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*Original Article*

# Giving Patients a Choice Improves Quality of Life: A Multi-centre, Investigator-blind, Randomised, Crossover Study Comparing Letrozole with Anastrozole

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**ABSTRACT:**
*Aims:* Although the third-generation aromatase inhibitors are generally well tolerated, side-effects still occur in up to 40% of women. As more women are taking these drugs for longer, the issue as to which version is better tolerated is now a significant patient concern. This study aimed to assess whether tolerance for either letrozole or anastrozole can differ for each individual in terms of early quality of life (QoL), whether patients welcome being given a preference and whether this correlated with formal toxicity scoring.
*Materials and methods:* A single-blind, crossover trial, with 72 women with breast cancer who had experienced tamoxifen failure. Randomised to either letrozole 2.5 mg or anastrozole 1 mg, for 4 weeks, 1 week off, then crossover for 4 weeks.
*Results:* Patients were confidently able to choose which drug suited them best (letrozole 68%, anastrozole 32%; $P < 0.01$). Fewer patients, when taking letrozole, experienced adverse events than when taking anastrozole (43% vs 65%; $P = 0.0028$). QoL was better when patients were taking letrozole than when they took anastrozole ($P = 0.02$).
*Conclusions:* As toxicity and QoL strongly correlated with patient preference for either drug, albeit with a tendency towards letrozole, this suggests that patient preference is now a legitimate and useful end point for future crossover studies. In routine practice, women would warmly welcome extra involvement in the decision-making process via a crossover manoeuvre if side-effects develop, whichever aromatase inhibitor is prescribed initially. Thomas, R. *et al*. (2004). *Clinical Oncology* **16,** 485–491


**Key words:** Aromatase inhibitors, breast cancer, post-menopausal, quality of life

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## Introduction

Letrozole and anastrozole are non-steroidal aromatase inhibitors that suppress oestrogen production more selectively and potently than earlier inhibitors [1,2]. In post-menopausal women with advanced breast cancer for whom tamoxifen had failed, letrozole and anastrozole were more effective and better tolerated than either first-generation aminoglutethimide or the progestin megestrol acetate [3–5]. As first-line therapy for advanced breast cancer, letrozole achieved longer survival than tamoxifen during the first 2 years of treatment [6,7], whereas anastrozole and tamoxifen had equivalent activity [8–10]. In the neoadjuvant setting, letrozole was more effective than tamoxifen in tumour downstaging [3]. As first-line adjuvant treatment for breast cancer, letrozole, given after tamoxifen and examestane [11], has demonstrated advantages over tamoxifen alone [12], and other adjuvant trials are in progress [2,13]. Early results also indicate that anastrozole is significantly superior to tamoxifen in disease-free survival, and that there is a significantly lower risk of anastrozole-treated patients developing contralateral primary breast tumours [14].

For these reasons, aromatase inhibitors have been moved into the first-line metastatic and neoadjuvant settings and, in the near future, may well have a role in adjuvant therapy of post-menopausal women. Consequently, increasing numbers of women are taking these drugs earlier and for longer periods in their treatment pathway [15]. Although letrozole and anastrozole are generally well tolerated [16], nearly half of treated patients may experience some adverse effects [1,3,4]. The issue of whether an individual patient

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would tolerate one aromatase inhibitor over another is, therefore, now a significant patient concern, particularly for those with little or no symptoms of their disease and attempting to lead a normal lifestyle. Patients with advanced or metastatic breast cancer, who are already burdened by disease symptoms, would also benefit from agents that minimise additional adverse events resulting from treatment.

Letrozole and anastrozole inhibit the aromatase enzyme in similar ways [17,18], but they have different chemical formulations and result in different levels of oestradiol suppression. It cannot be assumed that they are equally tolerated, especially as quality of life (QoL) has not been compared directly in a clinical setting. It also cannot be assumed that an individual patient has similar tolerance to both drugs or that patients are not able to decide for themselves. Therefore, we conducted a randomised, investigator-blind, crossover trial in post-menopausal patients with breast cancer who had failed, or were intolerant to, tamoxifen therapy to compare the tolerability and QoL associated with the two aromatase inhibitors. This crossover design allowed a within-patient comparison of the two agents. It enabled patients to choose which drug suited them best and tested the hypothesis that giving patients a choice leads to greater QoL scores.

## Methods

### *Patient Selection and Treatment*

Eligibility requirements for this multi-centre, randomised study were as follows: oestrogen and/or progesterone receptor-positive breast cancer that had either progressed on tamoxifen or become intolerant to that agent; post-menopausal status; World Health Organization (WHO) performance status 0–2; life expectancy of at least 6 months; no central nervous system metastasis or extensive liver metastasis; and no prior treatment with aromatase inhibitors. Enrolled patients ($n = 72$) were initially randomised (blocked within centre) to receive either letrozole (Femara®) 2.5 mg daily or anastrozole (Arimidex®) 1 mg daily, as oral tablets. Treatment was blinded to the investigator, but not to the patient. After 28 days (phase 1), followed by a 6-day washout period to permit systemic clearance of the first agent, patients were crossed over to the other agent for 28 days of treatment (phase 2) conducted in the same single-blind fashion. At the end of phase 2, patients were given the choice of continuing off-study with either of the two agents.

### *Quality of Life Assessment*

QoL was measured with the Functional Assessment of Cancer Therapy-general scale together with the breast cancer (FACT-B) and endocrine (FACT-ES) subscales, which cover physical as well as psychological symptoms and, in combination, are designed specifically for women with breast cancer who receive hormonal therapy [19,20]. The instrument has been validated in the advanced breast cancer setting, with good internal consistency, reliability, patient acceptability and sensitivity to clinically significant change [19]. A questionnaire was circulated on days 0, 7 and 28 for phase 1, and days 34, 41 and 62 for phase 2. Patients completed the questionnaire at home and then posted it back to the trial centre. At all visits, adverse effects were evaluated by the physician according to US National Cancer Institute common toxicity criteria, using a 0–4 scale (0 = no symptoms; 1–4 = progressive grade, or degree, of symptoms).

The primary end point of this trial was a comparison of total QoL scores after 1 month on each drug. Secondary analyses included comparison of final total scores after adjustment for baseline values and comparison of the individual subscale scores. All randomised patients who received trial medication, and from whom at least one evaluation was obtained after crossover, were included in the analysis. At the end of the study, patient preference for one of the two agents was determined by their choice of continuing treatment. To avoid possible bias at the end of the trial, this choice was stated in writing by patients before consultation with the physician. Similarly, completed QoL questionnaires were posted to the trial centre after completion.

### *Statistical Methods*

The computer package used for this trial analysis was STATA (www.stata.com) version 7. Mean total QoL scores were compared between the two treatment arms. Mean total QoL scores were compared after adjustment for differences in baseline QoL scores between the two treatment arms. Patient demographics and baseline characteristic data from all participating centres were combined and summarised. Adverse events and patient preference data were analysed using the Wilcoxon signed ranks, Chi-square test and t-test.

Individual questions were more than 90% complete except for the sex-related questions, and 94% of questionnaires had five or fewer missing items. Missing data were imputed per protocol by carrying forward the value from the previous questionnaire, to enable calculation of a summary score (excluding sex-related questions) for all patients who provided QoL responses for both agents. The modal score of the responses in the same arm was imputed for questions never answered by a respondent. Analysis was undertaken blind to treatment allocation. A higher score indicated a poorer QoL in this study.

A power calculation was undertaken before the start of the study. For a power of 80% and two-sided significance level of 5%, it was estimated that 66 patients were required to allow the detection of a difference in mean score of 8.1 between the two drugs. In the event, there was less within-patient variability in the scores than we anticipated, and a difference of 5.1 points reached statistical significance at the 5% level. Ten per cent more patients were recruited to maintain adequate numbers in the event of missing data.

**Table 1 – Patient demographics**

| | | Initial treatment | |
|---|---|---|---|
| | Both arms | Letrozole | Anastrozole |
| All patients, *n* (%) | 72 (100) | 37 (51) | 35 (49) |
| Patients with progressive disease on tamoxifen, *n* (%) | 61 (85) | 34 (56) | 27 (44) |
| Patients intolerant of tamoxifen, *n* (%) | 11 (15) | 3 (27) | 8 (73) |
| Patients with bone-only metastasis, *n* (%) | 22 (31) | 11 (50) | 11 (50) |
| Patients with visceral metastasis in the lungs or liver, *n* (%) | 15 (21) | 9 (60) | 6 (40) |
| Evaluable patients, *n* (%) | 65 (90) | 34 (52) | 31 (48) |
| Mean age, years (range) | 67 (45–95) | 66 | 68 |

## Results

### *Patient Demographics*

Of the 72 patients accrued to this study, 61 (85%) had disease progression on first-line tamoxifen, whereas 11 (15%) developed intolerance to that agent without evidence of progressive disease (Table 1); 59% had distant metastasis. Five of the 72 patients enrolled were not evaluable in the final analysis because of death (one patient) and patient withdrawal before crossover ( four patients, two taking letrozole and two taking anastrozole). A further two patients could not be included in the QoL analysis despite completing the study and the preference questionnaire because they failed to complete a QoL questionnaire. Of the seven patients excluded, three had been randomised to letrozole and four to anastrozole. For the remaining 65, the two arms were well balanced in patients with bone-only metastasis and those with metastasis in the lungs or liver, in age and in initial QoL score (Tables 1 and 2).

### *FACT-ES Quality of Life Scores*

QoL mean total scores were significantly better in the combined letrozole treatment phases (1 + 2) than for combined anastrozole treatment, as determined by comparing FACT-ES questionnaires from the end of each. After adjusting for baseline differences in mean QoL scores, there was a difference in mean score of 5.1 favouring letrozole (95% confidence interval [CI]: 1.0 to 9.3) (Table 2). Comparison of scores in six QoL categories revealed that letrozole was significantly favoured over anastrozole in two FACT-ES categories: additional concerns and endocrine symptoms (Table 3). For presentation purposes, it is worth emphasising that a higher score related to a lower QoL, but in other trials, such as the ATAC study, a higher score related to a better QoL, which also presented FACT-ES as a trial outcome index, which excludes the emotional and social well-being subscales of the FACT-B (breast cancer scale) [13]. Our main outcome measure was the total of the FACT-B plus the endocrine subscale (FACT-ES). This made no difference to the statistical comparison of letrozole or anastrozole (see discussion), but produced figures in the 40s (Table 2) rather than 60s [13].

**Table 2 – Quality of life scores* comparing phase 1 and 2 treatments with letrozole vs anastrozole**

| QoL | Letrozole | Anastrozole | Mean difference (95% CI) | *P* value |
|---|---|---|---|---|
| Baseline mean total score | 44.2 | 43.4 | | |
| Final mean total score, unadjusted | 43.8 | 48.2 | 4.5 (0.9 to 8.1) | 0.03 |
| Final mean total score, adjusted for baseline | 43.4 | 48.5 | 5.1 (1.0 to 9.3) | 0.02 |

CI, confidence interval; QoL, quality of life.
*A higher score indicates a poorer QoL.

**Table 3 – Quality of life subscale differences between letrozole and anastrozole treatment**

| QoL subscale | Mean difference* | 95% CI | *P* value |
|---|---|---|---|
| Physical well-being | 1.0 | −0.2 to 2.2 | 0.1 |
| Social/family well-being | −0.3 | −1.0 to 0.3 | 0.3 |
| Emotional well-being | 0.6 | −0.3 to 1.4 | 0.2 |
| Functional well-being | 0.7 | −0.2 to 1.7 | 0.1 |
| Additional concerns | 0.9 | 0.1 to 1.7 | 0.03 |
| Endocrine symptoms | 2.0 | 0.6 to 3.4 | <0.01 |

CI, confidence interval; QoL, quality of life.
*Positive differences favour letrozole, and negative differences favour anastrozole.

### *Tolerability of Letrozole Compared with Anastrozole*

Table 4 summarises the incidence and grade of adverse effects associated with letrozole or anastrozole, for 63 of the 65 patients evaluable for QoL (in two patients questionnaires were incomplete). Overall, significantly fewer patients while on letrozole experienced adverse events than patients on anastrozole (43% vs 65%, respectively; $P = 0.0028$). Letrozole was significantly better for all grades of lethargy (8% vs 19%; $P = 0.007$), nausea (10% vs 22%; $P = 0.021$), joint pain (3% vs 11%; $P = 0.025$), abdominal discomfort (3% vs 11%; $P = 0.025$), poor appetite (2% vs 8%; $P = 0.04$) and headache (5% vs 14%, $P = 0.05$). Anastrozole was not significantly better for any type of adverse event. Letrozole was also better tolerated in general than anastrozole in grade 2 and 3 adverse events (Table 4).

Symptoms associated with adverse events required medical intervention in nine patients: six taking letrozole, and three taking anastrozole. For five of the patients treated with letrozole, concomitant medication was prescribed while treatment continued; the other patient permanently discontinued treatment because of nausea. All three patients treated with anastrozole continued therapy while

**Table 4 – Percentage of patients reporting adverse effects associated with initial letrozole or anastrozole treatment, based on National Cancer Institute criteria for toxicity and grade**

| | Letrozole, % | | Anastrozole, % | | |
|---|---|---|---|---|---|
| Adverse event | All | Grade 2/3 | All | Grade 2/3 | *P* value* |
| Lethargy | 8 | 3 | 19 | 11 | 0.007 |
| Nausea | 10 | 2 | 22 | 8 | 0.02 |
| Joint pain | 3 | 0 | 11 | 3 | 0.025 |
| Abdominal discomfort | 3 | 0 | 11 | 3 | 0.025 |
| Poor appetite | 2 | 0 | 8 | 5 | 0.04 |
| Headache | 5 | 0 | 14 | 5 | 0.05 |
| Hot flushes | 14 | 5 | 19 | 8 | 0.16 |
| Fluid retention/weight gain | 3 | 2 | 3 | 2 | 1.00 |
| Thrombophlebitis | 0 | 0 | 2 | 0 | 0.32 |
| Wakefulness | 2 | 0 | 2 | 0 | 1.00 |
| Vaginitis | 2 | 0 | 0 | 0 | 0.32 |
| Any adverse event | 43 | | 65 | | 0.0028 |

*Comparison of all grades of adverse events associated with initial letrozole treatment compared with those associated with initial anastrozole treatment, Wilcoxon signed ranks test.

receiving concomitant medication for nausea and gastrointestinal discomfort.

### *Patient Preferences*

At the end of this trial, 44 (68%) patients who completed both treatment phases preferred to continue treatment with letrozole, whereas 21 (32%) chose anastrozole ($P < 0.01$). A preference for letrozole was also seen among the 11 patients who were intolerant to tamoxifen: seven opted to continue letrozole treatment, and four chose anastrozole; none opted to go back on to tamoxifen. Mean final QoL scores corresponded with patient preference for continuing treatment (Table 5), an internal consistency that validates patients' preferences. Thus, among patients preferring letrozole, mean QoL scores favoured letrozole, and among patients preferring anastrozole, mean QoL favoured anastrozole. Reasons for patient preference are given in Table 6.

**Table 5 – Relationship between final mean quality of life scores* and patient preferences for continuing treatment with letrozole or anastrozole†**

| | Preference for continuing treatment | |
|---|---|---|
| | Letrozole | Anastrozole |
| Mean QoL total score on letrozole | 41.6 | 48.3 |
| Mean QoL total score on anastrozole | 49.0 | 46.6 |

QoL, quality of life.
*A higher score indicates a poorer QoL.
†Choice of drug correlated with higher QoL whilst on that drug, t-test: $P = 0.02$.

**Table 6 – Reasons given for patient preference of letrozole or anastrozole for continuing treatment**

| | Reason for preference, number of patients* | | | |
|---|---|---|---|---|
| Preferred agent | Better overall QoL | Less nausea | Fewer hot flushes | Less abdominal discomfort |
| Letrozole | 24 | 14 | 16 | 10 |
| Anastrozole | 14 | 7 | 6 | 6 |

QoL, quality of life.
*Some patients specified more than one reason.

### *Patients' Attitudes to a Crossover Manoeuvre*

An additional feature of the final questionnaire was to ask patients their views on whether a crossover manoeuvre in routine clinical practice would be welcomed by future patients prescribed aromatase inhibitors. There was a positive agreement that women want to be involved in the decision-making process, as 92% agreed (51% strongly), whereas only 8% neither agreed nor disagreed.

## Discussion

This study was the first to evaluate the correlation between patient choice and formal QoL assessments within a randomised, crossover design. It also provided a useful insight into the enthusiasm women with breast cancer have for greater involvement in the treatment decisions that influence their daily lives. It was also the first direct, within-patient comparison of letrozole and anastrozole primarily addressing tolerability and QoL. Within this trial cohort, letrozole was significantly better tolerated than anastrozole as second-line treatment for post-menopausal breast cancer patients, in the incidence and severity of adverse side-effects reported and in overall final QoL scores. These results were also reflected in the nearly two-fold higher proportion of patients who chose to continue treatment with letrozole over anastrozole after study completion.

Why there should be better patient tolerability of letrozole than anastrozole is uncertain and warrants further discussion. First, although both drugs are classified as third-generation non-steroidals exerting their selective aromatase inhibition in the same manner [17,18], there are significant differences in chemical structure (Fig. 1). These structural

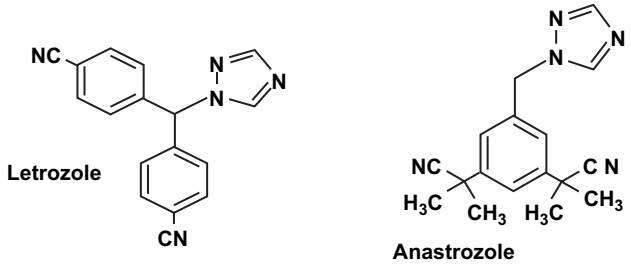


Fig. 1 – Structures of letrozole and anastrozole.

differences may produce varying non-endocrine effects leading to events such as lethargy, joint pain and gastrointestinal disturbances, which become evident with careful examination of spontaneously reported adverse events and the use of a sensitive QoL scale. Second, the better endocrine symptom profile of letrozole, despite its greater potency in oestradiol suppression than anastrozole (84–98% vs 81–94%) for plasma oestrone, oestradiol and oestrone sulphate in a recent comparative study by Geisler *et al.* [21] suggest a non-linear (or even inverse) relationship between symptoms and oestradiol levels in post-menopausal women. A comparable situation may occur during natural menopause, with hot flushes and other endocrine symptoms occurring as oestradiol levels fall, but becoming reduced upon reaching post-menopausal status. This report therefore highlights that the relationship between oestradiol and endocrine symptoms is not certain. It may be possible that greater suppression at this range may improve, not worsen, symptoms — a relationship that is worthy of further investigation. Third, a recent study demonstrated better response rates for letrozole in a direct comparison with anastrozole as second-line therapy in post-menopausal women with advanced breast cancer [22]. We believe, however, that this difference in effectiveness would only have had a small influence on our data, as treatment in our trial was too short for significant responses to affect QoL, as responses often require more than 3 months of treatment and follow-up to identify and confirm [6]. Furthermore, patients at trial entry were required to be asymptomatic or have stable disease symptoms while on appropriate supportive therapy. Changes in symptoms were therefore most likely related to side-effects of the aromatase inhibitors.

A recent direct comparison of letrozole and anastrozole failed to show significant differences in patient tolerability favouring letrozole as in our study [22]. There are several possible reasons why we detected a statistical difference despite smaller patient numbers. First, our trial was designed with QoL and toxicity as primary end points, and investigators were encouraged to report all new symptoms. Second, our tools for detecting a difference were much more sensitive: the FACT-ES has been specifically designed for use in patients with breast cancer on endocrine therapy and patient preference. Third, the crossover design ensured that patients served as their own controls, so our trial was asking if there was a difference in QoL and preference for the individual patient based on that individual's experience of both drugs, which is a different yet more realistic question than whether there is a difference in mean QoL scores between a group of patients taking one drug and another group taking the other drug. Fourth, an eligibility criterion for our study required stable or asymptomatic disease. As a consequence, our patient cohort had less advanced disease and were relatively asymptomatic at trial entry (only 57% having systemic metastatic disease compared with 78% in the other study) [22]. Differences in toxicity, as opposed to disease morbidity, were likely to have been more easily discerned in our study.

Although clinicians were blinded to treatment, patients knew which drug they were taking. Ideally, double-blinding would have enhanced the trial data, but the vastly greater cost of repackaging was prohibitive. The trial design committee, part of the Information for Patients Research Group, instigated other measures to avoid bias, particularly that patients complete the QoL and patient preference questionnaires at home, away from potential influences within the oncology departments. Nevertheless, we were concerned that media articles relating to the two large metastatic trials of letrozole or anastrozole vs tamoxifen [7,9] may have influenced patient choice. A comprehensive review of the UK national press during the relevant period, January 2000 to July 2001, however, showed similar numbers of citations for each drug (18 consumer articles with a total of 57 letrozole mentions, for an average of 3.2 mentions per article; 37 consumer articles with a total of 100 anastrozole mentions, giving an average of 3.7 mentions per article).

Dropout from our trial was similar in the two arms, and the baseline score of these patients was similar to that of patients who completed the study. Half of the patients expressly recorded a preference not to answer the question about satisfaction with sex life, and more than 70% of those who did not tick this box did not respond anyway. It was thus thought, by the independent statistical panel while the data were still blind, preferable to exclude these questions rather than make assumptions about these missing data. However, if the sex questions were included, the results remained substantially the same (i.e. a mean difference of 5.2 points in favour of letrozole [95% CI: 1.0 to 9.4]).

The remaining questions were well completed. The trial design of multiple questionnaires per patient in this trial allowed the method of last value carried forward to be used in preference to imputing the mean value of the remaining questions of a subscale ( prorating). However, if prorating were used, the results were more strongly in favour of letrozole, with a mean difference in score of 6.4 (95% CI: 1.0 to 11.9).

Patient preference as a trial end point has been used in a number of recent trials, but none of these had previously validated it against formal QoL measurement [23–25]. We demonstrated a strong correlation between patient preference and QoL on each drug. Women choosing letrozole had significantly better QoL while taking letrozole, whereas those choosing anastrozole had significantly better QoL while taking anastrozole. We believe these data validate, for the first time in a randomised clinical trial, the authenticity of patient choice as a trial end point, paving the way for its use in future crossover trials. Furthermore, it is clearly an end point that patients can relate to when trying to understand their treatment options. It has long been known that women who share in decision-making and are better informed report greater autonomy, reduced psychological morbidity and improved satisfaction [19,23,26].

This trial also supports the suggestion of introducing a crossover manoeuvre into routine clinical practice, particularly for drugs that may be taken for a long time.

Despite increasing the complexity of treatment, this option seems to be welcomed by patients; the additional questionnaire completed at the end of this study showed that 92% of patients wanted the opportunity to test both drugs, and they recommended this option to future patients. Needless to say, patients in trials are likely to be more receptive to novel strategies, but as only three eligible patients declined trial entry within the four units over the trial period, this attitude is likely to reflect those of many post-menopausal women with breast cancer.

The 4-week duration of the trial phases was arrived at from two considerations. First, steady-state plasma levels for both drugs are achieved within 4 weeks [1,21,27]. Second, as the trial design centre had extensive experience with letrozole and anastrozole, both routinely and as part of the randomised effectiveness study [22], patients were able to feed back to the Information for Patients Research Group. A clear clinical impression from this extensive experience is that intolerance is evident within a week or so, and relief from toxicity is usually evident within a week or so of stopping the drug. As the terminal elimination half-life is identical for both drugs (about 48 h) [17,21], and the order of phases was randomised, a washout period longer than 6 days was not deemed necessary or desirable to physician and patient alike.

Another interesting observation relates to the side-effects of letrozole and anastrozole in the 11 tamoxifen-intolerant patients entered into this trial. Although previous studies suggested a small toxicity advantage of aromatase inhibitors over tamoxifen, these data suggest that the magnitude of benefit may be greater in the tamoxifen-intolerant subgroup, as none of these 11 patients opted to go back on tamoxifen. A further study with patients who are experiencing marked side-effects when taking tamoxifen is under way to help establish if an early switch to aromatase inhibitors is warranted on QoL grounds alone.

## Conclusion

This trial raises questions about how patient preference for treatments should be assessed. As toxicity and QoL strongly correlated with patient preference for either drug, this suggests that patient preference is now a legitimate and useful end point for future crossover studies. In routine practice, although it is not practicable to offer all women a choice initially, it is clearly an option that women would welcome more often. Furthermore, this desire for involvement in the decision process, complements reports that more choice also attributes to a greater sense of well-being [19,23,26]. This trial certainly suggests a justification for the extra effort of a crossover manoeuvre in those women experiencing troublesome side-effects on an aromatase inhibitor, whichever is prescribed initially. In view of the rapidly increasing numbers of patients receiving long-term aromatase inhibitor treatment, particularly those in the adjuvant setting, even small improvements in well-being could benefit large numbers of women. Whether letrozole or anastrozole is prescribed initially remains the discretion of each physician. These data, however, suggest that letrozole is better tolerated but within the caveats of a single-blind trial design addressing early morbidity, and therefore there is clearly scope to build on the lessons learned from this study with a confirmatory double-blind trial design.

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