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ORIGINAL ARTICLE

Risk factors for bisphosphonate-associated osteonecrosis of the jaw in the prospective randomized trial of adjuvant bisphosphonates for early-stage breast cancer (SWOG 0307)

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Abstract

Purpose Bisphosphonates reduce bone metastases in postmenopausal women with early-stage breast cancer but carry the risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ). We describe risk factors for BRONJ and compare BRONJ provoked by infection or trauma with spontaneous lesions, which carry a better prognosis.

Methods SWOG 0307 randomized women with stage I–III breast cancer to receive zoledronic acid (ZA), clodronate (CL), or ibandronate (IB) for 3 years, implemented BRONJ prevention guidelines, and collected information about dental health and development of BRONJ. All statistical tests were two-sided.

Results Of 6018 women, 48 developed BRONJ. Infection was present in 21 (43.8%). Median time to BRONJ was 2.1 years for ZA, 2.0 years for IB, and 3.4 years for clodronate ($p = 0.04$). BRONJ was associated with bisphosphonate type (28/2231 (1.26%) for ZA, 8/2235 (0.36%) for CL, 12/1552 (0.77%) for IB), dental calculus (OR 2.03), gingivitis (OR 2.11), moderate/severe periodontal disease (OR 2.87), and periodontitis > 4 mm (OR 2.20) ($p < 0.05$). Of 57 lesions, BRONJ occurred spontaneously in 20 (35.1%) and was provoked by dental extraction in 20 (35.1%), periodontal disease in 14 (24.6%), denture trauma in 6 (10.5%), and dental surgery in 2 (3.5%). Spontaneous BRONJ occurred more frequently at the mylohyoid ridge. There were no differences in dental disease, infection, or bisphosphonate type between spontaneous and provoked BRONJ.

Conclusion ZA and worse dental health were associated with increased incidence of BRONJ, with a trend toward additive risk when combined. BRONJ incidence was lower than in similar studies, with prevention strategies likely linked to this.

Clinical trial number NCT00127205

Registration date July 2005

Keywords Clinical trials · Breast cancer · Bisphosphonate · Osteonecrosis of the jaw

Introduction

Bisphosphonates reduce the risk of bone metastases in a low-estrogen environment [1] and are recommended as adjuvant therapy in post-menopausal women with early-stage breast cancer [2–4]. Bisphosphonates inhibit the ability of osteoclasts to resorb bone, decreasing local metabolic activity and making for a less hospitable environment for metastasized

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cancer cells [5]. Amino-bisphosphonates, characterized by the addition of a nitrogen atom, block osteoclast activity and induce apoptosis by inhibiting farnesyl pyrophosphate synthase, an enzyme crucial to cell growth and division, while non-amino-bisphosphonates do so through formation of cytotoxic metabolites [6]. Bisphosphonates block tumor cell growth and angiogenesis, inducing apoptosis and immune system activation, and act in synergy with other anti-cancer agents [5, 7–9].

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is an uncommon but serious side effect [10]. BRONJ is defined as an area of non-healing exposed bone in the mandible or maxilla in the setting of bisphosphonate use, without exposure to radiation at the lesion site, and no other identifiable cause [11].

BRONJ can result in mouth pain, unsatisfactory diet, self-consciousness, and decreased life satisfaction [12]. Healing occurs faster in spontaneous BRONJ and BRONJ provoked by trauma and slower if provoked by dental extraction [13] and in patients with autoimmune conditions, diabetes, corticosteroid use, or tobacco smokers [14–16]. Based on our clinical experience, many cases resolve in 1–3 years. Treatment can vary from basic oral hygiene to repeated antibiotics, with rare advanced cases requiring hospitalization, intravenous antibiotics, and extensive oral surgery [13].

While the pathogenesis of BRONJ is poorly elucidated, and more studies are needed in this area, it is likely multifactorial. Decreased bone turnover and ability to repair bone due to the presence of bisphosphonates results in impaired healing after injury induced by a dental procedure, trauma, or infection (as evidenced by pain, swelling, gum erythema, numbness, purulent drainage, or fistula) that necessitate bone healing to resolve [17].

BRONJ can arise spontaneously without a clear provoking factor [14, 18]. Suggested causes include inflammation from microcracks [19], thin mucosal covering at the mylohyoid ridge [20], and bisphosphonate toxicity alone or in combination with anti-angiogenics [21]. The oral microbiome and its interplay with the local immune response [22] and genetic differences related to immune barrier [23, 24] and osteoclast functions may play a role [25]. In animal models, intravenous bisphosphonates and tooth extraction alone [25] or in combination with inoculation by bacteria [24] or cyclophosphamide [26] resulted in BRONJ.

BRONJ is twice as likely to occur in the mandible as in the maxilla [20]. Drug-specific risk factors include bisphosphonate potency [16], intravenous administration, and cumulative dose [20, 27]. Local factors include tooth extraction [28], tooth abscess or infection [29], periodontitis [30], denture trauma, periodontal surgery, root canals, or dental implants [21]. Other risk factors include ethnicity [31] and following BRONJ prevention guidelines [32].

Conservative treatment of BRONJ with chlorhexidine rinses and antibiotics frequently resulted in resolution of symptoms, while local curettage/debridement led to recurrence or progression [30]. Thus, treatment recommendations for early-stage BRONJ emphasize conservative management. Advanced surgical techniques are effective when there is progression, extensive necrosis, osteolysis, fistula, or pathologic fracture [10]. Treatment with pentoxifylline and tocopherol has shown promise [33].

Wide resection of necrotic bone to "bleeding margins" with smoothing of sharp bony edges and primary tension-free multi-layer wound closure has shown cure rates of 80–90% for early-stage BRONJ [34]. Outcomes are similar in patients treated with conservative management and up-front surgery for early-stage BRONJ, with faster healing in the latter [15]. Based on our clinical experience, oral surgeons are more likely to utilize up-front surgery, while dentists start with more conservative treatment.

Research about BRONJ in post-menopausal women with early-stage breast cancer taking adjuvant bisphosphonates is limited to reports of BRONJ incidence [35–38]. In the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) and Austrian Breast Cancer Study Group (ABCSG) trial-12 studies, both of which randomized patients with breast cancer to zoledronic acid or not, BRONJ prevention guidelines were not implemented and participants' dental health was not explored [15, 35, 36].

The SWOG S0307 randomized controlled trial of adjuvant bisphosphonates in women with early-stage breast cancer compared three bisphosphonates, zoledronic acid (ZA), ibandronate (IB), and clodronate (CL), and reported no difference in efficacy in reducing recurrence or death. S0307 reported the incidence of BRONJ in these patients after following recommended BRONJ prevention guidelines and was the first to report the incidence of BRONJ in women taking clodronate or ibandronate at doses intended to prevent breast cancer bone metastases [38]. While neither oral CL nor IB at the adjuvant dose used in S0307 is available in the USA, they are used at these doses in other countries to treat bone metastases. ZA and CL are included in guidelines as adjuvant therapy for post-menopausal women with early-stage breast cancer, and IB is supported by S0307 primary outcome data [2–4, 38].

Given the negative influence of BRONJ on quality of life, it is especially important to elucidate time to onset and risk factors associated with BRONJ in women who are taking adjuvant bisphosphonates to prevent breast cancer recurrence. We conducted a pre-planned secondary analysis of the data collected during S0307 to determine the time to onset of and risk factors for BRONJ and compare characteristics of spontaneous and provoked BRONJ to improve BRONJ outcomes.

Materials and methods

In S0307, 6097 patients diagnosed with stage I–III breast cancer who had undergone surgery and were receiving adjuvant systemic therapy were randomized to receive zoledronic acid 4-mg IV monthly for 6 months, then every 3 months,

clodronate 1600 mg by mouth daily, or ibandronate 50 mg by mouth daily for 3 years. Accrual started in November 15, 2005, and completed February 1, 2010.

The diagnosis of BRONJ was made clinically when there was presence of exposed non-healing bone for at least 8 weeks without history of radiation exposure or metastasis at the lesion site without another attributable cause [10].

Informed consent was obtained from all patients and demographic and clinical information collected as described previously [38]. All patients provided written informed consent. The study was approved by the National Cancer Institute Central Institutional Review Board (IRB), as well as by IRBs of participating institutions.

A baseline dental examination form was required to be completed by a dental health professional within 6 months of starting bisphosphonate. Instructions stated that the exam should include a visual inspection, periodontal probing, and an evaluation of BRONJ risk factors. X-rays were not required, but it was recommended that they be performed to assess the degree of periodontal involvement and endodontic (root canal) problems. The following dental health measures were collected: dental plaque levels, calculus, gingivitis, periodontitis, overall dental disease, presence of dentures, and number of teeth with deep caries, failing root canals, fractures/restorations, or endodontic treatment. Financial assistance was available for baseline dental exams for patients with severe financial need and without dental insurance. Patients were encouraged to complete planned dental procedures prior to starting the study drug, undergo regular dental exams while on study, maintain good oral hygiene, and report any dental symptoms to their oncologist and dentist. Patients who plan to undergo oral surgery were discouraged from enrollment. An off-study dental examination was required at study completion.

Participants were monitored for BRONJ with dental exams as part of routine medical care every 6–12 months. Information about BRONJ development was collected every 6 months and for up to 5 years after completing bisphosphonate treatment. For patients who developed BRONJ, completion of the Osteonecrosis Jaw (ONJ) Lesion Form was required, including the following: time since enrollment, number of lesions, lesion location, size, and evidence of infection. BRONJ was judged to be either spontaneous or provoked by one or more of the following: periodontal infection, dental extraction, other dental surgery, or denture trauma. Consultation with the S0307 dental health coordinator (MS) was recommended. Because it was not clear that stopping the bisphosphonate therapy would aid in ONJ healing, this was decided on a case-by-case basis.

Outcome dichotomous variable was set to development of BRONJ during follow-up. Independent dichotomous variables included the following: prior bisphosphonate use, chemotherapy, dental plaque, calculus, gingivitis, periodontitis, overall dental disease, and creatinine. The number of teeth with deep caries, failing root canals, fractured teeth/restorations, and endodontically treated teeth was grouped into none, 1, 2–3, and > 3. All other dental health variables categorized were categorized as none/mild v. moderate/severe. Independent categorical variables included bisphosphonate type and ethnicity.

Relative risk was calculated for all dichotomous variables, and odds ratios (OR) for categorical variables in this intent to treat analysis. Crude and adjusted ORs with 95% confidence intervals were calculated by univariate and multivariate logistic regression, respectively. Pearson's chi-squared/Fisher's exact test and Student's *T* test were used to test differences in categorical and continuous variables, respectively. Logistic regression was used test independent association. Survival analysis methods include Kaplan-Meier plots, log-rank tests, and Cox regression analyses. All *p* values were two-sided.

All statistical calculations were made using SAS program, version v94.

Results

BRONJ incidence and time to onset

Median follow-up was 7.5 years for ZA and CL and 8 years for IB (range 0–11.1 years). Of 6018 eligible women, 48 developed BRONJ (0.8%), with median duration to onset of 2.3 years (range 0.1–6.3). ONJ incidence was 1.26% (28/2231) for ZA, 0.77% (12/1552) for IB, 0.36% (8/2235) for CL (p = 0.0034), with median time to onset of 2.1 years for ZA, 2.0 years for IB, and 3.4 years for CL (p = 0.0447). (Table 1, Fig. 1)

BRONJ characteristics and risk factors

Of the 48 patients with BRONJ, 40 (83.3%) developed one lesion, 7 (14.6%) two, and one (2.1%) three lesions. Mean size was 7.0 mm (5.0–9.0). Infection was present in 21 (43.8%), absent in 22 (45.8%). Of 57 lesions, 42 (73.7%) occurred in the mandible and 14 (24.6%) in the maxilla.

BRONJ was associated with moderate/severe dental calculus, gingivitis, periodontal disease, and periodontitis > 4 mm (Table 2), but not with dentures at enrollment, plaque, chemotherapy use, baseline creatinine, or ethnicity. The same variables were also associated with BRONJ at the exit dental health assessment, except for periodontitis. At the exit assessment, the BRONJ was 5/190 (2.7%) among patients with complete dentures compared with 0.8% (30/3847) among those with no or partial dentures (p = 0.002). BRONJ incidence was higher among patients who reported bisphosphonate use prior to study enrollment, presumably for osteoporosis (1.53% (5/326) compared with 0.76% (43/5692)) (p = 0.18).

Table 1 Time to onset of BRONJ by bisphosphonate (years)

Time to ONJ onset	CL (n = 8/2235)	IB (n = 12/1552)	ZA (n = 28/2231)	Total (n = 48)
Mean (95% CI)	3.9 (3.0, 4.9)	2.4 (1.2, 3.6)	2.2 (1.6, 2.8)	2.5 (2.0, 3.0)
Median (range)	3.4 (2.8, 5.6)	2.0 (0.2, 6.3)	2.1 (0.1, 5.6)	2.3 (0.1, 6.3)

Eleven of the 48 patients (22.9%) developed BRONJ after finishing 3 years of the study drug. There was a trend toward higher risk of BRONJ in those with worsening periodontitis (though not worsening gingivitis or overall periodontal disease) compared with enrollment (p = 0.11).

BRONJ incidence ranged from 0.59–0.67% in patients with no or mild dental disease to 1.30–1.74% in patients with moderate or severe disease (Table 2). In multivariate analysis, only bisphosphonate type was associated with BRONJ (p = 0.039). The incidence of BRONJ increased in both none/mild and moderate/severe dental disease in patients who were taking ZA compared with CL and IB ($p > 0.05$). BRONJ incidence in patients with moderate/severe periodontitis who were taking ZA was 6/282 (2.13%) compared with 4/277 (1.44%) in patients who were taking CL and 3/188 (1.6%) in patients who were taking IB. BRONJ incidence in patients with none/mild calculus was 1.06% in patients taking ZA compared with 0.73% for IB and 0.23% for CL.

BRONJ incidence in patients with none or one deep caries was 0.61% (34/5588) compared with 3.45% (14/406) in patients with two or more. Incidence in patients with fractured teeth/restorations was 0.61% (29/4710) for those with no fractured teeth/restorations compared with 1.48% (19/1284) in one or more. Incidence was not increased in patients with failing root canals or endodontically treated teeth (Table 3).

Characteristics of provoked and spontaneous BRONJ

BRONJ was considered provoked by dental extraction in 20 (35.1%), periodontal disease in 14 (24.6%), denture trauma in 6 (10.5%), other dental surgery in 2 (3.5%), and with no cause identified in 20 lesions (35.1%). There was no difference in the amount of dental disease or bisphosphonate type between provoked and spontaneous BRONJ. Spontaneous BRONJ was significantly more likely to occur at the mylohyoid ridge (lingual and mylohyoid plate, some posterior mandible) (Tables 4 and 5). Infection was present in 13/27 (48.1%) provoked BRONJ and 7/18 (38.9%) spontaneous BRONJ (p = 0.41).

Discussion

BRONJ incidence and time to onset

While we did not evaluate adherence to oral bisphosphonates, the percentage of patients completing 3 years of therapy was similar, with 63% for ZA, 61% for IB, and 57% for CL [38].

The incidence of BRONJ was 1.26% (28/2231) in women taking ZA 4-mg IV monthly for 6 months, then every 3 months for 3 years after a median follow-up of 7.5–8 years.

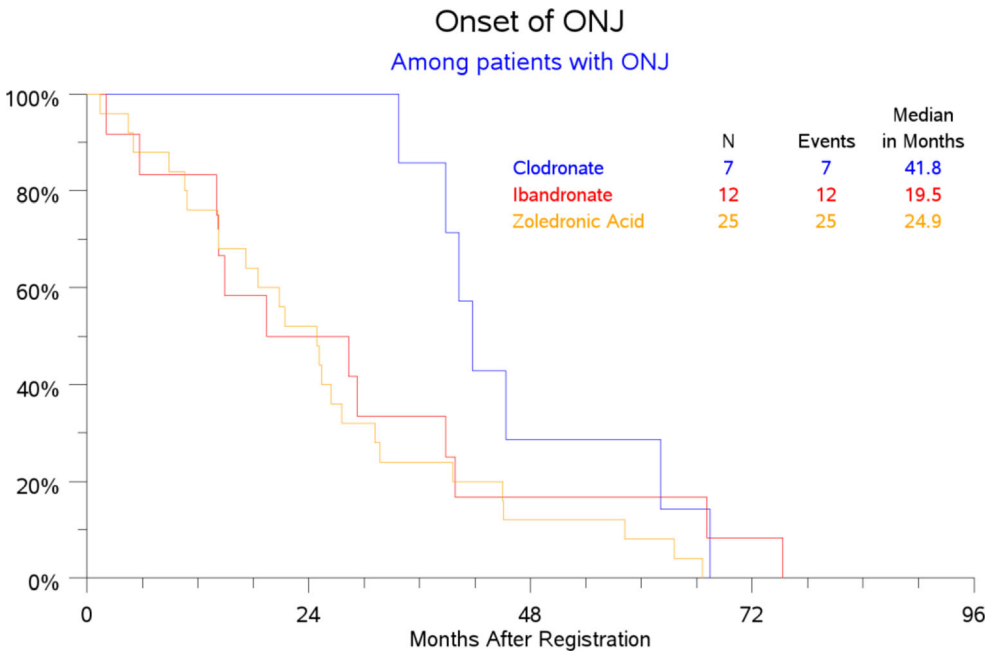

Fig. 1 ONJ onset among patients with ONJ (months)

Table 2 Factors associated with BRONJ

Variable	Ref.	OR for ONJ	95%CI	*p* value	Risk rate of ONJ in the reference group	Risk rate of ONJ in the exposure group
Calculus (n = 5837)	None or mild	2.03	(1.08, 3.81)	0.028	0.67%	1.34%
Gingivitis (n = 5759)	None or mild	2.11	(1.12, 3.98)	0.021	0.65%	1.37%
Periodontitis (n = 5516)	< 4 mm	2.20	(1.18, 4.08)	0.013	0.59%	1.30%
Overall periodontal disease (n = 5636)	None or mild	2.87	(1.49, 5.53)	0.002	0.61%	1.74%
Type of bisphosphonate (IB)	ZA	0.61	(0.31, 1.21)	0.158	1.26%	0.77%
Type of bisphosphonate (CL)	ZA	0.28	(0.13, 0.62)	0.002	1.26%	0.36%

This dose is higher than the current recommended dosing of adjuvant ZA for post-menopausal women with early-stage breast cancer, 4-mg IV every 6 months for 2–5 years [2–4]. In the AZURE trial, where ZA 4-mg IV was given monthly for 6 months, then every 3 months for 8 doses, followed by every 6 months for five doses, BRONJ incidence was 1.4% (26/1681) after 5 years [15] and 1.8% after 10 years [36]. There were no reports of BRONJ in the ABCSG trial-12, where half of the 1803 premenopausal women with early-stage breast cancer received ZA 4-mg IV every 6 months for 3 years and were followed for a median of 5.2 years [36]. In a meta-analysis of nine prospective clinical trials where ZA was given as adjuvant therapy in women with early-stage breast cancer, 0.33% (13/3987) developed BRONJ [39]. In all but two trials, ZA was administered at 4-mg IV every 6 months. Three trials had a follow-up period of 1 year, whereas BRONJ can occur 3 years after bisphosphonate discontinuation [40].

The incidence of BRONJ with oral clodronate 1600 mg daily was 0.36% (8/2235). In the National Surgical Adjuvant Breast and Bowel Project protocol B-34 study, one possible case of BRONJ (0.06%) was observed among 1662 women randomized to receive clodronate 1600 mg daily for 3 years with median follow-up of 7.6 years. Adherence in the clodronate arm was 56% [41]. In another study of adjuvant CL 1600 mg daily for 2 years with a 5.5-year follow-up, no cases of BRONJ were reported, likely due to shorter exposure and smaller sample size of 530 [42]. Examining patients for BRONJ in a prospective manner could have resulted in more accurate recognition of lesions in S0307.

The incidence of BRONJ with ibandronate 50 mg daily was 0.78% (12/1552). Prior studies have examined BRONJ prevalence in women taking ibandronate 150 mg by mouth monthly for osteoporosis. Time to BRONJ onset was similar between ZA and IB and significantly shorter than for CL,

Table 3 Association between dentition and BRONJ

Baseline dental health status	ONJ (% incidence) (n = 48)	No ONJ (n = 5946)	*p* value
Deep caries			< 0.0001
None	32 (0.62%)	5144	
1	2 (0.49%)	410	
2–3	10 (3.79%)	254	
> 3	4 (2.82%)	138	
Fractured teeth			0.0108
None	29 (0.61%)	4681	
1	7 (1.35%)	511	
2–3	6 (1.87%)	314	
> 3	6 (1.34%)	440	
Endodontically treated teeth			0.7834
None	27 (0.74%)	3621	
1	9 (0.81%)	1098	
2–3	8 (0.93%)	854	
> 3	4 (1.1%)	373	
Failing root canals			0.4652
None	46 (0.80%)	5729	
1	1 (0.63%)	159	
2–3	1 (2.22%)	44	
> 3	0 (0%)	14	

Table 4 Location of provoked and spontaneous BRONJ

Site (one patient could have > 1)	Provoked (n = 27)	Spontaneous (n = 18)
Maxilla: anterior	0	1
Maxilla: posterior	2	1
Maxilla: buccal	2	0
Maxilla: lingual	0	1
Maxilla: alveolar ridge	4	0
Maxilla: palate	2	0
Mandible: anterior	6	0
Mandible: posterior	12	8
Mandible: buccal	1	1
Mandible: lingual, mylohyoid plate	7	12
Mandible: alveolar ridge	6	2

likely because both are more potent amino-bisphosphonates [6]. Median time to onset of 2 years for ZA was similar to that of studies with similar or more frequent dosing done in the metastatic setting [43].

S0307 is the first to report median time to BRONJ onset with oral ibandronate and clodronate at the adjuvant dosing schedule, at 2.0 and 3.4 years, respectively. In a study of patients taking ibandronate 150 mg monthly for osteoporosis, median time to BRONJ onset was 2.1 years [43].

Since time to BRONJ onset for ZA or IB did not depend on frequency of administration or dose, respectively, compared with other studies, time to BRONJ onset is likely initially related to the potency of the amino-bisphosphonate, though accumulation of bisphosphonate in bone is likely important.

Risk factors for BRONJ

Our study is the first to describe risk factors associated with BRONJ in women with early-stage breast cancer who were taking adjuvant bisphosphonates to prevent bone metastases while following BRONJ prevention guidelines. While all subjects were required to have dental exams at the start of the study and encouraged to complete planned dental procedures prior to study entry, we did not require that all "necessary" dental treatments be carried out and did not track their outcome. However, it was likely that ongoing BRONJ surveillance and support from dental providers resulted in improved dental health and decreased risk of BRONJ.

Similar to other studies, we found that ZA carries a higher risk of BRONJ compared with CL and IB [16, 20, 27], that BRONJ was more likely to occur in the mandible [20], and that tooth extraction, dental trauma, dentures, and periodontitis were risk factors for BRONJ [21, 28–30]. We found that

Table 5 Bisphosphonate type and periodontal disease association with provoked and spontaneous BRONJ

Variable	Provoked ONJ (n = 27)	Spontaneous ONJ (n = 18)	p value
Bisphosphonate type			
Clodronate	4 (15%)	3 (17%)	0.27
Ibandronate	9 (33%)	2 (11%)	
Zoledronic acid	14 (52%)	13 (72%)	
Calculus (missing = 2)			0.46
None	2 (8%)	4 (22%)	
Mild	15 (60%)	8 (44%)	
Moderate	5 (20%)	5 (28%)	
Severe	3 (12%)	1 (6%)	
Gingivitis (missing = 3)			0.53
None	6 (24%)	8 (47%)	
Mild	9 (36%)	6 (35%)	
Moderate	5 (20%)	1 (6%)	
Severe	3 (12%)	1 (6%)	
Generalized	2 (8%)	1 (6%)	
Periodontitis (missing = 6)			0.25
< 4 mm	11 (52%)	13 (72%)	
4–6 mm	7 (33%)	2 (11%)	
> 6 mm	3 (14%)	3 (17%)	
Periodontal disease (missing = 5)			0.035
None	8 (36%)	12 (67%)	
Mild	7 (32%)	0	
Moderate	5 (23%)	4 (22%)	
Severe	2 (9%)	2 (11%)	

gingivitis and dental calculus were associated with increased BRONJ incidence, with increasing severity associated with higher incidence. Similarly, deep caries and fractured teeth/restorations increased the risk on BRONJ. If not treated, progression could lead to infection, necessitating dental interventions that could result in BRONJ. Consistent with this, we found a trend toward a higher risk of BRONJ among patients with progressive periodontitis on the exit dental exam. We found a trend toward additive risk for BRONJ when more potent bisphosphonates were combined with more severe dental disease. Thus, drug accumulation in alveolar bone, when combined with relative potencies of each bisphosphonate and a subsequent insult to bone or mucosa, helps explain BRONJ incidence and risk.

Similar to one study [27] and contrary to another [16], we did not find any association between BRONJ and chemotherapy. Animal models where BRONJ was induced by cyclophosphamide and ZA [26] suggest that the specific chemotherapy, dose, and timing would be especially critical for BRONJ development. Unlike a study that found increased BRONJ risk in Caucasian patients, we did not find an association between BRONJ and ethnicity [31]. We did not find a link between renal adverse events and BRONJ, likely due to stopping bisphosphonates in grade 3 or 4 renal toxicity.

Characteristics of provoked and spontaneous BRONJ

Twenty (30.7%) BRONJ lesions were spontaneous, compared with 0–50% in other studies [18]. As we did not train community dentists to evaluate whether BRONJ was spontaneous or provoked, a higher rate of spontaneous BRONJ could be due to incomplete data collection [18]. Our participants may have better dental health than the general population, resulting in a higher rate of spontaneous BRONJ.

Spontaneous BRONJ was more likely to occur at the mylohyoid ridge, consistent with our clinical experience. We expected provoked and spontaneous BRONJ to differ with respect to risk factors given faster healing of spontaneous BRONJ in one study [14] and in our clinical experience. However, provoked and spontaneous BRONJ did not differ in terms of dental health or bisphosphonate type. This could be due to BRONJ prevention measures that resulted in a more even distribution of risk factors or failure to capture differences between these as a result of BRONJ characterization done without specific training.

Limitations

Our results are limited by the small number of patients with BRONJ (likely in part due to following BRONJ prevention guidelines) and lack of specific training about BRONJ for community dentists who treated our patients. Results were limited by an older definition of BRONJ that required bone to be exposed (11). In our view, the data still provide useful insights into this significant complication of adjuvant bisphosphonate use.

Conclusion

S0307 is the first study to report BRONJ incidence and time to onset in a prospective cohort of women with early-stage breast cancer randomized to adjuvant ZA, IB, or CL to prevent bone metastases. While dental disease has long been implicated as risk factor for BRONJ, our study is the first to involve a comprehensive dental health assessment, implement BRONJ prevention measures, and measure the association between dental disease severity and BRONJ incidence. More advanced dental disease led to increased BRONJ risk; there was a trend toward additive risk when it was combined with more potent bisphosphonates. We are not aware of other prospective multi-center studies of bisphosphonates that have incorporated a similar degree of dental assessment and have found similar associations.

Given the variable progression and time to resolution of BRONJ, randomized controlled studies comparing outcomes in patients with early-stage BRONJ receiving conservative vs early surgical treatment are urgently needed. Future studies that rely on community dentists for early identification and treatment of provoked and spontaneous BRONJ should provide uniform training to community dentists to ensure internal validity of the collected data. It would be important to design protocols that followed standards of care for preventing BRONJ, trained and supported medical and dental providers in preventing BRONJ, and measured dental health, including type and site of disease, treatment received and its outcome, and adherence to regular dental check-ups throughout the length of the study.

Spontaneous and provoked BRONJ represent a spectrum of disease severity, and it would be important to determine whether patients with spontaneous BRONJ would be good candidates for conservative treatment given their tendency for faster healing. Given their proven efficacy, current recommendations for BRONJ prevention should be implemented widely and refined further to reflect recent research related to BRONJ prevention in patients who are taking bisphosphonates and require tooth extractions [32]. Given our finding of a higher risk of BRONJ in patients with moderate/severe periodontitis, gingivitis, calculus, deep caries, fractured teeth/restorations, and a trend toward higher risk of BRONJ with worsening periodontitis, treatment and follow-up of these conditions should be encouraged.

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Data availability Does not apply

Compliance with ethical standards

Conflict of interest Dr. Ingle reports grants from U.S. National Cancer Institute, during the conduct of the study. Dr. Falkson reports grants from Seattle Genetics, grants from Pfizer, other from Biotheranostics, other from Agendia, grants from Genentech/Roche, other from ExactSciences/OncotypeDx, outside the submitted work. Dr. Barlow reports grants from the National Cancer Institute, during the conduct of the study. Dr. Hortobagyi reports grants and personal fees from Novartis, outside the submitted work. Dr. Gralow reports other from Roche/Genentech, other from Novartis, other from Radius, other from Astra Zeneca, other from Pfizer, other from Puma, other from Immunomedics, other from Seattle Genetics, other from Sandoz/Hexal AG, outside the submitted work. All other authors declare no conflicts of interest.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. All patients provided written informed consent. The study was approved by the National Cancer Institute Central Institutional Review Board (IRB), as well as by IRBs of participating institutions and monitored by an independent data safety monitoring committee.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Does not apply

Code availability Does not apply

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