis	12 (5.3)	16 (7.2)
Headache	15 (6.6)	10 (4.5)
Insomnia	9 (3.9)	11 (5.0)
Fatigue	5 (2.2)	14 (6.3)
Neutropenia	8 (3.5)	11 (5.0)
Anxiety	6 (2.6)	10 (4.5)
Constipation	5 (2.2)	11 (5.0)
Leukopenia	6 (2.6)	10 (4.5)
Anemia	5 (2.2)	10 (4.5)
Diarrhea	8 (3.5)	6 (2.7)

PROACT: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) Trial.

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