Cancer Patients Receiving Bone-Modifying Agents Show Different Rates of Anti-Resorptive Agent-Related Osteonecrosis of the Jaw Depending on their Primary Disease

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Abstract

The continuing development of anti-resorptive drugs, called Bone-Modifying Agents (BMAs), is improving the medical management of metastatic bone disease and improving patients' Quality Of Life (QOL). However, Anti-Resorptive Agent-Related Osteonecrosis of the Jaw (ARONJ) is a known refractory oral adverse event. Effective measures to treat or prevent ARONJ have not been established, and the current best approach to preventing ARONJ is pre-BMA oral screening and peri-BMA oral management by a dentist. In this study, the incidence of ARONJ and survival time after starting BMAs were examined in lung cancer and breast cancer patients with bone metastases, and the oral management of such patients was considered. The objective of this study is to discuss how oral management should depend on possible survival periods in cancer patients to maintain better QOL. This was a nonrandomized, retrospective study involving 104 lung cancer patients (mean age: 66.5 ± 10.5 y; 62 men, 42 women) and 42 breast cancer patients (mean age: 57.8 ± 9.3 y, 42 women) from January 2013 to December 2017 in our hospital. After the oral screening, oral management was planned and performed, including tooth extraction, periodontal treatment, and/or endodontic treatment to eliminate infectious lesions in the jaw, as needed. The patients were followed-up every three months for oral screening and oral management. ARONJ developed within 5 years after starting treatment with bone-modifying agents (zoledronic acid and/or denosumab) in 5.8% (n=6/104) of lung cancer patients and 16.7% (n=7/42) of breast cancer patients. ARONJ occurred from 4 to 34 months after the first dose of BMAs. For year 2-3 ($p<0.05$), 3-4 and year 4-5 (both $p<0.01$), there were significant differences in the incidence of ARONJ between lung and breast cancer patients due to the short survival time of lung cancer patients. In order to minimize the deterioration of patients' oral quality of life due to measures to prevent ARONJ such as tooth extraction, oral management of patients starting BMAs should differ depending on their anticipated survival time.

Key Words: BMA, Cancer patient, ARONJ, Oral management

Introduction

Bone metastases are common in advanced cancer, and they lead to debilitating skeletal complications, including severe pain, an increased fracture rate, and spinal cord compression. The incidence of bone metastases varies by cancer, and recent medications for advanced disease are expected to lead to longer survival times.

The continuing development of anti-resorptive drugs, called Bone-Modifying Agents (BMAs), is improving the medical management of metastatic bone disease across many tumor types and making a major impact on patients' quality of life. BMAs, such as bisphosphonate, zoledronic acid, or denosumab, are used in patients with bone malignancies [1]. The effectiveness of BMAs for the treatment of lung cancer, breast cancer, prostate cancer, multiple myeloma, and other cancers is noted in each section of the guidelines, where the evidence for the suppression of Skeletal-Related Events (SREs) is also presented. The bisphosphonates zoledronic acid and denosumab were licensed for use in metastatic bone cancer in Japan, and they appear to yield a great benefit in terms of SRE reduction. The use of intravenous anti-resorptive agents, such as BMA, zoledronic acid, and denosumab, was started in a revision of medical services in the fiscal year 2006 and 2012 in Japan, respectively. Since then, these BMAs for metastatic bone lesions of several solid cancers have been adopted for use in many hospitals in Japan.

On the other hand, Osteonecrosis of the Jaw (ONJ), first reported in patients receiving bisphosphonates in 2003, is known to be a severe possible adverse effect of BMAs [2]. Anti-resorptive Agent-Related Osteonecrosis of the Jaw (ARONJ) caused by zoledronic acid and/or denosumab is known as a refractory oral adverse event. Effective treatment or measures for prevention of ARONJ have not been established, and the current best management for prevention of ARONJ is strongly suggested to be pre-BMA oral screening and peri-BMA oral management by a dentist [3]. It has been reported that eliminating possible infectious lesions in the jaw is important to prevent ARONJ. In the pre-BMA oral screening to eliminate odontogenic infectious lesions in the jaw, infectious tooth extractions, periodontal treatment, or endodontic treatment may be necessary. In cases of severe periapical or periodontal disease, tooth extraction before the start of BMAs could occasionally be necessary, leading to loss of teeth. The loss of teeth generally results in deterioration of the Quality Of Life (QOL) of oral functions for patients, although QOL improved partially after a new denture [4,5]. Many patients reported that their ability to chew, ability to open the mouth, and enjoyment of food were affected by tooth extraction, along with deterioration in their speech and cosmetic changes in their appearance [6].

The survival rates of cancer patients vary after detection of metastatic bone cancer. For example, the survival rate of lung cancer patients with bone metastasis is much shorter than that of prostate or breast cancer patients with bone metastasis [7,8]. As described, pre-BMA oral screening and peri-BMA oral management is suggested, and eliminating possible infectious lesions in the jaw has been uniformly suggested to

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be important to prevent ARONJ. However, the incidence of ARONJ could vary by cancer type with different possible survival times. Therefore, oral management for prevention of ARONJ depending on cancer type with various possible survival times could differ. There has not been any discussion of how oral management should depend on possible survival periods in cancer patients to maintain better QOL.

The incidence of ARONJ and survival time after the administration of BMA were examined in two types of cancer patients, lung and breast cancer patients, with bone metastases, and the oral management of patients with these two cancer types was considered.

Patients and Methods

This was a nonrandomized, retrospective study. A total of 104 lung cancer patients (mean age: 66.5 ± 10.5 y (range: 36-87 y), 62 men and 42 women) and 42 breast cancer patients (mean age: 57.8 ± 9.3 y (range: 39-75 y), 42 women) who were referred to the Department of Oral and Maxillofacial Surgery for pre-BMA oral screening starting from January 2013 to December 2017 in our hospital were investigated. All lung cancers and breast cancers were histologically diagnosed, with radiographic evidence of bone metastases classified as Stage IV by the UICC classification. Surviving patients with follow-up periods shorter than 4 years after BMA administration were excluded.

As instructed by the Health, Labour and Welfare Ministry of Japan, patients planned to start BMAs, zoledronic acid and/or denosumab, should be requested to undergo oral screening before BMA administration. After the oral screening, oral management was planned and performed depending on the interventional necessities of the patient's condition. In practical terms, in the dental section, if needed, patients underwent tooth extraction, periodontal treatment, and/or endodontic treatment to eliminate infectious lesions in the jaw in our hospital or their primary dental office. Additionally, patients who did not need any pre-BMA treatment were instructed how to brush their teeth and tongue and how to maintain a high level of oral hygiene, and they were followed-up every three months for removal of dental plaque and calculus. The patients were scheduled for longitudinal follow-up every three months for oral screening and oral management. The incidence of ARONJ was assessed through the examination period with study durations of more than four years after the first BMA administration.

The definition of ARONJ was taken from the AAOMS position paper. The outcome of this study was the incidence of ARONJ. Possible development of ARONJ was noted and classified into four different stages according to the criteria defined in the AAOMS position paper [3]. Stage 0 is characterized by no clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms. Stage 1 features asymptomatic exposed and necrotic bone or fistulas that probe to bone and have no evidence of infection. Stage 2 features exposed and necrotic bone or fistulas that probe to bone associated with infection evidenced by pain in the region of the exposed bone. Stage 3 is characterized by exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and more than one of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus of the mandible, maxillary sinus, and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor. The more severe staging was recorded when the patient showed the different stages in the same assessment year-period. Once ARONJ was reported as an adverse oral event, the patients were queried and received anti-inflammatory management such as lavage or sequestrectomy during the follow-up period.

The survival rate after administration of BMA was assessed in both lung cancer and breast cancer patients. Data were collected and analyzed with a combination of software packages [Microsoft Excel and SigmaPlot (Systat Software, San Jose, CA)]. Survival analysis was performed using Kaplan-Meier's method, and comparison of mean values was performed with the log-rank test, with $p<0.05$ considered significant. Results are reported as means ± SD unless indicated otherwise. This retrospective study was approved by the review board of our institution.

Results

Among the lung cancer patients examined in the present report, 35 (33.7%) were treated with zoledronic acid, and 69 (66.3%) were treated with denosumab, while among the breast cancer patients, 21 (50.0%) were treated with zoledronic acid, 18 (42.9%) were treated with denosumab, and 3 (7.1%) were given both BMAs.

Overall, in 5.8% (n=6/104) of lung cancer patients and 16.7% (n=7/42) of breast cancer patients, ARONJ developed within 5 years after treatment with BMAs, zoledronic acid and/or denosumab. ARONJ occurred from 4 to 34 months after patients received the first dose of BMA. The mean times of drug exposure before ARONJ in lung cancer and breast cancer patients were 12.3 ± 9.7 and 23.8 ± 15.1 months, respectively. *Figure 1* shows the cumulative incidence of ARONJ in both types of patients. The cumulative incidences of ARONJ for years 0-1, 1-2, 2-3, 3-4, and 4-5 in lung cancer patients were 2.9%, 3.8%, 3.8%, 1.0%, and 0.0%, respectively. Similarly, the cumulative incidences of ARONJ for years 0-1, 1-2, 2-3, 3-4, and 4-5 in breast cancer patients were 4.8%, 9.5%, 14.3%, 16.7%, and 16.7%, respectively. For year 2-3, 3-4 and year 4-5, there were significant differences in the incidence of ARONJ between lung and breast cancer patients (year 2-3: $p<0.05$, year 3-4 and 4-5: both $p<0.01$). The treatment for ARONJ performed in our institution was conservative, which was nonsurgical treatment including the use of an antiseptic mouth rinse, systemic antibiotics, or the debridement of separated necrotic bone, or the removal of necrotic bone only. Surgical treatment that includes the removal of necrotic and surrounding bone (i.e., marginal mandibulectomy or partial maxillectomy) was not performed.

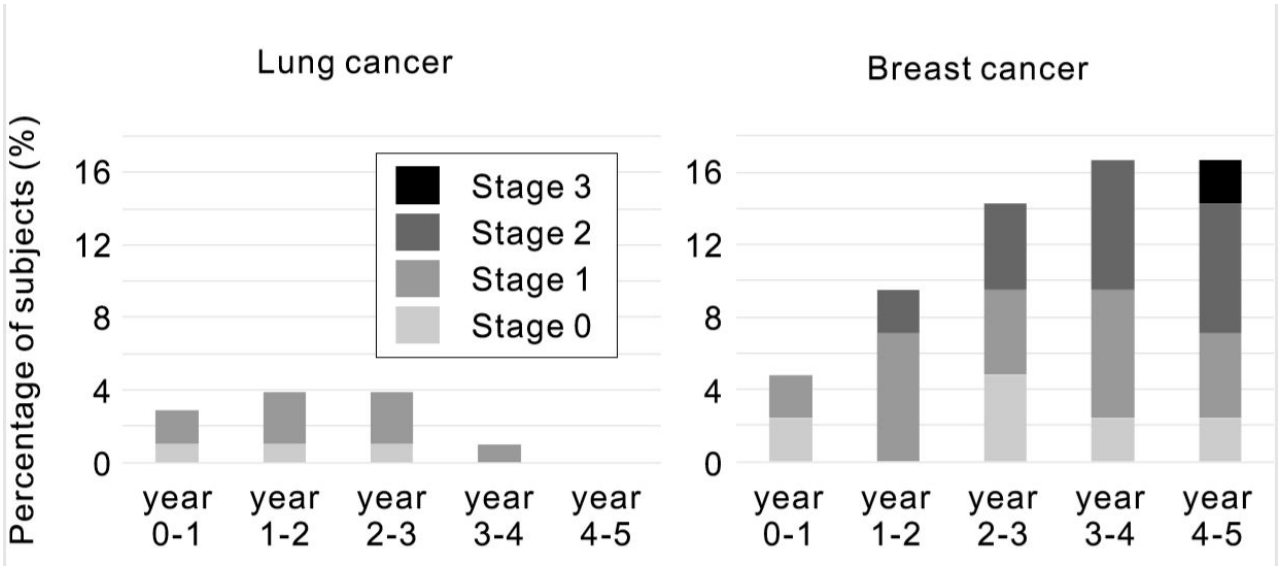

Figure 1. *Cumulative incidences of ARONJ for lung (left) and breast (right) cancer patients with bone metastases. The incidences of ARONJ for years 0-1, 1-2, 2-3, 3-4, and 4-5 were assessed, classified by ARONJ stage 0-3. There are significant differences in ARONJ occurrence after 2 years between lung and breast cancer patients (year 3-4: $p<0.05$, year 3-4 and 4-5: $p<0.01$, chi-squared test).*

Figure 2 shows the survival curves for lung and breast cancer patients with bone metastases after the start of BMA administration. The survival rates at 12, 24, and 36 months after the start of BMA administration were 28.8%, 12.5%, and 6.7%, respectively, in lung cancer patients. The survival rates at 12, 24, and 36 months after the start of BMA administration were 81.0%, 66.7%, and 59.5%, respectively, in breast cancer patients. In these two patient groups, there was a significant difference in survival rates after the start of BMA administration ($p<0.001$).

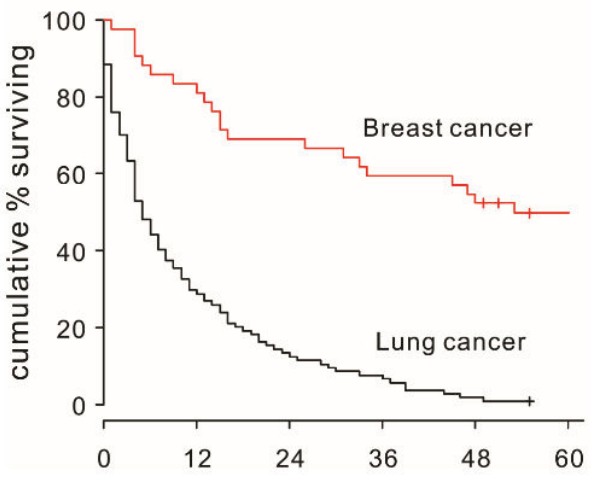

Figure 2. *Kaplan-Meier curves of overall survival for lung and breast cancer patients with bone metastases after starting BMA administration.*

Discussion

The present study offers the first report of the clinical assessment of ARONJ occurrence and survival times after the start of BMA administration in different cancer patients depending on their primary disease; lung cancer patients' vs. breast cancer patients. The objective of this study is to discuss how oral management should depend on possible survival periods in cancer patients to maintain better QOL. In this report, the lung cancer patients with bone metastases had a short potential survival time, while the breast cancer patients with bone metastases had a long potential survival time, and the clinical assessment of ARONJ occurrence and survival time after the start of BMA administration in these two different types of cancer patients were shown, and oral management after pre-BMA oral screening was discussed.

Longitudinal follow-up was conducted every three months after initial oral screening. After the pre-BMA oral screening, oral management was performed for all patients to maintain a high level of oral hygiene, with longitudinal follow-up every three months. BMA has a clear role in reducing SREs associated with bone metastases, while ARONJ has been documented and discussed as an oral adverse effect of BMAs worldwide. Appropriate oral management is the most important, and control of oral health is suggested to prevent the occurrence of ARONJ before the initiation of BMAs. Infection control is the most important factor in preventing ARONJ [9]. Tooth extraction for the active elimination of infectious lesions is occasionally required depending on the patients' oral health situation. With the great improvement provided by BMAs, breast cancer or prostate cancer patients with bone metastases have a long life expectancy from the time of diagnosis of bone metastases [10]. Additionally, there are several case reports of ARONJ that produced lethal sepsis in patients who had been taking BMAs long-term [11,12]. ARONJ is generally an intractable disease. Therefore, appropriate oral management and elimination of infectious lesions to control oral health and prevent the occurrence of ARONJ before initiation of BMA is important for these patients who have a long life expectancy. Because the occurrence of ARONJ and the severity of ARONJ depend on the duration of BMA therapy, active elimination of infectious

lesions could be reasonable and recommended, considering the future occurrence and development of ARONJ during the patients' possible long lifetime.

On the other hand, the cumulative incidence of ARONJ 2 years after BMA administration in lung cancer patients was significantly lower compared with that of breast cancer patients. At follow-up later than 2 years, the occurrence of ARONJ in lung cancer patients became less, as shown in *Figure 1*. In the 4-5 years period, there were no ARONJ patients. Additionally, there were no lung cancer patients with stage 2 or 3 ARONJ during the assessment period. This is because few lung cancer patients survived more than one year after the start of BMAs. During the continuous oral management, most lung cancer patients were lost to follow-up within very short periods because they died. In order to make this clearer, the survival rates after the start of BMAs for both lung cancer and breast cancer patients were assessed. As shown in *Figure 2*, after the start of BMA medication, about half of the lung cancer patients died within six months, while the survival rate at 12 months of breast cancer patients was greater than 80%. The life expectancy of lung cancer patients from the time of diagnosis of bone metastases is very short, with up to about 30% of patients surviving 12 months. This showed that lung cancer patients with their metastases live significantly shorter than breast cancer patients.

Thus, the possible occurrence and development of ARONJ during their lifetime could be very low. The necessity of active elimination of infectious lesions, such as by tooth extraction, can have a considerably negative impact on oral health-related QOL. Loss of teeth causes negative oral impacts that are most frequently experienced in eating, smiling, and when emotionally disturbed. The chewing disability caused by the loss of teeth especially produces a negative impact on oral health-related QOL [5]. For these patients, for example, even if there were teeth with chronic periapical lesions, which are considered an indication for tooth extraction, conservative treatment could give the patient, better oral health-related QOL.

The mean duration of administration of intravenous BMAs until the onset of ARONJ was reported to be from one to two years [13,14]. Most patients with bone metastases who start taking BMAs are predicted to have limited survival time to some extent, depending on their primary cancer. The advantages and disadvantages of oral health-related QOL to patients and their family members must be considered. Survival time is not the only factor when considering oral management, but it is a key factor to maintain oral health-related QOL. While trying to minimize deterioration of patients' oral QOL, oral management of patients starting BMAs should thus differ depending on their possible future survival time.

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