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CLINICAL STUDY

Bone mineral density in early breast cancer patients

Spanik S[1], Spanikova B[2]

1st Dept of Clinical Oncology, Faculty of Medicine, Comenius University, Bratislava, Slovakia.
sspanik@ousa.sk

Abstract: *Purpose:* Recent data indicate that women with breast cancer receiving aromatase inhibitors (AIs) are at increase risk of osteoporosis.
Patients and methods: We evaluated 263 patients in our study, 42 receiving AI (22 – Arimidex, 20 – Femara), 69 selective estrogen receptor modulater (SERM – Tamoxifen), in 72 the therapy with SERM was changed for AI and 80 were in follow-up without hormonal therapy. We measured BMD by whole-body densitometer Hologic explorer. BMD of proximal femur and L spine was measured and evaluated and in case of degenerative changes also the region of distal forearm. We evaluated T-score. 43.
Results: 35 % of the patients had decline of BMD to T-score of osteoporosis and only 13.31 % of patients had normal bone density. 53.13 % of the treated patients had BMD level of osteoporosis versus 40.2 % of untreated patients or patients treated for less than one year. 3.13 % of treated patients had normal BMD versus 16.58 % of untreated patients (p=0.015).
Conclusions: We confirm the influence of adjuvant AI therapy on decline of BMD in early breast cancer patients in our study. The bone loss was statistically significant in patients whose therapy lasted at least one year *(Fig. 6, Ref. 20).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: early breast cancer, adjuvant endocrine therapy, bone marrow density.

Epidemiologic data are continuously showing inreasing number of newly diagnoed patients with osteoporosis. This is partly due to increase in absolute number of new patients and partly due to continualy improving diagnostic procedures. The new generation of equipments and laboratory techniquesmore precisely identify patients with bone loss. At the same time improvement in public information leads to increasing number of densitometric examinations. The most important risk groups were identified. Cancer patients, especially breast cancer, are not negligible part of them. Postmenopausal breast cancer patients are in high risk of osteoporosis due to many reasons – primary diagnosis of breast cancer, side-effects of anticancer therapy, postmenopausal status. These factors mean not just elevated risk of bone loss, osteoporosis, but especially risk of pathological fractures. Many of postmenopausal breast cancer patients, especially those with early stage, with aromatase inhibitors (AI) adjuvant therapy have very good prognosis. The elevated risk of osteoporosis can lead to pathological fractures which may markedly worsen their quality of life.

Antagonizing estrogen in hormone-dependent breast cancer is well-known method of reducing tumor growth. Five years of treatment with tamoxifen, an antiestrogen of selective estrogen-receptor modulators (SERMs), has been shown to reduce the risk of recurrence and breast cancer mortality by 41 % and 34 %, respectively and is still recommended as one of several options for early-stage hormone receptor-positive breast cancer.

New data from clinical trials comparing third-generation aromatase inhibitors (AI) with tamoxifen have confirmed tha AI offer significant efficacy and tolerability advantage over tamoxifen. Aromatase inhibitors are recommended as adjuvant treatment for postmenopausal women with hormone-receptor positive early breast cancer. The group of clinicaly used AI contains non-steroidal AI letrozole and anastrozole and steroidal-AI exemestane. The primary mechanism of action of AI is inhibition of aromatase activity. Aromatase is the most important enzyme responsible for conversion of androgens to estrogens, mainly in tissues outside endocrine system. This is the most important mechanism of estrogen production in postmenopausal women. Estrogen production blockade influences bone metabolism directly via osteoclastogenesis stimulation. Survival extension of osteoclasts is the main mechanism. Cytokines, intreleukines 1 and 6, osteoprotegerin, bone resorption potentiation, osteocytes and osteoblasts apoptosis are other important mechanisms resulting in osteosynthesis inhibiton. AIs also play key role in calcium metabolism. Their action influences calcium absorption in small bowel and renal elimination. It is very similar to estrogens level decrease after menopause leading to postmenopausal osteoporosis.

AIs in breast cancer treatment are used as adjuvant therapy – it means after radical surgery in early breast cancer, stages I–III or as palliative therapy of locally advanced or metastatic disease. Standard duration of adjuvant hormonal therapy is now 5

[1]1st Dept of Clinical Oncology, Faculty of Medicine, Comenius University, Bratislava, Slovakia, and [2]Outpatient Department of Medicine and Osteology, St. Elisabeth Cancer Institute, Bratislava, Slovakia

Address of correspondence: S. Spanik, MD, PhD, 1st Dept of Clinical Oncology, Faculty of Medicine, Comenius University, Heydukova 10, SK-812 50 Bratislava, Slovakia.
Phone: +421.2.59249275

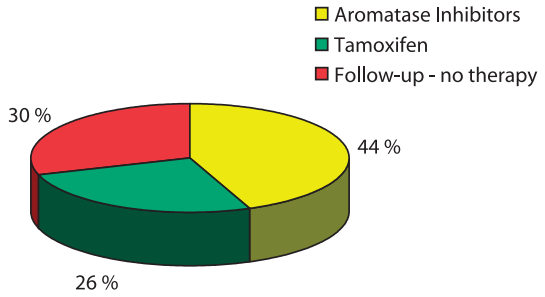
years. Recently published results of large international multicenter clinical studies (including more than 15 000 pacients) such as ATAC (4) and BIG (5) have shown that adjuvant hormonal therapy using AIs and lasting 5 years is more effective than adjuvant therapy using selective estrogen receptor modulators (SERMs), mainly tamoxifen. Substudies of these and many other similar studies dealing with bone mineral density (BMD) in early breast cancer patients on adjuvant hormonal therapy are consistently showing higher decrease of BMD during treatment with AIs than that with tamoxifen. This is the reason why regular BMD measurements at the beginning and during AIs adjuvant therapy were implemented into new recommendations for early breast cancer therapy published in July 2007 as a result of panel consensus of the most important international leaders in the field during the 10th St Gallen Conference (6).

Patients and methods

We started regular bone mineral density (BMD) measurement of postmenopausal early breast cancer patients treated either with aromatase inhibitors (AIs) or tamoxifen in St. Elisabeth Cancer Institute in September 2005. The most important goal of our study was to determine bone mineral density decrease in early breast cancer patients treated with (AIs). We measured BMD at the begining of treatment and during therapy (after one year or two depending on initial results) with AIs and a group of patients who have their hormonal therapy switched from tamoxifen to AIs for different reasons (intolerance or toxicity).

As a comparative group BMD was measured in group of early breast cancer patients treated with tamoxifen and patients after finished hormonal therapy without any anticaner therapy, only in regular follow-up. The study is sitll active, in this preliminary evaluation we analysed a group of 263 consecutive patients with early breast cancer, 42 on active AIs therapy – 22 on letrozole on oral daily dose 2.5 mg, 20 on anastrozole on oral daily dose 1 mg, 72 patients with "switched" therapy from tamoxifen to AIs, 69 on active tamoxife therapy on oral daily dose 20 mg and 80 patients just in follow-up after finishing active hormonal treatment.

In all our patients the BMD measurement was performed using total body densitometer Hologic Explorer. We measured and evaluated the region of proximal femur and Lumbar spine (L spine). In cases of degenerative changes which may cause false positivity of the resulrs the region we measured and evaluated the region of forearm. T scores were used for comparissons. All patients enrolled in our study were assessed for height, weight, age, duration of menopause, hormonal replacement therapy and history of other risk factors and previous fractures. In all patients calcium blood level was measured. Markers of bone turnover were also measured, CTX (CrossLaps – C telopeptide of alfa chain 2(I) colagen) as marker of osteoporosis measured by ELISA method and isoensyme of ALP as marker of osteoproduction. In patients with BMD values in the osteoporosis range differential diagnostic examinations were performed to exclude secondary osteoporosis. This is important especially in patients with breast cancer to exclude bone marrow metastases, which are



Aromatase Inhibitors (AIs)	
Anastrozole	22
Letrozole	20
A/L (after first line TMX)	72
AIs total	**114**
Tamoxifen	**69**
Follow-up – no therapy	**80**

Fig. 1. Patients Characteristics.

most frequent sites of generalised disease.Cancer markers, X-ray, CT scans MRI or bone scans – sceletal gamagraphy were used.

For the statistical analysis standard methods of descriptive statistics were used, test of data independency and multiple regression was used to verify influence of separate factors especially to exclude possible secondary influences in case of interactive correlation among parameters.

Results

From the whole study group of 263 postmenopausal early breast cancer patients, 114 patients in the group treated with AIs (72 of them switched from previous tamoxifen to AIs), 69 on tamoxifen therapy and 80 patients without hormonal therapy only on follow-up after finishing hormonal treatment (Fig. 1). Normal BMD was detected only in 13.31 % from all evaluated patients, 43.35 % patients had BMD value in osteoporosis range. Analyzing the localizations of measured osteoporosis it was detected s in 5.25 % in proximal femur, 63.1 % in L spine and 31.58 % in the forearm region (Fig. 2) – those were patients with defor-

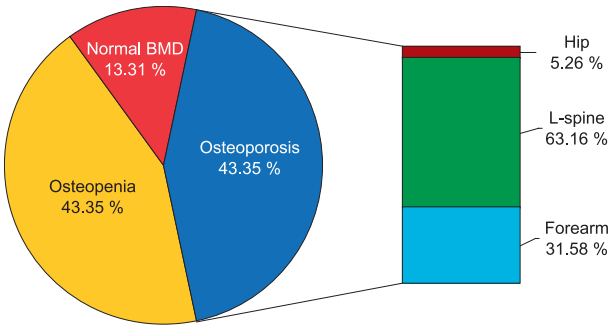


Fig. 2. BMD in Patients with Breast Cancer.

mations or degenerative changes in the region of spine, who cause false positive results.

Median age of the whole group of patients was 61 years. The BMD loss to levels of osteoporosis was found in group of patients under 50 years of age in 26 %, 50 % of them had osteoporosis in the region of L spine, 38 % in the region of proximal femur and only 13 % in the region of forearm. The rate of osteoporosis was higher in the group of patients older than 70 years – 73 % and most of them had osteoporosis in the region of forearm – 49 %. The region of L spine was overestimated by degenerative and deformative changes in this age group of patients. The group of patients in age between 50 to 70 years had BMD levels of osteoporosis in 34 %, most frequently in the region of L spine – 80 %. These findings are in correlation with many clinical studies confirming rising incidence of osteoporosis with rising age. We confirm the influence of menopause duration on osteoporosis as well as negative correlation of weight and osteoporosis in our study. All these findings are in consensus with literature data.

The impact of therapy on BMD losses was also analyzed. In the group of patients with AI therapy BMD loss to level of osteoporosis was diagnosed in 43.86 % and normal BMD had

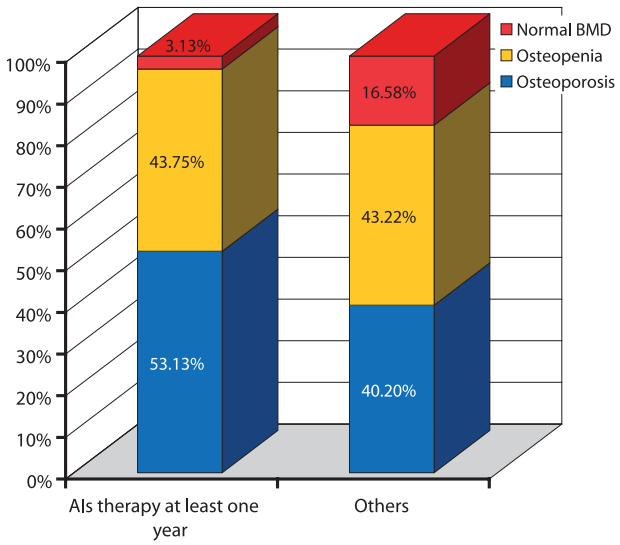


Fig. 3. BMD in Patients with Aromatase Inhibitors Therapy and Others.

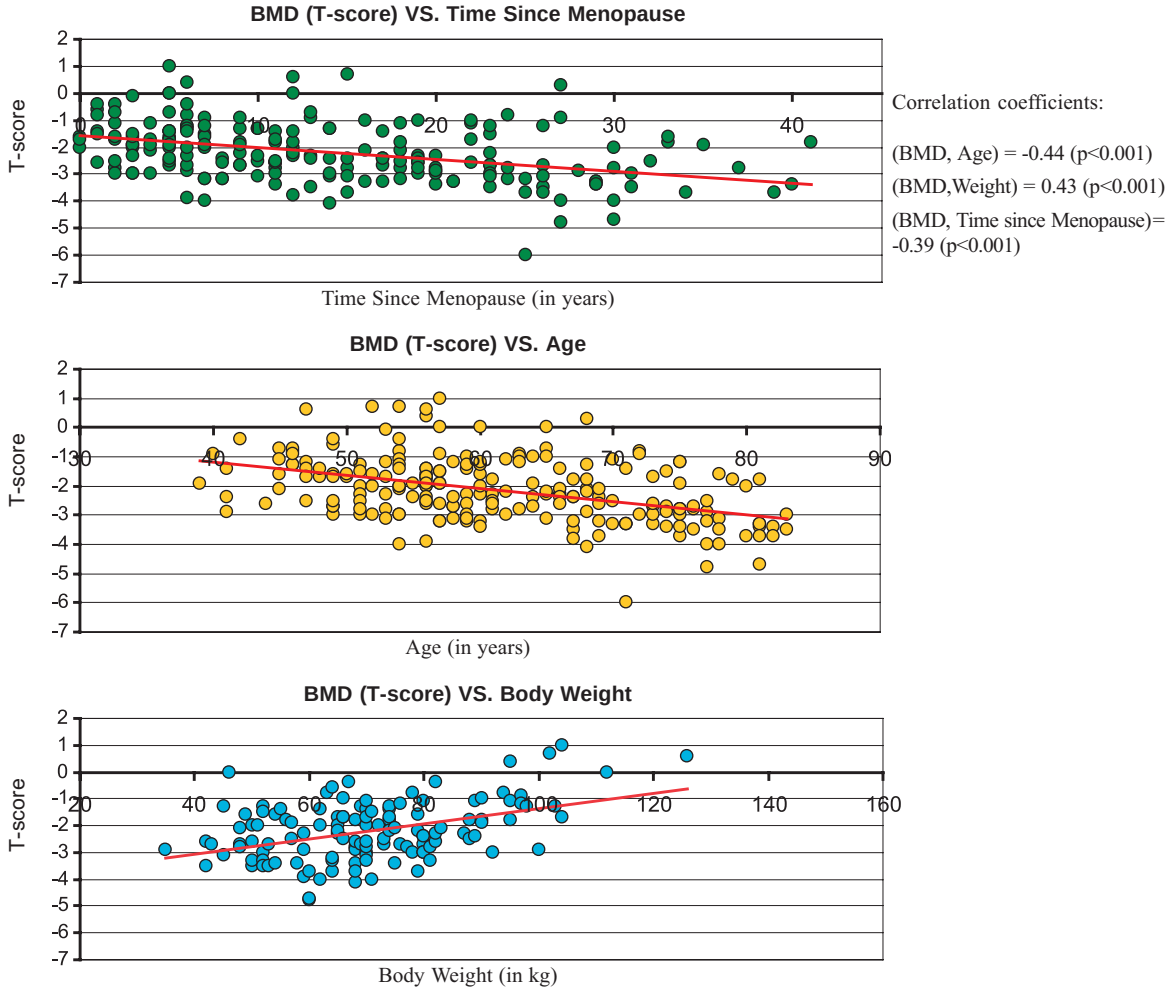
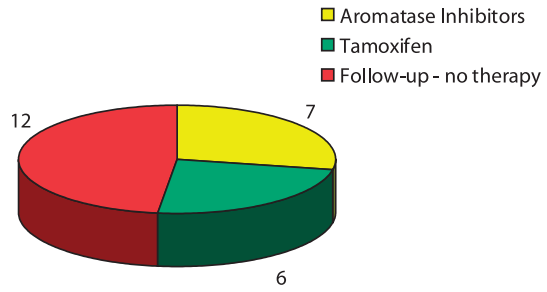


Fig. 4. Correlation of BMD with Age, Weight and Time since Menopause.



Osteoporosis	
E loco typico	10
Spine	5
Hip	0
Osteopenia	
E loco typico	3
Spine	2
Hip	0
Normal BMD	
E loco typico	2
Spine	0
Hip	0

Fig. 5. Pathological Fractures Rate.

13.16 % of patients, in the group with tamoxifen therapy the rate of osteoporosis was 30.43 % and normal BMD had 18.84 % of patients, in the group in follow-up without hormonal therapy the rate of osteoporosis was 53.75 % and normal BMD had 8.7 % of patients. The correlation between BMD loss and hormonal therapy was not proven statistically significant despite the tendency of tamoxifen protective effect on BMD maintenance – ($p=0.0610$). In a subanalysis, BMD loss was correlated only in subgroup of patients treated by AIs at least one year and patients treated less than 1 year or just in follow-up without hormonal therapy (Fig. 3), the difference was statistically significant. The rate of BMD loss to level of osteoporosis was 53.13 % in the first group and only 40.2 % in the latter and normal BMD rate was only 3.13 % in the first group versus 16.58 % in second ($p=0.0150$).

Other risk factors were analyzed and from those risk factors the highest rate had diabetes mellitus (33 patients), but no statistically significant influence of diabetes mellitus on BMD losses was confirmed – ($p=0.816$).

Correlation of BMD loss and increased levels of CTX as a marker of bone resorption was not confirmed in our study.

We tested all above mentioned risk factors statistically also (Fig. 4) using the method of multiple linear regression to eliminate potential secondary influences in cross interactions among factors. Correlations of BMD level with age ($p<0.0001$ and weight ($p<0.0001$) were confirmed by multiple linear regression. Borderline statistical significance was shown in correlation with AIs therapy ($p=0.0476$). The influence of time from menopause ($p=0.3410$) seemed to be secondary regarding to high correlation with the age of patients ($r=0.89$, $p<0.0001$).

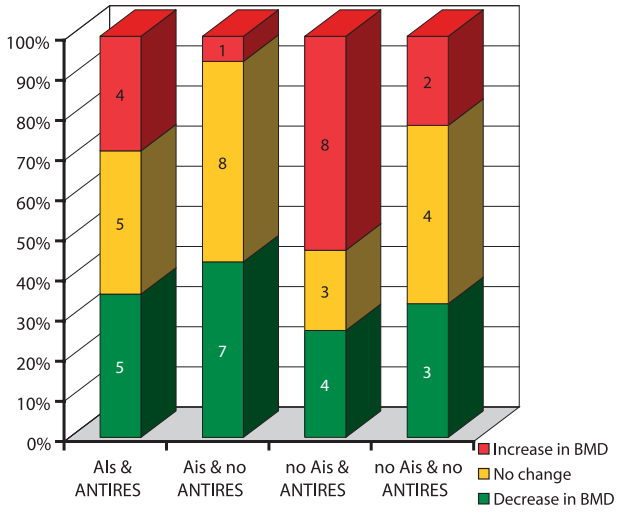
The rate of pathological fractures was also analyzed (Fig. 5). The highest incidence was in group of patients with osteoporosis. Fracture e loco typico was found in 10 patients and 5 had fractures in the region of L spine. In the group of patients with BMD in osteopenia range, 5 patients had pathological fractures, 3 of them e loco typico and 2 in region of L spine. There were only 2 pathological fractures in patients with normal BMD levels, both in the region of forearm. The whole group of patients is considered to be too small to make statistical analysis of risk factors of pathological fractures.

The last was the analysis of influence of antiresorptive therapy on BMD changes (Fig. 6). The analysis seemed to be preliminary as in the control group (control BMD measurement after 1 year of duration of antiresorptive therapy) were only 53 patients. This did not allow us to make relevant statistical analysis, although we found a trend toward protective effect of antiresorptive therapy in this group of patients.

The standard indication fro the use of antiresorptive therapy, mainly bisphosphonates in breast cancer patients, is prevention of bone events in bone metastatic disease. There is rapidly growing evidence from many clinical trials showing protective effect of bisphosphonates used in concomitance with AIs in early breast cancer. A protective effect on t bone loss was observed, longer period to bone metastases occurence and suspected direct anticancer effect as well. These results will probably lead very soon to a change in current standards and bisphosphonates will be used together with AIs in adjuvant therapy of early breast cancer patients.

Discussion

The AIs are becoming new standard in adjuvant hormonal therapy of early breast cancer postmenopausal patients. As the results of many large international multicentre clinical trials are more mature and results of substudies focused on BMD loss more



AIs – Aromatase Inhibitors; ANTIRES – Antiresorptive therapy

Fig. 6. Impact of Antiresorptive Therapy on BMD in patients with Breast Cancer.

and more consistent, new standards for BMD examination are evolving. The prognosis of early breast cancer patients is continuosly improving. BMD loss means increasing risk of osteoporosis and it means increasing risk of pathological fractures. There are many risks factors for this group of patients – age, postmenopausal status, breast cancer, AIs therapy. Adjuvant hormonal therapy is one of the most important factors leading to significant improvement in patient survival and the same important is quality of life which may be markedly decreased by pathological fractures from osteoporosis.

Identification of all risk factors of origin and progression of osteoporosis as well as exact examination procedures to find them is as important as prevention and therapy of BMD loss. Generally confirmed risk factors for pathological fractures of osteoporosis in breast cancer patients are:

AIs therapy
T-score <1. 5
Age >65 years
Low body mass index (BMI <20 kg/m^2)
Family history of hip fracture
Personal history of fracture from osteoporosis after age of 50
Oral corticosteroid therapy lasting >6 months
Smoking (in present or in past)

In multicenter international clinical trial "ATAC", where the postmenopausal early breast cancer patients were randomised (final design) to AI anastrozole (A) versus tamoxifen (T) showed that after 5 years of therapy (10) there were significantly more bone fractures on arm A (11 % versus 7 % p<0.001). In clinical trial "BIG 1-98" the same postmenopausal early breast cancer patients were randomised to AI letrozole (L) versus tamoxifen (T). With median of follow-up of 26 months (11) there were significantly more bone fractures in arm L (5.7 % versus 4.0 % p<0.001). Very similar results were reached in the clinical study "IES" where the postmenopausal early breast cancer patients were randomised to AI exemestane (E) versus tamoxifen (T) and with median of follow-up 56 months (12 there were significantly more bone fractures in arm E (7 % versus 4.9 % p=0.003). In combined clinical study "ABCSG-8 and ARNO 95" the patients were "switched" after anastrozole (A) therapy to tamoxifen (T) vs continuing T therapy. With median of follow-up of 28 months (13) there was similar significant difference against arm A (2 % versus 1 % p=0.015). In the clinical study "MA.17" were the patients after 5 years on tamoxifen (T) therapy were randomised to "switch" to anastrozole (A) versus only follow-up without hormonal treatment. With median of follow-up of 30 months (14), there were more patients with newly diagnosed osteoporosis in arm A (8.1 % versus 6.0 % p=0.003), and more bone fractures (5.3 % versus 6.0 %, this difference was however not statistically significant p=0.25).

In comparison of patients on AI anastrozole (A) therapy from the clinical study "ATAC" to their healthy counterparts matched in age, postmenopausal status, with osteopenia, the incidence of bone fractures was nearly doubled (10, 15).

We confirmed the prognostic importance of age, duration of menopause, AIs treatment in comparison to tamoxifen treatment or no therapy in follow-up group in our clinical observation. All these results are in concordance with world scientific literature.

According to WHO and NOF (National Osteoporotic Foundation) guidelines is the value of T-score in BMD measurement critical in distribution to normal BMD (T-score ≥ -1.0), osteopenia (T-score between -1.0 and -2.5) and osteoporosis (T-score ≤-2.5) (16, 17). According to international general guidelines is this classification universally accepted and it is recognised that with decreasing BMD level the risk of pathological bone fractures is rising. That is why the results and observations of the clinical study NORA (National Osteoporosis Risk Assessment) are so interesting. They observed 200 000 healthy postmenopausal women and found that 82 % pathological bone fractures occurrein women with T-score > -2.5, which means that they did no have osteoporosis and 52 % fractures were in women with osteopenia (T-score -1.0 to -2.5) (18).

All these results and findings confirm the importance of BMD measurement before AIs therapy initiation and importance of preventive measurements as components of adjuvant AIs therapy as well. Calcium and vitamin D supplementation and appropriate physical activity are standard components of these recommendations (7). Preventive bisphosphonates application is being evaluated in many running clinical studies. Especially zoledronic acid is showing excellent results and it seems to be incorporated into standard combination with AIs in adjuvant therapy of postmenopausal early breast cancer patients very soon as osteoporosis and bone fracture prevention (20).

The influence of antiresorptive therapy on BMD was part of our study as well. This analysis is difficult to interpret as our control group (control BMD measurement after 1 year of duration of antiresorptive therapy) was very small (only 53 patients) and median of follow-up very short. This did not allow us to make relevant statistical analysis but we found trend toward protective effect of antiresorptive therapy in this group of patients.

We did not confirm correlation of BMD decrease and CTX elevation. Probably the reason was small analysed group of patients and low specificity of CTX as osteoporosis marker.

Conclusions and future directions

The most important goal of our study was to confirm the importance of BMD measurement and evaluation in group of postmenopausal early breast cancer patients on AIs therapy. Even the study group is not very large, all the patients are from single institute and we have planned to follow-up them throughout the AIs therapy and thereafter. Preliminary analysis of our data confirmed significant BMD loss in this group of patients. The AIs therapy influence on BMD loss was statistically significant after one year of therapy. For more valid data we need more patients and longer time of follow-up. Our plan is to continue in evaluation of influence of antiresorptive therapy on BMD as we observed a trend of protection of BMD. Evaluation of importance of BMD loss for increased risk of patho-

logical bone fractures also needs more patients and longer time of follow-up.

Our observational study confirmed the importance of BMD measurement and evaluation in postmenopausal early breast cancer patients on AIs therapy. This is in concordance with new recommendations for early breast cancer therapy published in July 2007 as a result of consensus conference (10th St Gallen Conference) and other important international guidelines.

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