Influence of prostate cancer status on the prevalence of medication-related osteonecrosis of the jaw

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Objective. The aim of this study was to evaluate the risk of osteonecrosis of the jaw (ONJ) in patients with prostate cancer, particularly the relationship between prostate cancer progression and ONJ development.

Study Design. This single-center, retrospective, observational study included 113 patients who received zoledronic acid or denosumab for prostate cancer with bone metastasis between January 2012 and March 2020. The risk of ONJ was evaluated regarding age; antiresorptive drugs; duration of antiresorptive treatment; prostate cancer status, including castration-resistant prostate cancer (CRPC) and prostate-specific antigen level; chemotherapy; radium-223 treatment; corticosteroid treatment; diabetes mellitus; and dental extractions.

Results. Overall, 28 patients had ONJ; 10 patients received zoledronic acid and 18 patients received denosumab. Multiple logistic regression analysis demonstrated that CRPC (odds ratio = 6.01; 95% confidence interval, 1.76-20.05; $P = .004$) and dental extractions (odds ratio = 12.40; 95% confidence interval, 3.42-44.70; $P < .001$) were significantly associated with ONJ. In addition, antiresorptive treatment lasting more than 1 year partially mediated between CRPC and development of ONJ.

Conclusion. CRPC and dental extraction are risk factors for developing ONJ, and antiresorptive treatment lasting more than 1 year is a partial mediator between CRPC and ONJ. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:312−318)

Prostate cancer is the second most frequently diagnosed cancer in men worldwide, and it progresses relatively slowly.[1] Primary androgen deprivation therapy is often used as an initial treatment for advanced prostate cancer.[2] When the effect of androgen deprivation therapy is diminished, the disease status shifts from hormone-sensitive prostate cancer to castration-resistant prostate cancer (CRPC). Docetaxel (DOC), a taxane-type anticancer drug, has been used as a therapeutic for CRPC. Recently, enzalutamide and abiraterone, which are new hormone agents, and cabazitaxel (CBZ), which is a novel taxane-type anticancer drug, have been used for CRPC. In Japan, these drugs were approved in 2014 and have since been used in addition to conventional drugs.[3] Advanced prostate cancer often metastasizes to bone as it progresses, and bone metastases occur in more than 80% of patients with CRPC.[4] Exacerbation of bone metastases causes skeletal-related events (SREs), which are defined by pathologic fractures, spinal cord compression, or the need for palliative irradiation or orthopedic surgery.[5] SREs limit patients' activities of daily living, decrease quality of life, and pose a threat to survival. SREs occur in 46.1% of patients with prostate cancer with bone metastases within 1 year after the discovery of bone metastases.[6] Antiresorptive drugs, such as zoledronic acid (ZA) and denosumab (Dmab), are used early to prevent SREs.[3] Strong evidence suggests that antiresorptive drugs are beneficial in preventing SREs. Many randomized controlled trials have demonstrated that ZA and Dmab significantly reduce the incidence of SREs.[7,8] Dmab is considered highly effective, because it significantly prolongs (by 4 months) the time to the first onset of SREs compared to ZA.[7] Therefore, antiresorptive drugs play an important role in preventing SREs. However, an adverse effect of antiresorptive drugs is medication-related osteonecrosis of the jaw (MRONJ),[9] a pathologic condition that causes distress to the patient and may necessitate interruption of treatment of the underlying disease. Among patients with prostate cancer with bone metastases, the incidence of osteonecrosis of the jaw (ONJ) is 1.26% to 20.93%, and the frequency of ONJ is higher with Dmab treatment than with ZA treatment.[7,10-12]

The development and risk factors of ONJ in patients with prostate cancer have been examined in many

Statement of Clinical Relevance

The incidence of osteonecrosis of the jaw increases in patients with castration-resistant prostate cancer who receive antiresorptive treatment for more than 1 year.

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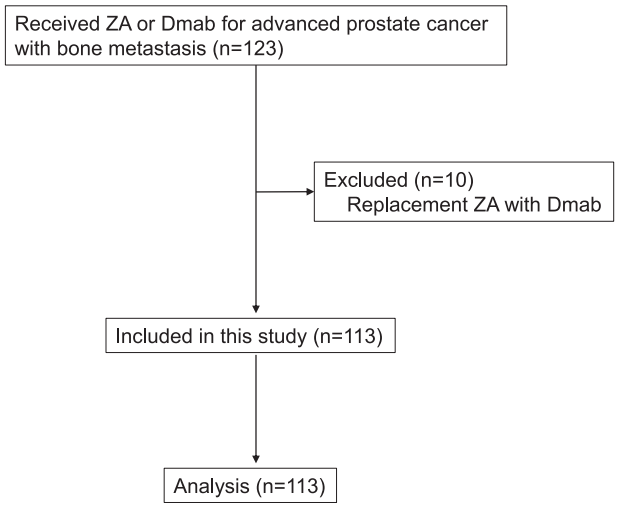

Fig. 1. Patient selection flowchart. *ZA*, zoledronic acid; *Dmab*, denosumab.

studies;[12-14] however, the relationship between the aspects of prostate cancer, such as CRPC and prostate-specific antigen (PSA) value, and the development of ONJ has not been examined in detail. If the risk for ONJ changes in accordance with the status of advanced prostate cancer, this information will be useful in decisions regarding whether to perform invasive treatment of the jaw, such as tooth extraction. In this study, we retrospectively evaluated the development of MRONJ in patients with prostate cancer with bone metastases; in particular, we assessed risk factors, including the relationship of CRPC, with regard to prostate cancer progression and ONJ development.

MATERIALS AND METHODS

Study design

This single-center, retrospective, observational study was conducted to evaluate the risk of the development of ONJ according to age; antiresorptive drugs (ZA or Dmab); duration of antiresorptive treatment; prostate cancer status, including PSA value and CRPC; chemotherapy; radium-223 dichloride treatment; corticosteroid treatment; diabetes mellitus; and dental extractions. The Institutional Review Board and Research Ethics Committee of Kawasaki Municipal Kawasaki Hospital, Kawasaki, Japan, approved this study (Approval No. 2019-31).

Patients

One hundred twenty-three patients received ZA or Dmab for advanced prostate cancer with bone metastasis between January 2012 and March 2020 at Kawasaki Municipal Kawasaki Hospital. Records for all consecutive patients who received at least 1 dose of ZA or Dmab were extracted from the dispensary records at the Department of Pharmacy. Observation was started from the beginning of ZA or Dmab administration. For patients who had received ZA or Dmab before January 2012, we observed data by returning to the date of first administration. After excluding patients in whom ZA was replaced with Dmab, the final study population included 113 patients (Figure 1). ZA (Zometa; Novartis Pharmaceuticals Corp., East Hanover, NJ, USA) was administered at a dose of 4 mg every 4 weeks by intravenous injection. For each patient, the dosage was adjusted on the basis of renal function. Dmab (RANMARK, Daiichi Sankyo Company Ltd., Tokyo, Japan) was administered at a dose of 120 mg every 4 weeks by subcutaneous injection. None of the patients received antiangiogenic agents or radiation therapy to the head and neck regions. Oral management was performed at our affiliated dental clinic.

Diagnosis and staging of MRONJ

MRONJ was diagnosed and staged according to the criteria of the 2014 update of the position paper of the American Association of Oral and Maxillofacial Surgeons.[9] Observation for ONJ began when ZA or Dmab was first administered, and patients who were diagnosed with ONJ through March 2020 were included in this study. Urologists or dentists referred patients to the Department of Oral Surgery based on the findings of bone scintigraphy and the clinical findings in the oral and maxillofacial regions, and oral surgeons made the diagnosis of ONJ.

Analysis of the relationship between characteristics of patients and development of ONJ

We selected ONJ risk factors in accordance with the position paper of the American Association of Oral and Maxillofacial Surgeons and the factors related to prostate cancer.[9] The duration of antiresorptive treatment

was the period from the first administration to the last administration of antiresorptive drugs through March 2020. The duration of antiresorptive treatment in patients with MRONJ was the period from the beginning of antiresorptive drugs administration to the date when ONJ was diagnosed.

Statistical analysis

First, to assess the association between each variable and the development of ONJ, univariable analysis was performed using the Mann-Whitney *U* nonparametric test for continuous variables and the chi-square test for categorical variables. Subsequently, for risk factors with $P < .05$ in univariable analysis, multivariable analysis was performed with logistic regression. The sample size for multiple logistic regression was estimated according to Peduzzi et al.'s study of the number of events per variable.[15] At least 10 outcomes were required for each independent variable included in the analysis.

A mediation analysis was performed using Baron and Kenny's method to identify a mediator variable that might influence the relationship between independent and dependent variables and to exclude it from confounding variables in the multivariable analysis by logistic regression analysis.[16] A variable was considered a mediator when 4 conditions were met: (1) the independent variable was significantly related to the dependent variable, (2) the hypothesized mediator was significantly related to the independent variable, (3) the mediator was significantly related to the dependent variable, and (4) the relationship between the independent variable and the dependent variable was reduced when the mediator was controlled. The 4 conditions were tested by means of 4 logistic regression analyses, with adjustment for the confounding variables. If the independent variable did not affect the dependent variable after the mediator was controlled and all 4 conditions were met, then the mediation was complete. If the influence of the independent variable on the dependent variable was attenuated after the mediator was controlled, then the mediation was partial.

To perform these analyses, we used EZR (Easy R) software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is based on R and R commander.[17]

RESULTS

Characteristics of patients and ONJ (location and clinical stage)

The characteristics of patients and the stage and location of ONJ are summarized in Table I. ZA was administered to 33 patients and Dmab was administered to 80 patients. ZA was administered for 1-3374 days (median, 866 days) and Dmab was administered for 1-2149 days (median, 537.5 days). The median PSA value at the beginning of antiresorptive treatment for all patients was 24.7 ng/mL, and 61 patients (54.0%) had CRPC. Overall, 28 patients (24.8%) had ONJ. The frequency of ONJ development in the maxilla (18 patients) was the same as that in the mandible (17 patients). Eight patients had stage 0 ONJ, 9 had stage 1, 15 had stage 2, and 3 had stage 3.

Table I. Characteristics of patients and ONJ (location and clinical stage)

Characteristics	*All patients*	*ZA treatment*	*Dmab treatment*
Number of patients	113	33	80
Age (years)			
Median	73	72	73
Range	47-93	57-93	47-90
Duration of antiresorptive treatment (days)			
Median	630	866	537.5
Range	1-3374	1-3374	1-2149
Cumulative dose of antiresorptive drugs (mg)			
Median		92	2040
Range		4-208	120-8040
PSA (ng/mL)			
Median	24.7	16.6	26.6
Range	0.1-35,377.0	0.1-35,377.0	0.1-2425.6
CRPC	61	17	44
Chemotherapy (docetaxel, cabazitaxel, or both)	24	12	12
Radium-223 dichloride use	11	1	10
Corticosteroid use	58	18	40
Diabetes mellitus	29	11	18
Dental extraction	19	6	13
No. of patients with ONJ	28	10	18
Location of ONJ			
Total	35	13	22
Maxilla	18	10	8
Mandible	17	3	14
Clinical stage of ONJ			
Stage 0	8	3	5
Stage 1	9	2	7
Stage 2	15	7	8
Stage 3	3	1	2

ONJ, osteonecrosis of the jaw; *ZA*, zoledronic acid; *Dmab*, denosumab; *PSA*, prostate-specific antigen; *CRPC*, castration-resistant prostate cancer.

Univariable analysis of the risk factors and development of ONJ

The results of univariable analyses of risk factors and development of ONJ are shown in Table II. The

Table II. Univariable analysis of the risk factors and development of ONJ

Characteristics	*Presence of ONJ (n = 28)*	*Absence of ONJ (n = 85)*	*P value*
Age			.636*
Median	73.5	72	
Range	63-90	47-93	
Antiresorptive drugs			.526†
ZA	10	23	
Dmab	18	62	
Duration of antiresorptive treatment (days)			.005*
Median	863.5	532	
Range	245-2289	1-3374	
Antiresorptive treatment lasting >1 year			.005†
>1 year	26	53	
<1 year	2	32	
PSA (ng/mL)			.489*
Median	16.2	37.5	
Range	0.1-35,377.0	0.1-3768.7	
CRPC			.001†
Present	23	38	
Absent	5	47	
Chemotherapy (docetaxel or cabazitaxel)			.768†
Received	7	17	
Not received	21	68	
Radium-223 dichloride use			.192†
Received	5	6	
Not received	23	79	
Corticosteroid use			.173†
Received	18	40	
Not received	10	45	
Diabetes mellitus			.031†
Present	12	17	
Absent	16	68	
Dental extraction			<.001†
Yes	14	5	
No	14	80	

ONJ, osteonecrosis of the jaw; *ZA*, zoledronic acid; *Dmab*, denosumab; *PSA*, prostate-specific antigen; *CRPC*, castration-resistant prostate cancer.
*Mann-Whitney *U* test.
†Chi-square test.

development of ONJ did not significantly differ by age (P = .636) or antiresorptive drugs (Dmab vs ZA; P = .526); however, of the patients who developed ONJ, the proportion of patients treated with ZA (30.3%) was higher than that of patients treated with Dmab (22.5%). The antiresorptive treatment duration (P = .005) and antiresorptive treatment lasting for longer than 1 year (P = .005) were significantly associated with the development of ONJ. The PSA value at the beginning of antiresorptive treatment was not significantly associated with the development of ONJ (P = .489), but CRPC was (P = .001). There were no significant differences in the development of ONJ according to chemotherapy (P = .768), radium-223 dichloride treatment (P = .192), and corticosteroid treatment (P = .173). Diabetes mellitus and dental extraction were significantly associated with the development of ONJ (P = .031 and P < .001, respectively).

Table III. Univariable analysis of the duration of antiresorptive treatment and CRPC

Duration	*Presence of CRPC (n = 61)*	*Absence of CRPC (n = 52)*	*P value*
Duration of antiresorptive treatment (days)			.027*
Median	792	480	
Range	1-2289	1-3374	
Antiresorptive treatment lasting >1 year			.016†
>1 year	49	30	
<1 year	12	22	

CRPC, castration-resistant prostate cancer.
*Mann-Whitney *U* test.
†Chi-square test.

Univariable analysis of the duration of antiresorptive treatment and CRPC

Table III shows the results of the univariable analysis of the duration of antiresorptive treatment and CRPC. Because antiresorptive treatment was expected to be longer in patients with CRPC, we analyzed the relationship between the duration of antiresorptive treatment and CRPC. The duration of antiresorptive treatment (P = .027) and antiresorptive treatment lasting for longer than 1 year (P = .016) were significantly associated with CRPC.

Multivariable logistic regression analysis of the risk factors for ONJ

Table IV shows the results of multivariable logistic regression analysis based on the risk factors derived from univariable analysis. Because antiresorptive treatment lasting for longer than 1 year was significantly associated with CRPC, we used Baron and Kenny's[16] method to determine whether antiresorptive treatment lasting more than 1 year was a mediator between CRPC and the development of ONJ (Figure 2). Four conditions were met: (1) CRPC (independent variable) was significantly related to ONJ (dependent variable)

Table IV. Multivariable logistic regression analysis of the risk factors and development of ONJ

Risk factor	*Odds ratio (95% confidence interval)*	*P value*
CRPC	6.01 (1.76-20.05)	.004
Diabetes mellitus	2.30 (0.71-7.45)	.165
Dental extraction	12.40 (3.42-44.70)	<.001

ONJ, osteonecrosis of the jaw; *CRPC*, castration-resistant prostate cancer.

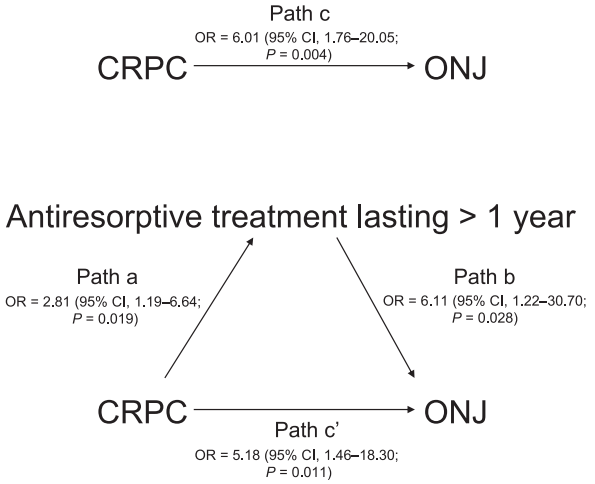

Fig. 2. Mediational model showing the pathways of the relationship between castration-resistant prostate cancer (CRPC) and development of osteonecrosis of the jaw (ONJ). Four conditions are shown: (1) CRPC (independent variable) is significantly related to ONJ (dependent variable) in path c (odds ratio [OR] = 6.01), (2) antiresorptive treatment lasting >1 year (hypothesized mediator) is significantly related to CRPC in path a (OR = 2.81), (3) antiresorptive treatment lasting >1 year is significantly related to ONJ in path b (OR = 6.11), and (4) the relationship between CRPC and ONJ is weakened when antiresorptive treatment lasting >1 year is controlled in path c′ (OR = 5.18). This mediation analysis demonstrates that antiresorptive treatment lasting for more than 1 year is a partial mediator between CRPC and the development of ONJ.

in path c (odds ratio [OR] = 6.01; 95% confidence interval [CI], 1.76-20.05), (2) antiresorptive treatment lasting >1 year (hypothesized mediator) was significantly related to CRPC in path a (OR = 2.81; 95% CI, 1.19-6.64), (3) antiresorptive treatment lasting >1 year was significantly related to ONJ (OR = 6.11; 95% CI, 1.22-30.70) in path b, and (4) the relationship between CRPC and ONJ was weakened when antiresorptive treatment lasting >1 year was controlled in path c′ (OR = 5.18; 95% CI, 1.46-18.30). These 4 conditions were tested via 4 logistic regression analyses, with adjustments for the confounding variables (diabetes mellitus and dental extraction). The results of this mediation analysis demonstrated that antiresorptive treatment lasting more than 1 year was a partial mediator between CRPC and the development of ONJ. Multivariable analysis was performed with 3 outcomes that were significant in the univariable analysis—CRPC, diabetes mellitus, and dental extraction—but not with antiresorptive treatment lasting more than 1 year (the mediator variable between CRPC and ONJ). The multivariable analysis revealed that CRPC (P = .004) and dental extraction (P < .001) were significantly associated with the development of ONJ. Furthermore, the ORs for CRPC (6.01; 95% CI, 1.76-20.05) and dental extraction (12.40; 95% CI, 3.42-44.70) were high. No significant difference in the development of ONJ was observed among patients with and without diabetes mellitus (OR = 2.30; 95% CI, 0.71-7.45; P = .165).

DISCUSSION

In this study, patients with CRPC were at a significantly higher risk for developing ONJ (P = .004), and the OR was high (6.01; 95% CI, 1.76-20.05). Previous reports also indicated that, among patients with prostate cancer with bone metastases, the incidence of ONJ was high (11.4%-20%), but the incidence of ONJ was not compared between CRPC and hormone-sensitive prostate cancer.[13,14] The risk factors for MRONJ include glucocorticoid use, maxillary or mandibular bone surgery, poor oral hygiene, chronic inflammation, diabetes mellitus, ill-fitting dentures, treatment with other drugs such as antiangiogenic agents, and treatment duration with antiresorptive drugs.[9] Among these factors, treatment duration is especially important. The frequency of ONJ increases with long-term antiresorptive treatment according to many reports.[10,18,19] A study of MRONJ in rats demonstrated that the incidence of ONJ increased with a longer duration of ZA treatment.[20] In this study, in agreement with previous reports, antiresorptive treatment lasted longer in patients with ONJ. In addition, our mediation analysis suggested that antiresorptive treatment lasting for more than 1 year was a partial mediator between CRPC and ONJ development. Therefore, we suggest that the incidence of ONJ increases in patients with CRPC who undergo long-term antiresorptive treatment. However, we also believe that other factors are responsible for the high frequency of ONJ in such patients, considering that the duration of antiresorptive treatment is a partial but not complete mediator between CRPC and development of ONJ.

In cases of CRPC in which androgen deprivation therapy is not effective, therapeutic agents such as novel hormone therapies (enzalutamide and abiraterone), radium-223 dichloride, and anticancer agents (DOC and CBZ) have been used. Chemotherapy with DOC and CBZ causes neutropenia (grade 3 or higher) in 32.0% and 82.0% of patients, respectively.[4,21] Grade 3 or higher neutropenia has been reported to occur in 93.0% of Japanese patients receiving DOC and in 100% of those receiving CBZ.[22,23] In addition, bacterial infection is considered one of the major triggers of MRONJ.[24-26] Hence, it is possible that bacterial infection may contribute to the development of ONJ in the setting of immunosuppression caused by chemotherapy. However, we found no significant correlation between chemotherapy and the development of ONJ in this study. In addition, corticosteroids are used in

combination, depending on the type of treatment for CRPC. Although corticosteroids were previously suggested to be a risk factor for ONJ,[9,27] we found no significant difference in this study.

The overall incidence of ONJ in this study was 24.8%, which was higher than that reported in previous reports. The reasons for this were as follows: First, our study included many patients with low-stage ONJ, such as stage 0, compared to previous reports.[28,29] These patients showed almost no subjective symptoms. Bone scintigraphy was performed in all patients for the evaluation of bone metastasis, and the uptake of the pathologic tracer was found to be high in the maxilla and mandible. Of these patients, several were diagnosed with ONJ. With longer survival for patients with prostate cancer, duration of antiresorptive treatment tends to be longer than with other carcinomas, and this may be the second reason for the high incidence of ONJ in this study.[30] Third, long-term antiresorptive treatment may increase the incidence of ONJ because it prolongs overall survival as a result of treatment with new drugs. In recent years, new drugs such as enzalutamide, abiraterone, CBZ, and radium-223 have been used, and overall survival has been extended.[4,31-33] Fourth, diabetes mellitus has been listed as a risk factor for ONJ in previous reports.[9,19] In our study, the high proportion of patients with diabetes (25.2%) was considered to be partly responsible for the increased incidence of ONJ, but multivariable analysis revealed no significant correlation.

Regarding the incidence of ONJ for ZA and Dmab, it has been previously reported that Dmab had a higher prevalence than ZA.[7,10-12] Contrary to previous studies, our study showed that the frequency of ONJ is higher with ZA treatment (30.3%) than with Dmab treatment (22.5%). ZA has a different mechanism and duration of action from Dmab. ZA strongly binds to bone minerals and has long-term persistence of effect.[34,35]

We found that dental extraction was significantly associated with the development of ONJ, similar to previous studies, which have suggested that dental extraction during antiresorptive treatment is a risk factor.[9] However, it remains unclear whether dental extraction itself or insufficient treatment of infection, such as periodontal and periapical diseases, induces the development of ONJ.[24]

Because this study was a single-center retrospective and observational evaluation, medical information may have been missing, and the number of cases was limited. Moreover, ZA was administered to patients mainly before 2014 and Dmab mainly since 2014. Consequently, the observation period for ONJ and the treatment for CRPC in patients who received ZA may have differed from those in patients who received Dmab. Hence, prospective and multicenter studies are necessary to determine the risk factors of ONJ and the exact incidence of ONJ among patients receiving ZA and Dmab.

CONCLUSION

Our study of the risk factors for developing ONJ, including the status of prostate cancers, is unique in that the incidences of ONJ in CRPC and hormone-sensitive prostate cancer have not been previously compared. CRPC and dental extractions are risk factors for developing ONJ, and antiresorptive treatment for longer than 1 year is a partial mediator between CRPC and ONJ.

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