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Breast Cancer and Osteoporosis—A Bridge at Last

BOTH BREAST cancer and osteoporosis have a major impact on the life expectancy and quality of life of women. Since oestrogens play important roles in the physiology of breast and bone, prevention of these diseases might be achieved by oestrogenic modulation. However, while an early menopause or oophorectomy can reduce the incidence of breast cancer it leads to an acceleration of bone loss resulting in osteoporosis and pathological fractures. In parallel, oestrogen replacement therapy protects bone, but its prolonged use may increase the risk of breast cancer. Thus, it would appear that the aims of prevention of breast cancer and osteoporosis are irreconcilable. However, results from recent studies suggest that this may not be the case and that there is a meeting point for treatment of the two disease groups. This bridge is formed by the drug tamoxifen.

Because tamoxifen stimulates ovulation, it had a very brief run in its first role as an oral contraceptive. Shortly thereafter it was rediscovered and used to treat advanced breast cancer in postmenopausal women [1]. Up to that time the standard treatment was oestrogen (stilboestrol or ethinyloestradiol) in pharmacological doses which could be associated with severe side-effects. Tamoxifen proved to be equi-efficacious but with a much lower profile of side-effects, so much so that it was used as an adjuvant treatment after surgery [2]. The long-term value of adjuvant tamoxifen has been confirmed by a recent meta-analysis of all such clinical trials [3]. In postmenopausal women given adjuvant tamoxifen, usually for 2 years, there was a 20% reduction in the risk of dying of breast cancer, which persisted for up to 10 years after diagnosis. At the same time there was a 39% reduction in contralateral breast cancers.

Apart from the benefits to women with breast cancer, tamoxifen has also been shown to be a useful treatment for premenopausal women with severe cyclical mastalgia. Clinical trials have confirmed that it is more effective than placebo [4] or danazol [5], and that it is effective at a dosage of 10 mg once daily, with minimal side-effects at this dose [6].

Animal studies have shown that tamoxifen can block the uptake of tritiated oestradiol by the rat uterus [7] and because of this the agent was dubbed an anti-oestrogen, and it was assumed that its beneficial effects in patients with breast cancer were mediated in this way. However, subsequent work in humans has suggested that this is an oversimplification. Tamoxifen administration induces hepatic synthesis of sex hormone binding globulin (SHBG) and cortisol binding globulin (CBG) both of which are also stimulated by oestrogen [8].

In addition, tamoxifen intake leads to an increase in high density lipoproteins and a reduction in serum cholesterol [9, 10], which are the actions of an oestrogen agonist. This lowering of cholesterol may have been responsible for the reduction in deaths from cardiovascular disease observed in patients given adjuvant tamoxifen [3].

However, if tamoxifen is blocking the effects on the breast of oestrogens for those with cyclical mastalgia or malignancy, it follows that a similar effect might occur in bone. This might lead to demineralisation, osteoporosis and risk of pathological fracture which could markedly offset the benefits of tamoxifen.

Five years ago, preliminary data were presented which suggested that tamoxifen did not have an adverse effect on bone mineral content in women treated for cyclical mastalgia [11]. Since then additional evidence has emerged from women given tamoxifen as adjuvant therapy, which supports the initial observation that this agent is protecting against bone loss.

There have been six peer-reviewed publications relating to tamoxifen use and bone density [12–17]. In the four studies which used single photon absorptiometry (SPA) to measure cortical bone density in the distal radius, no bone loss was seen [12–15]. Three studies used dual photon absorptiometry (DPA) of trabecular bone in the lumbar spine/femoral neck [15–17], (one study used both SPA and DPA)[15]. In premenopausal women followed by DPA scans over a 2-year period, no bone loss was seen [16]. In the two studies of postmenopausal women, there was a gain in bone mineral content among those given tamoxifen, amounting to approximately 1% per year of follow-up.

Additional indirect evidence that tamoxifen does not cause demineralisation comes from serial measurements of alkaline phosphatase and osteocalcin (gla), both of which are markers of bone metabolism, reflecting bone formation. In premenopausal women receiving tamoxifen, no change in osteocalcin was seen whereas alkaline phosphatase fell [16]. In postmenopausal women both osteocalcin and alkaline phosphatase levels fell, compatible with suppression of bone remodelling following inhibition of absorption and consistent with an osteoprotective effect. Furthermore, serum levels of both 1,25-dihydroxyvitamin D and parathyroid hormone were unchanged in those given either tamoxifen or placebo [15]. Further evidence of the oestrogenic activity of tamoxifen is presented in this issue (pp. 497–500). In postmenopausal women given adjuvant tamoxifen there was no bone loss and a significant reduction in serum osteocalcin levels.

Further data supporting an osteoprotective role for tamoxifen have emerged from a trial of adjuvant therapy conducted at Guy's Hospital and the Christie Hospital, Manchester. Postmenopausal women with operable breast cancer who were at risk of relapse were entered into a trial in which they received either tamoxifen alone (20 mg daily) for 5 years, or tamoxifen and prednisolone (7.5 mg daily) for the same length of time [18]. Sequential DPA scans were performed, and after 2 years of follow-up, no bone loss was observed in either spine or femur among the tamoxifen-treated group, and equally importantly no loss occurred in those given additional prednisolone. Previous work suggested that a dosage of 7.5 mg prednisolone daily to postmenopausal women would induce bone loss within 6 months [19]. Thus under these circumstances tamoxifen appears to protect against steroid-induced bone loss.

As the value of tamoxifen in an adjuvant role has been confirmed it is likely that the majority of postmenopausal

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patients (with tumours greater than 1 cm in diameter) will be given the drug, possibly on a lifetime basis. The cost/benefits of such an approach are still being debated but an additional benefit may now be a reduction in cases of osteoporosis and pathological fractures. If this is confirmed then such patients will not require long-term bone mineral monitoring as part of their follow-up. Secondly, provided that the forces of irrationality do not prevail, it is likely that a U.K. trial of tamoxifen as a prevention agent for breast cancer will be underway shortly. Volunteers taking part, many of whom will be premenopausal, can be reassured that they are not putting their bones at risk should they be given tamoxifen.

A variety of patients have to take long-term steroids as part of treatment in chronic conditions. Consideration should be given to prospective randomised trials using tamoxifen for such cases.

Tamoxifen, however, is not a potential replacement for hormone replacement therapy (HRT). There are numerous reasons why perimenopausal women are given HRT, but the spectre of osteoporosis is probably a dim one for the majority. The troublesome hot flushes and night sweats which are relieved by oestrogens or progestins can be exacerbated by tamoxifen. Nevertheless under circumstances where oestrogen and progestins are contra-indicated or unacceptable to the patient, tamoxifen could be considered in its role as an osteoprotective, cardioprotective and mammoprotective agent. An alternative approach might be the joint administration of both HRT and tamoxifen. A reduced dosage of both HRT and tamoxifen might be achievable. Pure oestrogens and pure anti-oestrogens have mutually incompatible indications with regards to breast and bone. By chance, tamoxifen's blend of oestrogen agonist/antagonist activity provides the bridge for the protection of breast and bone.

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