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Original research

Risk factors and treatments for medication-related osteonecrosis of the jaw: A 10-year single-institution experience

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ABSTRACT

Objective: Medication-related osteonecrosis of the jaw (MRONJ) decreases patients' quality of life. There is still room for argument about the risk factors, etiology, and treatment methods of MRONJ. The purpose of this study was to consider risk factors and treatments for MRONJ.
Methods: We designed a retrospective study, and analyzed the clinical data of 50 patients (15 men and 35 women) with a mean age of 75.1 years diagnosed with MRONJ at the University of Fukui Hospital.
Results: Seventeen patients suffered from malignant disease, and 33 patients suffered from osteoporosis. All patients had received antiresorptive medications such as bisphosphonates and/or denosumab. There was a statistically significant relationship between the treatment methods and the treatment outcome; namely, the patients who received surgical therapy showed more positive outcomes than those who received conservative therapy. *Actinomyces* was pathologically observed in the operatively resected specimens of 17 patients. However, there was no statistically significant relationship between the presence of *Actinomyces* in the operatively resected specimens and the treatment outcome.
Conclusions: The results of this study suggest that surgical therapy may be a more effective treatment method than conservative therapy for MRONJ, and that *Actinomyces* in the operatively resected specimens was not a predictor of treatment outcome after surgical therapy.

1. Introduction

Osteonecrosis of the jaw (ONJ) related to intravenous bisphosphonates (BPs) was first reported by Marx in 2003 [1]. Many cases of ONJ related to BPs have subsequently been reported, and the close relationship between BPs and ONJ has been widely recognized among clinicians. In recent years, the relationship between ONJ and denosumab or antiangiogenic medications has been clarified [2]. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has recommended changing the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in the light of these reports, and they named ONJ associated with antiresorptive medications (ie, BPs and denosumab), or antiangiogenic medications, medication-related osteonecrosis of the jaw (MRONJ) in 2014 [3]. Previous studies have suggested that MRONJ is related to a reduction in bone turnover and infection [4]. Furthermore, some studies have reported an association between MRONJ and *Actinomyces* infection [3–6]. However, there is still room for argument about the risk factors, etiology, and treatment methods for MRONJ. Because the progression of MRONJ decreases patients' quality of life, progress in MRONJ research is desired by both clinicians and patients with MRONJ. Therefore, it is important to accumulate more clinical reports to determine potential risk factors and treatment options.

It has been nearly 10 years since the first article on BRONJ was published in Japan. The purpose of this study was to consider the risk factors and treatments for MRONJ by analyzing the clinical data of the patients diagnosed with MRONJ in the past 10 years. In addition, we present a case of MRONJ that was particularly difficult to treat.

2. Methods

We designed a retrospective study and analyzed all patients diagnosed with MRONJ who had received treatment at the University of Fukui Hospital from April 2006 to March 2016. Patients

☆ AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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Table 1
The General Characteristics of Patients.

Gender			Cases (n)	(%)
	Male		15	30
	Female		35	70
Age			Cases (n)	(%)
	≦29		0	0
	30–39		1	2
	40–49		1	2
	50–59		3	6
	60–69		6	12
	70–79		20	40
	80–89		18	36
	90≦		1	2
Disease associated with MRONJ			Cases (n)	(%)
	Malignant disease		17	34
	Osteoporosis		33	66
Medication associated with MRONJ			Cases (n)	(%)
	Oral BPs		33	66
		Etidronate disodium	1	2
		Alendronate sodium hydrate	23	46
		Sodium risedronate hydrate	15	30
		Minodronic acid hydrate	5	10
	Intravenous BPs		14	28
		Ibandronate sodium hydrate	1	2
		Zoledronic acid hydrate	13	26
	Denosumab		9	18
The presence or absence of initiation factor			Cases (n)	(%)
	Presence		18	36
	Absence		32	64
Location of MRONJ			Cases (n)	(%)
	Mandible		30	60
	Maxilla		17	34
	Mandible and maxilla		3	6
Disease Stage			Cases (n)	(%)
	1		7	14
	2		35	70
	3		8	16

who had received radiation therapy for head and neck malignancy were excluded from the study. The staging of MRONJ at initial evaluation was performed on the basis of the position paper released by AAOMS in 2014 [3]. We investigated the general characteristics of patients, the clinical characteristics of MRONJ, the diseases and medications related to MRONJ, the presence of *Actinomyces* in operatively resected specimens, the treatment methods, the duration of discontinuation of a drug before surgical therapy, and the treatment outcome. All drugs used were recorded if there was a history of multiple drug use. The treatment methods were analyzed after dividing them into surgical therapy (for example, tooth extraction, sequestrectomy, and jaw resection) and conservative therapy (non-surgical therapy). The period from the final administration to the surgical therapy was counted as the discontinuation of a drug before surgical therapy. In addition, antibiotics were administered to all patients. The treatment outcome was analyzed according to the diagnostic method of Ruggiero et al. [7] as follows: 1) Healed, if complete mucosalization of the exposed bone had occurred with pain relief; 2) Improved, if the patient was symptomatically better or had moved to a lower disease stage after treatment; 3) Stable, if the disease had not advanced to a higher stage, and 4) Worse, if the patient demonstrated progressive pain, infection, or persistent bone exposure after treatment, with advancement to a higher stage. The patients were analyzed after being divided into the healed/improved group or the stable/worse group [7]. Patients who died during follow-up were classified in the stable/worse group. The treatment methods and the treatment outcome were analyzed up to March 2016.

We also analyzed the relationship between the treatment outcome and the medication after excluding the patients who had a history of multiple drug use related to MRONJ. Consequently, these patients were divided into the following 3 groups as follows: patients who had received only oral BPs, patients who had received only intravenous BPs, and patients who had received only denosumab.

Fisher's exact probability test was used for analysis. Furthermore, we performed a multivariate analysis on the treatment outcome of patients who had received only oral BPs or only intravenous BPs considering the follow-up periods using a Cox proportional hazard model with the following covariates: female gender (reference, male), age, intravenous BPs (reference, oral BPs), absence of over 2 months of drug discontinuation before surgery (reference, presence), presence of chemotherapy (reference, absence), and conservative therapy (reference, surgical therapy). $P < 0.05$ was considered statistically significant.

This study was approved by the Institutional Research Board (Ethical Committee of the University of Fukui, Faculty of Medical Sciences; No. 20160043).

3. Results

Fifty patients (15 men and 35 women) were included in the study (Table 1). The youngest was 38 years old, and the oldest was 90 years old. Their mean age and standard deviation was 75.1 ± 10.3 years. The largest age group comprised patients aged 70–79 years (n = 20). Seventeen patients with malignant disease, and 33 patients with osteoporosis were included in the study. Thirty of the 33 patients with osteoporosis were women. All patients had received antiresorptive medications; 33 patients had received oral BPs, 14 patients had received intravenous BPs, and 9 patients

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