S31. Endocrine Prevention of Breast Cancer

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It is likely that most breast cancers depend on oestrogen in order to develop from into clinical cancer. A clinically beneficial risk reduction for breast cancer should therefore result from the use of the anti-oestrogen, tamoxifen, in healthy high risk women. Four large clinical trials involving over 25,000 healthy women were undertaken starting in 1986.

A meta-analysis of these trials has shown that tamoxifen given for 5 years reduced the risk of breast cancer by approximately 40% [1]. However, there was 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 using tamoxifen has not been clearly established.

An approach to improve the benefits of antioestrogenic intervention is to use more active, less toxic agents. The selective oestrogen receptor modulator (SERM), raloxifene, used in an osteoporosis clinical trial (MORE trial) in post-menopausal women with osteoporosis has been shown not only to reduce the risk of fractures, and myocardial infarcts, but (as a secondary outcome) to also substantially reduce the risk of breast cancer. The 4 year continuation of this trial with breast cancer as a primary outcome (CORE trial) has confirmed the substantial risk reduction for breast cancer [2]. Raloxifene is also being investigated in a heart disease trial (RUTH trial) with breast cancer as an outcome.

Unlike tamoxifen, raloxifene is not oestrogenic on the endometrium, and does not cause endometrial cancer.

The NSABP P2 trial comparing raloxifene with tamoxifen for risk reduction has completed accrual of 16,000 healthy postmenopausal women at a Gail risk of $\geq$1.66. Other SERMs, such as lasofoxifene and arzoxifene, are now also being evaluated in multiple outcome trials with breast cancer risk reduction as a primary outcome.

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. The IBIS II trial has started randomizing 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.

In conclusion, the results of the adjuvant and prevention trials show that endocrine prevention of breast cancer with SERMs or aromatase inhibitors is possible. However, in order to achieve clinical benefit in the prevention setting. it will be necessary to use more active, and less toxic, agents than tamoxifen in women with an increased risk of breast cancer because of established oestrogen dependant risk factors.

References

[1] Cuzick J, et al. Overview of the main outcomes in the breast cancer prevention trials. Lancet, 2002 [in press].

[2] Martino S, Cauley J, Barett-Connor E, Powles T, et al Continuing Outcomes Relevant to Evista: Breast Cancer in Postmenopausal Osteoporotic Women in a Randomised Trial. JNCI, 2004, 96, 1751-1761.