Assessment and management of bone health in women with early breast cancer receiving endocrine treatment in the DATA study

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The phase III DATA study investigates the efficacy of adjuvant anastrozole (6 *vs.* 3 year) in postmenopausal women with breast cancer previously treated with 2–3 years of tamoxifen. This planned side-study assessed patterns of care regarding detection and treatment of osteopenia/osteoporosis, and trends in bone mineral density (BMD) during and after therapy. We registered all BMD measurements and bisphosphonate-use. Time to osteopenia/osteoporosis was analysed by Kaplan Meier methodology. For the trend in *T*-scores we used linear mixed models with random patients effects. Of 1860 eligible DATA patients, 910 (48.9%) had a baseline BMD measurement. Among patients with a normal baseline BMD (n = 417), osteopenia was observed in 53.5% and 55.4% in the 6- and 3-year group respectively ($p = 0.18$), during follow-up. Only two patients (3-year group) developed osteoporosis. Of the patients with osteopenia at baseline (n = 408), 24.4% and 20.4% developed osteoporosis respectively ($p = 0.89$). Three years after randomisation 18.3% and 18.2% used bisphosphonates in the 6- and 3-year groups respectively and 6 years after randomisation this was 23.7% and 20.9% respectively ($p = 0.90$) of which the majority used oral bisphosphonates. The yearly mean BMD-change during anastrozole in the lumbar spine showed a *T*-score decline of 0.075. After bisphosphonate addition the decline became less prominent (0.047 ($p < 0.001$)) and after anastrozole cessation, while continuing bisphosphonates, the mean BMD yearly increased (0.047 ($p < 0.001$)). In conclusion, extended anastrozole therapy was not associated with a higher incidence of osteoporosis. Anastrozole-use was associated with a BMD decrease; however, the decline was modest and partially reversible after anastrozole cessation.

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What's new?

Loss of bone mineral density (BMD) is a side effect of aromatase inhibitor treatment, a class of drugs that stops estrogen production in postmenopausal women with breast cancer. Here the authors examined BMD loss during and after extended adjuvant endocrine therapy, following a 2-3 year treatment with tamoxifen, subsequent aromatase inhibitor treatment was associated with BMD decrease, but the decline was modest and partially reversible after treatment cessation. The authors concluded that extended endocrine therapy was not associated with a higher incidence of osteoporosis.

Introduction

Osteoporosis is estimated to affect 200 million women worldwide and the proportion of osteoporosis increases with advancing age - approximately in 3.3% for age 45–49, 6.4% for age 50–54, 13.5% for age 55–59, up to 50.3% in the highest age group of 85 years and above.[1] In both Europe and the United States, 30% of women have osteoporosis, and at the age of 50 roughly 40% of post-menopausal women will experience an osteoporotic fracture during their remaining life.[2,3]

A reduction of the bone mineral density (BMD) is a well-known side effect of aromatase inhibitors (AI), which is of substantial clinical concern in early breast cancer patients for whom endocrine therapy is indicated, because they survive for many years after treatment. As these women age, any early decrease in BMD puts them at a clear disadvantage with an increased fracture risk. In general, a 10–12% loss in BMD can be compared to a 1 point drop in T-score, and an increase of the fracture risk by 2.6 times.[4] Hence maintenance of BMD during endocrine therapy is important. Currently, very few data are available on how the BMD develops during and after cessation of (extended) endocrine therapy with aromatase inhibitors.[5,6] The DATA study investigated the efficacy of 6 *vs.* 3 years of adjuvant anastrozole after a prior treatment with 2–3 years of tamoxifen in postmenopausal women with hormone receptor positive early breast cancer.[7] We pre-planned a side study to evaluate patterns of care considering bone health in these women, and the trend of BMD over time during and after cessation of anastrozole treatment. These research questions are addressed in the current report.

Methods

Study design

The DATA study (NCT00301457) is a prospective randomised phase III study in which postmenopausal women with early breast cancer were assigned to different durations of anastrozole therapy (6 *vs.* 3 years) after 2 to 3 years of tamoxifen as adjuvant endocrine therapy.[7] The study included a total of 1860 eligible postmenopausal women from June 2006 till August 2009. The protocol of the bone-health side study was approved by the Medical Ethical Committee of the Radboud University Nijmegen at November 22, 2009.

Guidelines and definitions

In the DATA study it was advised to adhere to (inter)national guidelines on the management of bone health, including lifestyle recommendations. In 2008 the Dutch guidelines on osteoporosis were updated, with more stringent recommendations on BMD evaluations and (prophylactic) treatment with calcium, vitamin D, and lifestyle advices on smoking, alcohol, and exercise. In 2012 the guideline recommended evaluating BMD every 2 years and starting bisphosphonates from a T-score of −2.0 instead of −2.5. BMD measurements were done by dual-energy X-ray absorptiometry (DEXA) scans of the lumbar spine and/or total hip. The BMD was considered normal when the measurement was less than 1 standard deviation (SD) below the average value for young healthy women (T-score >−1), osteopenia when the BMD was between 1 and 2.5 SD below the average (T-score between −1 and −2.5), and osteoporosis when the BMD was more than 2.5 SD below the average (T-score <−2.5).[8] Only DEXA scans before appearance of a distant recurrence were analysed.

Data collection

Data on bone health issues were collected by local data managers in the 79 participating hospitals in the Netherlands, partly retrospectively and partly prospectively from 2 years before until 7 years after randomisation irrespective of treatment arm. We registered the absolute BMD measurements and the T score for both the total hip and lumbar spine. Patient records were checked for the presence of risk factors of reduced BMD at study entry. In addition, the use of calcium, vitamin D supplements, and bisphosphonates was collected. Finally, the date of bone fractures was registered.

Study objectives

The primary study objective was to assess patterns of care regarding prevention, detection and treatment of osteoporosis in postmenopausal breast cancer patients without distant recurrences who were treated with adjuvant anastrozole after prior tamoxifen. Therefore, we evaluated the frequency of BMD assessments, the follow-up assessments of BMD depending on the result of the baseline scan, and the prescription of bone protective medication, all related to the duration of endocrine treatment (6 *vs.* 3 years anastrozole). Moreover, we analysed the linear trend of the BMD measurements over time during and after anastrozole therapy and the effect of bone protective medication, and the number of fractures.

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Statistical analyses

Figure S1 shows the patient selection for the performed analyses. The time from randomisation to first or second DEXA scan and the time period to the prescription of bisphosphonates were analysed by the Kaplan Meier method, considering distant recurrences or death a competing risk. The time periods were censored at the date of last follow-up. The baseline DEXA scan was defined as the last scan in the period between 2 years before, and 1 year after randomisation. If the event of interest (first DEXA scan, start bisphosphonates) occurred before randomisation, it was set at day 1 after randomisation. For the analysis on the time to first DEXA scan, the first scan reported could be a baseline scan or performed later on. The number of scans in the 6- and 3-year arm were compared to the Wilcoxon rank sum test.

Diagnosis of osteopenia and osteoporosis was based on the lowest *T*-score available in either the hip or the lumbar spine. Time to osteopenia or osteoporosis was censored at the last

Table 1. Baseline characteristics of all eligible randomised patients in the DATA study comparing 3 and 6 years of anastrozole after 2 to 3 years of tamoxifen (n = 1,860)

	Total group	6 years anastrozole	3 years anastrozole
	n = 1,860 (%)	n = 931 (%)	n = 929 (%)
Age (years) (median (IQR))		58.1 (51.9; 64.8)	57.8 (51.5; 64.6)
‹60 n (%)	1,063 (57.2)	531 (57.0)	532 (57.3)
≥60 n (%)	797 (42.8)	400 (43.0)	397 (42.7)
Duration of post menopause at randomisation (years) n (%)			
‹5	805 (43.3)	392 (42.1)	413 (44.5)
5–10	242 (13.0)	116 (12.5)	126 (13.6)
10–20	345 (18.5)	181 (19.4)	164 (17.7)
›20	331 (17.8)	164 (17.6)	167 (18.0)
Unknown	137 (7.4)	78 (8.4)	59 (6.4)
BMI (kg/m^2) n (%)			
≤24.9	689 (37.0)	345 (37.1)	344 (37.0)
25.0–29.9	712 (38.3)	368 (39.5)	344 (37.0)
30.0–34.9	298 (16.0)	142 (15.3)	156 (16.8)
≥35.0	93 (5.0)	48 (5.2)	45 (4.8)
Unknown	68 (3.7)	28 (3.0)	40 (4.3)
Smoking n (%)			
Current/previous smoker	943 (50.7)	465 (50.0)	478 (51.5)
Prior (neo) adjuvant chemotherapy n (%)			
Yes	1,259 (67.7)	628 (67.5)	631 (67.9)
Prior Tamoxifen duration (years) n (%)			
≤2.5	1,344 (72.3)	677 (72.7)	667 (71.8)
›2.5	516 (27.7)	254 (27.3)	262 (28.2)
History of bone fractures at baseline (%)[1]			
Yes	106 (5.7)	65 (7.0)	41 (4.4)
Baseline BMD measurement (n (%))[1]			
Not done	950 (51.1)	470 (50.5)	480 (51.7)
Done	910 (48.9)	461 (49.5)	449 (48.3)
Normal	417 (45.8)	201 (43.6)	216 (48.1)
Osteopenia	408 (44.8)	216 (46.9)	192 (42.8)
Osteoporosis	85 (9.3)	44 (9.5)	41 (9.1)
Actual treatment at baseline[1]			
Vitamin D and/or Calcium (%)			
Yes	445 (23.9)	241 (25.9)	204 (22.0)
Bisphosphonates			
Yes	168 (9.0)	89 (9.6)	79 (8.5)

BMI: Body Mass Index, BMD: Bone Mineral Density.
[1]Baseline was considered −2 years before randomisation until 1 year after randomisation.

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DEXA scan available for the patient when osteopenia or osteoporosis was not detected.

For assessing the effect of anastrozole on BMD we used a linear mixed model for the T-score, separately analysed for the hip and the lumbar spine. Dependency of measurements within the same patient was modelled by a random factor for patient. The time from anastrozole start to BMD measurement was included as a continuous covariate with a linear time effect that changed after stopping anastrozole. In addition, the linear effect of the time since start of bisphosphonate was incorporated in the model. Residual plots were used to verify the model assumptions of homogeneity and normally distributed errors.

For each year of follow-up, the annual fracture rate was calculated for patients being distant recurrence free and plotted at the midpoint of the interval. Multiple fractures could be reported in a single patient. A univariate Cox regression analysis was used to identify risk factors for developing fractures. The 6- and 3-year treatment groups were compared for the incidence of fractures starting after 3 years of anastrozole treatment because until that time both groups received the same treatment by using the log-rank test. All reported p-values are two-sided and a p-value ≤ 0.05 was considered statistically significant. All analyses were performed using SAS version 9.2.

Results

Patients

In the DATA study, 1860 patients were considered eligible. At randomisation, the median age was 58.1 years (interquartile range (IQR) 51.9–64.8) in the 6-year arm and 57.8 years (IQR 51.5–64.6) in the 3-year arm. Of these patients, 67.7% had received (neo-) adjuvant chemotherapy, and 32.5% of patients had node-negative disease. All patients had hormone receptor positive disease and 2.6% HER2 positive disease. Table 1 shows the risk profile and prior history regarding BMD. The baseline characteristics were well balanced.

BMD assessments

During 7 years of follow-up, the BMD was measured in 730 patients (78.0%) in the 6-year and in 650 (69.6%) in the 3-year arm (Fig. 1a). More measurements were performed in
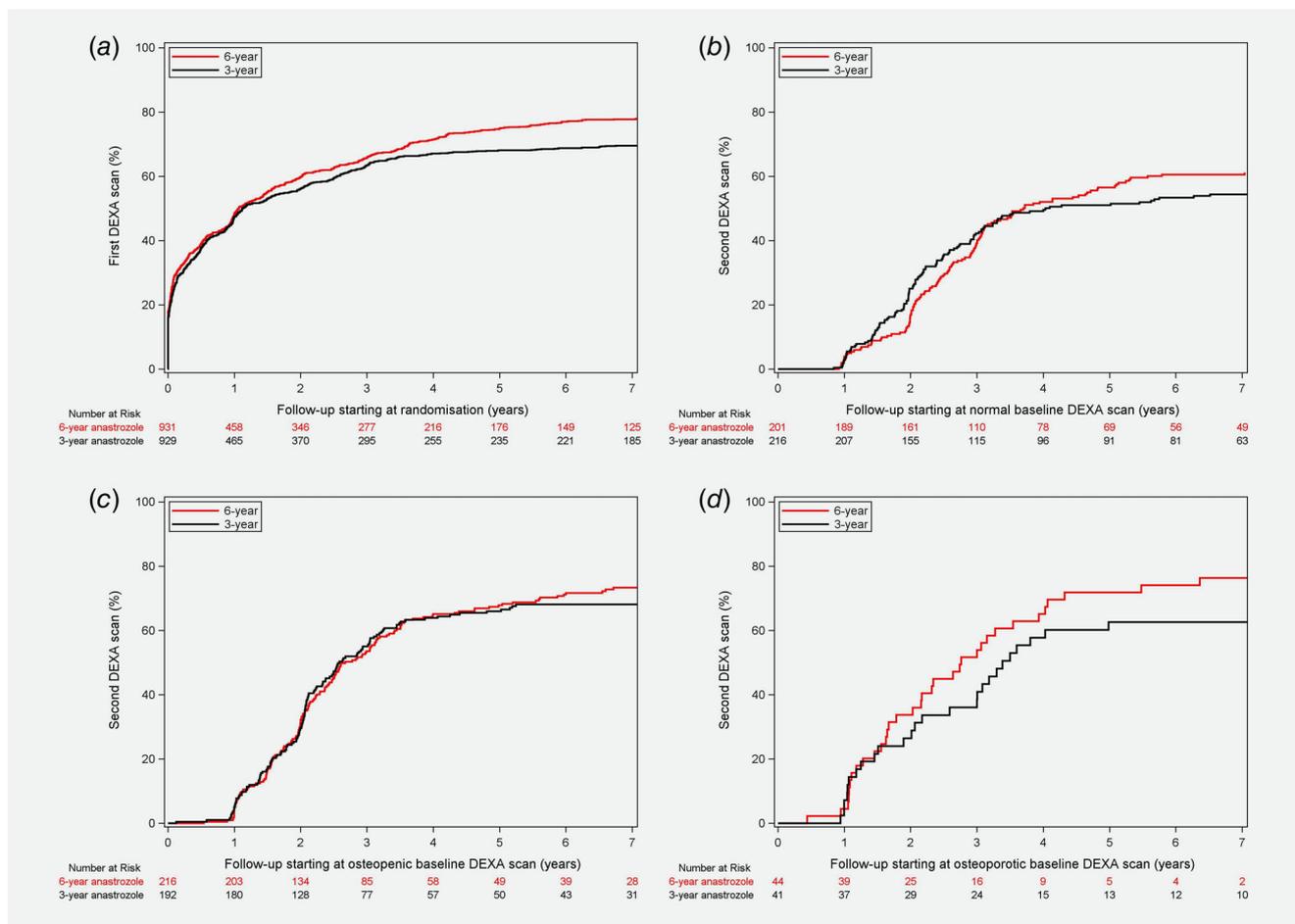

Figure 1. (a) Time to first DEXA scan, related to duration of Anastrozole therapy (3 vs. 6 years). Time to the second DEXA scan if the baseline scan showed a (b) normal BMD (c) osteopenia (d) osteoporosis. Overall, 30.2% of the patients had one BMD measurement, 20.3% had two measurements, 13.7% had three measurements, 10.0% had four or more measurements, and in 25.8% of the patients no BMD measurement was performed in the period from 2 years before randomisation until 7 years after randomisation.

the 6-year treatment arm in comparison with the 3-year arm ($p < 0.001$). The baseline characteristics of the patients with a BMD measurement (n = 1,380) were comparable to the total study population (n = 1,860; Table S1).

Follow-up assessments BMD after baseline scan

Overall, 910 (48.9%) patients had a baseline BMD measurement, which indicated a normal BMD in 417 (45.8%) patients, osteopenia in 408 (44.8%), and osteoporosis in 85 (9.3%). At sixth year, after the baseline scan, a second DEXA scan was performed in 60.6% of the patients in the 6-year and 54.4% in the 3-year group if the baseline scan was normal (Fig. 1b), and in 73.3% and 68.1% respectively if the baseline scan showed osteopenia (Fig. 1c), and in respectively 76.4% and 62.6% if the baseline scan showed osteoporosis (Fig. 1d).

If the baseline measurement showed a normal BMD, osteopenia was observed in the following 6 years in 53.5% of patients in the 6-year group and in 55.4% of the 3-year group ($p = 0.18$),

while osteoporosis developed in only two patients in the 3-year arm (Figs. 2a–2b). If the baseline measurements showed osteopenia, 24.4% developed osteoporosis in the 6-year group and 20.4% in the 3-year group ($p = 0.89$) within 6 years after baseline measurement (Fig. 2c).

Of the 1,380 patients with at least one DEXA scan, 59.4% in the 6-year arm *vs.* 67.4% in the 3-year arm had either osteopenia or osteoporosis at 3 years after randomisation. Six years after randomisation these percentages were 84.9% and 86.3% for the 6- and 3-year arm respectively ($p = 0.08$). Osteoporosis was diagnosed in 12.9% *vs.* 15.5% at 3 years after randomisation and 25.1% *vs.* 27.4% 6 years after randomisation in the 6- and 3-year groups respectively ($p = 0.24$).

Prescription of bone protective medication

Three years after randomisation 18.3% and 18.2% used bisphosphonates in the 6- and 3-year groups respectively and 6 years after randomisation this was 23.7% and 20.9% respectively
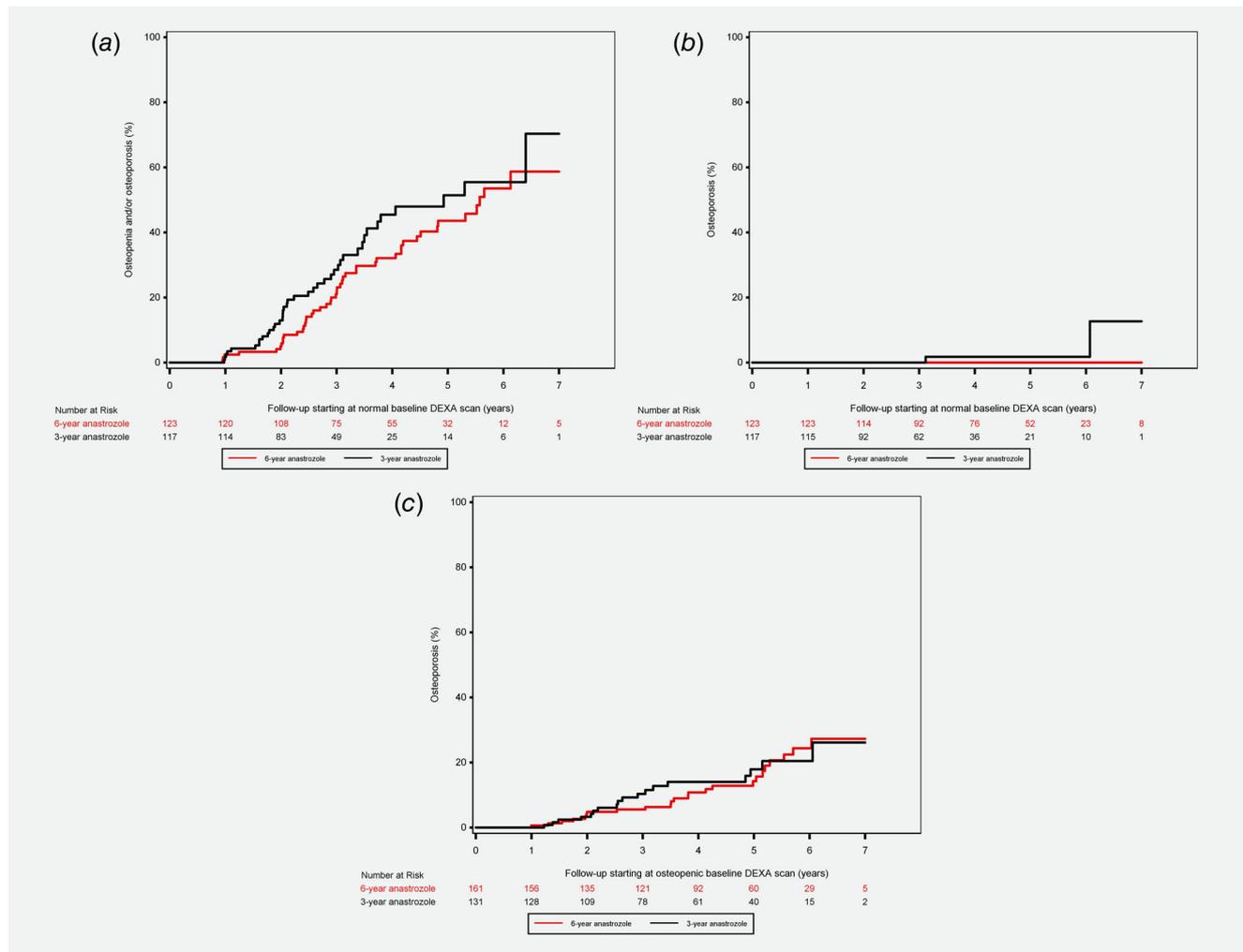

Figure 2. (*a*) Time to the development of osteopenia or osteoporosis if the DEXA scan at baseline showed a normal BMD. (*b*) Time to the development of osteoporosis if the DEXA scan at baseline showed a normal BMD. (*c*) Time to the development of osteoporosis if the DEXA scan at baseline showed osteopenia. At the beginning the lines remain horizontal because of the time interval between the baseline scan and the second scan. The scan performed within 1 year after randomisation was by definition the baseline scan.

(p = 0.90). Of the patients in whom bisphosphonates were prescribed, the majority used oral bisphosphonates (59.3% alendronate, 27.0% risedronate, 0.6% clodronate, 6.6% ibandronate) and few used intravenous bisphosphonates (3.2% pamidronate, 2.7% zoledronate). Only 0.6% received denosumab.

BMD outcome

The annual change of the mean T-score in the hip and the lumbar spine is shown for the average patient not treated with bisphosphonates (Fig. 3a) and the average patient treated with bisphosphonates (Fig. 3b).

Fractures

The annual incidence of fractures per treatment arm as of randomisation is shown in Figure 4. Fractures, as of 3 years after randomization, occurred in 67 (7.9%) and 52 (6.1%) patients in the 6- and 3-year treatment arms, respectively (p = 0.85). We identified age above 60 years, a decreased BMD at baseline (osteopenia/osteoporosis), previous fractures, and a family history for osteoporosis as risk factors for experiencing fractures.

Discussion

In this planned side-study of the phase III DATA study investigating the efficacy of 6 vs. 3 years of adjuvant anastrozole after 2–3 year of tamoxifen in postmenopausal women with breast cancer we assessed patterns of care regarding detection and treatment of osteopenia/osteoporosis and linear trends over time in BMD both during and after anastrozole therapy. Only 48.9% of all eligible patients had a baseline BMD measurement. It showed osteopenia in 44.4% and osteoporosis in 9.3% of them which is comparable with the general population.[9] Although subsequent anastrozole use was associated with a BMD decrease, in patients with a normal baseline BMD only two patients in the 3-year arm developed osteoporosis, none in the 6-year arm. The BMD decline was seen regardless of assigned treatment arm. Of the patients with osteopenia at baseline, about a fifth developed subsequent osteoporosis. Interestingly, the average yearly absolute decrease in mean T-score during anastrozole therapy seemed rather limited (−0.075 in the lumbar spine, −0.079 in the hip; ~1%). Bisphosphonate use partially compensated this effect in the lumbar spine, but not in the hip. After cessation of anastrozole and continuation of bisphosphonates, the T-score stabilised in the hip, whereas it actually increased in the lumbar spine. The fracture rate was quite low and during the 6-year observation period not related to the assigned anastrozole treatment duration.

Healthy women experiencing natural menopause undergo an accelerated, transient phase of bone loss of ~3% per year during the first 1–2 years, slowing to ~1% annually thereafter.[10] AI-associated bone loss occurs at approximately twice the rate of physiologic postmenopausal bone loss at an average of ~2% per
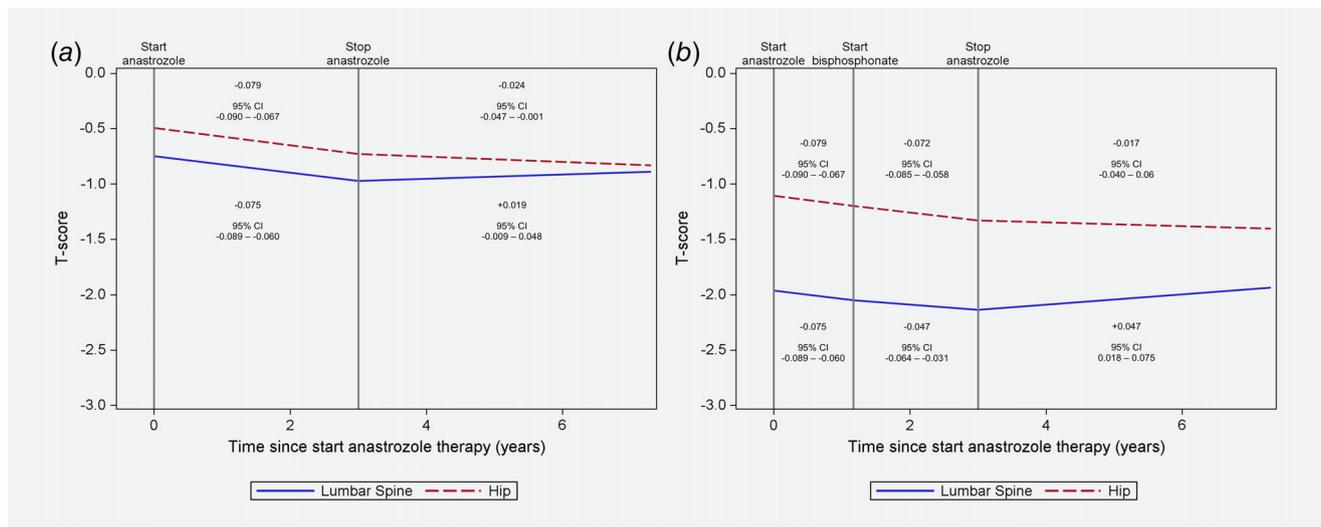

Figure 3. The annual change in mean T-score showing the effects of anastrozole and bisphosphonates on the hip and lumbar spine (a) in patients not receiving bisphosphonates, (b) in patients in whom bisphosphonates were started during the use of anastrozole. This figure shows the trend of the mean BMD in T-score for an average patient. In the linear mixed models with random effects, the development of the BMD in the hip during anastrozole use over time showed a decrease of the mean T-score of −0.079 (95% CI −0.090 to −0.067). When anastrozole was stopped the yearly decline was −0.024 (95% CI −0.47 to −0.001), which was a statistically significant change (p < 0.001) (a). During anastrozole-use, the prescription of bisphosphonates failed to stop the decrease of the mean T-score (yearly decrease of −0.072 (95% CI −0.085 to −0.058)) (p-value for change = 0.21). When anastrozole was stopped and bisphosphonates were continued the T-score stabilised (yearly decrease of −0.017 (95% CI −0.040 to 0.006)) which was a statistically significant change (p < 0.001) (b). The development of the BMD in the lumbar spine during AI use over time showed a yearly decrease of the mean T-score of −0.075 (95% CI −0.089 to −0.060). When anastrozole was stopped, the T-score stabilised to a yearly change of 0.019 (95% CI −0.009 to 0.048), which was a statistically significant change (p < 0.001) (a). During anastrozole-use, the prescription of bisphosphonates resulted in a less steep decline of −0.047 (95% CI −0.064 to −0.031) per year (p-value for change <0.001), and when the AI was stopped the T-score increased yearly with 0.047 (95% CI 0.018–0.075) (p-value for change <0.001) (b).
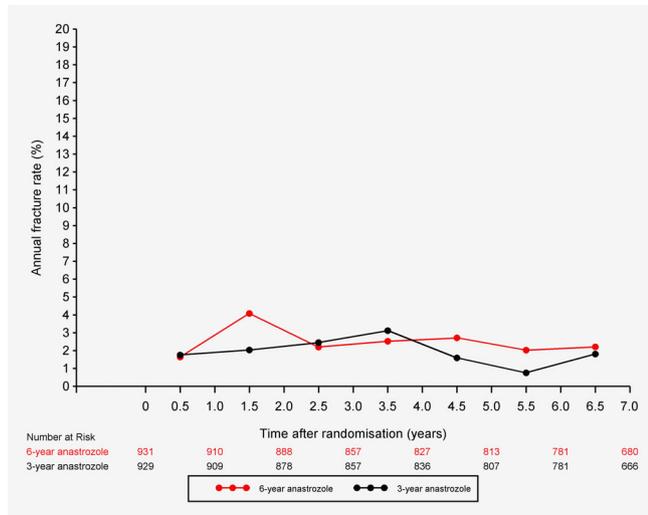
Figure 4. Annual fracture rate for the patients in the 6- *vs.* 3-year anastrozole treatment group. The total number of fractures during the 7 years after randomisation was 217 (n = 118 in the 6-year group and n = 99 in the 3-year group). Patients could have multiple fractures.

year which continues throughout the duration of therapy.[11,12] The extent of AI-associated bone loss was studied in several trials. The ATAC trial found significant BMD reductions in patients during 5 years of anastrozole treatment: −6.1% at lumbar spine and −7.2% at the hip.[12,13] Treatment with letrozole resulted in comparable bone loss in the MA.17 trial: at 24 months showing a significant additional decrease in total hip BMD (−3.6% *vs.* −0.7%; $p = 0.044$) and lumbar spine BMD (−5.4% *vs.* 0.7%; $p = 0.008$).[14] Also the ZO-FAST trial showed a median loss in lumbar spine BMD of −5.4% after 5 years of letrozole treatment without bisphosphonate use ($p < 0.0001$).[15] Decrease in BMD was apparently lower in patients treated with exemestane in the Intergroup Exemestane Study (IES), possibly related to its steroidal structure: −1.0% (lumbar spine) and −0.8% (total hip) at 24 months.[16] In our study, we also observed a decline of ~1% per year.

Moreover, it is important to realise that premenopausal women, who experience chemotherapy-induced ovarian function failure and receive ovarian suppression, pass through a much more distinct decrease in BMD within a short period of time (up to −7.7% in the first year).[17,18] The effect of ovarian suppression in combination with AIs is even worse, with reports of up to −17.3% BMD loss within 3 years compared to baseline ($p < 0.0001$).[5,17,19]

Hence, several prospective randomised studies observed negative consequences of AI-therapy on BMD in pre- and postmenopausal women. However, only few data are available on how BMD changes after adjuvant endocrine therapy is ended. In the ABCSG-12 trial, patients receiving endocrine therapy alone (i.e., goserelin plus tamoxifen or anastrozole) had a partial BMD recovery 2 years after completing therapy, but their BMD remained significantly lower than baseline BMD (mean for lumbar spine −6.3%, $p = 0.001$).[5] The ATAC trial also

showed a recovery at 2 years after completion of anastrozole treatment (+4.0% at the lumbar spine and +0.5% at the hip).[6] Our study is the first trial to specifically investigate bone health during and after extended AI therapy after initial tamoxifen treatment. Even though approximately half of the women with a normal BMD developed osteopenia, we showed no clinically relevant differences in the occurrence of osteopenia, osteoporosis, or fractures between 6 and 3 years of anastrozole treatment. Therefore for women with a normal BMD at the start of AI therapy being postmenopausal at breast cancer diagnosis, the time interval between DEXA scans can be longer than the 2 year currently advised in (inter)national guidelines.[20]

Moreover, we showed that after the start of anastrozole the yearly decrease in absolute *T*-score was −0.079 and −0.075 in the hip and lumbar spine respectively (absolute decrease of ~0.23 in *T*-score over a 3-year treatment and ~0.45 over a 6-year treatment), which was partially compensated if bisphosphonates were prescribed. Consequently, we consider a decreased BMD not as a major reason for disregarding extended endocrine therapy. Several trials demonstrated that treatment-induced bone loss could be successfully prevented if bisphosphonates were started immediately at the initiation of endocrine therapy not depending on actual BMD.[5,15,21,22] Yet, it remains unknown whether upfront use of bisphosphonates also reduces the incidence of fractures. More recently, denosumab was shown to increase BMD and reduce fractures into a great extent.[23] However, discontinuation of denosumab in patients with osteoporosis or vertebral fractures is associated with a strong decrease in BMD, exceeding the initial increase in BMD shown over a period of 7–10 years, and an increased risk of vertebral fractures.[24–26] Therefore, denosumab should not be stopped in these patients without considering alternative treatment.

When we compared the fracture rates of our study (6.1–7.9%) with those of the ABCSG-18 trial, the NSABP B42, and the IDEAL trial, all concerning postmenopausal breast cancer patients receiving aromatase inhibitor treatment, these were comparable.[23,27,28] Only the fracture rate in the placebo arm from the ABCSG-18 trial had a higher incidence of fractures (9.6%). We believe this is possibly due to the fact that these patients were not allowed to receive bisphosphonates which is in contrast with both treatment arms in the DATA trial.

In our study, we identified an age above 60 years, osteopenia or osteoporosis at baseline, a history of fractures, and a family history of osteoporosis as risk factors for experiencing fractures during and after adjuvant anastrozole therapy. These risk factors match with the factors implemented in the WHO fracture risk assessment tool (FRAX®; http://www.sheffield.ac.uk/FRAX/).[29] Therefore we suggest that the management of bone health during adjuvant endocrine therapy should be based on the baseline BMD measurement and the presence of risk factors for developing fractures according to FRAX®.

In our study anastrozole therapy was started after 2–3 years of tamoxifen, which is known to counteract BMD loss and decreases

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bone fracture rate in postmenopausal women.[30] Therefore it can be questioned into which extend our results are influenced by the positive effect of tamoxifen on bone health. A sub-study of the BIG 1–98 trial, comparing four 5-year regimens of endocrine therapy, looked at the effect of each regimen on BMD.[31] They found that the sequenced treatment of tamoxifen followed by letrozole had the worst effect on BMD and that letrozole followed by tamoxifen appeared to preserve BMD. They hypothesized that the interruption of tamoxifen combined with the rapid fall in oestrogen levels induced by letrozole promotes an accelerated bone turnover and loss of BMD following the switch as was confirmed by bone turnover biomarkers.[31]

Limitations

Our study has several limitations. The evaluation of BMD was not standardised but left at the discretion of the treating physician. The reason not to perform a DEXA scan at baseline in more than half of the women and no DEXA scan at all in a quarter of the patients is unknown. Moreover, the DEXA scans were not standardised since patients were treated in different hospitals. Selection based on patient characteristics (e.g. fractures, and familial osteoporosis) could not be ruled out. In our study, we report on the linear change of BMD over time during the use of anastrozole with or without bisphosphonates. In our model we could not evaluate if the BMD decrease over time was more profound in the early years of menopause and/or directly after the start of anastrozole because the minimum interval between DEXA scans was 1 year and scans were not performed at set times.

Conclusion

This is one of the first studies reporting on bone health during and after extended endocrine therapy. We conclude from our study, that although subsequent anastrozole use was associated with a BMD decrease, extended endocrine therapy was not associated with a higher incidence of osteoporosis or fractures. Nowadays, an increasing number of postmenopausal women are treated with bisphosphonates in the adjuvant setting, which also showed to compensate the negative effect of AIs on BMD. Therefore, with the availability of bisphosphonates, we believe bone health should not be a major argument in disregarding extended endocrine therapy.

Disclosure statement

IEGvH, SCL and ACPS report grants from AstraZeneca during the conduct of the study. MdB reports research grants from Roche, Eisai, Novartis, Pfizer, and Lily during the conduct of the study; and consultation/speakers fee from Roche, Novartis, and Pfizer. SCL reports research grants from AstraZeneca, Genentech, Roche and Tesaro; and advisory board membership of AstraZeneca, Cergentis, IBM and Philip Health BV. VCGT-H reports grants to the institute for research from AstraZeneca, Roche, Novartis, Pfizer, Eisai, Lilly during the conduct of the study; Honoraria/travel grants from Roche, Novartis, Pfizer, Lily, and Accord Healthcare. All other authors declare no competing interests.

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