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Letrozole versus tamoxifen in the treatment of advanced breast cancer and as neoadjuvant therapy☆

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Abstract

Letrozole, a third generation aromatase inhibitor, has been compared with tamoxifen in the treatment of advanced breast cancer and as neoadjuvant therapy. In a first-line trial in advanced disease, 939 post menopausal women were randomised double blind to receive treatment with letrozole 2.5 mg daily or tamoxifen 20 mg daily. Letrozole was significantly superior in terms of median time to progression (9.4 months versus 6.1 months, $P = 0.0001$), objective response (30% versus 20%, $P = 0.0006$), and clinical benefit (49% versus 38%, $P = 0.0001$). Superiority of letrozole was independent of disease site, receptor status, or prior adjuvant anti-oestrogen therapy. In an extended phase of this trial, 200 patients were crossed over to tamoxifen after letrozole, compared with 197 crossed over to letrozole after tamoxifen. Median overall survival was 34 months for letrozole versus 30 months for tamoxifen (not significant).

In a similar randomised double-blind neoadjuvant trial, 337 post menopausal patients with large ER/or PgR positive T2–T4 cancers, either requiring mastectomy or locally advanced, were randomised to preoperative letrozole or tamoxifen for 4 months prior to surgery. Overall response was 55% for letrozole versus 36% for tamoxifen ($P < 0.001$). Conservative surgery was possible in 45% of patients treated with letrozole versus 35% with tamoxifen ($P = 0.022$).

In both trials, both treatments were well tolerated with no significant differences in side effects.

These results indicate that letrozole is more active than tamoxifen both as neoadjuvant therapy and as first-line treatment in advanced disease. They support the importance of current adjuvant trials comparing the two treatments.

Keywords: Letrozole; Tamoxifen; Breast cancer

1. Introduction

The first clinical aromatase inhibitor, aminoglutethimide, was developed for the treatment of advanced breast cancer around 25 years ago. For many years, this class of drugs had only a minor role as second or third-line palliative therapy while tamoxifen remained unchallenged as first-line treatment for both early and advanced breast cancer. Recently, all this has changed. Letrozole, one of a new group of so-called third-generation aromatase inhibitors many times more specific and potent than aminoglutethimide, is rapidly changing standards of care in patients with advanced breast cancer. There is also good evidence that it may be more active than tamoxifen as neoadjuvant therapy in the treatment of large operable breast cancer. This article will review recent trials comparing letrozole with tamoxifen in advanced disease and as neoadjuvant therapy.

1.1. Letrozole as first-line endocrine therapy for advanced breast cancer

1.1.1. Background

Until recently tamoxifen has been the undisputed gold standard in the treatment of advanced breast cancer, significantly superior to or at least as good as all other forms of endocrine therapy including progestagens [1–6], diethylstilbestrol [7], androgens [8], other anti-estrogens [9,10], and first- and second-generation aromatase inhibitors including aminoglutethimide [11–13], fadrozole [14,15] and formestane [16]. In retrospect, these trials were clearly small and underpowered but there was nevertheless a tendency to interpret them as suggesting that tamoxifen through estrogen-receptor blockade was achieving the maximum possible endocrine control of advanced breast cancer.

Results from a recent trial comparing letrozole with tamoxifen as first-line therapy for advanced breast cancer have entirely changed this view.

1.1.2. Patients and methods

In this trial, the largest of its kind, letrozole 2.5 mg daily was compared with tamoxifen 20 mg daily in 939

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Table 1
Patient characteristics in trial of letrozole vs. tamoxifen in advanced/metastatic disease

	n	
	Letrozole	Tamoxifen
Mean age (range) (years)	65 (31–96)	64 (31–93)
Hormone receptor status		
ER and/or PgR positive	294 (65%)	305 (67%)
Both unknown	156 (34%)	149 (33%)
ER or PgR negative	3 (<1%)	0
Adjuvant tamoxifen (%)	19	19
Performance status (WHO)		
0/1	423 (93%)	414 (91%)
2	30 (7%)	39 (9%)

postmenopausal women recruited from 201 centres in 29 countries [17]. The core phase of the trial had a double dummy, double-blind, parallel group cross-over design, powered for superiority. Subsequently, an extended non-randomised phase was planned, allowing for cross-over at the time of progressive disease. This phase remained double-blind.

In the core phase, the primary efficacy end point was time to progression (TTP), defined as the time from randomisation to the earliest date of disease progression. Secondary endpoints included overall response rate (ORR), duration of ORR, clinical benefit, duration of clinical benefit, TTF, time to response (TTR) and tolerability. The concept of combining stable disease for at least 24 weeks with response into the overall term clinical benefit is a valid one because endocrine therapy studies have shown this to have the same clinical outcome as objective response [18–20]. Postmenopausal women with locally advanced, loco-regional recurrent or metastatic breast cancer whose tumours were ER and/or PgR positive or unknown and whose Karnofsky Performance Status was $\geq$50 were included. Patient characteristics are given in Table 1.

1.2. Results

1.2.1. Core phase

At a median 18 months follow-up, median TTP on letrozole was significantly longer than for tamoxifen (9.4 months versus 6.1 months: hazard ratio 0.70; 95% CI, 0.60–0.82; $P = 0.0001$). Objective response rate was also significantly superior with letrozole (30% versus 20%; $P = 0.0006$), as was rate of clinical benefit (49% versus 38%; $P = 0.001$). Response duration was 24 months for each agent and duration of overall clinical benefit likewise did not differ significantly between the two agents. Median time to respond was 14 weeks for both treatments [17].

The superiority of letrozole in TTP and ORR was observed consistently, regardless of disease site, receptor status or prior adjuvant anti-estrogen therapy. Notably, in patients with visceral-dominant disease, responses were seen in 26% treated with letrozole compared with 16% treated with tamoxifen ($P = 0.0001$) with respective response durations of 36 and 20 weeks ($P = 0.001$).

Table 2
Comparison of most frequent side effects in trial of letrozole vs. tamoxifen in advanced/metastatic disease ($n = 455$)

	Letrozole (%)	Tamoxifen (%)
Bone pain	20	18
Hot flushes	18	15
Back pain	17	17
Arthralgia	14	13
Nausea	6	6

This trial currently provides the largest source of comparative toxicity data between letrozole and tamoxifen. Both agents were well tolerated and no significant differences were seen in side effects (Table 2).

1.2.2. Extended phase

In the subsequent extended phase, cross-over analysis carried out at a median of 32 months after start of treatment, 200 patients (44%) randomised to first-line letrozole had been crossed over to tamoxifen compared with 197 patients (43%) randomised to first-line tamoxifen. At that time, a predicted 11% of patients randomised to letrozole were still on core therapy out to 5 years compared to 6% of the patients randomised to tamoxifen. For this extended phase, the statistical methods employed were the same as those for the primary analysis of the core study, except that here adjustment was made only for receptor status and dominant site of disease (and not for prior adjuvant anti-estrogen therapy). The primary analysis of overall survival was by the logrank test with estimates of the survivor function by the Kaplan-Meier product-limit method.

Median overall survival was 34 months for letrozole compared with 30 months for tamoxifen [21]. This difference was not significant but when the data were broken down by 6-month intervals, patients receiving letrozole had a significant early survival benefit during the first 2 years of treatment ($P < 0.02$).

One possible explanation for the subsequent convergence of the median survival curves was the cross-over design of the study. The objective response rates to second line treatment were similar (9% letrozole versus 7% tamoxifen) but median response duration was 35 weeks for letrozole compared with 16 weeks for tamoxifen. Thirty percent achieved clinical benefit with second line letrozole compared with 26% for tamoxifen but the respective median durations of benefit were 24 weeks compared with 12 weeks.

1.3. Neoadjuvant therapy with letrozole

1.3.1. Background

The concept of neoadjuvant endocrine therapy before, or even instead of, surgery is not a new one. Tamoxifen has been assessed as an alternative to surgery in elderly women

Table 3
Comparative side effects in 4-month neoadjuvant trial of letrozole compared with tamoxifen

	Letrozole	Tamoxifen
Patients	157	170
Hot flushes (%)	20	24
Nausea (%)	5	5
Leukorrhea	0	4
Weight gain (%)	2	2

in several trials, but this approach has consistently shown high local relapse rates in the no surgery arm [22–26]. The option of pre-operative endocrine therapy before rather than instead of surgery still remains clinically attractive however, as a means of downstaging primaries to reduce the need for mastectomy in elderly women, and as an in vivo measure of tumour responsiveness [27]. In small non-randomised studies letrozole and the other third-generation aromatase inhibitors anastrozole and exemestane have each been shown to achieve higher tumour regression rates than previously reported for tamoxifen when given pre-operatively to older women with large primaries [28–31].

1.3.2. Patients and methods

Recently, a randomised double-blind clinical trial of 337 postmenopausal patients recruited from 55 centres in 16 countries compared tamoxifen to letrozole as pre-operative treatment for ER and/or PgR positive untreated primary breast cancer. Patients had large stage T2–T4 cancers either requiring mastectomy or locally advanced and inoperable (14%). All had tumours which were ER and/or PgR positive. Details of patient characteristics are in Table 3.

1.3.3. Neoadjuvant results

The overall clinical response measured by calipers was 55% for patients treated with letrozole compared to with 36% for tamoxifen ($P < 0.001$). Likewise significantly more breast-conserving surgical procedures were carried out in patients treated with letrozole than with tamoxifen (45% versus 35%; $P = 0.022$). Apart from tumour size, the only factor that influenced the chances of undergoing breast-conserving surgery was choice of treatment. Letrozole was also significantly superior to tamoxifen in assessment of efficacy with ultrasound ($P = 0.042$) and mammography ($P < 0.001$) [32].

Both treatments were well tolerated. The most common side effects included hot flushes (20 and 24% for letrozole and tamoxifen, respectively), nausea (5 and 5%), leukorrhea (0 and 4%) and weight gain (2 and 4%). These are the only comparative toxicity data between the two agents so far available in patients with early disease, uncomplicated by the potential of tumour-related symptoms; results are summarised in Table 3.

This neoadjuvant trial also provided an important opportunity to investigate the predictive value of strength of ER expression and of EGFR/HER2 over-expression in relative response rates [33] and these results are updated in a separate paper in this volume.

2. Discussion and conclusions

The results of these two trials demonstrate convincingly that first-line letrozole is more active than tamoxifen in terms of tumour response. This therefore refutes the implication from a large series of earlier trials that tamoxifen, through oestrogen-receptor blockade, was achieving maximum possible clinical benefit through endocrine means; these new findings open up possibilities for further clinical endocrine therapy development.

The relatively low objective response rate of 20% for tamoxifen compared with earlier studies is unexpected but is probably a simple reflection of the strict criteria used to assess response here. Even in this strictly defined context, it is notable that almost 50% of patients treated with letrozole achieved clinical benefit, with median duration of 18 months. For patients achieving a response the median duration was 2 years, and the follow-up analysis showed that a predicted 11% of patients would still be on letrozole after 5 years of treatment. Given that side effects occurred only in a small minority of patients and were usually very mild, this represents a very impressive form of long-term palliation.

Traditional teaching has it that endocrine therapy is unlikely to be of benefit in the management of visceral disease. In this context, it is again worth noting that 26% of patients with predominantly visceral metastases responded to letrozole compared with 16% treated with tamoxifen. This supports a clinical management policy whereby patients with visceral disease which is not immediately life-threatening might benefit from a therapeutic trial of letrozole prior to a more standard approach with chemotherapy.

Cross-over data from the extended phase of the trial showed low objective second-line response rates for both treatments, but nevertheless clinical benefit was still seen in 30% of patients treated with letrozole and 26% with tamoxifen. The median duration of clinical benefit with letrozole used as second-line treatment was almost a year (24 weeks) compared to only 12 weeks with tamoxifen, providing further evidence that the mechanisms of acquired resistance to the two agents may differ.

Results with the neoadjuvant therapy trial confirm the impression from earlier non-randomised studies that aromatase inhibitors may be more active than tamoxifen in this clinical context. Letrozole therefore seems an effective and well tolerated alternative to mastectomy for older and less fit patients with large ER positive cancers, with a 45% chance of sufficient downstaging to allow simpler breast-conserving surgery.

Finally, these results bode well for the outcome of adjuvant letrozole trials currently running. Trials with anastrozole in advanced breast cancer have shown this to be at least as good as tamoxifen but the evidence for superiority

is less convincing and is supported in only one of two trials [34,35]. Nevertheless, first results from the adjuvant anastrozole ATAC trial have already shown a small but statistically significant improvement in disease-free survival [36]. By analogy, the more convincing results with letrozole in advanced disease suggest that adjuvant letrozole is likely to show at least as good a gain.

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