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A Retrospective Analysis of Predictors of Anti- Resorptive Agents-related Osteonecrosis of the Jaw (ARONJ) in General Hospitals

Yoshiyuki Kashiwagi

Department of Nursing, Sagamidai Hospital, Japan

Corresponding Author's Email: newstyle.clubana@gmail.com

ABSTRACT

Background: The aim of this study is to analyze predictive factors of ARONJ and the purpose is to examine intervention methods to prevent ARONJ. **Methods:** This study is a case control study. Regarding the diagnosis of ARONJ, since the research target hospital did not have dentistry or oral surgery, it was decided to define the patients diagnosed with ARONJ at other dental clinics as a case group. Risk factors include age, gender (male and female), ECOG performance status, cancer type, chemotherapy combination status, diabetes history, smoking and drinking history, number of oral cares per day, denture usage, medications, medications Period, hormone therapy, and blood tests (total protein, albumin, calcium, neutrophils). The Chi-square test and *t*-test were used to determine significant relation between variables. **Results:** According to the results of univariate analysis of ARONJ, calcium (p=0.015), history of smoking (p=0.006), the number of oral care/ day (p=0.013) and diabetes (0.023) have significant differences with ARONJ. **Conclusion:** This study suggested that daily life factors such as oral care and physical factors such as smoking history and diabetes were predictors. This result suggests that mandibular dentures are more likely to cause denture ulcers, leading to ARONJ. Nurses need to detect risk factors early, to continuously monitor the oral cavity and promote oral care.

Keywords: ARONJ; Bisphosphonate; Anti-RANKL Monoclonal Antibody Drug; Oral Care

INTRODUCTION

Recently, the incidence rate of cancer is increasing even in developed countries (Ferlay *et al.*, 2014). In terms of treatment, multidisciplinary therapy (combination of operation, chemotherapy, radiation therapy and palliative care) has now become the mainstream of many cancer treatments.

However, even if multidisciplinary therapy is applied, it is often seen that cancer patients in advanced stages of cancer with metastasis in other organ. Metastatic bone tumor is one of the major cancers. This is because bone is one of the target organs of malignant tumor like lung and liver (Shibata *et al.*, 2016).

Bone metastatic starts to destroy of bones and, as a result, many patients suffer from severe pain related to pathological fracture or compression fracture (Urade, 2010). One characteristic of bone metastatic is that it does not lead to vital prognosis. However, metastatic cancer cell of bone releases Parathyroid hormone-related protein (PTHrP) which revitalizes osteoblastic cell and osteoclast. As a result, bone resorption occurs along with osteolysis (Urade, 2010; Tanaka *et al.*, 2007; Yamaguchi *et al.*, 2008).

Bone modifying agent (BMA), which is used along with radiation therapy, is one of the treatment methods for bone metastatic, and bisphosphonate (BP) and RANKL inhibitor are examples of this (Urade, 2010; Urade *et al.*, 2011; Shibahara *et al.*, 2018; Morag *et al.*, 2009). Even though BMA has strong effect on bone resorption, it tends to cause osteonecrosis of the Jaw as a side effect (Urade, 2010).

According to guideline of American Association of Oral and Maxillofacial Surgeons (Force, 2007),

medical professions should spread awareness about risk factors and symptoms of Anti-resorptive agents-Related Osteonecrosis of the Jaw (ARONJ) to patients. It is said that at a hospital without dentistry or dental surgery, medical professions need to cooperate with dentists from the initial screening to the time when ARONJ symptoms appear. A high rate of occurrence of ARONJ compared with the data of phase III trial (anti-RANKL monoclonal antibody drug: Abroad 1.8%, Japan 1.4%) was reported (Coates, 2011).

Although there are some studies related to ARONJ by oral surgeon, we could not find any studies by general hospital without dental surgery. The aim of this study is to analyze predictive factors of ARONJ and the purpose is to examine intervention methods to prevent ARONJ at the general hospital without oral surgery.

METHODOLOGY

This survey used a case-control study and was carried out from April 2011 to January 2016 in a general hospital in Japan. The inclusion criteria were cancer patient metastasis bone and using ARONJ. Exclusion criteria was patient who had been treated by radiation therapy.

This study is a case control study. In terms of diagnosis of ARONJ, since there was no dentistry or dental surgery at the target hospital, the patient was defined with respect to being diagnosed with ARONJ at other dentistry as a case group. Data was collected from electronic medical records. All data on side effects of cancer patients on electronic medical records are entered using the CTCAE grade scale. All data were collected in the presence of an oncologist other than the researcher.

Age, sex, ECDG performance status, type of cancer, use of chemotherapy together, diabetes, history of smoking and drinking, the number of oral care per day, using denture, medication, period of medicine, hormonal therapy and values of blood test (total protein, albumin, calcium, neutrophil) as other risk factors were recorded based on previous studies (Matsuo *et al.*, 2008; Shimahara *et al.*, 2007), BRONJ position paper (Yoneda *et al.*, 2016) and the BRONJ manual issued by Ministry of Health, Labor and Welfare in Japan (Ministry of Health, Labor and Welfare, 2017).

The data were analyzed by SPSS v.23. The Chi-square test and *t*-test were used to determine significant relation between variables. The ethical approval was obtained from the target hospital's research ethics committee permitted on 03 April, 2017.

RESULTS

The total number of patients who participated in this study was 25. The mean age was 71 years. Among them, 19 patients had been diagnosed with prostate cancer and 6 patients had been diagnosed with breast cancer (Table 1).

Table 1: Characteristics of Participants

	n	%
Age mean (SD) Years	72(10.6)	
Gender		
Men	21	84
Women	4	16
Diagnosis		
Prostate Cancer	21	84
Breast Cancer	4	16
BMA		
RANKL Inhibitor	21	84
BP	4	16

About 24% of the patients had diabetes. 52% of them had a history of drinking and 36% of them had a history of smoking. As for oral care, 44% of them performed less than two times of oral cleanings a day and 56% of them performed three times a day.

It was estimated that 48% of those 25 patients used denture. Among those patients who used dentures, 38.5% used full denture, 46.2% used maxillary partial dentures and 15.4% used the partial dentures of the lower jaw. In the mean length of BMA use was 12 months. About 83% of the patients were using RANKL inhibitor and the rest were using BP.

Results of univariate analysis of ARONJ showed that calcium (p=0.015), history of smoking (p=0.006), the number of oral cares per day (p=0.013) and diabetes (0.023) have significant differences with ARONJ (Table 2).

Table 2: Association between Predictor Variables and ARONJ

	Yes	No	*t* value	
	N(%)=6	N(%)=19	Chi-square (df)	*p*-value
Age, mean (SD) years	72.5(4.2)	71.8(12.0)	0.064(23)	0.890a
Gender				
Men	6(100)	15(78.9)	1.504(1)	0.54b
Women	0(0)	4(21.1)		
Diagnosis				
Prostate Cancer	6(100)	15(78.9)	1.504(1)	0.306b
Breast Cancer	0(0)	4(21.1)		
Smoking				
Yes	5(83.3)	4(21.1)	7.677(1)	0.006b
No	1(16.7)	15(78.9)		
Alcohol Drinker				
Yes	4(66.7)	9(47.4)	0.6801(1)	0.645b
No	2(33.3)	10(52.6)		
Oral Care				
Below 2times	5(83.3)	5(26.3)	6.177(1)	0.013b
3times	1(16.7)	14(73.7)		
Denture				
Yes	5(83.3)	5(26.3)	6.177(1)	0.023b
No	1(16.7)	14(73.7)		
Performance Status	1.33(0.5)	1.05(0.2)	-1.904(23)	0.07a
Period of Medicine	14.1(6.8)	11.4(5.5)	-0998(23)	0.329a
Calcium	8.2(0.3)	8.8(0.5)	2.622(23)	0.015a
Total Protein	6.5(0.6)	6.7(0.6)	0.662(21)	0.515a
White Blood Cell	4250(809.3)	5777(1753.8)	2.039(22)	0.054a
Neutrophils	58(9.8)	62(12.1)	0.654(13)	0.524a
Albumin	4.1(0.36)	3.9(0.52)	-0.313(15)	0.753a

After ARONJ diagnosis, 3 patients needed surgical treatment; one of them took segmental mandibulotomy and the rest underwent debridement. Follow-up observations are required for other patients.

DISCUSSION

Through this study, it is shown that the amount of calcium in blood had significant differences with ARONJ. However, hypocalcemia is one of the common side effects with BMA, and the calcium values of both control and case group patients were within reference value. Therefore, it is difficult to say that the amount of calcium in blood is related to ARONJ.

Talking about risk factors, the number of times oral care performed per day, diabetes and history of smoking had significant differences with ARONJ. In the case group oral care was less than two times a day then it causes increase in oral bacteria. Then, using glue for dentures may lead to oral infection. With the results from this study, it is assumed that exacerbation of oral infection are caused due to the lack of proper oral care and ulceration due to use of denture causing necrosis of jawbone.

Although there was no significant difference between using chemotherapy together, hormonal therapy and ARONJ, given to two prostate cancer patients who treated by both of treatment resulted in ARONJ. It depends on patient wearing denture and adds to the risk factor of the denture and cases decrease in immunity function with adrenal cortex steroid used by preliminary medication in docetaxel and the chemotherapy that are standard including the castration resistance prostate cancer as an associated factor. Chemotherapy in combination with internal use may result in oral bacterial infection, and it is thought that it is a risk factor of ARONJ (Shibata *et al*, 2016; Yoneda *et al.*, 2010; Yokomizo *et al.*, 2009). However, qualitative evaluation was not performed for the detection of the oral environment of each patient in this study. Therefore, it would be necessary to analyze oral infection in future.

Although there were significant differences between history of smoking and ARONJ in this study, in addition it is thought that it can become the poor-prognosis factor (Urade, 2010). If a patient is associated with risk factors such as steroid dosage or diabetes, smoking cessation and moderation in drinking may prevent increase in additional risk factors of ARONJ (Urade, 2010).

In this study, about 60% of ARONJ patients had diabetes. As for patients who have diabetes, the apoptosis instructions of the microvasculature of the bone tend to be ischemic, the malfunction of the blood vessel endothelium, an obstacle of the remodeling of the bone and a bone cell or osteoblasts are risk factor of ARONJ (Khamaisi *et al.*, 2007). Talking about Docetaxel Predonine Therapy (DP) in the castration-resistant prostate cancer, since adrenal cortex steroid is applied it is assumed that impaired glucose tolerance could be caused possibly (Miura *et al.*, 2013). From the above, it is easily concluded that combination of local, systematic and drug-related factors increases risk factors of ARONJ.

In addition, as for prostate cancer, most of the patients are elderly, and it seems that there are body function changes such as decrease in oral purification ability with less amount of saliva and weakened immunity function. These are risk factors of ARONJ. Medical professionals, especially nurses, should give proper instructions about ARONJ to patients.

Self-care instruction in daily life, early detection of ARONJ symptoms and general disease management would be some examples of intervention to patients by medical profession. In addition, it is necessary to take oral examination before starting the treatment for ARONJ since dental treatment often becomes difficult after treatment begins. Also, it is considered that oral observation and oral environment check with medical examination for out-patients and cooperation with dental surgery are necessary (Tateishi *et al.*, 2008).

This study aimed to analyze intervention methods for prevention and early detection of ARONJ at a hospital with no oral surgery, focusing on some factors of drug-related necrosis of jawbone. Thus, at the hospital without dental surgery, it could be said that the cooperation with dental surgery is necessary.

As well as communalization of medical treatment information between a medical doctors and dentists, cooperation with nurses and dental hygienists through sharing of consultation and information about patient care would be necessary.

CONCLUSION

This study suggests that there were significant relationship between the number of times oral care per day, diabetes, history of smoking, amount of calcium in blood with ARONJ. As nursing interventions like, 1. discovery of risk factors, 2. continuous observation in the oral cavity, 3. guidance and promotion of oral care are necessary. If there is a risk factor, it is advisable to consult with oral surgent before treatment.

The perioperative oral cavity function management charges addition was introduced by a medical treatment reward revision from 2012 in Japan. When the researcher used the BMA at a hospital which does not provide oral surgery, active cooperation with local oral surgery would be necessary.

As a limitation of this study, not only the number of oral care but also evaluation of oral environment must be considered in future studies.

Conflict of interest

The author has no conflicts of interest directly relevant to the content of this article.

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