Replacing zoledronic acid with denosumab is a risk factor for developing osteonecrosis of the jaw

Tomoko Higuchi, DDS,[a,b] Yoshihiko Soga, DDS, PhD,[a] Misato Muro, DDS,[a] Makoto Kajizono, Ph, PhD,[c] Yoshihisa Kitamura, Ph, PhD,[c] Toshiaki Sendo, Ph, PhD,[c] and Akira Sasaki, DDS, PhD[b]

Objective. Intravenous zoledronic acid (ZA) is often replaced with subcutaneous denosumab in patients with bone metastatic cancer. Despite their different pharmacologic mechanisms of action, both denosumab and ZA are effective in bone metastasis but cause osteonecrosis of the jaw (ONJ) as a side effect. ZA persists in the body almost indefinitely, whereas denosumab does not persist for long periods. This study evaluated the risks of developing ONJ when replacing ZA with denosumab.

Study Design. In total, 161 Japanese patients administered ZA for bone metastatic cancer were enrolled in this single-center, retrospective, observational study. The risk of developing ONJ was evaluated by logistic regression analysis using the following factors: age, gender, cancer type, angiogenesis inhibitors, steroids, and replacement of ZA with denosumab.

Results. Seventeen patients (10.6%) developed ONJ. Multiple regression analysis indicated a significant difference in rate of ONJ associated with replacement of ZA with denosumab (odds ratio = 3.81; 95% confidence interval 1.04-13.97; P = .043).

Conclusions. Replacing ZA with denosumab is a risk factor for the development of ONJ. Both binding of bisphosphonate to bone and receptor activator of nuclear factor-κ B ligand inhibition could additively increase the risk of ONJ. We bring the replacement of ZA with denosumab to the attention of clinical oncologists. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018; 125:547–551)

Denosumab has recently been applied clinically to replace administration of bisphosphonates (BPs) in patients with bone metastasis. BPs require intravascular injection, and administration of the major BP, zoledronic acid (ZA), takes over 15 minutes, whereas denosumab requires only a single subcutaneous injection. Denosumab has advantages with regard to clinical load for both patients and medical staff. However, we found an increase rate of osteonecrosis of the jaw (ONJ) after switching to denosumab.

BPs, which have high chemical affinity for bone and specifically inhibit osteoclastic bone resorption, have been widely and safely used for the treatment of bone metastasis in which excessive osteoclastic bone resorption occurs.[1] BP-related ONJ is caused by high levels of BP accumulation, leading to suppression of intracortical remodeling (which is high in the jaw) and accumulation of large regions of dead/apoptotic osteocytes, which constitute necrotic bone.[2-4] However, its pathophysiology remains unclear.

Denosumab, a human immunoglobulin G2 (IgG2) monoclonal antibody against receptor activator of nuclear factor-κ B ligand (RANKL),[5] is a new therapeutic agent that has been shown to decrease skeletal-related events associated with metastatic bone disease from solid tumors,[6,7] with a half-life of approximately 1 month. Unlike BPs, which promote apoptosis in osteoclasts, denosumab inhibits osteoclastic bone resorption without causing apoptosis.[5] Furthermore, denosumab is not deposited in bone and therefore does not persist for long periods, as is the case with BPs, and therefore the effects of denosumab are reversible.[5] These pharmacologic properties initially suggested that denosumab treatment would be unlikely to result in ONJ. Surprisingly, however, patients treated with denosumab also developed ONJ, which was clinically indistinguishable from BP-related ONJ and occurred at almost the same rate.[8]

Both BPs and denosumab are related to ONJ, but their pharmacologic mechanisms are completely different. It should be noted that the effect of BPs on bone is almost permanent, whereas that of denosumab does not persist for long periods. Therefore, we hypothesized that replacing BPs with denosumab may have an influence on the development of ONJ; the effect of denosumab is additive to the permanent effect of BPs in the development of ONJ. Previously, increasing duration and/or total dose of ZA administration, concomitant use of angiogenesis

Statement of Clinical Relevance

Replacing the bisphosphonate zoledronic acid with the receptor activator of nuclear factor-κ B ligand inhibitor denosumab in patients with bone metastatic cancer appears to elevate the risk for the development of osteonecrosis of the jaw.

This study was supported by the management expenses grant for the Okayama University from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

[a]Division of Hospital Dentistry, Okayama University Hospital, Okayama, Japan.
[b]Department of Oral and Maxillofacial Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.
[c]Department of Pharmacy, Okayama University Hospital, Okayama, Japan.

Received for publication Oct 22, 2017; returned for revision Feb 11, 2018; accepted for publication Feb 17, 2018.

2212-4403/$ - see front matter
https://doi.org/10.1016/j.oooo.2018.02.010

inhibitors,[9-11] and concomitant use of steroids[8,12] were indicated as factors for development of ONJ. This study was performed to evaluate the risk of developing ONJ following replacement of ZA with denosumab, taking the known medication-related risk factors into consideration.

PATIENTS AND METHODS

Study design

This was a single-center, retrospective, observational study to evaluate the risk of developing ONJ by logistic regression analysis using the following factors: age, gender, death within the study period, cancer type, angiogenesis inhibitors, steroids, and replacement of ZA with denosumab. The Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences approved this study (Approval No. ken 1509-021).

Patients

A total of 161 consecutive patients (males 68; females 93) administered ZA for bone metastatic cancer between 2012 and 2015 in our hospital were included in this study. The observation was started from the date of ZA administration. Patients who had already been administrated ZA before 2012 were observed by going back to the beginning of ZA administration. All cases of BP administration for bone metastasis involved use of ZA only; other BPs were not administered in our hospital. All patients were Japanese. All consecutive patients administered ZA according to the dispensary records of the Department of Pharmacy were included in the study. Denosumab was approved for use in Japan in 2012; therefore, ZA was replaced with denosumab in many patients between 2012 and 2015. Our hospital has well-established medical–dental collaboration. All patients underwent a dental examination before ZA administration and were followed up. Dental examination was also performed in cases in which ZA was replaced with denosumab to confirm that the patients did not have ONJ.

Zoledronic acid or denosumab administration

ZA (Zometa; Novartis Pharmaceuticals Corp., East Hanover, NJ) was administered at a dose of 4 mg every 3 to 6 weeks for the duration of 15 minutes by intravenous injection, and denosumab (RANMARK; Daiichi Sankyo Company, Limited, Tokyo, Japan) was administered at a dose of 120 mg every 4 to 5 weeks, by subcutaneous injection. ZA dose adjustment was carried out on the basis of the patient's calcium level and/or renal function.

Diagnosis of medication-related ONJ

The diagnosis of medication-related ONJ was made according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper, 2014 update.[13] Patients were considered to have medication-related ONJ if all of the following characteristics were present:

- Current or previous treatment with antiresorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease in the jaws

Medication-related ONJ diagnosis was made clinically by the doctor/dentist in charge. When charts were reviewed, an investigator of this study also checked and verified the diagnosis of medication-related ONJ.

Analysis of relationship between subject characteristics and risk of ONJ

Before analysis of the relationship between medication and risk of ONJ, the relationship between each of the following subject characteristics and risk of ONJ were analyzed: increasing age at start of ZA administration, gender, death within the study period, and cancer type (lung, breast, prostate, kidney, colorectal, and others). Univariate logistic regression analysis was performed.

Analysis of relationship between medication and risk of ONJ

After analysis of the relationship between subject characteristics and risk of ONJ, we analyzed the relationship between medication and risk of ONJ.

First, univariate logistic regression analysis was performed. The relationship between each of the following medication-related potential risk factors, which were suggested in AAOMS position paper,[13] and the development of ONJ were analyzed: administration of ZA (increasing duration and total dose), administration of denosumab (increasing duration and total dose), concomitant use of angiogenesis inhibitors, and concomitant use of steroids. In addition, the relationship between replacement of ZA with denosumab and the development of ONJ was also analyzed.

Second, medication-related risk factors for the development of ONJ, with $P < .05$ on univariate logistic regression analysis, were subjected to multivariate logistic regression analysis. Multivariate logistic regression models were prepared to estimate the risks of medication-related ONJ associated with potential medication predictors. Inclusion of variables in the models was based on existing knowledge of risk factors for medication-related ONJ and our hypothesis that replacement of ZA with denosumab was a potential risk factor.

Statistical analysis

Univariate logistic regression analysis and multivariate logistic regression analysis were performed using STATA statistical software (release 12; Stata Corp, College Station, TX).

RESULTS

Development of ONJ

Seventeen of 161 patients (10.6%) administered ZA developed ONJ. We performed comparisons between the ONJ development group [ONJ(+), n = 17] and the non–ONJ development group [ONJ(–), n = 144]. There were no patients in stage 0, defined as no clinical evidence of necrotic bone, but presenting with nonspecific symptoms or clinical and radiographic findings.

Table I. Characteristics of patients and risks of ONJ: univariate logistic regression analysis

Characteristics	*ONJ(+) (n = 17)*	*ONJ(–) (n = 144)*	*P*
Increasing age at start of ZA administration	Median: 63 Range: 42-73	Median: 60 Range: 24-86	.676
Gender (M/F)	4/13 (23.5%/76.5%)	64/80 (44.4%/55.6%)	.100
Cancer type (*n*)			
Lung	3	39	NA
Breast	10	29	.001*
Prostate	1	16	NA
Kidney	1	10	NA
Colorectal	1	8	NA
Others	1	42	-

F, female; *M*, male; *NA*, not applicable to statistical analysis because of the small number of patients in the ONJ(+) group; *ONJ*, osteonecrosis of the jaw; *ZA*, zoledronic acid.
*P <.05.

Characteristics of patients and risk of ONJ

The results of univariate logistic regression analysis of the characteristics of the patients and risk of ONJ are shown in Table I. There was no significant difference in the age at commencement of ZA administration between the ONJ(+) and ONJ(–) groups. The development of ONJ tended to be more common in females than in males, although the difference was not significant ($P = .100$), reflecting the observation that breast cancer patients had significantly elevated risk of ONJ development ($P = .001$).

Medication and risk of ONJ: univariate logistic regression analysis

The results of univariate logistic regression analysis of medication and risk of ONJ are shown in Table II. Increases in the period of ZA administration and total dose of ZA were significantly related to the risk of ONJ ($P = .009$ and $P = .011$, respectively), but their odds ratio (OR) and 95% confidence interval (CI) were low (OR 1.00, 95% CI 1.00–1.00; OR 1.00, 95% CI 1.00-1.01, respectively). Increases in the period of denosumab administration and total dose of denosumab were not significantly related to the risk of ONJ ($P = .418$ and $P = .166$, respectively). Concomitant use of angiogenesis inhibitors was significantly related to the risk of ONJ ($P = .004$) with high OR (4.77) and 95% CI (1.65-13.75). Concomitant use of steroids was not significantly related to the risk of ONJ ($P = .855$). Notably, replacement of ZA with denosumab was significantly related to the risk of ONJ ($P = .014$) with high OR (3.68) and 95% CI (1.30-10.40).

Medication and risk of ONJ: multiple logistic regression analysis

On the basis of the results of univariate logistic regression analysis, we performed multiple logistic regression

Table II. Medication and risk of ONJ: univariate logistic regression analysis

Medication	*ONJ(+) (n = 17)*	*ONJ(–) (n = 144)*	*OR (95% CI)*	*P*
Administration of ZA				
Duration (d)	Median: 1031 Range: 79-2225	Median: 416 Range: 56-3466	1.00 (1.00–1.00)	.009*
Total dose (mg)	Median: 92 Range: 12-252	Median: 20 Range: 4-408	1.00 (1.00-1.01)	.011*
Administration of denosumab				
Duration (d)	Median: 617 Range: 166-1179	Median: 235 Range: 37-1301	1.00 (1.00–1.00)	.418
Total dose (mg)	Median: 2400 Range: 720-3840	Median: 780 Range: 120-5520	1.00 (1.00–1.00)	.166
Concomitant use of angiogenesis inhibitors (+/–)	11/6 (64.7%/35.3%)	37/107 (25.7%/74.3%)	4.77 (1.65-13.75)	.004*
Concomitant use of steroids (+/–)	1/16 (5.9%/94.1%)	6/138 (4.2%/95.8%)	1.22 (0.14-10.59)	.855
Replacement of ZA with denosumab (+/–)	8/9 (47.1%/52.9%)	28/116 (19.4%/80.4%)	3.68 (1.30-10.40)	.014*

ONJ, osteonecrosis of the jaw; *OR*, odds ratio; *ZA*, zoledronic acid.
*P <.05.

Table III. Medication and risk of ONJ: multiple logistic regression analysis

	OR (95% CI)	*P*
Administration of ZA		
Increasing duration	1.00 (1.00–1.00)	.376
Total dose	1.01 (1.00-1.02)	.069
Concomitant use of angiogenesis inhibitors (+/–)	5.02 (1.56-16.17)	.007*
Replacement of ZA with denosumab (+/–)	3.81 (1.04-13.97)	.043*

ONJ, osteonecrosis of the jaw; *OR*, odds ratio; *ZA*, zoledronic acid.
*P <.05.

analysis to evaluate the relationship between medication and risk of ONJ. We followed standard methods to estimate sample size for multiple logistic regression, with at least 10 outcomes needed for each independent variable included in the analysis.[14] Four outcomes were examined simultaneously: increasing duration of ZA administration, total dose of ZA administered, concomitant use of angiogenesis inhibitors, and replacement of ZA with denosumab, all of which were significant ($P < .05$) on univariate logistic regression analysis.

The results of multiple logistic regression analysis of medication and risk of ONJ are shown in Table III. Replacement of ZA with denosumab was significantly related to the risk ONJ development ($P = .043$) with high OR (3.81) and 95% CI (1.04-13.97).

DISCUSSION

Replacement of ZA with denosumab was significantly related to the risk of developing ONJ ($P = .043$) with OR (3.81) and 95% CI (1.04-13.97). Our results showed that this risk is greater than or equal to other previously identified medication risk factors. Replacement could increase the risk of ONJ, and clinical oncologists should be careful in their consideration of the need for replacement.

Inhibition of osteoclast function seems to be part of the pathophysiology of medication-related ONJ because the agents most commonly linked to medication-related ONJ— BPs and RANKL inhibitors (denosumab)—both reduce bone resorption, although through different mechanisms.[15] One reasonable mechanism for our results is that denosumab is a fully human monoclonal antibody with a half-life of several weeks[16] and is not eliminated via the kidneys, in contrast to BPs, which primarily show renal elimination, bind to hydroxyapatite, and may remain sequestered in bones for many years.[17] The effects of ZA on bone are persistent, whereas those of denosumab do not persist for long periods. Denosumab prevents RANKL from binding to its receptor, RANK, thereby inhibiting the development, activation, and survival of osteoclasts.[5] This is different from the mechanism of action of BPs, which bind to bone mineral and probably inhibit osteoclast function mainly by being taken up by osteoclasts at the sites of bone resorption.[5] A major difference in the effects of denosumab and BPs on osteoclasts is that BPs must be internalized to act on the cells, whereas denosumab acts in the extracellular milieu.[5] Functional osteoclasts could be decreased additively, and turnover of bone metabolism would be reduced. This may contribute to control bone metastasis cancer but increase the risk of ONJ.

Our results indicated high medication-related ONJ risk in patients with cancer. It was reported that the cumulative incidence of medication-related ONJ is in the low single digits (range 0.7%–6.7%) in cancer patients exposed to zoledronate.[18,19] When limited to studies with Level 1 evidence (i.e., systematic reviews or randomized controlled trials), the risk of medication-related ONJ in patients exposed to zoledronate is approximately 1% (100 cases per 10,000 patients).[18,20-22] In our study, however, ONJ developed in 17 of 161 patients (10.56%) administered ZA. Although this was a single-center, retrospective, observational study, the cases were consecutive, the primary endpoint was the development of ONJ, and all patients had been referred to dentists. The higher incidence of ONJ could be explained as follows: (1) Generally, the results obtained from the primary endpoint show a high incidence compared with those from a secondary endpoint if the item evaluated is the same, and some large-scale studies set ONJ as a secondary endpoint; (2) all patients were under the primary care of a dentist, and therefore, development of ONJ was detected diligently. Even so, the rate of ONJ incidence was high, and there may be ethnic differences in risk, with Japanese patients likely having a higher risk of ONJ. The reported incidence rate was not different from the impression in daily clinical practice. Our results regarding the frequency of ONJ development reached double digits, and the impact of this finding could not be ignored. Both ZA and denosumab control bone metastasis well, and the greatest advantage of replacing ZA with denosumab would be reduction in clinical load. However, the difference was small (intravenous or subcutaneous route of administration), and therefore continuation of ZA administration would be better in patients that have received this agent.

We speculated that the mechanism underlying the additive effect of denosumab in patients administered BPs is that the effects of ZA on bone are highly persistent, whereas those of denosumab do not persist for long periods. To confirm this speculation on mechanism, further in vitro and/or in vivo studies on osteoclast behavior are required. It would also be interesting to evaluate not only ONJ but also other effects of denosumab and BPs. These agents may have better ability to control bone metastasis, whereas other well-known side effects, for example,

atypical femoral fractures and hypocalcemia, could occur frequently.

We attempted to avoid bias by selecting patients consecutively, and the relationship between each of the medication-related potential risk factors, which were suggested in the AAOMS position paper,[13] and the development of ONJ was analyzed. However, the retrospective nature of this study, which was a limitation, may have resulted in important clinical information being missed. Furthermore, as the total number of incidents of ONJ was limited, it was not possible to compare the denosumab group and the group of continued ZA administration without switching. Therefore, we are currently planning further prospective, multicenter studies in this area.

CONCLUSIONS

Replacing ZA with denosumab is a risk factor for the development of ONJ. Both binding of BPs to bone and RANKL inhibition could additively increase the risk of ONJ. We thus bring the replacement of ZA with denosumab to the attention of clinical oncologists because of the increase in clinical load.

REFERENCES

1. Japanese Allied Committee on Osteonecrosis of the Jaw, Yoneda T, Hagino H, et al. Antiresorptive agent-related osteonecrosis of the jaw: position paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. *J Bone Miner Metab*. 2017;35:6-19.
2. Allen MR, Burr DB. The pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses, so few data. *J Oral Maxillofac Surg*. 2009;67:61-70.
3. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med*. 2006;144:753-761.
4. Reid IR, Bolland MJ, Grey AB. Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone*. 2007;41:318-320.
5. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. *Bone*. 2011;48:677-692.
6. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377:813-822.
7. Stopeck AT, Fizazi K, Body JJ, et al. Safety of long-term denosumab therapy: results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. *Suppor Care Cancer*. 2016;24:447-455.
8. Saad F, Brown JE, Van Poznak C, et al. 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. *Ann Oncol*. 2012;23:1341-1347.
9. Antonuzzo L, Lunghi A, Petreni P, et al. Osteonecrosis of the jaw and angiogenesis inhibitors: a revival of a rare but serous side effect. *Curr Med Chem*. 2017;24:3068-3076.
10. Pakosch D, Papadimas D, Munding J, Kawa D, Kriwalsky MS. Osteonecrosis of the mandible due to anti-angiogenic agent, bevacizumab. *Oral Maxillofac Surg*. 2013;17:303-306.
11. Guarneri V, Miles D, Robert N, et al. Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. *Breast Cancer Res Treat*. 2010;122:181-188.
12. Tsao C, Darby I, Ebeling PR, et al. Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. *J Oral Maxillofac Surg*. 2013;71:1360-1366.
13. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72:1938-1956.
14. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49:1373-1379.
15. Allen MR. Medication-related osteonecrosis of the jaw: basic and translational science updates. *Oral Maxillofac Surg Clin North Am*. 2015;27:497-508.
16. Doshi S, Sutjandra L, Zheng J, et al. Denosumab dose selection for patients with bone metastases from solid tumors. *Clin Cancer Res*. 2012;18:2648-2657.
17. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int*. 2008;19:733-759.
18. Coleman R, Woodward E, Brown J, et al. Safety of zoledronic acid and incidence of osteonecrosis of the jaw (ONJ) during adjuvant therapy in a randomised phase III trial (AZURE: BIG 01-04) for women with stage II/III breast cancer. *Breast Cancer Res Treat*. 2011;127:429-438.
19. Vahtsevanos K, Kyrgidis A, Verrou E, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J Clin Oncol*. 2009;27:5356-5362.
20. Qi WX, Tang LN, He AN, Yao Y, Shen Z. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. *Int J Clin Oncol*. 2014;19:403-410.
21. Mauri D, Valachis A, Polyzos IP, Polyzos NP, Kamposioras K, Pesce LL. Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a meta-analysis. *Breast Cancer Res Treat*. 2009;116:433-439.
22. Scagliotti GV, Hirsh V, Siena S, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. *J Thorac Oncol*. 2012;7:1823-1829.

Reprint requests:

Yoshihiko Soga, DDS, PhD
Division of Hospital Dentistry
Okayama University Hospital
2-5-1 Shikata-cho
Okayama 700-8525
Japan
y_soga@okayama-u.ac.jp