

Effect of Adjuvant (Hormonal) Therapy on Bone Mineral Density in Caucasian Women with Breast Cancer

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Abstract

Background and Aim: Aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs) are important components of adjuvant endocrine therapy in postmenopausal women with estrogen receptor positive breast cancer. The aim of our study was to assess the effect of AIs and SERMs on bone mineral density (BMD) in Caucasian postmenopausal women with breast cancer. **Patients and Methods:** 118 postmenopausal Caucasian women were enrolled in the study. 60 patients were receiving AIs and 58 patients – SERMs-Tamoxifen. Patients were also divided into two sub groups: 1) patients with more than 3 years of last menstrual period (LMP) and 2) patients with less than 3 years of last menstrual period. **Results:** Among Aromatase inhibitors treated patients, there was a decrease in median BMD from baseline to 5 years in lumbar spine and total hip compared with the Tamoxifen group. No patients with normal BMD at baseline became osteoporotic at 5 years. **Conclusion:** Aromatase inhibitors are associated with accelerated bone loss over the 5-year treatment period. In postmenopausal women, treatment with tamoxifen is associated with preservation of the bone mineral density of the lumbar spine

Keywords: Aromatase inhibitors; Selective estrogen receptor modulators; Bone mineral density; Dual Energy X-ray Absorptiometry; Last menstrual period.

Introduction

Estrogens play an important role in female bone homeostasis (Leslie, et al., 1995); in the estrogen deficient state, bone resorption is increased (Chapurlat, et al., 2000; Ettinger, et al., 1998; Rogers, et al., 2002). As a result of these predictable postmenopausal findings, estrogens have been extensively used as the main therapy to prevent bone loss in postmenopausal women. Estrogens reduce bone turnover rate and, as an antiresorptive, clearly improve bone density (Rossouw, et al., 2002) .

In the 10 years following the menopause, there is a reduction in BMD averaging 2% per annum, and osteoporosis is a major cause of morbidity in postmenopausal women.

Tamoxifen is a synthetic antiestrogen that, since its introduction for the treatment of patients with breast cancer in the early 1970s, has come to have a major role in the management of all stages of the disease (Love, et al., 1989). More recently, tamoxifen has been proved to have a favorable effect on disease-free and overall survival when given as adjuvant therapy after primary treatment for invasive breast cancer.

Aromatase inhibitors: Anastrozole and Letrozole -nonsteroidal aromatase inhibitors are hormone therapy drugs that can slow or stop the growth of hormone receptor-positive tumors. They lower estrogen levels in the body by blocking aromatase, an enzyme that converts other hormones into estrogen. This prevents the cancer cells from getting the hormones they need to grow.

Aromatase inhibitors cause a loss of bone density, which leads to higher rates of osteoporosis and bone fractures compared to tamoxifen (Perez, et al., 2006; Amir, et al., 2011).

Tamoxifen is not a pure antiestrogen; it has some estrogen-agonist properties, such as the ability to decrease the serum concentrations of cholesterol and increase those of sex-hormone-binding globulin (Love, et al., 1990) .

The beneficial effects of tamoxifen on BMD are most apparent at sites of trabecular bone, such as the lumbar spine (Grey, et al., 1995); such protective effects are associated with decreased bone resorption and formation (Marttunen, et al., 1999) .

In our study, we report the 5-years results of adjuvant (hormonal) therapy on bone mineral density in Caucasia women with breast cancer.

Materials and Methods

Patients

118 Caucasian postmenopausal women (between 46-74 years) were enrolled in this study at the National Institute of Endocrinology, Metabolic Disorders in Georgia. The study was approved by the ethical committee of

the National Institute of Endocrinology according to the declaration of Helsinki.

60 patients were receiving Aromatase inhibitors - Anastrozole or Letrozole, 58 patients - selective estrogen receptor modulators - Tamoxifen. We have measured Lumbar Spine (LS) and Total Hip (TH) BMDs, values were obtained using Dual Energy X-ray absorptiometry (DXA).

38 postmenopausal women with invasive breast cancer were also enrolled in the study as control group. These patients were not receiving any treatment after primary surgery.

T-score > -2.5 was exclusion criteria, so patients with osteoporosis were not enrolled in our study.

Assessments

Lumbar spine and Total hip BMD assessments were done at baseline, after 1, 2, and 5 years of therapy by dual energy x-ray absorptiometry.

For the lumbar spine, DXA measurement was derived by taking an average of the L1, L2, L3, and L4 values. Total hip BMD was calculated from the ratio of the total bone mineral content and bone area from the trochanteric, intertrochanteric, and femoral neck regions of the hip.

Results

Patients

60 postmenopausal Caucasian women received AI and 58 Tamoxifen. 38 postmenopausal women (as control group) with invasive breast cancer not receiving any treatment after primary surgery. They all had a baseline DXA.

The mean age at entry was 56 years. At baseline, approximately 58% patients from anastrozole or letrozole group, 22% patients from tamoxifen group and 29 % of the control group had osteopenia of the lumbar spine. Both treatment groups and control group had osteopenia also in total hip (28% in AI group; 10 % in Tamoxifen group and 21% in control group).

Most of the patients in the tamoxifen and the control group were within 3 years of menopause compared with the anastrozole and letrozole group.

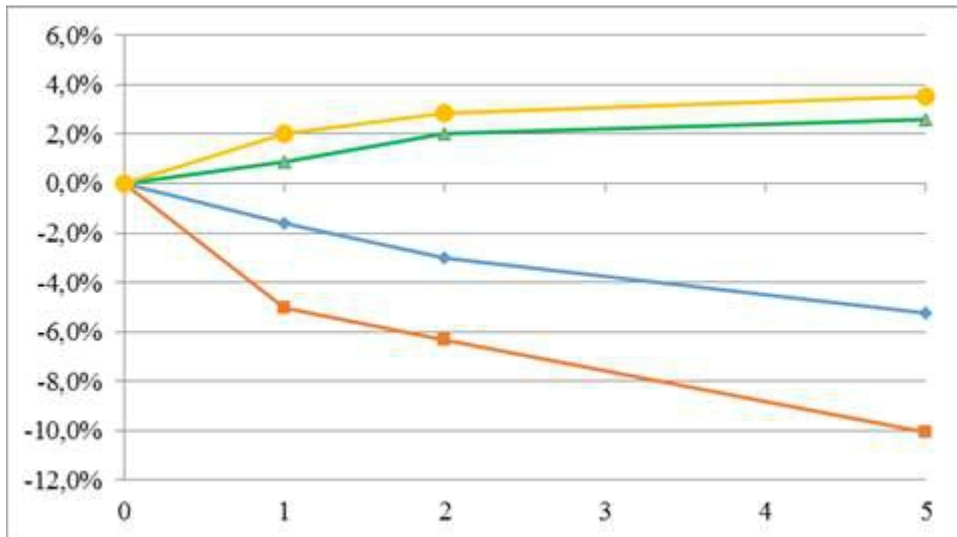
Effect of Treatment on BMD

Among Aromatase inhibitors treated patients, there was a decrease in median BMD from baseline to 5 years in lumbar spine (patients with > 3 years of LMP -5,22% and patients with < 3 years of LMP - 10,08%) and total hip (patients with > 3 years of LMP -6,52% and patients with < 3 years of LMP - 6,10 % compared with the Tamoxifen group (lumbar spine : patients with > 3 years of LMP +2,62 % and patients with < 3 years of LMP

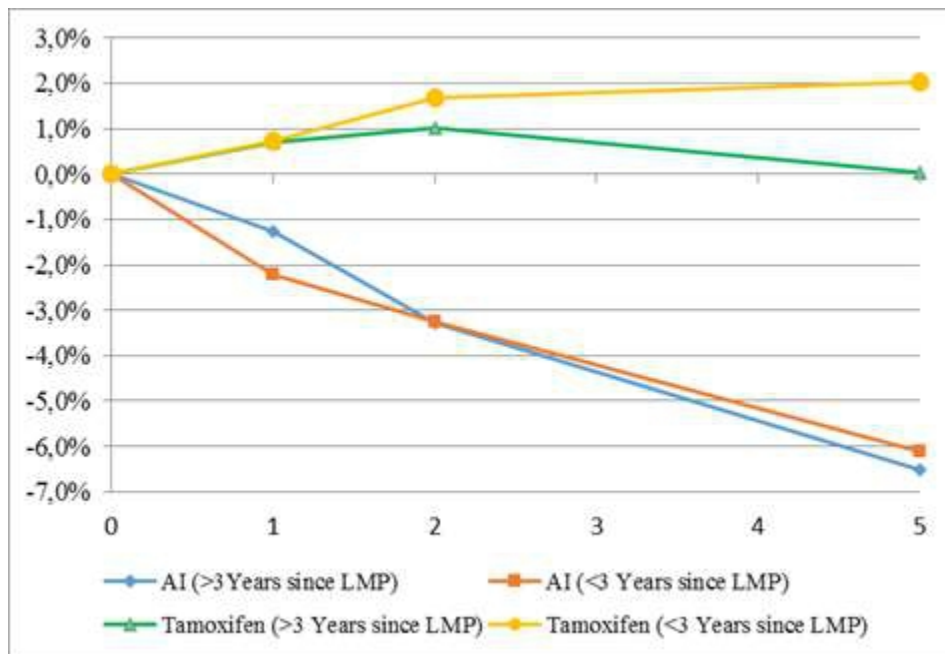
+3,54 %; total hip: patients with > 3 years of LMP +0,03 % and patients with < 3 years of LMP +2,03 %). No patients with normal BMD at baseline became osteoporotic at 5 years. BMD changes are listed in Table 1 and Figure 1.

Table 1. Percentage change in Lumbar spine and Total hip according to time since LMP

| | Treatment groups | Number of patients | Median % change from baseline | | |
|--------------|--|--------------------|-------------------------------|---------|---------|
| | | | 1 Year | 2 Years | 5 Years |
| Lumbar spine | Aromatase inhibitor (>3 Years since LMP) | 46 | -1,61% | -3,02% | -5,22% |
| | Aromatase inhibitor (<3 Years since LMP) | 14 | -5,01% | -6,32% | -10,08% |
| | Tamoxifen (>3 Years since LMP) | 16 | 0,87% | 2,03% | 2,62% |
| | Tamoxifen (<3 Years since LMP) | 42 | 2,01% | 2,87% | 3,54% |
| Total hip | Aromatase inhibitor (>3 Years since LMP) | 46 | -1,25% | -3,27% | -6,52% |
| | Aromatase inhibitor (<3 Years since LMP) | 14 | -2,20% | -3,27% | -6,10% |
| | Tamoxifen (>3 Years since LMP) | 16 | 0,71% | 1,03% | 0,03% |
| | Tamoxifen (<3 Years since LMP) | 42 | 0,72% | 1,69% | 2,03% |



A



B

Fig 1. Mean percentage changes in bone mineral density after 1, 2 and 5 years. Lumbar spine change over time and B. total hip change over time

The control group showed changes in median BMD over the 5-year period (lumbar spine +1,29%; total hip +2,31%).

Patients with normal BMD at baseline, who received treatment (anastrozole or letrozole - n 60; or tamoxifen- n 58), none had become osteoporotic (T-score <-2.5) at 5 years. Only 3 women with osteopenia at baseline developed osteoporosis on AI treatment.

Discussion

At the end of our study all BMD data showed significant bone loss in aromatase inhibitors treated patients relative to SERMs treated postmenopausal women. The rapid bone loss occurred in lumbar spine from baseline to 2 years compared with 2 to 5 years.

It is known that bone loss accelerates substantially in the late perimenopause and continues at a similar pace in the first postmenopausal years (Joel, et al., 2008).

We also found out that the rate of BMD loss at 1, 2, and 5 years at the lumbar spine for AI group was greater for women in the immediate postmenopausal period (within 3 years of their last menstrual period) than for patients more than 3 years since their menopause.

Breast cancer patients treated with tamoxifen showed protection against postmenopausal bone loss (Powles, et al., 1996).

We noticed that at 1, 2, and 5 years BMD increase was greater in Tamoxifen group patients within 3 years of their last menstrual period. Patients in the control group experienced little change in lumbar spine and total hip BMD.

The current analysis shows that no woman with a normal BMD at baseline had become osteoporotic at 5 years and the data suggest that only those women with a T-score of less than - 1.5 are at risk of developing osteoporosis during the treatment period.

Based on this, we can say that if pre-existing osteopenia is excluded no further preventive actions are required for all postmenopausal women.

For patients with pre-existing osteopenia (and risk factors including age, family history, smoking, and concomitant use of drugs such as corticosteroids), who are on AI treatment regular monitoring of BMD and bone-protection strategies are necessary.

Clinical trial evidence indicates that intravenous (Gnant, et al., 2009; Stephanie, et al., 2010; Brufsky et al., 2007) and oral bisphosphonates (Delmas, et al., 1997; Lester, et al., 2008; Van Poznak, et al., 2005) are effective in maintaining BMD in breast cancer patients receiving hormonal (endocrine) therapy.

Given that AIs reduce estrogen levels by approximately 90%, it might be expected that bone loss would be accelerated. However, it is critical to understand the relationship between AIs and fracture risk (Eastell, et al., 2005).

Overall, findings from our study suggest that adjuvant anastrozole/letrozole therapy for postmenopausal women with early breast cancer leads to accelerated bone loss. Many studies suggest that the risk of developing treatment-related osteoporosis seems to be confined to those patients already osteopenic at baseline, and other data suggest that bone loss can be managed in this group by DXA scanning and use of bisphosphonates as needed.

Conclusion

The present study showed that Aromatase inhibitors are associated with accelerated bone loss over the 5-year treatment period. The rapid bone loss occurred in lumbar spine from baseline to 2 years compared with 2 to 5 years. In postmenopausal women, treatment with tamoxifen is associated with preservation of the bone mineral density of the lumbar spine.

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