Exemestane for early-stage ER-positive breast cancer

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KEY FINDINGS AND IMPLICATIONS FOR POLICY

Since breast cancer is the leading cause of cancer death among Filipino women, the Department of Health (DOH) has prioritized programs and policies that will make treatment for breast cancer, alongside other measures, more accessible to patients. Considering this, the Formulary Executive Council (FEC) has prioritized to assess an application for the inclusion of an aromatase inhibitor (AI), exemestane, for early-stage estrogen-receptor-positive (ER+) breast cancer in the Philippine National Formulary (PNF). Given that 2 hormone therapies for early-stage breast cancer are already in the PNF, it is important to be able to justify the inclusion of another treatment for the same indication.

Based on the results of the clinical trials obtained through a systematic search, supplemented by several rounds of consultation with local specialists, the clinical effectiveness of exemestane compared with other AIs and tamoxifen is comparable. The only significant difference between the therapies is the observed adverse events, mainly bone thinning for all AIs, which can be prevented by intake of calcium and bisphosphonate therapy. When cost is taken into consideration, exemestane remains to be the most expensive option among all AIs and tamoxifen, as no generic equivalent is available in the market. Given that exemestane has very limited added clinical benefit relative to other treatments, it may only be recommended for listing for early-stage breast cancer if its price is to be significantly reduced.

This technology appraisal was limited to the indication that was prioritized by the FEC during the initial scoping meeting, which is early-stage breast cancer. Exemestane was not assessed for efficacy and safety in patients who have metastasis or progressed to advanced stages of ER+ breast cancer. There is an unmet clinical need for this population, as government financing mechanisms are limited only to those in early stages. Exemestane may be reconsidered for listing for other indications when public budgets will allow for coverage of patients in the advanced stages.

BACKGROUND

Definition and Burden of Disease

Breast cancer is the malignant proliferation of epithelial cells lining the ducts or lobules of the breast. In the Philippines, breast cancer is the top leading cause of cancer death among Filipino women. In 2015, approximately 61,142 newly diagnosed breast cancer were reported. Majority of cancer-related deaths (23%) are from breast cancer[1]. At the time of initial diagnosis, 63.3% to 76.7% of Filipino women are classified as having early-stage breast cancer, which is defined as locally confined breast tumor with possible nodal involvement that correspond to TNM Stages I to IIIA. Specifically, early-stage breast cancer shows no signs of extension to the chest wall or skin, has possible ipsilateral axillary node involvement that is not matted or fixed to other structures, and show no signs of metastasis. Patients with late stage breast cancer correspond to TNM Stage IIIB to IV or those identified with metastasis, disease recurrence, or disease progression.

Understanding Local Practice

Due to the absence of a locally developed guideline, specialists usually follow the 2017 National Comprehensive Cancer Network (NCCN) guidelines[2]. Strategies that address early-stage breast cancer involve the treatment of locoregional disease and systemic disease.

For locoregional invasive breast cancer, both mastectomy and breast conservation surgery with radiotherapy have equivalent prognosis based on NCCN guidelines. However, in the Philippines, patients in the early-stage breast cancer are commonly treated with mastectomy.

Systemic therapy involves endocrine (hormone) therapy and cytotoxic chemotherapy. While selective estrogen receptor modulators (SERMs) and AIs are the two most common categories of endocrine therapy, the choice of therapy would depend on the patient's menopausal status[3]. Adjuvant endocrine therapy include the following: SERMs (tamoxifen), AIs (anastrozole, letrozole, and exemestane), and ovarian ablation or suppression. The NCCN guidelines suggest three main treatment strategies: upfront/monotherapy, sequential/switch therapy, and extended therapy. Between monotherapy and sequential therapy, local medical oncologists recommend monotherapy strategy due to better tolerability and patient compliance, while the latter is limited to patients who experience adverse events. Monotherapy for premenopausal women commonly use tamoxifen treatment for 5 years. On the other hand, postmenopausal women are offered 5-year monotherapy of AIs or tamoxifen. In consideration of higher treatment availability and better accessibility, tamoxifen and letrozole remain the standard treatment for early-stage breast cancer. Alongside endocrine therapy, chemotherapeutic agents such as anthracyclines, taxanes, and antimetabolite-based drug class are also utilized to optimize health outcomes.

Government Financing

There are 2 national government programs supporting treatment for early breast cancer: DOH Medicine Access Program for early-stage breast cancer (DOH-BCMAP) and the PhilHealth Z-benefit Package for early-stage breast cancer (i.e., stages I to IIIa). The DOH-BCMAP currently finances adjuvant chemotherapy, chemotherapy cycles, hormone therapy, and psychosocial support for women with operable early-stage breast cancer. The program is available in government hospitals with priority given to indigent patients with limited financial resources. The Z-benefit Package of PhilHealth covers for both surgical and medical treatment including laboratory examinations. Payment is divided into two tranches: the first tranche (PHP 75,000) covering for primary surgical treatment and the second tranche (PHP 25,000) covering for chemotherapy and hormone therapy. Radiotherapy is excluded from the PhilHealth Z-benefit package and is financed under the all-case-rate scheme. In 2016, PhilHealth Z-benefit Package reported 302 claims amounting to PHP 27,150,000. Since its inception, PhilHealth has already paid PHP 91,800,00 for the treatment of 1,049 breast cancer patients. At present, there is no formal government financing mechanism that supports the treatment of late stage breast cancer or those with recurrences.

AROMATASE INHIBITORS

Aromatase inhibitors lower estrogen levels by blocking the aromatase enzyme active site leading to the enzyme inactivation resulting to the inhibition of androgen to estrogen conversion in the peripheral tissue. Treatment strategy with AIs is individualized based on patient preference, concomitant comorbidities, and drug tolerability[4]. The most common adverse effects associated with AI therapy are vasomotor (e.g., hot flushes) and musculoskeletal symptoms (e.g., arthralgia and arthritis)[5–7]. Patients who are prescribed AIs are usually given bisphosphonates, which may avert or lessen bone thinning caused by AIs[8]. The adverse effects associated with AIs have been identified as the primary factor for discontinuation of treatment. Frequent monitoring of patient status is required to help identify those at high risk for discontinuation and those that will be required to change treatment regimens[9,10].

EXEMESTANE

Exemestane (Aromasin®) is an irreversible steroidal AI. The 25-mg tablet is given once daily after meals for a total duration of 5 years as an adjuvant treatment of postmenopausal women with early-stage breast cancer. Premature discontinuation of exemestane treatment is commonly due to the occurrence of musculoskeletal symptoms and worsening quality of life.

CONTEXT AND POLICY ISSUES

In January 2017, the FEC Secretariat received an application from the Philippine Society of Medical Oncology (PSMO) to list exemestane in the PNF for early-stage ER+ breast cancer. The proponent also applied for other indications: as first-, second-, and third-line treatment for advanced breast cancer.

In the Philippine setting, tamoxifen remains to be the most commonly prescribed hormone therapy due its affordability and accessibility to patients. AIs are commonly used as a second-line hormone therapy after disease progression from tamoxifen, with letrozole as a primary choice. Other AIs, such as anastrozole and exemestane, are used if the patient progresses further. As the choice of AI therapy depends largely on cost; exemestane is usually reserved as a last option after further disease progression.

The tamoxifen citrate 20-mg tablet has a reference price of PHP 16.31 based on the 2017 Philippine Drug Price Reference Index. Because letrozole was just recently listed in the PNF, no reference price is available, but it has a retail market price of PHP 152.50. A generic version of anastrozole is also available in the Philippine market; however, anastrozole is not available in the PNF. Its current retail price is PHP 165.00 per tablet. The current price offer for exemestane is PHP 376.24 per tablet.

Table 1. Price comparison of aromatase inhibitors in the Philippines

Aromatase inhibitor	**Price (PHP)**
Letrozole	152.50*
Anastrozole	165.00*
Exemestane	376.24**

* denotes retail market price

** denotes price offer of manufacturer

As the price of exemestane is significantly higher than the two other AIs available in the market (with one already listed in the PNF), evidence on its superiority, whether on efficacy or safety, versus the other two must be established to justify its inclusion in the PNF.

REVIEW OF CLINICAL EFFICACY & EFFECTIVENESS

Literature search strategy

Research articles were searched in HERDIN, PubMed, Scopus, and Cochrane databases. The search was conducted from January to February 2018. Keywords and MeSH terms used were “exemestane”, “aromatase inhibitors”, “adjuvant”, and “breast cancer.” Combination of these keywords with Boolean operators were also used. Systematic review and meta-analysis were also searched. 185 potential studies were found using the MeSH terms stated above. The objective of the assessment was to identify the efficacy and safety of exemestane in contrast to the other AIs.

Selection criteria and methods

The study selection criteria are randomized controlled trials study design reported in the English language that meets the PICO criteria. The PICO criteria are as follows: Population: ER+ postmenopausal women with early-stage breast cancer; Intervention: adjuvant sequential exemestane treatment; and Control: adjuvant tamoxifen or letrozole or anastrozole as monotherapy or sequential therapy. The exclusion criteria are premenopausal women, ER- postmenopausal women, and advance/metastatic breast cancer. All abstracts were assessed based on the selection criteria.

Literature Review

From the literature search, several systematic reviews and meta-analysis combined the trial efficacy and safety results of each AI and reported the outcome as a drug class effect. No systematic review/meta-analysis fit the selection criteria therefore the search proceeded to explore randomized clinical trials (Annex A). Out of the 185 potential studies, only the FATA-GIM3 and Intergroup Exemestane Study (IES) trial were able to fit the selection criteria.

FATA-GIM3

FATA-GIM3 trial compared adjuvant upfront/monotherapy treatment strategy with sequential/switch therapy for hormone receptor-positive postmenopausal women with early-stage breast cancer. It is also the first trial that compared all three AIs. Strengths of this study include the generalizable results due to the inclusivity of the criteria used and funding support was from academic source. Furthermore, centralized randomization and intention to treat (ITT) analysis is consistent across all groups and lost to follow up cases were low in numbers; therefore, selection bias is highly improbable. One limitation of this trial is the reduced analysis power due to a slow enrollment process. Despite this, the proportion of patients with events related to breast cancer and

malignancies due to other causes were comparable to other trials. In addition, minimal information bias was reported since treatment arms assignment was not concealed to both patient and provider, however only blinding of individuals conducting the statistical analysis was done. The trial also compared the individual drug efficacy and the treatment strategy for hormone receptor-positive postmenopausal women with early-stage breast cancer. The three AIs showed a similar efficacy in improving both disease free survival and overall survival. Additionally, adjuvant endocrine sequential therapy (2 years of tamoxifen followed by 3 years of AI) showed non-inferiority to the 5 years adjuvant AI monotherapy[11].

IES Trial

The IES study is a randomized, double blind phase 3 trial assessing the efficacy and safety of switch therapy with exemestane versus tamoxifen upfront monotherapy. There are four studies showing results from different follow-up period on the efficacy of sequential therapy of exemestane compared to tamoxifen. Eligibility criteria for this trial includes postmenopausal women (≥ 55 years old with ≥ two years of amenorrhea or >1 year of amenorrhea at initial diagnosis) with early-stage breast cancer alongside 2-3 years of tamoxifen treatment. Participants were centrally randomized to receive exemestane or tamoxifen daily for up to 2-3 years to have a total duration adjuvant endocrine therapy of 5 years. The IES trial reported disease free survival and overall survival as the primary and secondary outcomes, respectively. Breast cancer free survival was reported in consideration of consistency with other trials. The IES trial is mainly funded by the pharmaceutical company, Pfizer[12].

The latest follow up (120 months) study on the IES trial showed no statistically significant absolute difference on the overall survival between exemestane and tamoxifen. However, the absolute difference for breast cancer free survival (4.0%, 1.2 -6.7%) and disease-free survival (3.8, 0.9-6.6%) at 10 years were significant. Additionally, patients who were on exemestane are less likely to develop recurrences (HR 0.80, 0.71-0.90; p<0.001) and are more likely to show improved disease-free survival (HR 0.83, 0.75-0.93%; p=0.001). Nodal status, history of hormonal replacement therapy use, and previous chemotherapy were adjusted for in the multivariable analysis[13]. After 55.7 months of follow up, venous thromboembolic events, cramps, vaginal bleeding, uterine dilation and curettage, endometrial hyperplasia, uterine polyp/fibroids were significantly higher with tamoxifen use while arthralgia, carpal tunnel syndrome, osteoporosis, musculoskeletal pain, joint stiffness, diarrhea, and paresthesia were more commonly seen with exemestane treatment[14]. Furthermore, after 91 months follow up, there was no statistical significant difference in rate of adverse events with exemestane and tamoxifen[15].

Exemestane showed little to no significant improvement on the disease-free survival of hormone-positive postmenopausal patient with early stage breast cancer. Table 1 summarizes the primary outcome result of the two aforementioned trials.

Table 1. FATA-GIM 3 and IES Trial primary outcome results

		Disease-Free Survival Hazard Ratio (95% CI)
FATA-GIM 3*	Exemestane VS Anastrazole	1.24 (0.97-1.57)
	Exemestane VS Letrozole	1.05 (0.82-1.35)
IES**	Exemestane VS Tamoxifen	0.83 (0.75-0.93)

*After 5 years follow up[11]

**After 10 years follow up[13]

Studies evaluating the efficacy of exemestane compared to tamoxifen and other AIs are limited. Only the IES trial was able to compare sequential therapy of tamoxifen to exemestane with upfront tamoxifen monotherapy. Further direct head to head comparative studies are necessary to assess efficacy of exemestane in improving outcomes. There is no difference in efficacy among the three AIs. In addition, the different treatment strategies illustrated similar efficacy. Consequently, treatment regimen for hormone receptor-positive postmenopausal women with early-stage breast cancer is individualized based on drug tolerability, patient preference and financial capability.

VALIDATION OF FINDINGS WITH SPECIALISTS

Several clinical specialists in the files of medical oncology, surgical oncology, and pharmacology were consulted to understand local practice and effectiveness of the hormone therapies in the real-world setting. Based on their clinical practice, the clinical effectiveness of tamoxifen versus AIs was comparable. Although the clinical trials reported significant difference in the nature of adverse effects, the specialists stated that adverse events among Filipino patients taking tamoxifen are nil, with limited to no thromboembolic neither events nor significantly morbid adverse bone events observed.

In terms of efficacy among AIs, when compared with each other, the clinical experts confirmed that all have similar effectiveness and adverse event profile. The main adverse event observed was bone thinning, hence, patients are given calcium and bisphosphonates to prevent this effect. They added that the choice

between the three AIs would ultimately depend on cost, giving preference to anastrozole and letrozole as they have generic counterparts making them more affordable to patients.

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ANNEX A. Summary of studies on Aromatase Inhibitors

Trial Name	Intervention	Comparator
Monotherapy		
ATAC	ANA	TAM
MA 27*	EXE	ANA
Face	LET	ANA
BIG	LET	TAM
Sequential therapy vs. TAM		
BIG	TAM-LET	TAM
BIG	LET-TAM	TAM
ABCSG-8	TAM-ANA	TAM
ARNO-95	TAM-ANA	TAM
ITA	TAM-ANA	TAM
IES*	TAM-EXE	TAM
Sequential therapy vs. AI		
BIG	TAM-LET	LET
BIG	LET-TAM	LET
TEAM*	TAM-EXE	EXE
Extended therapy		
MA 17	LET	PLA
ABCSG-6 and ABCSG-6a	ANA	PLA
NSABP B-33*	EXE	PLA

*denotes trials that included EXE in their study.

ANA: anastrozole; EXE: exemestane; LET: letrozole; PLA: placebo; TAM: tamoxifen.