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Adjuvant bisphosphonate use in patients with early stage breast cancer: Patient perspectives on treatment acceptability and potential de-escalation

Sharon McGee [a,b], Mashari AlZahrani [a], Carol Stober [b], Terry L. Ng [a,b], Katherine Cole [a], Gail Larocque [c], Arif Awan [a,b], Sandeep Sehdev [a,b], John Hilton [a,b], Lisa Vandermeer [b], Brian Hutton [d], Gregory Pond [e], Deanna Saunders [b], Mark Clemons [a,b,*]

[a] Department of Medicine, Division of Medical Oncology, The Ottawa Hospital and the University of Ottawa, Ottawa, Canada
[b] Cancer Therapeutics Program, Ottawa Hospital Research Institute, Ottawa, Canada
[c] The Ottawa Hospital Cancer Program, The Ottawa Hospital, Ottawa, Canada
[d] Clinical Epidemiology Program, The Ottawa Hospital Research Institute and University of Ottawa, Ottawa, Canada
[e] Department of Oncology, Juravinski Cancer Centre and McMaster University, Hamilton, Canada

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ABSTRACT

Background: Despite the increasing use of adjuvant bisphosphonates for early stage breast cancer (EBC), little is known about the patient experience with such treatments. A patient survey was performed to identify current prescribing practices, perceptions around the role of treatment, the impact of treatment on patients' quality of life, and future trial designs.

Methods: EBC patients who had either completed or were currently receiving adjuvant bisphosphonates were sent an anonymized survey. The survey collected information on patient and disease characteristics, bisphosphonate scheduling, compliance, and tolerance. Questions also assessed patient interest in trials of de-escalated bisphosphonate therapy.

Results: A total of 255 patients were contacted, with 164 eligible respondents (eligible response rate 164/255, 64.3%). Median patient age was 52 years (range 28 to 82 years). The majority (111/163, 68.1%) were postmenopausal at the time of diagnosis, 23.3% (38/163) were premenopausal, and 7.4% (12/163) were perimenopausal. Most patients (78%) had received chemotherapy. Zoledronate was the most commonly used bisphosphonate (92%), with the majority receiving treatment every 6 months for 3 years (73%). While 66% (107/161) of respondents had experienced side effects with treatment, most had, or expected to, complete treatment (154/163, 94%). Provided there was no detriment in breast cancer outcomes, there was strong interest in future studies of de-escalating adjuvant bisphosphonate therapy.

Conclusion: While most patients tolerate their treatment, there is interest in performing trials of de-escalation of these agents.

1. Introduction

Early stage breast cancer (EBC) patients are at risk of skeletal morbidity, reflected through an increased incidence of bone metastases and fragility fractures. Clinical trials and a meta-analysis have evaluated the adjuvant role of bone-modifying agents such as bisphosphonates. The results showed reduced rates of distant breast cancer recurrence, reduced bone recurrence, and improved breast cancer-specific survival. Hence evidence-based guideline groups now recommend adjuvant bisphosphonate (usually intravenous zoledronate or oral clodronate) use in postmenopausal (natural or with medically induced ovarian suppression) women, with high risk EBC [1–4].

Despite these recommendations, and the widespread use of zoledronate, the meta-analysis [1] was unable to identify the optimal agent, dose or duration of therapy. With adjuvant zoledronate trials utilising different numbers of zoledronate infusions (7 to 19), different durations of treatment (2 to 5 years), different doses and dosing intervals [5–8], many physicians recommend 6-monthly zoledronate over 3–5 years. Of interest, uptake of these recommen-

* Corresponding author at: Division of Medical Oncology, The Ottawa Hospital Cancer Centre, 501 Smyth Road, Ottawa, Canada.
E-mail address: mclemons@toh.ca (M. Clemons).

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dations has been variable. At the 2019 St Gallen Consensus Conference, only 42.6% of the international panel reported routine use of BMAs in eligible EBC patients [9,10]. Similarly, data obtained from Cancer Care Ontario (14/April/2020, personal communication, CCO Data Disclosure Team) shows that only about 20% of eligible breast cancer patients are receiving adjuvant bisphosphonate therapy [8].

Given the rapid evolution of adjuvant bisphosphonate use, and the variable uptake of these agents, a survey targeting EBC patients was conducted to identify current bisphosphonate prescribing practices, patient perceptions of the indications for treatment, and their impact on patient quality of life. In addition, as an increasing number of trials have evaluated the effects of less frequent administration of BMAs in metastatic disease [11–20], AI-induced bone loss [21–23], and osteoporosis [24–26], we also asked patients about their interest in further de-escalation trials of adjuvant bisphosphonate therapy. Responses from this survey will help devise a pragmatic clinical trial to answer these questions and ensure that trial results are relevant to patients.

2. Materials and methods

2.1. Study population

The target population was postmenopausal (including pre- and perimenopausal women considered postmenopausal because of ovarian suppression) EBC patients who were either currently receiving, or had previously received, a BMA as part of their treatment for breast cancer. In Ontario, funding for adjuvant zoledronate follows the CCO-ASCO guideline that, "recommended that administration of bisphosphonates as adjuvant therapy be considered for postmenopausal patients with breast cancer (including patients premenopausal before treatment who have menopause induced by ovarian suppression deemed candidates for adjuvant systemic therapy" [1–4]. The original study plan was to accrue approximately 200 participants from 3 Canadian cancer centres (Ottawa, Brampton and Southlake). This sample size was chosen to ensure a broad perspective on treatment. Patients had to be able to provide verbal consent and be willing and able, to complete the survey, which was available in English only. The main exclusion criterion was the presence of metastatic breast cancer.

2.2. Study outcomes

Information sought in the survey aimed to obtain insights on real world adjuvant BMA prescribing practices, patient perceptions and actual experiences of treatment. In addition, we wished to determine patient interest in the design of future adjuvant BMA studies and which endpoints should be considered the most important for such studies.

2.3. Survey development

The survey was designed by a multidisciplinary team with established expertise in survey development and performance [27–31]. While the survey was not validated it was pilot tested on a limited number of oncologists (MZA, KC), one advanced practice nurse (GL) and one non-healthcare professional (LV) before launch. The first section of the survey was devised to collect pertinent patient demographic information [age, menopausal status at time of breast cancer diagnosis, tumour receptor status, chemotherapy/LHRH analogue use]. Section two determined information on adjuvant BMA prescribed (i.e. agent, dose, schedule, duration), patient understanding of the indications for treatment, and their tolerance of therapy, including the types of side effects experienced and their impact on quality of life. In the final section, respondents were asked about their interest in de-escalation trials of adjuvant bisphosphonate therapy, specifically conducting a pragmatic trial of adjuvant zoledronate comparing 6-monthly dosing for 3 years to a single injection.

2.4. Survey implementation

Patients were approached to participate in the survey, by either their medical oncologist or clinic nurse. Once permission was given, the study clinical research associate would contact the patient. Interested patients were provided with the option of completing written or electronic versions of the survey. Written copies were sent via mail, with directions on return. Patients requesting electronic surveys were sent an email with a link to the anonymous survey on Microsoft Forms (on the secure, Ottawa Hospital SharePoint site), and completed online. Alternatively, patients could request to receive the questionnaire by email as a Word file or PDF file for completion. No reminders were sent to patients. The survey was approved by the Ontario Cancer Research Ethics Board (OCREB).

2.5. Data analysis

All the data were summarized descriptively. The frequency of each answer choice was tabulated as a proportion of the total number of respondents for that category. Data were analyzed using Microsoft Excel.

3. Results

3.1. Patient and disease characteristics

The survey was initiated on 1 September 2020 and closed 6 November 2020. Unfortunately, the survey launch was delayed by the Covid-19 pandemic and the reduction in clinical research staff at all sites. This also meant that two centres could not open the study and patients were therefore only accrued from the Ottawa centre. A total of 255 patients were contacted, of which 164 of 169 respondents met the study eligibility criteria (response rate 164/255, 64.3%). Overall, 169 patients responded to the survey, the majority preferring to do so electronically (156/169, 92.3%) while a small number (13/169, 7.7%) responded on paper copies. Of the five patients that were ineligible, 2 patients had never been prescribed a BMA / bisphosphonate as part of the treatment for their breast cancer (2 respondents) and 3 patients had been prescribed an oral bisphosphonate for the treatment of osteopenia/osteoporosis rather than for breast cancer. The characteristics of the 164 eligible and responding patients are shown in Table 1. The median age at breast cancer diagnosis was 52 years (range 28 to 82 years). The majority (111/163, 68.1%) of patients were post-menopausal while 23.3% (38/163) were premenopausal and 7.4% (12/163, 7.4%) were perimenopausal at the time of breast cancer diagnosis, with 20 respondents receiving ovarian suppression (medical or via oophorectomy) as part of their treatment. Chemotherapy was received by the majority of respondents (127/162, 78.4%). Most respondents reported having hormone receptor positive disease (99/162, 61.1%), with 28.4% (46/162) reporting HER2 positive, 6.2% (10/162) with triple negative disease and 17.9% (29/162) were unsure.

3.2. Bone-modifying agent therapy received

Overall, zoledronate was the most common BMA prescribed (150/163, 92.0%). No respondents received oral clodronate (Table 2). The majority received treatment as an injection every

Table 1
Patient & disease characteristics.

Question	Options	Number of responses (N = 163)	N (%)
Age at time of breast cancer diagnosis		162	Median 52 yrs (range 28–82 yrs)
Menopausal status at time of diagnosis		163	
	Postmenopausal		111 (68.1%)
	Premenopausal		38 (23.3%)
	Peri-Menopausal		12 (7.4%)
	Don't remember		2 (1.2%)
If pre/peri-menopausal at the time of diagnosis was additional treatment given to make patient menopausal		47	
	Yes		20 (42.6%)
	No		27 (57.4%)
chemotherapy administered		162	
	Yes		127 (78.4%)
	No		35 (21.6%)
Tumour receptor status		162	
	Hormone responsive		99 (61.1%)
	HER2 positive		46 (28.4%)
	Triple negative		10 (6.2%)
	Not sure		29 (17.9%)

6 months, for 3 years (117/163, 71.8%) or 5 years (21/163, 12.9%). Ninety-four percent (154/163) of respondents had completed (28/163, 17.2%), or planned to complete (126/163, 77.3%), their treatment, and 5.5% had either stopped treatment early (5/163), or are considering stopping early (4/163). Overall, 6% of respondents had either stopped treatment early (5/163, 3.1%) or were considering stopping (4/163, 2.4%). The 5 respondents who stopped treatment cited concerns about long term complications and side effects as reasons for discontinuation. The latter included dental issues, bone pain, and hypophosphatemia. One respondent stopped due to concerns about receiving treatment during the COVID-19 pandemic.

Respondents' understanding of the purpose or benefit of bone targeted therapy in the treatment of early stage breast cancer was varied. The majority reported that it was given to reduce the risk of breast cancer recurrence in the bone (109/163, 68.9%), to prevent osteopenia/osteoporosis (100/163, 61.3%) or to improve survival (38/163, 23.3%) (Table 2).

3.3. Tolerance of Bone-Modifying agent therapy

Table 3 shows data on patient tolerance of bisphosphonate therapy. Most respondents (103/162, 64%) did not find the requirements of adjuvant bisphosphonate therapy bothersome i.e. getting bloodwork prior or attending the treatment appointment. Sixty-six percent of respondents (107/161) did, however, experience some type of side effect with treatment. These side effects were, to some extent, bothersome to 63% of respondents ("a *bit bothersome*" for 20%, "*somewhat bothersome*" for 29%, "*quite bothersome*" for 7%, and "*very bothersome*" for 7%). The most common side effects reported were flu-like symptoms (72/163, 44%) and bone pain (68/163, 42%). Thirty-six percent (58/163) of respondents reported other side effects, which included fatigue, dizziness, nausea, dental problems, headaches and hair loss. Osteonecrosis of the jaw was reported by 4 respondents (4/163, 2%).

Table 2
Bone-Modifying Agent Therapy Received.

Question	Options	Number of responses (N)	N (%)
Bone modifying agent received		163	
	Zoledronic acid		151 (92.6%)
	Clodronate		0 (0%)
	Don't remember		11 (6.8%)
	Other:		3 (1.2%)
Treatment schedule		163	
	Daily by mouth for 2-3yrs		2 (1.2%)
	6-monthly as injection for 3yrs		120 (73.6%)
	6-monthly as injection for 5yrs		21 (12.9%)
	Don't know		8 (4.9%)
	Other		12 (7.3%)
Has treatment been completed?		163	
	I plan to finish my treatment		126 (77.3%)
	I'm considering stopping early		4 (2.4%)
	Yes, I completed treatment		28 (17.2%)
	No, I stopped treatment early		5 (3.1%)
If stopped early, reason		5	
	Side effects were bothersome		0 (0%)
	Concern about potential complications		1 (20%)
	Extra appointments were bothersome		0 (0%)
	Other:		4 (80%)
	- Dental issues		1
	- Bone pain		1
	- Hypophosphatemia		1
	- Concerns about COVID		1
Purpose of treatment		163	
	Reduce risk recurrence in bone		109 (66.9%)
	Reduce risk recurrence in organs		39 (23.9%)
	Prolong survival		39 (23.9%)
	Prevent bone loss		100 (61.3%)
	Prevent cancer treatment complications		27 (16.6%)

3.4. Interest in studies de-escalating adjuvant Bone-Modifying agent therapy

The majority of respondents stated they would be willing to receive fewer adjuvant bisphosphonate treatments if they were expected to obtain the same adjuvant breast cancer benefits (130/163, 80%). Sixty-four percent (104/161) would accept fewer treatments if it meant there would be less side effects. Fifty-six percent of respondents (90/162) stated they would be willing to participate in a trial comparing a single injection of zoledronic acid to injections given every 6 months over 3–5 years, understanding that the exact benefit in improving breast cancer outcomes with fewer treatments is yet unknown (Table 4).

3.5. Additional comments from respondents

Seventy respondents made additional comments, summarized in Appendix 1. Some common themes included the fact that with respect to side effects, the first bisphosphonate treatment was typically the worst, with subsequent treatments having fewer, or no, associated side effects (9 respondents). Four respondents

Table 3
Bisphosphonate therapy tolerance.

Question	Options	Number of responses (N)	N (%)
Was going for treatments bothersome?		162	
	Not at all		103 (63.6%)
	A bit		41 (25.3%)
	Somewhat		16 (9.9%)
	Quite bothersome		2 (1.2%)
	Very bothersome		0 (0%)
Side effects with BMA treatment		161	
	Yes		107 (66.4%)
	No		54 (33.5%)
Were side effects bothersome?		160	
	Not at all		59 (36.9%)
	A bit		33 (20.6%)
	Somewhat		46 (28.8%)
	Quite bothersome		11 (6.9%)
	Very bothersome		11 (6.9%)
What side effects did you experience? Select all that apply.		116	
	Flu-like symptoms		72 (62.1%)
	Bone pain		68 (58.6%)
	Fracture		0 (0%)
	Renal impairment		0 (0%)
	Electrolyte alterations		4 (3.4%)
	Osteonecrosis of jaw		4 (3.4%)
	Other, including:		58 (50%)
	- Fatigue		8
	- Dizziness		2
	- Nausea		2
	- Dental problems		2
	- Headaches		1
	- Hair loss		1

Table 4
Interest in adjuvant bisphosphonate de-escalation studies.

Question	Options	N	N(%)
If it was possible to receive fewer treatment with same benefits, would you agree to less?		163	
	Yes		130 (79.8%)
	No		17 (10.4%)
	Don't know		16 (9.8%)
If less treatments meant you could have less side effects, would you agree to less?		161	
	Yes		104 (64,6%)
	No		30 (18.6%)
	Don't know		27 (16.8%)
Would you participate in a trial comparing a single zoledronic acid treatment to 6 given twice yearly for 3 yrs?		162	
	Yes		90 (55.6%)
	No		72 (44.4%)

wished to re-iterate that they would only participate in trials of de-escalation of adjuvant bisphosphonate therapy if efficacy, specifically breast cancer benefits, were the same. Three respondents stated that they would be willing to endure side effects if it meant a better outcome for their breast cancer.

4. Discussion

We present survey data regarding the real-world use of adjuvant bisphosphonate therapy from a large sample of patients with EBC, treated at a single tertiary referral cancer center in Ontario, Canada. We are not aware of any other publications reporting similar data outside of the clinical trial setting that evaluates compliance with and acceptance of adjuvant intravenous bisphosphonates. The patient population in the survey reflects those seen in clinical practice, with median age of 52 years, and the majority being postmenopausal, with hormone receptor positive disease (Table 1). Respondents also had higher risk disease, as suggested by the high rates of chemotherapy exposure (78%). While there is clinical trial evidence for the use of oral clodronate and ibandronate, intravenous zoledronate was the most-commonly prescribed BMA. For most patients zoledronate was given every 6 months for 3 years, although evidence, and guidelines, allow for treatment over 3 to 5 years. This suggests physician comfort, and preference, for shorter prescribing durations. This is important as data from a recent trial showed 5 years of adjuvant bisphosphonate has the same clinical benefit compared to 2 years while the risk of developing BMA-related toxicities increase [32].

The logistical requirements of treatment (bloodwork, attendance at the cancer centre) was not bothersome to the majority of patients. Of note, while side effects were common and caused, "*some degree of bother*" to roughly 2/3rds of patients, few patients actually stopped, or considered stopping, their treatment. The side effect profile was as expected, with the majority reporting flu-like symptoms (44%), and bone pain (42%). The rate of self-reported osteonecrosis of the jaw was double that commonly reported in the literature [33], however, this is based on only 4 self-reported cases so would be within the margin of expectations. This data suggests that patients have a high tolerance for treatment related side effects. Reasons for this may be, as suggested by additional patient comments (Section 3.5, Appendix 1), that side effects are more common with the first treatment, and later improve, or that patients are willing to endure toxicities if there is a potential breast cancer benefit.

Patient understanding of the purpose, or benefit, of adjuvant bisphosphonate therapy was varied, likely related to what was conveyed to them, or emphasized, by their prescribing physician. There is in fact evidence supporting all the provided indications (question 15), including reduction in the risk of breast cancer recurrence in the bone, and elsewhere, improving breast cancer survival, and preventing osteopenia/osteoporosis, both age and treatment related [1,21–26]. The majority of patients (67%) were aware of benefits in reducing the risk of breast cancer recurrence in the bone. Interestingly, a large proportion of respondents (61%) also highlighted a reduction in the risk of osteopenia/osteoporosis, although this is not emphasized by guidelines as an indication for treatment in EBC patients. Potential strategies to increase patient understanding of the indications for adjuvant bisphoshonate use in their care could also be explored in future studies.

Finally, more than 50% of respondents were interested in participating in clinical trials of de-escalation of adjuvant bisphosphonate therapy in EBC. Responses, and additional comments (Section 3.5, Appendix 1), did however suggest that proof of maintained breast cancer efficacy was an important endpoint for patients, and not just impacts on treatment related toxicities.

The authors were unable to identify other studies evaluating real world patient experiences with adjuvant intravenous bisphosphonates. An interesting study from the UK evaluated patients experiences with adjuvant oral ibandronate [34]. As ibandronate had ben embedded in their local routine practice for early stage

breast cancer patients they surveyed patients about their compliance and tolerability of treatment. This study used the validated Osteoporosis Patient Treatment Satisfaction Questionnaire [35] and showed that the oral ibandronate patients were older, more likely to be postmenopausal and less likely to have received chemotherapy than our own patient population. Similar to our study these patients reported a low incidence of severe side effects. Despite this however, 16% of their respondents had discontinued their oral ibandronate compared with 3.1% of our patients receiving intravenous zoledronate. These cross-study comparisons should be interpreted with caution especially as only one study [36] has compared oral clodronate, oral ibandronate and intravenous zoledronate in the adjuvant setting, while other studies compared bone-targeted agent tolerability in patients with metastatic disease [37].

There are limitations of the current study. Despite initially being a 3 centre study, COVID-19 related challenges lead to this being changed to a single centre study. This reduced the number of patients enrolled and somewhat reduced generalizability of results. Greater patient numbers across more centres would have provided broader insights into prescribing patterns and patient experience. The survey also focused on patients who received adjuvant bisphosphonate therapy for breast cancer, and thus gives no insights into the proportions of patients who were approached but refused treatment, or those treated with bisphosphonate therapy to reduce fragility fracture risk, rather than breast cancer specific benefits. Another limitation/observation from the current study is that while 50 women reported themselves as being pre/perimenopausal prior to receiving a bisphosphonate, LHRH analogues were used in only 20 patients. This is important because the defined population for adjuvant bisphosphonates is those patients who are either naturally postmenopausal or if pre/perimenopausal they should also be on concurrent LHRH analogues. Similar observations have been reported elsewhere [38]. Another, limitation of any survey that is completed by patients themselves is the issue of missing data. As this was an anonymous survey we were unable to link individual questionnaire responses to the individual patient's electronic health record. Similarly, as the survey was restricted to patients who were either receiving or had received adjuvant zoledronate we do not know the number of patients eligible for adjuvant bisphosphonate use who were actually approached about treatment, and received it.

All results are self-report, and the usual limitations of self-reported surveys apply, including the potential for recall bias or response bias. In addition, it is clearly very challenging to compare the incidence of side effects we report with those from the literature. The literature is predominantly based on toxicity reporting from clinical trials using validated toxicity scores. In the current study our questions were far broader. For example, "Did you experience any side effects with the medication?", is a challenging question as breast cancer patients are often on multiple treatments with multiple adverse effects and it is therefore difficult for patient to separate these effects from those of the bisphosphonate. Similarly, we did not specifically ask patients how many zoledronate infusions they had received when they completed the survey, or, if they had completed bisphosphonate treatment and how long ago they had finished treatment. These questions could be addressed in future studies as ultimately, the answers to toxicity questions could be significantly affected by these variables. Similar the reported incidence of ONJ (4 patients, 3.4%) would appear higher than one would expect from the literature [39]. However, as above as this was an anonymous survey we cannot clarify questionnaire answers with individual patients EMRs. Finally, decisions regarding patients approached for treatment, bone targeted agents prescribed, and their duration, are typically made by physicians, thus readers may be interested in the results of a similar survey we are currently conducting with physicians, which will provide additional important insights not seen here.

5. Conclusion

Adjuvant bisphosphonates are now an established component of the treatment of postmenopausal women with high risk breast cancer [1–3]. It is evident from this survey that 6-monthly zoledronate is the most commonly selected treatment and although 60% of patients report bothersome toxicities, most patients feel they are able to complete their planned treatment schedule. Despite this, patients were interested in trials to evaluate fewer bisphosphonate treatments to see if less treatment could decrease the risk of treatment-related toxicities, with equivalent impacts on bone density, and potentially similar benefits for breast cancer outcomes (i.e. survival and disease recurrence).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SMG reports receipt of honorarium from Novartis for insights on management of breast cancer patients. AAA reports Advisory board: Eli Lily, Exact Sciences, Exactis, Novartis, Pfizer, Honoraria: Apotex, Roche, Travel: Roche. BH and MC reports consulting fees from Cornerstone Research, outside the submitted work. GP reports consulting fees from Merck, Astra-Zeneca, Profound Medical, outside of submitted work; honorarium for DSMB membership from Takeda outside of submitted work; a close family member works for Roche Canada Ltd and owns stock in Roche Ltd. All other authors declare no competing interests.

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Author contributions

SMG, KC, GL, LV, GP and MC designed the study and prepared the protocol. CS and DS collected the data and LV coordinated the study. SMG, MA, CS, TN, GL, AA, SS, JH and MC approached patients for the trial. SMG, LV and MC did the statistical analysis. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SMG, LV, DS and MC wrote the manuscript. All authors were involved in the critical review of the manuscript and approved the final version.

Ethics committee approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of each institution Research Ethics Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Completion of the survey implied consent to participate. All data has been anonymized to protect the identities of subjects involved in the research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2021.100351.

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