Prognosis of Medication-Related Osteonecrosis of the Jaw with Surgical Treatment

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Abstract: In 2014, the American Association of Oral and Maxillofacial Surgery (AAOMS) recommended surgical treatment for medication-related osteonecrosis of the jaw (MRONJ) patients classified as Stage 3. In 2016, the Japanese position paper recommended surgical treatment classified as Stage 2. Some systematic review reported effectiveness of surgical treatment for MRONJ. However there is no concerted consciousness on the treatment methods of MRONJ patients in the present. This study aimed to retrospectively elucidate clinical outcomes of the surgical treatment of MRONJ patients under the same criteria. This study included 86 patients in 40 osteoporosis patients (5 men and 35 women, average age: 78.8 years) and 46 cancer patients (18 men and 28 women, average age: 67.7 years). The outcome was classified into two categories: Healing or No healing in each stage. Among 86 patients, MRONJ was found in 91 jaws, of which 69 jaws (75.8%) were surgically operated. Total healing rate of surgical treatment was 85.5%, and total healing rate of conservative treatment was 4.5%. It was suggested that surgical treatment for MRONJ had a high clinical response rate in all stages.

Key words: Medication-related osteonecrosis of the jaw, Treatment, Prognosis, Surgical treatment, Conservative treatment

Introduction

Bisphosphonates and denosumab (RANKL inhibitor) are widely used to treat hypercalcemia caused by bone metastases and multiple myeloma and malignancies, and metabolic bone disease such as osteoporosis and Paget’s disease. Since Marx1 first reported that bisphosphonates cause bone necrosis of the jaw in 2003, osteonecrosis of the jaw due to RANKL inhibitor which is monoclonal antibody against receptor activator of nuclear factor-κB ligand (Denosumab-induced osteonecrosis of jaw; DRONJ) was reported2. Currently, it is called MRONJ, including osteonecrosis caused by angiogenesis inhibitors such as bevacizumab and sunitinib.

For treatment, the American Association of Oral and Maxillofacial Surgeons (AAOMS)3 recommends surgical treatment such as debridement or section from Stage 3. On the other hand, in Japan, a revised position paper which was issued in 2016 by the five Society (the Japanese Society for Bone and Mineral Research, the Japan Osteoporosis Society, the Japanese Society for Oral and Maxillofacial Radiology, the Japanese Society of Periodontology, and the Japanese Society of Oral and Maxillofacial Surgeons) recommends surgical treatments such as bone removal, curettage of necrotic bone, and bone resection from Stage 2. Some papers had reported effectiveness of surgical treatment and recommended surgical treatment for MRONJ4-6. However there is no concerted consciousness on the treatment methods of MRONJ patients in the present. As MRONJ is considered to be one of the infectious diseases, the stage gradually progresses from Stage 1 to Stage 2 and 3. Our clinic is actively performing surgical treatment from Stage 1. This study aimed to retrospectively elucidate clinical outcomes of the surgical treatment of MRONJ patients under the same criteria.

Materials and Methods

Patients

The subjects were MRONJ 86 cases who visited the Clinic for Medication Related Osteonecrosis of the Jaw, The Nippon Dental University Niigata Hospital during the two years and nine months from July 1, 2017 when the clinic was opened, to March 31, 2020.

The extent of necrosis area was evaluated using panoramic image and computed tomography (CT) and magnetic resonance imaging (MRI) and bone imaging using SPECT/CT scans with Tc-99m hydroxymethylene diphosphonate.

The criteria were to perform surgical treatment aggressively from the Stage 1 and prevent it from progressing up stage. Before the surgery, patients had not stopped the oral bisphosphonate drugs, but the bisphosphonate and RANKL inhibitor used for injection had stopped from 2 months before the surgery if there is no affect with the general condition after consulting with the treatment medical doctor.

Oral care before surgical treatment is important because surgery with remaining inflamed conditions disturb healing of the wound and causes dehiscence. Therefore, before surgery, as oral care, 0.025 benzalkonium chloride solution and 2.0% hydrogen peroxide soluto were alternately irrigated until the inflammation of the mucous membrane
around the necrosis bone improved. The surgical method was divided into three. (1) Sequestrum removal and curettage, which were selected for cases of local necrosis bone had separated, (2) Marginal resection of maxilla or mandible, which were selected for cases of necrosis bone had extended to the upper part of the mandibular canal or part of the maxilla, (3) Segmental resection, which were selected for cases of necrosis bone had progressed to the inferior margin of the mandible. Conservative treatment was selected for cases with poor general condition or disagreement for surgery.

**Outcomes**

Histopathological analysis of the bone specimens demonstrated no metastatic disease, and confirmed a diagnosis of MRONJ in all cases. The postoperative clinical statuses of patients were assessed for 6 months or longer using clinical and radiographical examinations. The evaluation method proposed by Okuyama et al. was used and includes the following:

- **a)** healing: resolution of all clinical symptoms, including bone exposure
- **b)** no healing: reduction, no change, or increased clinical stage but some symptoms are remained and/or infection is out of control.

**Statistical analysis**

Statistical analyses for the patients with MRONJ data were evaluated with the Mann–Whitney U test and χ²-test. These statistical analyses were performed using the Bell Curve for Excel version 3.20 (Social Survey Research Information, Tokyo, Japan). P value lower than 0.05 was considered as statistically significant.

**Results**

**The cause drugs**

Bisphosphonates occupied for 33 of 40 cases (82.5%) in osteoporosis patients, while in cancer patients, 22 of 46 (47.8%) cases were RANKL inhibitors, followed by bisphosphonates in 13 cases (28.2%), angiogenesis inhibitor in 8 cases (17.4%), BP preparation + angiogenesis inhibitor in 1 case, RANKL inhibitor + angiogenesis inhibitor in 2 cases.

**Table 1. Characteristics of patients with medication-related osteonecrosis of the jaw**

| Characteristics | Patients with osteoporosis (n = 40) | Patients with bone metastases (n = 46) | Total (n = 86) | P-value |
|-----------------|-------------------------------------|---------------------------------------|----------------|---------|
| **Age (years)** | 78.8 ± 8.1                          | 67.7 ± 8.3                            | 72.9 ± 9.9     | < 0.01  |
| Range           | 59 - 93                             | 51 - 88                               | 51 - 93        |         |
| **Sex**         |                                     |                                       |                |         |
| Male            | 5                                   | 18                                    | 23             | 0.01    |
| Female          | 35                                  | 28                                    | 63             | 0.01    |
| **The cause drugs** |                                    |                                       |                |         |
| Bisphosphonates | 33                                  | 13                                    | 46             | < 0.01  |
| RANKL inhibitor | 7                                   | 22                                    | 29             | < 0.01  |
| Angiogenesis inhibitor | 0                          | 8                                     | 8              | < 0.01  |
| Bisphosphonates + angiogenesis inhibitor | 0                        | 1                                     | 1              |         |
| RANKL inhibitor + angiogenesis inhibitor | 0                     | 2                                     | 2              |         |
| **Triggering factor** |                            |                                       |                |         |
| (The 91 jaws in all 86 cases) |                                    |                                       | (n = 91)       |         |
| Tooth extraction | 26                                  | 23                                    | 49             |         |
| Periodontal disease | 8                         | 14                                    | 22             |         |
| Denture incompatibility | 8                         | 3                                     | 11             |         |
| Dental implantitis | 0                           | 1                                     | 1              |         |
| Unknown         | 1                                   | 7                                     | 8              |         |
| **MRONJ Stage** |                                     |                                       |                |         |
| Stage 0         | 0                                   | 0                                     | 0              |         |
| Stage 1         | 3                                   | 3                                     | 6              |         |
| Stage 2         | 30                                  | 39                                    | 69             |         |
| Stage 3         | 10                                  | 6                                     | 16             |         |

SD: standard deviation

**Patient consent**

Written consent was obtained from the patients to publish the photographs.

**Ethical Approval**

All the procedures performed in studies were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained by the Ethics Committee of Nippon Dental University, School of Life Dentistry at Niigata, Japan (Approval No. ECNG-R-318).
Triggering factor

Among the 91 jaws in all 86 cases, the following triggering factors of MRONJ were identified: tooth extraction (n=49, 53.8%) periodontal disease (n=22, 24.2%), denture incompatibility (n=11, 12.1%), dental implantitis (n=1, 1.1%) and unknown cause (n=8, 8.8%).

Stage of the MRONJ

Among the 91 jaws in all 86 cases, the following Stage of MRONJ were identified: Stage 1 (n=6, 6.6%), Stage 2 (n=69, 75.8%), Stage 3 (n=16, 17.6%). There was no patient in the Stage 0.

Figure 1. Extraoral (a) and intraoral view (b), panoramic X-ray (C), and CT photographs (d) at MRONJ case in 85 years old osteoporosis women at Stage 3. Bone exposure was found in the right mandibular molar area, and drainage was found from the right mandibular molar area and from the extraoral fistula. CT indicated that the right mandible destroyed to the inferior border of mandible, and clinically right mental nerve palsy was observed.
Figure 2. MRI and SPECT-CT imaging examination. MRI (T1) indicated a decreasing bone marrow signal from the lower left premolar to the right molar, and SPECT-CT showed high uptake at the same area.

Figure 3. Surgical findings with tracheostomy (a), segment resection of mandible (b), reconstruction by the metal titanium plate (c), and excised mandible and fistula (d).
Treatment results

The healing rate by treatment method at MRONJ each stages on patients with osteoporosis and patients with bone metastasis are shown in Table 2. The surgery was performed actively on 69 jaws of all 91 jaws (75.8%). The remaining 22 jaws were treated conservatively because of poor general condition or disagreement for surgery.

The healing rate of surgical treatment was 100% in Stage 1, 81.8% in Stage 2, and 100% in Stage 3. On the other hand, the healing rate of conservative treatment was 0% in Stage 1, 7.1% in Stage 2, and 0% in Stage 3. Total healing rate of surgical treatment was 85.5%, and total healing rate of conservative treatment was 4.5%. Additionally, there were significant difference between surgical treatment and conservative treatment in Stage 2, 3 at patients with osteoporosis and patients with bone metastasis, and significant difference between surgical treatment and conservative treatment in Stage 1, 2, 3 at total patients.

Figs.1-4 show MRONJ treatment case in 85 years old osteoporosis women at Stage 3. Fig. 1 displays extraoral (a) and intraoral view (b), panoramic X-ray (c), and CT photographs (d). Bone exposure was found in the right mandibular molar area, and drainage was found from the right mandibular molar area and from the extraoral fistula. CT indicated that the right mandible destroyed to the inferior border of mandible, and clinically right mental nerve palsy was observed.

Fig. 2 displays MRI and SPECT-CT. MRI (T1) indicated a decreasing bone marrow signal from the lower left premolar to the right molar, and SPECT-CT showed high up take at the same area.

Fig. 3 exhibits the surgical findings. Surgery was performed under general anesthesia, with tracheostomy (a), segment resection of mandible (b), and reconstruction by the metal titanium plate (c). After reconstruction, laryngeal was elevated to metal titanium plate with nylon thread as a taking measures for miss swallowing. Excised mandible and fistula (d).

Fig. 4 displays extraoral (a) and intraoral view (b), panoramic X-ray (c), and CT photographs (d) 3 months after surgery. The extraoral and intraoral fistulas were closed.

Discussion

Currently, increasing number of patients with MRONJ has been reported in recent years. However, there is no general consensus for treatment of MRONJ, and it is still controversial.

There are some reports on the usefulness of surgical treatment, but in the conventional reports, there are biases by institutions and surgeons such as different criteria and different surgical methods. Therefore there are only few report comparing the superiority and inferiority of surgical treatment and conservative treatment under the same conditions. Even though in our clinic, the same doctor had performed surgical treatment in principle under the same criteria. As a result, we considered that it would be possible to compare the treatment results of conservative therapy and surgical therapy in this study.

Rupel et al. reported comparison of the healing rates of nonsurgical approach, conservative surgery, extensive surgery, and laser surgery in a systematic review of BRONJ treatment methods, and found that surgical treatment was effective in all Stages. In Stage 2, healing rates of the nonsurgical approach 24%, conservative surgery 79%, extensive surgery 96%, laser surgery 83%, showing the superiority of surgical treatment, especially extensive surgery. This report is a systematic review, that's why there were biases by institutions and surgeons.
Hayashida et al.\(^9\) reported healing rate of the surgical treatment is better than conservative treatment for MRONJ, and the healing rate of surgical treatment which removes necrotic bone with the surrounding bone is better than only removing the necrotic bone, and 361 cases were collected through a multicenter joint study, and statistical analysis by the propensity score method revealed that surgical therapy provided a significantly higher healing rate than conservative therapy. This paper had performed under joint study, hence there were biases by institutions and surgeons such as different criteria and different surgical methods.

Although in our clinic, the same doctor had performed surgical treatment in principle under the same criteria. In our results, the healing rate of surgical treatment was 100% in Stage 1, 81.8% in Stage 2, and 100% in Stage 3. On the other hand, the healing rate of conservative treatment was 0% in Stage 1, 7.1% in Stage 2, and 0% in Stage 3. Total healing rate of surgical treatment was 85.5%, and total healing rate of conservative treatment was 4.5%. There were significant difference between surgical treatment and conservative treatment in all stages. So, it was clear that surgical treatment was superior to conservative treatment.

Conservative therapy also has the advantage of being non-surgical invasion, but conservative therapy does not have a high healing rate, and many patients suffer significantly longer periods of illness. In particular, the general condition of cancer patients with bone metastases changes from moment to moment, so considering their life expectancy, it is important to heal them as soon as possible. In addition, MRONJ stage may get worse during conservative therapy, eventually requiring greater surgical invasion, such as segmental resection, so first treatment plan of the MRONJ in our clinic is surgical therapy, and select conservative therapy when surgery cannot be performed because of poor general condition or disagreement for surgery.

In the future, as a standard treatment for MRONJ, we will continue to perform surgical treatment, and judge the comprehensively (general condition, clinical symptoms, expected prognosis of life, patient’s opinion) and then decide the treatment method.

About the cause drugs in this report, bisphosphonates were the most common cause drug in osteoporosis patients and exceeded 80%, while RANKL inhibitors accounted for about half of the cancer patients. Lifemones et al. reviewed the MRONJ incidence and risk of zoledronic acid and denosumab, and reported that denosumab had a higher incidence and risk.\(^30\) This time, we have not examined the difference in healing rate by drug, so we would like to examine the difference in healing rate by drug in the future.

In conclusion, it was suggested that surgical treatment for MRONJ had a high clinical response rate in all stages.

**Competing Interests**

The authors have no conflicts of interest.

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