Bone Reports 16 (2022) 101160

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Adherence to bone health guidelines in patients with hormone receptor-positive early breast cancer: Status and clinical impact in a Swiss cohort experience

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ARTICLE INFO

Keywords:
Osteoporosis
Aromatase inhibitor
Breast cancer
Postmenopause
Bone targeted therapies
Denosumab
Bisphosphonates
Calcium
Vitamin D
Public health
Oncology

ABSTRACT

Aim: In patients with postmenopausal hormone receptor-positive breast cancer (ER + eBC), aromatase inhibitors (AIs) are widely used for effective relapse prevention. However, AIs reduce bone density and increase bone-related events (BREs). Alongside calcium and vitamin D3 supplementation, bisphosphonates and denosumab are well-known options for improving outcomes in bone health and breast cancer prognosis. This study aimed to evaluate the practice patterns of bone health guideline-based management in real-world patients with ER + eBC.
Material and methods: In total, 68 patients with ER + eBC treated between 2009 and 2014 at the University Hospital Basel were included in this retrospective cohort study. Chart reviews were analyzed. Baseline, clinicopathological, treatment, and BRE data were extracted. Each patient was specifically reviewed for therapy adherence to the Swiss bone health guidelines (Swiss Association against Osteoporosis 2010 [SVGO]).
Results: The mean patient age was 66.5 (range, 56–74) years, all post-menopausal. The most frequent tumor characteristics were tumor size of pT1–pT2 (N = 53, 77.9%) and treatment with letrozole (N = 35, 51.5%), followed by tamoxifen as a switch strategy (N = 27, 40.3%). The median treatment time with AIs was 47 (range, 30–60) months. Five patients (7.8%) experienced a fracture during or after AI treatment. Moreover, 51 (75%) patients were treated according to the SVGO recommendations.
Conclusion: The fracture rate in our retrospective cohort was comparable to that in the larger phase III randomized trials. The adherence to bone health guidelines was satisfactory but still suboptimal. Clinicians should strictly adhere to the current bone health guidelines to ensure the best possible prevention of BREs and maintain bone health and cancer prognosis in patients with ER + eBC.

1. Introduction

Breast cancer is the most common cancer among women worldwide. Switzerland reports approximately 6250 new cases of breast cancer annually, accounting for 32.5% of all newly diagnosed cancers (Schweiz Krebsliga, 2016). Over the last decades, the prognosis of breast cancer has markedly improved due to early detection, better diagnostic tools, surgical interventions, radio- and systemic therapy approaches, and systemic follow-up of breast cancer survivors. More recently, bone health has become an important cornerstone of adjuvant treatment for

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https://doi.org/10.1016/j.bonr.2021.101160
Received 19 September 2021; Received in revised form 8 December 2021; Accepted 8 December 2021
Available online 11 December 2021

early breast cancer (Onishi et al., 2010; Salmen et al., 2015).

In postmenopausal women with hormone receptor-positive breast cancer, anti-estrogen therapy with tamoxifen or aromatase inhibitors (AIs) is the standard of care, with AIs being superior to tamoxifen with regard to disease-free survival (DFS), as shown, for example, in the BIG-98 study with a cohort of over 8010 patients with letrozole being associated with a significant improvement in DFS, overall survival (OS), and time to recurrence compared to tamoxifen (Thurlimann et al., 2005; Brufsky et al., 2007; Ruhstaller et al., 2019). Since the disease-related benefits of AIs outweigh their adverse effects, they are commonly present in the therapy course in postmenopausal patients with receptor-positive breast cancer (Regan et al., 2011; Jones et al., 2008; Coleman et al., 2010; Reid et al., 2008; Ellis et al., 2009; Kilbreath et al., 2011). The results of the ZO-FAST study comprising 1064 postmenopausal patients with breast cancer receiving AI therapy have shown that the addition of zoledronic acid at the start of AI therapy improves bone density (Coleman et al., 2013).

However, the toxicity profile of AIs is complex and needs to be addressed in each patient requiring AIs. The most common side effects of AIs are bone density loss and musculoskeletal pain. Gnant et al. showed that an overall bone loss that was significantly more severe in patients receiving anastrozole/goserelin (BMD, 17.3%; mean T score reduction, 2.6) compared with patients receiving tamoxifen/goserelin (BMD, 11.6%; mean T score reduction, −1.1) (Gnant et al., 2007). Thus, it is important to consider concomitant bisphosphonate therapy for patients undergoing endocrine therapy, individually, in order to prevent severe bone density loss. The etiology of AIs is related to the role of estrogen in bone metabolism, which has been extensively described (Sambrook and Cooper, 2006).AIs inhibit the aromatase gene (CYP19) found in the ovaries and peripheral tissues, such as fat, muscle, and bone. Thus, decreasing the estrogen level in the blood. Estrogen plays an important role in bone metabolism by inhibiting osteoclast progenitor cells and stimulating osteoblasts to produce osteoprotegerin. A lack of estrogen causes a local disturbance in the microclimate of the bone: osteoclasts are activated, and osteoblasts decrease the production of osteoprotegerin, causing RANK-L binding to RANK, activating osteoclasts, and increasing bone resorption (Kilbreath et al., 2011; Chien and Goss, 2006). Studies have shown that during the first 5 years of treatment, an average of 10% reduction in bone mass density (BMD) can be observed (Hadji et al., 2011). An even higher percentage of BMD loss is observed in patients treated with the combination of AIs and GnRH analogues. These detrimental effects were mostly additive. Bone-related events (BREs), especially fractures, significantly diminish a patient's quality of life. In large randomized controlled trials, AIs in early breast cancer have resulted in a fracture rate of approximately 2–8% (Jones et al., 2008; Coleman et al., 2010; Dhesy-thind and Centre, 2012; Tabane and Vorobiof, 2011; Rozenberg et al., 2009; Amir et al., 2010; Gralow et al., 2009). In contrast, in patients treated with tamoxifen, there was a lower rate of fractures, demonstrating the bone protective effects of this agent.

Therefore, the use of bone-protecting agents, including calcium, vitamin D, denosumab, and bisphosphonates, has been intensively studied in the last decade, and various oncological societies have provided concise guidelines addressing bone health in this specific population, strongly encouraging the use of these agents. In addition, the Swiss Association against Osteoporosis (SVGO) has developed guidelines for the monitoring and therapy of BMD loss, osteopenia, and osteoporosis. The SVGO guidelines 2010 recommend the treatment of all patients, including those with a diagnosis of breast cancer and with a T-score −2.5, according to the Fracture Risk Assessment Tool score or after an osteoporotic fracture. This includes (1) prescription of calcium and vitamin D3 (CaD3) for osteopenic patients with a T-score between −1 and −2.5, (2) prescription of CaD3 and denosumab or bisphosphonates for patients with a T-score −2.5 or lower, and (3) a regular dual-energy X-ray absorptiometry (DXA) scan every 2 years (Stute et al., 2014).

These guidelines were implemented at our center. Until 2014, the recommendation for patients with breast cancer under AIs was a prophylactic prescription of CaD3, independent of the T-score. After 2014, for all postmenopausal women, denosumab or bisphosphonates were used in the adjuvant setting, regardless of the T-score.

This study aimed to analyze real-world data from a large Swiss breast cancer cohort of patients with stage I–III hormone receptor-positive breast cancer. The primary objectives of the study were to determine the effects of different treatment modalities (chemotherapy, AIs, tamoxifen, and lifestyle factors) on BMD, to quantify the adherence to the SVGO guidelines for each patient with breast cancer, and to establish whether there is a positive correlation between adherence and positive outcomes: higher BMD and fewer BREs. The secondary objective was to determine if the endpoint BREs depends on the development of osteopenia and osteoporosis during AI therapy.

2. Materials and methods

2.1. Study design

A comprehensive retrospective analysis of all female patients with breast cancer who were de novo diagnosed with invasive stage I–III breast cancer between 2009 and 2014 was performed. The main inclusion criteria of the study were: adjuvant therapy with a daily intake of aromatase inhibitors such as letrozole, anastrozole, or exemestane (switch strategy to or from tamoxifen was allowed), two or more DEXA scans (at least one baseline scan), all breast cancer subtypes, UICC/AJCC Stages I-III, and all patients have undergone surgery for breast cancer. All patients were either first diagnosed or were referred as therapy-naive patients to our hospital and underwent subsequent treatments and follow-up at our institution. A comprehensive chart review was performed, including the interdisciplinary notes and archival documents of each patient. Thus, the relevant data originated both from the internal medical information system and paper charts. In addition to formal reports, detailed data and images of the DXA scan examinations were available from the internal electronic system of the Department of Radiology, University of Basel. The study was approved by the local ethics committee (Ethikkommission Nordwest-und Zentralschweiz Basel).

2.2. Bone mass density measurements with DXA scans

BMD was quantified with DXA using a Hologic Discovery (QDR Series) scanner. All patients included in the study underwent a pretreatment DXA scan and at least two (annual) follow-up scans. Overall, at least three measurements were noted: T1 at baseline (before AI treatment), at 24 (T2), and at 48 months (T3) after AI initiation. All values were calculated and documented as bone density (g/cm^3) and T- and Z-scores of the femoral neck, total hip, and lumbar spine (median of 2–4 for each examination, reference values as per internal standards).

2.3. Study population

Data from all recorded patients with breast cancer (N = 357) were screened by two independent team members. Any divergence was evaluated by a senior investigator. In addition to clinicopathological characteristics, specific risk factors for bone health were documented, including age, menopause status, early menopause, use of chemotherapy, tumor stage, family history, previous fractures, tobacco use, alcohol consumption, body mass index (BMI), and activity/inactivity status.

2.4. Adherence to SVGO guidelines

Hospital-based bone health guidelines for patients with early breast cancer in accordance with the adapted SVGO guidelines are summarized in Table 1. Each patient's treatment was verified for guideline adherence and compliance. The patient care was considered compliant to the SVGO

Table 1
The Swiss Association against Osteoporosis guidelines 2010.

1. Staying active
2. Prevention of falls (>70 years, annual risk assessment)
3. At least 1000-mg calcium and 800 IE vitamin D intake per day
4. 1-g protein per kg body weight
5. Sustained vertebral fracture ➔ medication
6. Sustained peripheral fracture ➔ FRAX assessment
7. T-score lower −2.5 ➔ medication
8. DXA scan after 2 years
9. Bone turnover markers 3–6 months after medication administration

(Adapted from Osteoporose Empfehlungen 2015, Schweizerische Vereinigung gegen die Osteoporose, 2019, https://www.svgo.ch/userfiles/downloads/SVGO%20Empfehlungen%202015.pdf.)

guidelines in Table 1, if 5 or more recommendations were met, as assessed retrospectively by the investigator. Each guideline was considered equally clinically impactful. Patients had regular follow-ups according to recent ESMO/NCCN guidelines: every 3 months in years 1–2, every 6 months in years 3–5, and every 12 months in years 6–10. During visits, all patients receiving AIs were encouraged to take regular vitamin D3 and calcium supplementation. Junior doctors/resident doctors supervised the senior oncologists. Accordingly, AI-treated patients were expected to receive calcium/vitamin D3 supplements, and patients with a hip T-score lower than −2.5 were expected to additionally receive bone-targeted therapies with bisphosphonates or denosumab.

2.5. Statistical analyses

Patient characteristics were summarized using descriptive statistics. Quantitative variables are presented as the mean and median values. Qualitative variables were expressed as frequencies and percentages. All statistical analyses were performed using R statistical software (version 3.1.1). For ordinal and metric variables, comparisons between subgroups were performed using Mann-Whitney *U* tests. For categorical variables, Fisher's exact test was performed. Statistical significance was considered at $p < 0.05$, and a p-value < 0.1 was considered as a trend.

2.6. Ethics

This study was approved by the Ethics Committee Nord-West-Schweiz, Basel (No. AGMA 2015/195). All data were collected and kept anonymously; the key to decipher and re-identify the patients was at the sole discretion of the principal investigator.

3. Results

In total, 68 patients were identified as eligible for inclusion in the study. Of a total of 357 patients with breast cancer diagnosed during the study period, 289 were excluded due to chronic rheumatic diseases, chronic use of corticosteroids, stage IV disease, or missing data, with no regular DXA scans or external DXA scans (Fig. 1).

3.1. Clinicopathological characteristics and DXA measurements

The mean age of the included patients was 66.5 (range, 56–74) years, all post-menopausal (natural). The majority of the patients had breast cancer stage pT1 (33/68, 49.3%) and pT2 (29/68, 43.3%), with node stage pN0 (30/68, 44.1%) or pN1 (23/68, 33.8%) (Table 2). In total, 46 (69.7%) patients underwent chemotherapy, and 55 (84.6%) underwent radiotherapy to the breast or local lymph nodes. The most common AIs were letrozole (35 [51.5%]), anastrozole (14 [20.6%]), and exemestane (4 [5.9%]). Moreover, 22% of the patients received multiple AIs due to intolerance. Furthermore, 40% of the patients had a switch with either TAM to AI or AI to TAM (Fig. 2A). The median times to tamoxifen

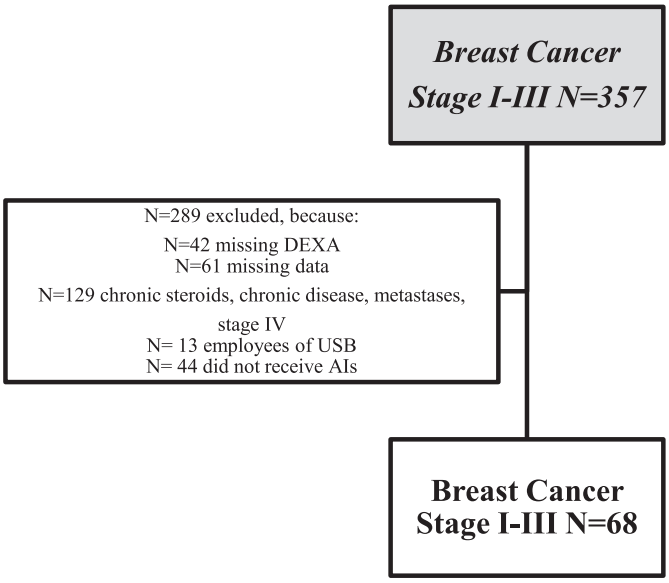

Fig. 1. Chart illustrating the eligibility assessment for the inclusion of patients in the study.

Table 2
Baseline clinicopathological characteristics of patients.

Number of patients	68
Age	
Median (years)	66.5
Range (years)	57–74.2
Stage at diagnosis	
pT1	33 (49.3%)
pT2	29 (43.3%)
pT3	2 (3%)
NA	3 (4.5%)
Node stage	
pN0	(30/68, 44.1%)
pN1	(23/68, 33.8%)
Chemotherapy	
Yes	46 (69.7%)
No	20 (30.3%)
Radiotherapy	
Yes	55 (84.6%)
No	10 (15.4%)
Used aromatase inhibitors	
Letrozole	35 (51.5%)
Exemestane	4 (5.9%)
Anastrozole	14 (20.6%)
Multiple	15 (22.1%)
Time on treatment	
Mean	47 months
Range	2–120 months

therapy were 28.5 (range, 2–114 months) months and 47 (range, 30–60) months with AIs (Fig. 2B). Fifteen women (23.1%) had a BMI of 20 kg/m^2 and below. At baseline, 44 (64.7%) patients had an osteopenia (T-score between −1.0 and −2.5), and 16 women were osteoporotic with a T-score below −2.5 (Fig. 2C). In the second DXA measurement, 59 patients remained stable, one osteopenic patient reached normalized BMD levels, and four osteoporotic patients became osteopenic. Two women progressed from osteopenia to osteoporosis (Fig. 2C).

3.2. Bone-related events

Five patients (7.81%) had fractures during or after treatment with AIs. One female patient was osteoporotic, and two patients had osteopenia in their first DXA examination. Their average T-score was lower (1.65, −2.65) than that of women with no fractures (−1, −1.65). Three

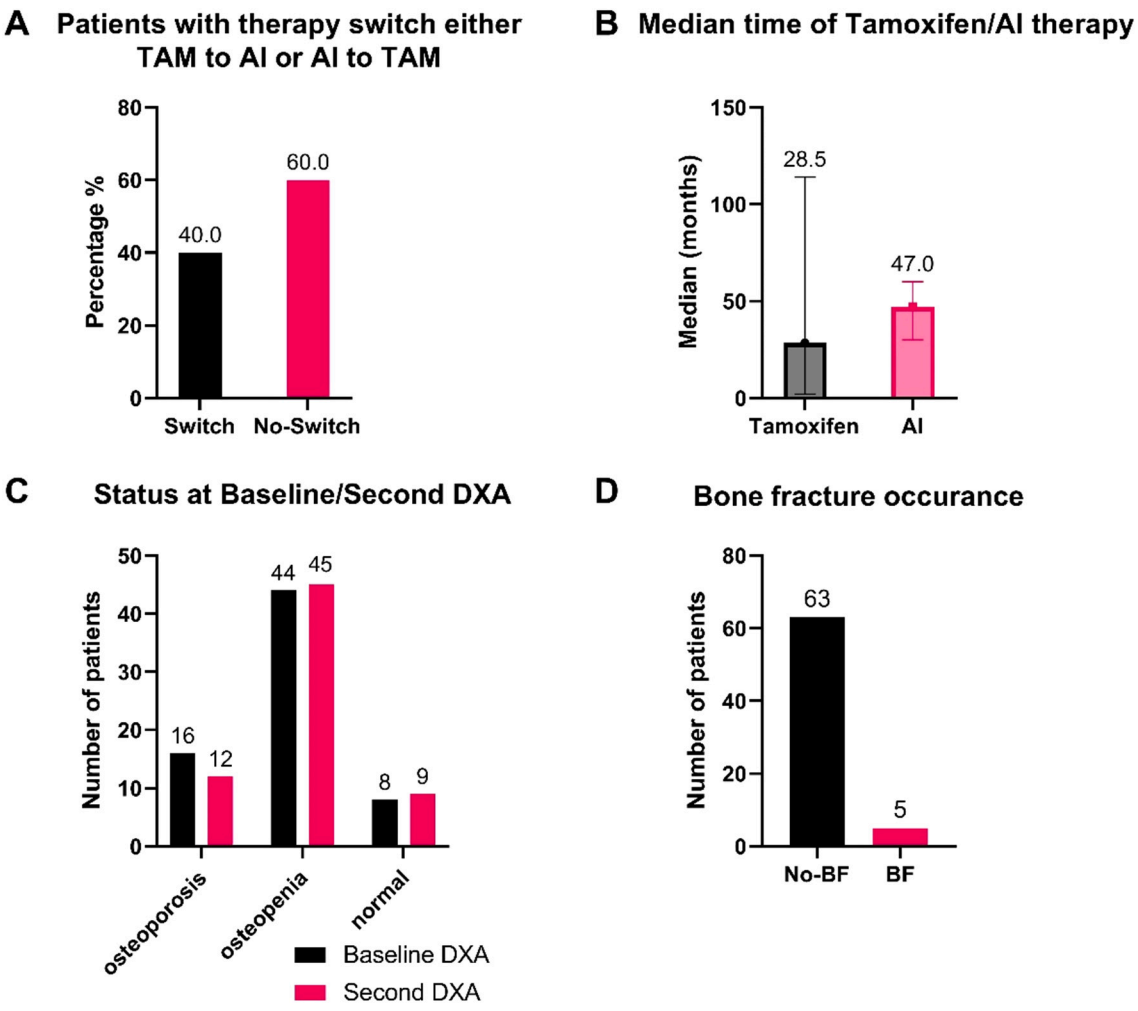

Fig. 2. A. 40% of the patients had a switch with either TAM AI or AI to TAM; B. the median times to tamoxifen therapy were 28.5 (range, 2–114 months) months and 47 (range, 30–60) months with AIs; C. distribution of baseline versus post-treatment T-scores (DXA) in the cohort of patients receiving aromatase inhibitor treatment. At baseline, 44 (64.7%) patients had an osteopenia (T-score between −1.0 and −2.5), and 16 women (23.5%) were osteoporotic with a T-score below −2.5. Eight patients (11.8%) had normal age-adopted t-score. In the second DEXA measurement, 59 patients remained stable, one osteopenic patient reached normalized BMD levels, and four osteoporotic patients became osteopenic. Two women progressed from osteopenia to osteoporosis; D. fracture rate in the complete cohort (in red). No-BF = no bone fractures (N = 63, 92.2%) (the mean T-score in this groups was −1.65), in the BF = bone fractures group (N = 5, 7.8%) (the mean T-score was −2.65). In this group, two of the five women (40%) were treated according to the Swiss Association against Osteoporosis guidelines. All patients received aromatase inhibitors.

of these five patients received tamoxifen for a mean of 25.7 (range, 11–36) months. Two out of five women (40%) with fractures were treated in accordance with the SVGO guidelines (Fig. 2D). Four out of five women experiencing a fracture were treated with letrozole, and the fifth patient received multiple AIs. As there was no evidence of trauma or breast cancer recurrence to bone in these patients, all 5 fractures were considered osteoporotic.

3.3. Adherence to the SVGO guidelines

Fifty-five (75%) women were treated according to the SVGO recommendations. Sixty women (87.9%) received adequate CaD3 supplementation.

Women receiving bisphosphonates showed a significant increase in delta T-score, whereas those not receiving bisphosphonates experienced a significant decline in delta T-score measured both in the spine (+0.25 [0.02, 0.06] vs. −0.1 [−0.4, 0.27], p = 0.017) and in the femur (+0.1 [0.00, 0.2] vs. femur −0.2 [−0.4, 0.0, p = 0.012]).

Women who received denosumab (13) showed a significant increase in T-scores of the femur of 0.2 ([0.0, 0.2] p = 0.046) and 0.2 ([−0.2, 0.6] p = 0.026) vs. 0.00 ([−0.35, 0.15]) and −0.2 ([−0.4, 0.00]). These women experienced a nonsignificant increase in delta T-scores in the spine (0.1 [−0.6, 0.5]) compared to those not receiving denosumab (−0.1 [−0.3, 0.25], p = 0.907).

Overall, there was no significant BMD loss in patients treated according to the SVGO 2010 guidelines (p = 0.094, 0.994). There was a strong trend and an almost statistical significance for women not treated according to the guidelines to experience a BMD loss (T-score reduced from −0.03 [−0.05, −0.01] vs. 0.00 [−0.03, 0.02], p = 0.058) (Table 3).

4. Discussion

Breast cancer is the most frequent type of neoplasm in women. Most patients are diagnosed with a hormone receptor-positive type (often after menopause). As a result, accompanied by improved OS, an increasing number of cancer survivors are treated with AIs. These agents, while contributing to a better prognosis (DFS and lower rate of recurrence), have a number of side effects.

International societies, including the SVGO, created concise guidelines to help leading physicians in bone health management of patients

Table 3
BMD increase/loss in patients with different treatments quantified by the T-score.

	T-score measured in the spine	T-score measured in the femur
Treatment		
Bisphosphonates		
Yes	+0.25 [0.02, 0.06]	+0.1 [0.00, 0.2]
No	−0.1 [−0.4, 0.27] p = 0.017	−0.2 [−0.4, 0.0] p = 0.012
Denosumab		
Yes (n = 13)	+0.1 [−0.6, 0.5]	+0.2 [0.0, 0.2]
No	−0.1 [−0.3, 0.25] p = 0.907	-0. 0[−0.35, 0.15] p = 0.046
Treatment according SVGO 2010		
Yes	−0.03 [−0.05, −0.01]	
No	0.00 [−0.03, 0.02], p = 0.058	

with breast cancer. Although several significantly recent studies have investigated the effects on adherence to guidelines in Germany, Croatia, and Saudi Arabia, such evidence was missing for Switzerland (Zekri and Farag, 2016; Link et al., 2019; Bošković et al., 2017). In general, there has been awareness about osteoporosis and complications in Switzerland for years. Thus, we performed a comprehensive retrospective analysis at a major Swiss university center.

We identified 357 patients with ER+ early breast cancer. A total of 68 patients (19%) who met all the inclusion criteria were included in the study. Eighty-one patients did not meet the inclusion criteria because of missing data, chronic disease, and no use of AI. Moreover, 75% (N = 51) of the women in the cohort were treated according to the SVGO recommendations. Besides being treated with the correct bone-targeted therapy, all patients received DXA scans at the beginning (within 3 months of starting AI treatment (Reid et al., 2008)) and patients at risk received DXA scans during the treatment with AIs and bisphosphonates. Five patients (7.81%) experienced a fracture during or after treatment with AIs (mostly letrozole), and two of these five patients (40%) were not treated according to the SVGO guidelines. Interestingly, although almost all patients received prophylactic bone health therapy, they did not fully conform to the guidelines. In terms of bisphosphonates and denosumab, our results were consistent with those of previous studies, showing that both agents prevent bone loss in postmenopausal patients with breast cancer undergoing AI therapy. The reasons why not each of the 9 points in Table 1 could be identified clearly in the chart review are related to the fact that the exact working is not ubiquitously known among all treating oncologists and, since the SVGO guidelines were not a golden standard in the regular oncological protocol, thus the alertness of their implications was not a priority, especially in charting. As a consequence, the records in the patients' charts would be less clear or incomplete. Furthermore, bone health guidelines might be rather misrepresented in the oncological setting, as the bone health management was previously heavily referred to the general practitioners.

Our data showed a significant correlation between adherence to the SVGO guidelines and an increase in T-scores, whereas 64.7% of included women were osteopenic, and 23.6% of the patients were osteoporotic at their baseline DXA scan, which corresponds to the real-world average (Hadji et al., 2013). Furthermore, we were able to show a significant increase in the T-score in women treated with bisphosphonates and a significant decrease in those not using bisphosphonates. This supports the reports about the bone-protective characteristics of bisphosphonates and their recommended application in patients treated with AI (Gralow, 2007; Rodan et al., 1996).

Twenty-seven patients in our cohort received tamoxifen before AI therapy. This selective estrogen receptor modulator has been shown to lead to bone loss in premenopausal women and bone gain in postmenopausal women (Powles et al., 1996). The cessation of tamoxifen in postmenopausal patients leads to BMD decline in the femoral neck. This can be prevented by the addition of alendronate (Cohen et al., 2008).

SVGO recommendations include Ca and Vitamin D supplementation together with physical activity. CaD3 is known to have a positive effect on bone metabolism, reducing bone resorption and thus bone density loss. In our cohort, all patients were adequately prescribed CaD3. Also, physical activity is a major protective factor of bone loss in patients with cancer. Various studies have shown that activity and weight-bearing exercises improve or preserve bone density (Gralow, 2007; Knobf et al., 2008; Irwin et al., 2009; Muslimani et al., 2009).

Our data showed that fifty-five (75%) women were treated according to the SVGO recommendations, and sixty women (87.9%) received adequate CaD3 supplementation, which demonstrates a high guideline adherence.

Our study has several limitations. First, the study population was relatively small; therefore, the statistical significance was limited. However, the number of patients is considered to be representative of the country's setting. To ensure a better quantification, we only included patients for whom all objective measurements were available and who did not experience comorbidities that essentially affected the skeletal system. Therefore, out of the nearly 357 evaluated individuals, we had to exclude a large number of patients because they only had one DXA scan, had an additional disease/tumor, and had rheumatic disease, or their breast cancer had metastasized. Second, the increased fracture rate during the intake of AI is confounded by a variety of other clinicopathological factors, and the T-score alone is not a direct predictor of fractures, as reported previously (Jones et al., 2008; Coleman et al., 2010; Kilbreath et al., 2011; Cheung et al., 2012). The majority (68.8%) of our study patients received chemotherapy and were thus affected by BMD before the onset of AIs. We considered these confounders in the study planning and documented the clinicopathological values and baseline DXA score. Some studies have mentioned that DXA reproducibility might be challenged, for example, by degenerative vertebral changes or a small change in the lighting angle that can generate a difference in the BMD measurement. The most continuous measurements were obtained from the proximal femur (Reid et al., 2008; Noon et al., 2010). In addition, DXA reference values programmed in the machine are based on a US cohort and can cause a significant difference in z-score calculation if applied to Swiss patients. The European Vertebral Osteoporosis Study conducted in 1997, along with other studies, has shown that z-score and reference values differ regionally (Noon et al., 2010; Lunt et al., 1997). Moreover, patients with fractures might have reported to a different hospital for fracture care, and not all fracture data were recorded. Therefore, we cannot exclude the possibility that the actual fracture number might be higher. Finally, bone turnover markers could have provided additional and more specific information about bone remodeling and hence show the responses to various bisphosphonates (Coleman et al., 2010; Swenson et al., 2009). As this study was retrospective, we could not revert to bone turnover markers as these tests were not routinely and significantly less frequently performed until 2014.

In conclusion, we provided data for Swiss breast cancer patients regarding adherence to bone health guidelines and its objective impact on patients' bone density. Overall, adherence is observed in the majority of patients and leads to stabilization or even improvement of the bone density in patients at risk (treated with AIs). Noncompliance with the guidelines leads to a higher number of AI-associated BREs, specifically fractures. Further validation of our findings in a larger prospective cohort is necessary and warranted.

Funding sources

This research received funding from Krebsliga, Schweiz, via a grant awarded to EB (BIL KFS 4261-08-2017).

CRediT authorship contribution statement

Evelyne Bischof: Investigation, Writing – original draft, Visualization. **Fabienne D. Schwab:** Writing – original draft, Visualization, Writing – review & editing. **Elena Laura Georgescu Margarint:**

Writing – review & editing, Visualization. **Céline Montavon:** Data curation, Formal analysis, Investigation. **Iris Zünti:** Data curation, Formal analysis, Investigation. **Anna Schollbach:** Data curation, Formal analysis, Investigation. **Andreas Schötzau:** Data curation, Formal analysis, Investigation **Anna Hirschmann:** Data curation, Formal analysis, Investigation. **Julia Landin:** Data curation, Formal analysis, Investigation. **Christian Meier:** Data curation, Formal analysis, Investigation. **Kurzeder Christian:** Data curation, Formal analysis, Investigation. **Marcus Vetter:** Writing – review & editing, Project administration, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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