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REVIEW

Novel Aromatase Inhibitors

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Oestrogen receptors are expressed in 2/3rd of all breast cancers and the oestrogen mediated growth stimulation through these receptors causes the progression of hormone sensitive breast tumours. Tamoxifen has played a significant role in the treatment of metastatic and early breast cancers, as well as in preinvasive ductal carcinova in situ. The occurance of adverse effects like hot flushes, vaginal dryness, thromboembolism and endometrial cancer with the use of tamoxifen, together with the fact that some patients are refractory to treatment or may develop resistance, generated interest in the inhibition of oestrogen synthesis by aromatase inhibitors (AI) and inactivators . There are two types of AI- irreversible steroidal activators and reversible nonsteroidal imidazole-based inhibitors. The three novel third generation oral AI and inactivators like, anastrozole, letrozole and steroidal exemestane are very effective in reducing oestrogen levels in postmenopausal women, with minimum toxicity. Moreover, their long half life allows once daily administration, leading to better patient compliance. Inhibition of the aromatase system, in particular, with third-generation aromatase inhibitors and inactivators, appears to be associated with statistically significant improved survival of patients with advanced breast cancer, as compared to standard hormonal treatments. Introduction of the novel AI in the treatment of breast cancer has truly increased the hope of longer and better disease-free survival for these patients.

Key Words: Anastrozole, Letrozole, Exemestane.

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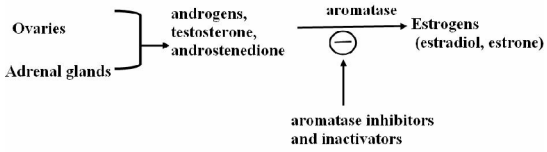
Oestrogen receptors (ER) are expressed in 2/3rd of all breast cancers and oestrogen mediated growth stimulation through these receptors causes the progression of hormone sensitive breast tumours. This can be ameliorated either by receptor blockade with the use of antioestrogens or by the inhibition of oestrogen synthesis by aromatase inhibitors (AI) and inactivators, which blocks oestrogen production in both the tumour cells as well as in the surrounding tissues [1].

Since it's introduction in 1973, tamoxifen has played a significant role in the treatment of metastatic and early breast cancer, as well as in preinvasive ductal carcinova in situ. Though it has beneficial effects on the bone and in lipid metabolism, the occurence of adverse effects like hot flushes, vaginal dryness, thromboembolism and endometrial cancer with the use of tamoxifen, together with the fact that some patients are refractory to treatment or may develop resistance to it, justify the need to develop new agents with an improved therapeutic index [2],[3].AIs act by suppressing the conversion of androgen substrates into oestrogen by inhibition of aromatase, thereby leading to regression of ER positive tumour cells [4] [Table/Fig. 1]



(Table/Fig 1) Mechanism of action of aromatase inhibitors and inactivators

AIs can be categorized by their generation and by their mechanisms of action. The

aromatase enzyme is required for the last step in oestrogen biosynthesis[5].There are two types of AIs, irreversible steroidal activators and reversible nonsteroidal imidazole-based inhibitors. Steroidal agents such as exemestane, have an androgen structure and they bind irreversibly to the catalytic site of aromatase (competing with the natural aromatase substrate androstenedione) [5]. Nonsteroidal imidazole-based agents like the second-generation agent aminoglutethimide and the third-generation agents, anastrozole and letrozole, reversibly interact with the cytochrome P450 moiety of the enzyme [5].

Both the first generation AIs, aminoglutethimide and the second generation steroidal AI formestane (introduced in late 1970's and early 1990's respectively), were less potent inhibitors of aromatase and oestrogen suppression, which provided the incentive for the development of the third generation Ais [4]. The three novel third generation oral AI and inactivators approved for use by FDA – USA, include nonsteroidal agents anastrozole (Arimidex), letrozole (Femara) and steroidal exemestane (Aromasin) [2].These are more potent and safer than progestins and aminogluthetimide. Moreover, these are highly selective for the aromatase enzyme without affecting mineralocorticoid or glucocorticoid synthesis .These are very effective in reducing oestrogen levels in postmenopausal women, with minimum toxicity [6]. Moreover, their long half life allows once daily administration, leading to better patient compliance [1]. In the present article, we are reviewing the novel third generation AIs.

Search Methodology

Prominent oncology and general/internal medicine journals (MEDLINE, EMBASE and PUBMED) were searched for review papers and clinical trials published on AIs. The data was collected and summarized in the present article.

Anastrozole

It is well absorbed orally with Cmax (maximum concentration) at 3 hours and with a terminal half life of 40-50 hours. More than 80% is metabolized by the liver by N-dealkylation and hydroxylation. 10% is excreted unchanged in urine. It is a potent AI (~ 97%) and provides near maximal suppression of oestrogen to below detectable levels. It is well tolerated [1].

A major clinical programme consisting of two large multicentre trials viz. the North American trial and TARGET (tamoxifen or anastrozole randomised group efficacy and tolerability) trial has demonstrated the superiority of anastrozole over standard endocrine therapy tamoxifen for first line treatment of post menopausal women with hormone sensitive advanced breast cancer[7],[8]. Clinical trials have also demonstrated significant benefits with anastrozole, as compared to the standard second line agent megestrol acetate, which led to its approval by US FDA for second line use in post menopausal women with advanced breast cancer, progressing after prior tamoxifen treatment[9]. In the long term, prospects may also exist for using anastrozole as a neo-adjuvant agent [4].The two studies comparing the efficacy of anastrozole (1 mg daily) with that of megestrol acetate (160 mg daily), did not report a statistically significant difference between the two groups, although results for each end point were numerically superior for anastrozole [10],[11]. In a subsequent pooled analysis of these two trials conducted at a median follow-up of 31 months, a statistically significant survival advantage was found for anastrozole [12].The most common adverse events reported in women taking anastrozole, were asthenia, nausea, headache, hot flashes, and pain [13].

Letrozole

It is an oral, highly potent (>99.1%) and reversible AI. It's bioavailability is 100% and it is unaffected by food. It is rapidly absorbed, with a half life of 48 hours. It has a high volume of distribution and 60% plasma protein binding. It is metabolized by P450 (CYP3A4 and CYP2A6) to a secondary alcohol, which is excreted in urine. Its levels are suppressed by tamoxifen by a mean of 35-40%, when administered together [1].On comparison with aminoglutethimide and megestrol acetate respectively, in different trials in post menopausal women with metastatic breast cancer previously treated with tamoxifen, letrozole demonstrated clinical superiority in terms of prolonged time to progression and treatment failure, as

well as in improved survival [6]. Dombernowsky, et al compared two doses of letrozole with megestrol acetate as second-line therapy in postmenopausal women [14]. Letrozole, at a dose of 2.5 mg, produced a significantly higher overall objective response rate (ORR) (24%) than megestrol acetate (16%; p = 0.04) and 0.5mg of letrozole (13%; p = 0.004). A significant dose effect on overall survival was observed with the higher letrozole dose, as compared to the lower dose of letrozole. However, Buzdar and colleagues showed no statistically significant differences among the three treatment groups for overall objective tumour response [15]. A dose-response relationship was not noted in the second study. However, 0.5 mg of letrozole was found to be superior to megestrol acetate in TTP and TTF (time to treatment failure). The most frequent adverse events reported in women treated with letrozole were hot flashes, nausea, diarrhoea, musculoskeletal pain, dyspnea, and headache [14], [15].

In an open-label, randomized, phase IIIB-IV study, anastrozole (1 mg daily) was compared with letrozole (2.5 mg daily) in 713 postmenopausal women with advanced breast cancer, whose disease became resistant to tamoxifen used, either as adjuvant therapy or for advanced disease [16]. Approximately half the patients had an unknown oestrogen-receptor status, TTP, clinical benefit, TTF, duration of response and duration of clinical benefit. However, the secondary end point OR rate statistically significantly favoured letrozole; but, this benefit was not seen in women with oestrogen-receptor-positive disease [17].Nausea was more common with anastrozole (11%) than with letrozole (8%) [16]. Letrozole was compared with tamoxifen in one study, in which it demonstrated statistically significant superiority in ORR, clinical benefit, TTP and TTF [18],[19].

In the National Cancer Institute of Canada (NCIC) MA17 trial, a double-blinded, placebo-controlled trial designed to test the effectiveness of 5 years of letrozole therapy in postmenopausal women with breast cancer who had completed 5 years of tamoxifen, an estimated 4-year disease-free survival rate of 93% was noted in the letrozole group, versus 87% in the placebo arm [20]. No statistically significant difference in overall survival was apparent at the time of this analysis. Low-grade hot flashes and arthritis were more common in the letrozole arm. No statistically significant difference in the new diagnosis of osteoporosis was observed (5.8% in the letrozole arm versus 4.5% in the placebo arm; p = 0.07). Given the positive results of the trial, it was terminated.

In a retrospective analysis of 95 patients with breast cancer who were postmenopausal and had failed after tamoxifen therapy, 2.5 mg of letrozole daily was quite effective as second line therapy in postmenopausal patients [21].Median TTP time to progression was 10 months and overall ORR was 21%, with a complete response rate of 9%. Th median overall survival was 36 months. Treatment failure was seen in 76% of patients.

Exemestane

It is an analogue of the aromatase subtrate androstenedione and is an irreversible AI (97.9%). Because of their steroidal structure, exemestane and its 17-hydroexemestane metabolite have the potential for androgenic effects. The binding of exemestane to the androgen receptor is about 0.2% that of dihydrotestosterone, but the affinity of 17-hydroexemestane for the androgen receptor is about 100 times that of the parent compound [5]. The recommended dosage of exemestane is 25 mg orally, once daily, after a meal[21]. It is rapidly absorbed, with peak plasma concentrations of 17 μg/L within one to two hours [21].A steady state concentration is achieved within seven days. Exemestane is extensively metabolized by cytochrome P450 3A4 and aldoketoreductases [21]. The metabolites are either of lower potency or inactive and are excreted equally in urine and faeces [22]. Exemestane has a half-life of 27h [22],[23].Oral clearance of exemestane is reduced in the presence of significant hepatic or renal disease. The therapeutic implications of this are considered minor because of its relatively large safety margin and minor side-effects [24].

It has been demonstrated that exemestane has a better clinical efficacy as compared to aminoglutethimide or megestrol acetate in phase II and III trials,. In a clinical trial, 25 mg of exemestane, daily, was compared with

40 mg of megestrol acetate, four times daily [5]. Exemestane was associated with statistically significant benefits in the duration of clinical benefit, TTP, TTF and survival time. The most frequently reported adverse events in women treated with exemestane were low-grade hot flashes, nausea, and fatigue. Greater weight gain was reported in patients treated with megestrol acetate [5]. The steroidal agent, exemestane was compared with tamoxifen in a randomized European Organization for Research and Treatment of Cancer (EORTC) phase II/III trial [25]. In the phase II portion of the study, exemestane produced an ORR of 40.9% and a clinical benefit of 55.7% as compared to 13.6% and 42.4%, respectively in the tamoxifen group [25]. However, the results of ongoing phase III clinical trials comparing it with tamoxifen, are awaited [26].

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. Exemestane produced 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 groups [27].

In another two-year trial enrolling 147 patients, exemestane reduced HDL levels by 6-9%, with no major effects on serum lipids, coagulation factors or homocysteine levels [28].

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 [29]. After a study period of one year, exemestane was found to have a neutral effect on total cholesterol and LDL and HDL levels. However, tamoxifen on the other hand, increased triglyceride levels, while exemestane resulted in a beneficial reduction[29].

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 [30]. Exemestane is marketed for use only in postmenopausal women. It is contraindicated in pregnant or lactating women [21].No dose adjustment is required in the geriatric population [21]. There is no cross-resistance between exemestane and other nonsteroidal Ais [21]. 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) as end points, are being evaluated in these studies [21] [Table/Fig 2].

(Table/Fig 2) Third generation Aromatase Inhibitors

Parameters	ANASTROZOLE	LETROZOLE	EXEMESTANE
Absorption	Well absorbed orally Tmax =3hrs	Oral bioavailability is 100% and is unaffected by food. Rapidly absorbed	Rapidly absorbed with peak plasma concentrations of 17 µg/L Tmax=1-2hrs
Half life	40-50hrs	48hrs	27hrs
Metabolism	More than 80% is metabolized by liver by N-dealkylation and hydroxylation. 10% is excreted unchanged in urine.	Metabolized by P450 (CYP3A4 and CYP2A6) to a secondary alcohol which is excreted in urine. Levels are suppressed by tamoxifen by a mean of 35-40% when administered together	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.
Adverse effects	Asthenia, nausea, headache, hot flashes, pain	Nausea, low-grade hot flashes and arthritis	Low-grade hot flashes, nausea, and fatigue. *positive beneficial effect on lipids

Sequential Use of Aromatase Inhibitors:[5]

There is evidence to suggest that steroidal aromatase inhibito, exemestane, is effective after the failure of tamoxifen and megestrol acetate and after failure of tamoxifen and a nonsteroidal aromatase inhibitor (e.g., aminoglutethimide, anastrozole, letrozole). The nonsteroidal aromatase inhibitors were effective after the failure of exemestane . The reason for non-cross-resistance among various AIs, is possibly due to structural differences among aromatase inhibitors (i.e., steroidal versus nonsteroidal imidazole), which may lead to different pharmacokinetic and pharmacologic profiles, or differences in the ways in which these agents interact with the aromatase enzyme. As an example, because of their steroidal structure, exemestane and its 17-hydroexemestane metabolite may have androgenic effects that contribute to antitumour activity. Although clinically important, androgenic adverse events have not been reported at the

recommended exemestane dose of 25 mg daily, hypertrichosis, hair loss, hoarseness and acne were reported in about 10% of patients treated with daily exemestane doses of 200 mg or more. It is possible that, although not clinically apparent, recommended doses of steroidal agents may have some androgenic effects.

Breast Cancer Prevention [5],[31],[32],[33]

There is a link between oestrogen exposure and breast cancer development and the antioestrogen tamoxifen has been shown to prevent the development of breast cancer in women with above average cancer risks. As there is evidence that both oestrogens and oestrogen metabolites may initiate breast cancer, AIs may have a role in preventing breast cancer. Moreover, antioestrogens block the action of oestrogens, leaving potentially carcinogenic oestrogen metabolites available to exert their effects. AIs block the formation of oestrogens and therefore, oestrogen metabolites. Data from the ATAC trial demonstrate a greater reduction in the incidence of contralateral breast cancer with anastrozole, than with tamoxifen, particularly in women with hormone-positive disease. However, several trials are currently under way to assess the role of aromatase inhibitors in breast cancer prevention.

Conclusion

The three novel third generation oral AI and inactivators like anastrozole, letrozole and steroidal exemestane are very effective in reducing oestrogen levels in postmenopausal women, with minimum toxicity. Moreover, their long half life allows once daily administration, leading to better patient compliance.

Inhibition of the aromatase system, in particular, with third-generation aromatase inhibitors and inactivators, appears to be associated with statistically significant improved survival of patients with advanced breast cancer as compared to standard hormonal treatments [34]. Introduction of the novel AIs in the treatment of breast cancer has truly increased the hope of longer and better disease-free survival for these patients.

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