Evidence that Tamoxifen Preserves Bone Density in Late Postmenopausal Women with Breast Cancer

Alexandra Resch, Eva Biber, Michael Seifert and Heinrich Resch

From the Departments of Radiotherapy (A. Resch, E. Biber), Gynecology & Obstetrics (M. Seifert), School of Medicine, Vienna University, KH Barmherzige Schwestern (St. Vincent Hospital), Medical Department II (H. Resch), and the Ludwig Boltzmann-Institute of Aging Research (H. Resch), Vienna, Austria

Correspondence to: Heinrich Resch MD, Medical Department II, Krankenhaus Barmherzige Schwestern (St. Vincent), Stumpergasse 13, A-1060 Vienna, Austria. Tel: + 43 1 59 98 82 104. Fax: + 43 1 59 98 84 041

Acta Oncologica Vol. 37, No. 7/8, pp. 661–664, 1998

Tamoxifen, which is used for treating breast cancer, exhibits estrogenic and antiestrogenic characteristics, depending on the tissue. In the human breast it acts as an antiestrogen, whereas estrogenic effects have been reported on endometrium and bone. The purpose of this study was to determine whether tamoxifen (TAM) prevents bone loss in elderly, postmenopausal women. Bone mineral density of the lumbar spine (SBD) was measured in elderly women (at least 10 years after menopause) 5 years after stage I or II breast cancer ($n = 111$). The results showed that SBD in untreated patients ($n = 74$) was significantly lower ($p < 0.05$) than SBD in patients ($n = 37$) treated with TAM over 5 years. In a subgroup of patients ($n = 24$) with positive estrogen receptor status, changes in SBD 12 months after discontinuation of 5-year TAM therapy were measured and compared with the changes of extended TAM treatment over a sixth year. Twelve months after withdrawal of 5-year TAM medication ($n = 11$) bone density decreased significantly ($-4.8 \pm 2.5\%$; $p > 0.05$), whereas in the group of women ($n = 13$) receiving extended TAM medication (20 mg) for an additional 12 months, SBD ($+1.9 \pm 3.5\%$) was maintained during the observation period, and was significantly higher when compared with the group of untreated patients ($p < 0.05$). We conclude that tamoxifen has a preventive effect on trabecular bone loss at the lumbar spine, when compared to age-matched data and to untreated women with breast cancer in the late menopause. Our data give evidence of benefits to bone density provided by prolonged administration in patients after breast cancer and at risk of osteoporosis.

Received 23 February 1998
Accepted 18 August 1998

Tamoxifen is widely used after surgery in the treatment of primary breast cancer. The chemotherapeutic effect of the estrogen antagonist in postmenopausal women with advanced estrogen receptor-positive cancer of the breast is well-documented, showing a significant reduction in the incidence of contralateral breast cancer (1, 2). As prolonged therapy is required for breast cancer treatment or prevention, the long-term effects of TAM require further investigation. TAM exhibits estrogenic and antiestrogenic characteristics, depending on the tissue. In the human breast it acts as an antiestrogen, whereas estrogenic effects have been reported on the endometrium. If tamoxifen exerts antiestrogenic effects on bone, women receiving long-term treatment may be at a greater risk of osteoporotic fracture (3). On the other hand, there is a partial estrogenic function of estrogen agonists/antagonists, such as TAM, so that an estrogen-like osteogenic action in women in the late menopause could be expected.

A number of clinical investigations (4–11) sought to define the effect of TAM on bone metabolism in pre- and postmenopausal women after breast cancer. However, the effects of TAM on bone have not been adequately evaluated in women in the late menopause. It is generally accepted that treatment with TAM should be stopped after 5 years of adjuvant therapy on the recurrence of the disease (12, 13). In those patients the question arises, irrespective of the age-dependent fracture risk per se in elderly patients, whether the discontinuation of TAM with a partial estrogenic action on bone in the late menopause causes increased bone resorption and, consequently, bone loss. In this case, TAM therapy should be maintained in patients with breast cancer and osteoporosis or at risk of osteoporosis. To answer this question, at least in part, and to determine whether tamoxifen preserves bone loss in elderly, postmenopausal women with breast cancer, we performed measurements of trabecular bone mineral density of the lumbar spine (SBD) with quantitative computed tomography after 5 years of adjuvant therapy with TAM and after discontinuation of TAM therapy.

MATERIAL AND METHODS

Two studies were conducted: 1) evaluations of spinal bone density (SBD) measurements in a large cross-sectional

 ISSN 0284-186X

population of untreated (estrogen receptor-negative) and tamoxifen-treated (estrogen receptor-positive) age-matched females 5 years after breast cancer stage I or II, and 2) evaluations of SBD measurements in a longitudinal follow-up of a smaller subset of females, treated with TAM for 5 years, 12 months after withdrawal of TAM.

Cross-sectional population

In this retrospective study, cross-sectional assessment was made from the records of 111 patients after stage I or II breast cancer referred for osteoporosis evaluation after 5 years of adjuvant therapy with tamoxifen. In all women, a breast-conserving therapy with lumpectomy or quadrantectomy, lymphadenectomy of the axilla and consecutive adjuvant radiotherapy (50 Gy on the remaining breast tissue with tangential fields) were performed. Roentgenograms of the lateral spine were taken to exclude females with osteoporotic spine deformities (anterior, central or total collapse of at least 20% of the vertebral height). Skeletal scintigram, routine blood and urinary analyses were obtained in all patients to rule out progressiveness of the disease or other metabolic bone disease. None of the patients had been treated with specific osteogenic therapy (e.g. calcitonin, bisphosphonates, fluoride, calcitriol, estrogens, anabolics). We further divided the females in two groups:

(I) Estrogen receptor-negative patients ($n = 74$; mean age: 67 ± 8 years) and therefore not treated with TAM; 20 out of 74 were lymph node positive and were treated with adjuvant chemotherapy (CMF).
(II) Estrogen receptor-positive patients ($n = 37$, mean age 68 ± 7 years) treated with TAM 20 mg/d.

Longitudinal follow-up

In a subgroup of 24 out of the 37 estrogen receptor-positive patients (mean age: 68 ± 7 years), a second measurement of spinal bone density was performed 12 months later (year 6). Group 1 ($n = 13$) remained on TAM (20 mg/d) treatment over the observation period, but in Group 2 ($n = 11$) TAM was withdrawn after 5 years. The patients received 500 mg of elementary calcium for the next 12 months and served as a control group.

Bone density measurements

Trabecular bone density in the lumbar spine was measured in milligrams per cc, using a mineral reference for calibration by quantitative computed tomography (QCT) with the single energy technique (120 kVp) of L1 to L4. The coefficient of variation of our method was less than 5%.

Statistical analysis

Results are given as the mean $\pm$ SD, cross-sectional data are expressed as Z-score (i.e. number of standard deviations below or above age- and sex-adjusted mean values established in a large cohort of normal adults). Data were analyzed by analysis of variance, Students's *t*-test, and regression analysis using CSS, a commercial statistical computer program (StatSoft); $p < 0.05$ was required for statistical significance.

Table 1

Subject characteristics of 111 elderly postmenopausal women after stage I or II breast cancer

Characteristics	TAM (n = 37)	Without TAM (n = 74)
Age (years)	67 ± 8	68 ± 7
Years since menopause	15 ± 5	16.2 ± 5.5
BMI (kg/m^2)*	26.4 ± 5.2	25.9 ± 4.9

* Body mass index

RESULTS

Cross-sectional population

All patients treated with tamoxifen and without TAM were well balanced in terms of age, menopausal status and body weight (see Table 1).

Bone density in 111 patients with stage I or II breast cancer 5 years after mastectomy was 84.2 ± 20.1 mg/cc, corresponding to a Z-score of -1.3 ± 0.8. When osteoporosis was defined by a QCT value below our established densitometric fracture threshold value of 100 mg/cc (14), 82 out of 111 patients (75%) could be classified as osteoporotic, regardless of whether they were treated with TAM or not. Twenty-nine women were considered not to suffer from osteoporosis, but those without osteoporosis were statistically significantly younger women. Calculating the data of bone mineral density (BMD) measurements as the number of standard deviations below or above an age- and sex-matched mean value (Z-score, as shown in Fig. 1),

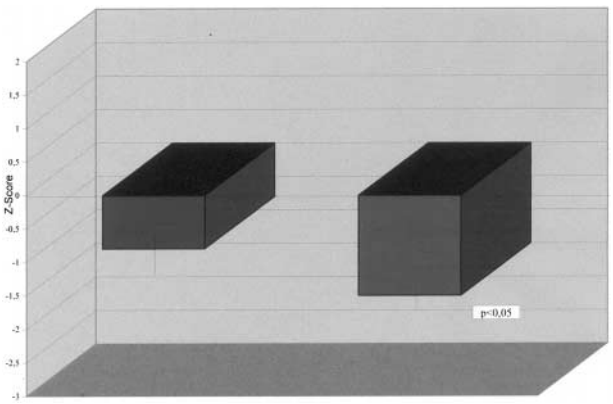

Fig. 1. Spinal bone density (SBD) as the number of standard deviations below or above an age and sex-matched mean value (Z-score) in elderly postmenopausal women after breast carcinoma treated over 5 years with 20 mg TAM and untreated ($n = 74$) (right) ($p < 0.05$).

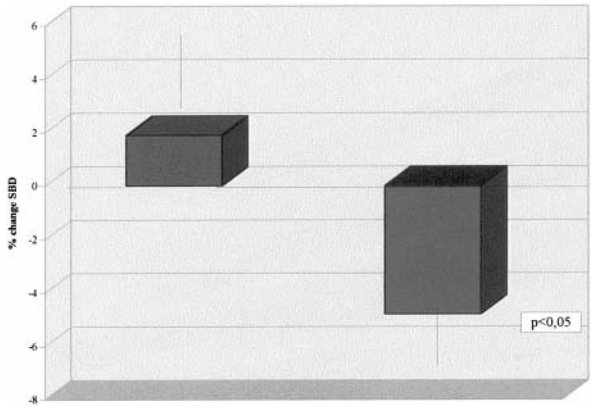

Fig. 2. Percentage changes of SBD 12 months after discontinuation of 5-year TAM therapy (n = 11) (right) compared with the group of women (n = 13) (left) receiving extended TAM medication (20 mg) for an additional 12 months.

SBD in untreated patients (n = 74) was significantly lower than SBD in patients (n = 37) treated with TAM over 5 years (-1.5 ± 0.7 vs. -0.8 ± 0.7; $p < 0.05$).

Longitudinal follow-up

In the subgroup of 24 elderly, postmenopausal women showing estrogen receptor-positive tissue and stage I or II breast carcinoma, a second BMD measurement was performed after 12 months. In Group I with extended TAM therapy (20 mg tamoxifen daily) over a sixth year, trabecular bone density at the lumbar spine was maintained, showing a rate of change in bone density of $1.9 \pm 3.5\%$ (N.S.). In Group II (withdrawal of TAM and continuing with 500 mg CA daily over the sixth year), statistically significant bone loss of $-4.8 \pm 2.5\%$ ($p > 0.05$) could be observed. After 12 months there was also a statistically significant difference in lumbar bone density between the two groups (Fig. 2).

DISCUSSION

Our results present evidence to show that TAM preserves bone loss in elderly, late-postmenopausal women showing estrogen receptor-positive tissue. Trabecular bone density was significantly higher at the lumbar spine in the females treated with tamoxifen, compared with age-matched untreated patients. Bone loss could be observed when measurements of SBD were performed 12 months after the withdrawal of 5-year TAM medication, whereas bone density could be maintained by prolonged TAM administration during the additional 12-month observation period. The results are similar to those found for estrogen action on bone mineral density, and are consistent with an estrogen-like effect of TAM. Furthermore, our data confirm previous studies in elderly women in the late menopause, which have examined the effects of TAM in healthy women and women with breast cancer (7–10, 15). Twelve months after withdrawal our effects of TAM are similar to accelerated bone turnover observed after discontinuation of hormone replacement therapy (10, 11). Although it has been reported that antiestrogens, such as tamoxifen, induce bone mineral loss, resulting in an increased susceptibility to fractures, evidence from animal studies suggests that TAM has a partial estrogen-agonist activity on the skeleton and actually assists in maintaining BMD (16, 17). From preclinical data we know that osteoclast apoptosis is not only promoted by 17β-estradiol but also by TAM and by transforming growth factor (TGF-β). It has been shown that both estrogen and TAM increase the production of the cytokine by osteoblasts (18). Antibodies to TGF-β inhibited the apoptotic effects of both estrogens and TAM as well as those of TGF-β itself, suggesting that TGF-β was mediating the apoptotic effects of those substances. However, the effects of TAM are complex and vary according to the species and tissue being studied. TAM is estrogenic in the mouse (19) and antiestrogenic in the chicken (20); it has mixed effects in the rat (21–23). In studies performed on rat skeletal tissue in vitro, TAM acts as an estrogen agonist and suppresses parathyroid hormone-mediated bone resorption. In the ovarectomized rat in vivo TAM inhibits the resorption of bone (24), notably at trabecular sites, and preserves bone mass as measured by femur ash density (16). In view of these considerations, a number of studies have sought to address the effects of TAM on BMD in humans. In this context, it was found that women treated over 5 years with tamoxifen daily had increased BMD, compared with those treated over 2 years, but the differences were not statistically significant. Our results confirm those of other studies which failed to show any reduction in BMD with adjuvant tamoxifen (4, 25). A large randomized double-blind prospective study showed that 2 years of TAM caused an increase in lumbar BMD, whereas a decrease of 1% per year was seen in the controls (7). In contrast to our study population, the subjects were heterogeneous with up to 27% of TAM-treated women being premenopausal at the commencement of therapy, and 80% of women having been in the menopause for more than 4 years. Furthermore, the biochemical changes in bone turnover parameters are indicative of an estrogen-like effect of tamoxifen on bone remodeling. A rise in serum osteocalcin and urinary hydroxyproline occurs following the menopause (26–29), reflecting an increased level of bone remodeling. Love (7) observed a decrease in osteocalcin levels after 1 year of TAM therapy that was maintained for a further 12 months. Ward et al. (11) found a similar decline in osteocalcin levels evident after 6 months of therapy. Moreover, the data describe a significant fall in urinary hydroxyproline markers of bone resorption that was also evident after 6 months. These data are again consistent with an effect of TAM on bone remodeling in postmenopausal women, similar to that observed with oral estrogen. In a histologic study per-

formed by Wright et al. (6) it has been shown that long-term TAM treatment does not adversely affect bone turnover in women with breast cancer. The preservation of the normal trabecular bone area is consistent with most densitometric data, which indicate either neutral or estrogenic effects of TAM on bone.

In conclusion our results show that long-term tamoxifen treatment preserves trabecular bone density at the lumbar spine in patients in the late menopause after breast carcinoma. The effects on bone density may be attributed to a partial estrogen-like effect of tamoxifen on bone in elderly women. Further prospective long-term studies are expected to show whether the administration of TAM in elderly women with breast carcinoma is able to prevent osteoporotic fractures of the spine and thus the morbidity associated with these events.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomized trials involving 31000 recurrences and 24000 deaths among 75000 woman. Lancet 1992; 339: 1–15, 71–85.
2. Fisher B, Brown A, Wolmark N, et al. Prolonging tamoxifen therapy for primary breast cancer: findings from the National Surgical Adjuvant Breast and Bowel Project clinical trial. Ann Intern Med 1987; 106: 649–54.
3. Riggs BL, Melton LJ III. Involutional osteoporosis. N Engl J Med 1986; 314: 1676–86.
4. Gotfriedsen A, Christiansen C, Palshof T. The effect of tamoxifen on bone mineral content in premopausal women with breast cancer. Cancer 1984; 53: 853–7.
5. Wright CDP, Mansell RE, Gazet J-C, et al. Effect of long-term tamoxifen on bone turnover in women with breast cancer. Br Med J 1993; 306: 429–30.
6. Wright CDP, Garrahan NJ, Stanton M, et al. Effect of long-term tamoxifen therapy on cancerous bone remodelling and structure in women with breast cancer. J Bone Miner Res 1994; 9: 153–9.
7. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Engl J Med 1992; 326: 852–6.
8. Fornander T, Rutqvist LE, Sjoberg HE, Blomqvist L, Mattsson A, Glas U. Long-term adjuvant tamoxifen in early breast cancer: effect on bone mineral density in postmenopausal women. J Clin Oncol 1990; 8: 1019–24.
9. Love RR, Mazess RB, Tormey D, Barden HS, Newcomb PA, Jordan VC. Bone mineral density in women with breast cancer treated with adjuvant tamoxifen for at least two years. Breast Cancer Res Treat 1988; 12: 297–301.
10. Prestwood KM, Pilbeam CC, Burleson JA, et al. Short-term effects of conjugated estrogen on bone turnover in older women. J Clin Endocrinol Metab 1994; 79: 366–71.
11. Ward RL, Morgan G, Dally D, Kelly PJ. Tamoxifen reduces bone turnover and prevents lumbar spine and proximal femoral bone loss in early postmenopausal women. Bone Miner 1993; 22: 87–94.
12. Fisher B, Dignam J, Bryant J, et al. The worth of 5 versus more than 5 years of tamoxifen therapy for breast cancer patients with negative nodes and estrogen receptor positive tumors: an update of NSABP B–14. JNCI 1996; 88: 1529–42.
13. Scottish Cancer Trials Breast Group, Edinburgh. Randomized comparison of five years of adjuvant tamoxifen with continuous therapy for operable breast cancer. Br J Cancer 1996; 74: 297–9.
14. Odvina CV, Wergedal JE, Libanati CR, Schulz EE, Baylink DJ. Relationship between trabecular vertebral body density and fractures: a quantitative definition of spinal osteoporosis. Metabolism 1988; 3: 221–8.
15. Turken S, Siris E, Seldin D, et al. Effects of tamoxifen on spinal bone density in 10 postmenopausal women with breast cancer. J Natl Cancer Inst 1989; 81: 1086–8.
16. Jordan C, Phelps E, Lindgren U. Effects of antioestrogens on bone in castrated and intact female rats. Breast Cancer Res 1987; 10: 31–5.
17. Turner R, Wakley G, Hannon K, Bell N. Tamoxifen inhibits osteoclast mediated resorption of trabecular bone in ovarian hormone deficient rats. Endocrinology 1988; 122: 1146–50.
18. Hughes DE, Aihua D, Tiffee JC, He Hiu L, Mundy G, Boyce BF. Estrogen promotes apoptosis of murine osteoclasts mediated by TGF-β. Nat Med 1996; 2: 1132–5.
19. Terenius L. Structure-activity relationships of anti-oestrogens with regard to interaction with 17 β-oestradiol in the mouse uterus and vagina. Acta Endocrinol 1971; 66: 431–47.
20. Sutherland R, Mester J, Bauer EE. Tamoxifen is a potent 'pure' anti-estrogen in chick oviduct. Nature 1977; 267: 434–7.
21. Jordan VC, Dix CJ, Naylor KE, et al. Non-steroids: their biological effects and potential mechanisms of action. J Toxicol Environ Health 1978; 4: 363–90.
22. Jordan VC. Biochemical pharmacology of antioestrogen action. Pharmacol Rev 1984; 36: 245–76.
23. Steward PJ, Stern PH. Effects of the antioestrogens tamoxifen and clomiphene on bone resorption in vitro. Endocrinology 1986; 118: 125–31.
24. Turner RT, Walkey GK, Hannon KS, et al. Tamoxifen prevents the skeletal effects of ovarian hormone deficiency in rats. J Bone Miner Res 1987; 2: 449–56.
25. Cuzick J, Allen D, Baum M, et al. Long-term effects of tamoxifen. Eur J Cancer 1992; 29: 15–21.
26. Kelly PJ, Pocock NA, Eisman JA, Sambrook PN. Age and menopause related changes in indices of bone turnover. J Clin Endocrinol Metab 1989; 69: 1160–5.
27. Yasamura S, Alioa JF, Gundberg CM, et al. Serum osteocalcin and total body calcium in normal pre- and postmenopausal women and postmenopausal osteoporotic patients. J Clin Endocrinol Metab 1987; 64: 681–5.
28. Johansen JS, Riis BJ, Delmas PD, Christiansen C. Plasma BGP: an indicator of spontaneous bone loss and the effect of estrogen treatment in postmenopausal women. Eur J Clin Invest 1988; 18: 191–5.
29. Stock JL, Coderre JA, Mallette LE. Effects of a short-term course of estrogen on mineral metabolism in postmenopausal women. J Clin Endocrinol Metab 1985; 61: 595–600.