The Efficacy of 3rd Generation Aromatase Inhibitors in Breast Cancer Chemoprevention

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Abstract

Background: Currently, tamoxifen and raloxifene are the only FDA-approved and USPSTF recommended pharmacologic treatments for breast cancer chemoprevention in high-risk postmenopausal women. Despite their widely recognized efficacy at reducing the incidence of breast cancer, the risk of potentially significant adverse effects may limit patient allocation. Consequently, research on the efficacy of third-generation aromatase inhibitors (AIs) as breast cancer preventives has emerged, especially since their value as adjuvant and combination therapy for breast cancer is well-established. The safety profile of anastrozole and exemestane potentially provide an appealing alternative to postmenopausal patients with a higher risk of developing breast cancer. Studies have successfully demonstrated the efficacy of AIs at reducing the incidence breast cancer, and further research will help to validate the FDA-approval of AIs for this indication.

Methods: An exhaustive search of medical literature included MEDLINE, Web of Science, CINAHL, and the National Institute of Health Clinical Trials using the key words: aromatase inhibitors, anastrozole, letrozole, exemestane, and chemoprevention. Relevant articles were critically appraised and GRADE was used for qualitative assessment.

Results: An extensive literary search rendered 262 relevant articles from January 2000 to February 2014. After screening several articles, two randomized control trials met inclusion criteria. The NIH clinical trials site yielded 36 results, and one trial met inclusion criteria. The LIBER trial, listed under NCT00673335, is in Phase III with a predicted completion date of February 2017.

Conclusion: Third generation AIs, such as anastrozole and exemestane, are very effective at reducing the incidence of invasive breast cancer, ductal carcinoma in situ, and certain tumors in high-risk postmenopausal women. Although both AIs demonstrate adverse effects, their overall safety profiles may be more favorable than other pharmacologic chemoprevention alternatives. More research, larger scale studies, and a longer follow-up after concluding treatment will be valuable to the prospective FDA-approval of AIs in breast cancer prevention.

Keywords: aromatase inhibitors, anastrozole, letrozole, exemestane, chemoprevention

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Degree Name
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Keywords
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The Efficacy of Third-Generation Aromatase Inhibitors in Breast Cancer Chemoprevention

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A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 9, 2014

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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

**Background:** Currently, tamoxifen and raloxifene are the only FDA-approved and USPSTF recommended pharmacologic treatments for breast cancer chemoprevention in high-risk postmenopausal women. Despite their widely recognized efficacy at reducing the incidence of breast cancer, the risk of potentially significant adverse effects may limit patient allocation. Consequently, research on the efficacy of third-generation aromatase inhibitors (AIs) as breast cancer preventives has emerged, especially since their value as adjuvant and combination therapy for breast cancer is well-established. The safety profile of anastrozole and exemestane potentially provide an appealing alternative to postmenopausal patients with a higher risk of developing breast cancer. Studies have successfully demonstrated the efficacy of AIs at reducing the incidence breast cancer, and further research will help to validate the FDA-approval of AIs for this indication.

**Methods:** An exhaustive search of medical literature included MEDLINE, Web of Science, CINAHL, and the National Institute of Health Clinical Trials using the key words: aromatase inhibitors, anastrozole, letrozole, exemestane, and chemoprevention. Relevant articles were critically appraised and GRADE was used for qualitative assessment.

**Results:** An extensive literary search rendered 262 relevant articles from January 2000 to February 2014. After screening several articles, two randomized control trials met inclusion criteria. The NIH clinical trials site yielded 36 results, and one trial met inclusion criteria. The LIBER trial, listed under NCT00673335, is in Phase III with a predicted completion date of February 2017.

**Conclusion:** Third generation AIs, such as anastrozole and exemestane, are very effective at reducing the incidence of invasive breast cancer, ductal carcinoma in situ, and certain tumors in high-risk postmenopausal women. Although both AIs demonstrate adverse effects, their overall safety profiles may be more favorable than other pharmacologic chemoprevention alternatives. More research, larger scale studies, and a longer follow-up after concluding treatment will be valuable to the prospective FDA-approval of AIs in breast cancer prevention.

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Table I: Summary of Findings
Table II: GRADE Quality Assessment of Reviewed Articles

List of Abbreviations

ADH………………………………………………………………Atypical ductal hyperplasia
AIs………………………………………………………………Aromatase inhibitors
ALH…………………………………………………………….Atypical lobular hyperplasia
ASCO………………………………………………American Society of Clinical Oncology
DCIS…………………………………………………………Ductal carcinoma in situ
ECOG…………………………………………….Eastern Cooperative Oncology Group
GRADE…………Grading of Recommendations, Assessment, Development and Evaluations
HR…………………………………………………………Hazard ratio
IBIS-II…………………………………………International Breast cancer Intervention Study II
LCIS………………………………………………………..Lobular carcinoma in situ
MAP.3……………………………………………………….Mammary Prevention.3
NNT…………………………………………………………Number needed to treat
QOL…………………………………………………………Quality of life
RR……………………………………………………………Risk ratio
SERM………………………………………………….Selective estrogen receptor modulator
USPSTF……………………………………………United States Preventive Services Task Force
The Efficacy of Third Generation Aromatase Inhibitors in Breast Cancer

Chemoprevention

BACKGROUND

Currently, tamoxifen and raloxifene are the only FDA-approved\textsuperscript{1,2} and USPSTF recommended\textsuperscript{3} treatments for breast cancer chemoprevention in high-risk postmenopausal patients. Albeit their efficacy as widely recognized preventive agents, neither comes without statistically significant adverse events, such as venous thromboembolism, endometrial cancer, or stroke.\textsuperscript{4-6}

Third generation aromatase inhibitors (AIs) have proven not only their efficacy as adjuvant and combination treatment of breast cancer, but also exhibit a favorable safety profile.\textsuperscript{6,7} Despite their association with accelerated bone loss and prolonged use,\textsuperscript{7,8} AIs provide a potentially more appealing alternative to postmenopausal patients who are unable to take selective estrogen receptor modulators (SERMs), decline the use of SERMs due to significant adverse effects or other reasons, or are considering surgical options for breast cancer prophylaxis. The favorable advent of AIs in the chemopreventive setting has even led the American Society of Clinical Oncology (ASCO) to refine treatment recommendations.\textsuperscript{9}

Based on the current ASCO guidelines for pharmacologic intervention for breast cancer risk reduction, the recommendation for third generation aromatase inhibitors extends only to exemestane in the preventive setting. As of 2013, the new recommendation for exemestane is that it should be considered a breast cancer risk-reducing alternative to tamoxifen and raloxifene in postmenopausal patients who have a higher risk of developing breast cancer, especially those who are estrogen-receptor positive or have a history of lobular
carcinoma in situ or atypical hyperplasia. The benefits and risks of exemestane should be discussed with the patient, as should the use of any preventive pharmacologic agent.\textsuperscript{9}

The purpose of this systematic review is to investigate the efficacy of third generation aromatase inhibitors as chemopreventive agents in postmenopausal women who have a greater risk of developing breast cancer.

**METHODS**

An exhaustive search of medical literature included MEDLINE, Web of Science, CINAHL, and the National Institute of Health Clinical Trials registry using key words: aromatase inhibitors, anastrozole, letrozole, exemestane, and chemoprevention. Inclusion criteria were clinical studies on high-risk post-menopausal women, using aromatase inhibitors, evaluating chemoprevention, measuring incidence of breast cancer, and published in the English language. Exclusion criteria consisted of studies containing adjuvant or combination therapy or concomitant hormone-replacement therapy. Once pertinent articles were identified, the bibliographies were thoroughly examined. Articles that met inclusion criteria were critically appraised and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to qualitatively assess each study.\textsuperscript{10}

**RESULTS**

An extensive literary search of various databases initially rendered 262 relevant articles from January 2000 to February 2014. After omitting duplicates and screening the remaining articles, two randomized control trials\textsuperscript{11,12} were identified as meeting eligibility criteria. A search of the National Institute of Health Clinical Trials database yielded 36 active
clinical trials, with one that has yet to be published.\textsuperscript{13} Tables I & II provide a summary of findings and quality assessment of reviewed articles.

\textbf{IBIS-II Trial}

The International Breast cancer Intervention Study II (IBIS-II)\textsuperscript{11} is a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of anastrozole as a breast cancer preventive in high-risk postmenopausal women. Over a nearly 10-year period beginning in 2003, a total of 3864 eligible participants were selected. Women were postmenopausal, aged 40-70 years old, and had a greater risk of developing breast cancer. Those considered high-risk included women aged 40-44 years with four times the relative risk, aged 45-60 years with greater than twice the relative risk, those aged 60-70 years with greater than 1.5 times the relative risk of breast cancer, or women who had a 10-year risk of breast cancer greater than 5\% based on the Tyrer-Cuzick model.\textsuperscript{11}

Women excluded from the study were premenopausal, had a personal history of breast or other cancer, used hormone replacement therapy for greater than 6 months, had a prophylactic mastectomy, had severe osteoporosis, had a less than 10-year life expectancy, had a history of gluten and/or lactose intolerance, intended to continue hormone replacement therapy, or had a physiological or psychological reason that would confound the trial. The study took place throughout 153 centers in 18 countries. Over a period of 5 years, 1914 randomized participants were given 1 mg of anastrozole orally per day.\textsuperscript{11}

The primary endpoint was occurrence of breast cancer. Secondary endpoints included estrogen-receptor positive breast cancer, other cancers, cardiovascular disease, death contributed to breast cancer or other causes, and adverse episodes. Endpoints were monitored via interval clinic visits, a mammogram at baseline and then at a minimum of
every 2 years, baseline dual energy x-ray absorptiometry scan and spinal radiographs, and blood work for possible biomarkers at baseline, 1 year, and 5 years.\textsuperscript{11}

Cuzick et al\textsuperscript{11} concluded that anastrozole is effective at reducing the incidence of invasive breast cancer and ductal carcinoma in situ (DCIS) (HR 0.47, 95% CI 0.32-0.68; p<0.0001; NNT =36 in 7 years). The authors determined that anastrozole was particularly effective at reducing the incidence of high-grade invasive breast cancer (HR 0.35, 95% CI 0.16-0.74) when compared to low-grade invasive breast cancer (HR 0.86, 95% CI 0.31-2.38). Cuzick et al further reported that anastrozole was effective at reducing the incidence of estrogen-receptor positive tumors (HR 0.42, 95% CI 0.25-0.71) when compared to placebo.\textsuperscript{11}

The most commonly reported side effects included vasomotor (RR 1.15, 95% CI 1.08-1.22) and musculoskeletal symptoms (RR 1.10, 95% CI 1.06-1.16), which were more prevalent in the anastrozole group versus the placebo group. Other symptoms significant in the anastrozole group included vaginal dryness, hypertension, influenza, and otitis media (95% CI, RR 1.19 [1.03-1.37], 1.64 [1.18-2.28], 2.11 [1.06-4.19], and 3.04 [1.21-7.64], respectively). Although more hypertensive events occurred in the anastrozole group, authors reported no discernible difference in cardiovascular or stroke events between the groups. Furthermore, Cuzick et al\textsuperscript{11} conveyed no dissimilarity in the event of fractures when comparing the two groups (RR 1.11, 95% CI 0.90-1.38), despite 16% of participants simultaneously taking a bisphosphonate (330 [17%] in anastrozole group versus 297 [15%] in placebo group).\textsuperscript{11}

Regarding adherence, authors projected that 68% of the anastrozole group and 72% of the placebo group had completed the entire 5-year treatment period. Reasons listed for early termination of treatment were adverse effects (375 [20%] in anastrozole group; 298
[15%] in placebo group) and the elective withdrawal of participants from treatment (94 [5%] in anastrozole group; 98 [5%] in placebo group).\textsuperscript{11}

Cuzick et al\textsuperscript{11} endorse the use of anastrozole as a breast cancer preventive in high-risk postmenopausal women.

**MAP.3 Trial**

The NCIC Clinical Trials Group Mammary Prevention.3 (MAP.3)\textsuperscript{12} is a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of exemestane as a breast cancer preventive in high-risk postmenopausal women. Over a nearly 6-year period that began in 2004, a total of 4560 participants were recruited. Participants eligible for the trial included postmenopausal women aged 35 or older and at least one qualifying risk factor: aged 60 or older, Gail score >1.66%, personal history of lobular carcinoma in situ or atypical ductal hyperplasia, or ductal carcinoma in situ treated with mastectomy. Ineligible participants included carriers of the BRCA1 or BRCA2 gene, premenopausal, history of cancer, uncontrolled thyroid disease, or chronic liver disease.\textsuperscript{12}

The study took place in the United States, Canada, Spain, and France. Over a median follow-up period of almost 3 years, 2285 randomly assigned participants were given 25mg of exemestane, taken orally each day. The primary endpoint was occurrence of invasive breast cancer. Secondary endpoints included invasive breast cancer with associated DCIS, estrogen-receptor negative breast cancer, lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), number of clinical breast biopsies, cardiovascular events that also included those resulting in death, clinical fractures, other cancers, development of side effects, and menopause-specific quality of life (QOL).\textsuperscript{12}
Screening for breast-related events included interval clinical evaluations at 6 months and then each year, plus annual mammograms. Study data was reviewed every 6 months by an independent safety and data monitoring committee.\textsuperscript{12}

After the median follow-up of 35 months, the trial proved that exemestane is effective at reducing the incidence of invasive breast cancer and DCIS (HR 0.47, 95% CI 0.27-0.79; p<0.004; NNT = 94 in 3 years). Goss et al\textsuperscript{12} noted a decrease in the incidence of precancerous breast events, such as HER2-neu positive tumors (HR N/A) and estrogen-receptor positive tumors (HR 0.27, 95% CI 0.12-0.60, p<0.001), when compared to placebo. The total number of breast-related events was 66, and authors reported a 65% relative incident reduction of invasive breast cancers, from 0.55% to 0.19%.\textsuperscript{12}

The most commonly reported adverse effects were vasomotor and joint-related symptoms. Symptoms more prevalent in those taking exemestane versus placebo included hot flashes, fatigue, sweating, arthritis, and arthralgia (p<0.001, p=0.03, p=0.046, p=0.01, p=0.04, respectively). Goss et al\textsuperscript{12} also reported that no critical side effects, such as fractures, end-organ damage, other cancers, or death were directly contributed to exemestane.\textsuperscript{12}

Upon closure of the trial, 32.8% of participants in the exemestane group and 28.7% of participants in the placebo group had discontinued the medication. Goss et al\textsuperscript{12} remarked notable reasons for untimely treatment cessation included completion of the drug, adverse effects, and patient refusal.\textsuperscript{12}

Goss et al\textsuperscript{12} concluded that exemestane is effective at reducing the incidence of invasive breast cancer in postmenopausal women with a higher risk than the general population. The MAP.3 trial determined that key components of this study were the risk-to-benefit ratio and safety profile of exemestane.\textsuperscript{12}
LIBER Trial: Phase III

The purpose of the LIBER trial\textsuperscript{13} is to determine the efficacy of letrozole versus placebo in breast cancer prevention in postmenopausal women with the BRCA1 or BRCA2 gene. The projected active treatment period is 5 years, and the intended observation period for long-term effects after concluding treatment is 5 years.\textsuperscript{13}

Eligible participants must be postmenopausal, aged 40-69 years or older, ECOG or WHO performance status 0-1, normal complete blood count and labs as specified by certain criteria, or no history of osteoporosis or fractures within the past 2 years of enrollment. Exclusion criteria are personal history of invasive cancer within the past 5 years, history of cardiovascular disease such as myocardial infarct or ischemia, hypersensitivity to letrozole, hepatic or renal insufficiency, prior hormone therapy in the past year, or any other psychological or social reason that would be interfere with the study.\textsuperscript{13}

The LIBER trial is currently in Phase III with a predicted completion date of February 2017.\textsuperscript{13}

DISCUSSION

Third generation aromatase inhibitors, specifically anastrozole and exemestane, are effective at reducing the incidence of invasive breast cancer and DCIS in high-risk postmenopausal women. According to the IBIS-II trial,\textsuperscript{11} 47% of the placebo group developed invasive breast cancer or DCIS compared to the anastrozole group (HR 0.47, 95% CI [0.32-0.68]). Of particular significance, 35% of the placebo group developed a high-grade invasive tumor (HR 0.35, 95% CI [0.16-0.74]), and 42% of the placebo group developed an estrogen-receptor positive invasive tumor (HR 0.42, 95% CI [0.25-0.71]) when
compared to the anastrozole group. Overall, of 36 people treated with anastrozole in a 7-year period, one person will develop invasive breast cancer or DCIS.

The MAP.3 trial\textsuperscript{12} demonstrated the significant efficacy of exemestane in breast cancer prevention. In the placebo group, 47\% developed invasive breast cancer or DCIS compared to the exemestane group (HR 0.47, 95\% CI [0.27-0.79]). Additionally, 36\% of the placebo group developed precancerous tumors such as LCIS, ADH, and ALH (HR 0.36, 95\% CI [0.11-1.12]). Overall, one person out of 94 treated with exemestane will develop invasive breast cancer or DCIS in a 3 year period.

Additionally, both trials\textsuperscript{11,12} also demonstrate the relative safety of aromatase inhibitors, especially with regard to fracture risk and concomitant use of bisphosphonates.

Although the trials\textsuperscript{11,12} have proven the efficacy of anastrozole and exemestane as breast cancer chemopreventive agents in high-risk postmenopausal women, each have limitations. The most profound limitation of both studies is the loss to follow-up: 30\% of participants in the IBIS-II trial\textsuperscript{11} and 30.3\% of participants in the MAP.3 trial\textsuperscript{12} (Tables I & II). Further limitations of the MAP.3 trial\textsuperscript{12} included a lack of precision, considering only 66 breast-related events, a median follow-up of only 35 months, and the amount of participants who received exemestane was less than anticipated.\textsuperscript{12} The limitations of each trial, and the lack of precision in the MAP.3 study were factored into the GRADE qualitative assessment and have been downgraded as deemed necessary (Table II).

Further GRADE analysis\textsuperscript{10} of the IBIS-II and MAP.3 studies\textsuperscript{11,12} did not yield any serious concerns with inconsistency, indirectness, or risk of bias. Although the GRADE of the IBIS-II trial\textsuperscript{11} is considered “moderate” and the MAP.3 trial\textsuperscript{12} is considered “low,” the overall quality of evidence is modestly supportive. Clinicians should be encouraged by the
fact that AIs are efficacious at reducing the incidence of breast cancer in postmenopausal women at a higher risk.

The results of the IBIS-II and MAP.3 trials\textsuperscript{11,12} and the anticipated results of the LIBER trial\textsuperscript{13} are encouraging for the future of AIs as chemopreventive agents in high-risk postmenopausal women. Recommendations for future study of aromatase inhibitors include investigating a larger outcome and evaluating the lasting effects of treatment, including their long-term efficacy and safety at reducing the incidence of breast cancer after the treatment period has concluded.

**CONCLUSION**

Third-generation aromatase inhibitors, such as anastrozole and exemestane, are remarkably effective at reducing the incidence of invasive breast cancer and DCIS in high-risk postmenopausal women. Anastrozole demonstrates extended efficacy at reducing the incidence of high-grade and estrogen-receptor positive invasive tumors, while exemestane also proves to be effective at decreasing the number of HER2-neu positive and estrogen-receptor positive tumors. Although both anastrozole and exemestane exhibit adverse effects, the overall safety profile of each may be more favorable than other chemoprevention alternatives. Further research on AIs, such as the publication of the LIBER trial, investigating larger scale studies, and evaluating the lasting effects of treatment after the established 5-year completion, will substantiate the evidence for prophylactic use of AIs in breast cancer prevention.
References


Table I. Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Participants</th>
<th>Age of Participants</th>
<th>Loss to Follow-Up</th>
<th>Effect HR (95% CI)</th>
<th>Duration of Follow-Up</th>
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<tbody>
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<td>Control Group</td>
<td>Placebo Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuzick et al(^1)</td>
<td>IBIS-II: Anastrozole</td>
<td></td>
<td>55-64 yrs</td>
<td>1155 (30%)</td>
<td>36 in 7 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.47 (0.32-0.68)</td>
<td></td>
</tr>
<tr>
<td>Goss et al(^2)</td>
<td>MAP.3: Exemestane</td>
<td></td>
<td>37-90 yrs</td>
<td>1381 (30.3%)</td>
<td>94 in 3 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.47 (0.27-0.79)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Hazard Ratio: Invasive breast cancer and DCIS

Table II. GRADE Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Studies</th>
<th>Design</th>
<th>Incidence of Breast Cancer</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Risk of Bias</th>
<th>Quality</th>
<th>Importance</th>
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</thead>
<tbody>
<tr>
<td>Cuzick et al(^1)</td>
<td>RCT</td>
<td>Serious(^a)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>MODERATE</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>Goss et al(^2)</td>
<td>RCT</td>
<td>Serious(^a)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^7)</td>
<td>Not serious</td>
<td>LOW</td>
<td>Critical</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Downgraded for large loss to follow-up
\(^7\)Downgraded due to duration of follow-up (3 years) and amount of breast-related outcomes (66)