Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases


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Background: Osteonecrosis of the jaw (ONJ) has been reported in patients receiving bisphosphonates for metastatic bone disease. ONJ incidence, risk factors, and outcomes were evaluated in a combined analysis of three phase III trials in patients with metastatic bone disease receiving antiresorptive therapies.

Patients and methods: Patients with bone metastases secondary to solid tumors or myeloma were randomly assigned to receive either s.c. denosumab (120 mg) or i.v. zoledronic acid (4 mg) every 4 weeks. On-study oral examinations were conducted by investigators at baseline and every 6 months. Oral adverse events were adjudicated by an independent blinded committee of dental experts.

Results: Of 5723 patients enrolled, 89 (1.6%) patients were determined to have ONJ: 37 (1.3%) received zoledronic acid and 52 (1.8%) received denosumab (P = 0.13). Tooth extraction was reported for 61.8% of patients with ONJ. ONJ treatment was conservative in >95% of patients. As of October 2010, ONJ resolved in 36.0% of patients (29.7% for zoledronic acid and 40.4% for denosumab).

Conclusions: In this combined analysis of three prospective trials, ONJ was infrequent, management was mostly conservative, and healing occurred in over one-third of the patients. Educating physicians about oral health before and during bone-targeted therapy may help reduce ONJ incidence and improve outcomes.

Key words: bone metastases, denosumab, osteonecrosis of the jaw, zoledronic acid

introduction

Osteonecrosis of the jaw (ONJ) was first reported in patients with a broad range of cancers receiving chemotherapy and i.v. bisphosphonates in the early 2000s. In retrospective studies, the incidence of ONJ has been reported to occur with variable frequency [1–9]. A recent meta-analysis reported a mean incidence of ONJ of 6.1% in these patients [10]. Recent guidelines issued by the American Academy of Oral and Maxillofacial Surgeons (AAOMS) define bisphosphonate-related ONJ as an area of exposed bone in the jaw persisting for >8 weeks in patients without prior craniofacial radiation to the jaws [11, 12]. Symptoms of ONJ include pain, swelling and infection of soft tissues, loosening of teeth, drainage, and a feeling of heaviness or numbness in the jaw. Current recommendations by AAOMS are that ONJ be managed conservatively through the use of antibiotics, oral rinses, and limited debridement. More aggressive treatment, including surgery and bone resection, may be needed in patients with more severe stages of ONJ [11–13].

Previous studies have attempted to identify both local and systemic risk factors associated with the development of ONJ in an advanced cancer population with bone metastases receiving antiresorptive therapy. Local risk factors, such as invasive...
dental procedures (e.g. tooth extraction) or concomitant oral disease, may increase the risk of ONJ [5, 14, 15]. Indeed, ONJ often occurs at the site of the procedure, although cases can occur spontaneously without a precipitating oral event [16, 17]. Epidemiology reports and retrospective studies have described multiple factors potentially associated with the development of ONJ, including chemotherapeutic agents, comorbid conditions (e.g. diabetes and anemia), and possibly, exposure to antiangiogenic agents [8, 9, 16–19].

Studies suggest that the risk of ONJ may increase with the potency of the antiresorptive agent and duration of treatment [1, 3, 5, 14, 15, 18, 20]. ONJ is more common in patients receiving i.v. than oral bisphosphonates [21]. The incidence of ONJ may vary by type of primary cancer, with higher incidence reported in patients with multiple myeloma or metastatic breast cancer [20, 21]. While the precise etiology of ONJ is unknown, leading hypotheses include impaired bone repair, suppression of osteoclast activity, infection and inflammation, and impaired angiogenesis or vascular repair [22–24].

The incidence of ONJ was collected prospectively from 5723 patients with metastatic bone disease enrolled in three registration trials comparing the efficacy and safety of denosumab (XGEVA®; Amgen Inc., Thousand Oaks, CA) with zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation, East Hanover, NJ). For these studies, ONJ was predefined as a lesion in the oral cavity of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found, associated with nonhealing after appropriate care for 8 weeks in a patient without prior history of radiation to the head, face, or mouth. Data from these trials were used to define the incidence, risk factors, and outcomes of ONJ in this study population.

patients and methods

patients

Patients (N = 5723) with bone metastases and solid tumors or multiple myeloma were enrolled in one of three identical designed phase III, parallel, double-blind double-dummy trials [25–27]. These trials compared the efficacy of denosumab (s.c., 120 mg) given every 4 weeks (Q4W) with zoledronic acid (i.v., 4 mg, adjusted for renal function) Q4W. A key secondary objective of these trials was to assess the safety and tolerability of denosumab compared with zoledronic acid. The identical designs of these trials allowed the data from each to be pooled and analyzed at a patient level.

Eligible patients were ≥18 years old with histologically or cytologically confirmed solid tumors or myeloma and radiographic evidence of one or more bone metastases or osteolytic lesions. Patients with prior exposure to oral or i.v. bisphosphonates for treatment of advanced cancer were excluded, but prior treatment with oral bisphosphonates for other bone loss conditions (e.g. osteoporosis) was permitted. Additionally, patients with prior history or current evidence of ONJ or osteomyelitis of the jaw; an active dental or jaw condition requiring surgery; planned invasive dental procedures over the course of study; or nonhealed oral or dental surgery were excluded from these trials.

Investigators were educated on the signs and symptoms of ONJ at study initiation and were provided additional training on carrying out detailed oral examinations for the purpose of evaluating ONJ. A visual examination of the oral cavity, including the teeth, mucosa, and jaws, was conducted by study investigators at screening and every 6 months while the patient was on study.

Patients provided written informed consent before any study-related procedures were carried out. These studies were approved by the institutional review board or ethics committee at each site.

identification of potential cases of ONJ

Potential ONJ events were identified by a number of mechanisms including spontaneously reported cases of ONJ by investigators, regularly carried out automated searches of clinical and safety databases using a predefined list of 36 Medical Dictionary for Regulatory Activities (MedDRA)-preferred terms (supplemental data, available at Annals of Oncology online), and clinical review of all adverse oral events. The terms included on the MedDRA-preferred terms list were discussed during an oncology drug advisory committee [28], and additional terms were added in consultation with the ONJ Adjudication Committee (ONJAC). Once a reported adverse oral event was considered to be a potential ONJ event, the investigator was notified and queried for further clinical information. All available relevant information required to facilitate adjudication decisions was collected including dental records, radiographs, and imaging reports; photographs or progress notes describing the event; and discharge summaries. For patients with positively adjudicated ONJ, follow-up on the status of ONJ was collected every 3 months until ONJ resolved or the patient withdrew consent or died.

adjudication committee and process

The ONJAC was an external independent panel of dental health care specialists who are experts in the field of ONJ diagnosis and treatment. The ONJAC was blinded to treatment assignment and was responsible for reviewing and adjudicating all conditions identified as suspicious for ONJ. All cases referred to the ONJAC were reviewed by two adjudicators; if their opinion was discordant, the case was sent to a third adjudicator for a majority decision.

data analysis

To assess the relative importance of potential risk factors, patients with positively adjudicated ONJ were compared with patients without ONJ. Data for patients with ONJ included information solicited from the sites after ONJ diagnosis as outlined above as well as data collected in the clinical trials database. Data for patients without ONJ were collected in the clinical trials database only. Systemic risk factors evaluated included comorbid conditions and concomitant therapies previously associated with ONJ development. Health-related quality of life (HRQoL) was evaluated using the Brief Pain Inventory-Short Form (BPI-SF) [29] and the general version of the Functional Assessment of Cancer Therapy (FACT-G) survey. The incidence of ONJ was assessed through the end of the primary analysis cut-off date for each of the three studies [6 March 2009 (breast cancer), 30 April 2009 (other solid tumors and myeloma), and 30 October 2009 (prostate cancer)]. ONJ treatments and outcomes are reported through 1 October 2010. The Cochran–Armitage test [30] was used to evaluate the difference in ONJ incidence between treatment groups. The cumulative incidence of ONJ is presented as a histogram. The frequency and percentage of ONJ are provided by baseline demographics, systemic risk factors, oral events, and location. The impact of ONJ on HRQoL was assessed from 6 months before ONJ diagnosis to the end of study or primary cut-off date, whichever occurred first.

To evaluate the benefit–risk of denosumab compared with zoledronic acid, the number of patients needed to treat (NNT) to prevent a skeletal-related event (SRE) and the NNT to experience an ONJ event (number needed to harm) were calculated for denosumab in comparison with zoledronic acid.

results

Study durations (first enrollment date to primary analysis cut-off date) ranged from 34 to 41 months. For the overall study
population, the median (Q1, Q3) time on study was 12.1 (5.4, 19.4) months for patients in the zoledronic acid group and 12.6 (5.6, 19.4) months for patients in the denosumab group. The median (Q1, Q3) number of doses of active product received was 11.0 (5.0, 19.4) for patients randomly assigned to receive zoledronic acid and 13.0 (6.0, 20.0) for patients randomly assigned to receive denosumab. The fewer doses of zoledronic acid received by patients were primarily because of dose withholding due to increased serum creatinine levels.

number of adjudicated cases and baseline demographics

Overall, 287 oral adverse events from 276 (4.8% of the overall population) patients were referred to the adjudication committee: 89 (approximately one-third) patients referred for adjudication (1.6% of the overall patient population) had positively adjudicated ONJ (Figure 1). Among patients with positively adjudicated ONJ, 37 (1.3%) were in the zoledronic acid group and 52 (1.8%) were in the denosumab group. The cumulative incidence of ONJ was not significantly different between treatment groups ($P = 0.13$; Figure 2). ONJ occurred from 4 up to 30 months after patients received the first dose of study drug. The median time of drug exposure before ONJ was 14 months for both treatment groups. Baseline characteristics of patients with ONJ were similar to those of patients without ONJ and reflected those of the overall trial population (Table 1).

systemic risk factors

Similar percentages of patients with ONJ and without ONJ had anemia, diabetes, or received chemotherapy (Table 2). A slightly greater proportion of patients with ONJ than those without received corticosteroids, while this proportion was higher for patients receiving antiangiogenic agents (bevacizumab, sunitinib malate, and sorafenib), although only a small number of ONJ patients were exposed to the latter ($n = 14$).

associated oral events

Among patients with ONJ, jaw pain was reported in nearly three-quarters, tooth extractions were reported for nearly two-thirds, and coinciding oral infections were reported for nearly one-half (Table 3). The mandible was the most common site of ONJ, while ONJ was observed less frequently in the maxilla. In a small number of patients ($<5\%$), ONJ was observed in both the mandible and the maxilla.

patient-reported outcomes

Data from the BPI-SF indicated that pain at worst, pain severity, and pain interference were stable over time in patients with ONJ (Figure 3A–C). In addition, the mean FACT-G overall and subscale scores did not change over time in patients with ONJ (Figure 3D; data not shown). The instability in pain and quality-of-life scores at later time points was because few patients remained on study at the later time points.

treatments, outcomes, and resolution

All patients with positively adjudicated ONJ received care for ONJ from a dental health expert. Over half of patients with positively adjudicated ONJ (54%) were treated conservatively for ONJ (oral monitoring, oral rinses, and/or antibiotics). Approximately 41% of patients with ONJ underwent limited surgery, which included sequestrectomy, extraction, or debridement (Table 4). Only four patients ($<5\%$) underwent resection of the affected bone. Of these patients, two had resolution of ONJ, one was lost to follow-up, and one had ONJ until death.

In 64% of patients with positively adjudicated ONJ, ONJ was either ongoing, present at the time of death, or the outcome was unknown as of 1 October 2010 (Table 4). Resolution of ONJ occurred in 36.0% (32 of 89) of patients [29.7% (11 of 37) for zoledronic acid; 40.4% (21 of 52) for denosumab] as of this date. Among the 32 patients who had resolution of ONJ, 25 (78.1%) discontinued blinded treatment, while 7 (21.9%)

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**Figure 1.** CONSORT diagram. Outcome of ONJ adjudication process. CONSORT, Consolidated Standards of Reporting Trials; ONJ, osteonecrosis of the jaw.

**Figure 2.** Cumulative incidence of ONJ. The crude incidence of ONJ reported for month 0–12, 0–24, and 0–36. ONJ, osteonecrosis of the jaw.
to prevent one additional SRE compared with zoledronic acid. In contrast, 212.2 patients need to be treated with denosumab for 1 year to incur one more event of ONJ compared with zoledronic acid. The benefit of denosumab in preventing an SRE compared with zoledronic acid outweighs the risk of ONJ by a factor of 17.

discussion

Initial reports of ONJ suggested a highly morbid and untreatable condition [31]. Over the past several years, a better understanding of the natural history of ONJ has developed, and it is now recognized that ONJ can present with a range of severities and can frequently resolve. As experience with diagnosis and management of ONJ has emerged, the plan of care has become focused on conservative measures. Whereas the initial medical management of ONJ typically involved more aggressive surgical intervention [32], it has evolved to a less invasive interventional approach as awareness of the condition has increased.

In agreement with published reports [2, 17, 21–23, 33], tooth extraction in this analysis of prospective studies was the predominant oral factor associated with the development of ONJ. This finding emphasizes the importance of assessing oral health of patients and implementing preventive dentistry if necessary before initiating therapy. Two recent studies showed that the incidence of ONJ decreased after routine preventive dental measures were implemented [34, 35]. Once antiresorptive therapy has been initiated, the aim should be maintenance of good oral health and avoidance of elective extractions as recommended by AAOMS and European Medicines Agency (EMA) [12, 13].

The association of systemic risk factors with ONJ was less pronounced than the association observed with oral factors. There was some association of ONJ with the use of corticosteroids and a near doubling of cases of ONJ in association with the use of antiangiogenic agents but no association with the use of chemotherapeutic agents, anemia, or diabetes. Antiangiogenic agents may potentially contribute to the development of ONJ by inhibiting vascular repair of the frequent microdamage sustained by the jaw. However, a recent analysis of ONJ incidence in patients with breast cancer...
and bone metastases found no association between development of ONJ and exposure to these agents [36]. The immunosuppressant effects of corticosteroids may slow wound healing and alter the oral microflora, thus increasing the risk of oral infection and ONJ.

It is unclear if demographic factors are associated with ONJ [1, 8, 14, 15, 18, 20], and they were not associated with ONJ in this analysis. As the vast majority of patients in these studies were white and nearly three-quarters of patients were enrolled in the United States or Europe, any differences in ONJ incidence by race or geographic region could not be interpreted.

Pain and HRQoL levels were stable from baseline over time in patients who developed ONJ. These data suggest that ONJ did not noticeably impact patients’ HRQoL. It should be noted that the instruments used in these studies are limited by not being specifically designed to capture oral events.

An important goal for physicians who are treating patients with metastatic bone disease with antiresorptive agents is to minimize the complications of this beneficial therapy including reducing the occurrence and severity of ONJ. The investigators for these trials were educated on the signs and symptoms that are indicative of potential development of ONJ and were also educated to treat active oral conditions before enrollment. Additionally, the patients had frequent and regular on-study oral examinations carried out by study investigators. As such measures could have either prevented ONJ to develop or resulted in earlier detection of ONJ, this suggests that these practices should be considered part of the standard of care in routine practice.

Figure 3. Patient-reported changes in pain and among patients with positively adjudicated ONJ. (A) Pain at worst; (B) pain severity; (C) pain interference; and (D) FACT-G total score. Data shown are the mean (SD) of patient-reported levels of pain (A–C) or HRQoL (D) at monthly intervals from 6 months before diagnosis of ONJ up to the time the patient discontinued the study for patients with positively adjudicated ONJ. HRQoL, health-related quality of life; FACT-G, Functional Assessment of Cancer Therapy - General; SD, standard deviation; ONJ, osteonecrosis of the jaw.
If a patient develops ONJ, current recommendations are to treat ONJ conservatively and avoid additional invasive surgeries [11, 12]. Investigators were counseled on the conservative treatment approach, and indeed, most patients in these trials received conservative treatment. This may have lead to the overall ONJ resolution rate of 36% observed in these trials. The resolution rate was somewhat greater in the denosumab group (40.4%) as compared with the zoledronic acid group (29.7%). One possible explanation for the difference in resolution rates between the treatment groups may be related to the different mechanisms of action of these agents. Denosumab selectively inhibits RANKL and the osteoclast inhibition caused by denosumab is reversible [37]. Bisphosphonates accumulate within bone and are released upon bone resorption, potentially recirculating to cause further suppressive effects on osteoclast function [38].

Currently, no evidence exists that discontinuing antiresorptive therapy improves the outcome of ONJ [39–41]. As all patients with positively adjudicated ONJ stopped antiresorptive therapy for a period of time, this analysis is unable to shed further light on this question.

One of the strengths of this analysis is that this is the first prospective evaluation of ONJ in patients with a broad spectrum of advanced cancer types using a large dataset from randomized phase III trials of antiresorptive agents. Also, rigorous processes were in place to capture and identify ONJ; this is clear from the high number of events referred to the ONJAC compared with those ultimately judged positive for ONJ. For these reasons, it is possible to have a high level of confidence in the accuracy of the incidence data.

In summary, this prospective analysis provides assessment of ONJ incidence, risk factors, and outcomes in the context of current therapies used to treat patients with advanced cancer. In these studies, ONJ was an infrequent event, and the incidence of ONJ did not significantly differ between the zoledronic acid and denosumab treatment groups. Most patients who developed ONJ had associated oral events, including jaw pain, tooth extraction, coinciding oral infection, or systemic risk factors such as the use of corticosteroids or antiangiogenic agents. It is possible that the incidence and severity of ONJ were minimized in these studies through proactive education of investigators. This would suggest that with wider education of health care providers about the need to resolve outstanding dental issues before administration of antiresorptive therapy, as well as training on the recognition of the signs and symptoms of ONJ, a lower incidence of ONJ and resolution of ONJ with conservative treatments may be achieved.

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disclosure
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tables

<table>
<thead>
<tr>
<th>Treatment, n (%)</th>
<th>Zoledronic acid (N = 37)</th>
<th>Denosumab (N = 52)</th>
<th>All (N = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited surgery</td>
<td>16 (43.2)</td>
<td>21 (40.3)</td>
<td>37 (41.6)</td>
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<tr>
<td>Sequestrectomy</td>
<td>5 (13.5)</td>
<td>10 (19.2)</td>
<td>15 (16.8)</td>
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<tr>
<td>Extraction</td>
<td>3 (8.1)</td>
<td>5 (9.6)</td>
<td>8 (9.0)</td>
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<tr>
<td>Debridement</td>
<td>3 (8.1)</td>
<td>3 (5.8)</td>
<td>6 (6.7)</td>
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<tr>
<td>Curettage</td>
<td>1 (2.7)</td>
<td>2 (3.8)</td>
<td>3 (3.4)</td>
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<tr>
<td>Othera</td>
<td>4 (10.8)</td>
<td>1 (1.9)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Bone resection</td>
<td>1 (2.7)</td>
<td>3 (5.8)</td>
<td>4 (4.5)</td>
</tr>
</tbody>
</table>

Outcomesb, n (%)

| Present at time of death | 15 (40.5) | 20 (38.5) | 35 (39.3) |
| Ongoing                 | 8 (21.6)  | 8 (15.4)  | 16 (18.0) |
| Unknown                 | 3 (8.1)   | 3 (5.8)   | 6 (6.7)   |
| Resolved                | 11 (29.7) | 21 (40.4) | 32 (36.0) |

Median (range) time to resolution, months

<table>
<thead>
<tr>
<th>Zoledronic acid</th>
<th>Denosumab</th>
<th>All</th>
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</thead>
<tbody>
<tr>
<td>8.7 (3.7–18.3)</td>
<td>8.0 (0.2–25.6)</td>
<td>8.2 (0.2–25.6)</td>
</tr>
</tbody>
</table>

aOther includes bone grinding, infundibulotomy, reduction in bone height, laser therapy, and sinusotomy.
bAs of 1 October 2010.
cResolved referred to complete mucosal coverage of exposed bone.

references
4. Dimopoulos MA, Kastritis E, Moulopoulos LA et al. The incidence of osteonecrosis of the jaw (ONJ) in patients with multiple myeloma who receive


