Letrozole is Superior to Anastrozole in Suppressing Breast Cancer Tissue and Plasma Estrogen Levels

Jürgen Geisler,¹ Hildegunn Helle,² Dagfinn Ekse,² Nhat K. Duong,² Dean B. Evans,³ Yngve Nordbø,⁴ Turid Aas,⁴ and Per E. Lønning²

Abstract

Purpose: To evaluate the influence of the third-generation aromatase inhibitor letrozole (Femara) on breast cancer tissue levels of estrone (E₁), estradiol (E₂), and estrone sulfate (E₁S) in postmenopausal women undergoing primary treatment for locally advanced estrogen receptor/progesterone receptor-positive breast cancers.

Experimental Design: Breast cancer tissue samples were collected before and following 4 months of neoadjuvant therapy with letrozole (2.5 mg o.d.), and tissue estrogen levels measured using a highly sensitive RIA after high-pressure liquid chromatography purification.

Results: Letrozole suppressed pretreatment tumor levels of E₂, E₁, and E₁S by 97.6%, 90.7%, and 90.1%, respectively. These data reveal that letrozole suppresses tissue estrogen levels significantly below what has previously been recorded with anastrozole (89.0%, 83.4%, and 72.9% suppression, respectively) using the same methods. To confirm the differential effect of letrozole and anastrozole on each plasma estrogen fraction, we re-analyzed plasma samples obtained from a previous intrapatient cross-over study comparing letrozole and anastrozole using an improved RIA (detection limits of 0.67, 1.14, and 0.55 pmol/L for E₂, E₁, and E₁S, respectively). Letrozole consistently suppressed each plasma estrogen fraction below the levels recorded for anastrozole: E₂ (average suppression by 95.2% versus 92.8%; P = 0.018), E₁ (98.8% suppression versus 96.3%; P = 0.003), and E₁S (98.9% suppression versus 95.3%; P = 0.003).

Conclusion: Our data reveals that letrozole (2.5 mg o.d.) is more effective compared with anastrozole (1.0 mg o.d.) with respect to tissue as well as plasma estrogen suppression in patients with postmenopausal breast cancer.

Contemporary clinical studies have shown that three third-generation aromatase inhibitors (anastrozole, letrozole, and exemestane) improve time to progression in metastatic disease (1–3) and relapse-free as well as overall survival compared with tamoxifen for adjuvant therapy of patients with postmenopausal breast cancer (4–6). These results are most likely related to their improved potency. The third-generation compounds inhibit total body aromatization by ≥98% in vivo (7–10). In contrast, compounds belonging to the first and second generation of inhibitors cause 80% to 90% (11–14) aromatase inhibition and do not improve clinical outcome compared with tamoxifen or megestrol acetate (see ref. 15).

An ongoing controversy relates to potential differences between the three third-generation aromatase inhibitors with respect to mechanism of action (16) and resistance (17), as well as clinical efficacy and safety. Thus, studies in metastatic breast cancer have revealed a lack of complete cross-resistance between nonsteroidal aromatase inhibitors and the steroidal aromatase inactivators (18–22). However, except for a single study comparing anastrozole and letrozole as second-line therapy in metastatic disease (23), we lack results from direct head-to-head comparisons.

Although plasma estrogen measurements have been considered suitable surrogate markers for aromatase inhibition, they do not necessarily reflect tumor estrogen levels due to extensive local production (24, 25). Thus, direct measurement of estrogen levels in tumor tissue will improve our understanding of breast cancer intracrinology and add to our understanding of the biochemical effects of these compounds. Although a few pioneering studies have revealed suppression of intratumor estrogen levels during treatment with aromatase inhibitors (26–28), some of these studies faced substantial methodologic problems when assessing estrogen levels in the ultra low range. As a consequence, we have developed a novel, highly sensitive high-pressure liquid chromatography–RIA method (29) suitable for the detection of tissue estrogen fractions during...
treatment with aromatase inhibitors. Using this method, we have previously evaluated the effects of anastrozole treatment on intratumor estrogen levels (30). This article provides the results of a second tissue study, which investigates the effects of letrozole on tumor estrogens.

In a previously published study (10), we compared total body aromatization with anastrozole and letrozole using a randomized, intrapatient cross-over design allowing us to evaluate the endocrine effects of letrozole versus anastrozole without the disturbing effects of interpatient variation. Although letrozole (2.5 mg o.d.) consistently suppressed total body aromatization below the levels measured for anastrozole (1.0 mg o.d.), many patients experienced suppression of estradiol below the detection limit of the method (11 out of 12 on anastrozole and 12 out of 12 on letrozole). To solve this problem related to methodologic limitations, we developed a novel, highly sensitive assay for plasma estrogen analysis characterized by the lowest detection limits for plasma estrogens reported thus far (31). Using this improved method, we re-analyzed plasma samples from our cross-over trial (10), comparing anastrozole and letrozole on a head-to-head basis to see whether more sensitive assays may allow a better discrimination between the compounds in this setting. The findings presented here reveal letrozole to be a consistently more potent aromatase inhibitor, translating into a significantly better suppression of plasma as well as tissue estrogen levels compared with anastrozole in patients with postmenopausal breast cancer.

### Materials and Methods

**Patients.** To evaluate the influence of letrozole on breast cancer tissue levels, postmenopausal women with locally advanced (T\(_3\), T\(_4\) and/or N\(_1\), and/or N\(_2\)), noninflammatory, estrogen receptor and/or progesterone receptor–positive breast cancer, with or without limited distant metastasis, were eligible. All in all, 16 patients matched the inclusion criteria and started treatment in accordance with the protocol. Pathologic examination of the biopsies revealed no tumor tissue in the mastectomy sample for three patients, excluding these patients from further evaluation. Thus, 13 patients (median age, 76 years; range, 62-83 years) completed all procedures according to the study protocol and were eligible for analysis (Table 1).

**According to the protocol, postmenopausal status was defined by amenorrhea for a duration of >1 year with follicle-stimulating hormone levels in the postmenopausal range or >5 years of amenorrhea. Exclusion criteria included hormone replacement therapy, systemic treatment with glucocorticoids, or treatment with any other drug known to influence estrogen metabolism (e.g., phenytoin, carbamazepine, or rifampicin, etc.). Concerning the patient data from the intrapatient cross-over trial, all details were given in the original publication (10). Briefly, 12 postmenopausal women (median age, 72 years; range, 54-79 years) with estrogen receptor–positive, metastatic breast cancer, suitable for treatment with an aromatase inhibitor were enrolled. All previous cancer treatments had been terminated at least 4 weeks before starting therapy on protocol. Each patient received anastrozole (1 mg orally) or letrozole (2.5 mg o.d.) in a double-blind cross-over study. Blood samples for plasma estrogen measurement were obtained after 6 weeks on each regimen to obtain steady state levels.**

**Treatment.** In the present neoadjuvant study, each patient received letrozole (Femara) given as an oral dose of 2.5 mg once daily. In general, treatment was given for 16 weeks, followed by surgery (mastectomy in 11 cases and breast-conserving surgery in 2 cases) and radiation. Each breast tumor (and, if present, palpable axillary nodes), was measured prior to therapy and following 4, 8, 12, and 16 weeks on letrozole therapy. Tumor size was calculated as the product of the largest diameter and its perpendicular. Clinical response was classified according to the International Union Against Cancer criteria, with the exception that tumors reduced by ≥25% but <50% in size were classified as “minimal change.” All patients who experienced at least a minimal change were defined as responders, whereas all patients with stable disease or progressive disease were defined as nonresponders. Patients that responded to treatment with letrozole in this trial continued with letrozole as adjuvant therapy for up to 5 years. The protocol was approved by the local ethical committee, and each patient gave written informed consent prior to enrollment.

**Tissue collection.** Breast tumor tissue was collected prior to treatment by an open biopsy, after 3 days on treatment (true-cut biopsy), and during final surgery (mastectomy). All tissue samples were stripped for adhering fat and divided into several pieces of ~100 mg each and one single piece of ~300 mg. Tissue samples to be used for estrogen measurements were immediately snap-frozen and stored in liquid nitrogen until analysis.

**Measurement of intratumoral estrogen levels.** Tissue estrogen levels were measured using a novel, highly sensitive RIA method subsequent to a multistep purification process involving high-pressure liquid chromatography as described previously (29). Briefly, tissue homogenates (200-300 mg) were incubated with \(^{3}H\)-labeled estrogens

### Table 1. Neoadjuvant letrozole study: patients’ characteristics

<table>
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<tr>
<th>No.</th>
<th>BMI</th>
<th>Age</th>
<th>TNM</th>
<th>Histology</th>
<th>Grade</th>
<th>ER (%)</th>
<th>PgR (%)</th>
<th>HER-2</th>
<th>Met.</th>
<th>Clinical response</th>
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<td>No</td>
<td>PR</td>
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<td>100</td>
<td>Negative</td>
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<td>PR</td>
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<td>No</td>
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<td>100</td>
<td>100</td>
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<td>No</td>
<td>PR</td>
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<td>&gt;50</td>
<td>Negative</td>
<td>No</td>
<td>PR</td>
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<tr>
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<td>83</td>
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<td>1-2</td>
<td>80-100</td>
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<tr>
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<td>82</td>
<td>T(_3)N(_0)M(_0)</td>
<td>Infr. duct. ca</td>
<td>2</td>
<td>&gt;80</td>
<td>&gt;80</td>
<td>Negative</td>
<td>No</td>
<td>PR</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; TNM, tumor-node-metastasis; ER, estrogen receptor; PgR, progesterone receptor; Met., distant metastasis; Muc. adenoc., mucinous adenocarcinoma; Inf. duct. ca, infiltrating ductal carcinoma; Inf. lob. ca, infiltrating lobular carcinoma; Lu, metastasis to lung; Li, liver metastasis; B, bone metastasis; PR, partial response.
estrone (E₁), estradiol (E₂), estrone sulfate (E₁S) as recovery controls and crude fractions were separated by ether extraction. The E₁S fraction was hydrolyzed with sulfatase followed by ether extraction and column purification of E₁. High-pressure liquid chromatography was used to purify the individual estrogen fractions prior to RIA analysis. E₁ and E₁S (after hydrolysis) were converted into E₂, and all three estrogen fractions were finally measured by the same highly sensitive RIA using estradiol-6-carboxymethyloxime-[2-¹²⁵I]-iodohistamine as a tracer ligand. These methods have also been improved by using solvents with higher purity in all steps and optimizing the procedures. The detection limits for E₂, E₁, and E₁S in plasma samples were calculated to be 0.67, 1.14, and 0.55 pmol/L, respectively (31), which improved from our previous limits of 2.7, 6.3, and 2.1 pmol/L, respectively (32, 33).

Statistics. Plasma and tissue estrogen levels are described by their geometric means with 95% confidence intervals (CI). Whenever estrogen levels (either in plasma or tissue samples) were below the detection limits given above, the value for the respective detection limit was ascribed to the sample for statistical analysis. Before-treatment and on-treatment values were compared using the Wilcoxon matched-pair signed-rank test. The mean value of percentage suppression from baseline for a variable was calculated as 100 - x, where x is the geometric mean value of the individual variables in the on-treatment situation expressed as a percentage of pretreatment values (8). All data handling was done independently from the sponsor of the study by the investigators (J. Geisler and P.E. Lønning) at the Haukeland University Hospital.

Results

The mean tumor tissue concentrations of E₂, E₁, and E₁S obtained from 13 postmenopausal patients at baseline were 475.8 fmol/g (95% CI, 282.2-802.2 fmol/g), 272.4 fmol/g (95% CI, 135.4-547.9 fmol/g), and 160.5 fmol/g (95% CI, 63.0-408.5 fmol/g), respectively. Neoadjuvant therapy with letrozole suppressed the tissue levels of E₂, E₁, and E₁S to 11.3 fmol/g (6.5-19.6 fmol/g), 25.3 fmol/g (18.2-35.2 fmol/g), and 16.0 (10.9-23.4 fmol/g), respectively. The individual estrogen tissue values at baseline and following 16 weeks on treatment with letrozole are given in Fig. 1A-C. The observed decrease in tissue estrogen levels while on letrozole therapy corresponded to a mean percentage suppression for tumor tissue levels of E₂, E₁, and E₁S by 97.6% (95% CI, 95.4-98.8%), 90.7% (95% CI, 81.3-95.4%), and 90.1% (95% CI, 74.1-96.2%), respectively. Several patients experienced a drop in tumor estrogen levels below the detection limits (marked with an asterisk).

Blood samples for hormone measurements were obtained into heparinized vials (two vials containing 10 mL each) immediately before commencing therapy with letrozole and following 3 days, 4 weeks, 8 weeks, 12 weeks, and 16 weeks (final sample just prior to surgery) on treatment. All blood samples were drawn after an overnight fast. Plasma was separated by centrifugation and stored at -20°C until processing. E₂ and E₁ were determined by a novel, highly sensitive RIA method established in our laboratory (31). Plasma levels of E₁S were determined by the same assay involving additional purification and derivatization into E₂ followed by RIA analysis using estradiol-6-carboxymethylxime-[2-¹²⁵I]-iodohistamine as tracer ligand. These methods have also been improved by using solvents with higher purity in all steps and optimizing the procedures. The detection limits for E₂, E₁, and E₁S in plasma samples were calculated to be 0.67, 1.14, and 0.55 pmol/L, respectively (31), which improved from our previous limits of 2.7, 6.3, and 2.1 pmol/L, respectively (32, 33).

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Influence of Letrozole and Anastrozole on Estrogen Levels

Fig. 3. Influence of anastrozole vs. letrozole on plasma estrogen levels in patients with postmenopausal breast cancer: percentage of pretreatment levels (given as geometric mean); data from the original comparison (in the first two, striped columns) and re-analysis (full color columns); the textbox gives the detection limits for E2, E1, and E1S of the original publication (year 2002) and the improved detection limits from the year 2006 (used for re-analysis).

Discussion

The third-generation aromatase inhibitors anastrozole, letrozole, and exemestane each inhibit total body aromatization by ≥98%, distinguishing these drugs from the previous first-generation and second-generation compounds (34). In contrast to the first- and second-generation compounds, the third-generation aromatase inhibitors improved clinical outcome compared with conventional therapy (1–5, 35). In the anastrozole study, we recorded breast cancer tissue levels of E2, E1, and E1S to be suppressed to 96.6%, 99.1%, and 99.5%, respectively.

In the anastrozole study, we recorded breast cancer tissue levels of E2, E1, and E1S to be suppressed to 96.6%, 99.1%, and 99.5%, respectively. Corresponding values for E2, E1, and E1S obtained with letrozole and anastrozole, the corresponding figure for anastrozole was reduced to 95.2% versus 92.8% for E2, 98.8% versus 96.3% for E1, and 97.6% (letrozole) and 89.0% (anastrozole) may seem modest, distinguishing these drugs from the previous first- and second-generation compounds (34). In contrast to the first- and second-generation compounds, the third-generation aromatase inhibitors improved clinical outcome compared with conventional therapy (1–5, 35). In the anastrozole study, we recorded breast cancer tissue levels of E2, E1, and E1S to be suppressed to 96.6%, 99.1%, and 99.5%, respectively.

Mean plasma estrogen levels at baseline in the present neoadjuvant letrozole trial were 19.9, 127.6, and 715.9 pmol/L for E2, E1, and E1S respectively. The finding of a mean plasma level of E2E1S higher than usual was due mainly to a high value of 3,290 pmol/L in a single patient (patient 11), something we have observed occasionally. Following 16 weeks on treatment with letrozole, these levels were reduced to a geometric mean level of 0.65, 1.14, and 3.9 pmol/L, corresponding to a mean suppression of 96.6%, 99.1%, and 99.5%, respectively.

Re-analysis of the plasma samples from our previously published cross-over trial (Fig. 2; ref. 10), using our improved plasma method (31), revealed plasma levels of E2, E1, and E1S that were consistently lower compared with what had been reported in the original publication (Fig. 3). During treatment with letrozole, E2, E1, and E1S fractions were suppressed to 0.7 pmol/L (0.6-0.8), 1.7 pmol/L (1.2-2.3), and 5.3 pmol/L (1.9-14.9), respectively. Corresponding values for E2, E1, and E1S during treatment with anastrozole were 1.1 pmol/L (0.7-1.7), 5.3 pmol/L (3.3-8.5), and 23.5 pmol/L (7.6-72.7). The mean percentage of suppression for estrogen plasma levels during treatment with letrozole and anastrozole averaged 95.2% versus 92.8% for E2, 98.8% versus 96.3% for E1, and 98.9% versus 95.3% for E1S, respectively.

Notably, the difference between the suppression of plasma levels of E2, E1, and E1S obtained with letrozole and anastrozole reached a level of statistical significance for all estrogen fractions (E2, P = 0.018; E1, P = 0.003; and E1S, P = 0.003). Although 11 out of 12 patients still had plasma E2 levels below the new detection limit (0.67 pmol/L) during treatment with letrozole, the corresponding figure for anastrozole was reduced to 5 out of 12. For plasma E1, 5 out of 12 samples revealed values below the detection limit of 1.14 pmol/L during letrozole treatment (0 out of 12 samples on anastrozole). Plasma E1S levels were found below the detection limit (0.55 pmol/L) for three patients during treatment with letrozole and for one patient while on anastrozole treatment.
measurements and clinical outcome (in terms of survival) was done in our study.

Similar to studies evaluating total body aromatase inhibition, studies on intratumor estrogen levels before and during treatment with aromatase inhibitors are laborious with respect to clinical as well as laboratory logistics. Although such studies may enroll only a limited number of patients, experience has thus far illustrated the feasibility of such studies to prove basic endocrine concepts and the effects of different compounds (34).

As tissue estrogen measurements demand comparatively large tumor tissue biopsies (100-200 mg), direct head-to-head comparison (intrapatient cross-over) involving multiple sampling is not an applicable approach. Thus, tissue estrogen measurements were done in two separate studies with the risk of a bias when it comes to the comparison of findings. However, the two neoadjuvant studies were performed as single-institution studies at our hospital using identical analytical methods. The patients participating in the studies were enrolled on similar inclusion and exclusion criteria, allowing indirect comparison.

In a previous publication (10), we showed letrozole to be more potent compared with anastrozole with regard to total body aromatase inhibition. However, comparing plasma estrogen suppression, only plasma levels of E₁ and E₁S were significantly better suppressed during treatment with letrozole compared with anastrozole. We postulated that this could be due to the lack of sensitivity of the analytical method at that time, as 11 out of 12 patients experienced E₂ plasma levels below the detection limit during anastrozole therapy, and the 12 out of 12 during letrozole therapy. With the improved analytical methods applied here (31), decreasing the detection limit for plasma E₂ from 2.7 to 0.67 pmol/L (Fig. 3), we were able to confirm that letrozole consistently suppressed all plasma estrogen fractions, including estradiol, more effectively compared with anastrozole in this study. This is mainly due to the fact that several patients experienced plasma E₂ levels above the new detection limit while on anastrozole therapy (7 out of 12), whereas letrozole still suppressed plasma E₂ levels below the detection limit in 11 out of 12 individuals.

The clinical effects of anastrozole and letrozole have previously been compared in an open randomized trial of second-line endocrine therapy in patients with advanced breast cancer (23). However, the results of this trial are somewhat difficult to interpret. Although letrozole turned out to be significantly superior to anastrozole in the overall response rate (19.1% versus 12.3%, \( P = 0.013 \)), there was no statistically significant improvement of the median time to progression. Remarkably, the benefits concerning the objective response rate were limited to the estrogen receptor–unknown patients with no statistically significant advantage for estrogen receptor–positive patients. The definite answer to whether letrozole is clinically superior to anastrozole is awaited from the large phase III trial called the “FACE study.” In this ongoing adjuvant trial enrolling 4,000 patients, a breast cancer population at high risk for relapse (node-positive) was randomized between anastrozole and letrozole in the adjuvant setting. Whatever the outcome of that study may be, our endocrine data, together with the data on clinical efficacy, should add significantly to our understanding of key issues such as the relation between the degree of estrogen suppression and clinical efficacy for potent aromatase inhibitors.

In conclusion, our results confirm that letrozole at 2.5 mg once daily is a more potent suppressor of both plasma and tissue estrogen levels in postmenopausal women with breast cancer compared with anastrozole at 1 mg once daily.

Disclosure of Potential Conflicts of Interest

J. Geisler and P. Lonning have both received speaker honoraria from Novartis Pharmaceuticals; D. Evans is employed by Novartis Pharmaceuticals.

Acknowledgments

We thank all the breast cancer patients in Bergen, Norway who participated in the clinical studies.

References


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