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Anastrozole and letrozole: an investigation and comparison of quality of life and tolerability

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This is original work performed in the Edinburgh Breast Unit. It has been presented in abstract form and in presentations at the San Antonio Breast Cancer Conferences.

Abstract

Purpose Previous studies have demonstrated that both anastrozole and letrozole are well tolerated. Letrozole suppresses estrogen to a greater degree than anastrozole in the serum and breast tumor. Concerns have been raised that greater potency may adversely affect patients' quality of life (QOL). *Patients and Methods* One hundred eighty-one postmenopausal women with invasive estrogen receptor-positive breast cancers were randomized to receive either 12 weeks of letrozole followed by 12 weeks of anastrozole or the reverse sequence. One hundred six received immediate adjuvant aromatase inhibitors (AIs) following surgery, and 75 received extended adjuvant therapy. The Functional Assessment of Cancer Therapy Endocrine Subscale (FACT-B-ES) QOL questionnaires were completed to assess QOL on each drug. Additional side-effect profiles were collected. Each patient completed a patient preference form. *Results* Twenty-one patients withdrew before study end, 10/179 (5.6%) while taking letrozole and 4/173 (2.3%) while taking anastrozole ($P = 0.12$). Tamoxifen-naïve patients had a higher mean ES score at entry versus those having extended therapy (66.0 vs. 61.9; $P = 0.001$). There was no significant change in FACT-B-ES (overall) scores or ES (endocrine symptoms subscale) scores while patients were taking anastrozole or letrozole and no significant differences between drugs. Nearly 80% of patients reported one or more side effects with either agent. No differences in frequency, grade, or range of side effects were seen between drugs. Of 160 patients, 49 (30.6%) preferred letrozole, 57 (35.6%) preferred anastrozole, and 54 (33.8%) had no preference ($P = 0.26$, Pearson's chi-squared test). *Conclusion* Both AIs are equally well tolerated. There were no significant differences in QOL scores between the two drugs.

Keywords: Anastrozole • Breast cancer • Letrozole • Quality of life • Tamoxifen

Introduction

Third-generation aromatase inhibitors (AIs) are approved as adjuvant endocrine therapy for postmenopausal women (PMW) with hormone-sensitive breast cancer [1]. The AIs include two broad categories, the reversible nonsteroidal agents, anastrozole and letrozole, and the irreversible steroidal inhibitor, exemestane [2]. These endocrine therapies have been developed to increase efficacy while decreasing the toxicities associated with more traditional estrogen receptor modulators (e.g., tamoxifen). AIs have been shown to improve disease-free survival (DFS) compared with tamoxifen [2]. Given this obvious benefit, the question of which AI to use is important.

Anastrozole and letrozole are now both widely used as adjuvant therapy in the treatment of breast cancer [3, 4]. While previous studies have demonstrated that both of these agents are well tolerated [3, 5–7], there are reported differences in the potency of estrogen suppression between these agents. Studies have consistently demonstrated that letrozole reduces plasma estradiol and estrone sulfate levels to a significantly greater extent than does anastrozole [8-10]. Direct head-to-head trials of AIs are ongoing and will determine the extent to which these differences in potency translate into differences in clinical efficacy. The MA.27 trial is comparing event-free survival in PMW with receptor-positive primary breast cancer treated with anastrozole or exemestane following surgery (ClinicalTrials.gov identifier: NCT00066573), and the Femara Anastrozole Clinical Evaluation trial compares DFS in PMW with hormone receptor-positive (HR+), node-positive breast cancer treated with anastrozole or letrozole following surgery (ClinicalTrials.gov identifier: NCT00248170).

Indirect information from available large-scale trials comparing AIs with tamoxifen indicates that there are differences in clinical efficacy between AIs. Initial adjuvant therapy with

AIs has been examined in the Arimidex, Tamoxifen Alone or in Combination (ATAC), Breast International Group 1-98, and the Tamoxifen, Exemestane Adjuvant Multicenter (TEAM) trials. In terms of efficacy, both anastrozole and letrozole have been shown to improve DFS compared with tamoxifen in patients with HR+ disease, although only letrozole significantly reduced early (at 2 years) distant metastases (DM) events in this population (hazard ratio [HR] 0.73, $P = 0.001$) [3]. A significant reduction in DM events was seen with anastrozole in the HR+ patients but only at 100 months of follow-up [4]. The early improvement in DM events with letrozole has resulted in what appears to be an improvement in overall survival in patients taking letrozole compared with those on tamoxifen [11]. No improvement in survival has emerged from the ATAC study (HR 0.97, $P = 0.7$) [4]. In the ongoing TEAM study, the first planned analysis at 2.75 years failed to demonstrate a significant difference between exemestane and tamoxifen with respect to DFS, although there was a reduction in breast cancer events (exemestane:tamoxifen, HR 0.89, $P = 0.12$) [12].

Patient tolerability and its potential influence on adherence and therapeutic outcome are an important concern [13]. As a class, all AIs are reported to have similar toxicity profiles [3, 5–7]; however, the adjuvant AI trials are not directly comparable because of differences in trial design, particularly with regard to the time at which AI treatment commenced and the variable methods used to collect safety and tolerability data. In the absence of direct comparative data, it is not clear whether the greater activity/potency of letrozole might translate into greater effects on a patient's quality of life (QOL). Differences between agents in terms of QOL and tolerability are likely to be important when selecting the optimal therapy for individual patients. QOL assessments are useful for the clinician to make informed treatment decisions and to identify supportive interventions that improve tolerability and adherence. The aim of this study was to

compare the effects of anastrozole and letrozole on patient tolerability and QOL as assessed by the Functional Assessment of Cancer Therapy - Breast - Endocrine Symptoms (FACT-B-ES, version 4) questionnaire and to determine if there is a patient preference for one agent over the other. Other aims, which are reported elsewhere, were to assess the effects of these two drugs on hormone levels and on markers of bone metabolism.

Methods

Study design

The Anastrozole versus Letrozole: Investigation into Quality of Life and Tolerability (ALQUOT) study was an open-label crossover study of PMW with estrogen receptor-positive breast cancer receiving adjuvant AI therapy [9]. The ALQUOT study examined the tolerability and side-effect profile associated with anastrozole and letrozole. One hundred eighty-five patients were randomized as part of their adjuvant endocrine therapy to receive either 12 weeks of letrozole followed by 12 weeks of anastrozole or 12 weeks of anastrozole followed by 12 weeks of letrozole. Assignment to treatment order was by randomized permuted blocks, undertaken manually using tables of random permutations. This crossover strategy was designed to allow direct comparison of anastrozole and letrozole in the same patient. Three patients withdrew before taking any drugs, and one patient withdrew because she was found to be premenopausal; therefore, a total of 181 patients were enrolled in the study and took one or the other drug. The current analysis was a limited-duration study comparing QOL, tolerability, and morbidity. The study was approved by the Lothian Research Ethics Committee in August 2003 and was conducted to comply with the principles laid down in the Declaration of Helsinki.

Assessments

Patient self-report

FACT-B-ES (version 4) QOL questionnaires were completed at trial entry, after 4 weeks, and after 12 weeks of each drug. FACT-B is a 38-item questionnaire with six subscales assessing physical, social, emotional, and functional well-being, relationship with doctor, and additional concerns more specific to women with breast cancer. The FACT-B has a 5-point Likert-type response scale ranging from 0 to 4 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much). The ES assesses endocrine side effects and comprises 18 items designed for use with the FACT-B [14, 15]. FACT-B-ES is the combined total of the FACT-B and the ES subscale scores.

Nurse interview

Graded adverse events (AEs) were collected using Common Terminology Criteria for Adverse Events (version 3.0) as reported directly by patients to study nurses at 1 month (by telephone), 2 months (by telephone), 3 months (at follow-up for trial), 4 months (by telephone), 5 months (by telephone), and 6 months (at trial follow-up), and for those receiving extended adjuvant therapy, at 9 months (at trial follow-up). At the end of the 24-week study period, each patient completed a patient preference form, which indicated drug preference and reasons for preference.

Statistical methods

Planned sample size

The typical standard deviation between patients using the FACT-B-ES QOL scale (the primary outcome) is 18. In order to have 80% power to detect a difference of 4 units between paired treatments, a sample size of 160 was required. As there was likely to be patient dropout, the sample size was increase by another 20 (12.5%) to allow for this.

Statistical testing

The primary outcome of QOL (FACT-B-ES) was analyzed by Student's t-test for the comparison of baseline data, and by paired t-test for the change from baseline at 3 and 6 months. Both tests were two-sided. The secondary outcomes of patient-reported side effects and individual patient preference were compared by McNemar's test of paired data and chi-squared test, respectively. Patients who withdrew following the first period were included in the comparisons of change to 3 months but excluded from the 6-month analysis and the paired analyses of side effects. Sufficient additional patients were recruited to ensure that the number available for analysis would still exceed 160, at a level of attrition of 5% every 3 months.

Results

Patients/demographics

A total of 181 women (excluding a woman subsequently found to be premenopausal) participated in the study and received at least one dose of trial medication (Table 1). Patients were recruited into the QOL study from November 24, 2003 to April 11, 2006 from the Edinburgh Breast Unit and Queen Margaret Hospital Breast Unit, Dunfermline. One hundred six received immediate adjuvant AIs following surgery, and 75 received extended adjuvant AI therapy following the completion of 5 years of adjuvant tamoxifen treatment. Thirty-eight patients received chemotherapy post surgery before receiving tamoxifen. Eighty-nine patients received letrozole therapy for 3 months followed by anastrozole therapy for 3 months. Ninety-two patients received the reverse sequence: 3 months of anastrozole followed by 3 months of letrozole. The mean age of patients was 63 years (range, 40 to 87 years), the mean height was 161 cm (range, 128 to 183 cm) and the mean weight was 72.8 kg (range, 48.0 to 140.0 kg).

Withdrawal rates

Although both drugs were well tolerated, there were withdrawals for drug-associated reasons; these included joint pain and nausea associated with anastrozole treatment and hot flushes, joint pain, tiredness, headache, hair thinning, and blurred vision associated with letrozole treatment. A total of 21 patients withdrew before study end. Ten of 179 (5.6%) withdrew while taking letrozole, and 4/173 (2.3%) withdrew while taking anastrozole ($P = 0.12$). Withdrawals were not related to drug sequence. Two women withdrew following vaginal bleeding after finishing tamoxifen and before starting letrozole. Similarly, two women withdrew when bleeding developed after the completion of tamoxifen and before the start of anastrozole (Fig. 1). When using the FACT-B questionnaire, if there is a missing item in a scale, then an overall score cannot be produced.

QOL scores and endocrine subscale results of the FACT-B-ES scores

Baseline scores for FACT-B-ES (overall quality of life score which is an additive of the FACT-B and the Endocrine Subscale Score) were 183.6 ($n = 92$; 95% confidence interval [CI], 179.4–187.8) for tamoxifen-naïve patients and 185.4 ($n = 74$; 95% CI, 181.6–189.3) ($P = 0.54$) for patients on prior tamoxifen. Mean changes in FACT-B-ES scores from baseline are shown in Table 2. Mean changes from baseline were recorded at 3 and 6 months. An increase in score indicates a better overall QOL. There was no significant change in overall FACT-B-ES score or endocrine symptoms subscale (ES) score while patients were taking anastrozole or letrozole, and no significant differences between the two drugs were observed. Neither AI had any measureable detrimental effect on overall QOL. Neither the drug sequence nor prior tamoxifen treatment had any influence on the results.

Endocrine Subscale scores for patients were subdivided by whether they had previously taken 5 years of tamoxifen. Tamoxifen-naïve patients had a mean ES score at entry of 66.0, compared with a score of 61.9 for those patients who had received prior tamoxifen ($P = 0.001$). The mean changes in ES scores from baseline are shown in Table 3 (an increase in score corresponds to fewer endocrine-related symptoms). There was a small but non-significant reduction in score in tamoxifen-naïve patients and a small but non-significant increase in score in patients who received prior tamoxifen therapy (A clinically meaningful score on the ES subscale is approximately 0.3 per item; with 18 items, this will be approximately 5). Overall, regardless of the sequence or prior tamoxifen, neither anastrozole nor letrozole significantly affected ES scores.

Side effect/symptom analysis

The percentages of patients with any reported side effect at any time are shown in Table 4. Reporting of side effects was similar for both drugs after the initial 12 weeks of treatment. There were no significant differences in the frequency or range of side effects between anastrozole and letrozole. Nearly 80% of patients complained of one or more side effects with either anastrozole or letrozole. Joint pain occurred with the highest frequency (from 40–52% depending upon the agent and previous tamoxifen exposure). Of the reported events of joint pain, 19–29% of patients experienced grade ≥ 2 pain. Hot flushes, lack of energy, and night sweats were also commonly reported by patients in both treatment arms. Table 5 reports the numbers of women with either no side effects or minimal (grade 1)/none on anastrozole or letrozole. Prior tamoxifen treatment did not significantly influence the reporting of side effects. When minimal (grade 1) side effects were excluded, this result did not change (Table 5).

Given the possibility that symptoms may increase or decrease over time irrespective of drug treatment, comparisons of first- and second-period side effects were performed. Only the number of hot flushes (more in the first period; $P = 0.0009$), joint problems (more in the second period; $P < 0.0001$), and rashes (more in the first period; $P = 0.003$) were influenced by time period. This result was found whether letrozole or anastrozole data were analyzed individually. These differences and the direction of the differences were still present when the subgroup of patients who had taken anastrozole first were analyzed ($P = 0.0164, 0.0009, \text{ and } 0.0253$, respectively) or when the subgroup of patients who had taken letrozole first were analyzed ($P = 0.02, < 0.0001, \text{ and } = 0.046$, respectively). This implies that the time period rather than the drug treatment is more of an influence on the presence of side effects and indicates that certain side effects take time to develop or improve.

Patient preference questionnaires

One hundred sixty patients completed a drug preference questionnaire. Forty-nine (30.6%) preferred letrozole, 57 (35.6%) preferred anastrozole, and 54 (33.8%) had no preference. These results indicate that more than two thirds of women have a preference for one or the other AI. Drug order and previous tamoxifen exposure had no effect on preference. Figure 2 (online) presents the comparison of patient preferences according to previous tamoxifen use. There was no statistically significant preference in any group for any drug. Preferences were based on factors such as generally felt better, fewer hot flushes, less joint pain, less nauseated, less stomach upset, less tired, less depression, less emotional, less flatulence, less vaginal dryness, less abdominal bloating, less hair thinning, less weight gain, and less increased appetite. Table 6 gives patients' reasons for preferring letrozole or anastrozole.

Discussion

The impact on patient QOL is an important consideration in the treatment of breast cancer. Since current treatment recommendations are based upon efficacy results from ≥ 5 years of therapy, it is vital for the clinician to appreciate the long-term impact on QOL parameters over the same timeframe. Deterioration in these parameters may affect adherence and, in turn, have a negative impact on overall treatment outcome. Patients should be able to actively participate in the selection of therapy, weighing the clinical benefit against the side-effect profile and impact on QOL. Regular and standardized QOL assessments will ensure that both the clinician and patient have enough information to make informed decisions about treatment intervention.

Sub-protocol assessments of patients' QOL are being incorporated into increasing numbers of breast cancer trials. To date, QOL sub-analyses have been included in trials comparing AI therapy with tamoxifen (the Intergroup Exemestane Study [IES], ATAC, the National Surgical Adjuvant Study of Breast Cancer [NSAS BC] 03, and the TEAM trial NSAS BC 01 sub-study) and in trials comparing AIs with placebo (MA.17) [16–23]. In general, the majority of results from these trials suggest that the superior efficacy benefits of AIs over tamoxifen are achieved without compromising overall QOL in the short term [16, 18, 20-24].

It has been well established that tamoxifen is associated with some potentially life-threatening AEs, while the third-generation AIs are associated with more predictable, manageable, and preventable side effects [3, 4, 16–18, 20, 21, 25]. This more favorable tolerability profile should translate into an improved impact on a patient's overall QOL, but there are adherence issues with AIs, and significant numbers of patients discontinue therapy because of side effects. This is potentially very worrying, because some symptoms, especially vasomotor symptoms and arthralgias, have been shown to be associated with better outcomes [26]. Given

the lack of direct head-to-head comparisons of different AIs and their impact on QOL, it is difficult for clinicians to make evidence-based decisions when choosing an AI. The results presented here compare anastrozole and letrozole directly in the same patients and assess the effects of these AIs on QOL. This design has significant advantages over comparing groups of women, as it removes a major variable, the patient. Despite the reported greater potency of letrozole, it was as well tolerated as anastrozole, and neither drug had a significant impact on overall QOL. Although patients who completed treatment had little if any measured impact on QOL, side effects with both drugs were common and were reported by 80% of women. These side effects were identical with both drugs and represent a class effect of AIs rather than effects that are limited/restricted to a specific drug. Most patients had a definite preference for either anastrozole or letrozole, with similar numbers of patients preferring each agent.

A similar crossover study by Thomas et al. comparing anastrozole and letrozole in women with breast cancer (N = 72) showed that a patient's preference for either anastrozole or letrozole was related to the patient's adverse events and QOL while taking the drug [27]. In contrast to the current study, which showed similar results for both drugs, the study by Thomas et al. showed that significantly more women chose letrozole, which was associated with significantly fewer adverse events and a significantly better QOL compared with anastrozole [27].

This study has several limitations. It was an open-label, single-institution design with short follow-up and limited patient numbers, and patient reporting is potentially subject to influence from family/friends, support groups, and publically available medical information. Anastrozole is the most widely and frequently used AI in the United Kingdom, and potential social influences for preference must be considered. Despite these limitations and potentially

confounding variables, the data reported here provide a useful framework within which physicians and patients can make informed decisions about initial adjuvant or extended adjuvant AI therapy. Larger-scale analyses in direct comparator trials will be required to confirm the current findings, but such studies have their own limitations. While treatment decisions cannot be made solely on the basis of QOL and reported side-effect profiles, such assessments are an important consideration, as adherence is likely to be significantly affected by a drug's impact on these parameters.

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491

Table 1 Baseline demographic and medical characteristics

Characteristic	Total	A to L	L to A
N	181	92	89
Adjuvant AI treatment			
Immediate, <i>n</i>	106 (59)	53 (58)	53 (60)
(%)			
Extended, <i>n</i> (%)	75 (42)	39 (42)	36 (40)
Age (years)	Mean: 63.6	Mean: 63.0	Mean: 64.2
	Median: 64	Median: 63	Median: 64
	Range: 41–87	Range: 41–84	Range: 41 – 87
Height (cm)	Mean: 161.19	160.34	162.07
	Median: 161.3	160.2	161.5
	Range: 128–182.9	(130-179.2)	(128-182.9)
Weight (kg)	Mean: 72.86	71.95	73.8
	Median: 69.9	69.7	70.2
	Range: 48–140	48-138	50-140
Tumor stage			
T1, <i>n</i> (%)	128 (71%)	66 (72%)	62 (70%)
T2, <i>n</i> (%)	47 (26%)	23 (25%)	24 (27%)
T3, <i>n</i> (%)	3 (2%)	2 (2%)	1 (1%)
T4b, <i>n</i> (%)	2 (1%)	1 (1%)	1 (1%)
T4d, <i>n</i> (%)	1 (0.5%)	0 (0%)	1 (1%)
Nodal status			

N0, <i>n</i> (%)	30 (17%)	15 (16%)	15 (17%)
N1, <i>n</i> (%)	151 (83%)	77 (84%)	74 (83%)
Prior chemotherapy, <i>n</i> (%)	38 (21%)	19 (21%)	19 (21%)
Prior HRT*, <i>n</i> (%)	57 (31%)	28 (30%)	29 (33%)

Abbreviations: AI, aromatase inhibitor; HRT, hormone replacement therapy.

*Patients who had received HRT within 6 months of diagnosis of breast cancer. Distribution of T and N stage within this group was similar to total group T1 42 (74%) and N0 54 (95%).

Table 2 Mean changes from baseline for the Functional Assessment of Cancer Therapy with Endocrine Subscale scores (FACT-B-ES) (overall quality of life score)

Patient population	Drug sequence	Mean change from baseline at 3 months	Mean change from baseline at 6 months
All patients (N = 181)	Letrozole to anastrozole	1.3 (<i>n</i> = 67; 95% CI, -2.2–4.8)*	0.2 (<i>n</i> = 67; 95% CI, -3.5–3.9)
	Anastrozole to letrozole	1.6 (<i>n</i> = 75; 95% CI, -1.8–4.9)	1.7 (<i>n</i> = 74; 95% CI, -1.8–5.2)
Tamoxifen-naïve patients (<i>n</i> = 106)	Letrozole to anastrozole	0.7 (<i>n</i> = 39; 95% CI, -4.1–5.6)	0.5 (<i>n</i> = 38; 95% CI, -4.5–5.5)
	Anastrozole to letrozole	1.3 (<i>n</i> = 40; 95% CI, -3.5–6.0)	0.6 (<i>n</i> = 39; 95% CI, -4.4–5.5)
Prior tamoxifen patients (<i>n</i> = 75)	Letrozole to anastrozole	2.1 (<i>n</i> = 28; 95% CI, -3.2–7.4)	-0.3 (<i>n</i> = 29; 95% CI, -6.0–5.5)
	Anastrozole to letrozole	1.9 (<i>n</i> = 35; 95% CI, -2.8–6.7)	2.9 (<i>n</i> = 35; 95% CI, 2.3–8.2)

Abbreviation: CI, confidence interval.

*Numbers of patients with fully completed data at baseline and 3 months.

Table 3 Mean changes in Endocrine Subscale (ES) scores from baseline

Patient population	Drug sequence	Mean change from baseline at 3 months	Mean change from baseline at 6 months
All patients	Letrozole to anastrozole	-0.5 (<i>n</i> = 74; 95% CI, -2.0–1.0)	-0.7 (<i>n</i> = 72; 95% CI, -2.2–0.9)
	Anastrozole to letrozole	-0.6 (<i>n</i> = 86; 95% CI, -2.0–0.8)	-0.1 (<i>n</i> = 80; 95% CI, -1.6–1.4)
Tamoxifen-naïve patients (<i>n</i> = 106)	Letrozole to anastrozole	-1.1 (<i>n</i> = 45; 95% CI, -2.7–0.6)	-1.1 (<i>n</i> = 42; 95% CI, -3.0–0.8)
	Anastrozole to letrozole	-2.1 (<i>n</i> = 48; 95% CI, -3.7 – -0.5)	-1.6 (<i>n</i> = 44; 95% CI, -3.4–0.3)
Prior tamoxifen patients (<i>n</i> = 75)	Letrozole to anastrozole	0.4 (<i>n</i> = 29; 95% CI, -2.3–0.1)	-0.1 (<i>n</i> = 30; 95% CI, -2.7–2.6)
	Anastrozole to letrozole	1.3 (<i>n</i> = 38; 95% CI, -1.1–3.7)	1.7 (<i>n</i> = 36; 95% CI, -0.7–4.1)

Abbreviation: CI, confidence interval.

An increase in score indicates fewer symptoms.

n = numbers of patients in each cell with complete data for analysis.

Table 4 Side effects as reported directly by patients to study nurses

Symptom	Group	Anastrozole	Letrozole	Anastrozole	Letrozole
		(%), any*	(%), any*	(%) grade $\geq 2^\dagger$	(%) grade $\geq 2^\dagger$
Alopecia	Tamoxifen- naïve	3 (3)	4 (4)	3 (3)	1 (1)
	Prior tamoxifen	2 (3)	3 (3)	0 (0)	0 (0)
Depression	Tamoxifen- naïve	5 (5)	4 (4)	2 (2)	1 (1)
	Prior tamoxifen	4 (5)	4 (6)	2 (3)	1 (1)
Diarrhea	Tamoxifen- naïve	4 (4)	9 (9)	1 (1)	1 (1)
	Prior tamoxifen	2 (3)	2 (3)	1 (1)	0 (0)
Headaches	Tamoxifen- naïve	12 (12)	8 (8)	5 (5)	6 (6)
	Prior tamoxifen	6 (8)	9 (13)	4 (5)	2 (3)
Hot flushes	Tamoxifen- naïve	32 (31)	37 (36)	12 (12)	18 (18)
	Prior	29 (40)	25 (35)	16 (22)	15 (21)

	tamoxifen				
Irritability	Tamoxifen-	3 (3)	3 (3)	–	–
	naïve				
	Prior	0 (0)	3 (4)	–	–
	tamoxifen				
Joint pain	Tamoxifen-	51 (49)	53 (52)	23 (22)	30 (25)
	naïve				
	Prior	29 (40)	37 (52)	14 (19)	14 (20)
	tamoxifen				
Joint stiffness	Tamoxifen-	6 (6)	2 (2)	–	–
	naïve				
	Prior	2 (3)	0 (0)	–	–
	tamoxifen				
Lack of energy	Tamoxifen-	15 (14)	25 (25)	1 (1)	5 (5)
	naïve				
	Prior	14 (19)	6 (8)	3 (4)	1 (1)
	tamoxifen				
Lightheaded/ dizzy	Tamoxifen-	4 (4)	6 (6)	0 (0)	3 (3)
	naïve				
	Prior	4 (5)	5 (7)	0 (0)	0 (0)
	tamoxifen				
Nausea	Tamoxifen-	9 (9)	6 (6)	1 (1)	1 (1)
	naïve				

	Prior	2 (3)	4 (6)	0 (0)	0 (0)
	tamoxifen				
Night sweats	Tamoxifen-	11 (11)	14 (14)	4 (4)	6 (6)
	naïve				
	Prior	4 (5)	7 (10)	2 (3)	4 (6)
	tamoxifen				
Sleeping	Tamoxifen-	2 (2)	8 (8)	1 (1)	4 (4)
difficulties	naïve				
	Prior	4 (5)	3 (4)	1 (1)	1 (1)
	tamoxifen				
Vaginal	Tamoxifen-	1 (1)	0 (0)	1 (1)	0 (0)
discharge	naïve				
	Prior	1 (1)	2 (3)	0 (0)	1 (1)
	tamoxifen				

*Numbers in these columns represent the number of side effects of any grade during each 12-week treatment period.

†Numbers in these columns represent the number of grade 2 side effects (graded using Common Terminology Criteria for Adverse Events Version 3.0) or higher reported at any time with either drug.

Table 5 Side effects as reported directly by patients to study nurses subdivided by prior tamoxifen status

Symptom	Group	Anastrozole (%)	Letrozole (%)
No side effects	Tamoxifen-naïve	23 (22)	20 (20)
	Prior tamoxifen	10 (14)	25 (35)
Minimal (grade 1) / no side effects	Tamoxifen-naïve	58 (56)	59 (58)
	Prior tamoxifen	48 (65)	34 (48)

Numbers represent the number of any grade side effects during each 12-week treatment period.

Table 6 Patients' stated reason for drug preference

Reason for preference	Patient preference	
	Letrozole	Anastrozole
Generally felt better	67% (16/24)	94% (30/32)*
Less tired	29% (7/24)	69% (22/32) [†]
Less sick	29% (7/24)	38% (12/32)
Less tummy upset	29% (7/24)	31% (10/32)
Fewer hot flushes	33% (8/24)	53% (17/32)
Fewer joint pains	42% (10/24)	50% (16/32)

* $P = 0.009$.

[†] $P = 0.003$.

Fig 1. CONSORT diagram.

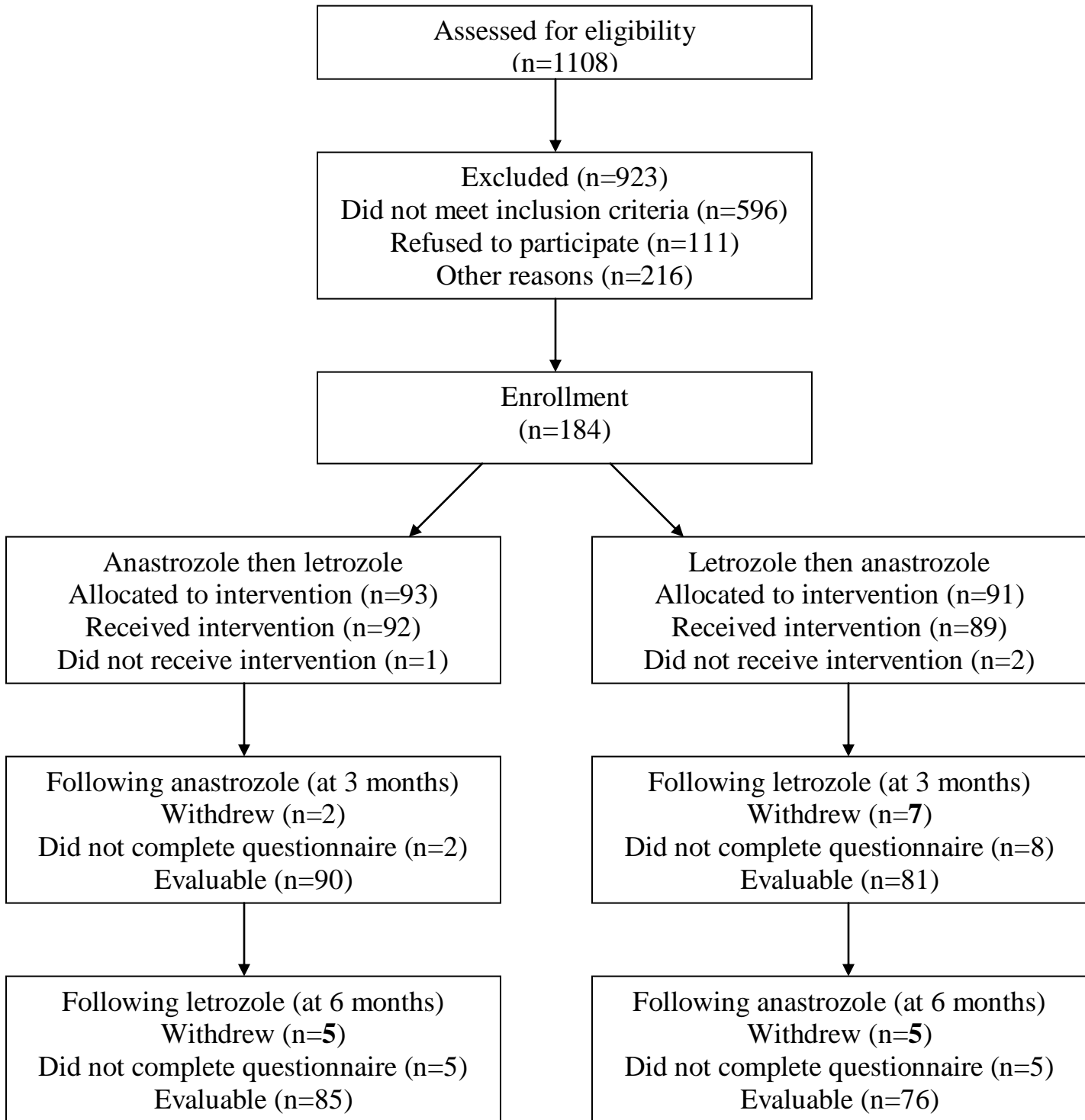


Fig 2. Results from the drug preference questionnaire (online only).

