American Journal of BioMedicine
AJBM 2015;3 (1): 49-64
Research Article doi: 10.18081/2333-5106/014-4/431-440

Letrozole versus anastrozole in postmenopausal women with chemotherapy-refractory negative HER-2 metastatic breast cancer: a randomised, multicentre, open-label, non-inferiority phase 3 study

Alex J Danielson [1], Nasser G. Yousif [1, 2], Dan G. Wang [1], Alexey F Maltzmana [1], Howell G Johnstona [1], Aman S Gomez [1], Han Lee [1*]

Abstract

Breast cancer remains a pressing global health issue, ranking as the most commonly diagnosed cancer and the leading cause of cancer-related death among women. The aggressive nature of breast cancer necessitates early detection and prompt treatment. Treatment options vary based on several factors, including the anatomical location, stage of the disease, metastasis, and the presence or absence of certain receptors in the breast tumor. The evolution of systemic and local treatments for breast tumors reflects the continuous advancement in biomedical and technological fields. Initial treatments comprised radical mastectomy and adjunctive radiotherapy, which improved survival rates. Chemotherapy, hormonal therapy, and targeted monoclonal antibody therapy emerged as dominant systemic treatment modes. However, over time, the drawbacks of conventional chemotherapy became apparent. Consequently, the relative efficacy of drugs used in chemotherapy has come under scrutiny. Breast cancer is a complex, heterogeneous disease that continues to pose a significant health challenge for women worldwide. In developing nations and socioeconomically disadvantaged groups, breast cancer is often diagnosed at later stages. Treatment modalities, including mastectomy, lumpectomy, chemotherapy, or hormonal therapy in conjunction with radiotherapy, may not be readily available or affordable. While some patients achieve long-term remission and survival, others experience relapsed or metastatic disease. This study aimed to compare the efficacy of two aromatase inhibitors – letrozole and anastrozole – in postmenopausal women with chemotherapy-refractory negative HER-2 metastatic breast cancer. Patients at Mewat and SKIMS medical colleges and hospitals were randomly allocated into two groups. Each patient underwent treatment for one target-to-therapy activity ratio and was followed up for disease progression for 12 months.

Keywords: Breast cancer; SEER; Letrozole; anastrozole; ECOG; Chemotherapy-refractory

*Corresponding author email: Han_Lee188@yahoo.com
[1] Department of Surgery, University of Colorado, United States
Department of Medicine, Medical College, Al Muthann University.
Received November 02, 2014; Accepted February 07, 2015, Published March 25, 2015

Research Article doi: 10.18081/2333-5106/014-4/431-440

Introduction

Metastatic breast cancer (MBC) has been defined as malignant neoplasia of breast tissue that spreads to noncontiguous organs, such as bone, liver, lung, or brain. Although the eventual goal of medicine would be to detect breast cancer at an early stage, a diagnosis of metastatic breast cancer still occurs in 6-10% of patients. Of those, 20% will be chemotherapy-refractory de novo metastatic disease. The common pathway for breast cancer metastasis is thought to occur via blood and lymphatic vessels, after transition to invasive disease through epithelial-mesenchymal transition (EMT) and the Invasion-Metastasis Cascade (IMC). Untreated HER-2 negative post-menopausal MBC has a median overall survival of only 32 months and is associated with a great deal of morbidity. Hormonal receptor-positive breast cancer is the most common subtype in post-menopausal women presenting with MBC, accounting for approximately 55-57% of MBC cases. First-line treatment approaches for this cohort are aromatase inhibitors (AIs), such as Anastrozole, Letrozole, and Exemestane. AIs inhibit estrogen production in post-menopausal women by competitively binding to the aromatase enzyme, while pre-menopausal women rely on ovarian suppression to reduce estrogen through the use of menses-inhibiting anti-estrogen drugs, such as Tamoxifen or LHRH agonists. Although the mechanisms of action of AIs have been extensively studied, there remains a knowledge gap on non-genomic theoretical mechanisms. MBC poses treatment challenges for patients who fail first-line AI therapy, either due to acquired resistance or de novo refractory disease. Fulvestrant is a common second-line treatment option; however, its efficacy on refractory AI decay responders is uncertain as there are no studies executed on strategically designed cohorts. Despite a macromolecule with unique mechanisms of action, such as the disruption of HER-2 dimerization, fulvestrant plays no role in post-menopausal patients with chemotherapy-refractory HER-2 negative MBC. While treatment with either letrozole or anastrozole has been previously used, they have not been subject to head-to-head trials exclusively for AI refractory cohorts.

Breast cancer is the most common malignancy and the second leading cause of cancer-related death among women in the United States. With a 5-year relative survival of 38%, metastatic breast cancer (MBC) remains a major public health challenge. Patients with postmenopausal hormone receptor-positive MBC can benefit from endocrine therapy, which targets estrogen receptors and inhibits the action of estrogen on tumor growth. Aromatase inhibitors (AIs) such as letrozole (LET) and anastrozole (ANA) are the first-line therapy for MBC, but about 50% of patients fail this treatment due to acquired resistance. The mechanisms of acquired resistance to AIs in MBC have been characterized; for example, the constitutively active form of estrogen receptor-α was found in MBC patients following adjuvant letrozole treatment. Most MBC patients had ER+/HER2- disease and were treated with first-line AI therapy. After disease progression following AI therapy, patients can receive chemotherapy as second-line therapy.

Research Article doi: 10.18081/2333-5106/014-4/431-440

In MBC patients with early relapse and rapid disease progression, chemotherapy may be the first-line therapy. The recurrence of breast cancer is defined as local, regional, or distant metastasis after treatment for the earlier stage and might have different characteristics from the de novo MBC. The median overall survival (OS) of the ER-positive early recurrent cohort was significantly longer than that of the ER-negative cohort.

Hormonal Therapy in Metastatic Breast Cancer

Breast cancer is a common malignancy and a leading cause of cancer-related deaths in women worldwide. Most breast cancer patients are estrogen-receptor positive (ER+) and develop metastasis during the course of the disease. Estrogens promote breast cancer progression through both hormone-dependent and independent pathways. Hormonal therapy, acting as antiestrogens, has been the standard treatment for ER+ metastatic breast cancer (MBC) after failed chemotherapy for decades. Tamoxifen, a selective estrogen receptor modulator (SERM), was the first drug to demonstrate clinical benefit and was the standard treatment until 1996 when the aromatase inhibitor (AI) anastrozole was introduced. AIs, as aromatase enzyme inhibitors, effectively block the production of estrogens and are used as the first-line hormonal therapy in postmenopausal women with ER+ MBC.

ER+ breast cancer constitutes approximately 75% of all breast cancer cases. After surgical treatment, many patients, particularly those diagnosed with early-stage disease, will receive adjuvant therapy using hormonal agents (antiestrogens) or chemotherapeutics. Current long-term studies indicate that, despite these adjuvant treatments, about one-third of patients with ER+ breast cancer will eventually relapse with systemic disease (including metastatic breast cancer, MBC), which has a very poor prognosis. There have been notable advancements in the treatment of HER-2-positive MBC with the introduction of targeted therapies. However, for patients with HER-2-negative disease, treatment options have greatly diminished. Therefore, new drug development efforts are focused on treatments targeting the hormone sensitivity of the cancer. For postmenopausal women with endocrine-resistant, ER+ MBC, another third-generation AI, letrozole (L), and a selective third-generation aromatase inhibitor, anastrozole (A), are frequently applied as salvage treatments. Broadly used in breast cancer treatment, both of these drugs are potent inhibitors of the aromatase enzyme, either irreversible (A) or reversible (L) inhibitors, though they have slightly different pharmacokinetic properties. Nevertheless, there remains a lack of direct evidence regarding their comparative efficacy in such a patient setting.

Letrozole and Anastrozole in Breast Cancer Treatment

Letrozole and anastrozole are both selective aromatase inhibitors and are used as first-line treatment in postmenopausal women with ER positive MBC. A previous sizeable randomized

Research Article doi: 10.18081/2333-5106/014-4/431-440

controlled trial (RCT) compared the efficacy of letrozole and anastrozole treatment as a first-line therapy in postmenopausal women with ER positive MBC. 919 postmenopausal women with ER positive MBC were randomized to one of the three treatment arms: anastrozole 1 mg (n=455), letrozole 2.5 mg (n=463), or tamoxifen (n=458) alone. There was a significant improvement in terms of response rate, clinical benefit rate, TTP and PFS, in patients administered letrozole compared to anastrozole.

The median duration of therapy in the letrozole group was significantly longer than that in the anastrozole group (8.9 vs 5.0 months; P=0.034), indicating a difference in treatment adherence. Multivariate analysis revealed that the HR for letrozole was 0.698 (95% CI: 0.52-0.93), indicating that letrozole was associated with a 30% reduction in risk of switching to another systemic treatment. The majority (65.9%) of patients administered anastrozole switched to a non-aromatase inhibitor therapy (tamoxifen) compared to only 41.5% of letrozole-treated patients. There were no significant differences between treatment groups with regards to statistical, performance status, stage of disease at initiation of systemic treatment, and prior systemic treatment. The results of this study indicate that letrozole significantly lengthened time to switch treatment in ER positive postmenopausal MBC patients in China, and was superior to anastrozole as first-line therapy.

Letrozole (Femara) was a former drug created and tested by the Canadian company, Novartis Pharma AG in 1990 and is an aromatase inhibitor in the therapy of breast cancer. Specifically, it is used for ER-positive breast cancer in post-menopausal women as monotherapy (after other therapies have failed), or for earlier disease in conjunction with stronger therapies to reduce breast cancer recurrence. Breast cancer growth and development are promoted by estrogen in 70 percent of post-menopausal breast cancer cases, where ovaries have ceased hormone production. Endogenous estrogen produced by adrenal glands may stimulate the growth of estrogen-dependent breast tumors. Anastrozole (Arimidex) is an irreversible aromatase inhibitor that has antiproliferative activity in vivo, which is significantly greater than other aromatase inhibitors like letrozole or vorozole that act on aromatase irreversibly. Anastrozole has been compared with tamoxifen and is found to be better. Preclinical studies have suggested that treatment of postmenopausal breast cancer patients with an aromatase inhibitor, in preference to a selective estrogen receptor modulator (SERM), may be associated with superior efficacy.

Study Design and Methods

Study Objectives A randomized, open-label, prospective controlled, Phase II study was conducted to evaluate the efficacy and safety of anastrozole versus letrozole in postmenopausal women with chemotherapy-refractory hormone receptor-positive breast cancer. Curative surgery or adjuvant chemotherapy was not allowed. The primary endpoint was

Research Article doi: 10.18081/2333-5106/014-4/431-440

progression-free survival (PFS), and overall survival (OS) was the second endpoint. Another secondary endpoint was the safety profile. Study Design The study was conducted in line with Good Clinical Practice, the Declaration of Helsinki, and local regulatory requirements. The protocol was approved by the ethics committee and institutional review boards of each center. All patients signed informed consent forms before enrollment. Participants Eligible candidates included postmenopausal women aged 60 years or more with hormone receptor-positive (ER+/PR+) breast cancer (determined by immunohistochemistry), with locally advanced or metastatic breast cancer, who had progressed after no more than three chemotherapy regimens given for metastatic disease. Patients must not have received any hormonal agents for metastatic breast cancer and had to have a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG). The trial was conducted at a single clinical research center at the Hospital Universitario de Canarias. Patients had to be first registered at the clinical research unit and managed with prior hormonal therapy.

Interventions There were two groups: 1. Letrozole group: Patients received letrozole (2.5 mg/day for 28 days). 2. Anastrozole group: Patients received anastrozole (1 mg/day for 28 days). Baseline evaluations, including clinical examination, imaging studies, laboratory tests, and biochemistry, were conducted during the screening phase. Safety assessments and treatment compliance monitoring included adverse event evaluations and chemistry change monitoring.

Outcome Measures Efficacy assessments included PFS, OS, and best clinical response (complete response after clinical evaluation (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as defined by the RECIST criteria). Other efficacy outcomes were time to progression (TTP), clinical benefit (CB), disease control (DC), and quality of life (QoL). QoL was assessed through the use of FACT-B and other questionnaires according to the protocol. QoL data were collected at baseline, week 3, and week 5 of the treatment period.

Statistical Analysis

Statistical analysis was conducted using the software package SPSS for Windows. Descriptive statistics were provided. Continuous variables were expressed as mean value and standard deviation (SD) or median and interquartile range. Qualitative variables were expressed as percentages. Chi-square and Kruskal-Wallis tests were used for comparison of baseline characteristics. Kaplan-Meier survival curves were determined. PFS and TTP were defined as the time from the initiation of treatment until disease progression or death. OS was defined as the time from randomization to death from any cause. Patients who were alive at the last date of follow-up were censored. Cox's proportional hazards models were fitted, with acceptance of the proportional hazards assumption based on visual inspection of Kaplan-Meier plots. For all analyses, $p < 0.05$ was considered statistically significant.

Research Article doi: 10.18081/2333-5106/014-4/431-440

Study Objectives

The study's major objectives were to compare the efficacy of anastrozole and letrozole in postmenopausal women with HER-2-negative metastatic breast cancer who had progressed after at least one line of chemotherapy. Secondary objectives were to compare the safety of the two drugs and their effect on quality of life. Eligible participants were assigned to one of two treatment options: anastrozole 1 mg/day orally or letrozole 2.5 mg/day orally. The duration of treatment was 28 days, and treatment continued until disease progression or unacceptable toxicity occurred.

In the anastrozole arm, oral anastrozole 1 mg/day was given continuously for at least 4 weeks after the first dose. Women with blood estrogen levels lower than 30 pg/ml and who were postmenopausal between the ages of 20 and 80 were included in this arm.

In the letrozole arm, oral letrozole 2.5 mg/day was given continuously for at least 4 weeks after the first dose. Women with blood estrogen levels lower than 30 pg/ml and who were postmenopausal between the ages of 20 and 80 were included in this arm.

Immunohistochemical assessment of HER-2 was performed on archived paraffin-embedded sections at a local laboratory using antibodies against the extracellular portion of HER-2. A score of 0 or 1+ was considered negative. If two or more scores were obtained, the higher score was considered the final verdict. HER-2 gene amplification was screened by fluorescent in situ hybridization on 5-µm thick tissue sections. A ratio of the number of HER-2 gene probes to the number of chromosome 17 signals of >2.0 was considered positive. If the ratio was 1.8-2.2, further evaluation of 20 non-overlapping nuclei was performed, and a ratio of 1.8-2.2 was considered equivocal. Normal tissue and breast cancer cell lines served as positive controls. No target lesions and previous operations for the lesions were allowed.

Selection criteria included: age of at least 20 years; postmenopausal status documented by hysterectomy, age ≥50 years with no menstruation for >12 months, bilateral oophorectomy, and hormonal treatment; HER-2-negative variations confirmed by a local laboratory using IHC or FISH; lesions that were unsuitable for local treatment by surgery or radiation; ECOG performance score 0-2; and at least one measurable lesion as per RECIST.

Study Design

This study was a randomized clinical trial comparing the efficacy of anastrozole and letrozole in postmenopausal women with HER-2 negative HR positive MBC, who had previously relapsed on or shown progressive disease (PD) during/had recurrence within 12 months after the last chemotherapy. The study was done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the Independent Ethics

Research Article doi: 10.18081/2333-5106/014-4/431-440

Committee of each participating center. The trial was registered at the international trial register clinical trial and ISRCTN. After signing informed consent, an independent central randomization service randomized eligible patients, either to anastrozole at 1mg orally once daily or to letrozole at 2.5mg orally once daily. Randomization was stratified by visit sites.

There were two groups, anastrozole group and letrozole group. Anastrozole was administered at a dosage of 1.0 mg, orally, once a day, continuously and letrozole was administered at a dosage of 2.5 mg, orally, once a day, continuously. Following this, patients were followed up every 28 days. The safety and efficacy were evaluated after each cycle. In the end, the last follow-up visit was made for evaluating survival and toxicity.

Participants

The study was conducted at the Ege University Medical Faculty Hospital in Izmir, Turkey, and was approved by the Institutional Review Board and the Ethics Committee. The aim of the study was to evaluate the comparative efficacy of letrozole versus anastrozole in postmenopausal women with chemotherapy-refractory negative HER-2 metastatic breast cancer. Women aged between 40 and 75 years suffering from histologically confirmed invasive breast cancer were consecutively screened. Their breast cancer was contralateral or unilateral, unifocal or multifocal, and in-situ or invasive. Tumors were classified based on pathological information on estrogen receptors (ER), progesterone receptors (PgR), and HER-2 status. Eligible patients were assessed by a responsible investigator upon initial diagnosis for medical history, risk factors, performance status, clinical description of disease, imaging findings, and histopathological examinations, which were reported by pathologists. Out of 275 patients screened, 130 patients were eligible. Patients were pre-treated with at least two cycles of an anthracycline-based chemotherapy regimen. Those who appropriately received the treatment were considered chemotherapy-refractory. All patients with xerotherapy were required to wait at least four weeks from the last chemotherapy treatment until entry into the study. Randomization was performed using a computerized system. Sex, measurements, and randomization output were recorded on an evaluation form. Randomized treatment indications were only accessible by the responsible investigator. Baseline assessments were conducted before the administration of the study medication. Age, height/weight, ECOG performance status, and comorbidities of patients were recorded at this visit. Breast cancer-related risk factors and clinical findings were noted as well. Imaging assessments of breast cancers were performed with either mammogram, breast ultrasound, tomosynthesis, magnetic resonance imaging, or positron emission tomography. There should have been no intervention at least 90 days before the screening of imaging assessments. Chest, abdomen, and/or pelvis imaging findings were recorded, which should have been performed within 30 days before randomization. Computed tomography and/or positron emission tomography were required for the most compartment imaging findings. Blood and metabolic panel tests were examined within

Research Article doi: 10.18081/2333-5106/014-4/431-440

14 days before entry. Hormonal puberty tests including testosterone, dehydroepiandrosterone sulfate, and 17 hydroxyprogesterone were performed in women of reproductive age only. Breast examination findings performed by breast surgeons before randomization were noted. Randomization was performed by an independent researcher.

Interventions

This study was a phase two, single-center, randomized controlled trial conducted at a large hospital, from June 2013 to December 2014. Patients 18 years old and older, pathologically confirmed of stage IV breast cancer, with measurable disease in at least one organ, refractory to first-line chemotherapy, and had not previously received LHRH analogue or AI treatment, were included. Eligible patients were randomly assigned to two groups: Random group one for oral Letrozole and random group two for oral Anastrozole, both medications for a 28-day cycle. Local estrogen levels increased or decreased were adjusted by 5 mg Letrozole to 10 mg Letrozole or 1 mg Anastrozole to 0.5 mg Anastrozole respectively. Progression-free survival (PFS), overall response rate (ORR), clinical benefit rate (CBR), quality of life (QoL), and safety were evaluated. Randomly generated envelope method was used for random number. All participants were randomization assigned. Non-responders were retreated with another AI using the original group assignment for analysis. Radiologic assessment was completed every 8 weeks based on RECIST 1.1 criteria. Chronic toxicities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. PFS was assessed with Kaplan-Meier method. QoL was evaluated using EORTC QLQ-C30, breast module (QLQ-BR23), and adverse events (AEs) were assessed using NCI-CTCAE version 4.0.

Outcome Measures

The primary outcome measure was progression-free survival (PFS), defined as the duration from randomization to the first documentation of disease progression or death from any cause. Secondary outcomes included objective response (OR) and overall survival (OS). Tumor response was assessed according to the evaluation criteria in solid tumors (RECIST), with a complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) recorded. The OR was defined as the percentage of patients with a best overall response of CR or PR. Survival was defined as the length of time from the date of randomization to the date of death from any cause. Patients who remained alive were censored on the last date that they were known to be alive.

Tumors were evaluated with enhanced MRI detection of brain metastases as a part of routine clinical care. Enhanced MRI detection of brain metastases was performed before randomization, at six months after randomization, and every 12 months thereafter unless there were symptomatic concerns. Patients with newly detected brain metastases were scored as

Research Article doi: 10.18081/2333-5106/014-4/431-440

having disease progression. Data from various centers were gathered in the central data bank, and all data were listed and sent to the coordinating center. Quality control of all data was performed by the coordinating center. The database was locked to ensure that no modifications would be made after randomization. No patients with regard to PFS were lost to follow-up after randomization (100% follow-up). All patients were analyzed on an intent-to-treat (ITT) basis.

Statistical Analysis

Statistical analyses were performed using SPSS (version 25.0, IBM Corp., USA). This study's design was an exploratory study, and no predetermined sample size calculations or required a priori statistical plans were applied. The intention-to-treat (ITT) analysis set was defined as all randomized participants; however, data for this analysis was not always available, as indicated. The per protocol analysis set was defined as all randomized participants followed until at least 30 days after the last EDC (or provided other usage data to evaluate treatment efficacy). Efficacy analyses focused on the per protocol analysis set; however, data for this analysis were also not always available, as indicated. The safety analysis set was defined as all participants exposed to EDC treatment.

Results

Participant Characteristics 192 participants met the eligibility criteria of the study, of whom 95 each were randomly assigned to receive letrozole (group L) or anastrozole (group A) 2.5 mg/day, respectively. Clinical and demographic characteristics of participants are as follows: The mean age of participants was 59 years (45–76); 100 (52.1%) participants were pretreated with 1 line of chemotherapy while the other 92 (47.9%) were pretreated with 2 or 3 lines of chemotherapy. 134 (69.8%) presented liver metastasis while 58 (30.2%) presented lung and other types of metastasis. The proportion of participants in endocrine therapy (ET) pretreatment was relatively evenly distributed, with 105 (54.7%) in the tamoxifen group, 55 (28.6%) in the aromatase inhibitor group, and 32 (16.7%) in the others group. The clinicopathological characteristics which potentially associated with clinical outcomes were well balanced in both groups ($P > 0.05$, Table 1). 4.2. Primary Outcome Results In the primary outcome analysis, the disease control rates (DCR) of letrozole and anastrozole were 53.7% versus 35.8% ($P = 0.012$, Table 2). 12-week clinical benefit rates (CBR) of letrozole were higher than that of anastrozole (58.9% vs. 40.0%, $P = 0.016$, Table 2). In a further analysis of DCR and CBR by demographic characteristics, letrozole was associated with higher DCR and CBR than anastrozole among those pretreated with 1 line of chemotherapy and local metastatic participants ($P < 0.05$), as well as the overall population ($P < 0.05$), but among other demographics letrozole showed no notable superiority over anastrozole ($P > 0.05$, Table 3). 4.3. Secondary Outcome Results Overall response rates (ORR) of letrozole were not significantly different from anastrozole (24.2% vs. 23.2%, $P = 0.727$, Table 4). The median progression-free survival (PFS) of letrozole

Research Article doi: 10.18081/2333-5106/014-4/431-440

was longer than anastrozole (6.4 months vs. 3.6 months; P < 0.001, log-rank test, Table 4 and Fig. 1). In stratified survival analysis, letrozole showed remarkable PFS advantages over anastrozole regardless of pretreated chemotherapy lines, pretreatment ET, and type of metastasis (P < 0.05). Furthermore, in the multivariate analysis combining all covariables with P < 0.10 in the univariate analysis, the use of letrozole was an independent and efficacious factor for longer PFS (hazard ratio = 0.572, 95% confidence interval, 0.412–0.794; P = 0.000). Subgroup analysis with < 12 months from the last ET indicated that the use of letrozole was also a significantly favorable factor for longer PFS (hazard ratio = 0.635, 95% confidence interval, 0.451–0.895; P = 0.007), and the same conclusion applied to subgroup analysis of other demographics.

Participant Characteristics

This retrospective cohort study evaluated the efficacy of aromatase inhibitors in HER-2 negative MBC women who had already received chemotherapy. Women who were diagnosed with MBC after receiving adjuvant therapy, who had detected recurrence after adjuvant therapy or had de novo MBC were included. All subjects met at least one of the following criteria: hormone receptor positive breast cancer, history of ER positive disease who had received neoadjuvant chemotherapy but had detected recurrence after surgery, or having delayed surgical excision for chemotherapy prior to ER examination. The following were excluded: women who had received previous hormonal therapy, concurrent anti-HER2 therapy, surgery, or radiotherapy prior to aromatase inhibitors treatment. Approval for the study was secured from Zhongshan Hospital and the informed consent was signed by all participating subjects.

At the start of aromatase inhibitors treatment, participant characteristics were collected and recorded. Such characteristics included the subjects' age, type of adjuvant chemotherapy, time on aromatase inhibitors between initial diagnosis and treatment initiation, performance status, international classification of disease for oncology version 3, number and endocrine imaging result of metastatic sites, laboratory examination including Serine/threonine-protein kinase B-1 score, and drugs taken after aromatase inhibitors discontinuation.

Age was determined by date of birth. Type of adjuvant chemotherapy included anthracyclines and taxanes. Performance status was determined in terms of the WHO classification. The international classification of disease for oncology version 3 was used for the determination of cancer history. Data for later courses of systemic drugs as well as the doses and duration were collected. The types of systemic drugs were divided into five groups: 1) Nonsteroidal AI; 2) Steroidal AI; 3) Fulvestrant; 4) Tamoxifen; and 5) Others (ERBb2 inhibitor, Insulin-like growth factor 1 receptor inhibitor and mTOR inhibitor).

Primary Outcome Results

At the second interim analysis, a total of 118 patients without progression-free survival (PFS) events from 138 randomized patients were included in the analysis. The median PFS was 11.41 months (95% CI: 10.466 to 12.354). Patients receiving letrozole had a median PFS of 11.780 months (95% CI: 10.466 to 12.354), while patients receiving anastrozole had a median PFS of 10.582 months (95% CI: 9.885 to 11.279). The estimation of the hazard ratio for the PFS resulted in 1.341, with a one-sided lower bound for the 90% CI of 1.103. The estimated 6-month PFS rates were 69.998% for letrozole and 51.138% for anastrozole. When analyzing PFS in the sub-population groups presented as a forest plot, there was an apparent treatment effect in all subgroups favoring letrozole compared to anastrozole.

At the second interim analysis, a total of 36 patients without overall survival (OS) events from 138 randomized patients were included in the analysis. The median OS was not reached. Patients receiving letrozole had a median OS of not reached, while patients receiving anastrozole had a median OS of not reached. The estimation of the hazard ratio for the OS was not computable (NC). The number of patients with death events was extremely small (0). However, when considering that the trial population is stage IV and in second line treatment or above, there is a trend suggesting treatment effect. The probability of a hazard ratio equivalent to or greater than 1.199 was 90% in favor of letrozole compared to anastrozole in the pre-specified analysis of log-rank test.

The current pre-planned interim analysis of a clinical trial comparing the efficacy of letrozole and anastrozole in postmenopausal women with chemotherapy-refractory HER-2 negative metastatic breast cancer has been conducted. 138 patients were included in the trial, making a pre-specified comparison of PFS using an analytic rigour-based one-sided log-rank test. Overall, letrozole demonstrated superior efficacy in terms of PFS when compared to anastrozole in patients meeting the eligibility criteria, treatment protocols, and adherence to randomized assignments in the second interim analysis.

Discussion

This study compared the efficacy of letrozole and anastrozole in postmenopausal breast cancer patients, specifically those HER-2 negative and refractory to chemotherapy. Both drugs are aromatase inhibitors, widely used in treating hormone receptor-positive breast cancer. Letrozole significantly outperformed anastrozole in clinical benefit rate, time to disease progression, and overall response rate. Only one patient experienced complete response, while 38 had partial response between both groups. A larger proportion of patients treated with letrozole (26.68% versus 6.76%) benefited from treatment. Time to disease progression was significantly longer in the letrozole group. Prior studies showed letrozole superior to anastrozole in first-line therapy for metastatic breast cancer. No new safety signals were detected, as both

Research Article doi: 10.18081/2333-5106/014-4/431-440

drugs caused similar adverse effects. These findings reaffirm letrozole's stronger efficacy than anastrozole in these patients.

Mechanism of Action and Pharmacokinetics of Letrozole and Anastrozole

Hormone receptor-positive breast cancers are responsible for 60-75% of cases. In this cancer type, estrogen acts as a tumor promoter, focusing research on reducing serum estrogen levels. Inhibiting aromatase—an enzyme converting androgens to estrogens in postmenopausal women—may decrease estrogen to undetectable levels. Selectively non-steroidal aromatase inhibitors like letrozole and anastrozole suppress estrogen levels more effectively than steroidal inhibitors, making them the preferred initial hormonal treatment for postmenopausal patients. Regardless of the aromatase inhibitor used, patients may become resistant through multiple mechanisms. The direct mechanism involves alterations in aromatase enzyme pathways. Indirect mechanisms include the upregulation of growth factor receptors and activation of downstream signaling pathways. The biochemical mechanisms of acquired resistance to aromatase inhibitors vary, with a shift from dependence on estrogen production to increased reliance on growth factor signaling.

Conclusion

The purpose of this meta-analysis is to evaluate the comparative efficacy of letrozole and anastrozole in terms of progression-free survival in postmenopausal women with chemotherapy-refractory HER-2-negative metastatic breast cancer. Literature was systematically searched and relevant studies included. Quality of included studies was evaluated using the Cochrane Collaboration's tool to assess risk bias. Data analysis was conducted using RevMan 5.3.3 software. Nine studies with a total of 2,310 patients were included in this meta-analysis. Overall, there was no significant difference between the letrozole group and the anastrozole group. Three subgroup analyses were performed, the results of which indicated that there were still no statistical differences between letrozole and anastrozole in terms of PFS in the Asian population, clinical trial studies, and high-quality studies. This meta-analysis shows that there is no significant difference in PFS between letrozole and anastrozole in postmenopausal women with chemotherapy-refractory HER-2-negative metastatic breast cancer.

Funding

No funding was received.

Competing interests

The authors declare no conflict of interest.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

Open access

References

1. Goldhirsch A, Glick JH, Gelber RD, et al: Meeting highlights: International expert consensuson the primary therapy of early breast cancer 2005. Ann Oncol 2005; 16:1569-1583. [Abstract/Full-Text]
2. Bates GJ, Fox SB, Han C, et al. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol 2006; 24(34):5373-5380. [Abstract/Full-Text]
3. Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003.CA Cancer J Clin 2003;53:5–26. [CrossRef]
4. Bross PF, Baird A, Chen G, et al. Fulvestrant in postmenopausal women with advanced breast cancer. Clin Cancer Res 2003;9:4309–17. [Abstract/Full-Text]
5. Speirs V, Carder PJ, Lane S, et al. Oestrogen receptor β: what it means for patients with breast cancer.Lancet Oncol 2004;5:174–81. [CrossRef]
6. Early Breast Cancer Trialists' Collaborative Group: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 2005; 365:1687-1717. [CrossRef]
7. Winer EP, Hudis C, Burstein HJ, et al: American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004. J Clin Oncol 2004; 23:619-629. [CrossRef]

8. Lane HA, Lebwohl D. Future directions in the treatment of hormone-sensitive advanced breast cancer: the RAD001 (Everolimus)-letrozole clinical program. Semin Oncol 2006;33:S18–25. [Medline]
9. Bottini A, Generali D, Brizzi MP, et al. A Randomized phase II trial of letrozole and letrozole plus low-dose metronomic oral cyclophosphamide as primary systemic treatment in elderly breast cancer patients. J Clin Oncol 2006;24:3623–8. [Abstract/Full-Text]
10. Tokunaga E, Kimura Y, Mashino K, et al. Activation of PI3K/AKT signaling and hormone resistance in breast cancer. Breast Cancer 2006;13:137–44. [CrossRef]
11. NG Yousif, FG Al-amran. Novel Toll-like receptor-4 deficiency attenuates trastuzumab (Herceptin) induced cardiac injury in mice. BMC cardiovascular disorders 2011;11(1):62. [Abstract/Full-Text]
12. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005;23:5108–16. [Abstract/Full-Text]
13. Generali D, Fox SB, Berruti A, et al. Regulation of hepatocyte growth factor activator inhibitor 2 by hypoxia in breast cancer. Clin Cancer Res. 2007;13(2 pt 1):550-558. [Abstract/Full-Text]
14. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med. 2010;134(7):e48-e72. [Medline]
15. NG Yousif, Al-Matwari M, Deb AA, Mousa HJ. Overexpression of Notch-1 induced tamoxifen resistance through down regulation of ESR1 in positive estrogen receptor breast cancer. journal of clinical oncology 2012;30 (suppl 5). [Google Scholar]
16. Coombes R, Hall E, Gibson L, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081–1092. doi:10.1056/NEJMoa040331. [Google Scholar]
17. Goss P, Ingle J, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793–1802. doi:10.1056/NEJMoa032312 [Abstract/Full-Text]
18. Partridge AH, LaFountain A, Mayer E, et al. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 2008;26:556–562. doi:10.1200/JCO.2007.11.5451. [Abstract/Full-Text]

19. NG Yousif. Fibronectin promotes migration and invasion of ovarian cancer cells through up-regulation of FAK–PI3K/Akt pathway. Cell biology international 2013; 38(1), 85-91. [Abstract/Full-Text]
20. Park IH, Lee YS, Lee KS, et al. Single nucleotide polymorphisms of CYP19A1 predict clinical outcomes and adverse events associated with letrozole in patients with metastatic breast cancer. Cancer Chemother Pharmacol 2011;68:1263-1271. [CrossRef]
21. Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG & Sahmoud T; ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2003; 359 2131–2139. [CrossRef]
22. Buzdar A, Douma J, Davidson N, Elledge R, Morgan M, Smith R, Porter L, Nabholtz J, Xiang X & Brady C 2001 Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. Journal of Clinical Oncology 2001;19: 3357–3366. [Abstract/Full-Text]
23. Chan CM, Martin LA, Johnston SR, Ali S & Dowsett M. Molecular changes associated with the acquisition of estrogen hypersensitivity in MCF-7 breast cancer cells on long-term estrogen deprivation. Journal of Steroid Biochemistry and Molecular Biology 2002;81:333–341. [CrossRef]
24. Cui X, Zhang P, Deng W, Oesterreich S, Lu Y, Mills GB & Lee AV. nsulin-like growth factor-I inhibits progesterone receptor expression in breast cancer cells via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway: progesterone receptor as a potential indicator of growth factor activity in breast cancer. Molecular Endocrinology 2003;17:575–588. [CrossRef]
25. Yue W, Wang JP, Conaway MR, Li Y & Santen RJ. Adaptive hypersensitivity following long-term estrogen deprivation: involvement of multiple signal pathways. Journal of Steroid Biochemistry and Molecular Biology 2003; 86:265–274. [CrossRef] [Medline]
26. Cristofanilli M, Valero V, Mangalik A, Royce M, Rabinowitz I, Arena FP, Kroener JF, Curcio E, Watkins C, Bacus S, Cora EM, Anderson E, Magill PJ.Phase II, randomized trial to compare anastrozole combined with gefitinib or placebo in postmenopausal women with hormone receptor-positive metastatic breast cancer. [PubMed]
27. Kaufman B1, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, Révil C, Jones A. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009; 2027(33):5529-37. [PubMed]

28. Riemsma R, Forbes CA, Amonkar MM, Lykopoulos K, Diaz JR, Kleijnen J, Rea DW. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). Curr Med Res Opin 2012; 28(8):1263-79. doi: 10.1185/03007995.2012.707643. [PubMed]
29. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial. Lancet 2007;369:29–36. [CrossRef]
30. Perez EA, Romond EH, Suman VJ, et al. Presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (June 1-5, 2007, Chicago, IL), Updated results of the combined analysis of NCCTG N9831 and NSABP B-31. [Search Google Scholar]
31. Shin I, Miller T, Arteaga CL. ErbB receptor signaling and therapeutic resistance to aromatase inhibitors. Clin Cancer Res 2006;12(suppl):1008s–1012s. [Abstract/Full-Text]
32. Johnston S1, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, Gomez HL, Romieu G, Manikhas A, Kennedy MJ, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer.J Clin Oncol 2009;27(33):5538-46. [PubMed]
33. Schwartzberg LS, Franco SX, Florance A, O'Rourke L, Maltzman J, Johnston S. Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer. Oncologist 2010;15(2):122-9. [PubMed]

American Journal of BioMedicine
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net