Journal of Bone Oncology 26 (2021) 100343

Contents lists available at ScienceDirect

Journal of Bone Oncology

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

Feasibility outcomes of a randomised, multicentre, pilot trial comparing standard 6-monthly dosing of adjuvant zoledronate with a single one-time dose in patients with early stage breast cancer

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ARTICLE INFO

Article history:
Received 10 November 2020
Revised 24 November 2020
Accepted 26 November 2020
Available online 13 December 2020

Keywords:
Breast cancer
Zoledronate
Adjuvant bisphosphonate

ABSTRACT

Background: Adjuvant zoledronate is widely used in patients with early stage breast cancer (EBC), but its optimal duration and dosing interval is still unknown. While a single-dose of zoledronate can improve bone density for many years, a proper evaluation of its effects on breast cancer-related outcomes would require a large trial. In this pilot study we evaluated the feasibility of performing such a trial.

Methods: Eligible patients with EBC were randomised to receive either one dose of zoledronate or 7 doses (6-monthly dosing for 3 years). Feasibility was assessed by a combination of primary outcomes including: activation of at least 6 Ontario sites within a year, active participation (i.e. approaching eligible patients for study participation) of at least half of the medical oncologists, and enrolment of at least 100 patients across all sites within 9 months of the sixth site being activated.

Results: All 6 sites were activated within 1 year and of 47 medical oncologists, 27 (57%) approached patients. Between November 2018 and April 2020, 211 eligible patients were randomised, 106 (50.2%) to a single dose of zoledronate and 105 (49.8%) to 6-monthly dosing. Baseline characteristics of randomised patients included; median age 59 (range 36–88), ER and/or PR positive (85%), Her2 positive (23%), menopausal status (premenopausal [19%], perimenopausal [6.7%] and postmenopausal [74%]) and 74% received neo/adjuvant chemotherapy.

Conclusions: All study feasibility endpoints were met in this trial comparing alternative schedules for adjuvant zoledronate. We will now seek funding for performing a larger efficacy trial.

Trial registration: NCT03664687.

1. Introduction

Patients with early stage breast cancer (EBC) are at an increased risk of skeletal morbidity, as reflected through both bone recurrences and fragility fractures. Many trials have evaluated bone-modifying agents such as bisphosphonates and denosumab as adjuvant therapy in EBC patients with variable results [1,2]. The findings of an individual patient data meta-analysis showed that in postmenopausal women adjuvant bisphosphonates reduced the rate of distant breast cancer recurrence, recurrence in the bone and improved breast cancer survival [3]. This publication, and evidence-based treatment guidelines recommend that bisphosphonates (usually zoledronate or clodronate) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy [3–5]. One guideline more specifically recommended bisphosphonates

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https://doi.org/10.1016/j.jbo.2020.100343
2212-1374/

for those patients treated with chemotherapy and/or a > 12% risk of breast-cancer death at 10 years [6].

Despite these recommendations and the widespread use of zoledronate, the meta-analysis [3] was unable to identify the optimal agent, its dose or duration. It is therefore not surprising that with adjuvant zoledronate trials utilising different numbers of zoledronate infusions (7 to 19) and different durations of treatment (2 to 5 years) [7–9] that many guidelines have recommended 6-monthly zoledronate over 3–5 years. Of interest, uptake of these recommendations has been variable. For example, in Ontario, Canada, zoledronate was approved for funding in 2016, the percentage of patients over the age of 50 receiving adjuvant chemotherapy for breast cancer (and would therefore be considered to have higher risk disease) who also received adjuvant zoledronate was 4% (135/3370) in 2016, 13.7% (343/2502) in 2017, 20% (516/2568) in 2017 and in 2019 was 20.1% (452/2239) [10].

A number of studies have shown that a single-dose of zoledronate results in increased bone density over 2 years [11,12], 3 years [13] and 5 years [14] in different patient populations, including those with cancer. Furthermore, pharmacokinetic data with intravenous bisphosphonates in post-menopausal women showed the terminal half-life to be over a decade [15]. We hypothesize that one dose of zoledronate will be non-inferior to dosing every 6 months over 3 years for a number of primary end points including, invasive disease free survival, bone metastasis-free survival and breast cancer specific overall survival. A single injection of zoledronate should also improve patient adherence to treatment, reduce visits to the cancer centre for treatment, lead to fewer bone modifying agent related adverse events, improve health-related quality of life, and reduce cost and health care resource utilization. However, given the bone-metastasis event-free survival rate of newly diagnosed breast cancer patients is around 5% at 3–5 years, a non-inferiority study would require enrolment of thousands of patients [3]. For such a large sample size to be achieved, a pilot study is required to assess whether a larger clinical trial could be completed. Thus, we proposed a pragmatic, multicentre, open-label, randomized clinical trial to demonstrate the feasibility of opening a trial comparing a single-dose of zoledronate to 6-monthly dosing of zoledronate over 3 years.

2. Methods

2.1. Study population

Patients with EBC who were to receive systemic neo/adjuvant treatment and for whom adjuvant zoledronate would also be prescribed were potentially eligible. Other inclusion criteria included: commencing zoledronate within 3 months of starting endocrine therapy or within 3 months of completion of neoadjuvant or adjuvant chemotherapy. Patients receiving prior intravenous or oral bisphosphonates, or subcutaneous denosumab for the treatment of osteoporosis discontinued treatment prior to baseline evaluation. Patients had to have an ECOG performance status ≤ 2, serum creatinine > 30 ml/min and serum calcium ≥ 2 mmol/l within 4 weeks before first zoledronate infusion and be able to provide written consent. Exclusion criteria included: metastatic disease, history of or current evidence of osteonecrosis of the jaw and pregnancy or risk of pregnancy in patients that were not willing to practice contraception for the duration of the study. Patients were assessed at their usual clinic visits. No radiological assessments beyond conventional practice were mandated by the study. The study was approved by Health Canada as well as both local and provincial Research Ethics Boards (Ontario Research Ethics Board, OCREB). The trial was registered on clinicaltrials.gov NCT03664687 [16].

2.2. Trial design

In this multi-center unblinded randomized trial, patients were approached by their medical oncologist during a routine clinic visit. Eligible and consented patients were randomised in a 1:1 ratio using permuted variable block size of 4 and 6 to either: Arm A: Zoledronate one dose (4 mg) or Arm B: Zoledronate 4 mg every 6 months for 3 years (i.e. 7 doses). Allocations were concealed until patients were registered and enrolled. Stratification occurred by centre. Patients were stratified by centre and by use of chemotherapy (yes, no). Commercially available stocks of drug were used and initial dose, dose modifications and method of administration were as per the product monographs. Patients were instructed to take calcium and vitamin D as per Health Canada guidelines.

2.3. Data collection

Endpoint data were collected from emails sent to the treating physician when the patient was expected back in clinic and from the patient's electronic medical record (EMR) at baseline, 6, 12, 18, 24, 30 and 36 months. If the patient was randomized and either the patient or physician refused the randomization selection, reasons for this were recorded. Data collected included: baseline characteristics (age, stage of disease and type of chemotherapy), laboratory results (i.e. serum creatinine, serum calcium before each zoledronate infusion), most recent bone mineral density reading (if performed, as not study mandated) and baseline menopause status.

2.4. Outcomes

Primary Outcome: The feasibility of performing this randomised trial was assessed by a combination of metrics: activation of at least 6 Ontario sites, activation of the sixth site within 12 months of the first site being open for accrual, active participation in the trial (i.e. approaching eligible patients for study participation) of at least half of the medical oncologists at each site and enrolment of at least 100 patients across all 6 sites within 9 months of the sixth site being activated. The results of the primary outcomes are presented in this manuscript. These endpoints were chosen as indicators of committed physicians across centers, such that it would be possible to reach the sample size of a larger definitive trial.

Secondary Outcomes: A combination of secondary endpoints were evaluated including: Health utilities and incremental cost-effectiveness ratios, bone-metastasis-free survival (BMFS), time to first bone metastasis, fragility fractures rates and toxicity. Significant toxicities including; acute phase responses, ONJ, impaired renal function resulting in either discontinuation of zoledronate or zoledronate dose adjustment, atypical femur fracture, and new diagnosis of atrial fibrillation were also assessed. As dental care is not free in Canada, dental examination were recommended but not mandated. Hospitalizations and ER visits related to zoledronate were also collected. Baseline FRAX (Fracture Risk Assessment Tool) scores were calculated for each patient using most recent bone mineral density (BMD) reading if available [17]. Baseline FRAX scores were also calculated without bone density values if these were not available [18]. FRAX scores calculate the 10-year probability of a major osteoporotic fracture (proximal part of the humerus, wrist, or hip or a clinical vertebral fracture) and of a hip fracture, calibrated to the fracture and death hazards [19–21]. As scores can vary between countries, the validated Canadian tool was used [22].

Exploratory outcomes: Disease free survival (DFS), defined as the percentage of people in the trial who were alive and cancer free

after a specified number of years, and overall survival (OS), defined as the number of people alive, with or without signs of cancer will also be evaluated. As these endpoints as well as the secondary outcomes will take many years to occur they will be published elsewhere.

2.5. Statistical methods

Descriptive analysis: Baseline characteristics are presented as means (continuous measures) or proportions (dichotomous or categorical data) with 95% confidence intervals.

Analysis of the primary outcome: If all four primary outcomes defined above were met, then the study will be deemed as having met its feasibility goals, and planning for a larger randomized clinical trial could begin. If any primary outcomes were not met, the study will be deemed unfeasible.

2.6. Sample size

Given that this study is an internal pilot, a specific sample size cannot be calculated. We estimate that by the time the final centre has been activated for 9 months, we would accrue between 100 and 200 patients.

2.7. Study populations

The intent-to-treat (ITT) population was used for all primary feasibility and secondary clinically important outcomes. The ITT population was comprised of all patients who consented to participate in the, met all eligibility criteria, and were randomized to treatment, regardless of whether they went on to receive any study treatment or regardless of the duration of follow-up. Patients were included in the per protocol (PP) population if they were included in the ITT population and went on to receive at least one dose of treatment as per their planned treatment allocation. The PP population would be used for supportive analyses.

3. Results

3.1. Baseline patient characteristics

Between November 1, 2018 and April 2, 2020, 287 patients were approached about the study (The CONSORT diagram is shown in Fig. 1). Of these, 51 declined study participation. In total, 235 patients consented and were then assessed for study eligibility. 25 patients withdrew from the study; the most common reasons were: ineligible (n = 3), patient choice (n = 9) and physician choice (n = 12). The reasons for withdrawal are shown in Fig. 1. Practice changes due to the Covid-19 pandemic significantly changed the ability of patients to start treatment within protocol mandated timelines (n = 10).

Of the 211 eligible and randomised patients, 106 (50.2%) were randomised to single-dose zoledronate and 105 (49.7%) to 6-monthly zoledronate treatment. Baseline characteristics of the randomised patients are shown in Table 1. For the randomised patients, median age was 59 (range 36–88), 85% were ER and/or PR positive, 23% were Her2 positive, 12% were triple negative, and 74% of patients were postmenopausal (19% premenopausal

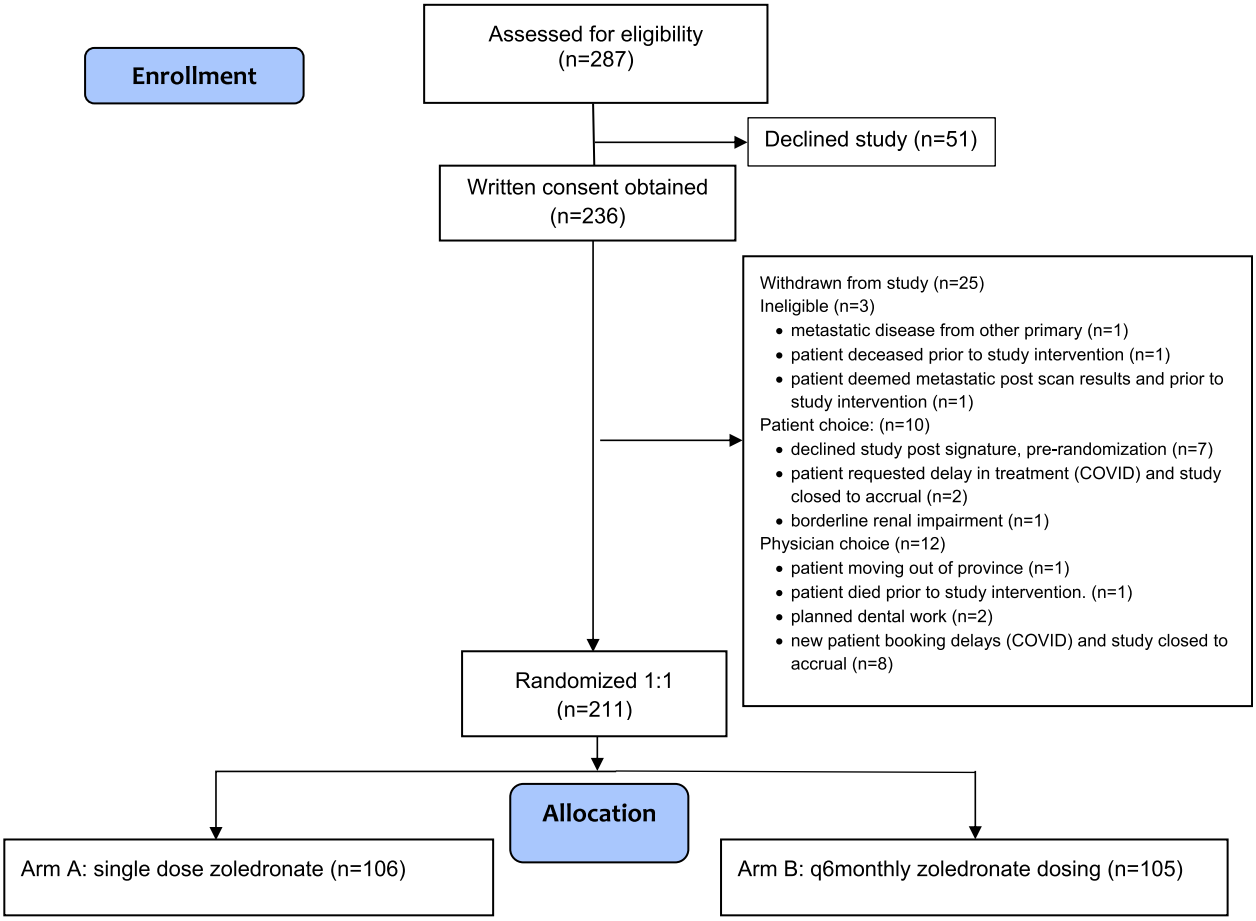

Fig. 1. CONSORT Diagram.

Table 1
Baseline patient and disease characteristics.

	N	Total	Single zoledronate N = 106	6-monthly zoledronate N = 105
Age, Mean, (sd)	211	59.5 (11.0)	59.7 (11.4)	59.2 (10.8)
Median (range)		59.8 (36.4, 88.5)	61.9 (37.0, 88.5)	58.3 (36.4, 86.1)
Sex, No. (% female)	211	209 (99.1)	106 (100)	103 (98.1)
Ethnicity:	211			
African Canadian		8 (3.8)	7 (6.6)	1 (1.0)
Asian		17 (8.1)	11 (10.4)	6 (5.7)
Caucasian		172 (81.5)	82 (77.4)	90 (85.7)
Native Canadian		1 (0.5)	1 (0.9)	0 (0)
Unknown		13 (6.1)	5 (4.7)	8 (7.6)
BMI Mean (sd)	210	28.9 (6.0)	28.8 (5.8)	28.9 (6.3)
ECOG:	211			
0		82 (38.9)	36 (34.0)	46 (43.8)
1		67 (31.8)	34 (32.0)	33 (31.4)
2		4 (1.9)	0 (0)	4 (3.8)
Unknown		58 (27.5)	36 (34.0)	22 (21.0)
Menopausal status at time of cancer diagnosis:	209			
Peri		14 (6.7)	7 (6.6)	7 (6.8)
Post		155 (74.2)	76 (71.7)	79 (76.7)
Pre		40 (19.1)	23 (21.7)	17 (16.5)
Disease characteristics				
ER positive N (%)	211	177 (83.9)	85 (80.2)	92 (87.6)
PR positive N (%)	211	139 (65.9)	68 (64.2)	71 (67.6)
ER and/or PR positive N (%)	211	180 (85.3)	86 (81.1)	94 (89.5)
Triple negative N (%)				
(ER-, PR-, Her2-)	211	26 (12.3)	18 (17.0)	8 (7.6)
Her2 positive N (%)	211	48 (22.8)	23 (21.7)	25 (23.8)
T stage:	210			
1		90 (42.9)	48 (45.3)	42 (40.4)
2		98 (46.7)	45 (42.4)	53 (51.0)
3		19 (9.1)	12 (11.3)	7 (6.7)
4		3 (1.4)	1 (1.0)	2 (1.9)
N stage:	210			
0		115 (54.7)	62 (58.5)	53 (51.0)
1		78 (37.1)	36 (34.0)	42 (40.4)
2		12 (5.7)	6 (5.6)	6 (5.8)
3		5 (2.38)	2 (1.9)	3 (2.8)
Overall stage:	210			
IA		55 (26.2)	35 (33.0)	20 (19.2)
IIA		89 (42.4)	38 (35.8)	51 (49.0)
IIB		40 (19.1)	17 (16.0)	23 (22.1)
IIIA		19 (9.1)	13 (12.3)	6 (5.8)
IIIB		2 (1.0)	1 (0.9)	1 (1.0)
IIIC		5 (2.4)	2 (1.9)	3 (2.9)
Baseline biochemistry				
Serum Creatinine (umol/L) Mean (sd)	211	67.7 (14.8)	66.7 (14.8)	68.6 (14.9)
Serum Calcium (mmol/L) Mean (sd)	211	2.33 (0.21)	2.34 (0.20)	2.31 (0.22)

and 6.7% were perimenopausal). With respect to disease stage, 129/210 (61%) patients had stage 2 disease and 26/120 (12%) had stage 3 disease. With respect to cancer treatment, 150/211 71% received chemotherapy with the majority (112/150, 74%) receiving it in the adjuvant setting (Table 2). 81.5% of patients were planned to receive endocrine therapy. This was either with an aromatase inhibitor (AI) (30.8%), tamoxifen (44.2%), or tamoxifen-AI switch strategy (20.9%). Overall, 4.1% of patients received a concurrent LHRH analogue.

Baseline characteristics related to fragility fracture risk are shown in Table 3. Median (MO) FRAX scores were 5.4 (range 0.9, 47) and HF scores 0.5 (range 0, 38). At baseline, 3.3% of patients had experienced a prior fragility fracture. Self-identified reports included osteopenia in 4.3% of study participants, osteoporosis 8.1% and 21% were unsure.

3.2. Primary outcome measures

The feasibility of performing this randomised trial was assessed according to three metrics. The study was able to open at 6 Ontario sites (Ottawa, Newmarket, Brampton, Kingston, Hamilton and Markham). The first site opened on October 23, 2018 and the sixth site opened on October 21, 2019. Thus, activation (i.e. study being open for accrual) of the sixth site occurred within 12 months of the first site being open for accrual.

Active participation in the trial was defined as the number of physicians who signed study logs for study participate who actually approached eligible patients for study participation. Of 47 physicians who signed study logs, 27 (57%) approached patients. By individual study site this ratio was: Ottawa (7/10, 70%), Newmarket (2/9, 22.2%), Brampton (3/8, 37.5%), Kingston (4/7, 57.1%), Hamilton (6/8, 75%) and Markham (5/5, 100%). The final feasibility endpoint evaluated whether we could enroll at least 100 patients across all sites within 9 months of the sixth site being activated. The sixth site was activated on October 21, 2019 and April 2020 when the study closed (7 months later) 211 patients had been randomised. Of these 211 patients 107 (50.7%) were randomised to a single dose of zoledronate and 104 (49.3%) to the 6-month dosing arm.

Table 2
Baseline treatment characteristics.

	N	Total	Single zoledronate	6-monthly zoledronate
			N = 106	N = 105
Chemotherapy N (%)	211			
Yes		150 (71.1)	79 (74.5)	71 (67.6)
Adjuvant N (%)	150			
Yes		112 (74.7)	53 (50.0)	59 (56.2)
Chemotherapy Regimen:	150			
AC-T		9 (6.0)	4 (5.1)	5 (7.0)
FEC-D		30 (20.0)	18 (22.8)	12 (16.9)
TC		58 (38.7)	26 (32.9)	32 (45.1)
dd AC-T		47 (31.3)	28 (35.4)	19 (26.8)
AC-carbo-T		1 (0.7)	0 (0.0)	1 (1.4)
Other		5 (3.3)	3 (3.8)	2 (2.8)
Trastuzumab N (%)	211			
Yes		46 (21.8)	23 (21.7)	23 (21.9)
Adjuvant endocrine therapy N (%)	211			
Yes		172 (81.5)	82 (77.4)	90 (85.7)
Planned endocrine therapy:	172			
AI		53 (30.8)	23 (28.1)	30 (33.4)
LHRH		7 (4.1)	4 (4.9)	3 (3.3)
Tamoxifen		76 (44.2)	38 (46.3)	38 (42.2)
Tamoxifen to AI		36 (20.9)	17 (20.7)	19 (21.1)

AC-T = AC-paclitaxel; dd AC-T = dose dense AC-paclitaxel

Table 3
Baseline bone health characteristics.

Bone Health characteristics	N	Total	Single zoledronate	6-monthly zoledronate
Osteoporosis N (%)	210			
Yes		17 (8.1)	8 (7.5)	9 (8.6)
Osteopenia N (%)	210			
Yes		9 (4.3)	1 (0.9)	8 (7.7)
I do not know		35 (16.7)	26 (24.5)	9 (8.6)
Current use of bisphosphonate N (%):	211			
Yes		5 (2.4)	1 (0.9)	4 (3.8)
No		206 (97.6)	105 (99.1)	102 (96.2)
Prior bone mineral density assessment within 3 years	211			
Yes		28 (13.3)	12 (11.3)	16 (15.2)
No		183 (86.7)	94 (88.7)	89 (84.8)
If yes:				
Femoral T-score:	28			
−1.0 or above (normal bone density)		12 (42.9)	6 (50.0)	6 (37.5)
Between −1.0 and −2.5 (osteopenia)		16 (57.1)	6 (50.0)	10 (62.5)
−2.5 or below (osteoporosis)		0 (0)	0 (0)	0 (0)
BMD Femoral Neck T-score:	28			
		28 (13.3)	12 (11.4)	16 (15.1)
		−1.01	−1	−1.01
Questions from FRAX				
Age, Mean, (sd)	211	59.5 (11.0)	59.7 (11.4)	59.2 (10.8)
Median (range)		59.8 (36.4, 88.5)	61.9 (37.0, 88.5)	58.3 (36.4, 86.1)
Sex, No. (% female)	211	209 (99.1)	106 (100)	103 (98.1)
Height (cm) Mean (sd)	210	162.3 (7.0)	161.6 (6.3)	163.0 (7.6)
Weight (kg) Mean (sd)	211	76.2 (17.1)	75.4 (6.3)	77.0 (17.5)
Previous fracture	209			
Yes		7 (6.4)	4 (3.8)	3 (2.9)
No		202 (96.6)	100 (96.2)	102 (97.1)
Parent fractured hip	209			
Yes		27 (12.9)	11 (10.5)	16 (15.3)
No		182 (87.1)	93 (89.5)	88 (84.7)
Current smoking N (%)	209			
Yes		9 (4.3)	3 (2.8)	6 (5.8)
Current or past glucocorticoid use N (%)	211			
Yes		14 (6.6)	8 (7.5)	6 (5.8)
Rheumatoid arthritis	211			
Yes		6 (2.8)	4 (3.8)	2 (1.9)
Secondary osteoporosis questions from FRAX				
Type 1 diabetes N (%)	211			
Yes		1 (0.5)	1 (0.9)	0 (0)

(*continued on next page*)

Table 3 (*continued*)

Bone Health characteristics	N	Total	Single zoledronate	6-monthly zoledronate
Osteogenesis imperfecta	211			
Yes		0 (0)	0 (0)	0 (0)
Untreated hyperthyroidism or hypogonadism N (%)	211			
Yes		1 (0.5)	0 (0)	1 (0.9)
Premature menopause (<45 years) N (%)	211			
Yes		6 (2.8)	4 (3.8)	2 (1.9)
Chronic malnutrition or malabsorption N (%)	211			
Yes		1 (0.5)	1 (0.9)	0 (0)
Chronic liver disease N (%)	211			
Yes		3 (1.4)	2 (1.9)	1 (0.9)
Alcohol (≥3units/day)	210			
Yes		7 (3.3)	4 (3.8)	3 (2.9)
No		103 (96.7)	101 (95.3)	102 (97.1)
FRAX score with BMD N, %	27/206		11 (10.7)	16 (15.5)
10-year risk of a hip fracture (≥3%)		3 (1.4)	1 (1.0)	2 (1.9)
10-year risk of another major osteoporotic fracture (≥ 20%)		2 (1.0)	0 (0)	2 (1.9)
FRAX score without BMD N, %	179/206		92 (89.3)	87 (84.5)
10-year risk of a hip fracture (≥3%)		22 (10.7)	12 (11.6)	10 (9.7)
10-year risk of another major osteoporotic fracture (≥20%)		10 (4.8)	5 (4.8)	5 (4.8)

4. Discussion

In view of their effects on reducing bone loss and improving disease-free survival bone-targeting agents are widely recommended for postmenopausal (including premenopausal women treated with ovarian suppression) patients with EBC [3,4,6,8,23–25]. Despite these recommendations, questions remain around the optimal choice of agent, its route of administration, dose and dosing schedule [26]. Indeed, the CCO and ASCO Practice Guideline, 'bottom line recommendations' specifically states, ''More research is recommended comparing different bone-modifying agents, doses, dosing intervals, and durations" [4].

Identifying the optimal agent, dosing interval and duration to evaluate is challenging for a number of reasons. First is the relatively low event rate of both fragility fractures and bone recurrences, and as such, the study would require a large sample size of over 5000 patients and years of follow up [7,8,23]. In addition, for zoledronate, different trials have used different durations. The ZO-FAST trial, evaluated zoledronate 4 mg every 6 months for 5 years [8]. The AZURE trial used zoledronate for 5 years (initially monthly to every 3 and 6 months) [7] while the ABCSG-12 trial evaluated zoledronate every 6 months for 3 years with concurrent goserelin in pre-menopausal breast cancer patients [9]. Despite different number of zoledronate doses at 4 mg with 11 doses in ZO-FAST, 19 doses in AZURE and 7 doses in ABCSG-12 the hazard ratio for disease-free interval was similar between 0.66 and 0.77 in these trials [7–9]. Recently the data from the SUCCESS trial was presented comparing 2 years of adjuvant zoledronate with 5 years of therapy [27]. The additional 3 years made no difference in the primary endpoint of bone metastasis free survival. The extra 3 years was however associated with a significantly higher incidence of renal toxicity and osteonecrosis of the jaw [28].

For all these reasons, we decided to perform a feasibility study to explore whether a definitive study was possible. In the current study we met all of our predefined feasibility endpoints and will now start the challenging journey of trying to find funding for such a definitive efficacy trial.

Clearly there are limitations with the current study. These include whether or not a single dose of zoledronate is enough. Indeed, of 287 patients who were approached about the study 51 declined study participation. While we could not collect individual patient reasons for declining, it was apparent that patients either wanted no zoledronate at all or did not want to be randomised to the single dose arm. In addition, there are challenges with performing any large trial in the current funding environment. The COVID-19 pandemic has significantly reduced in-person patient visits and our study methodology enabled patient assessment without requiring patients to attend the clinic in person. Such strategies will be essential for performing large, efficient adjuvant trials under the current environment [29]. However, as COVID-19 led to sudden restrictions in administration of zoledronate as well as clinic visits we had to make practical changes and this led to some patients being randomised after they had received their first zoledronate treatment. For example, some patients who wanted to consider study had planned to inform us of their consent at their next clinic visit, but as these were delayed, but in the mean time they were scheduled and given their first dose (before being seen again). In addition, while waiting for study amendment approval 9 patients had their first zoledronate treatment.

Another limitation/observation from the current study is that while 40 premenopausal and 14 perimenopausal women were recruited, LHRH analogues were used in only 7 patients. This is important because the defined population for adjuvant bisphosphonates is those patients who are either naturally postmenopausal or if pre/peri-menopausal they should also be on concurrent LHRH analogues. Another limitation of the current study could be the choice of endpoints, however this was a feasibility trial and different endpoints would be used for a definitive comparison trial. These endpoints could include; invasive disease free survival, bone metastasis-free survival and breast cancer specific overall survival for example. For this reason, we are currently performing surveys of both patients and health care providers to assess the optimal study endpoints for such a trial.

In conclusion, we have demonstrated the feasibility of opening a trial comparing a single injection of adjuvant zoledronate with 6-monthly treatment. Secondary endpoints results will take several years to evolve, but in the meantime, we will commence applications for funding for a larger definitive trial.

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.

Acknowledgements

We are grateful for patients and their families for their assistance with this study, as well as physicians for approaching patients. Accrual by site and physician was: Ottawa (159);

M. Clemons and B. Basulaiman (132), T. Ng (15), A. Awan (5), A. Srikanthan (2), J. Hilton (2), S. McGee (2). Newmarket (10); D. Simos (7) and Y. Rahim (3). Brampton (22); H Conter (12), W. Raskin (8) and J. Husain (2). Kingston (4); M. Mates (2), H. Ostic (1) and N. Hammad (1). Hamilton (11); S. Dhesy (4), L. Bordeleau (3), O. Levine (2) and G. Kazemi (2). Markham (5); V. Kumar (3), M. Trinkaus (1) and L. Hajra (1).

Conflicts of interest statement

AA has participated on an advisory board for Novartis, Eli Lily, Exactis innovation and Pfizer, has received honoraria from Apobiologix and Roche and has received travel funds from Roche. TN has received honoraria from Takeda Oncology, ARIAD, and Boehringer-Ingelheim, outside of this work. HC has provided Consulting for Janssen, Genomic Health, Acadia, Novartis, and has had employment at Roche. WR reports honoraria from Ipsen. DSi participated on an advisory board for Genomic Health. SDT is the co-lead author of CCO/ASCO adjuvant bisphosphonate guideline group, has received honoraria for developing educational material for Novartis (unrelated to bone modifying agents), and participates on the advisory board for Seattle Genetics Canada. MM participates on the advisory boards for Novartis, Pfizer, Seattle Genetics Canada and is a Member of the ASCO adjuvant bisphosphonate guideline group. VK reports Honoraria from Janssen and Genomic Health. BH consults for Cornerstone Research and has received honoraria from Eversana Inc for the provision of methodologic advice related to the conduct of systematic reviews and meta-analysis. MC has received honoria for speaking at a meeting funded by Apotex, is a co-I on SWOG 0307 and a member of the ASCO adjuvant bisphosphonate guideline group and UpToDate panel. The remaining authors declare no competing interests.

Funding

This work was supported through the Rethinking Clinical Trials Program (REaCT) at the Ottawa Hospital Research Institute, as well as funds donated from the CURE Foundation and the Ottawa Hospital Foundation and its generous donors. Participating sites also received accrual support from the Canadian Cancer Clinical Trials Network (3CTN).

Author's contributions

The protocol was designed and developed by AA, DF, GP and MC. Patients were entered into the study by AA, TN, HC, WR, DS, SD-T, MM, VK, MC.

MC, CS, DSa, LV and GP had access to all the raw data. Statistical analysis and data analysis was performed by AA, BH, GP and MC. First version of the manuscript was developed by AA, CS, DSa, LV, GP and MC. All authors were involved in the critical review of the manuscript and approved the final version.

References

[1] R. Coleman, D.M. Finkelstein, C. Barrios, M. Martin, H. Iwata, R. Hegg, J. Glaspy, A.M. Periañez, K. Tonkin, I. Deleu, Adjuvant denosumab in early breast cancer (D-CARE): an international, multicentre, randomised, controlled, phase 3 trial, Lancet Oncol. 21 (1) (2020) 60–72.

[2] M. Gnant, G. Pfeiler, G.G. Steger, D. Egle, R. Greil, F. Fitzal, V. Wette, M. Balic, F. Haslbauer, E. Melbinger-Zeinitzer, Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Oncol. 20 (3) (2019) 339–351.

[3] E.B.C.T.C. Group, Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, The Lancet 386(10001) (2015) 1353-1361.

[4] S. Dhesy-Thind, G.G. Fletcher, P.S. Blanchette, M.J. Clemons, M.S. Dillmon, E.S. Frank, S. Gandhi, R. Gupta, M. Mates, B. Moy, T. Vandenberg, C.H. Van Poznak, 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 (18) (2017) 2062–2081.

[5] P. Hadji, M.S. Aapro, J.J. Body, M. Gnant, M.L. Brandi, J.Y. Reginster, M.C. Zillikens, C.C. Gluer, T. de Villiers, R. Baber, G.D. Roodman, C. Cooper, B. Langdahl, S. Palacios, J. Kanis, N. Al-Daghri, X. Nogues, E.F. Eriksen, A. Kurth, R. Rizzoli, R.E. Coleman, 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.

[6] R. Coleman, P. Hadji, J.-J. Body, D. Santini, E. Chow, E. Terpos, S. Oudard, Ø. Bruland, P. Flamen, A. Kurth, Bone health in cancer: ESMO clinical practice guidelines, Ann. Oncol. (2020).

[7] R. Coleman, D. Cameron, D. Dodwell, R. Bell, C. Wilson, E. Rathbone, M. Keane, M. Gil, R. Burkinshaw, R. Grieve, P. Barrett-Lee, D. Ritchie, V. Liversedge, S. Hinsley, H. Marshall, Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial, Lancet Oncol. 15 (9) (2014) 997–1006.

[8] R. Coleman, R. de Boer, H. Eidtmann, A. Llombart, N. Davidson, P. Neven, G. von Minckwitz, H.P. Sleeboom, J. Forbes, C. Barrios, A. Frassoldati, I. Campbell, O. Paija, N. Martin, A. Modi, N. Bundred, Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results, Ann. Oncol. 24 (2) (2013) 398–405.

[9] M. Gnant, B. Mlineritsch, H. Stoeger, G. Luschin-Ebengreuth, M. Knauer, M. Moik, R. Jakesz, M. Seifert, S. Taucher, V. Bjelic-Radisic, M. Balic, H. Eidtmann, W. Eiermann, G. Steger, W. Kwasny, P. Dubsky, U. Selim, F. Fitzal, G. Hochreiner, V. Wette, P. Sevelda, F. Ploner, R. Bartsch, C. Fesl, R. Greil, Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12, Ann. Oncol. 26 (2) (2015) 313–320.

[10] Cancer Care Ontario, Data request to the Cancer Care Ontario Data Disclosure Team, 2020. https://www.ccohealth.ca/en/request-data-for-research. (Accessed April 14 2020).

[11] S.L. Greenspan, S. Perera, M.A. Ferchak, D.A. Nace, N.M. Resnick, Efficacy and safety of single-dose zoledronic acid for osteoporosis in frail elderly women: a randomized clinical trial, JAMA Int. Med. 175 (6) (2015) 913–921.

[12] I. Ofotokun, K. Titanji, C.D. Lahiri, A. Vunnava, A. Foster, S.E. Sanford, A.N. Sheth, J.L. Lennox, A. Knezevic, L. Ward, K.A. Easley, P. Powers, M.N. Weitzmann, A single-dose zoledronic acid infusion prevents antiretroviral therapy-induced bone loss in treatment-naive HIV-infected Patients: A Phase IIb Trial, Clin. Infect. Dis. 63 (5) (2016) 663–671.

[13] A. Grey, M.J. Bolland, A. Horne, B. Mihov, G. Gamble, I.R. Reid, Duration of antiresorptive activity of zoledronate in postmenopausal women with osteopenia: a randomized, controlled multidose trial, CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne 189 (36) (2017) E1130–E1136.

[14] J.E. Brown, S.P. Ellis, J.E. Lester, S. Gutcher, T. Khanna, O.P. Purohit, E. McCloskey, R.E. Coleman, Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid, Clin. Cancer Res. 13 (18 Pt 1) (2007) 5406–5410.

[15] S.A. Khan, J.A. Kanis, S. Vasikaran, W.F. Kline, B.K. Matuszewski, E.V. McCloskey, M.N. Beneton, B.J. Gertz, D.G. Sciberras, S.D. Holland, J. Orgee, G. M. Coombes, S.R. Rogers, A.G. Porras, Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis, J. Bone Mineral Res. 12 (10) (1997) 1700–1707.

[16] ClinicaTrials.gov, A randomised, multicentre, pragmatic trial comparing a single dose vs. twice yearly zoledronate in patients with early stage breast cancer (REaCT-ZOL), 2018. https://clinicaltrials.gov/ct2/show/NCT03664687?term=REaCT-ZOL&cntry=CA&city=Ottawa&draw=2&rank=1.

[17] W. FRAX, fracture assessment tool. Sheffield (UK): World Health Organization Collaborating Centre for Metabolic Bone Diseases. University of Sheffield; 2008, 2008.

[18] N.B. Watts, B. Ettinger, M.S. LeBoff, FRAX facts, J. Bone Miner. Res. 24 (6) (2009) 975–979.

[19] J.A. Kanis, Assessment of osteoporosis at the primary health-care level, WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield (2007).

[20] N. Zethraeus, F. Borgström, O. Ström, J. Kanis, B. Jönsson, Cost-effectiveness of the treatment and prevention of osteoporosis—a review of the literature and a reference model, Osteoporos. Int. 18 (1) (2007) 9–23.

[21] National Osteoporosis Foundation Clinician's guide to prevention and treatment of osteoporosis. http://www.nof.org/professionals/cliniciansguide_form.asp. (Accessed October 2 2009).

[22] J.A. Kanis, O. Johnell, C. De Laet, B. Jonsson, A. Oden, A.K. Ogelsby, International variations in hip fracture probabilities: implications for risk assessment, J. Bone Miner. Res. 17 (7) (2002) 1237–1244.

[23] M. Gnant, G. Pfeiler, P.C. Dubsky, M. Hubalek, R. Greil, R. Jakesz, V. Wette, M. Balic, F. Haslbauer, E. Melbinger, V. Bjelic-Radisic, S. Artner-Matuschek, F. Fitzal, C. Marth, P. Sevelda, B. Mlineritsch, G.G. Steger, D. Manfreda, R. Exner, D. Egle, J. Bergh, F. Kainberger, S. Talbot, D. Warner, C. Fesl, C.F. Singer, Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial, Lancet (London, England) 386 (9992) (2015) 433–443.

[24] G.K. Ellis, H.G. Bone, R. Chlebowski, D. Paul, S. Spadafora, J. Smith, M. Fan, S. Jun, Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer, J. Clin. Oncol. 26 (30) (2008) 4875–4882.
[25] R. Coleman, J.J. Body, M. Aapro, P. Hadji, J. Herrstedt, Bone health in cancer patients: ESMO Clinical Practice Guidelines, Ann. Oncol. 25 (Suppl 3) (2014) iii124-37.
[26] C. Jacobs, E. Amir, A. Paterson, X. Zhu, M. Clemons, Are adjuvant bisphosphonates now standard of care of women with early stage breast cancer? A debate from the Canadian Bone and the Oncologist New Updates meeting, J. Bone Oncol. 4 (2) (2015) 54–58.
[27] W. Janni, T.W. Friedl, T. Fehm, V. Mueller, W. Lichtenegger, J. Blohmer, R. Lorenz, H. Forstbauer, E. Bauer, V. Fink, Abstract GS1-06: extended adjuvant bisphosphonate treatment over five years in early breast cancer does not improve disease-free and overall survival compared to two years of treatment: phase III data from the SUCCESS a study, AACR (2018).
[28] C. Domschke, F. Schuetz, Side effects of bone-targeted therapies in advanced breast cancer, Breast care (Basel, Switzerland) 9 (5) (2014) 332–336.
[29] B. Basulaiman, A.A. Awan, D. Fergusson, L. Vandermeer, A. Arnaout, J. Hilton, B. Hutton, A.A. Joy, A. Robinson, N. Califaretti, Creating a pragmatic trials program for breast cancer patients: Rethinking Clinical Trials (REaCT), Breast Cancer Res. Treat. 177 (1) (2019) 93–101.