Accepted Manuscript

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PII: S8756-3282(18)30348-X
DOI: doi:[10.1016/j.bone.2018.09.010](https://doi.org/10.1016/j.bone.2018.09.010)
Reference: BON 11752
To appear in: *Bone*
Received date: 25 June 2018
Revised date: 13 September 2018
Accepted date: 13 September 2018

Please cite this article as: Marta Pineda-Moncusí, Sonia Servitja, Guillem Casamayor, Maria Lourdes Cos, Abora Rial, Jaime Rodriguez-Morera, Ignasi Tusquets, Adolfo Diez-Perez, Natalia Garcia-Giralt, Xavier Nogués, Bone health evaluation one year after aromatase inhibitors completion. *Bone* (2018), doi:[10.1016/j.bone.2018.09.010](https://doi.org/10.1016/j.bone.2018.09.010)

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Bone health evaluation one year after aromatase inhibitors completion

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Abstract

Introduction

Breast cancer patients treated with aromatase inhibitors (AIs) experience increased bone loss during their treatment. However, there is little information about bone mineral density (BMD) after completing AI-treatment. The present study aimed to assess BMD changes one year after AI-therapy completion.

Methods

Data were collected from 864 postmenopausal women treated with AI during 5 years (5y-AI group), or during 2-3 years after taking tamoxifen therapy (pTAM-AI group). Participants with osteoporosis were treated with oral bisphosphonates (BP). BMD changes in lumbar spine (LS), femoral neck (FN) and total hip (TH) between baseline, end of treatment, and at one year post-treatment were assessed using repeated-measures ANOVA.

Results

At the end of AI-treatment, 382 patients had available BMD values and 316 also had post-treatment BMD values. As expected, BMD levels were decreased at AI-completion in non-BP treated patients. After one year, LS BMD increased in both groups (5y-AI: +2.11% [95%CI: 1.55 to 2.68], $p<0.001$; pTAM-AI: +1.00% [95%CI: 0.49 to 1.51], $p<0.001$) compared with the end of AI-therapy, while values at FN and TH remained stable. On the other hand, BMD values of BP-treated patients were increased or maintained at the end of AI-treatment and also at post-treatment.

Conclusions

At one year after AI-completion, FN and TH BMD remained reduced in non-BP treated women, while LS BMD was recovered in the 5y-AI group and partially recovered in the pTAM-AI group. BP treatment increased or maintained BMD values at the end of therapy and at one year post-treatment.

Keywords: breast cancer, aromatase inhibitors, bone mineral density, bisphosphonates, B-ABLE cohort.

Introduction

Aromatase inhibitor (AI) is recommended by the American Society of Clinical Oncology as the adjuvant endocrine therapy to treat estrogen receptor positive (ER+) early breast cancer in postmenopausal women. Despite its great efficiency, compared to tamoxifen (TAM) as the alternative [1-3], AI has been associated with side effects that could affect the patient's quality of life and its adherence to treatment, being arthralgia and bone loss induction among the most common [4, 5].

Previous studies have described an accelerated decrease in bone mineral density (BMD) associated with AI therapy, leading to osteopenic or osteoporotic bone status, both of which are related to osteoporotic fracture [1, 4]. Clinical guidelines for the management of AI-related bone loss strongly recommend a close monitoring of BMD and other risk factors to reduce the fracture risk by means of antiresorptive therapies [6]. Treatment with bisphosphonates (BPs) is the current recommendation to avoid this bone loss [7-9].

Even though bone parameters have been monitored during AI treatment in many studies [10, 11], there is scarce information about bone status after completion of AI treatment. A small sub-analysis in the ATAC trial, with 23 evaluated patients, showed an increase of bone mass at lumbar spine after one year of AI-completion [12]. In the MA.17R trial [13], an increase in lumbar spine (LS) and total hip (TH) BMD was reported 5-7 years post-treatment in women mainly treated with TAM followed by AI; however, half of the patients were treated with BP, concealing the results. Despite the insights on bone behavior related to AI treatment gained from these previous randomized control trials (RCTs), bone health after AI cessation has not been explored in actual clinical conditions.

In the present study, we analyzed BMD changes at the end of treatment and at one year after AI-completion in an observational prospective cohort (B-ABLE). In this study, the effect of previous tamoxifen and/or BP treatment was taken into account.

Materials and Methods

Study design and participants

Caucasian postmenopausal woman diagnosed with ER+ early breast cancer and candidates for AI-treatment (letrozole, exemestane, or anastrozole) were consecutively recruited from January 2006 to January 2018 in B-ABLE cohort – a prospective, non-selected, observational, clinical cohort study – in Hospital del Mar (Barcelona, Spain). The study protocol was approved by the ethics committee of Parc de Salut Mar (2016/6803/I) and it was carried out in accordance with the Declaration of Helsinki. A written informed consent was obtained from all participants after

they had read the study information sheet and any questions had been answered. The privacy rights of human subjects must always be observed.

Participants were enrolled at point of starting AI therapy, either six weeks post-surgery or one month after the last cycle of chemotherapy (5y-AI group) or, alternatively, once starting menopause after taking TAM for two to three years (pTAM-AI group). End of treatment was considered a total of five years of hormonal adjuvant therapy, according to classic American Society of Clinical Oncology recommendations [14]. Follow-up was from the first day of AI intake to one year after AI-completion. Postmenopausal status was defined as patients >55 years old with amenorrhea for >12 months, or those ≤ 55 with levels of luteinizing hormone >30 mIU/mL or follicle-stimulating hormone values >40 mIU/mL. Eligible participants were excluded for previous history of any bone, metabolic or endocrine diseases, as well as alcoholism, rheumatoid arthritis, and concurrent or prior treatment with BP, oral corticosteroids, or any other bone-active drug except tamoxifen.

At the outset of the study, patients were stratified by the corresponding therapeutic regimen: 1) those with osteoporosis [T score < -2.5] or with a T score ≤ -2.0 at any site plus 1 major risk factor (i.e. family history of femoral fracture, or early menopause) or prevalent fragility fractures were treated with weekly oral risedronate or alendronate therapy (BP-treated patients) 2) all other patients were allocated to no active antiresorptive therapy (non-BP-treated patients). BMD was assessed every 12 months until one year after the end of AI therapy (post-treatment). Those who developed osteoporosis during the treatment were immediately offered oral BP treatment and were censored from the study at that point.

Additionally, all participants received supplements of calcium and 25(OH)vitD3 tablets (1000 mg and 800 IU daily, respectively), and those with baseline 25(OH)vitD deficiency (<30 ng/mL) received an additional dose of 16,000 IU of oral calcifediol (HIDROFEROL® FAES FARMA) every 2 weeks.

Variables

Bone Mineral Density

The main outcomes of the study are the absolute and cumulative percentage change in lumbar spine (LS), femoral neck (FN) and total hip (TH) BMD from baseline to the end of treatment and at one year post-treatment.

BMD measures were obtained using a DXA densitometer QDR 4500 SL® (Hologic, Waltham, MA, USA), according to manufacturer recommendations. In our department, in vivo coefficients of variation of these techniques are 1.0% at LS, 1.60 at TH, and 1.65% at FN. As a secondary analysis, non-BP-treated patients were categorized according to its LS-BMD shift, and their distribution was plotted.

Other variables

At the time of recruitment, data from large clinical variables were registered, including: age, body mass index (BMI), age of menarche and menopause, number of children, months of breastfeeding, and prior chemotherapy, among others.

Statistical methods

Significant differences between variables in the groups of the study were analyzed with One-way ANOVA, Kruskal-Wallis and Chi-square tests, according to variables' nature. In each group, BMD changes between baseline, end of treatment, and post-treatment were evaluated by repeated-measures ANOVA.

Statistical analysis was done with R for Windows version 3.3.3 (foreign, compareGroups, pgirmess, fitter, boot, ggplot2 and scales packages) and SPSS Statistics version 22.0. All statistical contrasts were corrected by Bonferroni test per multiple comparisons and *P* values lower than 0.05 were considered significant.

Results

Participants

From 864 participants included in the B-ABLE cohort, 382 patients completed AI treatment and had BMD values registered at this point, and 316 of those patients had BMD values at one year after AI-treatment completion (Fig. 1).

Fig. 1 Flowchart showing the number of patient records in each bone mineral density site at the end of aromatase inhibitors treatment and at post-treatment, according to antiresorptive therapy. Abbreviations: AI, aromatase inhibitors; BP, oral bisphosphonates.

Before the end of AI therapy, 32 patients became osteoporotic and started oral BP (5y-AI: n=22, 3.8%; pTAM-AI: n=10, 3.6%), who were censored from the study at this point; 122 participants were withdrawn from the study (Supplementary table 1), and 328 patients still remained in the follow-up and did not achieve the time of AI-treatment completion. Between end of treatment and one year post-treatment, 41 participants were withdrawn (Supplementary table 1), and 25 patients had not reached one year post-treatment at the end of data collection. Fracture events in participants during follow-up are reported in Supplementary table 2. Baseline characteristics of selected patients are described in Table 1.

Table 1 Baseline characteristics of patients

Variables	Non-BP-treated patients (n=242)		BP-treated patients (n=74)	
	pTAM-AI group (n=127)	5y-AI group (n=115)	pTAM-AI group (n=44)	5y-AI group (n=30)
Mean age (years) $\pm$ SD	57.2 $\pm$ 8.65	62.8 $\pm$ 7.21	63.4 $\pm$ 9.42	60.8 $\pm$ 6.20
Mean BMI (g/cm ²) $\pm$ SD	28.5 $\pm$ 5.68	30.4 $\pm$ 4.78	27.3 $\pm$ 4.70	27.4 $\pm$ 4.45
Median age of menarche (years) [Q1;Q3]	13.0 [11.0;13.0]	12.0 [11.0;14.0]	12.0 [11.0;14.0]	13.0 [12.0;13.8]
Mean age of menopause onset (years) $\pm$ SD	48.7 $\pm$ 4.08	49.7 $\pm$ 4.40	49.5 $\pm$ 3.73	49.5 $\pm$ 3.04
Median number of children [Q1;Q3]	2.0 [1.0;2.0]	2.0 [1.0;3.0]	2.0 [1.7;3.0]	2.0 [2.0;2.7]
Median breastfeeding (months) [Q1;Q3]	3.0 [0.0;9.0]	3.0 [0.0;11.5]	3.0 [0.0;7.2]	0.0 [0.0;6.0]
Prior chemotherapy (n (%))	90 (70.9%)	58 (50.4%)	27 (61.4%)	16 (53.3%)
Abbreviations: 5y, treated during five years; AI, aromatase inhibitors; BMI, body mass index; BP, oral bisphosphonates; pTAM, previous tamoxifen treatment; Q, quartile.				

BP and non-BP treated patients were analyzed separately. In the BP-treated group, no significant differences were found between pTAM-AI and 5y-AI patients. In the non-BP-treated patients, the pTAM-AI group was significantly younger ($p < 0.0001$) and more likely to be treated with chemotherapy ($p = 0.0107$) than the 5y-AI group. Both groups did not differ in age of menarche, age of menopause, number of children, and months of breastfeeding.

BMD variation analysis

Mean percentage changes in BMD at LS, FN and TH from baseline to end of treatment and one year post-AI treatment are summarized in Fig. 2.

Fig. 2 Individual percent change in lumbar spine, femoral neck, and total hip bone mineral density from baseline to the end of aromatase inhibitors treatment and at post-treatment according to oral bisphosphonates and previous tamoxifen treatment. Mean $\pm$ 95%CI is reported. In ANOVA from baseline: * ($P < 0.01$); ** ($P < 0.001$). Abbreviations: 5y, treated during five years; AI, aromatase inhibitors; BMD, bone mineral density; BP, oral bisphosphonates; pTAM, previous tamoxifen treatment.

Absolute BMD values at the three evaluation points are reported in Table 2.

Table 2 Absolute LS, FN and TH BMD values at baseline, at the end of AI treatment, and at one year post-treatment, according to BP treatment and previous TAM use.

BP treatment	Patients group	Site	N	Visit		
				Baseline	End of treatment	Post-treatment
NO	pTAM-AI	LS	125	0.963 ± 0.099	0.925 ± 0.102	0.934 ± 0.106
		FN	125	0.765 ± 0.088	0.739 ± 0.087	0.740 ± 0.083
		TH	120	0.910 ± 0.095	0.882 ± 0.093	0.888 ± 0.095
	5y-AI	LS	114	0.965 ± 0.112	0.939 ± 0.117	0.958 ± 0.121
		FN	114	0.753 ± 0.094	0.727 ± 0.092	0.725 ± 0.090
		TH	113	0.901 ± 0.093	0.878 ± 0.092	0.879 ± 0.095
YES	pTAM-AI	LS	41	0.814 ± 0.104	0.828 ± 0.099	0.839 ± 0.103
		FN	44	0.649 ± 0.086	0.653 ± 0.083	0.654 ± 0.083
		TH	43	0.785 ± 0.103	0.792 ± 0.105	0.800 ± 0.105
	5y-AI	LS	30	0.768 ± 0.078	0.794 ± 0.086	0.806 ± 0.079
		FN	30	0.625 ± 0.083	0.644 ± 0.085	0.646 ± 0.083
		TH	30	0.769 ± 0.096	0.783 ± 0.113	0.798 ± 0.101

Abbreviations: 5y, treated during five years; AI, aromatase inhibitors; BMD, bone mineral density (g/cm² (Mean±SD)); BP, oral bisphosphonates; FN, femoral neck; TH, total hip; LS, lumbar spine; pTAM, previous tamoxifen treatment.

Lumbar spine BMD variation

In non-BP treated patients, LS BMD decreased significantly at the end of AI treatment in both 5y-AI and pTAM-AI patients: -2.62% [95%CI: -3.64 to -1.60] and -3.96% [95%CI: -4.79 to -3.12], respectively; $p < 0.001$. After one year of AI-treatment completion, BMD in 5y-AI patients significantly increased (+2.11% [95%CI: +1.55 to +2.68], $p < 0.001$), achieving values similar to baseline (-0.59% [95%CI: -1.69 to +0.50], $p = 0.732$). In contrast, baseline LS BMD values were not recovered in pTAM-AI patients (-3.01% [95%CI: -3.96 to -2.05], $p < 0.001$). However, a slight increase in BMD was detected between end of treatment and one year post-treatment (+1.00% [95%CI: +0.49 to +1.51], $p < 0.001$).

In the BP-treated group, all patients had continued bone mass gains at a) the end of treatment and b) one year post-treatment: a) 5y-AI group (+3.39% [95%CI: +1.39 to +5.40], $p = 0.005$); pTAM-AI group (+1.90% [95%CI: +0.31 to +3.48], $p = 0.145$); and b) 5y-AI (+5.16% [95%CI: +2.91 to +7.41], $p < 0.001$); pTAM-AI (+3.23% [95%CI: +1.62 to +4.84], $p = 0.002$).

Femoral neck BMD variation

In non-BP-treated participants, FN BMD diminished in both groups (5y-AI: -3.42% [95%CI: -4.36 to -2.47]; pTAM-AI: -3.33% [95%CI: -4.15 to -2.51]; $p < 0.001$) until the end of AI treatment; these BMD values were maintained at one year post-treatment.

In contrast, BMD improved with BP therapy (5y-AI: +3.17% [95%CI: +1.37 to +4.98], $p<0.003$; and pTAM-AI: +0.85% [95%CI: -0.73 to +2.44], $p=0.145$) up to the end of treatment; no significant changes were detected between AI-completion and post-treatment.

Total hip BMD variation

Similar to FN BMD behavior, a significant decrease in TH BMD was detected after AI-treatment completion in non-BP-treated patients (-2.53% [95%CI: -3.40 to -1.65], $p<0.001$ in 5y-AI group; and -3.01% [95%CI: -3.80 to -2.22], $p<0.001$ in pTAM-AI group). The decreased TH BMD levels remained stable at one year post-treatment.

In the BP-treated patients, BMD increases were detected only in the 5y-AI group at one year post treatment (+3.89% [95%CI: +2.14 to +5.64], $p<0.001$).

Patient distribution by LS BMD categories

As the major BMD variations were detected at the LS location in patients without BP between end of AI treatment and one year post-treatment, patient distribution according to LS BMD changes was explored (Fig. 2). A total of 65.8% of 5y-AI and 42.4% of pTAM-AI patients experienced an intra-individual BMD gain equal to or greater than 1%. In 19.3% and 32.8% of patients, respectively, BMD values remained constant (Fig. 3). However, in 14.9% and 24.8%, respectively, bone mass had continued to decrease, by 1% or more, at one-year follow-up.

Fig. 3 Participant distribution in non-BP-treated patients according to lumbar spine bone mineral density shift between end of treatment and post-treatment. Abbreviations: 5y, treated during five years; AI, aromatase inhibitors; BMD, bone mineral density; pTAM, previous tamoxifen treatment.

Discussion

In this prospective cohort study based on actual clinical conditions, bone health was evaluated after one year of AI-completion in women with early breast cancer, stratifying the analysis by bisphosphonates use.

Bone loss related to AI therapy was recovered at the LS location in 5y-AI patients, but mean BMD recovery in pTAM-AI patients was only 1%. In contrast, FN and TH BMD values

remained reduced at one year post-treatment even though the bone loss was stopped. In BP-treated patients, LS, FN and TH BMD levels were maintained or continued to gain at the end of follow-up.

About half of non-BP treated patients experienced a clinically significant gain (greater than or equal to 1%) in LS-BMD at one year after AI cessation, and half of this subgroup had gained more than 3%. Only 15% of 5y-AI and 25% of pTAM-AI patients continued to lose bone mass at the end of follow-up. Hence, in most patients the deleterious effect of AI in LS bone mass stopped, with a trend towards recuperation of baseline BMD after completing AI treatment. On the other hand, a lack of FN and TH BMD recovery was observed in the first year post-treatment. This could be due to the lower capacity for change at these locations [11].

Similar findings were reported in the bone sub-study of the ATAC trial [12], in which 65.2% of participants had increased their LS BMD one year after AI cessation. Similar to our study, LS BMD values increased (+2.35% [interquartile range: -5.34 to 8.19, $p=0.04$]) and remained stable in TH BMD (+0.71% [interquartile range: -9.42 to 4.63, $p=0.3$]). Their results, obtained from a small sample ($n=21$ in LS; $n=23$ in TH), were confirmed in our cohort.

In the Ma.17R trial [13], patients presented a mean gain in BMD of +4.5% in the spine and +22.4% in the hip at 5 to 7 years post-treatment. The higher increase observed in that trial could be explained by differences in length of follow-up and a lack of stratification by BP use and previous TAM treatment. In fact, one of the strengths of the present study is that we separate participants in different groups according to previous tamoxifen treatment and current BP use, which revealed differences in BMD behavior between treatment groups. In this regard, BP-treated patients improved their BMD values, as would be expected.

Bone mass loss during AI treatment is one of the most important adverse effects experienced by breast cancer patients on adjuvant endocrine therapy. In fact, the decrease of BMD has been described as the major factor of fragility fractures [15]. Moreover, some clinical trials with AI have reported an increase of fractures in both osteopenic and osteoporotic patients [13, 16]. Even though bone mass seems to be recovered after AI cessation, bone health should be evaluated in all patients since BMD in LS remained decreasing almost in 1/4 of patients after AI treatment was ended. In these cases, BPs could be a recommended option since BP treated patients in our study showed better BMD values.

In this line, patients from our cohort are subjected to strict monitoring of 25(OH)vitD levels and calcium diet intake. All patients receive a high 25(OH)vitD supplementation from baseline. Hence, 25(OH)vitD levels improved significantly in our cohort with the proposed repletion regimen raised until the normal range reaching an average >30 ng/ mL, and persisted by the

follow-up [17]. Data from previous studies strongly recommend that individuals in AI treatment, including those who are at low risk for fractures and not candidates for BP treatment, should receive calcium and 25(OH)vitD supplements [18], especially in cases where calcium intake is not enough. These supplementations could contribute to the recovery of BMD values observed after AI-completion in our study.

One limitation of our study is the limited tracking time after treatment completion, which precludes any predictions about how BMD will evolve during a longer-term follow-up, and in particular, whether FN and TH BMD will be recovered. Further research is needed to explain why patients previously treated with TAM experienced lower LS BMD recovery than patients receiving AI monotherapy. We hypothesize that the accelerated bone loss during AI treatment in pTAM-AI patients, as previously described in B-ABLE cohort [19], might delay LS BMD recovery. Likewise, we cannot know if this BMD could return to baseline levels at long term.

It is worth mentioning that although BMD measured by DXA is the gold standard surrogate for the diagnosis of osteoporosis, it is well-known that the increased risk of non-traumatic fractures is determined not only by the mineral content but also by bone quality and material properties, such as trabecular microarchitecture [10], the accumulation of microfractures, a disordered bone remodeling, bone affecting drugs, toxic habits or the influence of extra-skeletal risk factors [20].

In summary, AI-related bone loss stopped at one year after AI-completion and, in the lumbar location, BMD values were totally recovered in most patients who had received AI monotherapy and partially recovered in patients who were previously treated with TAM. However, monitoring of bone health and calcium and 25(OH)vitD supplementation is essential for the clinical management of patients after finalizing AI adjuvant therapy. Larger studies are needed to determine whether the observed BMD behavior persists beyond the one year post-treatment.

Conflicts of interest

Marta Pineda-Moncusí, Sonia Servitja, Guillem Casamayor, Maria Lourdes Cos, Abora Rial, Jaime Rodriguez-Morera, Ignasi Tusquets, Adolfo Diez-Perez, Natalia Garcia-Giralt, Xavier Nogués declare that they have no conflict of interest.

Acknowledgments

The authors thank Elaine M. Lilly, Ph.D, for providing language assistance, helpful advice and critical reading of the manuscript. This work was supported by the Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES, grant number

CB16/10/00245) and FIS Project (grant number PI16/00818); Instituto de Salud Carlos III (ISCIII), and FEDER funds.

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References

- [1] L. Ryden, M. Heibert Arnlind, S. Vitols, M. Hoistad, J. Ahlgren, Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials, *Breast* 26 (2016) 106-14. doi: <https://doi.org/10.1016/j.breast.2016.01.006>
- [2] A.T.A.C. Group, J.F. Forbes, J. Cuzick, A. Buzdar, A. Howell, J.S. Tobias, M. Baum, Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial, *Lancet Oncol* 9(1) (2008) 45-53. doi: [https://doi.org/10.1016/S1470-2045\(07\)70385-6](https://doi.org/10.1016/S1470-2045(07)70385-6)
- [3] E.B.C.T.C. Group, Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials, *Lancet* 386(10001) (2015) 1341-1352. doi: [https://doi.org/10.1016/S0140-6736\(15\)61074-1](https://doi.org/10.1016/S0140-6736(15)61074-1)
- [4] R. Eastell, J.E. Adams, R.E. Coleman, A. Howell, R.A. Hannon, J. Cuzick, J.R. Mackey, M.W. Beckmann, G. Clack, Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230, *J Clin Oncol* 26(7) (2008) 1051-7. doi: <https://doi.org/10.1200/JCO.2007.11.0726>
- [5] F. Laroche, J. Coste, T. Medkour, P.H. Cottu, J.Y. Pierga, J.P. Lotz, K. Beerblock, C. Tournigand, X. Decleves, P. de Cremoux, D. Bouhassira, S. Perrot, Classification of and risk factors for estrogen deprivation pain syndromes related to aromatase inhibitor treatments in women with breast cancer: a prospective multicenter cohort study, *J Pain* 15(3) (2014) 293-303. doi: <https://doi.org/10.1016/j.jpain.2013.11.004>
- [6] P. Hadji, J.J. Body, M.S. Aapro, A. Brufsky, R.E. Coleman, T. Guise, A. Lipton, M. Tubiana-Hulin, Practical guidance for the management of aromatase inhibitor-associated bone loss, *Ann Oncol* 19(8) (2008) 1407-16. doi: <https://doi.org/10.1093/annonc/mdn164>
- [7] P. Hadji, R.E. Coleman, C. Wilson, T.J. Powles, P. Clezardin, M. Aapro, L. Costa, J.J. Body, C. Markopoulos, D. Santini, I. Diel, A. Di Leo, D. Cameron, D. Dodwell, I. Smith, M. Gnant, R. Gray, N. Harbeck, B. Thurlimann, M. Untch, J. Cortes, M. Martin, U.S. Albert, P.F. Conte, B. Ejlersen, J. Bergh, M. Kaufmann, I. Holen, Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel, *Ann Oncol* 27(3) (2016) 379-90. doi: <https://doi.org/10.1093/annonc/mdv617>
- [8] F.A. Tremollieres, I. Ceausu, H. Depypere, I. Lambrinoudaki, A. Mueck, F.R. Perez-Lopez, Y.T. van der Schouw, L.M. Senturk, T. Simoncini, J.C. Stevenson, P. Stute, M. Rees, Osteoporosis management in patients with breast cancer: EMAS position statement, *Maturitas* 95 (2017) 65-71. doi: <https://doi.org/10.1016/j.maturitas.2016.10.007>
- [9] P. Hadji, M.S. Aapro, J.J. Body, M. Gnant, M.L. Brandi, J.Y. Reginster, M.C. Zillikens, C.C. Gluer, T. de Villiers, R. Baber, G.D. Roodman, C. Cooper, B. Langdahl, S. Palacios, J. Kanis, N. Al-Daghri, X. Nogues, E.F. Eriksen, A. Kurth, R. Rizzoli, R.E. Coleman, Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG, *J Bone Oncol* 7 (2017) 1-12. doi: <https://doi.org/10.1016/j.jbo.2017.03.001>
- [10] R.-S. María, P.-M. Marta, S. Sonia, G.-G. Natalia, M. Tamara, T. Ignasi, M.-G. Maria, R.-M. Jaime, D.-P. Adolfo, A. Joan, N. Xavier, TBS and BMD at the end of AI-therapy: A prospective study of the B-ABLE cohort, *Bone* 92 (2016) 1-8. doi: <https://doi.org/10.1016/j.bone.2016.08.008>
- [11] A.R. Hong, J.H. Kim, K.H. Lee, T.Y. Kim, S.A. Im, H.G. Moon, W.S. Han, D.Y. Noh, S.W. Kim, C.S. Shin, Long-term effect of aromatase inhibitors on bone microarchitecture and macroarchitecture in non-osteoporotic postmenopausal women with breast cancer, *Osteoporos Int* 28(4) (2017) 1413-1422. doi: <https://doi.org/10.1007/s00198-016-3899-6>

- [12] R. Eastell, J. Adams, G. Clack, A. Howell, J. Cuzick, J. Mackey, M.W. Beckmann, R.E. Coleman, Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial, *Ann Oncol* 22(4) (2011) 857-62. doi: <https://doi.org/10.1093/annonc/mdq541>
- [13] P.E. Goss, J.N. Ingle, K.I. Pritchard, N.J. Robert, H. Muss, J. Gralow, K. Gelmon, T. Whelan, K. Strasser-Weippl, S. Rubin, K. Sturtz, A.C. Wolff, E. Winer, C. Hudis, A. Stopeck, J.T. Beck, J.S. Kaur, K. Whelan, D. Tu, W.R. Parulekar, Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years, *N Engl J Med* 375(3) (2016) 209-19. doi: <https://doi.org/10.1056/NEJMoa1604700>
- [14] E.P. Winer, C. Hudis, H.J. Burstein, A.C. Wolff, K.I. Pritchard, J.N. Ingle, R.T. Chlebowski, R. Gelber, S.B. Edge, J. Gralow, M.A. Cobleigh, E.P. Mamounas, L.J. Goldstein, T.J. Whelan, T.J. Powles, J. Bryant, C. Perkins, J. Perotti, S. Braun, A.S. Langer, G.P. Browman, M.R. Somerfield, American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004, *J Clin Oncol* 23(3) (2005) 619-29. doi: <https://doi.org/10.1200/JCO.2005.09.121>
- [15] N. O'Flynn, Risk assessment of fragility fracture: NICE guideline, *Br J Gen Pract* 62(605) (2012) 667-8. doi: <https://doi.org/10.3399/bjgp12X659475>
- [16] M. Colleoni, A. Giobbie-Hurder, M.M. Regan, B. Thurlimann, H. Mouridsen, L. Mauriac, J.F. Forbes, R. Paridaens, I. Lang, I. Smith, J. Chirgwin, T. Pienkowski, A. Wardley, K.N. Price, R.D. Gelber, A.S. Coates, A. Goldhirsch, Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study, *J Clin Oncol* 29(9) (2011) 1117-24. doi: <https://doi.org/10.1200/JCO.2010.31.6455>
- [17] D. Prieto-Alhambra, S. Servitja, M.K. Javaid, L. Garrigos, N.K. Arden, C. Cooper, J. Albanell, I. Tusquets, A. Diez-Perez, X. Nogues, Vitamin D threshold to prevent aromatase inhibitor-related bone loss: the B-ABLE prospective cohort study, *Breast Cancer Res Treat* 133(3) (2012) 1159-67. doi: <https://doi.org/10.1007/s10549-012-2013-9>
- [18] C. Markopoulos, E. Tzoracoleftherakis, A. Polychronis, B. Venizelos, U. Dafni, G. Xepapadakis, J. Papadiamantis, V. Zobolas, J. Misitzis, K. Kalogerakos, A. Sarantopoulou, N. Siasos, D. Koukouras, Z. Antonopoulou, S. Lazarou, H. Gogas, Management of anastrozole-induced bone loss in breast cancer patients with oral risendronate: results from the ARBI prospective clinical trial, *Breast Cancer Res* 12(2) (2010) R24. doi: <https://doi.org/10.1186/bcr2565>
- [19] M. Rodriguez-Sanz, D. Prieto-Alhambra, S. Servitja, N. Garcia-Giralt, L. Garrigos, J. Rodriguez-Morera, J. Albanell, M. Martinez-Garcia, I. Gonzalez, A. Diez-Perez, I. Tusquets, X. Nogues, AI-related BMD variation in actual practice conditions: A prospective cohort study, *Endocr Relat Cancer* 23(4) (2016) 303-12. doi: <https://doi.org/10.1530/ERC-16-0025>
- [20] J.A. Kanis, A. Oden, H. Johansson, F. Borgstrom, O. Strom, E. McCloskey, FRAX and its applications to clinical practice, *Bone* 44(5) (2009) 734-43. doi: <https://doi.org/10.1016/j.bone.2009.01.373>

Highlights

- Bone mineral density (BMD) levels decrease during aromatase inhibitor (AI) therapy.
- At one year after AI-completion, femoral neck and total hip BMD remained reduced.
- At one year after AI-completion, lumbar spine BMD was recovered in patients treated with 5 years of AI and partially recovered in AI-patients previously treated with tamoxifen.
- Bisphosphonate treatment increased or maintained BMD values at the end of AI therapy and at one year post-treatment.