

Cost-effectiveness analysis review of exemestane in the treatment of primary and advanced breast cancer

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Abstract

Introduction: Exemestane was approved in 2005 for adjuvant treatment of breast cancer. In this study, we aimed to assess whether it is cost-effective in comparison to available alternatives.

Material and methods: To evaluate the efficacy of exemestane, a systematic review was conducted by searching electronic databases. The outcomes of interest were “clinical benefit”, “overall response” and “disease-free survival rate”. To evaluate the cost of treatments, costs of both domestic generic and imported brand medicines were taken into account, and the incremental cost-effectiveness ratio (ICER) was calculated for each comparison.

Results: Regarding primary breast cancer, based upon available evidence, exemestane could not be considered as a cost-effective medicine either in generic or brand form compared with placebo (ICER: 119,100 and 215,525), with tamoxifen after 2-3 years of therapy (ICER: 35,150 and 82,400) and with sequential treatment by tamoxifen and exemestane (dominated because of lower effectiveness and higher cost). In metastatic breast cancer, exemestane was not considered a cost-effective treatment compared with both anastrozole and megestrol acetate (dominated) and was highly cost-effective compared with tamoxifen (ICERs: 2,208 and 4,326 dollars per one more patient with an overall response for generic and brand medicines) although even in this case it was not cost-effective in terms of the 1-year survival rates (dominated).

Conclusions: Regarding current evidence and related costs in terms of Iranian pharmaceutical market prices, exemestane could not be considered a cost-effective treatment in primary and advanced breast cancer compared with available alternatives. However, more evidence is still needed for more certain decisions.

Key words: systematic review, cost-effectiveness, anastrozole, letrozole, megestrol acetate, exemestane, evidence based medicine.

Introduction

Breast cancer is the most common cancer among females all over the world [1]. Although its incidence is higher in developed countries, breast cancer is growing in developing countries because of multiple reasons including urbanization and changes in women's lifestyle [2]. Most of the mortality related to breast cancer (88%) is in developing countries [3]. Breast cancer is associated with a substantial economic burden, mostly

attributed to hospitalization and pharmacotherapy [4, 5]. According to a new study, direct medical costs of breast cancer in Isfahan (Iran) were 222.17, 224.61, 316.51 and 828.52 US dollars per patient per day for stage I to IV, respectively [6]. Cost of medications was indicated as a main component in this study. To reduce the burden of disease, policy makers should provide a strategy of dissemination of more cost-effective medicines and treatment guidelines. One of the important parts of the Iran national drug policy is to provide equal access of patients to essential drugs [7-9]. In order to implement equity in health, the affordability of medicines and the balanced utilization of medicines should be professionally managed [10].

Endocrine therapy (tamoxifen), aromatase inhibitors (anastrozole, letrozole (as a non-steroidal) and exemestane (steroidal), and progestins (megestrol acetate) as the main classes of medical treatment are available. These drugs in combination with other treatment strategies such as chemotherapy or radiotherapy are currently used for management of breast cancer.

Exemestane was approved in 1999 by the FDA [11] for the ancillary treatment of postmenopausal women with estrogen receptor positive early breast cancer who have already received 2-3 years of tamoxifen for completion of a total of 5 consecutive years of adjuvant hormonal therapy. Anastrozole [12] and letrozole [13] were also approved by the FDA for adjuvant treatment of postmenopausal women with estrogen receptor positive early breast cancer. Additionally, megestrol acetate is still a common treatment for advanced breast cancer [14].

In Iran, tamoxifen, letrozole, megestrol, anastrozole and exemestane are available for treatment of breast cancer patients [15]. Recently, the domestic generic exemestane entered into the market of Iran. Given the higher cost of treatment, to assess whether it is rational to add exemestane to the clinical practice guidelines and whether it is logical to be covered by national insurance, we were interested to analyze its cost-effectiveness [16-18]. In this study, cost-effectiveness of exemestane with other available alternatives such as tamoxifen, anastrozole, letrozole, and megestrol in primary and metastatic breast cancer was studied.

Material and methods

Data sources and searches

To evaluate the efficacy of exemestane, a systematic review was conducted by searching published studies in electronic databases including PubMed, Web of Science, Scopus, Google scholar and Cochrane review databases from 2000 to the end of 2012. The keywords were “exemestane”, “tamoxifen or letrozole or anastrozole or megestrol

and exemestane”, “breast neoplasm or breast cancer and exemestane”.

Outcomes of interest

The outcomes of interest were “overall clinical benefit”, which is defined as the proportion of patients who had a complete response (CR) or partial response (PR) or stable disease (SD), “overall response rate”, which is defined as the proportion of patients who had CR or PR, and “disease-free survival (DFS)”, which is defined as years of living without any events after treatment.

Process of study selection

The inclusion criteria included English language published articles of randomized controlled trials (RCTs) which compared clinical efficacy of exemestane with placebo, and also head-to-head RCTs comparing exemestane with tamoxifen, anastrozole, letrozole and megestrol acetate. The exclusion criteria were *in vivo* and animal studies, uncontrolled, observational and review studies, economic evaluations and studies evaluating biochemical effects. The search results were examined by two authors (ZG and MK) separately by reviewing titles and abstracts to eliminate duplicates and unrelated reports and those meeting exclusion criteria. Then the reports selected by each of them were rechecked whether to be included within the study or not. In the next step, the full texts of opted studies were reviewed to evaluate the inclusion and exclusion criteria in each of them to select final studies.

Assessment of trial quality

The quality of methodology in all included studies was evaluated by the Jadad score, which gives a score between 0 and 5 to each study based on randomization, blinding, and dropouts (withdrawals). Scores ≥ 3 were considered acceptable in terms of quality [19]. A Jadad score less than 3 was considered as an exclusion criterion.

Cost analysis

To calculate costs of treatment with exemestane and other medicines, regarding consulting professionals, only the direct medical costs were taken into consideration because there were tiny differences in the frequency and cost of laboratory monitoring and diagnostic tests between exemestane and other included alternatives. To calculate the cost of medicines, the cheapest combination of local generic dosage forms as the generic price and the most expensive combination of available brand dosage forms as the brand price were considered to cover all possible combinations of different dosage forms that a physician may prescribe. To

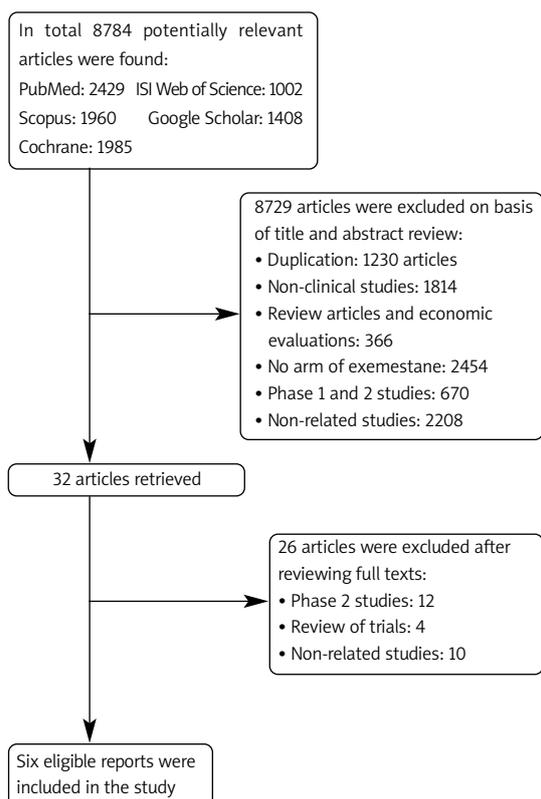


Figure 1. Flow of the process in selection of studies regarding the efficacy of exemestane in breast cancer

exchange prices from Iranian rials (IRR) to US dollars (USD), the time exchange rate declared by the central bank (12,260 IRR) was used (2012).

Data synthesis and analysis

Regarding the calculated local costs and extracted efficacy of exemestane and another alternative, the incremental cost-effectiveness ratio (ICER) was calculated for each generic and brand form of medicines. The ICER represents the cost (US dollars) per unit of difference in efficacy between two alternatives of intervention. A parametric one-way sensitivity analysis was performed based on the confidence intervals of the efficacy reports (if available). Given that there is no accurate threshold calculated for Iran, the ICERs were compared with one and

three times the GDP per capita according to the recommendation of WHO [20]. This procedure was done in order to evaluate just how the treatments of breast cancer with different doses are “highly cost effective” (when the ICER is less than GDP per capita), “cost-effective” (when the ICER is between one and three times the GDP per capita) and “not cost-effective” (when the ICER is more than three times the GDP per capita). The GDP per capita of Iran was considered to be 5608 USD based on 2010 statistics of the World Economic Outlook Database [21]. It has to be noted that the estimated threshold according to Iranian Health economists is approximately two times GDP per capita.

Results

Of a total of 8,784 searched articles, 2,429 were from PubMed, 1,960 from Scopus, 1985 from Cochrane review databases, 1002 from Web of Science, and 1408 from Google Scholar. Finally, six articles [22-27] met the inclusion criteria (Figure 1). The Jadad scores regarding all selected articles were calculated, and all studies were eligible to be included in the final analysis in light of getting a score more than 3 (Table I).

Characteristics of included studies

Exemestane and other alternatives in selected studies were evaluated in two indication categories of breast cancer. In some studies, the efficacy of exemestane was evaluated in early or primary breast cancer and in some others it was evaluated in advanced or metastatic breast cancer. In all investigated studies (on primary or advanced breast cancer), the methodology was confirmed by an institutional review board, and all patients had signed an approved consent form. Table II provides some key characteristics of studies and patients included in our analysis. Because of diversity in reporting outcomes, the pooling of results for efficacy was impossible. Thus we presented the extracted efficacy results and calculated ICER regarding each study and the treatment doses, one by one. The cost was calculated individually for each study due to different treatment duration.

Table I. Jadad score to evaluate the quality of included studies

Study	Randomization	Double blinded	Withdrawal and dropout	Total score
Coombes <i>et al.</i> , 2007 [23]	2	1	1	4
Mamounas <i>et al.</i> , 2008 [22]	2	1	0	3
Paridaens <i>et al.</i> , 2008 [27]	2	0	1	3
Campos <i>et al.</i> , 2009 [25]	2	0	1	3
Kaufmann <i>et al.</i> , 2000 [26]	2	1	1	4
Van de velde <i>et al.</i> , 2011 [24]	2	0	1	3

Early breast cancer

Exemestane-placebo

There was one study [22] comparing exemestane with placebo after 2-3 years of tamoxifen therapy. The ICERs for domestic generic and imported exemestane therapy were 119,100 and 215,525 (USD per one more patient with 4 years DFS from 100 patients), respectively. Both are more than three times the GDP per capita as the threshold and are considered as not cost-effective treatment.

Exemestane-tamoxifen

Based on one study [23] which compared exemestane with tamoxifen after 2-3 years of tamoxifen therapy, the ICERs of treatment with domestic generic and imported brand medicine were 35,150 and 82,400 (USD per one more patient with 5 years DFS from 100 patients), respectively. This means that switching to exemestane could be considered not to be a cost-effective intervention compared with continuing tamoxifen.

Based on another study [24] that compared 5 years of exemestane therapy with sequential treatment by tamoxifen (2-3 years) and exemestane (until 5 years), in spite of higher costs by the former strategy, no significant advantage was found, which makes the principal strategy dominated.

Metastatic breast cancer

Exemestane-anastrozole

One study evaluated the efficacy of exemestane in comparison with anastrozole in metastatic breast cancer [25], showing no significant advantage in terms of clinical benefit or overall response (effica-

cy). Thus given the higher cost of exemestane therapy, it is a dominated strategy. As mentioned in Table III, domestic generic anastrozole is not available in Iran.

Exemestane-megestrol acetate

Based on one study, which compared exemestane with megestrol acetate in metastatic breast cancer [26], no significant difference in clinical benefit and overall response of these two treatments was found. Therefore, considering the higher costs of exemestane, it is a dominated strategy compared to megestrol acetate.

Exemestane-tamoxifen

Regarding the results of one study comparing exemestane with tamoxifen in metastatic breast cancer [27], in terms of difference in all-inclusive response, the ICER for exemestane in comparison to tamoxifen was 2,208 and 4,326 for generic and brand medicines, respectively. When compared against the threshold, exemestane could be considered as highly cost effective. However, in terms of 1-year survival rates, the study showed no significant advantage of efficacy for exemestane compared with tamoxifen (Table IV). Therefore, it could be considered as a dominated strategy.

Discussion

Our analysis indicated that based upon available evidences and in spite of being more effective, switching to exemestane after 2-3 years is not cost-effective as an adjuvant treatment of primary breast cancer in post-menopausal women in comparison to continuing tamoxifen therapy. Furthermore, no weighty advantage is found in 5-year

Table II. Summarized characteristics of included studies

Study of patients	Number	Age (mean or distribution) [years]			Dosage [mg/day]		Treatment duration
		< 60	60-69	≥ 70	EXE 25	TAM 20 (30)	
Coombes <i>et al.</i> , 2007 [23]	4724	< 60 32.2%	60-69 42.8%	≥ 70 25%	EXE 25	TAM 20 (30)	30 months
Mamounas <i>et al.</i> , 2008 [22]	1598	< 60 50%	≥ 60 50%		EXE 25		5 years (for cost: 4 years)
Paridaens <i>et al.</i> , 2008 [27]	371	59.9 ±10.5			EXE 25	TAM 20	EXE: 7 months TAM: 9 months
Campos <i>et al.</i> , 2009 [25]	128	EXE 61.4 (10.5)		ANA 64.2 (10.1)	EXE 25	ANA 1	EXE: 17 weeks ANA: 18.5 weeks
Kaufmann <i>et al.</i> , 2000 [26]	769	EXE 64.3 ±8.1		MA 64.2 ±8.2	EXE 25	MA 160	17 weeks
Van de velde <i>et al.</i> , 2011 [24]	9779	< 60 34%	≥ 60 66%		EXE 25	TAM 20	5 years

TAM – tamoxifen, EXE – exemestane, MA – megestrol acetate, ANA – anastrozolea

Table III. Summarized results for the studies with “clinical benefit” and “overall response” as outcome

Study	Δ Clinical benefit in 100 patients	Δ Overall response in 100 patients	Δ Cost (USD) in 100 patients		ICER Cost per one more OR in 100 patients		Consideration based on comparing ICER with threshold	
			Generic	Brand	Generic	Brand	Brand	Generic
Paridaens <i>et al.</i> , 2008 [27] (EXE-TAM)	NR	14.4	31800	62300	2208	4326	HCE	HCE
Campos <i>et al.</i> , 2009 [25] (EXE-ANA)	N sig	N sig	NAv in Iran	46100	NA	NA	NA	Dominated
Kaufmann <i>et al.</i> 2000 [26] (EXE-MA)	N sig	N sig	18600	NAv in Iran	NA	NA	Dominated	Dominated

OR – overall response, N sig – not significant, NA – not applicable, NAv – not available, USD – United States dollar, HCE – highly cost effective, ICER – incremental cost-effectiveness ratio

Table IV. Summarized results for the studies with “disease-free survival rate” as outcome

Study	Δ DFS rate in 100 patients					Δ Cost (USD) in 100 patients		ICER Cost per one more OR in 100 patients		Consideration based on comparing ICER with threshold		
	1 y	2.5 y	2.75 y	3 y	4 y	5 y	Generic	Brand	Generic	Brand	Brand	Generic
Coombes <i>et al.</i> , 2007 [23]* (EXE-TAM)	-	4 (2-5)	-	-	-	4 (1-7)	140600	329600	35150 (140600-20086)	82400 (329600-47086)	NCE	NCE
Mamounas <i>et al.</i> , 2008 [22] (EXE-PLA)	-	-	-	-	2	-	238200	677600	119100	215525	NCE	NCE
Paridaens <i>et al.</i> , 2008 [27] (EXE-TAM)	N sig	-	-	-	-	-	31800	62300	NA	NA	Dominated	Dominated
Van de Velde <i>et al.</i> , 2011 [24] (EXE-TAM)	-	-	N sig	-	-	N sig	142500 (1710)	334200 (4010)	NA	NA	Dominated	Dominated

y – year(s), NCE – not cost effective, DFS – disease-free survival. *If more than one DFS is available, the longer time period is considered

exemestane therapy when compared with sequential tamoxifen-exemestane therapy. In treatment of metastatic breast cancer, no meaningful advantage in efficacy of exemestane in comparison to anastrozole and megestrol is found. Comparing exemestane and tamoxifen in advanced breast cancer led to two opposite results in terms of different outcome of interests that leaves the choice for policy makers.

Although exemestane has entered the Iranian pharmaceutical market since 2005 and its domestic generic has been available for more than 1 year, this study is the first economic evaluation of exemestane in treatment of breast cancer in Iran. The results of this study could be a good basis for policy makers in making logical decisions regarding the reimbursement and recommendations to clinical practitioners.

The results of our study are somewhat contradictory to other cost-effectiveness analyses con-

ducted in the USA which reported that switching to exemestane after 2 or 3 years of tamoxifen therapy is a cost-effective strategy versus continuing tamoxifen up to 5 years with an ICER of USD 20,100 per QALY (Quality Adjusted Life Year) gained [28]. Another economic evaluation to compare exemestane after 2-3 years of tamoxifen therapy for 5 years of tamoxifen therapy in a Swedish setting with a Markov transition model indicated that the ICER is Euro 31,000 per QALY gained, which means exemestane was considered a cost-effective treatment [29]. A cost-effectiveness analysis of exemestane versus megestrol acetate for metastatic breast cancer in post-menopausal women in Australia and European countries by a hazard-driven model showed that the ICER range is between Euro 3700 and 9,100 per life years gained, which in all cases means that exemestane could be considered a cost-effective treatment [30]. One rational reason for this inconsistency among present findings and those of

previous ones might concern the disparity in the threshold of different countries. Also it is notable that costs of medicines in developed countries and Iran differ a lot.

This study was done as a rapid health technology assessment (rHTA) and thus we used no decision model. Therefore, long-term and indirect effects and costs of each treatment strategy are not clear. The quality of life as an important outcome in cancer was also not considered in this study, which could be stated as a limitation of this study. Moreover, because of heterogeneous results from different trials, pooling of outcomes was impossible, and we were not able to conduct a meta-analysis. Although the results of this study could be cautiously used by policy makers, the use of decision models and full HTA for more precise estimation of efficacy and costs associated with each treatment strategy is recommended.

In conclusion, although based on the investigated trials, exemestane proved to be as effective as other alternatives in primary stage or metastatic breast cancer in postmenopausal women, higher costs of that treatment do not allow us to recommend it as a cost-effective treatment in Iran. However, designing better studies by considering decision models, quality of life, and adverse effects is felt to be essential before making a decision about adding or not adding exemestane to clinical practice guidelines and the reimbursement positive list.

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