ELSEVIER

EJC Supplements Vol 2 No. 9 (2004) 15–16

EJC Supplements

www.ejconline.com

E1. Endocrine prevention of breast cancer

Trevor J. Powles *

Parkside Oncology Clinic, London, UK

Four clinical trials, the Royal Marsden, the Italian, the American National Surgical Adjuvant Breast and Bowel Project (NSABP) and the United Kingdom (UK) IBIS (International Breast Intervention Study) trials, have been reported evaluating tamoxifen used in healthy women to prevent breast cancer [1–4]. After 10 years of follow-up, the Marsden trial shows no significant risk reduction for breast cancer. The Italian trial was also initially negative, but now shows a small risk reduction. The UK IBIS trial showed a risk reduction, but this was not significant for invasive breast cancer. The largest study, the NSABP trial, reported a very significant risk reduction for breast cancer.

The entry criteria for each of these trials were based on various risk factors. The Royal Marsden trial was a younger population-based subject group with a strong family history. The IBIS trial was similar to the Marsden trial, but included patients with a lower risk assessment. The NSABP trial was based on the Gail model and the Italian trial had no special risk criteria, but required all of the participants to have had a hysterectomy. These differences in entry criteria probably account for much of the variation in outcomes.

A meta-analysis of these trials has shown that tamoxifen given for 5 years will reduce the risk of breast cancer by approximately 40% [5]. However, there is significant toxicity with an increased risk of endometrial polyps and cancer, venous thrombo-embolism, vasomotor symptoms and cataracts. Clinical benefit from this risk reduction for breast cancer has not been clearly established.

Another selective oestrogen receptor modulator (SERM), raloxifene, has been used in an osteoporosis clinical trial in post-menopausal women and been shown to reduce the risk of fractures [6], myocardial infarcts [7] and breast cancer [8]. Unlike tamoxifen, raloxifene is not oestrogenic on the endometrium, due to an impeded agonist effect caused by a side-chain on the molecule [9] and therefore does not cause endometrial cancer. The NSABP P2 trial is now comparing raloxifene with tamoxifen for risk reduction effects. Due to its impeded oestrogenic activity, it is likely that raloxifene will be more active than tamoxifen for the prevention of breast cancer. Other SERMs, such as lasofoxifene, are also being evaluated.

The aromatase inhibitors, anastrozole, letrozole and exemestane have been shown to reduce the risk of contralateral breast cancer better than tamoxifen in the adjuvant breast cancer trials [10]. The IBIS II trial has started randomising healthy women with a family history of breast cancer to anastrozole or placebo, and other aromatase inhibitors are likely to be evaluated in primary prevention trials in the near future.

No trials at this time are directly comparing an aromatase inhibitor with a SERM. The relative merits of these two types of intervention for the chemoprevention of breast cancer needs to be addressed.

To date, the results of the adjuvant and prevention trials show that endocrine prevention of breast cancer is possible, but it will be necessary to use more active, and less toxic, agents than tamoxifen.

For future trials, an evaluation of the risk factors which predispose to the oestrogenic promotion of breast cancer, rather than using the Gail model, may allow the identification of those women likely to gain benefit from anti-oestrogenic intervention using SERMs or aromatase inhibitors.

References

1. Powles T, Tamoxifen's oestrogen-like effect in a breast cancer prevention trial. *Eur J Cancer* 1998, **34**(4), S17–S18.
2. Veronesi U, *et al.* Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet* 1998, **352,** 93–97.
3. Fisher B, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *JNCI* 1998, **90**(18), 1371–1388.

* Tel.: +44 20 8971 8000.
E-mail address: amccabe@parkside-hospital.co.uk.

doi:10.1016/j.ejcsup.2004.08.001

4. IBIS investigators, First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial. *Lancet* 2002, **360,** 817–824.
5. Cuzick J, *et al*. Overview of the main outcomes in the breast cancer prevention trials. *Lancet,* 2003, **361**, 296–300.
6. Ettinger B, *et al*. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999, **282**(7), 637–645.
7. Barrett-Connor E, Wenger NK, Grady D, Mosca L, Collins P, Kornitzer M, Cox DA, Moscarelli E, Anderson PW, Coronary heart disease in women, randomized clinical trials, HERS and RUTH. *Maturitas* 1998, **31**(1), 1–7.
8. Cummings S, *et al*. The effect of raloxifene on risk of breast cancer in postmenopausal women. Results from the MORE randomized trial. *JAMA* 1999, **281,** 2189-2197.
9. Shang Y, Brown M. Molecular determinants for the tissue specificity of SERMs. *Science* 2002, **295,** 2465–2468.
10. 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.