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E17. Are aromatase inhibitors superior to tamoxifen after the menopause?

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Tamoxifen has long been considered the endocrine therapy of choice for the treatment of women with hormone-sensitive breast cancer. The most recently published overview of adjuvant tamoxifen trials showed that in patients with hormone receptor-positive disease, the odds of recurrence and death were reduced by 47% and 26%, respectively, following about 5 years of therapy with tamoxifen [1]. Despite it is proven effectiveness, tamoxifen is associated with an increased risk of endometrial cancer, uterine sarcoma and thromboembolic disorders [2,3].

In postmenopausal women, the major source of oestrogen is from peripheral aromatisation of androgens; the rate-limiting step catalysed by aromatase enzyme. Anastrozole is a third generation aromatase inhibitor and has no partial oestrogenic activity like tamoxifen. Anastrozole has been established to be effective and well tolerated as first-line therapy for treatment of breast cancer [4]. The Armidex, tamoxifen, alone or in combination (ATAC) trial (N = 9366) is a large international, randomised, double-blind, multicentre study that compared the efficacy of anastrozole (N = 3125) against tamoxifen (N = 3116) or a combination of both drugs (N = 3125) [5]. The trial was designed to answer three important questions: (1) Is anastrozole at least as effective as tamoxifen in postmenopausal patients with early breast cancer? (2) Does anastrozole offer any safety or efficacy advantage over tamoxifen in this subset of patients? (3) Could the combination of anastrozole plus tamoxifen offer additional efficacy or safety benefits over tamoxifen alone? The initial data with a median follow-up of 33 months demonstrated that anastrozole significantly prolonged disease-free survival compared with tamoxifen in overall population (Hazard Ratio 0.83; 95% Confidence Interval 0.71–0.96, P = 0.013) with disease-free survival in patients receiving the combination not being significantly different from those receiving tamoxifen alone. Disease-free survival was further improved in patients with hormone receptor-positive disease; 84% of patients in the study population. There were no differences in patients with hormone receptor-negative disease between the three arms of the study. At a median follow-up of 47 months, the primary endpoint, disease-free survival was again significantly longer for patients who received anastrozole alone compared with those who received tamoxifen alone (Hazard Ratio 0.86; 95% Confidence Interval 0.76–0.99; P = 0.03) [6]. There were no significant differences in disease-free survival between tamoxifen and the combination arm. These data confirmed the results of the initial analysis. Relative Risk reduction was greater among patients with hormone receptor-positive disease. Hazard Ratio was 0.82 (95% Confidence Interval 0.70–0.96; P = 0.014) for anastrozole versus tamoxifen. Absolute differences in disease-free survival in favour of anastrozole increased over time.

At a median follow-up of 33 months, there was a significant reduction in primary contralateral breast cancer as a first event in the anastrozole group compared with tamoxifen (Odds Ratio 0.42; 95% Confidence Interval 0.22–0.79; P = 0.007). This reduction continued to be seen in anastrozole group after an immediate follow-up of 47 months and was statistically significant in the subgroup with hormone receptor-positive disease compared with tamoxifen, odds were reduced by 38% in overall population. Odds Ratio being 0.62 (95% Confidence Interval 0.38–1.02; P = 0.06), and by 44% in the

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hormone receptor-positive subgroup, Odds Ratio 0.56 (95% Confidence Interval 0.32–0.98; $P = 0.04$). Initial and updated safety analysis have shown that anastrozole therapy was associated with a significantly reduced incidence of hot flashes, vaginal bleeding, vaginal discharge, endometrial malignancies, ischaemic cerebral vascular events, venous thromboembolic events including deep vein thrombosis. Musculo-skeletal disorders and fractures were increased with anastrozole compared with tamoxifen. The Relative Risk data demonstrate that benefits from anastrozole were maintained with longer follow-up and the Relative Risk of fracture or musculo-skeletal disorders were unchanged, and did not worsen over time [6,7].

The results of the ATAC trial demonstrate the superiority of anastrozole over tamoxifen and confirmed that anastrozole significantly prolonged both disease-free survival and time-to-recurrence. Anastrozole treatment was also associated with a significant reduction in the risk of contralateral breast cancer compared with tamoxifen in postmenopausal patients with hormone receptor-positive early stage breast cancer. The absolute benefits of anastrozole compared with tamoxifen continued to increase over time and are expected to result in improvements in overall survival after additional follow-up. These data support the use of anastrozole over tamoxifen in the treatment of postmenopausal women with hormone-sensitive early breast cancer, as the overall therapeutic index of anastrozole is more favourable than tamoxifen.

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