Selective Oestrogen Receptor Modulators (SERMs) for Prevention of Breast Cancer

The likelihood that oestrogen is needed for the development of oestrogen receptor-positive (ER +ve) breast cancer has encouraged the concept that breast cancer could be prevented by using an anti-oestrogen such as tamoxifen.

In the 1970s, tamoxifen was shown to be safe and effective as an anti-oestrogen for treating metastatic breast cancer and as adjuvant treatment for primary breast cancer. In 1986, a feasibility trial was started at the Royal Marsden Hospital, London, UK using tamoxifen to prevent breast cancer in healthy pre- and post-menopausal women. The early results showed, rather surprisingly, that although tamoxifen was anti-oestrogenic on the breast, it was 'selective' and the drug had oestrogenic activity on other tissues in the body, lowering cholesterol and reducing bone loss.[1,2] As a result, the overall toxicity was low, compliance was high and recruitment of healthy women to large clinical trials was possible.

The Marsden trial finally recruited 2500 women followed by three larger trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 trial, the Italian National trial and the International Breast Cancer Intervention Study (IBIS-1) trial, all starting in 1992 recruiting a further 24 400 women.[3–6]

A meta-analysis of these trials in 2003 showed a 38% reduction in invasive breast cancer (48% for ER +ve, p=0.0001) for pre- and post-menopausal women. However, there was a significant increase in endometrial cancer and venous thromboembolism. Other side-effects included gynaecological problems, vasomotor symptoms and cataracts. A beneficial reduction in serum cholesterol, osteoporotic fractures, breast symptoms including cysts and pain, and headaches was also seen.[7]

Further follow-up of these trials indicated that the risk reduction continued for at least 10 years after completion of tamoxifen indicating a possible life-long risk reduction, whereas most side-effects resolved on completion of the medication.[6]

Breast cancer risk in women with no risk factors is about 1 per 1000 per year at age 40, rising to about 3 per 1000 per year at age 60 and increasing gradually after this. The tamoxifen trials selected women with various risk factors for breast cancer such as family history, previous benign biopsy, previous high-risk pathology such as lobular carcinoma *in situ* or atypia. The Marsden trial had a >3-fold increased risk and IBIS a 2-fold risk based on a family history of breast cancer. The NSABP had an estimated Gail risk of >1.66% at 5 years equivalent to >3.3 per 1000 per year.[8] Participants of the Italian trial did not show an increased risk.

Tamoxifen was approved by the US Food and Drug Administration (FDA) for reduction of breast cancer risk in the USA in 1998 for women at Gail risk >1.66% at 5 years.

Following the tamoxifen trials, the concept of selective oestrogen receptor modulation (SERM) allowed the development of the second generation SERM raloxifene as a treatment to reduce fractures in post-menopausal women with low bone density. The MORE (multiple outcome for raloxifene evaluation) trial randomized 12 512 women to raloxifene and reported a significant reduction in the primary outcome of vertebral fractures.[9] Breast cancer incidence as a secondary outcome of the trial was also significantly reduced.[10] The US FDA approved only the primary outcome of fracture risk reduction and, therefore, the trial continued as the CORE (COlchicine for REcurrent pericarditis) trial with 7700 of the original participants, with breast cancer as the primary outcome. After a further follow-up of 4 years, a 66% risk reduction (p<0.001) in invasive breast cancer was reported.[11]

The MORE/CORE trials showed a significant reduction in cholesterol and therefore a further raloxifene trial, the RUTH (Raloxifene) trial, designed to evaluate the effect of raloxifene on the heart was completed. This, disappointingly, showed no reduction in cardiovascular events but did confirm a convincing reduction of breast cancer risk.[12]

Then followed the Study of Tamoxifen and Raloxifene (STAR) trial which recruited 19 747 post-menopausal women in a direct comparison between raloxifene and tamoxifen. This showed that the reduction of breast cancer risk by both agents was the same with no difference in cardiac events, incidence of other cancers, osteoporotic fractures or stroke. Thromboembolic events, uterine abnormalities and cataract occurred less often with raloxifene.[13]

Two third-generation SERMs have been evaluated as possible osteoporosis drugs. The

Generation trial randomized 9354 post-menopausal women with osteoporosis or osteopenia to arzoxifene or placebo and showed a reduction in vertebral but not non-vertebral cancers. There was a significant reduction in ER +ve breast cancer but because of the disappointing non-vertebral bone fracture results the drug has not been developed further.[14]

The PEARL (protocol for a cluster randomized controlled trial) evaluated a direct comparison of lasofoxifene with placebo in 8556 post-menopausal women with osteoporosis and showed a significant reduction in ER +ve invasive breast cancer, vertebral and non-vertebral fractures, stroke, major coronary events, with no increase in endometrial cancers, atypia or hyperplasia but a similar increased risk of thromboembolism. Further development of lasofoxifene for use for reduction of breast cancer risk has not occurred at this time.[15]

A meta-analysis of all nine of these trials comprising 83 399 randomized women, with 306 307 women-years of follow-up has confirmed a significant 38% reduction in risk of breast cancer. The incidence of invasive (ER +ve cancers was decreased by 51%; HR=0·49) with no observed reduction in oestrogen-receptor-negative (ER –ve) breast cancers. With regard to side-effects there was a significant increase in endometrial cancer (HR=2.18) with tamoxifen but not other SERMs and an increase in thromboembolic effects with all SERMs (OR=1.73). Vertebral fractures were reduced by 34% but there was only a small reduction in non-vertebral fractures (OR=0.93). Overall, there was no effect on mortality from other cancers, stroke or myocardial infarction.[16]

For high-risk women because of a family history, the National Institute for Health and Care Excellence (formerly National Institute for Clinical Excellence), UK has recommended tamoxifen for all women and raloxifene for post-menopausal women who have not had a hysterectomy for prevention of breast cancer.[17]

All the SERM trials clearly show a failure to reduce the incidence of ER –ve breast cancer risk even long after completion of 5 years of treatment indicating that ER –ve cancers are not derived from ER +ve precursors. Research is therefore under way to identify those women at high risk of developing ER +ve breast cancers, by identification of commonly inherited moderate risk breast cancer predisposing single nucleotide polymorphisms (SNPs). The occurrence of multiple SNPs acting synergistically in combination and with environmental risk factors may substantially increase the process of endocrine promotion of breast carcinogenesis. These mutations may occur commonly because they give an oestrogenic advantage in early adulthood (such as fertility, lactation, etc.) and may give rise to phenotypic features of risk (such as breast density, endocrine measurements, etc.). Stored DNA from the trials may be needed to identify these markers of risk of ER +ve breast cancer and show that SERMs can reduce this risk.

In summary, the use for a few years of tamoxifen in pre-menopausal women and the next generation of SERMs in post-menopausal women, can give long term (even lifetime) risk reduction of breast cancers with only a relatively short period of—for the most part—low morbidity. In the foreseeable future we should be better able to identify those women at significant risk of getting ER+ve breast cancer for whom tamoxifen would be of benefit. This would reduce the number of women who need to be treated and thereby make the concept of breast cancer prevention more acceptable and less of a controversial issue.

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