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Which symptoms negatively affect the oral health-related quality of life in patients with osteonecrosis of the jaw?

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Declarations of interest

None.

Statement of Clinical Relevance

Quality of life was reduced because of painful aching in patients with osteoradionecrosis of the jaw. Moreover, worsened taste was experienced by patients with medication-related osteonecrosis of the jaw.

Abstract

Objectives. One of the treatment goals for osteonecrotic lesions of the jaw, such as medication-related osteonecrosis of the jaw (MRONJ) or osteoradionecrosis (ORN), is restoration of quality of life (QOL). This study aimed to identify symptoms that negatively affected QOL in patients with unhealed MRONJ or ORN.

Study Design. This cross-sectional study included patients who were previously diagnosed with MRONJ or ORN and who underwent treatment at our hospital between June 2015 and February 2016. Patient QOL was measured using the Oral Health Impact Profile (OHIP-14). **The predictor variable was the disease status (stage and healing). The outcome variable was OHIP-14**. One-way analysis of variance **and Tukey's test** were performed.

Results. 74 patients (37 men and 37 women; mean age, 70 years) were included. **Although there was no significant difference of OHIP-14 score among stage 1-3 of unhealed MRONJ and ORN and healed ones,** the "worsened sense of taste" result significantly differed among stages in patients with unhealed MRONJ (P=0.027) and the "painful mouth aching" in patients with unhealed ORN (P=0.041).

Conclusions. Worsened sense of taste and pain negatively affected the QOL in patients with unhealed MRONJ and ORN.

Key words: medication-related osteonecrosis of the jaw; osteoradionecrosis of the jaw; quality of life; Oral Health Impact Profile.

Introduction

Osteonecrotic lesions of the jaw, such as medication-related osteonecrosis of the jaw (MRONJ) and osteoradionecrosis (ORN), are uncommon but problematic adverse effects of medical treatments for malignant tumors. Anti-resorptive agents including bisphosphonates and anti-receptor activator of nuclear factor κ-β ligand antibody have been used as treatment for bone metastasis and osteoporosis; these drugs cause osteonecrosis in 1–15% of patients with cancer and 0.001–0.1% of patients with osteoporosis.[1] ORN of the jaw is a complication of radiation therapy for head and neck malignancy. Although ORN occurs in 5–15% of patients within the first 3 years after completion of radiation therapy,[2] ORN can occur regardless of the post-treatment interval.[3]

Although there is no defined treatment algorithm thus far, the treatment goals for osteonecrotic lesions of the jaw include controlling the following aspects: infection, bone necrosis, and pain.[4] Infection involves cutaneous fistula formation, persistent pus discharge, and intense pain; these characteristics greatly reduce quality of life (QOL) in patients with osteonecrotic lesions of the jaw, such that one of the primary goals of treatment for patients with osteonecrotic lesions of the jaw is maintenance and restoration of QOL. Therefore, a better understanding of QOL is essential for accurately evaluating treatment outcome in patients with osteonecrotic lesions of the jaw. Some studies have been performed regarding assessment of QOL in patients with osteonecrotic lesions of the jaw;[5-7] however, to the best of our knowledge, there have been no reports regarding assessment of QOL in both patients with MRONJ and in patients with ORN. **We hypothesized that the status of lesions (i.e., the staging of MRONJ and ORN and treatment outcome [healed or unhealed]) may affect patients' QOL. Thus, QOL among patients with each stage of unhealed lesions and healed patients was compared. Another specific aim of the current study was to identify symptoms that**

negatively affect QOL in patients with unhealed MRONJ or ORN.

Materials and Methods

Study design/participants

To address the research purpose, the investigators designed and implemented this cross-sectional study protocol which was approved by the Research Ethics Committee of Kobe University Hospital (Approval No. 170022). **P**atients who had been diagnosed with ORN or MRONJ and had undergone treatment at the Department of Oral and Maxillofacial Surgery, Kobe University Hospital between June 2015 and February 2016 **were included. Patients who could not complete the questionnaire because of impaired comprehension (e.g., dementia) were excluded.**

The guidelines of the American Association of Oral and Maxillofacial Surgeons were used for diagnosis and staging of MRONJ.[8] In brief, stage 0 MRONJ comprised radiographic changes alone; stage 1 comprised exposure of bone without symptoms; stage 2 comprised exposure of bone without infection; stage 3 comprised exposure of bone without pathological fracture, extraoral fistula, or osteolysis extending to the inferior aspect of the mandible or sinus floor. Patients with stage 0 MRONJ were excluded from this study. ORN was classified in accordance with the method used by Notani et al.[9] In brief, stage 1 ORN was confined to the alveolar bone; stage 2 ORN was limited to the alveolar bone and/or mandible above the level of the mandibular alveolar canal; stage 3 ORN involved the mandible below the level of the inferior alveolar canal and was accompanied by skin fistula and/or pathologic fracture.

Treatment was classified as conservative therapy (i.e., repeated local irrigation or antibiotic administration when necessary), minimal debridement (i.e., sequestrectomy under local or general anesthesia), and surgical resection (e.g., marginal or segmental

mandibulectomy) with or without reconstruction.

QOL was assessed in patients with MRONJ and ORN by using the Oral Health Impact Profile (OHIP), a commonly used questionnaire in dental therapeutic decision-making.[10] The short-form version of the Oral Health Impact Profile (OHIP-14) was developed by Slade,[11] and the reliability and validity of the Japanese version of the OHIP-14 have been confirmed.[12] In brief, OHIP-14 includes two question items from each of the impact sub-domains (i.e., functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap). Response options are "very often (= 4)," "fairly often (= 3)," "occasionally (= 2)," "hardly ever (= 1)," and "never (= 0)." The highest OHIP-14 score is 56, which indicates that a patient's QOL is greatly impaired. Upon administration of the OHIP-14 questionnaire in 2017, patients were stratified into healed and unhealed groups. Healed osteonecrosis of the jaw was defined as follows: 1) an absence of pain and infection; and 2) an absence of exposed or probable exposed bone.[13] Unhealed osteonecrosis of the jaw consisted of residual lesions after conservative treatments and recurrent or new lesions after minimal debridement or surgery.

The predictor variable was the status of osteonecrosis of the jaws (i.e., the staging of lesions and healing). The outcome variable was OHIP-14. Other confounding variables such as patient age, sex, primary disease, osteonecrosis location (when lesions were found in both maxilla and mandible, the more severe side was selected), and lesion number (i.e., single or multiple) were retrospectively gathered from electronic medical records.

Statistical analysis

Statistical analysis was performed using R (R Development Core Team, 2011). **Two groups were compared by Student's t test for continuos variables and by Fisher's exact**

test for categorical variables. Multiple groups were compared using one-way analysis of variance and Tukey's test. A *P*-value less than 0.05 was considered statistically significant.

Results

In total, 74 patients (37 men and 37 women) with a mean age of 70.0 (± 10.1) years were included. The clinical characteristics of patients with MRONJ and ORN are shown in Table 1. Patients with MRONJ were significantly older than patients with ORN (P=0.008) and the proportion of women was higher among patients with MRONJ (P<0.001). Patients with ORN had multiple lesions significantly more frequently, relative to patients with MRONJ (P=0.009). Conservative and minimal debridement were selected significantly more frequently for patients with MRONJ than for patients with ORN (P=0.004), resulting in a significantly higher rate of unhealed lesions (i.e., residual or recurrent) in patients with MRONJ than in patients with ORN (P=0.007).

At the time of OHIP-14 questionnaire acquisition, nine of 42 patients with MRONJ (21.4%) and 17 of 32 patients with ORN (53.1%) had been healed by various treatment approaches. The mean total OHIP-14 scores in all groups are shown in **Table 2**. Although OHIP-14 scores increased as MRONJ stage increased, the mean OHIP-14 score was highest in patients with stage 2 ORN. Multiple comparison showed no significant difference of OHIP-14 score among unhealed stage 1, stage 2, stage 3 MRONJ, unhealed stage 1, stage 2, stage 3 ORN, and healed MRONJ and ORN.

As shown in **Table 3**, among patients with unhealed MRONJ, only the "worsened sense of taste" result significantly differed among stages (P=0.027). In patients with unhealed ORN, only the "painful mouth aching" result significantly differed among stages (P=0.041); painful aching was most severe in patients with unhealed stage 2 ORN (Table **4**).

Discussion

Because one of the treatment goals for osteonecrotic lesions of the jaw is maintenance and restoration of QOL, a better understanding of QOL is essential for treatment decision-making and accurately evaluating treatment outcome in patients with MRONJ and ORN. This study aimed to identify symptoms that negatively affected QOL in patients with MRONJ or ORN, and found that worsened sense of taste and pain negatively affected the QOL in patients with unhealed MRONJ and ORN.

The results of the current study demonstrate the reliability and validity of using the OHIP-14 questionnaire to assess QOL in patients with osteonecrosis of the jaw; specifically, greater reduction of QOL was observed in patients with more severe MRONJ **(Table 2)**. The highest mean OHIP-14 score was 18.2 in patients with unhealed stage 3 MRONJ; this finding is similar to that of previous studies. Barrios et al. reported that, at ≥6 months post-treatment, the mean OHIP-14 scores of 142 patients who underwent treatment for oral cancer (mean age, 65.2 years) and age-matched controls (mean age, 67.5 years) were 18.9 (± 11.8) and 5.9 (± 6.2).[14] Schweyen et al. reported that the mean OHIP-14 score of patients who underwent radiation therapy for head and neck cancers (mean age, 57.7 years) before QOL assessment was 19.2 (± 16.1); moreover, patients with oral cavity cancers had a significantly higher mean OHIP-14 score (28.5 ± 14.4) compared with patients who had cancers in other head and neck regions.[15] The only specific questionnaire items for which results significantly differed among stages were "worsened sense of taste" in patients with unhealed MRONJ (Table **3**) and "painful mouth aching" in patients with unhealed ORN (Table **4**). Notably, the reduction of QOL was greatest in patients with unhealed stage 2 ORN; the pain score was also highest in patients with unhealed stage 2 ORN.

The severity of pain in maxillofacial osteonecrosis is sufficient to cause sleep

deprivation and awaken patients.[16] We previously analyzed pathological changes in the inferior alveolar nerve to understand the underlying mechanism of pain in maxillofacial osteonecrosis.[15] Patients with severe histopathological nerve degeneration (as determined by surgical resection of the mandibular ORN) exhibited slight pain before surgery. In contrast, patients with relatively normal fascicle morphology in the inferior alveolar nerve experienced extreme preoperative pain.[17] This pain pathology in patients with mandibular ORN appears similar to diabetic neuropathy. Patients exhibit positive symptoms (e.g., pain, paresthesia, and hypoesthesia) in the early and intermediate stages of diabetic neuropathy; in the later stages of disease progression, patients experience negative symptoms (e.g., sensory loss).[17] Oral surgeons more commonly encounter sensory loss due to pulpitis, which causes severe pain that interferes with sleep; without removal of the infected pulp, necrosis and apical periodontitis occur, which evoke no pain until the onset of acute infection-related inflammation. The current study showed that pain was most severe in patients with unhealed stage 2 ORN, which supports the above-mentioned hypothesis. Pain management may be difficult in patients with osteonecrotic lesions of the jaw. Minimal debridement (intended to preserve the mandibular canal) often fails, especially in patients with ORN.[18] As shown in Table 1, the proportion of patients who underwent surgical resection was higher in patients with ORN than in patients with MRONJ. This difference is likely because patients with ORN are younger and more often cancer-free than patients with MRONJ. Therefore, patients with ORN are more often eligible for radical surgery, whereas patients with MRONJ are not. However, OHIP-14 scores were high in patients with healed ORN (the majority of whom received surgical resection). **Reduction of QOL in healed ORN patients may be due to postoperative sequelae but also late sequelae of irradiation itself.** More conservative management approaches (e.g., pentoxifylline, α-tocopherol, and clodronate[19-21]) are necessary for management of ORN. Importantly, the only

specific questionnaire item for which results significantly differed among stages of unhealed MRONJ was "worsened sense of taste." This result is potentially because patients with MRONJ experience intraoral chronic purulent drainage and anaerobic odor. One of the causes of oral malodor is osteonecrosis.[22] Pathological halitosis, an offensive breath odor, negatively influences patients' QOL.[23] This finding indicates that odor management is important for improvement of QOL in patients with osteonecrotic lesions of the jaw.

There were some limitations in the current study. First, it involved a small sample size and heterogeneous population. To assess the efficacy of treatments for osteonecrosis of the jaw, QOL should be evaluated before and after treatment in the same patients, as performed in a previous study.[24] Second, the current study did not evaluate various other factors that have been reported to affect QOL in patients with osteonecrosis of the jaw such as dentition status, denture use, hyposalivation, and trismus. Poor dentition affects mastication; this can be evaluated by the questionnaire items: "unsatisfactory diet" and "frequent meal interruptions." These evaluation items can be affected by the statuses of both jaw osteonecrosis and dentition. Finally, the current study included many elderly patients. Although we excluded patients who could not complete the questionnaires because of impaired comprehension (e.g., dementia), some elderly patients required assistance to complete the questionnaires. Potential differences between elderly patients who require assistance and those who do not might have affected the results of the current study.

In conclusion, the current study demonstrated the usefulness of assessing QOL to better understand the statuses of patients with MRONJ and patients with ORN. **There was no significant difference of total OHIP-14 score among unhealed stage 1, stage 2, stage 3 MRONJ, unhealed stage 1, stage 2, stage 3 ORN, and healed MRONJ and ORN.** The specific questionnaire items for which results significantly differed among patients with

unhealed MRONJ and patients with unhealed ORN were “worsened sense of taste” and “painful mouth aching”, respectively. Therefore, odor management and pain management are important goals for treatment of patients with osteonecrosis of the jaw.

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Table 1. Clinical characteristics of patients with MRONJ and ORN who received treatment at our hospital during the study period

	MRONJ (n=42)	ORN (n=32)	*P*-value
Age	72.9 ± 10.5	66.9 ± 10.5	**0.008**
Sex			**<0.001**
Male	8 (19.0)	29 (90.6)	
Female	34 (81.0)	3 (9.4)	
Primary disease			**<0.001**
Malignant disease	22 (52.4)	32 (100)	
Location			0.243
Mandible	31 (73.8)	28 (87.5)	
Maxilla	11 (26.2)	4 (12.5)	
Lesion			**0.009**
Single	27 (64.3)	10 (31.2)	
Multiple	15 (35.7)	22 (68.8)	
Treatment			**0.004**
Conservative	27 (64.3)	21 (65.6)	
Minimal debridement	11 (26.2)	1 (3.2)	
Surgical resection	4 (9.5)	10 (31.2)	
Outcome			**0.007**
Unhealed	33 (78.6)	15 (46.9)	
Healed	9 (21.4)	17 (53.1)	

Bold font indicates differences that are statistically significant.

Data are reported as mean ± standard deviation or number (percentage) of study patients.

MRONJ, medication-related osteonecrosis of the jaw; *ORN*, osteoradionecrosis.

Table 2. Oral Health Impact Profile (OHIP-14) scores of patients in **unhealed and healed osteonecrosis of the jaws**

	MRONJ staging			ORN staging			Healed MRONJ	Healed ORN
	1 (n=16)	2 (n=12)	3 (n=5)	1 (n=2)	2 (n=3)	3 (n=10)	(n=9)	(n=17)
Total OHIP-14	10.12 (7.33)	13.75 (11.61)	18.20 (14.96)	8.50 (9.19)	15.00 (8.19)	13.40 (9.65)	11.00 (8.09)	13.94 (11.36)

Data are reported as mean ± standard deviation of study patients.

MRONJ, medication-related osteonecrosis of the jaw. *ORN*, osteoradionecrosis of the jaw.

Table 3. Oral Health Impact Profile (OHIP-14) scores of patients with unhealed MRONJ

	MRONJ staging*			*P*-value
	1 (n=16)	2 (n=12)	3 (n=5)	
Age	76.1 ± 10.2	71.7 ± 9.3	61.2 ± 12.6	**0.027**
Sex				0.1340
Male	5 (31.2)	1 (8.3)	1 (20.0)	
Female	11 (68.8)	11 (91.7)	4 (80.0)	
Primary disease				0.345
Malignant disease	9 (56.2)	5 (41.7)	4 (80.0)	
Location				0.437
Mandible	10 (62.5)	10 (83.3)	4 (80.0)	
Maxilla	6 (37.5)	2 (16.7)	1 (20.0)	
Lesion				**0.016**
Single	14 (87.5)	8 (66.7)	1 (20.0)	
Multiple	2 (12.5)	4 (33.3)	4 (80.0)	
Treatment				0.114
Conservative	13 (81.2)	8 (66.7)	2 (40.0)	
Minimal debridement	3 (18.8)	4 (33.3)	2 (40.0)	
Surgical resection	0 (0)	0 (0)	1 (20.0)	
OHIP-14				
Functional limitation				
Trouble pronouncing words	1.19 (1.05)	1.00 (1.29)	1.00 (0.71)	0.893
Sense of taste worse	0.50 (0.89)	1.08 (0.95)	2.00 (1.58)	**0.027**
Physical pain				
Painful aching in your mouth	0.75 (1.00)	1.25 (1.29)	1.40 (0.89)	0.367
Uncomfortable to eat foods	1.19 (1.33)	1.00 (1.35)	1.40 (1.67)	0.855
Psychological discomfort				
Been self-conscious	0.56 (0.81)	1.58 (1.73)	1.60 (1.82)	0.116
Felt tense	0.50 (0.82)	1.25 (1.48)	0.80 (1.10)	0.243
Physical disability				
Diet been unsatisfactory	1.31 (1.20)	1.17 (1.34)	1.80 (1.79)	0.675
Had to interrupt meals	0.75 (0.86)	0.50 (0.80)	1.00 (1.73)	0.621
Psychological disability				
Difficult to relax	0.62 (0.89)	0.92 (0.90)	1.00 (1.00)	0.602
Been embarrassed	0.31 (0.48)	0.83 (0.94)	1.20 (1.30)	0.076
Social disability				
Been irritable with other	0.31 (0.60)	0.67 (0.65)	1.00 (1.73)	0.260

Difficult doing usual jobs	0.38 (0.81)	0.42 (0.67)	1.40 (1.67)	0.099
Handicap				
Felt life less satisfying	1.00 (0.82)	1.08 (1.24)	1.40 (1.52)	0.778
Totally unable to function	0.75 (0.77)	1.00 (1.13)	1.20 (1.30)	0.632

Data are reported as mean ± standard deviation or number (percentage) of study patients.
MRONJ, medication-related osteonecrosis of the jaw.

Table 4. Oral Health Impact Profile (OHIP-14) scores of patients with unhealed ORN

	ORN staging			*P*-value
	1 (n=2)	2 (n=3)	3 (n=10)	
Age	60.5 ± 3.5	73.7 ± 9.3	70.5 ± 9.6	0.304
Sex				ns
Male	2 (100)	3 (100)	10 (100)	
Primary disease				ns
Malignant disease	2 (100)	3 (100)	10 (100)	
Location				0.659
Mandible	2 (100)	2 (66.7)	8 (80.0)	
Maxilla	0 (0)	1 (33.3)	2 (20.0)	
Lesion				**0.044**
Single	1 (50.0)	3 (100)	2 (20.0)	
Multiple	1 (50.0)	0 (0)	8 (80.0)	
Treatment				0.886
Conservative	2 (100)	3 (100)	8 (80.0)	
Minimal debridement	0 (0)	0 (0)	1 (10.0)	
Surgical resection	0 (0)	0 (0)	1 (10.0)	
OHIP-14				
Functional limitation				
Trouble pronouncing words	1.00 (1.41)	1.00 (1.00)	1.70 (1.57)	0.695
Sense of taste worse	0.50 (0.71)	0.67 (1.15)	0.90 (0.74)	0.784
Physical pain				
Painful aching in your mouth	0.50 (0.71)	2.33 (0.58)	0.80 (0.92)	**0.041**
Uncomfortable to eat foods	0.50 (0.71)	0.67 (1.15)	1.00 (0.82)	0.698
Psychological discomfort				
Been self-conscious	0.50 (0.71)	1.33 (0.58)	1.10 (1.10)	0.660
Felt tense	0.50 (0.71)	1.00 (1.00)	0.50 (0.53)	0.507
Physical disability				
Diet been unsatisfactory	0.50 (0.71)	1.00 (1.00)	1.50 (1.43)	0.614
Had to interrupt meals	0.50 (0.71)	1.00 (1.00)	1.10 (0.88)	0.690
Psychological disability				
Difficult to relax	0.50 (0.71)	0.85 (0.90)	0.80 (0.63)	0.750
Been embarrassed	0.50 (0.71)	0.77 (0.93)	0.80 (0.63)	0.750
Social disability				
Been irritable with other	0.50 (0.71)	1.00 (0)	0.90 (0.74)	0.698
Difficult doing usual jobs	0.50 (0.71)	0.67 (0.58)	0.90 (0.74)	0.725

Handicap				
Felt life less satisfying	1.00 (0)	1.00 (0)	0.80 (1.03)	0.921
Totally unable to function	1.00 (0)	1.00 (0)	0.60 (0.70)	0.503

Data are reported as mean ± standard deviation or number (percentage) of study patients.
ORN, osteoradionecrosis of the jaw; *ns*, not significant.