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Original Article

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The Frequency of and Risk Factors for the Use of Bisphosphonates in the Adjuvant Setting of Primary Breast Cancer in Germany

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Purpose

The aim of this cross-sectional health care study (use of bisphosphonates in primary tumors of the mammae, EBisMa) is to determine how often bisphosphonate medication is used in patients with non-metastatic primary breast cancer treatment, but who do not suffer from osteoporosis. Furthermore, we describe patients' characteristics and the most frequently used type of bisphosphonate in adjuvant therapy.

Materials and Methods

The study population included primary breast cancer patients of four breast centers in northern Germany. Data on bisphosphonate therapy were collected by use of patient questionnaires; clinical data were extracted from the registers. Patients with and without prescribed bisphosphonate adjuvant treatment were tested for statistically significant differences regarding their characteristics.

Results

Four hundred seventy-four of 663 contacted patients participated in the study. Thirty-nine out of 474 patients (9.6%) were on adjuvant bisphosphonate therapy. Zoledronic acid was the most frequently reported bisphosphonate used for prevention of bone metastases. Compared to patients who did not report bisphosphonate medication, women who did report bisphosphonate therapy had a significantly higher advanced tumor stage ($p < 0.001$). Both the T2-T4 stage and N+ stage remained significant predictors in multivariate-adjusted regression models.

Conclusion

Bisphosphonates are rarely used in the adjuvant treatment of primary breast cancer. Patients with advanced tumor stage were more likely to use bisphosphonates in the adjuvant treatment of primary breast cancer. Further research is needed to identify patients who may benefit most from adjuvant bisphosphonate treatment.

Key words
Breast neoplasm, Diphosphonates, Adjuvant chemotherapy

Introduction

Among women breast cancer is the most frequent cancer in Germany [1]. The therapy of breast cancer has been optimized during the past decades. In addition to standard therapies, bisphosphonates (BP) are another option for treatment of late stage breast cancer and breast cancer patients with osteoporosis. Since the nineties this group of substances is established in the treatment of bone metastases [2].

Currently, the adjuvant treatment of primary breast cancer with BPs is discussed controversially. However, there is no approval of BPs for primary breast cancer therapy without any skeletal-related event. Several clinical trials such as the ABCSG-12 trial [3] and the AZURE trial [4] using zoledronic acid (ZOL), or the study by Diel et al. [5] using clodronate have been conducted to examine a possible direct antitumor activity, a benefit in disease-free survival (DFS) and overall survival (OS) for patients with primary breast cancer. The different studies represent conflicting results concerning the

Table 1. Description of study population and comparison of breast patients with (BP+) and without (BP–) BP use

Characteristic	Overall (n=474)	Patients BP+ (n=39)	Patients BP– (n=366)	p-value
Age (yr)				0.217
Mean±SD	60.4±9.9	58.3±10.5	60.1±9.8	
Missing	0	0	0	
Tumor size (TNM-T)[a]				< 0.001
T1	295 (62.2)	10 (25.6)	246 (67.2)	
T2	144 (30.4)	25 (64.1)	93 (25.4)	
T3	16 (3.4)	2 (5.1)	11 (3.0)	
T4	7 (1.5)	0	7 (1.9)	
Tx	12 (2.5)	2 (5.1)	9 (2.5)	
Local lymph node involvement (TNM-N)[a]				< 0.001
N0	329 (69.4)	14 (35.9)	269 (73.5)	
N1	91 (19.2)	15 (38.5)	58 (15.8)	
N2	23 (4.9)	6 (15.4)	14 (3.8)	
N3	15 (3.2)	2 (5.1)	12 (3.3)	
Nx	16 (3.4)	2 (5.1)	13 (3.6)	
Grading[a]				0.002
G1	94 (19.8)	2 (5.1)	79 (21.6)	
G2	248 (52.3)	20 (51.3)	191 (52.2)	
G3	123 (25.9)	17 (43.6)	88 (24.0)	
Missing	9 (1.9)	0	8 (2.2)	
ER status[a]	n=436	n=38	n=334	0.609
Positive	355 (81.4)	29 (76.3)	274 (82.0)	
Negative	59 (13.5)	6 (15.8)	44 (13.2)	
Missing	22 (5.0)	3 (7.9)	16 (4.8)	
PR status[a]	n=436	n=38	n=334	> 0.999
Positive	316 (72.5)	26 (68.4)	239 (71.6)	
Negative	96 (22.0)	9 (23.7)	77 (23.1)	
Missing	24 (5.5)	3 (7.9)	18 (5.4)	
ER/PR status[a]	n=38	n=1	n=32	0.405
Positive	36 (94.7)	1 (100)	30 (93.8)	
Negative	1 (2.6)	0	1 (3.1)	
Missing	1 (2.6)	0	1 (3.1)	
Menopausal status[b]				0.319
Premenopausal	16 (3.4)	0	15 (4.1)	
Perimenopausal	13 (2.7)	2 (5.1)	10 (2.7)	
Postmenopausal	398 (84.0)	34 (87.2)	306 (83.6)	
Missing	47 (9.9)	3 (7.7)	35 (9.6)	
Surgery[a]				0.015
Breast preserving	379 (80.0)	25 (64.1)	299 (81.7)	
Mastectomy	87 (18.4)	13 (33.3)	61 (16.7)	
No surgery	4 (0.8)	1 (2.6)	3 (0.8)	
Missing	4 (0.8)	0	3 (0.8)	
Chemotherapy[c]				< 0.001
Yes	211 (44.5)	30 (76.9)	144 (39.3)	
No	246 (51.9)	9 (23.1)	208 (56.8)	
Discontinued	6 (1.3)	0	4 (1.1)	
Missing	11 (2.3)	0	10 (2.7)	

Table 1. Continued

Characteristic	Overall (n=474)	Patients BP+ (n=39)	Patients BP– (n=366)	p-value
Radiation[c]				0.375
Yes	407 (85.9)	32 (82.1)	315 (86.1)	
No	58 (12.2)	7 (17.9)	43 (11.7)	
Discontinued	1 (0.2)	0	1 (0.3)	
Missing	8 (1.7)	0	7 (1.9)	
Anti-hormone therapy[b]				0.844
Yes	368 (77.6)	31(79.5)	284 (77.6)	
No	103 (21.7)	8 (20.5)	81 (22.1)	
I don't know	1 (0.2)	0	0	
Missing	2 (0.4)	0	1 (0.3)	
Aromatase inhibitor[b),d]	n=368	n=31	n=284	0.367
Yes	196 (53.3)	18 (58.1)	146 (51.4)	
No	102 (27.7)	7 (22.6)	87 (30.6)	
I don't know	3 (0.8)	0	1 (0.4)	
Missing	67 (18.2)	6 (19.4)	50 (17.6)	
GnRH analogon[b),d]	n=368	n=31	n=284	0.640
Yes	1 (0.3)	0	0	
No	250 (67.9)	20 (64.5)	207 (72.9)	
I don't know	27 (7.3)	2 (6.5)	14 (4.9)	
Missing	90 (24.5)	9 (29.0)	63 (22.2)	

Cases with unknown answer concerning the BP treatment are only represented in the overall population (n=69). BP, bisphosphonate; SD, standard deviation; ER, estrogen receptor; PR, progesterone receptor; GnRH, gonadotropin-releasing hormone. [a)]Clinical data, [b)]EBisMa questionnaire data, [c)]Follow-up data from breast centers, [d)]Exclusive cases with anti-hormone therapy reported in EbisMa questionnaire.

improvement in DFS and OS.

The German working group of gynecological oncology (Arbeitsgemeinschaft Gynäkologische Onkologie e.V., AGO) first recommended the adjuvant use of ZOL and clodronate for primary breast cancer in February 2009 [6] and confirmed its recommendation in March 2014 [7].

The aim of this study is to estimate the frequency of BPs use for the treatment of primary breast cancer among female patients without clinical signs of metastases or osteoporosis, to describe the most frequently used compound of BP, as well as patient characteristics of women receiving BP medication.

Materials and Methods

1. Study design

EBisMa (use of BP in primary tumors of the mammae) is a cross-sectional health-care research study to examine the adjuvant use of BPs in patients with breast cancer without signs of bone metastases, hypercalcaemia and/or osteoporosis.

Patients selected from a clinical cancer care register including four breast cancer centers in the federal state of Schleswig-Holstein, Northern Germany. Participating breast centers were located in the cities of Luebeck, Pinneberg, Holstein, and Flensburg. Data on BP therapy were not available from the register and therefore collected by patient questionnaires; clinical data about tumor stage, tumor characteristics, and standard therapy were provided by the register. The questionnaire was send via postal mail together with the regular follow-up. All patients gave consent to be contacted by the clinical cancer care register for research purposes. The questionnaire was send with a cover letter explaining the aim of the study and an informed consent sheet to participate (upon request, the questionnaire is available from the authors). The Ethical Review Board of the University of Luebeck approved the study protocol in March 2012.

Table 2. Details of bisphosphonate (BP) treatment (n=39)

Bisphosphonate treatment (questionnaire data)	No. (%)
BP usage	
Current usage	15 (38.5)
Usage is terminated	24 (61.5)
Missing	0
BP name	
Zoledronic acid	35 (89.7)
Ibandronate	1 (2.6)
I don't know	1 (2.6)
Missing	2 (5.1)
BP reason for application	
Prevention of bone metastases	28 (71.8)
Treatment of bone pain	3 (7.7)
Different reason	2 (5.1)
I don't know	3 (7.7)
Missing	3 (7.7)
BP application	
Tablet/capsule	3 (7.7)
Infusion	33 (84.6)
Missing	3 (7.7)
BP treatment interval, current/last	
Daily	1 (2.6)
Every wk	1 (2.6)
Every 4 wk	2 (5.1)
Every 6 mo	28 (71.8)
Different	5 (12.8)
Missing	2 (5.1)
BP treatment interval at baseline	
No changes	19 (48.7)
Daily	0
Every wk	0
Every 4 wk	1 (2.6)
Every 6 mo	1 (2.6)
Different	2 (5.1)
Missing	16 (41.0)
Treatment duration (yr)	
< 1	3 (7.7)
1	6 (15.4)
2	9 (23.1)
Open end	8 (20.5)
Missing	13 (33.3)

2. Study population

A total of 1,015 female patients with breast cancer were treated in 2009 or 2011 at one of the four cooperating breast centers and were eligible for follow-up surveys. Criteria for inclusion into the study were as follows: age between 18 and 75 years, and an initial diagnosis either in the year 2009 or 2011. Patients were excluded from the study population if they had an initial diagnosis of (bone) metastasis, or if the tumor classification Tis or T0 had been notified to the register. Accordingly, a total of 638 patients were eligible for the study.

3. Statistical analyses

The study population has been divided into two groups: women who report BP treatment (BP+) and women who report no BP treatment (BP–). For 69 women (14.6%) the status of BP therapy was unknown. They were only considered in the description of the overall study population. The differences between the two groups (BP+ and BP–) were tested for significance by chi-square test respectively exact Fischer test (nominal scale) and Mann-Whitney U test (ordinal scale). For bivariate analyses t test (metric data) and Mann-Whitney U test (ordinal data) were used. The 95% confidence intervals (CIs) were calculated for the prevalence of BP+ patients in the overall population and in subgroups (T-stages, N-stages, grading, age groups). In the binary logistic regression (multivariable model) only those variables that showed a significant influence in bivariate analyses were included. The significance level was defined as p=0.05.

Results

Six hundred thirty-eight patients were eligible for the study. Of those 79.8% (n=509) responded and 474 patients (93.1% of 509) gave written informed consent to participate in EBisMa. Two hundred and three patients (55.5%) had their initial breast cancer diagnosis in 2009 and 211 patients (44.5%) in 2011.

1. Patient characteristics

The average age of the predominantly postmenopausal women was 60.4 years (Table 1). All patients had an invasive, not metastatic breast cancer (cM0). More than half of the patients had an estrogen and/or progesterone positive tumor. Furthermore, the most common TNM-staging was T1 and N0. A breast conserving surgery has been performed in 80% of all patients. The most frequently adjuvant standard therapies were radiotherapy and/or anti-hormonal therapy (AHT). The aromatase inhibitor (AI) has been reported by 53.3% of all patients with AHT.

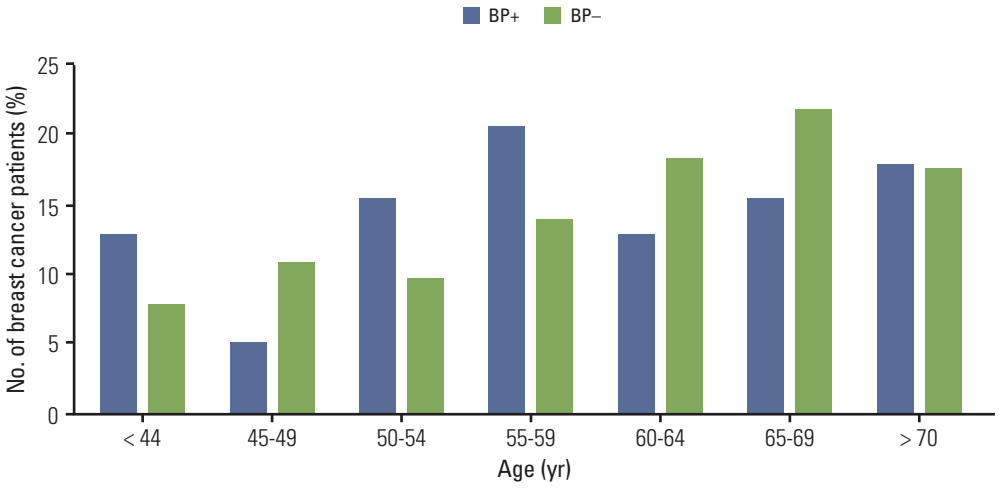

Fig. 1. Age distribution for breast cancer patients with (BP+) and without (BP–) bisphosphonate (BP) use.

Table 3. Prevalence in overall population and subgroups

Characteristic	No. of BP+ patients/subgroup	Prevalence (95% CI, %)
Overall population	39/405	9.6 (6.8 to 12.5)
Age (yr)		
≤ 49	7/76	9.2 (2.7 to 15.7)
50-64	19/172	11.0 (6.4 to 15.7)
≥ 65	13/157	8.3 (4.0 to 12.6)
Tumor size (TNM-T)		
T1	10/256	3.9 (1.5 to 6.3)
T2/T3/T4	27/138	19.6 (12.9 to 26.2)
Tx	2/11	18.2 (–4.6 to 41.0)
Local lymph node involvement (TNM-N)		
N0	14/283	4.9 (2.4 to 7.5)
N+	23/107	21.5 (13.7 to 29.3)
Nx	2/15	13.3 (–3.9 to 30.5)
Grading		
G1	2/81	2.5 (–0.9 to 5.8)
G2/G3	37/316	11.7 (8.2 to 15.3)
Missing	0/8	0

BP, bisphosphonate; CI, confidence interval.

2. BP treatment

A BP treatment was reported by 39 patients (9.6%; 95% CI, 6.8% to 12.5%) with known BP status (n=405) (Table 2). ZOL was reported by 89.7% (n=35). The most frequently self-reported indication for BP treatment was 'prevention of bone metastases.' In 69% of women BP treatment started after discharge from hospital, and 72% of women started BP medication 6 months after discharge.

3. Description of BP groups and risk factors for BP treatment

On average, BP+ patients were two years younger than BP– patients (Fig. 1). BP+ patients showed a significant worse grading, T- and N-staging compared with the BP– patients. Patients of the BP+ groups received mastectomy and chemotherapy more often compared to BP– patients ($p < 0.05$) (Table 1). The prevalence of BP treatment was higher in

Table 4. Odds ratio for the bisphosphonate use of bivariate and multivariate binary logistic regression

Variable	Bivariate regression analysis	Multivariate regression analysis
Age (yr)		
≤ 49	1	1
50-64	1.42 (0.54-3.71)	2.61 (0.90-7.60)
≥ 65	1.03 (0.38-2.83)	1.59 (0.53-4.75)
Tumor size (TNM-T)		
T1	1	1
T2/T3/T4	5.96 (2.79-12.74)	3.42 (1.44-8.12)
Tx	3.50 (0.39-31.23)	6.41 (0.49-83.56)
Local lymph node involvement (TNM-N)		
N0	1	1
N+	5.16 (2.52-10.53)	2.51 (1.06-5.93)
Nx	3.20 (0.65-15.71)	3.33 (0.58-19.16)
Grading		
G1	1	1
G2/G3	5.13 (1.21-21.79)	2.57 (0.56-11.84)
Missing	0	0
Surgery		
Breast preserving	1	1
Mastectomy	2.56 (1.24-5.26)	1.24 (0.54-2.81)
Missing	0	0
Chemotherapy		
Yes	1	1
No	4.62 (2.13-10.06)	1.62 (0.62-4.23)
Missing	0	0

Values are presented as odds ratio (95% confidence interval).

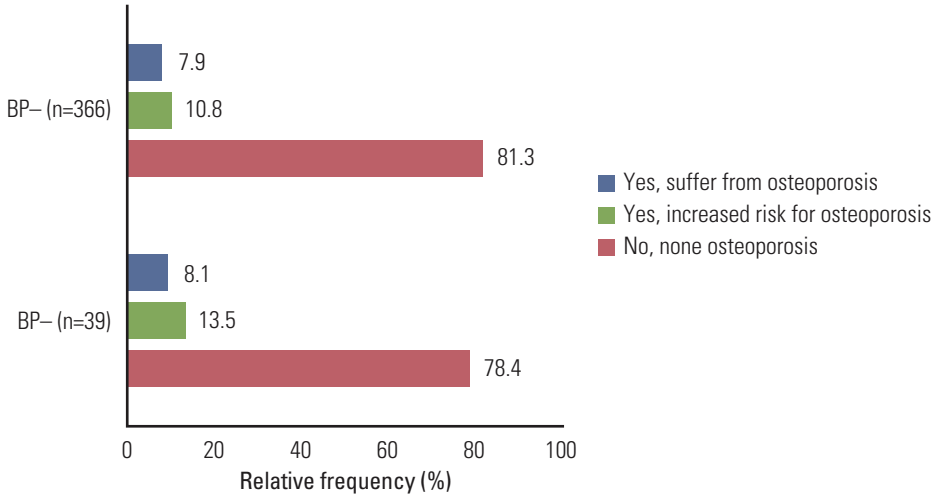

Fig. 2. Osteoporosis or risk of osteoporosis in breast cancer patients with (BP+) and without (BP–) bisphosphonate (BP) use.

the subgroups patients with T2-T4 stage, N+ patients and G2-G3 patients (Table 3). In the multivariable model, only T2-T4 stage and the N+ stage remained independent significant predictors, while chemotherapy and G2-G3 status became nonsignificant (Table 4).

BP+ patients did not differ from BP– patients regarding the prevalence of osteoporosis or the risk of developing osteoporosis (Fig. 2). Likewise, frequency and time of osteoporosis diagnosis differed not significantly between the two groups (osteoporosis before breast cancer diagnosis: BP+, 11.1%, BP–, 19.4%; after breast cancer diagnosis: BP+, 33.3%, BP–, 45.8%; p=0.387).

Discussion

The primary aim of this study was to describe the adjuvant therapy use of BPs in a group of primary breast cancer patients admitted to four breast centers in Germany. Frequencies of adjuvant BP use, as well as possible differences in clinical characteristics of the included patients were examined.

Currently, limited results from few clinical trials investigating the adjuvant use of oral and intravenous BPs have been published recently [3-5,8-14]. The results of EBisMa show that ZOL is the most frequently reported BP—one that has been studied in a number of studies (e.g., ABCSG-12 [3], AZURE [4]).

The ABCSG-12 trial [3], which included premenopausal women with hormone receptor positive tumors and endocrine therapy (gonadotropin-releasing hormone analogues and additionally either tamoxifen or AI), is one of the largest trials (n=1,803) showed a benefit in DFS for adjuvant BP treatment after 5-year follow-up for the ZOL group compared to the control group (DFS: ZOL group, 92%; control-group, 88%; hazard ratio [HR], 0.68; 95% CI, 0.51 to 0.91; log-rank, p=0.008) [3]. Another study in pos menopausal women with endocrine therapy (AI-Letrozol)—the ZO-FAST trial [11]—showed after 5-year follow-up a significant benefit in DFS for patients with immediate ZOL treatment compared to the group which received ZOL only after clinical relevant reduction of bone mineral density (BMD) (HR, 0.66; 95% CI, 0.44 to 0.97; log-rank, p=0.0375) [11]. A third large trial—the AZURE trial [4]—indicated no benefit in DFS for either post- or premenopausal patients treated with ZOL and standard therapy (HR, 0.98; 95% CI, 0.85 to 1.13; p=0.79). Nevertheless, a benefit for DFS in subgroup analyses of postmenopausal patients were demonstrated (ZOL group, 78.2%; control group, 71.0%; HR, 0.75; 95% CI, 0.59 to 0.96; p=0.02) [4]. Most of the clinical trials investigating adjuvant use of clodronate in primary breast cancer patients had smaller sample sizes (n=299-1,069) than the ZOL trials (n=1,065-3,360) and indicated no benefit DFS or OS [8-10]. Only the not-placebo controlled study by Diel et al. [5] indicated a significant lower incidence of bone metastases compared to standard follow-up (8% vs. 17%, p=0.003). Furthermore, the GAIN trial [12] investigating the adjuvant use of ibandronate and studies investigating the adjuvant use of pamidronate [13,14] indicate no benefits from the use of these two BPs.

In summary, results from studies about the adjuvant use of BPs are showing no clear treatment benefit. Overall, results of ZOL studies are most promising among those prescribing BPs for adjuvant therapy. This may explain our findings from EBisMa with most patients reporting use of ZOL (i.v.). Furthermore, conflicting results from clinical studies may explain the small number of patients reporting adjuvant use of BPs—in addition to our in- and exclusion criteria. The patients with BP treatment mainly report the indication 'prevention of bone metastases'—which is due to exclusion criteria of the study. There is no approval of BPs for primary breast cancer therapy, except for hypercalcaemia. In Germany, costs for adjuvant BP treatment are usually not covered by health insurance claims, but the patient has to pay for this medication. Another reason for the limited prescription of BPs might be physicians' skepticism because of conflicting results from clinical studies [3-5,8,11,12] particularly concerning the effect of BPs in not metastasized settings.

Most women reported application intervals of 6 months. The interval used in the ZO-FAST trial [11] was 6 months from the beginning of the study. The intervals used in the ABCSG-12 trial [3] were initial 8 mg ZOL every 4 weeks and afterwards 4 mg of ZOL every 6 months. There were no differences regarding side effects between the ZO-FAST [11] and ABCSG-12 [3] study. Moreover, the German AGO e.V. guideline 2012 [15] recommends a six month interval as well. In so far the observed BP treatment in our study followed the guideline.

Overall, it is remarkable that the tumor stage of BP+ women was more advanced as compared to BP– women in this study. The T-stage was significantly higher in BP+ group—there are obviously more T2-stage cases. In addition, lymph node involvement and the grading were higher in BP+ group. Moreover, the T2-T4 stage and N+ remained as predictors in the multivariate regression model. Hence, a mastectomy was more often performed in this group. It seems that BP treatment is more often recommended to women with a worse disease prognosis. Furthermore, it is possible that these women agree more often to novel, but not finally approved, treatment options.

In addition, women's age and menopausal status may be

important for treatment effect. The ABCSG-12 trial [3] indicated a significant increase in DFS only for BP patients older than 40 years who had a therapy induced low estrogen level (≤ 40 years: HR, 0.94; 95% CI, 0.57 to 1.56; > 40 years HR, 0.58; 95% CI, 0.40 to 0.83). The NSABP-B34 trial [8] investigating the adjuvant use of oral clodronate in postmenopausal women indicated a benefit in bone metastases free survival only for patients older than 50 years (HR, 0.62; 95% CI, 0.40 to 0.95; p=0.027). Although results of the clinical trials indicate a benefit for postmenopausal women [16], BP+ patients in our study were on average two years younger than BP– patients; however, about 87% and 84% in the respective subgroups were postmenopausal.

Treatment with AIs is often related with an aromatase inhibitor-induced bone loss (AIBL) and an increase number of skeletal-related events. Different studies as the E-ZO-FAST trial [17] show an increase in BMD for patients treated with an AI and ZOL [18]. Especially risk of tumor therapy-induced osteoporosis and the long-term risk of fractures has been reduced [17,18]. Patients treated with AIs or an increased risk for osteoporosis could not only benefit from the possible direct anti-tumor activity of BPs but also from prohibition of AIBL and increasing BMD [19]. However, results of EBisMa indicate that there is no difference between the two groups concerning therapy with AIs and reports concerning a greater risk for osteoporosis.

We observed differences in the frequency of chemotherapy between the two groups. The BP+ group more often reports chemotherapy. One reason could be to prevent the chemotherapy-induced bone loss of patients [20]. Another reason could be that different studies on breast cancer cell cultures determine a synergistic effect of giving BP in combination with chemotherapy [21,22]. In the AZURE study, a subgroup analysis of patients treated with neoadjuvant chemotherapy alone or additionally with ZOL indicated a significant difference in residual invasive tumor size (RITS) [23]. The group with chemotherapy alone had a median RITS of 27.4 mm and the group with additional ZOL treatment had a median RITS of 15.5 mm (95% CI, 3.5 to 20.4; p=0.0059) [23]. However, in the present study it is not clear whether the reported chemotherapy and the adjuvant BP treatment were prescribed simultaneously. In addition, the BP+ group had a more advanced tumor stage which is usually an indication for chemotherapy in itself. Also in the regression analyses chemotherapy was a significant predictor for BP treatment only in the bivariate, but not in the multivariate model.

Our study (EBisMa) is (one of) the first cross-sectional study investigating the adjuvant use of BPs for primary breast cancer in Germany. It was examined in a population setting and therefore our study is an important complement to existing (controlled) clinical trials. This study stands out due to a high response rate. A further strength is the collaboration with four large breast centers located across the federal state of Schleswig-Holstein, thus providing a representative health care sample of breast cancer patients. A possible limitation of the study is the fact that data concerning BP treatment were self-reported. However, other health-care studies have proven that patients are able to give valid [24] and reliable [25] information about their disease status and clinical therapy.

Conclusion

The prevalence of adjuvant use of BPs (9.6%) for primary breast cancer was relatively low. The conflicting evidence from clinical trials including missing information on treatment intervals, drug dosage, treatment duration, and respective medication costs to be covered by patients may have limited the adjuvant BP use so far. Patients with advanced tumor stage were more likely to use BP in the adjuvant treatment of primary breast cancer. Further studies are needed to identify those patients selected for adjuvant BP treatment who may benefit the most.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

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References

1. Kaatsch P, Spix C, Hentschel S, Katalinic A, Luttmann S, Stegmaier C. Krebs in Deutschland 2009/2010. Berlin: Robert Koch-Institut; 2013.
2. Russell RG. Bisphosphonates: the first 40 years. Bone. 2011;49:2-19.
3. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Heck D, Menzel C, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncol. 2011;12:631-41.
4. Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, et al. Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med. 2011;365:1396-405.
5. Diel IJ, Jaschke A, Solomayer EF, Gollan C, Bastert G, Sohn C, et al. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up. Ann Oncol. 2008;19: 2007-11.
6. Diagnostik und therapie primärer und metastasierter mammakarzinome: bisphosphonate [Internet]. Arbeitsgemeinschaft Gynäkologische Onkologie e.V.; 2009 [cited 2014 Dec 1]. Available from: http://www.ago-online.de/fileadmin/downloads/leitlinien/mamma/februar2009/g_mamma_09_1_0_d_26_bisphosphonates.pdf.
7. Diagnostik und therapie primärer und metastasierter mammakarzinome: osteoonkologie und knochengesundheit [Internet]. Arbeitsgemeinschaft Gynäkologische Onkologie AGO e.V.; 2014 [cited 2014 Dec 1]. Available from: http://www.ago-online.de/fileadmin/downloads/leitlinien/mamma/maerz2014/de/2014D_21_Osteoonkologie_und_Knochengesundheit.pdf.
8. Paterson AH, Anderson SJ, Lembersky BC, Fehrenbacher L, Falkson CI, King KM, et al. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial. Lancet Oncol. 2012; 13:734-42.
9. Powles T, Paterson S, Kanis JA, McCloskey E, Ashley S, Tidy A, et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. J Clin Oncol. 2002;20:3219-24.
10. Saarto T, Vehmanen L, Virkkunen P, Blomqvist C. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. Acta Oncol. 2004;43:650-6.
11. Coleman R, de Boer R, Eidtmann H, Llombart A, Davidson N, Neven P, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. Ann Oncol. 2013;24:398-405.
12. von Minckwitz G, Mobus V, Schneeweiss A, Huober J, Thomssen C, Untch M, et al. German adjuvant intergroup node-positive study: a phase III trial to compare oral ibandronate versus observation in patients with high-risk early breast cancer. J Clin Oncol. 2013;31:3531-9.
13. Kokufu I, Kohno N, Yamamoto M, Takao S. Adjuvant pamidronate therapy prevents the development of bone metastases in breast cancer patients with four or more positive nodes. Oncol Lett. 2010;1:247-52.
14. Kristensen B, Ejlertsen B, Mouridsen HT, Jensen MB, Andersen J, Bjerregaard B, et al. Bisphosphonate treatment in primary breast cancer: results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer. Acta Oncol. 2008;47:740-6.
15. Diagnostik und therapie primärer und metastasierter mammakarzinome: bisphosphonate und RANKL-antikörper [Internet]. Arbeitsgemeinschaft Gynäkologische Onkologie AGO e.V.; 2012 [cited 2014 Dec 1]. Available from: http://www.ago-online.de/fileadmin/downloads/leitlinien/mamma/maerz2012/16_2012D_Bisphosphonate_und_der_RANKL-Antikoerper_Denosumab.pdf.
16. Fick EM, Anzeneder T, Katalinic A, Waldmann A. Bisphosphonates and their role in therapy for breast cancer: results from the PATH Biobank. Geburtshilfe Frauenheilkd. 2013; 73:412-21.
17. Llombart A, Frassoldati A, Paija O, Sleeboom HP, Jerusalem G, Mebis J, et al. Immediate administration of zoledronic acid reduces aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer: 12-month analysis of the E-ZO-FAST trial. Clin Breast Cancer. 2012;12:40-8.
18. Bundred NJ, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. Cancer. 2008;112: 1001-10.
19. Winter MC, Coleman RE. Bisphosphonates in the adjuvant treatment of breast cancer. Clin Oncol (R Coll Radiol). 2013;25:135-45.
20. Hershman DL, McMahon DJ, Crew KD, Cremers S, Irani D, Cucchiara G, et al. Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol. 2008;26:4739-45.
21. Ibrahim T, Liverani C, Mercatali L, Sacanna E, Zanoni M, Fabbri F, et al. Cisplatin in combination with zoledronic acid: a synergistic effect in triple-negative breast cancer cell lines. Int J Oncol. 2013;42:1263-70.
22. Neville-Webbe HL, Rostami-Hodjegan A, Evans CA, Coleman RE, Holen I. Sequence-and schedule-dependent enhancement of zoledronic acid induced apoptosis by doxorubicin in breast and prostate cancer cells. Int J Cancer. 2005;113:364-71.
23. Coleman RE, Winter MC, Cameron D, Bell R, Dodwell D, Keane MM, et al. The effects of adding zoledronic acid to neoadjuvant chemotherapy on tumour response: exploratory evidence for direct anti-tumour activity in breast cancer. Br J Cancer. 2010;102:1099-105.
24. Ritterhoff N. Wie gut kennen patienten ihre krankheit und behandlung? Ein vergleich von patientenangaben, arztang-

aben und registerdaten in der onkologischen versorgung. Lübeck: Medizinische Fakultät, Institut für Krebsepidemiologie e.V., Universität zu Lübeck; 2010.
25. Waldmann A, Dreckschmidt J, Pritzkuleit R, Katalinic A. Test-retest reliability of the OVIS Questionnaire: an instrument to evaluate oncological care from a patient's point of view. Gesundheitswesen. 2010;72:707-13.