REVIEW

Aromatase inhibitors in the breast cancer therapy and their potential using in the prevention setting

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Abstract

Long term exposure to estradiol is associated with an increased risk of breast cancer. Aromatase inhibitors, suppressing tumour and plasma estrogen levels by blocking conversion of testosteron to estrogen, have been proven to provide the most effective endocrine therapy in metastatic and adjuvant setting in postmenopausal women. Questions remains about the long term side effects and safety profile of aromatase inhibitors. The effectiveness and safety of aromatase inhibitors therapy in premenopausal breast cancer patients is unknown, this needs to be further investigated. Although tamoxifen represents the gold standard for prevention therapy at present, results of ongoing studies may indicate a role of aromatase inhibitors in prevention of breast cancer *(Tab. 2, Ref. 22)*. Full Text (Free, PDF) *www.bmj.sk*.
Key words: aromatase inhibitors, breast cancer, treatment, chemoprevention.

Estrogens and their metabolites have been implicated in both the initiation and the progression of breast cancer. The prevailing theory postulates that estrogens increase the rate of cell proliferation by stimulating estrogen receptor-mediating transcription, thereby increasing the number of errors during DNA replication. An alternative theory suggests that estradiol is metabolized to quinone derivates, which directly remove base pairs from DNA through depurination resulting in point mutations. Theories mentioned above could represent two pathways which work in additive or synergistic fashion to induce cancer (1).

Endocrine therapy is one of the most effective treatments for breast cancer in the adjuvant, metastatic, and prevention settings. Endocrine agents have been designed to affect the supply of estrogens to the breast tumor, principally by blocking estrogen activity at the receptor level or by inhibition of estrogen production. Historically, tamoxifen was the first successful hormonal treatment and became the "gold standard" adjuvant endocrine therapy in postmenopausal women with estrogen receptor-positive breast cancers. It has been shown to be more effective than chemotherapy in women over 50 years of age with hormone receptor-positive early breast cancer and these findings have prompted its investigation as a chemo-preventive agent in women at risk of breast cancer. In 1998, Fisher et al showed that tamoxifen could reduce breast cancer incidence by 50 %. Subsequently, together with the overall toxicology database, tamoxifen was approved for the reduction of the incidence of breast cancer in high-risk women by the US Food and Drug Administration in 1998. This was the first time that women at increased risk for breast cancer have had an alternative to bilateral mastectomy for risk reduction. Despite having an approved indication for breast cancer risk reduction and a relatively substantial risk reduction, the use of tamoxifen as a breast cancer chemo-preventive agent is limited by its potential adverse effects, including an increased risk of endometrial cancer and sarcoma, and thromboembolic disorders, all of which are potentially life – threatening (2). This clearly limits its use both as adjuvant therapy (where it is usually recommended for up to 5 years) and, in particular, as a preventive therapy.

Aromatization is the major mechanism of estrogen synthesis in the postmenopausal women. In these women, aromatase inhibitors block biotransformation of adrenal androgens to estrogens in peripheral tissues (including breast, muscle, liver, and adipose tissue), resulting in undetectable levels of plasma estrogens. For that reason, aromatase inhibitors are primarily used in the postmenopausal population. Aromatase inhibitors have been

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used to treat metastatic breast cancer treatment for over 25 years. The first commercially available aromatase inhibitor aminoglutethimide demonstrated activity in the metastatic breast cancer when compared to establish second – line therapy with megestrol acetate (3). Because aminoglutethimide was associated with severe adverse effect, a lot of effort was invested into developing novel non-steroidal as well as steroidal compounds. Recently potent and specific aromatase inhibitors have been introduced: two non-steroidal anastrozole and letrozole, and the steroidal exemestane. There is overwhelming evidence that these new aromatase inhibitors are superior to tamoxifen as adjuvant treatment for postmenopausal women with estrogen receptor positive breast cancer. Emerging data suggest that there may be differences in effects of aromatase inhibitors on target organs, which may become evident with long term use, such as in adjuvant or prevention settings.

The aim of this study is to review the current clinical status and possible future application of aromatase inhibitors in breast cancer prevention. We will discuss advantages and disadvantages of aromatase inhibitors treatment in both pre- and postmenopausal women. Our data were obtained through a MEDLINE search of newest papers published in English.

Aromatase inhibitors in metastatic breast cancer

Several phase III studies have compared the efficacy of anastrozole (1 mg/day), letrozole (2.5 mg/day) and exemestane (25 mg/day) with tamoxifen (20 mg/day) as a first-line therapy for metastatic breast cancer postmenopausal women. The patients in these trials had hormone receptor positive or unknown breast cancers, respectively.

The Tamoxifen and Arimidex Randomized Group Efficacy and Tolerability (TARGET) trial was done simultaneously in the Europe (4) and in the North America (5). In the European TARGET trial, the overall response rate was 33 % in both tamoxifen and anastrozole groups. In the North American TARGET trial, anastrozole showed superior efficacy to tamoxifen in terms of time to progression in patients with hormone receptor-positive tumors. Combined median follow up of both trials was 18 months. Both treatments were well tolerated; anastrozole was associated with significantly fewer thromboembolic events and fewer reports of vaginal bleeding. On the basis of these two trials, anastrozole was approved as first-line therapy for metastatic breast cancer.

In the next trial of the International Letrozole Breast Cancer Group, letrozole showed superiority to tamoxifen with respect to time to progression, time to treatment failure, overall response rate and overall survival after median of 32 months (6). The nature and frequency of adverse events were similar for the letrozole and tamoxifen treatment arms. These data led to the approval of letrozole as first-line therapy for metastatic breast cancer.

Exemestane compared with tamoxifen in patients with no prior hormone therapy for metastatic disease showed better overall response rate (43 % vs 29 %) (7). Median progression-free survival time was significantly longer with exemestane compared to tamoxifen. There was a low incidence of severe flushing, sweating, nausea and edema in women who received exemestane.

Based on the trial results mentioned above, aromatase inhibitors could replace tamoxifen as the first line therapy of advanced breast cancer.

Tab. 1. Design of clinical trials with aromatase inhibitors in adjuvant treatment.

Trial	Treatment	n
ATAC	T (5 y) vs A (5 y) vs. T+A (5 y)	6241
ABCSG-8/ARNO–95	T (5 y) vs T (2 y)+A (3y)	3700
BIG 1–98	T (5 y) vs L (5 y) vs T (2 y)+L (3 y) vs L (2 y)+T (3y)	8028
MA-17	T (5 y)+L (5 y) vs. T (5 y)+P (5 y)	5187
IES T (5 y) vs	T (2-3 y)+E (3 y)	4742

A – Anastrozole, L – Letrozole, P – placebo, T – tamoxifen, n – number of patients

Aromatase inhibitors in adjuvant breast cancer treatment

Clinical trials on these agents in the adjuvant treatment of postmenopausal women with breast cancer are few but important due to comparative design with tamoxifen given for five years in a dose of 20 mg per day (with exception of 30 mg per day in IEC study). Designs of clinical trials with adjuvant aromatase inhibitors application in postmenopausal, hormone receptor-positive breast cancer are summarized in Table 1.

In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study, there was a direct comparison of adjuvant tamoxifen and anastrozole (1 mg/day), given 5 years as adjuvant therapy following primary local treatment in women with early-stage breast cancer (8). After median of 68 months, there was a significant reduction in distant metastases among those given anastrozole. Furthermore, there was a constant reduction in deaths after relapse in the anastrozole arm during the 5 years of treatment. Compared with tamoxifen, anastrozole was associated with fewer venous thromboembolic complications and ischemic cerebrovascular complications but more musculoskeletal symptoms and higher fracture rate. The endometrial cancer was significantly reduced in anastrozole arm (9).

Two German and Austrian Cooperative groups, reported results of The Austrian Breast Cancer Study Group (ABCSG-8) and Arimidex-Nolvadex (ARNO-95) studies. Trials were similar in design, and both were conducted to determine whether switching to anastrozole (1 mg/day) after 2 years of tamoxifen administration was more effective than continuing tamoxifen for the remaining 3 years of adjuvant therapy (10). After median of 28 months, there was a 40 % reduction in relapses in the anastrozole group. Higher treatment benefit was observed in patient with estrogen and progesterone receptor positive tumors. There were significantly more fractures and significantly fewer thromboses in women treated with anastrozole than with tamoxifen.

The Breast International Group (BIG) 1-98 trial is examining whether the aromatase inhibitor letrozole (2.5 mg/day) is more effective when used as primary adjuvant therapy or sequentially after tamoxifen in women with early breast cancer (11). The preliminary results after median of 26 months showed a small but significant benefit for women receiving the letrozole. The majority of adverse events were similar between the groups, with the exception of hypercholesterolemia, which was more frequent with letrozole. Bone fractures also occurred more frequently in the letrozole group. There was trend toward fewer invasive endometrial cancers in patients with letrozole.

Five year therapy with tamoxifen, followed by a second adjuvant therapy with letrozole (2.5 mg/day), was examined in MA-17 study of the National Cancer Institute of Canada's Clinical Trial Group. The results of this trial were reported after median of 30 months. There had been 127 relapses in the placebo group and 75 in the letrozole group with a 40 % risk reduction of distant metastases (12). Expected adverse effects were observed in the letrozole group, including hot flashes, arthralgia and myalgia. Osteoporosis, fractures and cardiovascular events were more frequent in the letrozole group, but differences did not reach significance.

The Intergroup Exemestane Study (IES) is a trial designed to compare 5 years of tamoxifen with 2–3 years of tamoxifen followed by 3–2 years of aromatase inhibitor exemestane (25 mg/day) (13). After median of 31 months, there was a 32 % reduction of relapse risk in the exemestane group. Switching to exemestane significantly reduced the risk of both contralateral and ipsilateral breast cancers. Adverse effects reported in this trial are preliminary. The use of exemestane was associated with a higher incidence of musculoskeletal side effects but a lower risk for adverse gynecologic and thromboembolic events.

The most common adverse events associated with adjuvant aromatase inhibitors therapy reported in above mentioned studies included hot flushes and musculoskeletal complaints (arthralgia, myalgia). There was a small but significant increase in the risk of osteoporosis and fractures in aromatase inhibitors therapy. These adverse events seemed to be manageable with appropriate pharmacological intervention (anti-inflammatory drugs in algias and bisphosphonates in osteoporosis). The incidence of endometrial cancer and thromboembolic events was significantly lower in aromatase inhibitors than in tamoxifen therapy. A potential negative effect on the cardiovascular system, specifically on lipid metabolism, has not been conclusively demonstrated. No significant differences in overall quality of life were observed in studies comparing aromatase inhibitors to tamoxifen or placebo.

Aromatase inhibitors in neoadjuvant therapy

The Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial was realized in 330 postmenopausal women with estrogen receptor positive, invasive and operable breast cancer. Preoperative treatment with anastrozole, tamoxifen, or both lasted 3 months. The significantly higher number of patients receiving breast conserving surgery were observed in anastrozole group in comparison to those given tamoxifen (46 % vs 22 %) (14).

In the phase III Preoperative Arimidex Compared with Tamoxifen (PROACT) trial, the efficacy of anastrozole versus tamoxifen as neoadjuvant therapy lasting 12 weeks was evaluated in 451 postmenopausal women with hormone receptor positive breast cancer. In the subset of patients who received only hormonal therapy, 43 % of those treated with anastrozole received breast conserving surgery compared to 31 % of those treated with tamoxifen ($p=0.04$) (15). Treatments in both trials were well tolerated.

Tab. 2. Ongoing prevention trials with aromatase inhibitors.

TrialDrug	
IBIS-2	Anastrozole vs placebo
Italian Aromasin prevention study	Exemestane vs placebo
NCIC CTG MAP.2	Exemestane vs placebo
NCIC CTG MAP.3	Exemestane vs placebo vs Exemestane + Celecoxib
Women with Increased Serum Estradiol (WISE)	Letrozole vs placebo

A – Anastrozole, L – Letrozole, P – placebo, T – tamoxifen

Aromatase inhibitors in breast cancer prevention

The aim of the chemo-preventive trials is to find a suitable efficient substance that can be administered for a long period. Results from the ATAC, MA-17 and IES trials showed that aromatase inhibitors reduced the incidence of contralateral breast cancer. Data of these trials highlight the fact that aromatase inhibitors could be useful in prevention in women with increased risk for developing the disease. In direct comparisons to tamoxifen in adjuvant therapy, aromatase inhibitors have a better toxicity profile with fewer patients stopping therapy due to drug related adverse effects. These data have prompted breast cancer chemoprevention trial with aromatase inhibitors. Results of ongoing trials may indicate a role of aromatase inhibitors in prevention of breast cancer.

Several phase III trials on aromatase inhibitors in breast cancer prevention are ongoing (Table 2). The National Cancer Institute of Canada's Clinical Trial Group (NCIC CTG) is conducting a pilot study of exemestane with or without celecoxib versus placebo in healthy postmenopausal women with increased breast density on mammogram or those with prior receptor-positive breast cancer and longer than 6 months from completing adjuvant tamoxifen. The primary end point of this trial is breast mammographic density and partial end points include bone and plasma lipid assessment and general toxicities. The Italian Aromasin prevention study, comparing exemestane to placebo, is enrolling BRCA 1 or 2 gene carriers who are postmenopausal and do not yet have breast cancer. The primary end point is incidence of breast cancer. The International Breast Cancer Intervention Study

(IBIS)-2 has been designed to investigate whether superiority of anastrozole over tamoxifen in the ATAC trial will translate into the prevention of breast cancer. IBIS-2 is realized in postmenopausal women with ductal carcinoma in situ (DCIS) or at a high risk of breast cancer.

Premenopausal versus postmenopausal aromatase inhibitors application

Aromatase inhibitor shave revolutionized the treatment of postmenopausal women with hormone receptor positive breast cancer. On the other hand, single agent therapy with aromatase inhibitors has not an established role in premenopausal women with breast cancer. However, approximately 22 % of all cases of breast cancer in the North America are diagnosed in women below the age of 50 and a substantial proportion of these women are premenopausal (16). For that reason, research on the use of aromatase inhibitors in premenopausal population with estrogen receptor positive breast cancer is required.

It is known, that premenopausal ovaries are relatively resistant to blockade with first generation aromatase inhibitors (1). Several experimental methods have been used to determine the biological importance of breast *in situ* estrogen production versus uptake of estradiol from plasma by breast tissue (17, 18, 19). Results of above cited experiments suggested the importance of *in situ* estrogen production in the breast and led to the hzpothesis that an important determinant of tissue estradiol levels is local production in the mammary gland. Also clinical evidence suggesting that local production of estrogens may contribute to breast tumour growth (20, 21). Based on this hypothesis, the estradiol levels in breast tissue itself would be an important predictor of later carcinogenesis in the mammary gland and therefore intratumoral aromatase could be a potential therapeutic target. This hypothesis, yet not proven, is attractive because it suggests that aromatase inhibitors can lower breast tissue estradiol levels without causing a reduction in plasma estradiol levels. This would protect a premenopausal patient treated with aromatase inhibitors from development of osteoporosis, urogenital atrophy, and vasomotor instability while still reducing the incidence of breast cancer. Adjuvant trials are planned to evaluate the role of luteinizing hormone releasing hormone agonists in combination with aromatase inhibitors in premenopausal women. The purpose of an ongoing phase II trial is to explore the anti-tumor activity of anastrozole against hormone receptor positive metastatic breast cancer in the treatment of premenopausal women who have been rendered functionally post-menopausal with the use of goserelin.

Aromatase inhibitors in postmenopausal women would also lower levels of tissue estradiol. No effects on negative feedback would be observed. The plasma estradiol levels also fall as has been shown in women treated with aromatase inhibitors. But the consequences on potential acceleration of osteoporosis, urogenital atrophy and on vasomotor instability would be expected in these women. These issues have not been addressed specially for women with advanced breast cancer with relatively short duration of aromatase inhibitors treatment. Similarly, in postmenopausal women in whom endometrial cancer risk, thromboembolism and urogenital dysfunction are most pronounced, the aromatase inhibitors may represent a logical alternative to tamoxifen in adjuvant treatment (22).

Conclusion

Aromatase inhibitors are now the first choice endocrine therapy in the metastatic setting in postmenopausal women. These endocrine agents also seem to soon become the standard adjuvant therapy for postmenopausal patients with hormone-responsive breast cancer, either alone or in sequence with tamoxifen, but monitoring and management of bone loss associated with their application are essential and are being addressed in ongoing trials. Further studies with longer follow up are required to clarify the effects of aromatase inhibitors on lipid metabolism and cardiovascular health. The results from the aromatase inhibitor prevention trials with the identification of breast cancer risk reduction are awaited with interest. The role of aromatase inhibitors in premenopausal breast cancer patients needs to be further investigated.

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