Exemestane: A milestone against breast cancer

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ABSTRACT

Rapid advances in the treatment of breast cancer, especially in the form of hormone therapy have truly increased the hope of longer and better disease-free survival for these patients. Exemestane, a third generation aromatase inhibitor has been extensively evaluated in metastatic as well as adjuvant therapy of breast cancer. It has also been evaluated for its safety profile, especially on bone and lipids. Exemestane provides hope to the patients with breast cancer both in early and metastatic disease. This review analyzes all the aspects of exemestane therapy.

KEY WORDS: Aromatase inhibitors, breast cancer, hormonal therapy

Methods used for locating, selecting, extracting and synthesizing data

The relevant articles published in the last 10 years were searched in Pubmed and Medline using the search terms "Exemestane", "Aromatase inhibitors", "Breast neoplasms". The full texts of the articles were procured from various libraries. The relevant material was collected and analyzed from these articles.

Breast cancer is the second leading cause of cancer death in women today. Late diagnosis and the resulting delay in treatment leads to high incidence of death (> 410,000 annually worldwide).[1] Hormonal therapy exhibits encouraging efficacy with minimal toxicity. Exemestane, a third generation aromatase inhibitor (AI), has been studied in early as well as metastatic hormone receptor-positive breast cancer. This review analyzes all the aspects of exemestane therapy in breast cancer.

Chemistry

Exemestane is an orally active irreversible steroidal aromatase inactivator. It has very high structural similarity with androstenedione[2,3] [Figure 1].

Pharmacokinetics

The recommended dosage of exemestane is 25 mg taken orally once daily after a meal which is rapidly absorbed reaching peak plasma concentrations of 17 μg/L within one to two hours. Steady state is reached within seven days. Exemestane is extensively metabolized by cytochrome P450 3A4 and aldoketoreductases. The metabolites are either of lower potency or inactive and are excreted equally in urine and feces.[3] Exemestane has a total clearance of 517L/h and a terminal elimination half-life of 27h.[3,4]

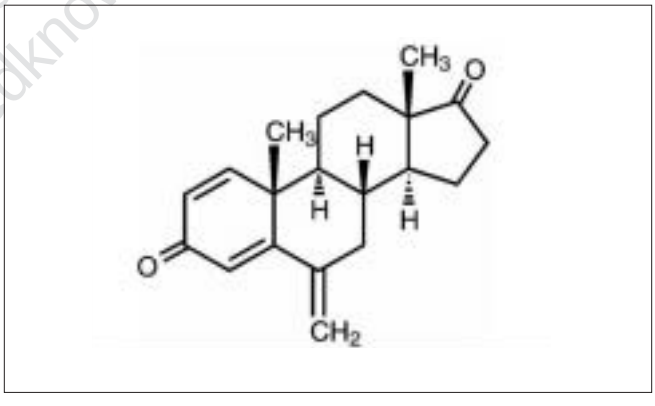

Figure 1: Structure of exemestane

Pharmacodynamics

Mechanism of action

In postmenopausal women, aromatase enzyme is responsible for the final step in estrogen synthesis. Exemestane is initially recognized by the aromatase enzyme as false substrate [Figure 2]. This is then transformed through an NADPH-dependent mechanism, to an intermediate that binds irreversibly to

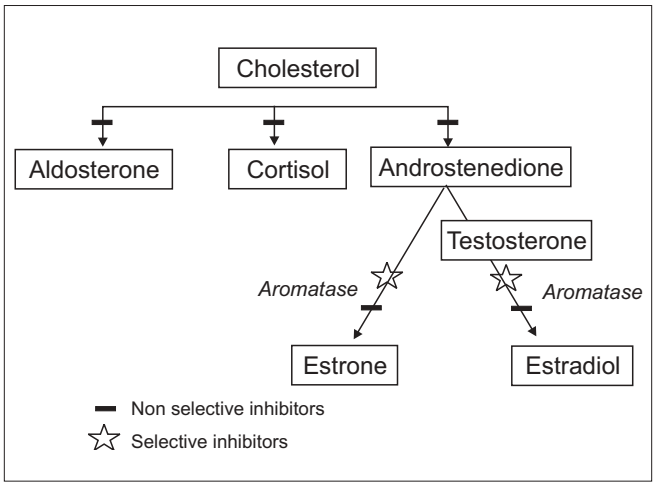

Figure 2: Selective versus nonselective inhibitors

aromatase, causing suicide inhibition and therefore *de novo* synthesis of aromatase is required for subsequent estrogen synthesis.[3,5] This is in contrast to other third generation inhibitors e.g., anastrozole and letrozole which are competitive inhibitors and hence can be displaced from the binding site.

Exemestane, at its clinically used dose of 25 mg/day suppressed aromatase activity by 97%, similar to that shown by anastrozole, at 1 mg/day dose.[6] *In vitro* studies have demonstrated a dose-related inhibition of aromatase activity with exemestane but other anti-aromatase agents (e.g., aminoglutethimide, anastrozole and letrozole) caused a paradoxical increase in aromatase activity under similar conditions.[7-9] This may in part explain the development of resistance with nonsteroidal, Type II agents and the ability of exemestane to induce a response when nonsteroidal agents fail.[10]

Exemestane - Clinical Application

Third line therapy

In a Phase II study, 80 patients, previously treated with endocrine treatments and/or chemotherapy, received 200 mg/day exemestane. The response rate was 26%, clinical efficacy 39% and average period achieving objective response was 52 weeks. A similar study with 25 mg exemestane showed clinical efficacy of 24.3%. In two studies, daily 25 mg exemestane was administered in relapse following tamoxifen and megestrol-acetate. The rate of clinical efficacy was 29% and 30%. These studies provide evidence that exemestane is effective in the treatment of repeatedly pretreated metastatic breast cancer patients.[11,12]

Second line treatment

Second line exemestane therapy decreases the risk of disease progression and the mortality in metastatic breast cancer by nearly 20%. Furthermore, in a study pain and symptoms associated with the tumor decreased more during exemestane therapy than during megestrol-acetate treatment. In case of visceral metastases, the objective response rate with exemestane was 14-29% and clinical efficacy was 36.3%, whereas with megestrol-acetate, it was 30.0%.[11]

In patients of metastatic disease who have progressed on tamoxifen, exemestane was equivalent to megesterol acetate in terms of response rate but it was superior to megesterol acetate in median time to progression (20 weeks *versus* 17 weeks) and median survival.[13]

First line treatment

In a long-term Phase II study comparing exemestane and tamoxifen, the overall response (OR) and clinical benefit (CB) rates were 41% and 57% respectively for the exemestane group. But in the tamoxifen group the OR and CB rates were 17% and 42% respectively.[14]

Adjuvant therapy

The Inter group Exemestane Study (IES) [Table 1] showed that exemestane therapy after two to three years of tamoxifen therapy significantly improved disease-free survival as compared with the standard five years of tamoxifen treatment.[15,16]

Neo-adjuvant therapy

Effect of exemestane on aromatization peripherally, in breast cancer and surrounding normal tissue, studied in 12 postmenopausal women with untreated large or locally advanced estrogen receptor-rich tumors, also showed a promising result [Table 2].[9]

Anastrozole and exemestane have been studied in smaller Phase II uncontrolled trials where the median reduction in tumor volume was 75-90% and the percentage of patients able

Table 1: Inter group exemestane study, intention to treat analysis[15]

Trial	Design	Total number of patients	Median follow-up (months)	Disease-free survival (Hazard ratio)	Absolute benefit	Overall survival
IES	switching	4724	55.7	0.76 (0.66-0.88)	3.3%	ITT:0.85 (0.71-1.02)

Table 2: Effects of neo-adjuvant therapy[9]

Duration of exemestane therapy	Total number of patients	Number of patients showing reduction in aromatization	Median reduction in tumor volume assessed by			Number of patients able to undergo breast conservation surgery
			Clinical examination	Ultrasound	Mammography	
3 months	12	11	85.5%	82.5%	84%	8 out of 10

to undergo breast-conserving surgery ranged from 80-88%.[17]

Aromatase inhibitors and inactivators should not be used in premenopausal women without concomitant ovarian blockade with gonadotropin releasing hormone analogues as ovarian aromatase escapes inhibition because of stimulation by gonadotropins.[2,18]

Safety Profile

Exemestane was generally well tolerated in clinical trials at once daily dosages up to 600 mg. Withdrawal due to adverse events occurred in 1.7-8% of patients.[3]

At a dosage of 25 mg once daily, adverse events were mainly Grade one to two in severity. The most commonly occurring adverse events were nausea (8-26%), hot flushes (7.5-24%), fatigue (7-12%), increased sweating (4.5-12%) and dizziness (3.4-12%). Significantly fewer patients receiving exemestane than megestrol experienced moderate to severe weight gain (7.6 *vs.* 17.1%).[3]

Androgenic events have been reported in some patients receiving once daily exemestane 200 mg, but were rarely reported at the recommended dosage. Symptoms that may have been androgenic in nature and related to exemestane 25 mg were reported in one study (alopecia two patients, acne one, hypertrichosis one).[3]

In two independent experiments conducted in female SD rats osteoporosis engendered by castration was completely alleviated by simultaneous administration of exemestane or its principal rat and human metabolite, 17-hydroexemestane which may be attributed to its androgenic action.[19]

Clinical studies have shown variable effects of exemestane on lipid profile. In a nine-week trial in advanced breast cancer and a 48-week study in postmenopausal woman with breast cancer, exemestane resulted in a significant decrease in both total cholesterol and HDL. Exemestane also decreased the total triglycerides levels in this study.[20]

In another European Organization of Research and Treatment of Cancer study, 24 weeks of exemestane therapy had no impact on the lipid profile.[20]

The Letrozole, Exemestane and Anastrozole Pharmacodynamics (LEAP) study was conducted in 96 healthy postmenopausal women to assess the pharmacodynamic differences between the three AIs at the 12th and 24th week. In the exemestane arm, there was a significant decrease in HDL-C levels associated with an increase in the ApoB:ApoA-1 ratio. However, no significant differences in the changes in nonHDL-C concentrations were observed between the treatment arms[21] [Table 3].

In another two-year trial enrolling 147 patients, exemestane was found to drop HDL levels by 6-9% with no major effects on serum lipids, coagulation factors or homocysteine levels.[22]

Table 3: LEAP study[21]

% Change in HDL-C levels	Exemestane	Letrozole	Anastrozole
At 12 weeks	-8.7	-3.9	-4.1
At 24 weeks	-12.3	-2.7	-1.3

The Greek sub-study of TEAM (Tamoxifen and Exemestane Adjuvant Multicenter) International trial evaluated the effects of either adjuvant exemestane or tamoxifen therapy on the lipid profile in 176 postmenopausal early breast cancer patients. After a study period of one year, exemestane was found to have a neutral effect on total cholesterol and HDL levels. Unlike tamoxifen's positive effect on LDL levels, exemestane did not significantly alter LDL levels. Tamoxifen on the other hand increased triglycerides levels, while exemestane resulted in a beneficial reduction.[23]

Unlike aminoglutethimide, exemestane does not influence plasma total homocysteine levels.[24]

In a randomized trial comparing megestrol acetate with exemestane as second-line hormonal treatment for metastatic disease in 366 patients, there was no incidence of thromboembolic events with the use of exemestane.[25]

Oral clearance of exemestane is reduced in the presence of significant hepatic or renal disease. The therapeutic implications of this is considered minor because of its relatively large safety margin and minor side-effects.[26]

Safety in case of pregnant women and the pediatric age group is not yet established but administration of exemestane in early stages of pregnancy in rats had shown detrimental effects on the fetus and with difficult labor process.[27] Exemestane is marketed for use only in postmenopausal women. It is contraindicated in pregnant or lactating women.[27]

No dose adjustment is required in the geriatric population.[26] There is no cross-resistance between exemestane and other nonsteroidal AIs.[28]

Exemestane is currently being evaluated extensively in several studies in postmenopausal women as upfront therapy versus tamoxifen in postmenopausal women with early breast cancer. Efficacy, safety and quality of life (QOL) end points are being evaluated in these studies.

Conclusion

Exemestane has been studied in patients of breast cancer who have progressed on tamoxifen and other hormonal therapy and in patients with early breast cancer after two to three years of initial tamoxifen therapy. In the latter, it is the only aromatase inhibitor to show an improved overall survival than tamoxifen. Emerging evidence from other patient subgroups will throw more light on exemestane's role in the entire spectrum of breast cancer.

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