ELSEVIER

EJC Supplements Vol 2 No. 9 (2004) 33–34

EJC Supplements

www.ejconline.com

E9. Side-effects of tamoxifen and solutions with aromatase inhibitors

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Tamoxifen is an effective drug, both for preventing and treating breast cancer, but its role in prevention is limited by its side-effect profile, particularly related to endometrial problems and thrombotic events. The aromatase inhibitors offer the promise of greater efficacy with fewer side-effects. Loss of bone mineral density leading to an increased fracture rate appears to be the major side-effect associated with aromatase inhibitors. It will be important to learn how to manage this outcome with DXA (dual energy X-ray absorptiometry) scans and bisphosphonates, where appropriate. New studies in this direction are ongoing.

1. Background

Tamoxifen is probably the most successful cancer treatment currently available and has a low side-effect profile. Data from the overview of all adjuvant trials [1] indicated that for every 1000 hormone receptor-positive women, 5 years of tamoxifen can be expected to lead to 78 fewer breast cancer deaths and only one extra endometrial cancer death, and one extra death from a pulmonary embolism. However, prevention trials [2,3] have clearly indicated that there are a range of less severe side-effects associated with tamoxifen and that the risk-benefit is not so clearly positive when used in the preventive setting. Recent studies in the adjuvant setting have suggested that the aromatase inhibitors may be more effective than tamoxifen in preventing recurrence and new contralateral tumours and have fewer side-effects than tamoxifen.

2. Results

The best comparative data on aromatase inhibitors *vs* tamoxifen come from the arimidex, tamoxifen, alone or in combination (ATAC) trial [4]. This trial randomised 9366 women into one of three arms: anastrozole alone, tamoxifen alone, or the combination for 5 years. The results on efficacy and side-effects have recently been published after a 47-month median follow-up [5]. For receptor-positive women, anastrozole had a 22% lower hazard ratio than tamoxifen (P=0.007). The frequency of predefined side-effects that differed significantly between these two treatments is shown in Table 1. Overall, anastrozole was better tolerated than tamoxifen (P<0.001). Many of the side effects known to be associated with tamoxifen were reduced to baseline levels (vaginal bleeding, endometrial cancer, thromboembolic events). The number of endometrial cancers is particularly low, and may reflect a protective effect against this cancer as well. It is too early to be confident, but the next analysis (due in December 2004) in which almost all women will have completed their 5 years of treatment will provide substantially more information on this outcome. Strokes and TIAs are also substantially reduced on anastrozole compared with tamoxifen (P<0.001). It is not clear yet if this represents a reduction in strokes due to oestrogen depletion from

Table 1
Adverse events in ATAC Summary relative rates for Anastrozole compared with tamoxifen

Reduced by anastrozole	
Hot flushes (34% *vs* 40%)	down 14%
Vaginal bleeding (4.5% *vs* 8.1%)	down 44%
Endometrial cancer (3% *vs* 15%)	down 80%
Strokes/TIAs (1% *vs* 2%)	down 50%
Thromboembolic events (2.1% *vs* 3.5%)	down 40%
Stopping treatment (5% *vs* 7%)	down 32%
Increased by qnastrozole	
Musculo-skeletal (28% *vs* 21%)	up 30%
All fractures (6% *vs* 4%)	up 50%

ATAC, arimidex, tamoxifen, alone or in combination.
TIA: transient ischaemic attack.

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doi:10.1016/j.ejcsup.2004.08.009

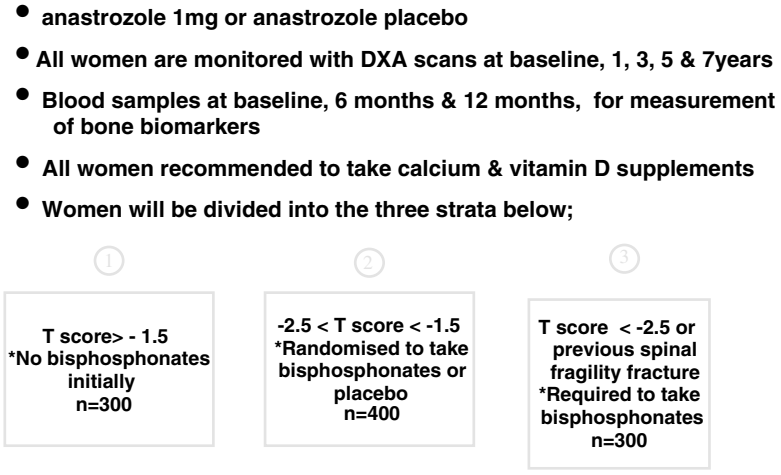

Fig. 1. IBIS II–Bone sub-study.

anastrozole or an increase due to tamoxifen, where the data are currently mixed [2,6]. The placebo-controlled prevention trial of anastrozole (IBIS-II) (International Breast cancer Intervention Study) will be needed to clarify this.

Against these favourable outcomes, one must weigh the unfavourable effects of oestrogen depletion on musculo-skeletal events and fractures. The former problem appears to be generally mild and has not led to stopping treatment in the ATAC trial. However, learning how best to manage bone loss and the attendant increase in fracture rates is probably the major new challenge for using aromatase inhibitors.

This is being addressed in the IBIS-II prevention trial in which 1000 women split into 3 strata will be evaluated by sequential DXA scans and treatment with the bisphosphonate risedronate (oral, weekly 35 mg) (Fig. 1). Adequate control of this side-effect would make an aromatase inhibitor a very useful agent, both for the treatment and prevention of breast cancer. The latter goal is the subject of the ongoing IBIS-II trial involving the use of anastrozole or placebo in 6000 post-menopausal women at increased risk of breast cancer.

References

1. Early Breast Cancer Trialists Collaborative Group. Favourable and unfavourable effects of long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000, **355**, 1757–1770.
2. Cuzick J. A brief review of the International Breast Cancer Intervention Study (IBIS), the other current breast cancer prevention trials, and proposals for future trials. In: Marietta Anthony, Barbara K. Dunn, Sherry Sherman (editors). Selective estrogen receptor modulators [SERMs], *Ann NY Acad Sci* 2002, **949**, 123–133.
3. Cuzick J, Powles T, Veronesi U, *et al*. Overview of the main outcomes in breast cancer prevention trials. *Lancet* 2003, **361**, 296–300.
4. The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen *versus* tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002, **359**, 2131–2139.
5. The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen *versus* tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer – Results of the ATAC (arimidex, tamoxifen alone or in combination) trial efficacy and safety update analysis. *Cancer* 2003, **98**, 1802–1810.
6. Fisher B, Costantino JP, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998, **90**, 1371–1388.