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Breast Cancer Prevention with Tamoxifen

The Role of Tamoxifen in the Prevention of Breast Cancer

THE ENDOCRINE sensitivity of breast cancer sets it aside from the other common malignancies. Early carcinogenic events have not yet been characterised, but subsequent promotional role of ovarian steroids is recognised [1]. Partial protection against breast cancer is acquired naturally in women who have a late menarche and early menopause, or unnaturally by early oophorectomy, albeit at the cost of side-effects of oestrogen withdrawal [2, 3].

It is fortuitous that tamoxifen blocks the effects of oestrogens on the breast, but does not act as a pure anti-oestrogen. Thus tamoxifen stimulates the hepatic synthesis of high-density lipoproteins, reduces levels of cholesterol in the blood and has no demineralising effect on bone [4, 5]. Indeed, it has been suggested that the drug protects against osteoporosis [6]. Furthermore, tamoxifen induces synthesis of TGF-β, a breast cancer inhibitory growth factor [7]. For these and probably other reasons, women with breast cancer given adjuvant tamoxifen are less likely to develop contralateral tumours [8, 9].

Which women should be considered for trials of prevention? Since no blood assays have yet been shown reproducibly to be markers of risk of breast cancer, clinicopathological or mammographic criteria have to be used. The most easily family history (first-degree relative developing the disease before age 50 or two first-degree relatives after age 50). Such individuals have a three-fold to four-fold increase in life-time risk. Such criteria have been used at the Royal Marsden Hospital and a carefully conducted randomised pilot study is underway. This has shown that tamoxifen is well tolerated with a compliance of around 80% for both placebo and treated groups at 2 years [10].

Those with a family history of breast cancer may not be the best group in which to test endocrine prevention. Tumours in younger women are more likely to be oestrogen receptor negative and thus might not be influenced by tamoxifen. Hereditary breast cancer represents only 5% of all cases, so that some other factors will need to be used to have a major impact on the disease [11]. An alternative risk factor is lobular carcinoma *in situ* (one in four risk), but this is a rare pathological finding [12]. An almost equally powerful but also rare histological change is atypical ductal hyperplasia [13]. With the combination of Wolfe grade P2/DY and nulliparity or first baby after age 28, a group with a two-fold increase in risk can be delineated [14]. However, to demonstrate an effect in this group would need a trial of 10,000 patients.

Extrapolation from the adjuvant studies indicates that a one-third or one-half reduction in incidence might be achieved. This might not be prevention but procrastination—if the disease is deferred for 20 years an individual may die of other causes. If, however, the malignant phenotype is inhibited for, say 2–5 years with subsequent emergence of a more aggressive hormone-

independent variant, the prognosis might be worse than if no tamoxifen had been given.

Another potentially sinister side to tamoxifen prevention is the risk of other cancers. Carcinoma of the endometrium was reported more frequently in the Swedish adjuvant study but not in the Scottish trial [9, 15]. Such malignant change would be consistent with an oestrogen agonist effect. Another theoretical risk of this effect is the development of hepatocellular carcinoma, which has been observed in rats given high dosages of tamoxifen. However, this is unlikely to be a problem in women given the agent [16]. Nevertheless these possibilities underline the need for close monitoring of volunteers taking part in these trials.

A simple study design is needed. Tamoxifen 20 mg daily has few side-effects. Treatment should continue for at least 5 and probably for 10 years. The control group would receive either placebo or be untreated. The foundations for a trial for prevention of breast cancer are now in place. A study of sufficient statistical power will require national and international cooperation and a European initiative would be timely. Recruitment needs to be rapid and extensive so that the momentum can be maintained. If enough centres make a commitment we may know in 5–10 years whether tamoxifen reduces the incidence of breast cancer. To ascertain the effect on mortality may take longer. However there is the intriguing possibility that tamoxifen might decrease mortality from coronary heart disease as well as reducing deaths from breast cancer.

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The Madison Meetings

THE POTENTIAL chemopreventive activity of tamoxifen (inhibition of initiation and growth of DMBA-induced mammary carcinomas) has been known since the mid-seventies [1]. Tamoxifen can reduce the incidence of contralateral primary cancers in patients already operated on for one breast cancer [2]. The issue of the feasibility of a large scale intervention study to verify the effectiveness of anti-oestrogens in preventing breast cancer is being increasingly addressed. Critical aspects are long-term tolerability of the drugs and the identification of the high-risk group of women which could benefit from the intervention.

The results of one pilot study were published in 1989 [3]: tamoxifen was compared to placebo and given to 200 women. Acute toxicity was suggested to be low and accrual and compliance satisfactory. Furthermore, biochemical monitoring of lipids and clotting factors suggested that anti-oestrogens may reduce the risk of cardiovascular disease (CVD). Trevor Powles and his colleagues report that their experience now includes over 400 women, and the findings of the pilot study have been confirmed and extended (p. 680).

To review all available data supporting the hypothesis of breast cancer prevention with tamoxifen, a workshop was held in Madison, Wisconsin, in October 1989 [4]. A second meeting, again in Madison, was held in June 1990, by which time new data had become available from the two-year toxicity study conducted at the University of Wisconsin.

Arguments in favour of breast cancer chemoprevention (perhaps chemosuppression is a better term) are the experimental studies in animals [5]; the reduction of incidence of contralateral tumours in patients treated with tamoxifen as an adjuvant therapy; the potential favourable effect on coronary heart disease and on bone density (prevention of osteoporosis and decreased number of bone fractures).

Major concerns are the risk of liver carcinogenesis (as shown by experimental studies conducted at ICI), uterine carcinogenesis (as suggested by the Stockholm study with 40 mgs of tamoxifen a day) and a series of other possible biological effects, namely increased risk of thrombophlebitis, and symptomatic effects, such as hot flushes and gynaecological symptoms. It has been argued that this 'co-morbidity' should be taken into account when considering cost-effectiveness; moreover it has been argued that tamoxifen could simply delay the onset of the tumour and not actually prevent them.

On the other hand, it has been argued that cancer of the liver is so rare that even if prolonged administration of tamoxifen could double the risk of this cancer, this might be balanced by a suggested potential reduction in ovarian cancer. Finally, it has been stated that prescription of tamoxifen in benign conditions (e.g. mastalgia, fibrocystic disease) has been increasing, and it is now evident that there is an urgent need for a better knowledge of the consequences of prolonged administration of this drug. For the moment, approval has been given to accrue 10–15,000 women into the U.K. national trial and a large clinical trial on hysterectomized women (to avoid the risk of endometrial cancer)