学 位 論 文 の 要 旨

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学 位 論 文 名　A Retrospective Observational Study of Risk Factors for Denosumab-Related Osteonecrosis of the Jaw in Patients with Bone Metastases from Solid Cancers

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論 文 内 容 の 要 旨

INTRODUCTION

Bone metastasis is commonly found in patients with solid cancers. Denosumab is a human monoclonal antibody that binds to, and interferes with, the activation of the receptor activator of nuclear factor kappa- ligand (RANKL), a potent stimulator of osteoclastogenesis. Denosumab is widely used as a substitute for BPs in patients with bone metastases, osteoporosis, and other bone diseases. Anti-resorptive agents may cause osteonecrosis of the jaw (ONJ), called anti-resorptive agent-related osteonecrosis of the jaw (ARONJ,) and medication-related osteonecrosis of the jaw (MRONJ), which includes denosumab-related osteonecrosis of the jaw (DRONJ) and BP osteonecrosis of the jaw (BRONJ). This ARONJ significantly affects QoL, and the decline in QoL is correlated with the ARONJ stage. The reported risk of developing DRONJ in oncology patients is 1–3%. However, the exact mechanisms underlying DRONJ remain unclear, and definitive treatment strategies have not yet been developed, although the dominant risk factors for DRONJ are the cumulative dose and the number of administrations, and typically following a local infection or trauma to the bone or soft tissue. Therefore, in this study, we retrospectively investigated the risk factors for DRONJ. The identification of such risk factors would facilitate the prediction and prevention of DRONJ onset, as well as improve the oral and maxillofacial QoL and treatment outcomes of patients with bone metastases from solid cancers.

MATERIALS AND METHODS

This was a retrospective single-center observational study to evaluate risk factors for developing DRONJ. The study protocol was approved by the Ethics Committee of Shimane University(No. 20181225-1) and the Ethics Committee of Matsue City Hospital (No. 2019A-0004). All patients received denosumab for bone metastasis of solid cancers between July 2014 and October 2018 at Matsue City Hospital, Shimane, Japan. The inclusion criteria were as follows: stage IV solid cancer with bone metastases, denosumab (RANMARK; Daiichi Sankyo Company, Ltd., Tokyo, Japan) administration by subcutaneous injection at a dose of 120 mg every 4 weeks at least twice, and denosumab dose adjustment based on the patient's calcium level and renal function. The exclusion criteria were patients with missing or inaccurate data. The surveyed items were as follows: patient characteristics, medical history, blood examination, underlying characteristics of the solid cancer, and intraoral findings (number of teeth, denture use, and apical periodontitis such as root apical lesions or periodontal disease with marginal periodontitis). All statistical analyses were performed using SPSS version 26.0 software (IBM Japan, Tokyo, Japan). Background factors in the two groups were analyzed using the chi-squared and Mann– Whitney U-tests. Univariate and multivariate analyses of the risk factors for the development of DRONJ were conducted using logistic regression analysis. All study variables were selected using the stepwise method.

RESULTS AND DISCUSSION

In total, 157 consecutive patients were enrolled in our study. Among them, 123 patients (57 males and 66 females) met the inclusion criteria. The demographics of DRONJ(n=14) and non-DRONJ patients(n=109) were compared. Statistically significant differences were found in sex, height, Brinkman index, use of chemotherapy/targeted molecular therapy, use of hormone therapy, presence of apical periodontitis/root apical lesions and periodontal disease with marginal periodontitis, and the duration of denosumab treatment. No other variables differed significantly between the two groups. In univariate analyses, statistically significant predictors of DRONJ onset included hormone therapy (odds ratio [OR], 5.81; 95% confidence interval [CI], 1.80–18.81), chemotherapy/molecular target drug (OR, 4.26; 95% CI, 1.35–13.40), apical periodontitis (OR, 5.52; 95% CI, 1.62–18.84), periodontal disease (OR, 9.57; 95% CI, 2.04–44.91), sex (OR, 6.11; 95% CI, 1.31–28.60), and body mass index (OR, 1.18; 95% CI, 1.02–1.37) (Table 3). Furthermore, in multivariate analysis, statistically significant predictors of DRONJ onset included hormone therapy (OR, 22.07; 95% CI, 2.86–170.24), chemotherapy/molecular targeted therapy (OR, 18.61; 95% CI, 2.54–136.27), and apical periodontitis (OR, 22.75; 95% CI, 3.20–161.73).

We then should recommend that oncologists highlight the importance of maintaining good oral hygiene and recognizing early signs of DRONJ in the context of denosumab treatment for stage IV advanced cancer bone metastases. Furthermore, we recommend the administration of denosumab as part of the management and care of cases with bone metastases from solid cancers, in combination with chemotherapy, targeted therapy, or hormonal therapy. All patients should undergo oral and dental examinations before the start of denosumab treatment, and should receive regular oral examinations while receiving denosumab. A previous report showed that the incidence and severity of ONJ could be minimized through proactive education. Therefore, a lower incidence, and higher rate of resolution, of DRONJ may be achieved by educating health care providers. It may also be helpful to encourage the patient's oral specialist, regular dentist, and oral and maxillofacial surgeons to ensure that the patient understands the risks of cancer treatment.

CONCLUSION

In conclusion, this retrospective observational study analysis revealed statistically significant correlations of DRONJ onset with hormone therapy, chemotherapy/molecular targeted therapy, and apical periodontitis. Close collaborative oral examination and regular maintenance of oral hygiene by oral specialists may reduce the incidence of DRONJ in cancer patients with bone metastases treated with denosumab.