A Case Report of Kampo Medicine Improving the Symptoms of Antiresorptive Agent-related Osteonecrosis of the Jaw (ARONJ)

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A 56-year-old woman visited an oral surgery clinic in October X with sudden pain in the left mandible. She was diagnosed with left mandibular osteomyelitis based on head computed tomography examination findings. The pain did not reduce even with amoxicillin and loxoprofen sodium hydrate. The patient was then referred to our clinic for treatment. Hainosankyuto (7.5 g/d), loxoprofen sodium hydrate (180 mg/d), and mecobalamin (1500 µg/d) alleviated the pain. However, numbness and tingling pain in the left part of the chin increased. Pregabalin 50 mg/week was then prescribed and then increased from 50 to 100 mg/d. The patient was diagnosed with antiresorptive agent-related osteonecrosis of the jaw (ARONJ). As the pain was exacerbated by discontinuation of the hainosankyuto, it was used continuously. The patient experienced no pain, even after discontinuing the mecobalamin and pregabalin. Platycodon root in hainosankyuto promotes drainage. The patient did not show any significant swelling because she took hainosankyuto during the early stages of inflammation. In addition, the pain resolved even when only hainosankyuto was used, possibly due to the analgesic effect of platycodon root, glycyrrhiza root, and peony root. Hainosankyuto may be an effective adjunctive treatment for patients with ARONJ whose pain is difficult to control with general treatment.

Key words—antiresorptive agent-related osteonecrosis of the jaw; Kampo; hainosankyuto

INTRODUCTION

Antiresorptive agent-related osteonecrosis of the jaw (ARONJ) is the comprehensive name for bisphosphonate-related osteonecrosis of the jaw (BRONJ) and denosumab-related osteonecrosis of the jaw (DRONJ). ARONJ develops when a bone resorption inhibitor is used to treat cancer or osteoporosis. However, its underlying mechanism remains unclear. The incidence of ARONJ is higher among cancer patients treated with bisphosphonates and denosumab than among patients without cancer. ARONJ can be treated conservatively or surgically. However, it is intractable in many cases. When the lesion becomes widespread, neuropathic pain may occur in addition to inflammatory pain, resulting in pain control difficulty.

Hainosankyuto is a traditional Japanese medicine created by combining Hainoto and Hainosan used in Chinese traditional medicine. Hainosankyuto effectively reduces redness, swelling, and pain in the affected area. To the best of our knowledge, no reports have described the use of hainosankyuto for ARONJ. This case report focused on the use of hainosankyuto for controlling the symptoms of ARONJ in the left mandible.

CASE REPORT

Past Medical History and History of Present Illness

The patient was a 56-year-old woman who underwent a cesarean section 11 years prior as well as fixed surgery for a fracture of the left femur 3 months prior. There were no special notes in her family history, and she had no allergies. The patient had undergone surgery for left breast cancer 8 years prior. The patient was administered zoledronic acid 1 year after surgery and had been using it for 4 years. She had also been using denosumab for the last 3 years and continued to receive it subcutaneously once a month.

The patient experienced pain in the left mandible after chewing hard food. She was examined at two dental clinics, but no dental-related causes of pain were identified. Two months later, her pain increased acutely, and she visited the Department of Oral Surgery, Tokyo Medical and Dental University Dental Hospital. Panoramic radiography and blood tests were performed. No obvious inflammatory findings were found on panoramic radiograph. Blood tests showed a C-reactive protein level of 0.22 mg/dL and a white blood cell count of 6020/µL, which were wi-
thin the normal range, and there were no signs of active inflammation. However, computed tomography (CT) revealed a periosteal reaction on the buccal side of the left mandible (Fig. 1), and she was diagnosed with left mandibular osteomyelitis. She was prescribed amoxicillin 750 mg/d and loxoprofen sodium hydrate 180 mg/d, but her pain did not change. To address the pain, the patient was referred to the Orofacial Pain Clinic of Tokyo Medical and Dental University Dental Hospital.

**Present Condition**  
At her first visit, the patient complained of spontaneous and persistent intense pain on the left side of her mandible. A swelling-like dysesthesia affecting her left chin was evident. The pain affected the entire left mandible, and its localization was unclear. Loxoprofen sodiumhydrate relieved the pain for about 6 hours, but the pain did not resolve. The same degree of pain returned. She was frustrated by the pain and refused to grade it on a visual analog scale (VAS). A physical examination revealed that the patient was lean with a good complexion, and she reported constipation but no stomach upset. Psychological findings suggested high anxiety, irritability, and frustration. We diagnosed left mandibular osteomyelitis and a left inferior alveolar nerve disorder.

**Progress**  
Hainosankyuto (TJ-122) (7.5 g/d), loxoprofen sodium hydrate (180 mg/d), and mecobalamin (1.5 mg/d) were administered to improve the patient's osteomyelitis, pain, and dysesthesia. One month later, the patient's jaw pain decreased, but numbness and tingling pain persisted in the left chin for which pregabalin was administered. Magnetic resonance imaging (MRI) performed in the Oral Surgery department revealed a low-signal area on the left mandible on T1-weighted images (Fig. 2). The patient was diagnosed with chronic sclerosing osteomyelitis of the left mandible for which amoxicillin and loxoprofen sodium hydrate were continued. Seven months after the initial visit, the numbness had largely resolved, and the mecobalamin was discontinued. The patient insisted that reducing the dose of hainosankyuto would increase her pain. Therefore, it was continued. However, the doses of amoxicillin, loxoprofen sodium hydrate, and pregabalin were gradually decreased. Approximately two years after her first visit, the patient used only hainosankyuto to control her pain. Subsequently, its dose was reduced over approximately one year and ultimately discontinued.

However, a few days after discontinuing the hainosankyuto, she experienced discomfort on the
left side of her lower jaw; thus, she resumed hainosankyuto 2.5–5.0 g/d. CT revealed sequestrum formation in the right maxilla and left mandible (Fig. 3). The patient was diagnosed with stage 2 ARONJ because she had a history of taking zoledronic acid and denosumab. Redness and swelling were observed in the gingiva around the implant replacing the second premolar of the left mandible, and a small area of bone was exposed in the oral cavity. However, antibacterial agents and non-steroidal anti-inflammatory drugs (NSAIDs) due to a lack of severe pain. Since the patient did not want to undergo surgery, a sequestrectomy was not performed. Instead, she received an oral cleaning and brushing instructions from a dental hygienist to keep her oral cavity clean. The patient was also advised to gargle with benzethonium chloride to disinfect the mucous membrane. The patient’s gingival condition improved, and the discomfort on the left side of the mandible also resolved.

RESULT

The patient’s symptoms were controlled by thorough oral cleaning and the use of hainosankyuto 5.0 g/d without antibacterial agents or NSAIDs. No adverse events such as liver dysfunction or pseudoaldosteronism due to long-term hainosankyuto use were observed. The patient was pleased to be able to control the symptoms with medication alone. The drug administration schedule and change in pain intensity in this case are shown in Fig. 4.

DISCUSSION

Hainosankyuto is a formula used in Kampo medicine. Kampo is defined in the WHO International Standard Terminologies in Traditional Medicine in the Western Pacific Region as “the medicine traditionally practiced in Japan based on ancient Chinese medicine.” Hainosankyuto, a combination of Hainoto and Hainosan, was first used by the Japanese doctor Todo Yoshimasu (1702–1773). The hainosankyuto formula consists of platycodon root, glycyrrhiza root, peony root, immature orange, jujube fruit, and ginger rhizome. Platycodon root have a heat-clearing function and promote drainage. Immature orange works to cure induration and eliminate inflammatory infiltration. Glycyrrhiza root and jujube fruit have anti-inflammatory effects. Some case reports have shown that hainosankyuto effectively treats perianal inflammation in children. Some Japanese case reports have demonstrated that hainosankyuto effectively alleviates osteomyelitis and radiation osteomyelitis. In our case, hainosankyuto exerted analgesic and anti-inflammatory effects that alleviated the symptoms of ARONJ. Notably, the patient’s pain resolved even when only hainosankyuto was used. This may be due to the analgesic effect of platycodon root, glycyrrhiza root, and peony root.

ARONJ is classified into stages 0–3 based on clinical symptoms and imaging findings. At the start of treatment, the patient was diagnosed with sclerosing...
Fig. 4. Drug Administration Schedule and Pain Intensity

The solid line indicates the duration of daily use of the drug, while the dotted line indicates the duration of intermittent use of the drug. The classification of pain intensity is as follows: severe = pain interferes with life; moderate = pain can be controlled by medicine but does not disappear; weak = pain is intermittent; and painless = no pain. Mecobalamin, amoxicillin, and loxoprofen sodium hydrate were not used for about 8 months after the initial use. After discontinuation of the pregabalin, the pain was controlled by taking hainosankyuto and gargling with benzethonium chloride. The pain recurred when the hainosankyuto was discontinued and was controlled when it was restarted.

Osteomyelitis because there was no exposed bone in the oral cavity and a high-density area was observed in the left mandible on CT images. However, her condition at that time was more likely ARONJ stage 0. The numbness and tingling pain of the left chin that occurred in the early stage of this case may have been Vincent’s symptoms. It is speculated that the early use of hainosankyuto prevented further inflammatory aggravation and promptly improved sensations. Unfortunately, bone exposure occurred after the discontinuation of hainosankyuto. Fedele et al. reported that 50% of cases of non-exposed bisphosphonate-associated osteonecrosis of the jaw would subsequently progress to frank exposed osteonecrosis. Poor oral hygiene is a risk factor for ARONJ. In this case, exacerbation of the inflammation became apparent because of poor cleaning around the implant and temporary discontinuation of the hainosankyuto. The patient’s symptoms subsided again following a thorough oral cleaning and resumption of the hainosankyuto.

The main limitation of this case is related to the patient’s concurrent use of several drugs rather than hainosankyuto alone and concomitant oral cleaning. Hence, the effect of hainosankyuto alone remains unclear. However, the discontinuation of hainosankyuto exacerbated her symptoms, whereas its resumption caused improvement. Hence, it is highly likely that hainosankyuto contributed to her symptom improvement.

A previous animal study reported that hainosankyuto did not have a direct antibacterial effect on *Streptococcus pyogenes* but increased the survival rate after *S. pyogenes* infection and upregulated both blood bactericidal activity and macrophage phagocytic activity by modulating inflammatory cytokines. It has been suggested that hainosankyuto alone cannot alleviate inflammation caused by infections; however, Kampo medicine may help improve inflammation adjunctively. There are also clinical reports that hainosankyuto improves inflammation. Kawahara et al. reported that 14 of 15 patients were cured using hainosankyuto for neonates and young infants with perianal abscess. A case report showed that hainosankyuto effectively treated suppurative osteomyelitis with repeated recurrence. Thus, hainosankyuto reportedly improves inflammation in both soft and hard tissues. It has been suggested that the symptoms of ARONJ, which is characteristic of chronic osteomyelitis, also improve. The use of hainosankyuto in this case minimized the continuous use of antibacterial agents and NSAIDs. Thus, its use for the treatment of ARONJ may prevent the development of resistant bacteria and the unnecessary
use of analgesics.

In conclusion, pain control using hainosankyuto was effective in our patient with ARONJ. The anti-inflammatory and analgesic effects of hainosankyuto controlled her symptoms. Thus, our findings suggest that hainosankyuto may be an effective adjunctive treatment for patients with ARONJ in whom pain control is difficult with general treatment.

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Conflict of interest The authors declare no conflicts of interest associated with this manuscript.

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