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Association of Osteonecrosis of the Jaw With Zoledronic Acid Treatment for Bone Metastases in Patients With Cancer

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IMPORTANCE Osteonecrosis of the jaw (ONJ) affects patients with cancer and metastatic bone disease (MBD) treated with bone-modifying agents (BMAs), yet the true incidence is unknown.

OBJECTIVE To define the cumulative incidence of ONJ at 3 years in patients receiving zoledronic acid for MBD from any malignant neoplasm.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, prospective observational cohort study (SWOG Cancer Research Network S0702) included patients with MBD with either limited or no prior exposure to BMAs and a clinical care plan that included use of zoledronic acid within 30 days of registration. Medical, dental, and patient-reported outcome forms were submitted at baseline and every 6 months. Follow-up was 3 years. Osteonecrosis of the jaw was defined using established criteria. Data were collected from January 30, 2009, to December 13, 2013, and analyzed from August 24, 2018, to August 6, 2020.

INTERVENTIONS/EXPOSURES Cancer treatments, BMAs, and dental care were administered as clinically indicated.

MAIN OUTCOMES AND MEASURES Cumulative incidence of confirmed ONJ, defined as an area of exposed bone in the maxillofacial region present for more than 8 weeks with no concurrent radiotherapy to the craniofacial region. Risk factors for ONJ were also examined.

RESULTS The SWOG S0702 trial enrolled 3491 evaluable patients (1806 women [51.7%]; median age, 63.1 [range, 2.24-93.9] years), of whom 1120 had breast cancer; 580, myeloma; 702, prostate cancer; 666, lung cancer; and 423, other neoplasm. A baseline dental examination was performed in 2263 patients (64.8%). Overall, 90 patients developed confirmed ONJ, with cumulative incidence of 0.8% (95% CI, 0.5%-1.1%) at year 1, 2.0% (95% CI, 1.5%-2.5%) at year 2, and 2.8% (95% CI, 2.3%-3.5%) at year 3; 3-year cumulative incidence was highest in patients with myeloma (4.3%; 95% CI, 2.8%-6.4%). Patients with planned zoledronic acid dosing intervals of less than 5 weeks were more likely to experience ONJ than patients with planned dosing intervals of 5 weeks or more (hazard ratio [HR], 4.65; 95% CI, 1.46-14.81; $P = .009$). A higher rate of ONJ was associated with fewer total number of teeth (HR, 0.51; 95% CI, 0.31-0.83; $P = .006$), the presence of dentures (HR, 1.83; 95% CI, 1.10-3.03; $P = .02$), and current smoking (HR, 2.12; 95% CI, 1.12-4.02; $P = .02$).

CONCLUSIONS AND RELEVANCE As the findings show, the cumulative incidence of ONJ after 3 years was 2.8% in patients receiving zoledronic acid for MBD. Cancer type, oral health, and frequency of dosing were associated with the risk of ONJ. These data provide information to guide stratification of risk for developing ONJ in patients with MBD receiving zoledronic acid.

Author Audio Interview

Supplemental content

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The bisphosphonates and denosumab are bone-modifying agents (BMAs) that reduce the risk of skeletal-related events (SREs), including fracture, need for surgery or radiotherapy to bone, spinal cord compression, and hypercalcemia of malignant neoplasm. Clinical care guidelines recommend use of BMAs in the management of metastatic bone disease (MBD).[1,2] These BMAs reduce SREs by 25% to 50%[3]; however, SREs continue to occur in approximately 15% to 29% of treated patients.[1] Use of BMAs are also associated with risk of osteonecrosis of the jaw (ONJ). Based on case reports and small cohort studies, the risk of ONJ in MBD ranges from 1% to 15%.[4] The etiology of ONJ remains undefined.

The SWOG Cancer Research Network S0702 trial[5] was a large, observational cohort study designed to prospectively assess the incidence of and predictive factors associated with ONJ in patients with cancer receiving zoledronic acid. The primary objective was to prospectively assess the cumulative incidence of ONJ at 3 years.

Key Points

Question What is the incidence of osteonecrosis of the jaw (ONJ) in patients treated with zoledronic acid for bone metastases from any cancer?

Findings In this cohort study of 3491 participants initiating zoledronic acid treatment for bone metastases, the cumulative incidence of ONJ was 0.8% at year 1, 2.0% at year 2, and 2.8% at year 3, with the highest incidence observed in multiple myeloma and the lowest in breast cancer. More frequent dosing of zoledronic acid and poor oral health were associated with higher rates of ONJ.

Meaning These findings suggest that cancer type, oral health, and frequency of dosing are associated with the risk of ONJ, which should help to guide stratification of risk for developing ONJ in patients receiving zoledronic acid.

Methods

Study Design

SWOG S0702 enrolled patients from January 30, 2009, to December 13, 2013. All patients in this cohort study provided written informed consent in accordance with institutional review board approval at participating centers and federal guidelines. Findings are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[6] Cancer care, use of BMAs, and dental care were performed as clinically indicated. The original design required a baseline dental examination within 6 months before registration, but early during accrual (November 1, 2011), baseline dental examinations were modified to be recommended only, consistent with guidelines, to improve accrual and better reflect community standards. Follow-up dental examinations were recommended every 6 months after registration. Study follow-up consisted of medical, dental, and patient-reported outcome form submissions every 6 months. If participants were diagnosed with ONJ during the study, recommended assessments changed to every 3 months. Maximum follow-up was 3 years. Dental reports were completed by the patient's oral health care clinicians. The absence of a dental examination was recorded.

The primary end point was the diagnosis of confirmed ONJ, defined as an area of exposed bone in the maxillofacial region that had been present for at least 8 weeks in a participant receiving or previously exposed to a bisphosphonate and who had not had radiotherapy to the craniofacial region; diagnoses were required to have been identified by a health care clinician. A suspected case of ONJ was defined by the same ONJ criteria but present for less than 8 weeks. All suspected and confirmed cases of ONJ were adjudicated by the study team (C.H.V.P., J.M.U., and A.K.D.).

Participants

Participants must have had bone metastases from a solid tumor, multiple myeloma, or other malignant neoplasm for which intravenous bisphosphonate has clinical indications in the treatment of MBD. Participants must have been planning to receive zoledronic acid for MBD within 30 days of registration. Prior exposure to BMAs was allowed, limited to oral bisphosphonates for osteoporosis and a limited number of doses of intravenous bisphosphonate or denosumab. Participants must not have had a history of ONJ or radiotherapy to the maxillofacial area administered for therapeutic intent in the treatment of cancer. A Zubrod performance score of 0 to 3 (where 0 indicates no disease restrictions and 5, death) was required. Participants with a history of more than 1 histological tumor finding (other than treated basal cell or squamous cell skin cancer or in situ cervical cancer) were excluded.

Variables

Data collected in the medical case report forms (CRFs) included demographic details, tumor type, use of zoledronic acid or other osteoclast inhibitor, cancer therapies, comorbid conditions, type and dates of any imaging that captured the head region, and 5 patient-reported outcome questions adapted from the Brief Pain Inventory.[7] Dental CRFs included whether dental encounters occurred in the reporting period and, if performed, dental history and dental, periodontal, or endodontic examinations. If ONJ was suspected or confirmed, a separate dental ONJ CRF was used to characterize the findings, interventions, and outcomes.

Study CRFs captured the categories of anticancer therapies used before and during study participation. Although eligibility required participants to be planning to use zoledronic acid, the protocol did not dictate clinical care. After the US Food and Drug Administration approved denosumab for preventing SREs in solid tumors, the S0702 protocol and CRFs were revised to capture use of denosumab.

Statistical Analysis

Data were analyzed from August 24, 2018, to August 6, 2020. The accrual goal was 3500 patients to allow estimation of the upper bound of the 95% CI to within 26% of the assumed incidence if the incidence was at least 2.0% and no

information was obtained from the 30% of patients anticipated to drop out.[8] Cumulative incidence was estimated to account for the competing risk of death. A 30-day window was allowed for the 3-year ONJ rate to account for reporting delays. Prior studies[8-10] indicated the median time to onset of ONJ among patients receiving zoledronic acid is 18 (range, 4-35) months, suggesting that 3-year maximum follow-up was sufficient to detect ONJ.

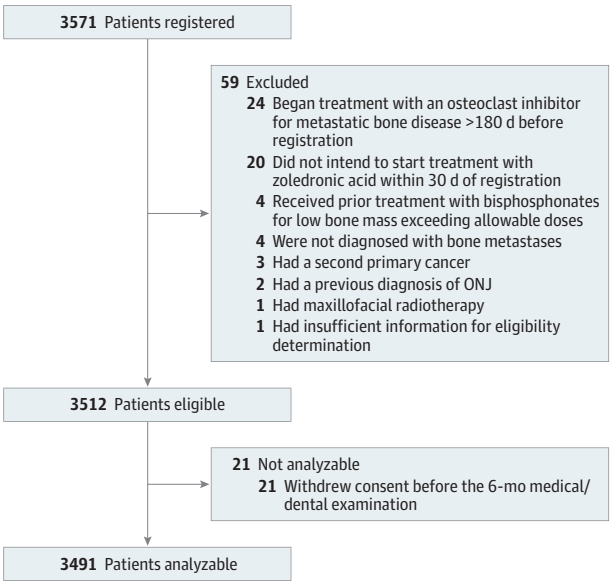
Secondary objectives included estimation of the 3-year cumulative incidence of ONJ for individual tumor types (eg, myeloma and breast, prostate, and lung cancers). Associations between individual baseline factors and the cumulative incidence of ONJ were explored, with baseline factors coded as binary indicator variables for consistency. Per protocol, we used multivariate Cox proportional hazards regression to generate cause-specific hazard ratios (HRs), emphasizing potential causal relationships, with adjustment for cancer type to limit potential bias.[11-15] Secondary examinations were hypothesis generating, and no adjustments for multiple comparisons were made; 2-sided $\alpha = .05$ indicated statistical significance. Factors with levels defining rare conditions (<5% of total eligible observations) were excluded. A sensitivity analysis of overall and disease-specific cumulative incidence, as well as of exploratory analyses of baseline factors, was also conducted using the combined end point of confirmed plus suspected ONJ if the number of suspected cases of ONJ at study conclusion was greater than 10% of all cases.

We described the clinical presentation, natural history, and management of ONJ cases and compared the change in oral health-related quality of life measures between baseline and follow-up for patients who did vs did not develop ONJ using 2-sample paired *t* tests. We estimated the incidence of ONJ in subgroups of patients according to the number of doses of zoledronic acid received. A landmark approach was used, testing the association of high vs low number of doses in the first 6 months (split at the median) with cumulative incidence of ONJ among patients still alive without ONJ after 6 months, using Cox proportional hazards regression. Landmark values of 1.0, 1.5, and 2.0 years were also evaluated.

Results

In total, 3571 patients were registered from 172 institutions in 3 countries (170 in the US; Instituto Nacional de Cancerología, Mexico City, Mexico; and King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia). A total of 2302 patients (64.5%) were enrolled after the study amendment, making the baseline dental examination recommended rather than required. Fifty-nine patients were not eligible, primarily because osteoclast inhibitor therapy was initiated more than 180 days before registration for patients with MBD (n = 24) or because patients did not initiate treatment with zoledronic acid within 30 days after registration (n = 20) (**Figure 1**). Among 3512 eligible patients, 21 were not analyzable because they withdrew consent before the 6-month examination, leaving 3491 patients evaluable for ONJ outcomes (1806 women [51.7%] and 1685 men [48.3%];

Figure 1. Consort Diagram



ONJ indicates osteonecrosis of the jaw.

median age, 63.1 [range, 22.4-93.9] years). The total amount of follow-up time examined for all eligible patients was 6153 years. In total, 1996 patients (56.8%) died before completing follow-up, and 327 (9.3%) were lost to follow-up; median follow-up time was 3.0 (range, 2.0-3.1) years among patients still alive at last contact. A total of 1228 eligible patients (35.0%) were enrolled without a baseline dental examination (108 [3.1%] before and 1120 [31.9%] after the study amendment).

Patient Characteristics

US study participation occurred in 41 states, with a plurality from Midwestern states (eFigure 1 in the Supplement). Among patients with data available, 368 (10.9%) were Black and 190 (5.6%) were Hispanic. Only 204 patients (6.1%) had no medical insurance. Dominant cancer types were breast (1120 [32.1%]), prostate (702 [20.1%]), and lung (666 [19.1%]); 580 (16.6%) had myeloma and 423 (12.1%) had other neoplasms. Few patients had any osteoclast inhibitor therapy within 6 months before registration (194 [5.6%]) or prior antiangiogenic therapy (417 [12.1%]). Most patients reported no alcohol use (2231 [67.5%]), and 430 (12.3%) were current smokers. Complete or partial dentures were observed in 515 patients (22.1%). Among patients with baseline dental examinations, severe cases of dental plaque (138 [6.2%]), calculus (126 [5.7%]), gingivitis (134 [6.1%]), and periodontal disease (133 [6.5%]) were reported (**Table 1**).

A total of 2263 patients (64.8%) had a baseline dental examination. Patients without a baseline dental examination were more likely to be Black (187 [15.2%] vs 181 [8.0%]), nonusers of alcohol (866 [70.5%] vs 1365 [60.3%]), and current smokers (221 [18.0%] vs 209 [9.2%]) and to have worse performance status (Zubrod score of 3, 32 [2.6%] vs 46 [2.0%]) (eTable 1 in the Supplement).

Table 1. Baseline Patient Characteristics

Characteristic	Data (n = 3491)[a]
Sociodemographic factors	
Age, median (range), y	63.1 (22.4-93.9)
Sex	
Female	1806 (51.7)
Male	1685 (48.3)
Race	
White	2942 (86.8)
Black	368 (10.9)
Asian	55 (1.6)
Pacific Islander	5 (0.1)
Native American	18 (0.5)
No. other or unknown	103
Ethnicity	
Hispanic	190 (5.6)
Non-Hispanic	3184 (94.4)
No. unknown	117
Medical insurance	
Private	1461 (43.7)
Medicare[b]	1271 (38.0)
Medicaid[c]	304 (9.1)
Military or Veterans	105 (3.1)
No insurance	204 (6.1)
No. other or unknown	146
Cancer and treatment factors	
Type of cancer	
Breast	1120 (32.1)
Multiple myeloma	580 (16.6)
Prostate	702 (20.1)
Lung	666 (19.1)
Other	423 (12.1)
Other osteoclast inhibitors within 6 mo before registration	
Yes	194 (5.6)
No	3296 (94.4)
No. unknown	1
Prior antiangiogenic therapy	
Yes	417 (12.1)
No	3020 (87.9)
No. unknown	54
Lifestyle factors	
Alcohol use within past 3 mo	
None	2231 (67.5)
≤1 Drink per week	542 (16.4)
2-6 Drinks per week	301 (9.1)
1-3 Drinks per day	204 (6.2)
≥4 Drinks per day	28 (0.8)
No. missing or unknown	185
Cigarette smoker	
None	1545 (44.3)
Former	1513 (43.4)
Current	430 (12.3)
No. missing or unknown	3
Periodontal factors	
No. of dental cleanings within 2 y before registration	
0	600 (26.5)
1	337 (14.9)
2	282 (12.5)
3	274 (12.1)
≥4	772 (34.1)
No. missing or unknown	1226
Baseline dental examination done	
Yes	2263 (64.8)
No	1228 (35.2)
Baseline dental imaging	
Yes	1935 (55.5)
No	1552 (44.5)
No. missing or unknown	4
Complete or partial dentures	
Yes	515 (22.1)
No	1816 (77.9)
No. missing or unknown	1160
Dental plaque	
None	230 (10.3)
Mild	1291 (57.9)
Moderate	571 (25.6)
Severe	138 (6.2)
No. missing or unknown	1261
Calculus	
None	342 (15.3)
Mild	1232 (55.3)
Moderate	529 (23.7)
Severe	126 (5.7)
No. missing or unknown	1262
Gingivitis	
None	571 (25.9)
Mild	1069 (48.5)
Moderate	430 (19.5)
Severe	134 (6.1)
No. missing or unknown	1287
Periodontal disease	
None	680 (33.4)
Mild	840 (41.2)
Moderate	385 (18.9)
Severe	133 (6.5)
No. missing or unknown	1453
Patient-reported dental pain/discomfort score, mean (SD)[d]	
Mean pain	0.81 (1.84)
Interference	
With eating	0.50 (1.55)
With smile	0.32 (1.36)
With speech	0.23 (1.07)
With quality of life	0.35 (1.28)

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients with data available. Percentages have been rounded and may not total 100.

[b] Includes Medicare alone (n = 406) and Medicare plus private (n = 865).

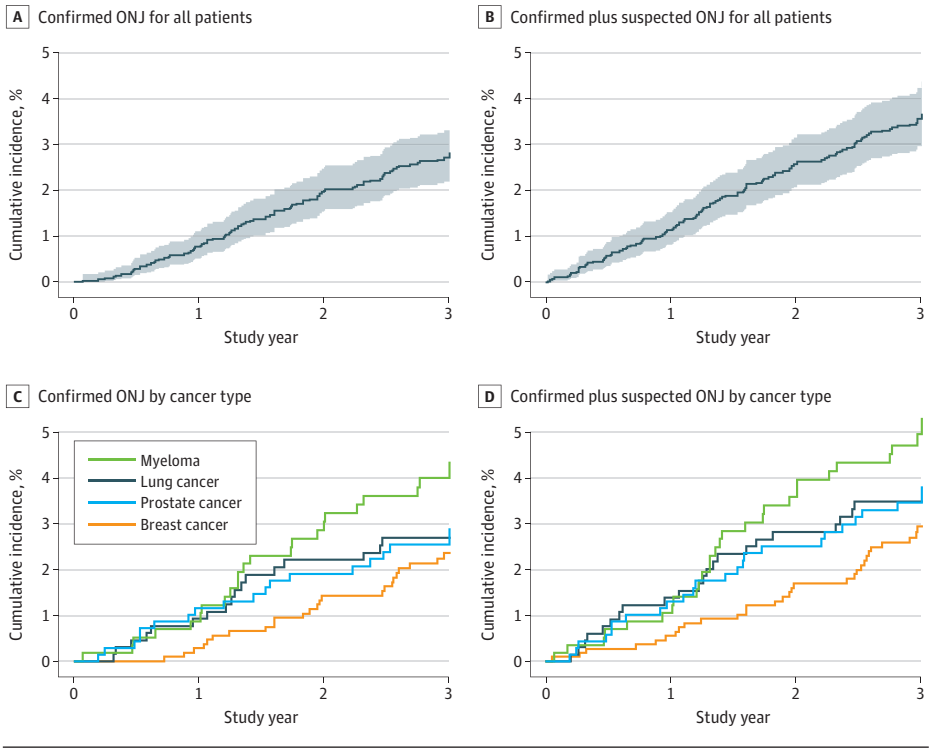
[c] Includes Medicaid alone (n = 205) and Medicaid plus Medicare (n = 9).

[d] Indicates within last 3 months, reported using the Brief Pain Inventory score. Scores for each question range from 0 to 10, with higher scores indicating greater pain or interference.

Cumulative Incidence of ONJ

Among the 3491 patients, 90 cases of ONJ were confirmed. The estimated cumulative incidence of confirmed ONJ at 3 years was 2.8% (95% CI, 2.3%-3.5%) (**Figure 2** and eTable 2 in the Supplement). Rates were 0.8% (95% CI, 0.5%-1.1%) at year 1 and 2.0% (95% CI, 1.5%-2.5%) at year 2. Rates of 3-year confirmed ONJ were highest in patients with myeloma (4.3%; 95% CI, 2.8%-6.4%) and lowest in those with breast cancer (2.4%; 95% CI, 1.5%-3.4%).

Figure 2. Cumulative Incidence of Osteonecrosis of the Jaw (ONJ)



A and B, The solid line represents the point estimate over time, and the blue area represents the uncertainty region, bounded by the 95% CIs indicated by the dashed lines to either side of the solid line. C and D, Point estimates over time by type of cancer. Exact data are given in eTable 2 in the Supplement.

One hundred eighteen patients had confirmed or suspected ONJ (3-year rate, 3.7%; 95% CI, 3.1%-4.4%). Three-year confirmed plus suspected rates of ONJ were highest in patients with myeloma (5.3%; 95% CI, 3.6%-7.5%) and lowest in patients with breast cancer (2.9%; 95% CI, 2.0%-4.1%) (Figure 2 and eTable 2 in the Supplement).

Hazard Risk of ONJ by Baseline Predictors

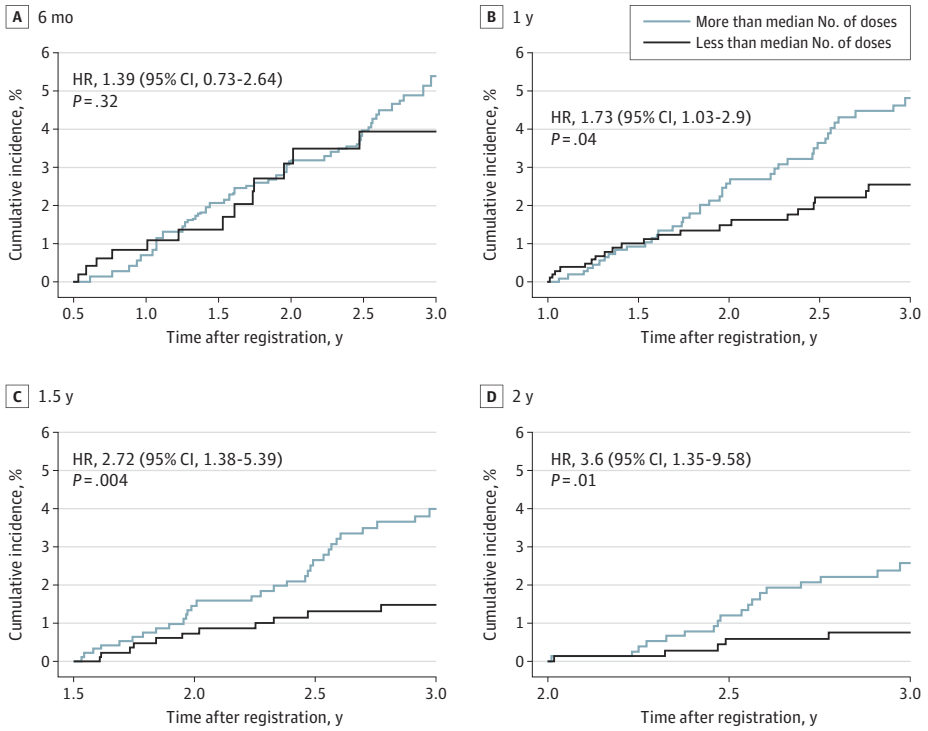
Factors associated with preexisting dental disease were most likely to be associated with confirmed ONJ (eFigure 2 in the Supplement). Patients with a total number of teeth at baseline greater than the median (25 [range, 0-32]) had an observed 3-year risk of ONJ of 2.4% (n = 1127) compared with 4.4% (n = 1142) for those with a total number of teeth less than the median (HR, 0.51; 95% CI, 0.31-0.83; *P* = .006). Findings for number of mandibular teeth and the number of maxillary teeth were consistent with these results although less extreme. Patients with any dentures (cumulative incidence, 5.0% [n = 508] vs 2.9% [n = 1791]; HR, 1.83; 95% CI, 1.10-3.03; *P* = .02) and removable dentures (cumulative incidence, 6.5% [n = 225] vs 3.0% [n = 2074]; HR, 2.02; 95% CI, 1.08-3.78; *P* = .03) were about twice as likely to experience ONJ compared with patients without any dentures or without removable dentures, respectively. Patients with baseline planned zoledronic acid dosing intervals of less than 5 weeks were more likely to experience ONJ (cumulative incidence, 3.2% [n = 3039]) than patients with planned dosing intervals of 5 weeks or longer (cumulative incidence, 0.7% [n = 447]; HR, 4.65; 95% CI, 1.46-14.81; *P* = .009). Patients with a baseline history of any oral surgery (cumulative incidence, 3.8% [n = 1682]) had about twice the risk of ONJ as patients without a baseline history of having had oral surgery (cumulative incidence, 2.2% [n = 592]), although this difference was not statistically significant (HR, 1.81; 95% CI, 0.97-3.38; *P* = .06). Last, current smokers (cumulative incidence, 3.7% [n = 430]) were more likely to experience ONJ than patients who were not current smokers (cumulative incidence, 2.4% [n = 1548]; HR = 2.12; 95% CI, 1.12-4.02; *P* = .02). Results were generally similar when both confirmed plus suspected ONJ cases were examined (eFigure 3 in the Supplement).

The 3-year cumulative incidence was higher for patients enrolled before (3.7% [n = 1256]) vs after (2.3% [n = 2235]) the amendment making the baseline dental examination recommended (HR, 1.65; 95% CI, 1.09-2.50; *P* = .02). Similarly, 3-year cumulative incidence was higher for patients with (3.4% [n = 2263]) vs without (1.9% [n = 1228]) a baseline dental examination (HR, 1.67; 95% CI, 1.02-2.75; *P* = .04).

Cumulative Incidence by Actual Dose Received

Patients receiving more than the median number of doses of zoledronic acid within the first 6 months had similar cumulative incidence of ONJ after 6 months (**Figure 3**) as those who received less. However, receipt of greater than the median number of doses within the first year (HR, 1.73; 95% CI, 1.03-2.90; *P* = .04), first 1.5 years (HR, 2.72; 95% CI, 1.38-5.39; *P* = .004), and first 2.0 years (HR, 3.60; 95% CI, 1.35-9.58; *P* = .01) was associated with higher rates of ONJ after each time.

Figure 3. Cumulative Incidence of Osteonecrosis of the Jaw (ONJ) by Dose Using Landmark Analysis



The blue lines indicate patients who received more than the median number of doses of zoledronic acid within the first 6 months, 1.0 year, 1.5 years, and 2.0 years after registration, respectively; the black lines indicate the complementary group of patients received less than the median number of doses. HR indicates hazard ratio.

Use of Denosumab

In the 460 participants for whom denosumab use was reported, 11 patients had confirmed ONJ (cumulative incidence at 3 years, 3.2%; 95% CI, 1.8%-5.1%). In those with denosumab exposure who had ONJ, the median number of on-study zoledronic acid doses was 2 (range, 0-5), and the median number of prestudy and on-study denosumab doses was 10 (range, 1-21).

Use of Antiangiogenic Therapies

Prior use of antiangiogenic therapy (eg, bevacizumab, sorafenib tosylate) was not statistically significantly associated with confirmed ONJ (HR, 1.42; 95% CI, 0.78-2.59; *P* = .25) (eFigure 2 in the Supplement). However, patients receiving antiangiogenic therapy within the first year after registration had a higher cumulative incidence of ONJ after 1 year (4.9%; 95% CI, 3.2%-7.2%) than patients receiving no antiangiogenic therapy by 1 year (2.5%; 95% CI, 1.8%-3.4%; *P* = .004) using landmark analysis.

Clinical Presentation, Management of ONJ Cases, and Description of Lesions

Seventy-eight cases with ONJ (86.7%) were staged and graded at presentation (**Table 2**).[16,17] Sixty-eight of these (87.2%) were stage 1 or 2 (exposed necrotic bone with none to mild symptoms or infection). Among 77 ONJ lesions with a known grade (reflecting the size of the ONJ lesion), 29 measured at least 1 cm (grades 3A-4B). Among 79 cases of ONJ with available data, management included oral rinses in 48 (60.8%), dental imaging in 17 (21.5%), debridement in 14 (17.7%), and invasive procedures in 4 (5.1%). Among 58 participants with ONJ outcomes data, 7 cases resolved, 8 improved, 33 remained stable, and 10 progressed. A minority of lesions were associated with periodontal infection, dental extraction, denture trauma, or other surgery or trauma (eTable 3 in the Supplement).

Patient-Reported Outcomes

At baseline, there were no significant differences in mean patient-reported outcome scores between patients who did vs did not develop ONJ (eTable 3 in the Supplement). However, the 83 participants with ONJ and available oral health–related quality of life measures showed a much worse oral health–related quality of life at the time of ONJ presentation for all 5 patient-reported outcome symptom items compared with noncases assessed at similar intervals. For instance, patients who went on to develop ONJ reported mean pain of 0.60 at baseline (on a scale of 0 to 10, where 0 represents no pain), whereas those who did not develop ONJ reported mean baseline pain of 0.71 (*P* = .57). In follow-up, at the time of ONJ diagnosis, mean pain was reported as 2.72. In contrast, for those who did not develop ONJ who were assessed for patient-reported outcomes at similar follow-up intervals, average pain was 0.64 (*P* < .001). Patterns for other patient-reported outcome items were similar (eTable 4 in the Supplement).

Discussion

This large, multicenter, prospective, observational cohort study of patients with MBD treated with zoledronic acid showed that

the 3-year cumulative incidence of ONJ was 2.8%. Patients with myeloma (4.3%), higher zoledronic acid exposure (3.2%), poor dentition (ie, fewer teeth [4.4%], dentures [5.0%], and prior oral surgery [3.8%]), and current smoking (3.7%) had higher observed rates of ONJ. Tooth loss, dentures, and need for oral surgery, as well as smoking, are associated with poor oral health. It is not yet known if an intervention made before initiating zoledronic acid treatment can modify these particular baseline risk factors for ONJ. The 3-year cumulative incidence differed between patients enrolled before (3.7%) vs after (2.3%) the study amendment that made the baseline dental examination recommended rather than required. Patients who developed ONJ reported more pain, interference with eating and speech, and worse oral health–related quality of life. Because osteoclast inhibition therapy, anticancer therapy, and dental care were performed as clinically indicated, these findings reflect ONJ as it occurs in clinical practice. Results from this study provide critical insights into the medical and dental care of patients with MBD and their risk of ONJ.

Our study used a uniform definition of ONJ, with more than 2000 participants having formal dental assessments. After an early amendment, standard baseline dental care was recommended, not mandated, to avoid biasing the cohort toward those with better dental care habits. This strategy enabled the study to better reflect clinically relevant care and generate widely generalizable findings. The overall rate of 35.2% of participants without a reported baseline dental examination is consistent with 2018 Centers for Disease Control and Prevention data that 36% of adults did not have a dental visit in the past year.[18]

Owing to the paucity of prospective data, current guidelines are based on expert opinion,[19,20] even as data suggest that optimizing oral health before initiating BMA can reduce the risk of ONJ.[21-23] The results of this study are likely to affect clinical care because we established both the overall risk of ONJ—vital for evaluating the risks and benefits of bisphosphonates—and identified potentially modifiable risk factors for developing ONJ, including optimizing oral health and use of longer zoledronic acid dosing intervals. Noninferiority studies[24-26] have demonstrated that, in some cancers, dosing zoledronic acid every 3 months has similar efficacy in preventing SREs as does monthly dosing.

Limitations

S0702 is unique for its large scale, pragmatic design, and comprehensive prospective data collection. However, there were limitations. The study lacked detailed information about antiangiogenic agents, sequence of therapies, additional supportive therapies, and socioeconomic data, including dental insurance, income, or educational level. The American Association of Oral and Maxillofacial Surgeons' position paper on ONJ[19] and a recent multiorganization ONJ guideline[20] use a definition of medication-related ONJ that includes exposure to antiangiogenic therapies. S0702 was designed before these publications and so was unable to use this definition. Although our study found no significant association between prestudy exposure to antiangiogenic therapy and occurrence of ONJ during BMA therapy, the use

Table 2. Clinical Presentation and Management of ONJ Cases

Factor	Patient data (n = 90)[a]
Initial presentation	
Stage[b]	
0	5 (6.4)
1	46 (59.0)
2	22 (28.2)
3	5 (6.4)
Grade[c]	
1A	18 (23.4)
1B	3 (3.9)
2A	22 (28.6)
2B	5 (6.5)
3A	22 (28.6)
3B	2 (2.6)
4A	2 (2.6)
4B	3 (3.9)
Infection signs or symptoms	
No	48 (63.2)
Yes	28 (36.8)
No. of lesions, median (IQR)	1 (1-1)
ONJ management	
Procedures	
No	16 (20.3)
Yes	63 (79.7)
Rinses	
No	31 (39.2)
Yes	48 (60.8)
Antibiotics	
No	46 (58.2)
Yes	33 (41.8)
Cultures taken	
No	79 (100)
Yes	0
Dental imaging	
No	62 (78.5)
Yes	17 (21.5)
Debridement	
No	65 (82.3)
Yes	14 (17.7)
Biopsy	
No	74 (93.7)
Yes	5 (6.3)
Invasive procedure	
No	75 (94.9)
Yes	4 (5.1)
Other	
No	69 (87.3)
Yes	10 (12.7)

Abbreviations: IQR, intraquartile range; ONJ, osteonecrosis of the jaw.

[a] Unless otherwise indicated, data are expressed as number (percentage) among those with known data. Percentages have been rounded and may not total 100.

[b] Zero indicates no evidence of necrotic bone but nonspecific signs and symptoms; 1, asymptomatic, exposed necrotic bone without evidence of infection; 2, exposed, necrotic bone with infection (pain and erythema with or without purulence); and 3, exposed, necrotic bone associated with pain and infection and 1 or more of the following: necrotic bone extending beyond the alveolar ridge, pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor.

[c] Graded by lesion size, where 1A (1B if multiple lesions with largest of this size) indicates single lesion less than 0.50 cm; 2A (2B if multiple lesions with largest of this size), single lesion of 0.50 to 0.99 cm; 3A (3B if multiple lesions with largest of this size), single lesion of 1.00 to 2.00 cm; and 4A (4B if multiple lesions with largest of this size), single lesion greater than 2.00 cm.

of antiangiogenic therapy within the first year after registration was associated with increased ONJ risk. Future studies are needed to assess the risk of ONJ with use of antiangiogenic therapies as well as additional novel therapies. In addition, S0702 may not have identified all ONJ cases owing to use of the older ONJ definition, the reliance on confirmed ONJ cases in the primary analysis, and the clinically directed oral examinations. If so, the true underlying rate may be closer to the upper bound represented by the estimate of both confirmed and suspected ONJ cases. The ONJ risk was higher among patients enrolled after implementation of an amendment recommending rather than requiring baseline dental examinations, suggesting the actual cumulative incidence rate of ONJ among patients with cancer receiving dental care under guideline recommendations may be somewhat higher. Finally, coding baseline factors as binary indicator variables enabled consistent interpretation of associations across different domains but could also result in loss of power. Additional analyses of risk factors are planned.

Denosumab was approved by the US Food and Drug Administration for reducing the risk of skeletal complications in patients with bone metastases from solid tumors almost 2 years after initiation of patient enrollment in S0702. The following year, S0702 was amended to capture its use in enrolled patients. Of note, fewer than 500 participants had exposure to denosumab during study follow-up, and of those who received treatment with denosumab, more than half were not exposed until they had already reached 2 years of study follow-up, complicating interpretation of the timing and magnitude of ONJ risk. Analysis of these participants will be reported separately.

Conclusions

This pragmatic, prospective cohort study of participants treated with zoledronic acid provides clinicians with critical information about the overall risk—and risk factors for—developing ONJ. Our findings suggest that, when clinically appropriate, consideration should be given to use of zoledronic acid dosing intervals of greater than 5 weeks to reduce the risk of ONJ. Going forward, this well-annotated trial and its corresponding biorepository may yield clues to mechanisms underlying development of this challenging toxic effect, as well as additional biochemical, genomic, composite risk score, or other predictive factors associated with ONJ risk.

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