Journal of Bone Oncology 15 (2019) 100226

Contents lists available at ScienceDirect

Journal of Bone Oncology

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

Research Paper

Compliance and patient reported toxicity from oral adjuvant bisphosphonates in patients with early breast cancer. A cross sectional study

C. Wilson[a,*], C. Martin[b], M.C. Winter[a]

[a] Weston Park Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Whitham Road, Sheffield, S10 2SJ, UK
[b] Medical School, University of Sheffield, Beech Hill Road, Sheffield, UK

ARTICLE INFO

Keywords:
Toxicity
Adjuvant bisphosphonates
Early breast cancer

ABSTRACT

Background: Adjuvant bisphosphonates (BPs) are recommended as part of routine early breast cancer treatment for many postmenopausal (PM) women within the past year. There is a paucity of 'real world' data on compliance and patient satisfaction with oral BPs in this population. The aim of our study was to investigate patient reported compliance and toxicity of these drugs in a retrospective cohort study.
Patients and methods: 413 patient were identified as receiving adjuvant oral BPs as part of their breast cancer treatment in the past 12 months from five NHS hospitals. The validated Osteoporosis Patient Treatment Satisfaction Questionnaire (OPSAT-Q) was sent to all suitable patients (n = 389).
Results: 295 (76%) of patients responded. Average age was median (range) 67 (35–89). The majority of patients had T1 (52%), N0 (61%) grade 2 (58%) ER positive (87%), HER2 negative (84%) breast cancer and were PM at diagnosis of breast cancer (93%). All patients had been prescribed at least 1 month of oral ibandronate 50 mg daily. Review of items rated on the 7-point scale (1 = very dissatisfied to 7 = very satisfied), the mean item scores ranged from 5.0 (lowest) for time required to take oral BPs, to 6.1 (highest) for how easy it is to remember to take the medication. <10% of patients were extremely bothered by heartburn or stomach upset. 16% of responders stopped oral BPs with 10% of those converting onto IV BPs.
Conclusions: Prevalence of severe side effects in a 'real world' population of PM women receiving adjuvant BPs is low and these drugs are generally well accepted and tolerated by patients.

1. Introduction

A significant percentage of women diagnosed with breast cancer develop metastatic disease, with bone representing the first site of metastasis in approximately 50% of patients. Bisphosphonates (BPs), as potent inhibitors of osteoclast-mediated bone resorption, significantly reduce the risk of skeletal complications in metastatic bone disease and have been used in this treatment setting for many years.

A wealth of pre-clinical data reported that BPs may modify disease course and disrupt the metastatic process by preventing tumour cell homing to bone, inducing tumour cell apoptosis in bone, maintaining dormancy of tumour cells in bone, modifying the bone microenvironment and interrupting the vicious cycle of bone metastasis by inhibiting the release of growth factors rendering it less fertile for metastatic tumour growth [1–4]. These data support the rationale for clinical metastasis-prevention studies. The first adjuvant study showing a benefit of clodronate in terms of bone-metastasis free survival and overall survival was published 20 years ago [5]. A larger oral clodronate trial initiated in the 1990s supported the findings from the Diel study [6] but a third trial reported a negative and potential harmful effect on disease outcome [7]. Over the last 10 years several further large adjuvant metastases prevention studies, including the use of oral ibandronate and intravenous zoledronic acid, have been conducted [8–11]. Whilst results were from these trials were not consistent, two of these trials, including ABCSG-12 and AZURE/BIG 1-04, gave the first indication that the benefits of adjuvant bisphosphonates are restricted to women with a low oestrogen environment, achieved either through menopause or treatment with ovarian suppression.

Subsequently, these findings have been corroborated by results from the Early Breast Cancer Trials Collaborative Group (EBCTCG) meta-analysis, published in 2015 [12]. This included data on 18,766 women treated in trials with 2–5 years of bisphosphonates, including 11,767 post-menopausal women in which bisphosphonates reduced the risk of recurrence (RR 0.86, 95% CI 0.78–0.94, $2p$ = 0.002), distant recurrence (RR 0.82, 95% CI 0.74–0.92, $2p$ = 0.0003), bone recurrence (0.72, 0.60–0.86, $2p$ = 0.0002) and a reduction in 10 year breast

* Corresponding author.
E-mail address: c.wilson@sheffield.ac.uk (C. Wilson).

https://doi.org/10.1016/j.jbo.2019.100226
Received 14 January 2019; Received in revised form 14 February 2019; Accepted 15 February 2019
Available online 19 February 2019

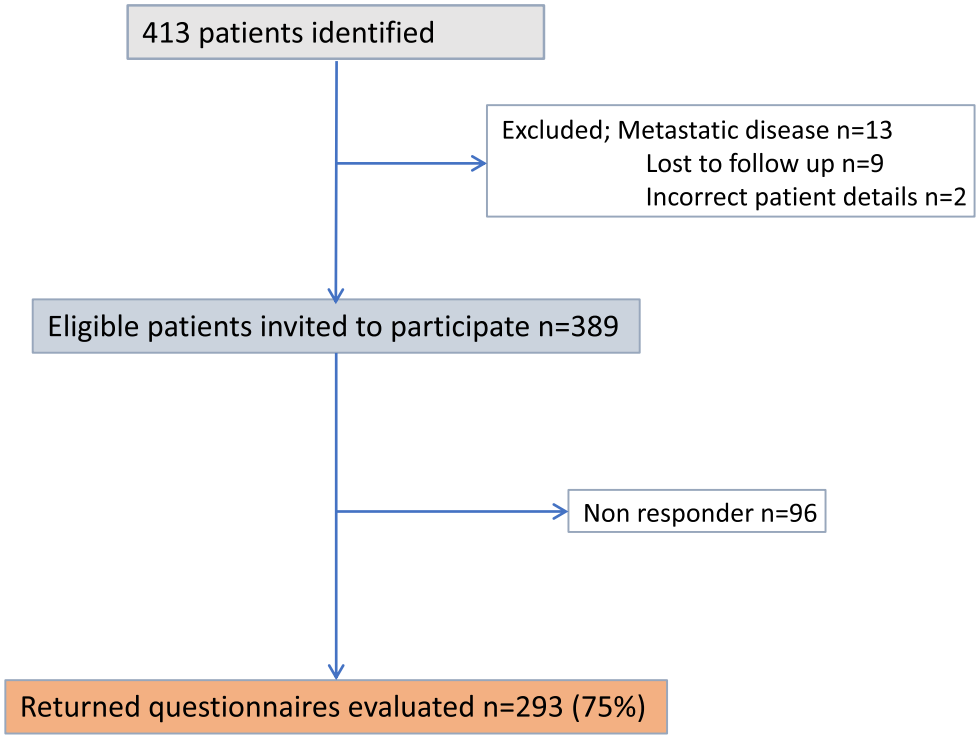

Fig. 1. Study consort diagram.

cancer mortality by 3.3% (RR 0.82, 95% CI 0.73–0.93, $2p = 0.002$) was observed. There was no beneficial survival outcome effect in pre-menopausal women. The benefits seen in post-menopausal women were similar irrespective of grade, ER status, axillary node status, receipt of chemotherapy or not. The meta-analysis was also not able to demonstrate any difference in terms of dosing regimen or type of bisphosphonate.

International consensus recommendations and guidelines have subsequently been published advocating the use adjuvant bisphosphonates in post-menopausal women with early breast cancer [13,14] and have recommended oral clodronate or IV zoledronic acid as choice of agent. Although only published in abstract form so far, the SWOG S0307 included 6097 patients with stage I-III breast cancer receiving adjuvant systemic therapy randomized to receive 3 years of clodronate (1600 mg daily), ibandronate 50 mg po daily or zoledronic acid 4 mg IV monthly for 6 months, then 3-monthly for 2.5 years. There was no difference in 5-year disease-free survival between the 3 arms (88% in the clodronate and zoledronic acid arms, and 87% in the ibandronate arms) [15]. These data indicate ibandronate is an additional choice of agent in the adjuvant setting. Of interest, prior to randomisation, 76% of patients expressed a preference for oral medication versus 24% for intravenous if the drugs proved equal in efficacy. Clodronate (a non amino-BP) has slightly difference gastrointestinal toxicity than ibandronate (an amino BP) in that the main side effects reported with clodronate over placebo are diarrhoea (15% vs 7%) with less excess of upper GI toxicity over placebo (22% vs 19%). Ibandronate however is reported to double the incidence of GI toxicity including abdominal pain, dyspepsia, nausea and oesophagitis compared to placebo [16].

Locally in our practice, adjuvant bisphosphonates were commissioned by Sheffield Clinical Commissioning Group (CCG) in 2016, followed by other local CCGs shortly after, and came into routine clinical practice between November 2016 and February 2017. Post-menopausal patients, either naturally or rendered post-menopausal by ovarian suppression therapy with GnRH analogues, were selected for treatment and patients receiving adjuvant chemotherapy also received zoledronic acid 6-weekly for 3 infusions and then on completion of chemotherapy switched to oral ibandronate 50 mg daily to complete three years of bisphosphonate treatment. Patients not requiring chemotherapy received oral ibandronate 50 mg daily from the outset, intended for a 3-year treatment period. From the literature, concerns do exist regarding oral bisphosphonate compliance in the osteoporosis treatment settings, in which bisphosphonates are most commonly given as a weekly oral dose [17], but limited data is available on the compliance with the daily oral dosing recommended for prevention of recurrence of breast cancer. Now that oral ibandronate has been embedded into our local routine practice for over 12 months, we aimed to evaluate the compliance and tolerability of oral ibandronate within our early breast cancer population.

2. Patients and methods

The OPSAT-Q is a validated questionnaire to assess patient satisfaction with BP treatment [18]. Convenience, confidence and daily functioning whilst on oral BPs and overall satisfaction items are rated on a 7-point scale from “very dissatisfied” to “very satisfied”. Side effect evaluation includes ‘heartburn/acid reflux”, “stomach upset” and any “other side effects” and are rated on a 5 point scale from “not bothered at all “ to “extremely bothered”. In addition we collected data on whether patients have “considered” or “already” stopped their medication. We also included a free text box to facilitate patient comments. The OPSAT-Q questionnaire was modified for our patient population and was reviewed and approved by the Clinical Effectiveness Unit at Sheffield Teaching Hospitals Foundation NHS trust.

Patients were included in this study if they had a diagnosis of invasive breast cancer, which had been treated with curative intent and they had been prescribed at least 1 month of oral ibandronate (50 mg daily) between November 2016 and January 2018 from secondary care pharmacy records. Patients were excluded if they had developed metastatic disease since their ibandronate was first prescribed or if they were non-compliant with follow up oncology appointments. 413 patients were identified from pharmacy records at Weston Park Hospital Sheffield, Doncaster Royal Infirmary, Rotherham District General Hospital, Barnsley Hospital and Chesterfield Royal Hospital. 389 patients were identified as eligible to take part (see Fig. 1).

Table 1
Patient demographics.

Patient demographic	Number (% of responders)
Age (mean and range)	67 (35–89)
T stage	
T1	152 (52%)
T2	127 (43%)
T3	17 (5%)
N stage	
N0	181 (61%)
N1	77 (25%)
N2	28 (10%)
N3	13 (4%)
NPI (mean and range)	4.33 (2.2–8.2)
Tumour grade	
1	17 (5%)
2	177 (58%)
3	113 (37%)
Menopausal status at diagnosis	
Pre	14 (4%)
Peri	8 (3%)
Post	273 (93%)
ER Allred score	
0–2	41 (13%)
3–5	7 (2%)
6–8	252 (85%)
Herceptin status	
Positive	43 (15%)
Negative	257(84%)
Not tested	4 (1%)
Systemic treatment	
Endocrine alone	137 (46%)
Chemotherapy	138 (47%)
Herceptin	37 (13%)

Statistical analysis was performed in graph pad PRISM v 7.0d and Excel v14.5.6. Average item scores were expressed as mean + 95% confidence interval. Other results were expressed as percentage of total study responders. Comparison of groups was evaluated using paired *t*-test for significance.

3. Results

3.1. Patient characteristics

Of 389 questionnaires sent out, 295 patients responded (76%). Mean (range) age was 67 years (35–89) and 273 (93%) were post-menopausal at the diagnosis of breast cancer. Those who were pre-menopausal were rendered chemically postmenopausal with goserelin prior to initiation of bisphosphonates. The majority of patients had T1 (52%), N0 (61%), grade 2 (58%) breast cancer giving a mean (range) Nottingham prognostic index of 4.3 (2.2–8.2)(see Table 1).

3.2. Patient satisfaction

The mean item scores for satisfaction where 1 reflects “very dissatisfied” and 7 reflects “very satisfied” were: 5.7 for how easy it is to take the medication, 6.1 for how easy it is to remember to take the medication, 5.5 for how well oral BPs fit into medication schedule, 5.0 for amount of time required to take oral BPs, 5.3 for overall satisfaction with the medication and 5.3 for how satisfied to continue taking the medication. We evaluated if there was any significant differences in satisfaction according to age, with the recognition that the majority of women ≤55years will still be in regular employment with caregiver responsibility [19]. There was no significant difference in mean item score for satisfaction with the exception of how well BPs fit into medication schedule with those ≤55 years scoring 5.3 and those >55years scoring 6.1 ($p = 0.045$) (see Fig. 2).

3.3. Patient reported side effects

The mean item scores for side effects where 1 reflects “not bothered at all” and 5 reflects “extremely bothered” were: 1.9 for heartburn/acid reflux, 1.7 for stomach upset other than heartburn/acid reflux and 1.8 for other side effects. Less than 10% of patients reported being extremely bothered by side effects (see Fig. 3). The predominant ‘other’ side effect reported by patients was aching muscles / joints / bones. 3 patients reported dental issues with no reports of osteonecrosis of the jaw, 4 reported skin irritation, 1 reported kidney problems.

3.4. Discontinuation of oral BPs

22% of patients reported they had considered stopping their oral bisphosphonates but only 16% of responders ($n = 47$) had stopped. Of those that had stopped, 10% converted onto IV zoledronic acid but the remaining 6% did not continue with adjuvant bisphosphonates either due to advice from the General Practitioner, Oncology team or patient choice. In the 47 patients who had to stop oral BPs, the majority of those ceased the medication in the first 6 months of use (see Fig. 4).

4. Discussion

Adjuvant BPs have now become standard of care to reduce breast cancer mortality in post-menopausal early breast cancer patients in Europe and America, supported by published guidelines on drug choice, duration and patient selection [13,14]. Clinicians have the option to prescribe intravenous or oral BPs for 3–5 years duration after consideration of side effect profile and according to local commissioning agreements.

Patient satisfaction and compliance with BPs is important to optimise the benefit of a 17% relative reduction in breast cancer mortality as demonstrated in the recent meta-analysis of adjuvant BP clinical trials [12]. In the present study we investigated patient reported tolerability with daily ibandronate in women with early breast cancer. Patient satisfaction overall was good and less than 10% of patients were extremely bothered by side effects. This data reflects better tolerability than patient data from the metastatic setting where 24% of patients expressed dissatisfaction with the constraints, especially the time required to be upright after taking the tablet [20].This may be due to differences between the patient cohorts with the patients in our study receiving curative breast cancer treatment compared to the metastatic setting where polypharmacy is more likely to occur, patients may be symptomatic of their metastatic disease and a duration for compliance with the tablets is not defined, all of which can impact on resilience to comply with daily oral medication that requires such a stringent administration process. In addition, the potential to prevent metastatic disease and improve survival may be a stronger driver to comply with medication in the adjuvant setting than the prevention of skeletal related events in the metastatic setting.

In the adjuvant setting, there is currently no patient reported data on compliance and tolerability of oral BPs administered as a daily dose to reduce breast cancer mortality in a ‘real world’ setting. In the context of a randomised controlled trial of adjuvant clodronate, adherence to treatment at 3 years was 56% [10]. In the present study, rates of discontinuation from medication were low (16%) in the 295 patients who responded. This is lower than discontinuation rates seen in the metastatic studies of daily oral BP with clodronate (1600 mg/day) where rates of discontinuation were ~35% due to GI side effects [21,22], but similar to metastatic studies with daily ibandronate (5–50 mg/day) with a 10% discontinuation rate [23]. Compliance with weekly oral BPs in the metastatic breast cancer setting has also been evaluated and showed poor persistence with 45.6% of patients stopping after 1 year of therapy [24]. Previous studies have suggested oncologists tend to overestimate patient compliance with oral bisphosphonates and a third of surveyed oncologists anticipated that adherence would be >70% in

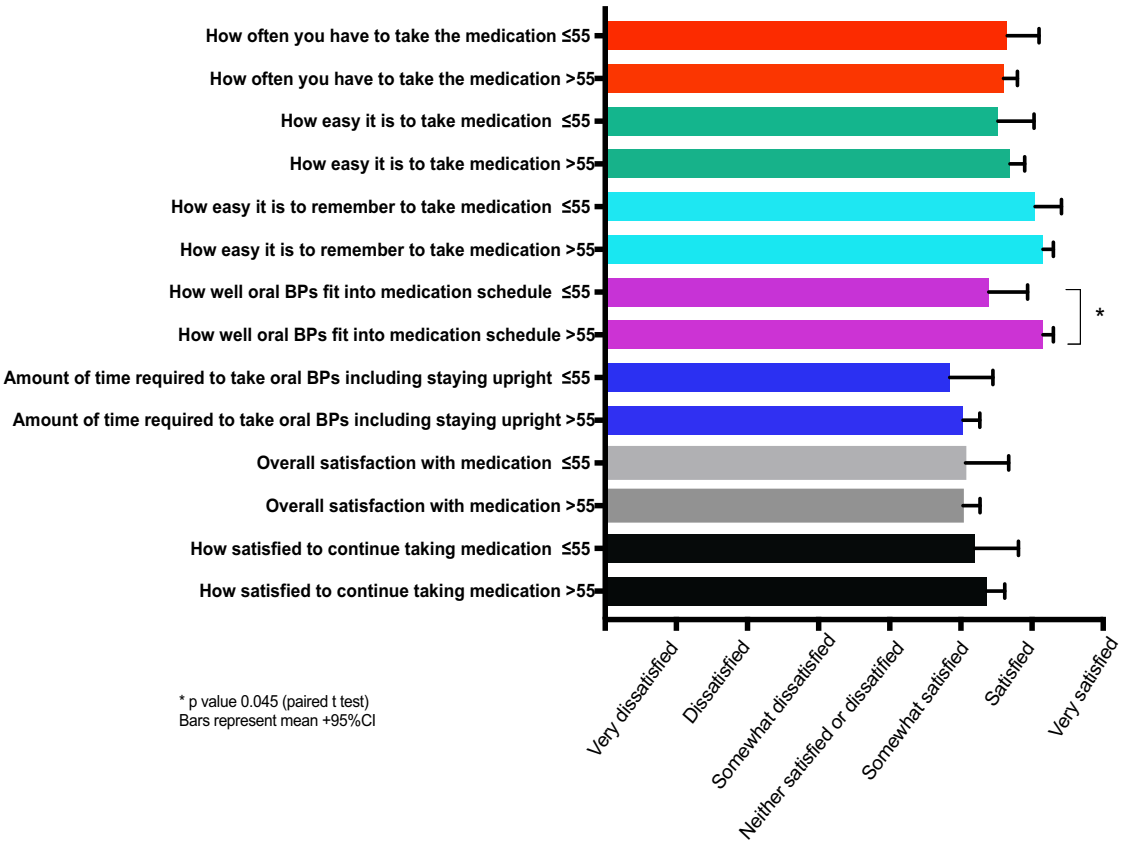

Fig. 2. Patient reported satisfaction stratified according to age. (1 represents "very dissatisfied", 7 "very satisfied"). Bars represent mean + 95%CI. *P-value < 0.05 (paired t-test).

the metastatic setting [25]. This has the potential to negatively impact on clinical outcomes and there is recognition amongst clinicians that strategies to improve compliance are needed [26].

In the osteoporosis setting, compliance is less with daily regimes compared to weekly regimes with a 40–60% higher discontinuation rate with daily compared to weekly regimes [27]. Compliance was evaluated in a systematic review of 27 studies in the osteoporotic setting and demonstrated persistence rates of 27.9–86.8% at 1 year with increased compliance in those patients who has experienced a fracture compared to those who were asymptomatic from their osteoporosis [28]. Compliance is higher in our population with a persistence rate of 84% at 1 year and may reflect patient perception of the importance of compliance with a medication that can improve survival after a breast cancer diagnosis.

Our adjuvant patient data is encouraging and can reassure clinicians that daily oral bisphosphonates in the early breast cancer setting are a viable option and adherence to the medication in the first year is 84%. If patients do stop, this is most likely to be in the first 6 months of treatment and is reflected in the reported early withdrawal from study rates (within 6 weeks of start) of 8% in the metastatic trials of ibandronate [16]. This is important clinical information that needs to be corresponded to primary care colleagues so that potential toxicities from this treatment are recognised and patients are referred back to secondary care for consideration of an intravenous BP regimen.

Our study does have limitations. We did not collect additional data on lifestyle factors that may have predisposed to poor compliance (including smoking, alcohol consumption, socioeconomic status, employment status). Additionally we did not record if the patient had pre-existing GI symptoms, which are not uncommon after adjuvant chemotherapy regimens containing oral steroids. We relied entirely on patient reported compliance with oral BPs and did not check primary care records of repeat prescriptions. The response rate to our questionnaire was 76% so it must be acknowledged that compliance rates may be lower than recorded. However, this is the first patient reported data to evaluate compliance with adjuvant daily oral BPs since they were introduced into routine clinical practice and provide useful data on which clinicians can base choice of drug and assess impact on local clinical practice.

In conclusion, prevalence of severe side effects in a 'real world' population of post-menopausal women receiving adjuvant oral BPs is low and these drugs are generally well accepted and tolerated by patients, but a proportion of patients will discontinue treatment. Further research is needed to understand if the compliance issues with oral BPs affect the clinical impact of adjuvant bisphosphonates on breast cancer mortality compared to an IV regimen.

Declaration of interest

CW declares speaker and consultancy fees from Amgen and Pfizer. MCW declares advisory board fees for Roche, Novartis and Genomic Health and speaker fees from Pfizer and Eisai. CM declares no interests.

Funding and acknowledgements

This study was funded by Weston Park Cancer Charity (grant reference number SG225 and CA140). We would like to acknowledge all the patients who kindly took time to complete the questionnaires and the consultants of the patients included in the study: Drs Purohit, Din, Walkington, Baldry, Taylor, Brown, Lee, Silva, Hatton, Dunn, Ramakrishnan.

Supplementary material

Supplementary material associated with this article can be found, in

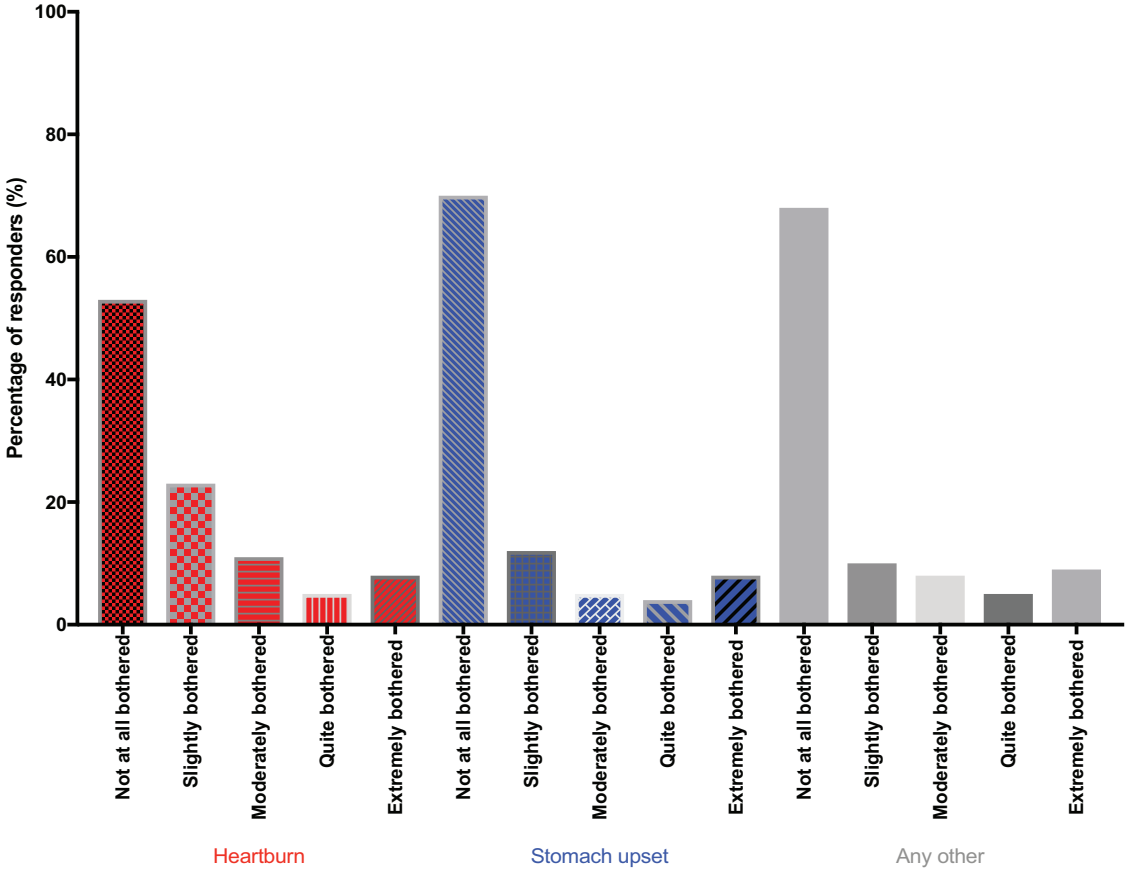

Fig. 3. Patient reported side effects of oral ibandronate.

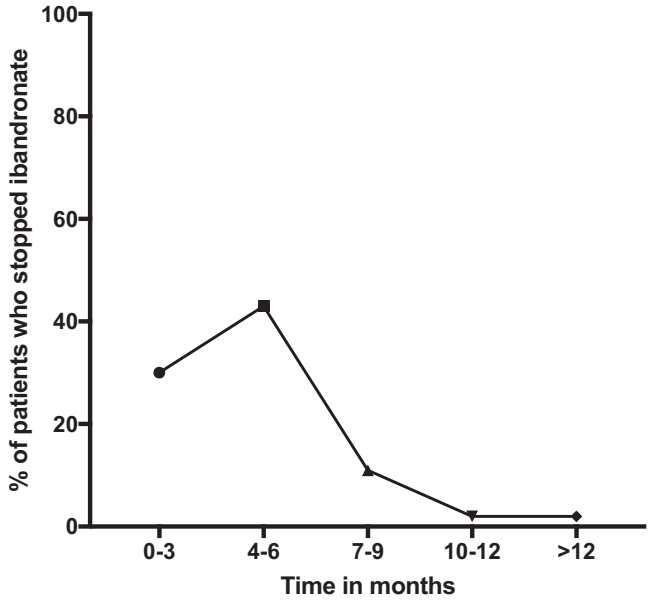

Fig. 4. Time to cessation of oral ibandronate.

the online version, at doi: 10.1016/j.jbo.2019.100226.

References

[1] M.C. Winter, I. Holen, R.E. Coleman, Exploring the anti-tumour activity of bisphosphonates in early breast cancer, Cancer Treat. Rev. 34 (2008) 453–475.
[2] F. Daubine, C. Le Gall, J. Gasser, J. Green, P. Clezardin, Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis, J. Natl. Cancer Inst. 99 (2007) 322–330.
[3] G. Mundy, Preclinical models of bone metastases, Semin. Oncol. 28 (2001) 2–8.
[4] G.R. Mundy, Metastasis to bone: causes, consequences and therapeutic opportunities, Nat. Rev. Cancer 2 (2002) 584–593.
[5] I.J. Diel, E.F. Solomayer, S.D. Costa, et al., Reduction in new metastases in breast cancer with adjuvant clodronate treatment, N. Engl. J. Med. 339 (1998) 357–363.
[6] T. Powles, S. Paterson, J.A. Kanis, et al., Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer, J. Clin. Oncol. 20 (2002) 3219–3224.
[7] T. Saarto, L. Vehmanen, P. Virkkunen, C. Blomqvist, Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients, Acta Oncologica 43 (2004) 650–656.
[8] M. Gnant, B. Mlineritsch, W. Schippinger, et al., Endocrine therapy plus zoledronic acid in premenopausal breast cancer, N. Engl. J. Med. 360 (2009) 679–691.
[9] R.E. Coleman, H. Marshall, D. Cameron, et al., Breast-cancer adjuvant therapy with zoledronic acid, N. Engl. J. Med. 365 (2011) 1396–1405.
[10] A.H. Paterson, S.J. Anderson, B.C. Lembersky, 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. 13 (2012) 734–742.
[11] G. von Minckwitz, V. Mobus, A. Schneeweiss, 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. 31 (2013) 3531–3539.
[12] R. Coleman, T. Powles, A. Paterson, et al., Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, Lancet 386 (2015) 1353–1361.
[13] S. Dhesy-Thind, G.G. Fletcher, P.S. Blanchette, et al., Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology clinical practice guideline, J. Clin. Oncol. 35 (2017) 2062–2081.
[14] P. Hadji, R.E. Coleman, C. Wilson, et al., Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel, Ann. Oncol. (2015).
[15] J. Gralow, W.E. Barlow, A.H.G. Paterson, D. Lew, A. Stopeck, D.F. Hayes, D.L. Hershman, M. Schubert, M. Clemons, C.H. Van Poznak, E.C. Dees, J.N. Ingle, C.I. Falkson, A.D. Elias, M.J. Messino, J.H. Margolis, S.R. Dakhil, H.K. Chew, R.B. Livingston, G.N. Hortobagyi, SWOG S0307 phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: comparison of toxicities and patient-stated preference for oral versus intravenous delivery, J. Clin. Oncol. 32 (2017) 558.

[16] P. Conte, V. Guarneri, Safety of intravenous and oral bisphosphonates and compliance with dosing regimens, Oncologist 9 (Suppl 4) (2004) 28–37.
[17] E.S. Siris, C.S. Fan, X. Yang, S. Sajjan, S.S. Sen, A. Modi, Association between gastrointestinal events and compliance with osteoporosis therapy, Bone Rep. 4 (2016) 5–10.
[18] E.M. Flood, K.M. Beusterien, H. Green, et al., Psychometric evaluation of the Osteoporosis Patient Treatment Satisfaction Questionnaire (OPSAT-Q), a novel measure to assess satisfaction with bisphosphonate treatment in postmenopausal women, Health Qual. Life Outcomes 4 (2006) 42.
[19] www.ons.gov.uk/employmentandlabourmarket/peopleinwork. Accessed 24 October 2018.
[20] L. Fallowfield, J. Stebbing, J. Braybrooke, C. Langridge, V. Jenkins, The preferences and experiences of different bisphosphonate treatments in women with breast cancer, Psychooncology 20 (2011) 755–761.
[21] A.H. Paterson, T.J. Powles, J.A. Kanis, E. McCloskey, J. Hanson, S. Ashley, Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer, J. Clin. Oncol. 11 (1993) 59–65.
[22] B. Kristensen, B. Ejlertsen, M. Groenvold, S. Hein, H. Loft, H.T. Mouridsen, Oral clodronate in breast cancer patients with bone metastases: a randomized study, J. Intern. Med. 246 (1999) 67–74.
[23] J.J. Body, I.J. Diel, M. Lichinitzer, et al., Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies, Br. J. Cancer 90 (2004) 1133–1137.
[24] P. Hadji, V. Ziller, J. Kyvernitakis, N. Schmidt, K. Kostev, Persistence with bisphosphonates in patients with metastatic breast cancer: a retrospective database analysis, J. Cancer Res. Clin. Oncol. 139 (2013) 1149–1155.
[25] L. Fallowfield, V. Jenkins, R. Coleman, Which bisphosphonates do oncologists prescribe for women with metastatic breast cancer and why? Results of a UK survey, Breast 17 (2008) 459–463.
[26] P. Hadji, M.S. Aapro, J.J. Body, et al., 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.
[27] C. Carbonell-Abella, A. Pages-Castella, M.K. Javaid, et al., Early (1-year) discontinuation of different anti-osteoporosis medications compared: a population-based cohort study, Calcif. Tissue Int. 97 (2015) 535–541.
[28] H.P. Vieira, I.A. Leite, T.M. Araujo Sampaio, et al., Bisphosphonates adherence for treatment of osteoporosis, Int. Arch. Med. 6 (2013) 24.