Chemoprevention of breast cancer using tamoxifen

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Clinical and experimental basis for tamoxifen chemoprevention

In many respects it is disappointing that it has taken more than 100 years to apply the quite remarkable observation of Beatson, of endocrine treatment of advanced breast cancer, to the possibility of endocrine prevention of the disease. More than 30 years ago it was shown that the carcinogenic induction of mammary cancers in rats depended on ovarian hormones and that ovariectomy would prevent the development of these tumours (Dao 1962). Further epidemiological data indicated that early ovarian failure in humans was associated with a reduced incidence of breast cancer (MacMahan & Feinlieb 1960, Hirayama & Wynder 1962). However, clinical trials to test for prevention by ovarian ablation in healthy women are ethically unacceptable, and therefore no further progress could be made in the possible endocrine prevention of breast cancer until the development of an acceptable safe alternative.

In 1967 Harper & Walpole reported the development of an antioestrogenic triphenylethylene by ICI which was shown to be an effective low toxicity treatment of advanced breast cancer (Cole et al. 1971, Ward 1973). Experimentally, tamoxifen was shown to inhibit the growth of oestrogen receptor-positive MCF7 cells in culture (Lippman & Bolan 1975) and could prevent the development of tumours in carcinogenically treated rats (Jordan 1974, 1976), irradiated rats (Welsch et al. 1981) and mice infected with the mouse mammary tumour virus (Jordan et al. 1990). This provided a sound experimental basis for using tamoxifen as a chemopreventative agent.

Use of tamoxifen as adjuvant therapy after surgical treatment for primary breast cancer developed during the mid to late 1970s and early results were encouraging (Nolvadex Adjuvant Trial Organisation 1983), showing a significant reduction in the risk of relapse and death, confirmed by an overview meta-analysis carried out in 1984 by the Oxford group (Early Breast Cancer Trialists’ Collaborative Group 1988). Of particular interest was the reported very low toxicity associated with long-term tamoxifen therapy and the possibility that the incidence of contralateral second primary cancers could be reduced by the use of such adjuvant therapy (Cuzick & Baum 1985). These results encouraged the view that tamoxifen could be an acceptable alternative to ovarian ablation for a clinical trial of endocrine chemoprevention of breast cancer in healthy women. This possibility was further strengthened by epidemiological data which indicated that a relatively high-risk group of women could be identified, based on a strong family history of the disease.

However, the jump from treatment of patients with breast cancer to chemoprevention in healthy women required considerable caution and much higher levels of safety monitoring than had been considered adequate for adjuvant trials. For this reason it was agreed that a small feasibility, randomised, double-blind, tamoxifen versus placebo trial involving 200 high-risk healthy women, with a strong family history of breast cancer, would be undertaken at the Royal Marsden Hospital, designed to evaluate accrual, compliance, acute toxicity and safety monitoring. Providing these were all satisfactory, the trial could be extended into a pilot programme involving 2500 healthy women aimed at leading into multicentre international trials accruing the 20-30 000 healthy women who would be required for a definitive answer on the possibility of tamoxifen chemoprevention.
The feasibility trial

After extensive consultation with breast cancer specialists and family doctors in the UK, funding bodies and ethical and patient groups, accrual to the feasibility trial started at the Royal Marsden Hospital in October 1986. Two hundred healthy pre- and post-menopausal women aged between 35 and 65 years were randomised to receive either tamoxifen (20 mg/day) or placebo for 5 years.

An interim analysis of this feasibility trial in June 1988 indicated that healthy women would be accrued to a tamoxifen chemoprevention trial, that acute toxicity was low and the safety monitoring was satisfactory (Powles et al. 1989a). Accrual of 200 women to this feasibility trial was therefore completed in October 1988. Evaluation at that time confirmed the very low acute toxicity with a correspondingly high compliance of over 80% at 1 year (Powles et al. 1989b). Safety monitoring of these 200 women indicated no evidence of loss of bone mineral density (BMD) measured by single photon absorption through the wrist, or adverse effects by tamoxifen on clotting factors. There was surprisingly a 15% drop in the serum cholesterol (Powles et al. 1989b).

These accrual, compliance, acute toxicity and safety data, particularly the lowering of serum cholesterol, indicated that it waslogistically possible, ethically acceptable, and sufficiently safe for the feasibility trial to extend into a pilot programme.

By October 1991, the first women who had been randomised into the feasibility programme had received 5 years of medication, and a review of the acute toxicity and safety monitoring data (Powles et al. 1990), together with experimental data which indicated that tamoxifen chemoprevention depended on the duration of medication (Jordan et al. 1990), encouraged agreement that the duration of medication in the pilot trial should be extended to 8 years, and the total number of women included in the pilot trial should be 2500. The accrual to this pilot trial was completed in 1995.

Pilot trial

Acute toxicity and compliance

In the completed pilot trial, the acute toxicity in these healthy women receiving either tamoxifen (20 mg/day) or placebo remained very low. The only significant side-effects for tamoxifen were hot flushes in 34% (placebo 20%), vaginal discharge in 16% (placebo 4%) and menstrual irregularities in 14% (placebo 9%) with a correspondingly high compliance at 5 years of 77% for tamoxifen versus 82% for placebo. This level of toxicity is extremely low and will allow the level of compliance required for a large multicentre chemoprevention trial.

Safety monitoring

Clotting and lipid monitoring

Although there has been one report of an increased risk of thromboembolism in women receiving adjuvant tamoxifen (Fisher et al. 1996), other trials have failed to confirm this and we have been unable to detect any adverse changes in clotting factors caused by tamoxifen in the pilot programme (Jones et al. 1992).

We have, however, confirmed our initial observation that total serum cholesterol is reduced by about 15% (Powles et al. 1989b) in pre- and postmenopausal women, associated with a fall in low-density lipoprotein but not high-density lipoprotein cholesterol with a corresponding fall in apolipoprotein A but not apolipoprotein B (Powles et al. 1990) maintained out to at least 5 years (Powles et al. 1994). This could account for a reported reduction in the incidence of fatal myocardial infarctions (MacDonald et al. 1991) and non-cancer deaths (Early Breast Cancer Trialists' Collaborative Group 1992) in patients on adjuvant tamoxifen. Therefore, at this time, the data indicate that the risk of cardiovascular death is not increased by the use of tamoxifen and may well be reduced.

Bone density studies

In postmenopausal women tamoxifen has been reported to cause an increase in BMD measured by dual energy X-ray absorption (Love et al. 1992, Kristensen et al. 1994, Powles et al. 1994) predominantly occurring, like hormone replacement therapy, during the first 2 or 3 years of medication. In contrast, in premenopausal women tamoxifen causes a transient, but significant, reduction in BMD, presumably by an antioestrogenic mechanism, which could have an impact on the subsequent risk of osteoporotic fractures (Powles et al. 1994). It is possible that this antioestrogenic effect on bone will not be maintained and that with continued medication the agonistic effect of tamoxifen on bone will predominate. Further follow-up involving longer monitoring of...
bone density is required in pre- and postmenopausal women in order to evaluate any potential long-term benefit or risk from continued tamoxifen treatment.

**Carcinogenic effect**

Experimentally, tamoxifen has been shown to be a genotoxic carcinogen (Han & Liehr 1992) causing development of liver cancer in rats (White et al. 1992) but not other animals. However, at the standard dose of 20 mg/day, there is no clinical evidence of any increase in non-endometrial cancers in women who have received adjuvant tamoxifen for up to 10 years in clinical trials, some of which were started in the early 1970s (Early Breast Cancer Trialists' Collaborative Group 1992).

At the higher dose of 40 mg/day an increase in the risk of gastrointestinal cancers has been reported in a retrospective study of adjuvant tamoxifen (Rutqvist et al. 1995), although considerable doubt has been cast on the statistical methods used for this analysis (Jordan 1995). Furthermore, in women on tamoxifen there is no evidence for any increase in DNA adducts in the liver (Martin et al. 1995). In the pilot programme only 15 non-endometrial, non-breast cancers have occurred so far, in women on tamoxifen or placebo, with no significant difference in incidence in the two arms.

At this time, it would therefore seem unlikely that there is a significant increased risk of non-endometrial cancers in women given tamoxifen and that the potential benefits are likely to outweigh any theoretical non-endometrial carcinogenic risks.

**Gynaecological effects**

The risk of endometrial cancer is, however, probably increased even at doses of 20 mg/day and probably by a non-genotoxic mechanism. This follows an initial report from Sweden that adjuvant tamoxifen given at a dose of 40 mg/day was associated with a sixfold increase in the risk of endometrial cancer in postmenopausal women (Fornander et al. 1989). However, at a dose of 20 mg/day various retrospective reviews and case-controlled studies indicate a possible increase of only about twofold in postmenopausal women receiving 2 to 5 years of tamoxifen treatment (Cummings et al. 1985, Stewart & Knight 1989, Andersson et al. 1991, van Leeuwen et al. 1994, Cuenca et al. 1996, Sasco et al. 1996). If this is a real effect, it would appear to be unrelated to the genotoxic properties of tamoxifen (Carmichael et al. 1996) and more likely due to the oestrogenic effect of tamoxifen on an atrophic postmenopausal endometrium, in a similar manner to unopposed oestrogen replacement therapy (Grady et al. 1995). Tamoxifen does have an oestrogenic effect on the normal endometrium in postmenopausal women, and will cause endometrial thickening in some postmenopausal women which can be detected using transvaginal ultrasound (Kedar et al. 1994).

In our pilot trial, over 40% of postmenopausal women on tamoxifen have an endometrium of >8 mm in thickness, measured using transvaginal ultrasound, compared with only 5% of women on placebo. This thickening is probably caused by tamoxifen-induced hyperplasia which may become atypical and give rise to an increased risk of endometrial cancer. At this time in the pilot trial, only five endometrial cancers have occurred in women on tamoxifen or placebo and any difference in incidence between the two arms is likely to be quite small (Powles & Ashley 1994). However, cysts, polyps and fibroids were detected in about 30% of women on tamoxifen by transvaginal ultrasound, indicating stromal changes in the uterus caused by tamoxifen, not necessarily related to endometrial hyperplasia, and presumably unrelated to the risk of endometrial cancer. Nonetheless, these gynaecological changes may cause symptoms and lead to a small but significant increase in the requirements for hysterectomy (Powles et al. 1994).

**International multicentre trials**

The accrual, compliance, acute toxicity and safety monitoring data from the pilot trial, together with the more comprehensive retrospective and prospective safety data from adjuvant trials, particularly the noted reduction in serum cholesterol in pre- and postmenopausal women, encouraged the Federal Drug Administration to approve tamoxifen for use in a national multicentre chemoprevention trial in the United States which was started under the auspices of the National Surgical Adjuvant Breast and Bowel Project and the National Cancer Institute in May 1992.

Healthy women over the age of 60 and at no special risk were considered eligible. Younger women aged between 35 and 59, however, had to have an increased risk of breast cancer because of a family history to a level at least that of a 60-year-old
woman. Initially, it was estimated that 16 000 women would be required for this trial, at the level of risk required for eligibility, but by 1996 over 12 000 had been randomised to tamoxifen or placebo and were found to have a significantly higher risk than required.

In Italy a similar randomised trial was started in 1991 and involved recruitment of healthy women aged over 45 who had had a hysterectomy but were not at special risk of breast cancer. By 1996 over 5000 women had been randomised to tamoxifen or placebo.

In the UK a multicentre international trial (International Breast Cancer Intervention Study) was started in 1992 of healthy women aged 40-65 years with at least a twofold increased risk of breast cancer and by 1996 nearly 3000 women have been accrued to this trial.

Incorporated in all of these trials (now involving over 20 000 healthy women) are various safety monitoring requirements which should provide further information on the spectrum of activity of tamoxifen in the body. Over the next 5-10 years the incidence of breast cancer in these trials will provide an accurate estimation of any chemoprevention activity by tamoxifen, and genetic and pedigree profiling of these women will allow distinction within genetic subgroups. For this, almost certainly, a meta-analysis overview of all the trials will be required.

**Conclusions**

Since Beatson's outstanding initial observations of endocrine response, we have come a long way in the medical treatment of breast cancer. Perhaps the most important development over the last 100 years was the discovery of the quite remarkable drug, tamoxifen, for treatment of breast cancer, which is now saving many thousands of lives per year. In comparison with any other effective cancer treatments, tamoxifen has a very high safety and low toxicity profile. The challenge has now been taken, before the start of the next century, to evaluate whether we can use tamoxifen to prevent breast cancer. There has been much debate and controversy about this initiative, and there is no doubt that involving many thousands of healthy women in a drug trial is not without risk. Nonetheless, it is probable that the only way that tamoxifen can be tested for chemoprevention is by undertaking a large clinical trial, and at this time it seems likely that the potential benefits for participants is likely to outweigh the established and potential risks.

If the results from these tamoxifen chemoprevention trials are encouraging, the future possibility of being able to identify the phenotypic and genetic subgroups of healthy women who gain benefit, together with the possibility of developing the next generation of tamoxifen-like drugs, with selective beneficial activity on bone, lipids, uterus and ovary, offers the Utopian potential of preventing many major diseases in women, apart from breast cancer (Tonetti & Jordan 1996). It may have taken over 100 years to achieve this, but if realistic, the wait will have been worth it.

**Acknowledgement**

The Royal Marsden pilot tamoxifen chemoprevention trial is supported in part by the Cancer Research Campaign.

**References**


