Dental Awareness and Barriers in Reducing the Risk of Medication-related Osteonecrosis of the Jaw (MRONJ) Among Non-head and Neck Cancer Patients

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Research Article

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Abstract

Objectives. The objectives of this study are to assess the dental awareness in reducing the risk of Medication-Related Osteonecrosis of the Jaw (MRONJ) among non-head and neck cancer patients and their barriers of attending pre-medication dental evaluation (PMDE).

Methodology: This study was conducted in the Department of Oncology of the University of Malaya Medical Centre. Non-head and neck cancer patients who are currently or will be undergoing anti-resorptive and/or anti-angiogenic therapy were interviewed using a questionnaire that consist of questions on patient's awareness, attitude, and barriers of receiving PMDE. Ethics approval was obtained.

Results. In total, 17 patients were interviewed. Only 6 patients were informed by the medical doctors about the risk of MRONJ. Nine patients were advised by the medical doctors to have the PMDE prior to the therapy, and most of them in this group follow the instruction and already had their PMDE done prior to the therapy. The other 8 patients, who did not attend a PMDE, thought it was not important because their medical doctors neither inform them about MRONJ, nor refer them for PMDE.

Conclusion. Patients' awareness of MRONJ risks and preventive strategies are poor. The main barrier for PMDE is the lack of referral and information on MRONJ from the medical doctors. Patients' attitudes were positive towards PMDE if they were referred by the medical doctors.

Introduction

Surgery, radiation and chemotherapy are the common treatment modalities for most cancer patients. To reduce the frequency of skeletal-related events, parenteral administration of antiresorptive (AR) therapy e.g., zoledronate and denosumab have been commonly used [1].

Bisphosphonate (BP) is a commonly used AR drug. It inhibits the osteoclast-mediated bone resorption and changes the bone marrow microenvironment, to make it less favourable for cancer cells to survive, thus preventing cancer recurrence [2]. In addition to its effect on osteoclasts, it also triggers the human T-cells in the immune pathway, which may be another potential mechanism in its anti-cancer activity [3]. It was used to treat patients with malignant bone disease such as multiple myeloma and bone metastases of various solid tumors such as breast, lung, and prostate cancer [2]. Recent data from clinical trials proved that adding nitrogen-containing bisphosphonate (N-BP) e.g., zoledronate to endocrine therapy or chemotherapy enhances disease-free survival rate of patients [3].

However, in 2003, Marx noted the complication of osteonecrosis of the jaw (ONJ) associated with the BP drug [4]. He first reported 36 ONJ cases among patients who mainly received BP as an adjuvant cancer therapy. They were presented with exposed avascular bone in the maxillofacial region [4]. Since then, bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been reported as an unusual, but consequential complication.

Denosumab, a new class of AR drug with a shorter half-life, was introduced as an alternative to BP. Denosumab is a human monoclonal antibody that inhibits the cytokine RANKL, which acts as a mediator within the formation and function of osteoclasts [5]. Correspondingly, this non-bisphosphonate AR drug can also lead to ONJ, which was first reported in 2010 [6]. The incidence of ONJ from denosumab and zoledronate fall in a range of 0.7-4% and 0.8-3%, respectively [7, 8].

Besides AR, in 2008, first ONJ associated with an anti-angiogenic agent (AA) drug was reported [9]. Therefore, in 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMSs) had updated the term 'BRONJ' to medication-related osteonecrosis of the jaw (MRONJ), in order to include all the medications that cause ONJ [10].

MRONJ is represented by painful necrotic exposed bone, or bone that can be probed through an intraoral or extraoral fistula, which occurred in the maxillofacial region that has lasted for more than 2 months, in which the patients had a history of AR/AA therapy but without history of radiation therapy and metastatic disease to the jaws [10]. The pathogenesis of MRONJ has been studied for several years, but it has not yet been fully understood. It is hypothesized that MRONJ are related to either bone remodeling inhibition, inflammation and infection, angiogenesis inhibition, soft tissue toxicity, or immunity dysfunction [10, 11].

There are numerous risk factors leading to MRONJ. Among dental operative procedures, tooth extraction is the most frequently reported predisposing event [12]. Other than extraction, periodontal disease, dental implant placement, endodontic treatment, oral surgery and maxillofacial trauma had also been reported to cause MRONJ [12, 13]. However, there were also cases of MRONJ which developed spontaneously [13].

When a patient is diagnosed with MRONJ, a multidisciplinary team approach is needed, including regular communication among oncologist, dentist, and oral and maxillofacial surgeon. According to AAOMSs, the treatment aims for patients with established MRONJ are to control pain, infection of soft and hard tissues, and the progression of bone necrosis, which may include surgical intervention, pain medication, antimicrobial mouthwashes, and antibiotic therapy [10]. However, the treatment of this condition is generally challenging, and the optimal therapeutic option is yet to be established. Due to this fact, it highlights the importance of measures to prevent MRONJ.

Risk of developing MRONJ can be significantly reduced if preventive measures are taken. Premedication dental evaluation (PMDE) has been reported as an effective MRONJ prevention measure, in which it comprises a thorough oral assessment together with radiographic examination, detailed patient education, and completion of the dental treatment needs prior exposure to AR/AA drugs [14]. The aim of PMDE is to achieve a good oral health condition by eliminating any possible oral pathology or risk factors [15, 16]. Treatment of dental caries and periodontal disease should be indicated at this point [14, 17]. Non-restorable tooth and tooth with hopeless prognosis need to be extracted [10, 17], as well as the partially erupted third molar [16, 17]. Furthermore, ill-fitting dentures should be examined and modified, particularly along the lingual flange region, in order to remove any pressure areas or sore spots [10, 16]. An appropriate oral hygiene instruction and the relevant information about MRONJ should be provided to the patients by the oral healthcare professionals [10, 14]. In a retrospective study, Owosho et al. reported a

10-year data in Memorial Sloan Kettering Cancer Center [14]. It was found that there was a 12-fold reduction in the incidence of MRONJ when patients received PMDE [14]. This was in accordance with several other studies which have proved that the implementation of PMDE had successfully reduced the development of MRONJ [18, 19].

Besides providing the dental treatments prior to the AR/AA therapy, creating dental awareness among these cancer patients is important to prevent and reduce the disease burden attributable to MRONJ. In a qualitative study, most of the patients demonstrated poor awareness and limited knowledge about the recommended preventive strategies of MRONJ [20] Patient education about prevention of MRONJ should be emphasized [21]. It is necessary for healthcare professionals to inform their patients about the possible complications of AR/AA drugs and refer the patients to receive PMDE [20]. Study has shown a remarkable reduction in the incidence of MRONJ when effective patient education and dental preventive measures were applied [22].

At present, the literature on patient awareness about the MRONJ and barrier to the PMDE are still scanty. Hence, the aims of this study are to assess the dental awareness in reducing the risk of MRONJ among non-head and neck cancer patients, and the barriers of them attending PMDE.

Material And Methods

Ethics approval

This study was approved by the Medical Ethics Committee, Faculty of Dentistry, University of Malaya (Reference number: DF CD2002/0012).

Methodology of recruiting participants

This study was conducted through a face-to-face interview. Two interviewers were stationed at the Day Care Unit of the Department of Oncology, University of Malaya Medical Centre (UMMC). Potential patients were identified by their drug prescription records and referred to the interviewers by the nurses on duty. Potential subjects were informed about the study and asked if they were interested in participating in a survey where they would be asked questions regarding PMDE. Consent was obtained from eligible patients who agreed to volunteer in the interview.

Questionnaire

The questionnaire consisted of demographic data such as age, sex, gender and cancer information. There were 10 questions which focused on the patient’s awareness and attitude on PMDE, as well as the barriers of attending PMDE (Appendix A).

Subject selection

The interviewers prescreened the oncology patients for eligibility. All eligible participants were approached by the interviewers to take consent for voluntary participation.

Inclusion criteria

1. Non head and neck cancer patient of the UMMC.
2. History of current/future use of anti-resorptive (AR) and/or anti-angiogenic (AA) drugs.

Exclusion criteria

1. Head and neck cancer patients.
2. Patients who do not speak and/or understand the common communicating language (English/Malay/Mandarin).

Statistical analysis

Data collected were analyzed using the IBM SPSS software. The mean age and frequency distribution for all categorical variables were calculated. Comparison of whether the patients were informed on the risk of MRONJ by medical practitioners and patients' awareness on PMDE was done using the chi-square test. In addition, the comparison of referral of patients to PMDE by medical practitioners and patients' perception on the importance of PMDE was carried out using the chi-square test.

Results

A total of 17 patients were interviewed. Fifteen participants were females, who were diagnosed with breast cancer, while the other 2 were male patients with prostate cancer. The participants' ages ranged from 30 to 81 years old, with the majority fall within the range of 51-70-years old (76.5%, n=13). Ten of the participants were Chinese and 7 were Malays. With regard to the drug use, 14 participants already started receiving AR therapy, i.e. zoledronate or denosumab, while the other 3 were preparing to receive AR therapy (Table 1). Although our inclusion criteria included the use of AA drugs, none of the patients in this study were receiving the AA drugs.

Table 1
Demographical data of participated subjects.

Variable	Responses	Frequency
Age	30-50	3
	51-70	13
	Gender	Male 2
Female		15
Race	Malay	7
	Chinese	10
Cancer information	Breast cancer	15
	Prostate cancer	2
Dental attendee	Regular	5
	Symptomatic	12
Use of drugs	Currently receiving	14
	Going to receive	3

Most patients (64.7%, n=11) were informed about the general risks of AR therapy such as hypocalcaemia, fever and flu-like symptoms, but only 6 patients were informed specifically regarding the risk of MRONJ. When asked about patients' awareness on visiting their dentist for PMDE prior to the AR therapy, more than half (n=9, 52.9%) responded that they did not know about it (Table 2). There was a significant relationship between whether the patients were informed about MRONJ, and patient's awareness on visiting to dentist prior to the AR therapy (p=0.002). When the medical doctors mentioned MRONJ to them, the patients are more likely visit to their dentists as a precautionary step to reduce the risk of MRONJ. Interestingly, 2 of the patients visited their dentists as told by the medical doctors, even though the medical doctors did not highlight the risk of MRONJ. It indicated that patients would normally follow the advice given by their doctors (Table 2).

Table 2
The relationship between patients' awareness of PMDE and oncology doctors' advice on MRONJ (p =0.002).

		Did the doctor mention about MRONJ?	
		Yes	**No**
Are you aware that you need to visit a dentist before the drug therapy?	**Yes**	6	2
	No	0	9

It is interesting to know that not all medical doctors will refer their patients for a PMDE. Only 9 patients (52.9%) were referred for PMDE by their medical doctors. Table 3 shows that there is a significant difference (p=0.000) between the referral for PMDE by medical doctors and the patients' perception on the importance of having a PMDE prior to the AR therapy. In fact, almost all the patients who were suggested for PMDE had already gone for a dental check-up, except one who has not yet gone during the interview, but she told us that she was planning to see her dentist soon (Table 4). This finding indicated that medical doctors play an important role in referring patients for PMDE. Without the referral, the patients do not perceive the need for them to visit their dentist prior to the AR therapy.

Table 3
Referral for PMDE by medical doctors and patients' attitude on PMDE prior to starting AR therapy (p=0.000).

		Does your doctor suggest or refer you to receive a dental assessment prior to starting one of these drugs?	
		Yes	**No**
Do you think it is important to do a dental check-up before starting one of these drugs?	**Yes**	9	0
	No	0	8

Table 4
Attitude towards PMDE in patients who were referred for PMDE.

Responses	Frequency
I already went for a dental check-up prior starting the drug.	8
I will go for dental check-up soon.	1
I am ok either to go for a dental check-up or not.	0
I want to go for dental check-up but I am unable to do so due to some reasons.	0
I feel there is no need for me to go for a dental check-up.	0

For the other group (n=8), when asked why they did not visit their dentists, all of them responded that their doctors did not mention so. Besides the lack of information from the medical doctors, some think that their cancer mattered more than their oral health (n=3), some don't think PMDE is necessary (n=3), and some say that they are lazy to go for a PMDE (n=3). The other reasons for not attending the PMDE were dental care is too expensive (n=2) and no transport to dental clinic (n=1). No one answered that dental treatments are painful or that there is no family support as reasons for not attending PMDE (Table 5).

When asked how often they normally visit their dentists, 12 said that they will only visit dentists when they have symptoms such as pain, while the other 5 were regular dental attendees who attended regular dental check-ups 6 monthly or yearly. Within the limitation of this study, it was suggested that the main

barrier of attending PMDE prior to AR therapy was due to the fact that the patients were not informed by their oncology doctors (Table 5).

Table 5
Barriers for attending PMDE in patients who were not referred for PMDE.

Responses	Frequency
My doctor did not mention about this to me.	8
I feel that my cancer matters more than my oral health.	3
I don't think that dental check-up is necessary.	3
I am lazy to go for a dental check-up.	3
Dental care is too expensive.	2
No transport to dental clinic.	1
Dental treatments are painful.	0
My family doesn't support me to go for dental check-up.	0

Discussion

In this pilot study, the level of awareness on MRONJ, barriers and attitude in receiving PMDE prior to the start of AR therapy, were evaluated among non-head and neck cancer patients, who may not be seen by the dental profession due to the nature of the disease. The ideal sample size of this study is 133 patients, with a confidence level of 80%. However, we were only able to recruit 17 patients to participate in this pilot study due to the COVID-19 pandemic. Despite the limited sample size, significant findings were noted.

MRONJ is a serious adverse effect of AR/AA therapy. Although its prevalence is low, it can cause a great deal of pain and is a difficult condition to treat [19]. In a recent study, Galis et al. stated that the morbidity of MRONJ may be underestimated [23].

Absence of dental preventive measures due to patients' lack of knowledge and awareness are key factors of MRONJ. A study conducted by Ripamonti et al. showed that there is reduction in the occurrence of MRONJ in patients who have undergone PMDE before starting AR therapy [24]. Similarly, several studies have proved that early oral health screening and the provision of appropriate oral and dental care prior to the medications, bring benefits to patients who were scheduled to receive AR therapy [25, 26].

In this study, only about one third of participants received information about MRONJ from their medical doctors. The other two-third of the participants, who were not informed by their medical doctors about the risk of MRONJ, showed limited awareness of PMDE before starting AR therapy. From this data, it seems that the main reason of patients' ignorance is because they did not receive the information from their

medical doctors. This finding was in line with Al Abdullateef A et al.'s statement [27]. Medical doctor is the main source for patients to acquire information about the adverse effects of BP [27].

Alshammari et al. showed that the side effects of medications could be reduced by providing patient education about drug safety by healthcare professionals [28]. AAOMS also suggested that to prevent the risk of MRONJ, it was important to educate patients in terms of the potential effects and precautions to be taken prior to the AR/AA therapy [10In addition, a study revealed that most people prefer to receive information including all possible side effects from the prescribing doctors, although the side effects might rarely occur [29]. Apparently, literature showed low awareness about the risk of MRONJ among patients, i.e. 66% and 80% as reported by Bauer et al. and Al Abdullateef A et al. respectively [27, 30].

In this study, it reveals that if patients are aware of the risk of MRONJ, they are ready to attend dental clinic for PMDE, especially if they are advised by their medical doctors. All the 9 participants (52.9%) who were advised by their medical doctors, attended PMDE. The attitudes of this group of patients toward receiving PMDE were considered positive. Interestingly, in this study, 2 patients obeyed to their medical doctors' instruction to attend PMDE, even though the medical doctors did not mention the risk of MRONJ. Sturrock A et al. highlighted that the patients usually have better understanding of their responsibility and own actions if they were provided information or advice from the healthcare professionals, which has been clearly demonstrated in our study [20].

Another group of patients (n=8) did not visit their dentist prior to the AR therapy. The main reason they gave was that their medical doctors did not mention PMDE to them. Furthermore, they were not aware of the importance of PMDE in relation to reducing the risk of MRONJ. It is obviously shown here, the main barrier for patients in accessing and receiving PMDE is due to lack of information from the medical doctors. This is consistent with the report by Sturrock et al., as only few participants (13%) received information about MRONJ from their medical doctors [20]. Most of their patients were not aware of the risks, as well as the preventive measures of MRONJ [20].

In 2019, MRONJ Clinical Practice Guidelines recommended that patients with cancer and are scheduled to receive AR therapy, should be referred by the medical professionals for PMDE [19]. However, physicians' perceptions regarding referrals to dentists are still very poor. One of the reasons behind the lack of PMDE referral might be due to the lack of awareness of MRONJ among the general medical practitioners (GMPs). In general, the MRONJ cases were usually presented to dental instead of medical practitioners. A survey conducted by Rahman Z et al. showed that in Birmingham, UK, only 11% of GMPs knew about the possible adverse effect of MRONJ upon prescribing AR medications [31]. Besides, a study also concluded that there is poor knowledge and awareness regarding MRONJ among medical doctors [32]. In contrast, Raj et al.'s study demonstrated that although 88% of GMPs in Victoria, Australia were aware of MRONJ, only 45% of the GMPs referred patients for PMDE [33]. Hence, medical practitioners' awareness and knowledge about MRONJ and their understanding of the importance of PMDE referral are the key factors to ensure they convey effective information to their patients to reduce the risk of MRONJ.

Those patients who did not attend PMDE, besides that they were not being informed by their medical doctors, several other reasons related to psycho-social factors were noticed. Most people have a low awareness of the needs of dental assessment, and some people are facing financial problems. It was suggested that patient's previous life experiences and psycho-social background reduce their ability to receive dental care [34].

MRONJ is a manageable and preventable disease with the implementation of preventive measures [24]. These preventive measures include a careful visual examination of the oral cavity, proactive management of any possible dental diseases, usage of antibiotic treatment, avoidance of invasive dental procedures and identification of risk factors [10, 24]. Prevention of MRONJ can be achieved mainly by improving patients' education on the adverse effects of BPs and taking preventive measures before starting AA/AR medications. The 10-year follow-up result in the Dental Service of Memorial Sloan Kettering Cancer Center showed a significant reduction in the incidence of MRONJ when PMDE was carried out [14].

Based on our finding, a collaboration of the dental team with the Department of Oncology to refer their patients for PMDE prior to AR/AA therapy is highly recommended. Patients should be well-informed about the risk of MRONJ, so that the patients understand the importance of PMDE and maintain good oral health. Drug manufacturers should provide clear and understandable information on the prevention and prophylaxis of ONJ in the package inserts of BPs [30].

Conclusion

Non-head and neck cancer patients have poor awareness of the risks and preventive strategies of MRONJ. The main barrier of patients attending PMDE is the lack of referral and information on MRONJ from the medical doctors. Patients' attitude was positive towards PMDE if they were referred by the medical doctors. Medical doctors have an important role to play in conveying effective education to the patients to reduce the risk of MRONJ.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Authors' contribution

XYL and ZC wrote the manuscript, designed the study, conducted the interview, coordinated data collection, assessed and analysed the data. WLC designed the study, assessed and analysed data and edited the manuscript. All authors read, edited and approved the final version of the manuscript.

Ethics approval

This study was approved by the Medical Ethics Committee, Faculty of Dentistry, University of Malaya (Reference number: DF CD2002/0012).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

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