Exemestane in the prevention setting

Jennifer Keating Litton, Therese B. Bevers and Banu K. Arun

Abstract: Aromatase inhibitors are well-established therapies in the neoadjuvant, adjuvant and metastatic settings for breast cancer. In adjuvant trials, this class of drugs has shown preventative properties by decreasing the rate of contralateral breast cancer. Recently, the National Cancer Institute of Canada Clinical Trials Group MAP.3 study evaluated exemestane as a breast cancer prevention agent for women with specified higher risks of developing breast cancer. We review the history of exemestane and evaluate the available evidence of its use for breast cancer prevention.

Keywords: aromatase inhibitors, breast cancer, exemestane, prevention

Introduction

Selective estrogen-receptor modulators (SERMs) have been the mainstay of therapeutic breast cancer prevention trials. The American Society of Clinical Oncology has published guidelines reviewing these agents in the prevention setting [Visvanathan *et al.* 2009]. Tamoxifen and raloxifene have been shown to have efficacy as breast cancer prevention agents. However, due to concerns of toxicities such as uterine cancer, thromboembolic events and cataract formation, only a very small portion of women eligible for SERM prevention therapy, estimated at only 4%, pursue this option [Ropka *et al.* 2010]. The aromatase inhibitors have shown improvement in disease-free survival when compared with tamoxifen and they do not carry the significant increased risks of thromboembolic events and uterine cancer when compared with tamoxifen [ATAC, 2008]. They have shown similar if not better evidence of prevention of contralateral breast cancers in adjuvant studies. Here, we review the development of exemestane in the prevention setting with the recent publication of the results from the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) Mammary Prevention.3 trial (MAP.3) [Goss *et al.* 2011] and make recommendations regarding its usage as a chemopreventative agent.

History of exemestane

Aromatase is the enzyme that is involved in the process of converting androstenedione to estrone

and estradiol [Santen *et al.* 2009]. High levels of circulating estrogens have been demonstrated in cancer models to promote tumorigenesis and growth [Endogenous Hormones and Breast Cancer Collaborative Group, 2011]. In postmenopausal women, the majority of estrogen synthesis occurs in the adipose tissue. In addition, postmenopausal obese women have higher rates of circulating estrogens [Grodin *et al.* 1973; Simpson *et al.* 1996]. Higher levels of aromatase have also been identified in breast tissue, both in benign as well as malignant breast tissue [Pasqualini *et al.* 1996; Santen *et al.* 2009; Szymczak *et al.* 1998]. Owing to the peripheral estrogen production in postmenopausal women as well as the significant estrogen production within breast tissue itself, aromatase was an attractive target for anti-breast-cancer therapy [Schwarzel *et al.* 1973]. Aminoglutethimide, the first aromatase inhibitor, was being developed simultaneously with tamoxifen in the 1970s [Santen *et al.* 2009]. However, the newer third-generation aromatase inhibitors (letrozole, anastrozole and exemestane) were found to be significantly more potent and specific with less toxicity than aminoglutethimide [Santen *et al.* 2009]. These agents should only be used in postmenopausal women, as their usage in premenopausal women, affects the peripheral conversion to estrogens, and can cause ovarian hyperstimulation in a woman with intact ovarian function, thus producing higher circulating estrogen levels [Casper, 2007; Dowsett *et al.* 1992; Johnston and Dowsett, 2003].

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Exemestane is a third-generation steroidal aromatase inhibitor. It is a type I inhibitor due to its mostly irreversible binding to aromatase. It is an oral medication that is rapidly absorbed. Steady-state levels of the medication are reached within 7 days at 25 mg oral daily dosing [Evans *et al.* 1992; Johannessen *et al.* 1997; Zilembo *et al.* 1995]. Higher levels did not provide significant further blockade of estrogen synthesis, therefore this dose was carried forward into therapeutic trials.

Exemestane as therapy in the metastatic setting for breast cancer

Multiple studies have been reported with the use of exemestane for women with metastatic breast cancer. Jones and colleagues treated 91 patients who had metastatic breast cancer that was refractory to tamoxifen with exemestane as a third-line therapy in a phase II clinical trial. There were four complete responses and eight partial responses with a clinical benefit rate (stable, partial or complete response) of 30%. They also showed significant reduction in circulating estrone and estradiol levels. The most significant side effects of nausea (20% and hot flashes (20%) [Jones *et al.* 1999].

Kvinnsland and colleagues treated 137 patients with differing responses to tamoxifen. There was an overall response rate of 23% and an overall success rate of 47% with a median time to progression of 25.1 weeks [Kvinnsland *et al.* 2000]. Several other studies also showed similar efficacy in the metastatic setting [Kaufmann *et al.* 2000; Paridaens *et al.* 2000].

Further evidence exists that women who have been treated with a nonsteroidal aromatase inhibitor such as letrozole or anastrozole, may still benefit from exemestane as there is evidence of lack of cross-resistance between these two classes of aromatase inhibitors [Beresford *et al.* 2010].

Exemestane as therapy in the adjuvant and neoadjuvant setting for breast cancer

With the activity of exemestane clearly established in the metastatic setting, its use in the adjuvant and neoadjuvant setting was also evaluated. The TEAM (Tamoxifen Exemestane Adjuvant Multinational) [van de Velde *et al.* 2011] and the IES (Intergroup Exemestane Study) [Coombes *et al.* 2007] studies evaluated exemestane in the adjuvant setting. In the IES study, 4724 postmenopausal breast cancer patients were eligible

after 2–3 years of tamoxifen therapy. They were randomized to either switch to exemestane or to continue with tamoxifen. Both groups completed 5 years of adjuvant endocrine therapy. In the intention-to-treat analysis there was a statistically significant improvement in breast-cancer-free survival and time to distant recurrence in those women who received exemestane. Interestingly, when looking at the risk of developing a contralateral breast cancer, there were 18 events in the group treated with exemestane *versus* 35 in those treated with tamoxifen alone. This translated to a hazard ratio (HR) of 0.57 (95% confidence interval [CI] 0.33–0.98) [Coombes *et al.* 2007].

The TEAM phase III trial enrolled postmenopausal women from nine countries and initially randomized women to receive exemestane *versus* tamoxifen for 5 years. However, after the IES study reported, the TEAM study was amended so that women who were started on tamoxifen were switched to exemestane after 2–3 years. In the intention-to-treat analysis at 5 years, there were no statistically significant differences in disease-free survival or overall survival between these two groups. There was also no difference in the percentage of new primary breast cancers reported (both were <1%) [van de Velde *et al.* 2011].

Exemestane has also been studied in the neoadjuvant setting. Lustberg and colleagues reported on the use of exemestane in combination with celecoxib [Lustberg *et al.* 2011]. Twenty-two women were enrolled with no pathological responses, but 36% partial response and 55% had stable disease. In the larger American College of Surgeons Oncology Group (ACOSOG) Z1031 study, 377 women were randomized to receive exemestane, letrozole or anastrozole preoperatively. In this study, the intention-to-treat clinical response rate was 62.9% for exemestane, 74.8% for letrozole and 69.1% for anastrozole [Ellis *et al.* 2011].

Toxicities in the adjuvant and neoadjuvant studies

In the IES study, between tamoxifen and exemestane, there was no statistically significant difference in hot flashes, depression, fatigue, ischemic heart disease or pain. However, exemestane had higher incidences of hypertension (35.8% *versus* 33.0%), fracture (4.3% *versus* 3.1%), arthritis (14.1% *versus* 12%), carpal tunnel syndrome (2.8% *versus* 0.3%), osteoporosis (7.3% *versus*

5.5%) and musculoskeletal pain (21% *versus* 16.1%). Tamoxifen had higher risks of serious gynecological events (9.0% *versus* 5.9%) and thromboembolic events (2.3% *versus* 1.2%). In the TEAM trial [van de Velde *et al.* 2011], there was no significant difference between the two groups with respect to all deaths and secondary malignancies. When comparing toxicities between tamoxifen followed by exemestane with the tamoxifen alone arm, tamoxifen had higher rates of hot flashes (40% *versus* 35%) and endometrial abnormalities (4% *versus* <1%), while the exemestane alone arm had higher rates of fractures (5% *versus* 3%), osteoporosis (10% *versus* 6%) and insomnia (13% *versus* 10%).

These trials had several other secondary end-points as well to aid in monitoring toxicity and quality of life. In the IES trial, bone mineral density (BMD) was followed and within 6 months of switching to exemestane, BMD was lowered by 2.7% (95% CI 2.0–3.4) at the lumbar spine and less significantly in the hip. It is important to note that no participant who entered the study with a normal BMD developed osteoporosis during the course of the study [Coleman *et al.* 2007]. Similarly, in the TEAM trial, women who were receiving tamoxifen had an increase in their BMD by 1.2% at month 12 and 0.2% at month 24, while women randomized to exemestane had a decrease of their BMD of 2.6% at baseline and 3.5% after 24 months [Hadji *et al.* 2011]. Cognitive functioning was also assessed in the TEAM trial. After 1 year of therapy, self reports of cognitive functioning, attention and concentration were reportedly in women who received tamoxifen *versus* exemestane (38% *versus* 27%, $p = 0.01$) [Schilder *et al.* 2011]. Fallowfield and colleagues also evaluated the switch from tamoxifen to exemestane as far as overall quality of life in the IES study, with no clinically meaningful differences between these two groups using several different validated metrics [Fallowfield *et al.* 2006]. Furthermore, Francini and colleagues, evaluated body composition and lipids after the switch from tamoxifen to exemestane in 55 patients and fat mass decreased by month 12 in women receiving exemestane *versus* no change in fat mass in the women receiving tamoxifen. There was no change in overall body weight or lipid profiles in women who received exemestane *versus* tamoxifen alone [Francini *et al.* 2006].

These studies demonstrated not only the efficacy of exemestane in the treatment of early breast

cancer, but also what appears to be a favorable toxicity profile when compared directly with tamoxifen. Although exemestane had higher rates of bone loss, arthralgias and myalgias, it also had lower incidences of severe gynecological disorders and thromboembolic disease. In addition, from the IES study, in conjunction with the decrease in contralateral breast cancers as seen in the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial [ATAC, 2008] aromatase inhibitors were felt to have a potential role in the prevention setting that should be investigated further.

Exemestane in the prevention setting

Several studies have evaluated the role of SERMs as chemopreventative agents for breast cancer. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study [Fisher *et al.* 2005], there was a 49% absolute risk reduction of breast cancer with tamoxifen *versus* placebo. In the subsequent NSABP STAR trial (P-2), tamoxifen was compared with raloxifene in women with a high risk of developing breast cancer. At the initial analysis, there was no statistically significant difference as far as prevention between these two SERMs, however, tamoxifen did have a higher rate of uterine hyperplasia and thromboembolic events [Vogel *et al.* 2006]. However, with the latest update on this trial, raloxifene was inferior to tamoxifen with regards to preventing invasive breast cancer (relative risk [RR] 1.24, $p = 0.01$), but tamoxifen still had higher rates of uterine cancer (RR 0.55, 95% CI 0.36–0.83), thromboembolic events (RR 0.75, 95% CI 0.60–0.93) and cataracts (RR 0.80, 95% CI 0.72–0.89) [Vogel *et al.* 2010].

With regards to ductal carcinoma *in situ* (DCIS), NSABP B-24 randomized women who had a wide excision and radiation therapy to either tamoxifen or placebo. With 1804 women initially included, tamoxifen decreased all breast events from 13.4% to 8.2% including subsequent diagnoses of both DCIS and invasive carcinoma at 5 years [Fisher *et al.* 1999].

With this mounting data surrounding SERMs in the preventative setting, aromatase inhibitors would also be an attractive choice for investigation. The aromatase inhibitors have a different toxicity profile, without as significant concerns as of uterine cancer and thromboembolic events, which mostly accounts for the only 4% of eligible high-risk women who decide to take tamoxifen [Ropka *et al.* 2010].

Exemestane, given its efficacy and favorable side effect profile, was chosen for the NCIC CTG Mammary Prevention.3 trial (MAP.3) [Goss *et al.* 2011]. This was a randomized, double-blind, placebo-controlled trial that started enrollment in September 2004 and continued until March 2010. Women who were 35 years of age or older were eligible if they were postmenopausal, age greater than 60, Gail 5-year risk score greater than 1.66%, prior atypia, lobular carcinoma *in situ* or DCIS status postmastectomy. A history of prior endocrine therapies was allowed, as long as they were not taken within 3 months of randomization. Women were excluded if they had a previous history of breast cancer, a known deleterious mutation in the *BRCA* 1 or 2 genes, a history of other malignancy or other uncontrolled thyroid or liver disease.

There were 4560 women included in the study, with 32.8% of the exemestane group and 28.7% of the placebo group off of therapy at the time of final data analysis. Only 5% in each group were due to completion of 5 years of the study drug. Approximately 85% of the women enrolled were compliant with study guidelines, with the major reasons for discontinuing being toxic effects (15.4% in exemestane and 10.8% in the placebo group). At a median follow up of 35 months, 11 invasive cancers were diagnosed in the exemestane group and 43 in the placebo group (HR 0.35, 95% CI 0.18–0.70). It is also important to note that with regard to exemestane in the prevention setting for DCIS, only 2.5% of participants had a history of DCIS with mastectomy at study entry and was not included in the planned subgroup analysis.

With regards to toxicity, exemestane had higher rates of any side effect (88% *versus* 85%), hot flashes (40% *versus* 32%), arthritis (11% *versus* 9%), and muscle and joint pain. There was no statistically significant difference in the rates of fracture, new osteoporosis or cardiovascular events.

Although a very well-conducted trial, this study had several limitations. The median follow up is short at only 35 months and longer follow up for trends will be needed to determine long-term efficacy. This study did not adequately address exemestane after a diagnosis of DCIS as only a small portion of women had actually had DCIS (2.5%). Those that did had to have had a unilateral mastectomy to be eligible to participate in this

study. In addition, women with *BRCA* mutations were also excluded and therefore this data should not be extrapolated at this point to this specific high-risk population. With this data, the number needed to treat is 94. Given the cost differential between tamoxifen and exemestane, exemestane may not prove to be our best cost-effective strategy at this point, especially with the addition of BMD monitoring. This may change as generic forms of exemestane are available, and further long-term follow up shows similar persistence of risk reduction as seen in the tamoxifen trials.

Future direction of endocrine prevention trials

In addition to the usage of exemestane, several other trials are ongoing and evaluating other endocrine prevention agents. The NSABP B-35 trial is evaluating the use of anastrozole *versus* placebo in women with DCIS who have had lumpectomy and radiation. The IBIS-II study is evaluating anastrozole *versus* placebo in high risk women. In addition, there is a French study currently accruing evaluating letrozole *versus* placebo in women with *BRCA*-deleterious mutations [ClinicalTrials.gov identifier: NCT00673335]. These trials are all evaluating anti-estrogen interventions in women at a high risk of developing breast cancer. They will likely have little, if any, effect on preventing hormone resistant breast tumors.

Conclusions

Exemestane is a well-tolerated and effective therapy for both early and advanced breast cancer. The MAP.3 trial shows at 35 months median follow up, exemestane demonstrates a 65% reduction in the incidence of breast cancer when compared with placebo. For women who are eligible for breast cancer prevention therapy, but for whom tamoxifen may be contraindicated (such as a history of a thromboembolic event or uterine cancer), exemestane may provide an alternative therapy. Further long-term follow up is needed, as well as cost assessment before exemestane gains widespread usage for this indication. Given the eligibility criteria for this study, we caution extrapolating this data to women with DCIS or known *BRCA*-deleterious mutations. There are ongoing trials accruing to evaluate aromatase inhibitors in the prevention setting for known *BRCA* mutation carriers and those studies will be better suited to answer that question. In addition, potential breast cancer prevention agents

will be chosen to potentially prevent hormone resistant breast cancers as well.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this manuscript.

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