EDITORIAL

Vishal R. Tandon, Sudhaa Sharma*

For many years, tamoxifen has been the gold standard amongst antioestrogen therapies for breast cancer. However, its estrogenic agonist effects in some tissues limit its use. Similarly, clinical data exists suggesting role of selective estrogen receptor modulators (SERMS) in breast cancer but they show minimal activity in tamoxifen resistant disease and show no superiority over tamoxifen. Hence, there is a need of drugs with better clinical profile. Aromatase inhibitors (AIs) are a new class of agents that are of considerable interest in the treatment of hormone-dependent breast cancer in postmenopausal women. Aromatase is an enzymic complex that catalyses the conversion of the adrenal androgens androstenedione and testosterone to estrone. In postmenopausal women, the process of peripheral aromatisation accounts for the majority of circulating estrogens. The selective inhibition of estrogen production by aromatase inhibitors is an efficient strategy for breast cancer treatment (1).

These drugs can be classified into first-generation (aminoglutethimide), second-generation (formestane and fadrazole), and third-generation (anastrozole, letrozole, and exemestane) agents. Second and third generation aromatase inhibitors are considerably more potent and more specific in their ability to inhibit aromatase, as compared to first generation compounds (1, 2).

Breast Cancer

There is a growing body of evidence supporting the role of third-generation aromatase inhibitors as first-line and second-line therapy for estrogen receptor (ER)- and/ or progesterone receptor (PgR)-positive advanced breast cancer in postmenopausal women, and as a neoadjuvant therapy in postmenopausal women unsuitable for breast-conserving surgery. Furthermore, the preliminary results of the ATAC (Arimidex, Tamoxifen, Alone and in Combination) study have shown that adjuvant anastrozole is superior to tamoxifen in terms of disease-free survival

(DFS), adverse effects, and prevention of contralateral breast cancer in postmenopausal women with early, ER-positive breast cancer (2).

In contrast to the oestrogen receptor blockade provided by tamoxifen, aromatase inhibitors result in deprivation of oestrogens in postmenopausal women both through paracrine/intracrine and endocrine modulation. Experimental evidence has shown a significant (97 - 99%) reduction of in vivo aromatase activity and an equal or sometimes better antitumour activity compared with megestrol acetate when these drugs are used as secondline treatment for metastatic breast cancer (3).

It has been recommended that adjuvant treatment with tamoxifen for 5 years should no longer be considered as the sole standard but a third-generation aromatase inhibitor should be used either alone or in a sequence with tamoxifen in the adjuvant treatment of postmenopausal women with hormone-receptor-positive breast cancer. Third generation aromatase inhibitors may be considered as the first line therapy for hormone-receptor-positive advanced breast cancer in postmenopausal women, and they may also be used for preoperative therapy of breast cancer (4).

Endometriosis

Endometriosis is an estrogen-dependent disorder mostly occurring in reproductive-age women. Various therapies have been used in an attempt to treat endometriosis, including ovarian suppression therapy, surgical treatment or a combination of these. However, in general, substantial surgery remains the primary treatment option for endometriosis at all stages. Recently, aromatase inhibitors and anti-estrogens have been proposed as novel potential candidates. The rationale for the use of aromatase inhibitors is mostly related to the high aromatase expression in endometriotic cysts and extra-ovarian endometriotic implants (5).

From The Postgraduate Deptt. of Pharmacology & Therapeutics and *Gynaecology & Obstetrics, Govt. Medical College, Jammu. Correspondence to: Dr. Sudhaa Sharma, Asstt. Professor, P.G Department of Gynae & Obstetrics, Govt. Medical College, Jammu (J&K).

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Ovulation Induction

Promising pregnancy rates are associated with the use of aromatase inhibitors by induction of ovulation in these women. In addition, the use of aromatase inhibition in conjunction with gonadotropin injection was associated with a significant reduction in the gonadotropin dose required for optimum controlled ovarian hyperstimulation. It is proposed that aromatase inhibitors will replace clomiphine citrate in the future as the new primary treatment for ovulation induction (6).

Vascular Effects

Als reduce circulating estrogen to a low concentration which may be deleterious to the vascular system since estrogen receptors are known to be in the cell walls of blood vessels and estrogen is thought to be important in maintaining blood vessel integrity.

Clinical trial evidence indicates that HRT increases risk of coronary heart disease (CHD) whereas, SERMs and AIs (to date) appear to be neutral (7). Cerebrovascular disease venous thromboembolic events and cognitive disfunction are increased by HRT and SERMs but appear to be unaffected by treatment with AIs. Hence, at present concerns about deleterious vascular side effects are confined to HRT and SERMs (8).

Concerns

Menopausal Symptoms

Endocrine treatment of breast cancer patients antagonize estrogen and may lead to consequences of estrogen deprivation including menopausal symptoms.First-line aromatase inhibitors induce an increase in the occurrence and severity of hot flashes. Musculoskeletal pain and dyspareunia significantly increases under first-line non-steroidal aromatase inhibitors (9).

Bone Loss

The risk of fracture in the postmenopausal woman given aromatase inhibitors may be increased by up to 60%. The likely mechanism for the increase in fracture risk is an increase in bone turnover (of about 20%) and an acceleration of bone loss. There is evidence to suggest that the residual levels of oestradiol present in the postmenopausal woman are important for bone health, and thus, the effect of these drugs is to remove this protective effect. Current clinical practice should include the measurement of bone mineral density in postmenopausal women taking these drugs and commencement of antiresorptive therapy if osteoporosis is already present (10).

In conclusion, aromatase inhibitors have emerged very useful class of drug and represent paradigm shift in the treatment of an early and advanced breast cancer in postmenopausal women as, they are better, selective more potent and even effective in resistant breast cancers in comparison to drugs like tamoxifen and SERM's. In addition, they have been proposed as novel agents for the treatment of endometerosis and for ovulation induction. **References**

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