

COMMENTARY

Focus on anastrozole and breast cancer

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SUMMARY

This commentary article provides an overview of recent clinical research trials involving anastrozole and its evolving role in the management of breast cancer.

Anti-aromatase agents inhibit the cytochrome P-450 component of the aromatase enzyme complex responsible for the final step of estrogen biosynthesis in peripheral tissues which are the main source of estrogen in postmenopausal women. Anastrozole is a third-generation non-steroidal aromatase inhibitor. It has been shown to be superior to megestrol acetate, in terms of survival and adverse effects, as a second-line therapy in postmenopausal women with estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive advanced breast cancer. Phase III clinical trials have also demonstrated that anastrozole significantly prolongs the time to tumour progression compared with tamoxifen as a first-line therapy for ER- and/or PgR-positive advanced breast cancer in postmenopausal

women. Furthermore, the preliminary results of the Arimidex*, Tamoxifen, Alone and in Combination (ATAC) study have shown that adjuvant anastrozole is superior to tamoxifen in terms of disease-free survival (DFS), non-musculoskeletal adverse effects and prevention of contralateral breast cancer in postmenopausal women with early, ER-positive breast cancer. Although longer follow-up is required to assess the long-term effects of anastrozole on bone mineral density, cognitive function and overall survival, the drug has been recently approved for adjuvant use in postmenopausal women with early, ER-positive breast cancer who are unable to tolerate tamoxifen or at an increased risk of developing thromboembolism or endometrial cancer.

The potential role of anastrozole in the neoadjuvant setting, the management of DCIS, premenopausal breast cancer and breast cancer prevention is currently being investigated.

Introduction

Estrogen plays a significant role in the development and growth of hormone-dependent breast cancer^{1,2}. The principal sites of estrogen biosynthesis in postmenopausal women include skin, muscle, fat, and benign and malignant breast tissue³⁻⁵. The aromatase enzyme complex in such tissues converts androgens

(C₁₉ steroids) into estrogen (a C₁₈ steroid). The conversion process of adrenal androstenedione to estrone by aromatase is related to body weight⁶. In normal-weight subjects, approximately 1% of androstenedione is converted to estrone, whereas in obese subjects this increases up to 10%. The increase in peripheral estrogen synthesis with weight in postmenopausal women is the most likely explanation

*Arimidex (anastrozole) is a registered tradename of AstraZeneca Pharmaceuticals, Concord Pike, Wilmington DE, USA

for the increased risk of breast cancer observed in obese postmenopausal women⁶. Aromatase activity also increases with age⁷. Aromatase inhibition has therefore become an important therapeutic modality for hormone-sensitive breast cancer in postmenopausal patients². Anti-aromatase agents such as anastrozole inhibit the cytochrome P-450 component of the aromatase enzyme complex by interfering with the electron transfer from NADPH. These drugs can be classified into first-generation (e.g. aminoglutethimide), second-generation (e.g. formestane and fadrazole) and third-generation (e.g. anastrozole, letrozole and exemestane) agents. Anti-aromatase agents can be also divided into type I and type II inhibitors. Type I inhibitors have a steroidal structure similar to androgens and inactivate the enzyme by blocking the substrate-binding site and are therefore known as aromatase inactivators. Examples of such drugs include formestane and exemestane. Type II inhibitors are non-steroidal and their action is reversible. Anastrozole is a third-generation non-steroidal aromatase inhibitor. It is the most extensively investigated third-generation aromatase inhibitor in the treatment of breast cancer. For clinical use the drug is administered orally (1 mg) once daily and the plasma steady state is reached in 41–48 h. It has no adverse influence on serum lipids and lacks androgenic side-effects⁸. Anastrozole contraindications include severe renal impairment (creatinine clearance < 20 ml/min), severe hepatic impairment, premenopausal patients (not receiving LHRH analogues such as goserelin) and concomitant use of estrogens. The present article provides an overview of the evolving role of anastrozole in the management of breast cancer.

Second-line therapy

Two international, phase III, randomised trials (0027 and 0030) have been conducted to compare the efficacy and tolerability of anastrozole with that of megestrol acetate (MA) in postmenopausal women who had relapsed/recurred on adjuvant tamoxifen treatment or following tamoxifen therapy for advanced breast cancer⁹. Megestrol acetate is a progestogen which has been used in the treatment of breast cancer. Unfortunately, the publication represents a combined analysis of two independently-conducted trials of the same protocol design with few details of the results of the individual trials. One study was carried out in Europe, Australia and South Africa and included 378 patients; the other study involved 386 patients from the USA and Canada. All patients had evaluable disease and 70% of them had ER-positive tumours. The remainder were ER-negative (5%) or of unknown ER status (25%).

The patients were randomised into three groups: anastrozole 1 mg once daily, anastrozole 10 mg o.d. and megestrol acetate 40 mg q.d.s. Both studies were double-blinded to anastrozole dose only but not to megestrol acetate. The end-points of the trials included objective response rate (complete and partial response), time to tumour progression (TTP), time to treatment failure (TTF), duration of response, survival and tolerability. The UICC criteria and computerised algorithms based on tumour measurements were used to assess response. Clinical benefit analyses were conducted after median follow-up periods of 6 and 31 months. Tolerability data were assessed at median follow-up periods of 6 and 12 months. The 6-month analysis revealed that both doses of anastrozole were as effective as megestrol acetate in terms of overall clinical benefit and time to disease progression. The 10-mg dose had no additional clinical benefit over the 1-mg dose, therefore it was decided that the 1-mg dose would be used after tamoxifen failure. At 31 months, the data were mature enough to allow survival analysis. The 2-year survival was 56.1% for the anastrozole group compared with 46.3% for the MA group (hazard ratio (HR) = 0.78, 97.5% CI = 0.6040–0.9996; $p = 0.0248$). The median survival was 26.7 months and 22.5 months for patients receiving anastrozole and MA, respectively. The survival benefit was not statistically significant in the North American study. There were no significant differences between the two treatments in terms of objective response and stable disease. The duration of overall clinical benefit for anastrozole was 18.3 months. Tolerability data showed that anastrozole was generally well tolerated with less weight gain ($p < 0.01$) than MA and less than 3% of patients withdrawing from the treatment due to unacceptable side-effects. Quality of life data were not reported in these studies. Anastrozole is currently widely used as a second-line therapy in postmenopausal women who relapse on (or fail to respond to) tamoxifen therapy.

First-line therapy

The role of anastrozole versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer (ER-positive and/or PgR-positive) was the focus of two identically designed multi-centre trials^{10,11}. The first trial¹⁰ showed that anastrozole was superior to tamoxifen in prolonging the median time to tumour progression, TTP (11.1 vs 5.6 months; $p = 0.005$). Furthermore there were fewer thromboembolic events (4.1 vs 8.2%) and vaginal bleeding episodes (1.2 vs 3.8%) in the anastrozole arm. The second trial¹¹ demonstrated that anastrozole was equivalent to

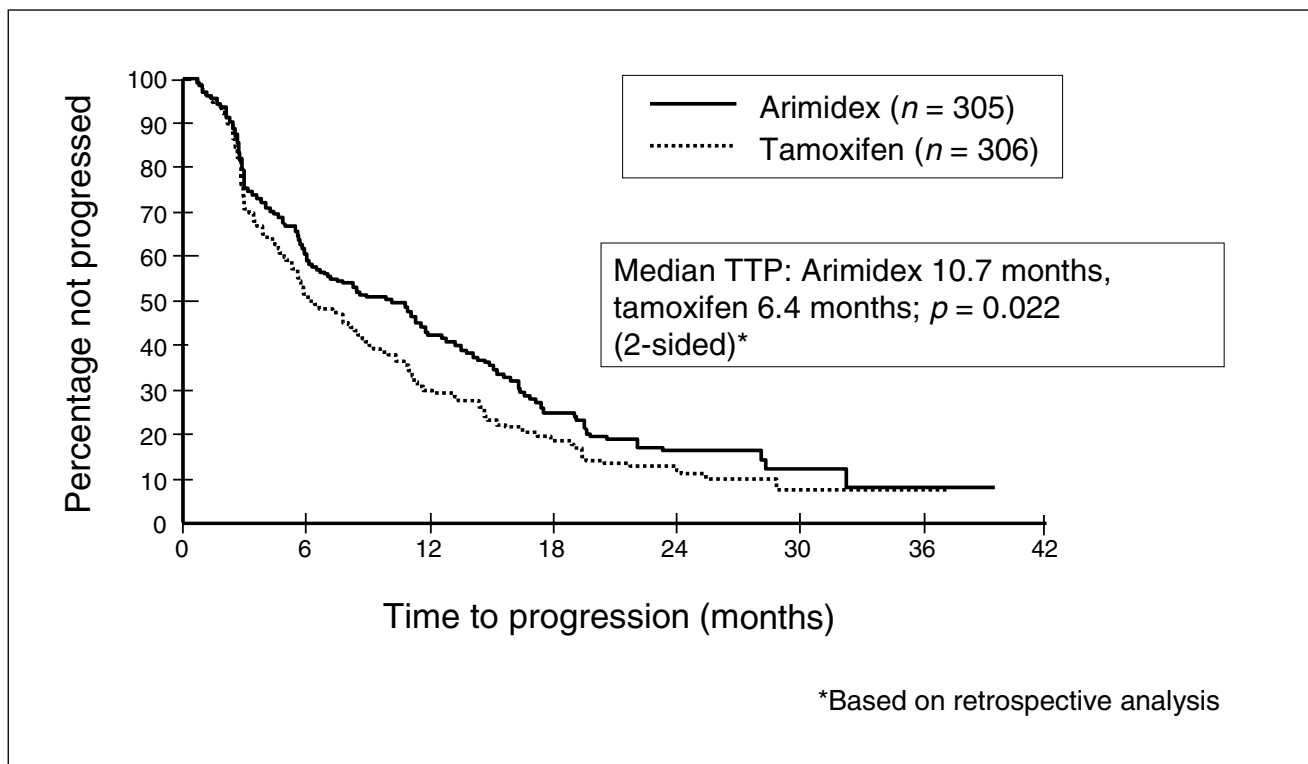


Figure 1. Kaplan-Meier Curve for TTP among the combined patients from trials 0030 and 0027 known to be receptor-positive

tamoxifen in terms of clinical benefit and TTP. Adverse effects were again significantly less frequent in the anastrozole group. The failure of the second trial to demonstrate that anastrozole is superior to tamoxifen in prolonging TTP can be attributed to the fact that a greater percentage of patients in the first trial had ER- and/or PgR-positive tumours. A combined analysis of both trials has shown that anastrozole was significantly superior to tamoxifen in relation to TTP (10.7 vs 6.4 months; $2p = 0.022$, Figure 1). These findings strongly suggest that anastrozole should be used as an alternative to tamoxifen in postmenopausal women with ER-positive advanced breast cancer, especially in patients at increased risk of deep venous thrombosis (DVT) and endometrial cancer.

Adjuvant therapy

The early results of the Arimidex*, Tamoxifen, Alone and in Combination (ATAC) trial have been recently reported¹². This multi-centre randomised trial is the largest trial in the field of cancer treatment. The study aims to compare tamoxifen and anastrozole alone and in combination in the adjuvant treatment of invasive breast carcinoma in over 9000 postmenopausal women. Patients were not excluded if they had chemotherapy and/or radiotherapy in the adjuvant or neo-adjuvant

setting. Approximately 80% of the tumours were ER-positive and 60% were T2. One-third of all patients had nodal disease. After a median of 33 months of follow-up and a median duration of treatment of 2.5 years, anastrozole was found to be significantly superior to tamoxifen in terms of DFS (HR = 0.83; $p = 0.0129$), adverse effects (vaginal bleeding, hot flushes, endometrial carcinoma, thromboembolism and weight gain) and prevention of contralateral breast cancer (HR = 0.42; $p = 0.0068$). The reduction in breast cancer recurrence was even more striking in patients with ER-positive tumours (HR = 0.78; $p = 0.0054$). However, musculoskeletal disorders and bone fractures were more frequently seen in the anastrozole group (27.8 vs 21.2% and 5.8 vs 3.7%, respectively). DFS was lessened when both drugs were given together than when anastrozole was given alone. This might be due to tamoxifen having greater estrogen agonist activity in the low estrogen environment produced by anastrozole. More recently, Dr Buzdar presented an updated analysis with a median follow-up of 47 months at the 25th San Antonio Breast Cancer Symposium¹³. The updated analysis showed that anastrozole's greater efficacy was maintained over time (Figure 2). In fact the absolute benefit increased from 1.7% at 3 years to 2.9% at 4 years for patients with ER-positive disease. The number of first events for the overall population was 413 (13.2%) for the anastrozole group, and 472 (15.1%) for the tamoxifen group. In ER-positive patients, the

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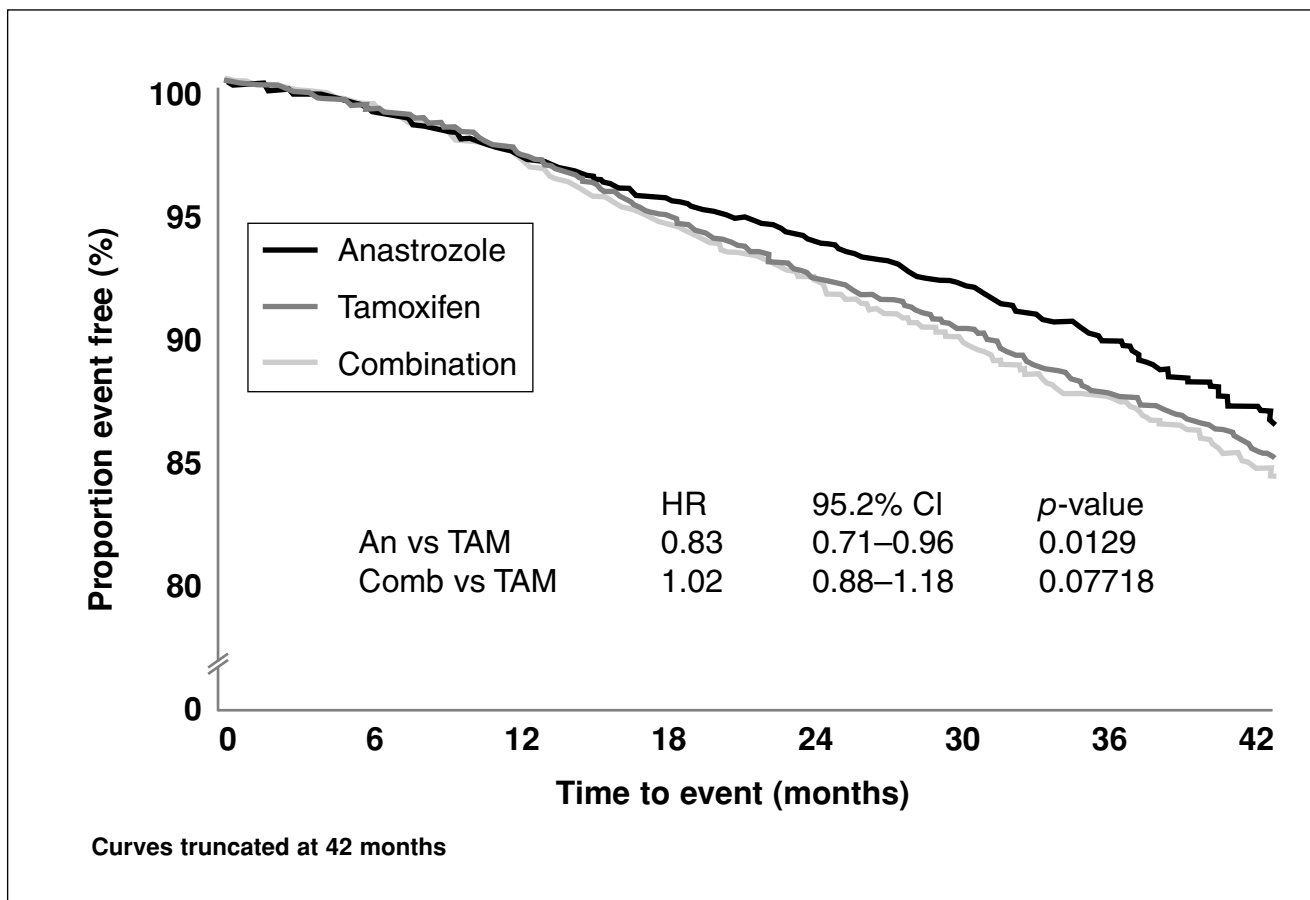


Figure 2. Kaplan–Meier survival curves for DFS in the ATAC study

number of first events was 290 (11.1%) for the anastrozole arm compared with 345 (13.3%) for the tamoxifen arm. The new data provide reassurance that anastrozole superiority is maintained, and predict that anastrozole's greater efficacy will continue. Anastrozole reduced the incidence of contralateral breast cancer by 38% ($p = 0.062$) in the overall population and by 44% ($p = 0.04$) in the ER-positive patients compared with tamoxifen. Anastrozole also maintained its superiority regarding tolerability and adverse effects, except for musculoskeletal side-effects (Figure 3). Reassuringly, there was no further increase in the number of fractures in the anastrozole arm. Although the absolute number of fractures continues to increase at a rate which is greater in the anastrozole arm than in the tamoxifen group, there is no evidence for an increase in rate with continuing therapy.

The recent evidence that letrozole, a third-generation aromatase inhibitor, is more effective than tamoxifen in patients with tumours which are positive for ErbB-1 and/or ErbB-2 and ER¹⁴ has stimulated a retrospective analysis of the ATAC study in relation to ErbB-2 status. This study is currently in progress. It is possible that the early recurrences in the tamoxifen arm are associated with ErbB-2-positive disease and a plot of hazards would be particularly informative.

A complete risk–benefit analysis requires longer follow-up and particular points of interest will be bone mineral density (BMD) and survival. Unfortunately, cognitive function was not a pre-defined parameter that was monitored in the ATAC study. It is likely that anti-osteoporosis measures such as the concomitant use of bisphosphonates and BMD measurement (DXA scan) will play an important role in the management of patients suitable for adjuvant anastrozole therapy. Although longer follow up is required prior to routine use of anastrozole in the adjuvant setting, it is currently indicated as an adjuvant therapy in women who are unable to tolerate tamoxifen or who are at an increased risk of DVT or endometrial cancer.

Neoadjuvant therapy

In a double-blind randomised trial, the effect of neoadjuvant anastrozole (1 mg once daily for 12 weeks) on tumour volume was assessed in 24 patients¹⁴. The median reduction in tumour volume, as measured by ultrasound, was 80.5%. Of the 17 patients who would have needed a mastectomy before treatment, 15 were suitable for breast conservation after receiving

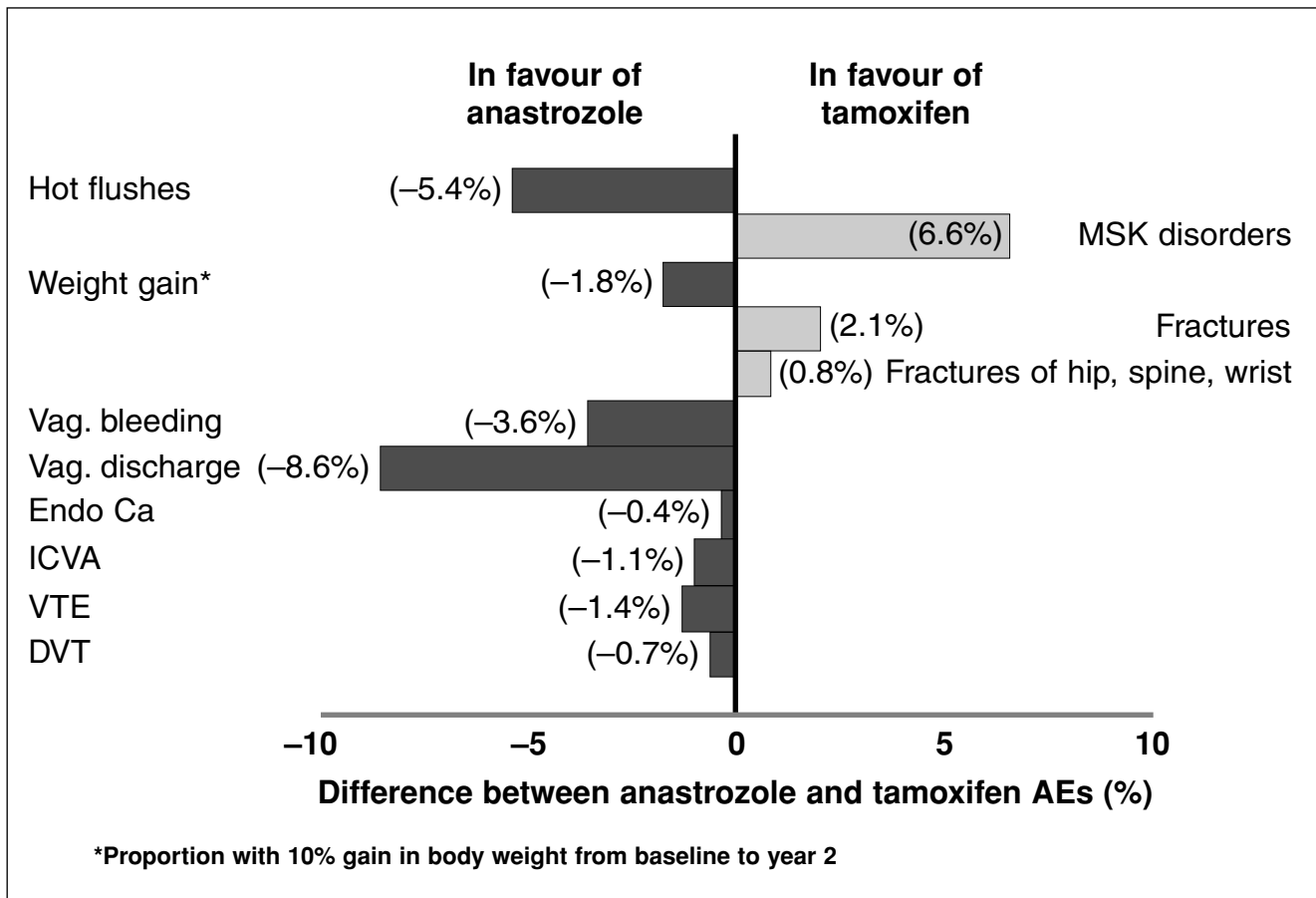


Figure 3. The adverse effects profiles for anastrozole and tamoxifen observed in the ATAC study
 Abbreviations used: MSK = Musculoskeletal; Vag. = Vaginal; Endo Ca = Endometrial cancer;
 ICVA = Ischaemic cerebrovascular adverse event; VTE = Venous thromboembolism; DVT = Deep venous thrombosis

anastrozole. Anastrozole was compared to letrozole and tamoxifen in a neoadjuvant trial¹⁵. Patients received daily doses of either 2.5 mg or 10 mg letrozole ($n = 24$), 1 mg or 10 mg anastrozole ($n = 24$ with 17 evaluable) or 20 mg tamoxifen ($n = 65$). Tumour volume was assessed after 3 months by ultrasound. The reduction in tumour volume (with 95% confidence limits) for anastrozole, letrozole and tamoxifen was 64% (52–76), 81% (69–86) and 48% (27–48), respectively. The authors concluded that aromatase inhibitors were highly effective agents in the neoadjuvant setting. As part of the ongoing clinical trial programme for anastrozole, there are studies in progress which are further investigating the use of Arimidex in the neoadjuvant setting. The double-blind Immediate Preoperative Arimidex, Tamoxifen, or Combined with Tamoxifen (IMPACT) trial is comparing neoadjuvant oral Arimidex 1 mg once daily with neoadjuvant oral tamoxifen 20 mg once daily or the two combined¹⁶. In the IMPACT trial, 300 postmenopausal patients with ER-positive, operable breast cancer are being followed for 12 weeks prior to surgery. The Preoperative Arimidex Compared to Tamoxifen (PROACT) study is also looking at the neoadjuvant use of Arimidex and tamoxifen and is in the process of

recruiting patients. A total of 6440 patients will be randomised 1:1 to two treatment arms. In this trial chemotherapy may be given, where required, during both the neoadjuvant and adjuvant periods. Assessment and surgery will be performed at 3 months, and patients will continue treatment for 5 years. The primary end-points are response rate, breast conservation rate and safety.

Pre-/peri-menopausal patients¹⁷

So far, there is limited data on the potential role of anastrozole in pre- or peri-menopausal women who are rendered postmenopausal at the time of anastrozole administration by endocrine or chemotherapeutic interventions. The Austrian Breast Cancer Study Group presented BMD data in 278 premenopausal women with ER- and/or PgR-positive breast cancer being treated with goserelin plus tamoxifen +/- zoledronate (4 mg or 6 mg) or with goserelin plus anastrozole +/- zoledronate (4 mg or 6 mg). The investigators observed a

decline in BMD as determined by DXA imaging (lumbar spine and greater trochanter) in patients receiving tamoxifen or anastrozole without zoledronate. BMD reduction was significantly greater for anastrozole ($p = 0.0125$). However, after 6 months of treatment with zoledronate, the cohorts receiving zoledronate had significantly higher BMD ($p < 0.0001$). Although longer follow-up is required to ensure that zoledronate benefits are maintained, it would be reasonable to consider zoledronate therapy (4 mg) in postmenopausal women receiving adjuvant anastrozole, who are at high risk of osteoporosis.

In a study involving 119 pre- or perimenopausal women with hormone-sensitive advanced breast cancer randomised to goserelin plus tamoxifen or goserelin plus anastrozole, the OR was significantly higher for the anastrozole plus goserelin arm compared with the tamoxifen plus goserelin arm (80 vs 53%; $p = 0.0023$). Furthermore, the time to death was also significantly longer for the anastrozole plus goserelin group (18.9 vs 14.3 months; $p = 0.0001$), suggesting that this combination should be considered for the treatment of pre- or perimenopausal women with hormone-sensitive advanced breast cancer.

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