Management of Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ): A Retrospective Clinical Study

Çenelerin Bifosfonat İlgili Kemik Nekrozunun (BRONJ) Yönetimi: Retrospektif Bir Klinik Çalışma

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ABSTRACT Objective: Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ) is typically a chronic soft tissue wound exposing the underlying jawbone, that persists over 8 weeks in patients taking bisphosphonates with no history of maxillofacial radiotherapy and other bone related disease. Contemporary research focuses on pathogenesis of the disease, various conservative and surgical treatment modalities and their clinical implications. In this retrospective study we aimed to evaluate our management of BRONJ cases. Accordingly case notes of BRONJ patients were evaluated and relevant data were collected. **Material and Methods:** Case notes of BRONJ patients were retrospectively reviewed over a period of four years (2010-2014). Seventy patients with established BRONJ were included in this study. Disease and treatment related parameters were reviewed and descriptively presented. **Results:** Most of the defects showed complete mucosal healing with no sign of recurrent infection. Few patients with persistent disease were re-operated or palliative treatment was commenced giving a surgical treatment success rate of 89.7%. **Conclusion:** Today, clinical guidelines allow a predictable treatment in most of the BRONJ cases. In a small group of patients with a favourable healing potential, extensive surgical treatment can be avoided through a wait and see approach that eventually leads to a more conservative treatment. An efficient communication between the oncologist and the dentist is imperative in the management of BRONJ patients, and ideally dental treatment should be completed before starting bisphosphonates.

Key Words: Bisphosphonate-associated osteonecrosis of the jaw; osteonecrosis

ÖZET Amaç: Bisfosfonata bağlı osteonekroz (BRONJ), bisfosfonat kullanan ve radyoterapi ya da ilgili kemik hastalığı hikayesi olmayan hastalarda, 8 haftadan uzun süren ve çene kemiğinin açığa çıktığı bir yumuşak doku yarasıdır. Güncel araştırmalar hastalığın patogenezi, çeşitli konservatif ve cerrahi tedavi yöntemler ve bunların klinik sonuçları üzerine yoğunlaşmıştır. Biz bu retrospektif çalışmada, 4 yıllık bir periyotta (2010-2014) BRONJ tanısı almış hastaların dosyalarını gözden geçirip, ilgili verileri toplayarak, BRONJ olgularının kliniğimizdeki yönetimini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Bu çalışmaya, Amerikan Oral ve Maksillofasiyal Cerrahi Derneği tarafından yayınlanmış olan kılavuz ilkelere göre tanısı kesinleşmiş 70 BRONJ hastası dahil edilmiştir. Hastalığın evreleri ve her birinin tedavisi ile ilgili kantitatif ve kalitatif parametreler incelenmiştir. Veriler istatistiksel olarak incelenmiş ve tanımlayıcı olarak sunulmuştur. **Bulgular:** Defektlerin çoğunda, yumuşak ve sert dokularda tekrarlayan enfeksiyonun klinik bulguları olmadan iyileşme görülmüştür. Yapılan operasyonlar sonucunda iyileşme sağlanamayan ve hastalığın devam ettiği birkaç hasta tekrar opere edilmiş veya operasyonu kabul etmeyen hastalara palyatif tedaviye başlanmıştır. **Sonuç:** Günümüz klinik kılavuz ilkeleri kullanılarak BRONJ olgularının çoğuna öngörülebilir bir tedavi imkanı sağlanmaktadır. Buna ilave olarak, iyileşme potansiyeli göreceli olarak daha yüksek olan az sayıdaki hastada radikal cerrahi müdaheleden kaçınmak mümkün olabilecektir. Bu grup hastaları klinik takibe alarak, sökestre oluşumu sonrasında daha konservatif bir cerrahi müdahale olan sökestrektomi ile tedavi etmek mümkün olabilmektedir.

Anahtar Kelimeler: Çenenin bifosfonat ilişkili osteonekrozu; osteonekroz

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Typically bone cells like osteoclasts, osteoblasts and osteocytes are activated for bone remodeling either independently or with inflammation seen during odontogenic infections. However bisphosphonates that are used for osteoporosis, paget, metastatic bone disease and hypercalcemia of malignancy change this delicate balance between the bone cells and can impair bone remodeling.[1,2]

BRONJ is typically a chronic soft tissue wound exposing the underlying jawbone, that persists over 8 weeks in patients taking bisphosphonates with no history of maxillofacial radiotherapy and other bone related disease.[3-5] In 2003, Marx was the first to report a series of osteonecrosis patients who were characterized by exposure of maxillary or mandibular bone and IV bishophonate usage.[6] This was followed by similar reports involving both oral and IV bisphosphonate usage and osteonecrosis.[6-8] It has significant morbidity and adversely affects the life quality of patients, that are already compromised by cancer as in most cases.

According to the final position paper by American Association of Oral and Maxillofacial Surgeons, the Special Committee recommends changing the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ) to the term medication-related osteonecrosis of the jaw (MRONJ), in order to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies.[7] However we prefer to use the term BRONJ in this paper, since all of the cases in our study were associated with bisphosphonate usage.

MATERIAL AND METHODS

This is a retrospective study that was conducted in line with Helsinki 2008 Declaration. Case notes of patients who were diagnosed to have BRONJ between 2010-2014 were retrospectively reviewed. Seventy-patients (47 women, 23 men) who were treated surgically for BRONJ were included in this study. Patients with a history of maxillofacial radiotherapy, co-existence of other bone related disease, absence of histopathological confirmation of BRONJ, were excluded. Inclusion criteria and the parameters studied were clear documentation of;

1. Conditions for which bisphosphonates had been used and types of bisphosphonates used (oral/injectable)

2. Number and anatomic locations of the sites involved

3. BRONJ classification[7]

4. Associated systemic risk factors[8,9]

5. Surgical technique used

6. Treatment outcomes including clinical and radiological review minimum 4 weeks after completion of mucosal healing as suggested by Ruggiero et al (Figure 1).[7]

The above given parameters were reviewed and the results were descriptively documented. Systemic risk factors namely, high BMI, Anaemia and DM, were statistically compared regarding their contribution to the occurrence of BRONJ (Chi Square Tests using SPSS 11.0)

RESULTS

Women were effected twice more than men. Most of the patients had only one BRONJ site and there were multiple BRONJ sites in 12 patients. The staging of the disease was advanced in most of the cases and unfortunately there were only a few cases that were diagnosed early. Mandible was affected more than maxilla. The reason for bishosphonate treatment was metastatic breast cancer in most of the cases followed by multiple myeloma, prostate cancer, and osteoporosis. Zoledronate was administered via IV route in most of the cases (4 cases also received ibandronate and 3 cases received clodronate before they were given zoledronate) and 3 cases were given oral alendronate only, for the treatment of osteoporosis. Most of the defects showed complete mucosal healing with no sign of recurrent infection. Few patients with persistent infection were re-operated or palliative treatment was commenced. Results of the study are given descriptively in Table 1.

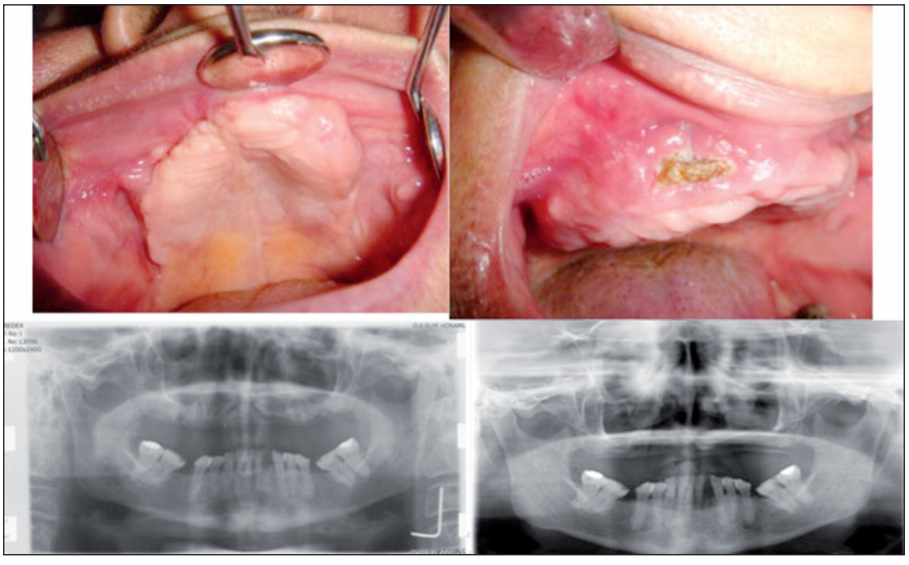

FIGURE 1: Pre-operative and post-operative intra-oral views and panoromic radiograps of a BRONJ (Bisphosphonate-related osteonecrosis of the jaw) patient.

Ten patients did not attend review appointments, treatment of BRONJ was unsuccessful in 2 cases, 2 cases refused treatment, 1 case was not suitable for operation because of systemic disease, 1 of the patients was referred to plastic surgery for resection of his mandible while 54 patients were treated successfully. Surgical treatment success rate was calculated as 89.7% while the combined treatment (including medical treatment) success rate was calculated as 77% (Table 1).

Associated risk factors and stratification of patients based on results acquired at patients' initial presentation are shown in Table 2. The comparison of systemic risk factors regarding their contribution to the occurrence of BRONJ did not yield statistical significance ($p=0.172>0.05$).

DISCUSSION

In the last decade tooth extraction was recognized as the main risk factor for precipitating BRONJ.[1,6,10,11] In general, a thorough dental examination is recommended, and if necessary dental treatment is completed before starting bisphosphonates.[10,12-14]

However, patients were usually late for referral to oral surgery as most of them had stage II or stage III BRONJ at presentation. This would easily be reduced if dental consultations start playing a role in the care pathway of all oncology patients.

Prevalence of BRONJ is reported to be more frequent in female patients, in patients with malignancies, especially those with breast cancer and multiple myeloma.[15-18] In our series most of the patients with BRONJ were females (67%) and, breast cancer was the most frequent cancer type ahead of other cancer types while BRONJ due to oral bishosphonates was less common, these findings are in accordance with the literature.

In our series mandible was affected more than maxilla and posterior more than anterior.[4,7,11] This could be attributed to the decreased vascularity of the mandible. This finding is similar to that reported by other authors.[19-21]

It is well known that IV bisphosphonates impose a greater risk of BRONJ formation then oral bisphosphonates as seen in our series. BRONJ formation increases with zoledronic acid application when compared with other IV bishophonates. In our series zoledronic acid was the only IV bisphosphonate applied to all of the cancer patients therefore it was not possible to compare the risk of BRONJ development after application of different IV bisphosphonates.[22]

Poor glycemic control, low haemoglobin levels, high BMI and smoking are well known risk factors for BRONJ. Most of the patients in this study were non-smokers; only 12 patients admitted to be smokers; therefore it is not possible to discuss the

TABLE 1: Descriptive presentation of clinical variables.

Clinical Variables		Women	Men	Total
Number of patients		47	23	70
Age, Means (Std. Deviation)		60.9 (12.1)	65.3 (10.8)	---
Number of patients without recreational habits		40	16	56
Tobacco users		7	5	12
Tobacco+Alcohol users		---	2	2
Distribution of BRONJ sites (1 site/2sites/3 or more)		40/5/2	18/5/---	58/10/2 (84sites)
Location and numbers of BRONJ sites (posterior/anterior)		Mandible 35 (32/3)	Mandible 17 (5/2)	52 (47/5)
		Maxilla 20 (19/1)	Maxilla 12 (11/1)	32 (30/2)
Classification of BRONJ/ number of sites per staging		Stage 0	Stage 0	Stage 0
		2	---	2
		Stage I	Stage I	Stage I
		3	2	5
		Stage II	Stage II	Stage II
		20	11	31
		Stage III	Stage III	Stage III
		30	16	46
Distribution of indications for bisphosphonates		Breast	Breast	33
		33	---	
		Multiple Myeloma	Multiple Myeloma	14
		5	9	
		Prostate	Prostate	12
		---	12	
		Other*	Other*	7
		5	2	
		Lung	Lung	1
		---	1	
		Osteoporosis	Osteoporosis	3
		3	---	
Routes of administration of bisphosphonates/ number of patients		IV	IV	IV
		43	24	67
		PO	PO	PO
		3	---	3
		Med./Surg./Resec.**	**Med./Surg./Resec.****	**Total**
Treatment strategies and successful outcomes for different stages of BRONJ	Stage 0	---	---	---
	Stage I	---/2√/---	---	2√
	Stage II	2√/11√/1√	---/8√/1√	23√
	Stage III	---/1√/18√	---/2√/8√	29√

*Thyroid, sarcoma, nasopharynx, renal.

**Medical/surgical debridement/rim resection or maxillectomy. ↔:Sucessfully treated patients.

contribution of smoking in the occurrence of BRONJ. Chi-Square comparison of the remaining risk factors regarding the occurrence of BRONJ did not yield statistical significance. ($p>0.05$). However more data is needed to statistically analyze the association of the disease with these risk factors.[5]

Generally speaking surgical debridement was applied to stage II disease patients, while stage III patients were treated with either rim resection or partial maxillectomy. A couple of stage III patients were treated with surgical debridement only, due to sequester formation that enabled easy removal of diseased bone.

TABLE 2: Chi-Square comparison of risk factors and stratification of patients based on results acquired at presentation (p=0.172>0.05).

Risk factors	Normal	Pathological
Glycemic control	Normo glysemic (n=44)	Pre-diabetes (n=16) DM (n=10) Total=26
Haemoglobin count*	Normal (n=33)	Mild (n=13), Moderate (n=24) Severe (n=0) Total=37
BMI**	Normal (n=36)	Underweight (n=3) Overweight (n=17) Obese (n=14) Total 34

*Anaemia according to WHO criteria.

**Normal (18.5-24.9), Underweight (ŧ18.5), Overweight (25-29.9), Obesity (30 or greater).

BMI: Body mass indeks; DM: Diabetes mellitus.

Surgical treatment of BRONJ according to AAOMS guidelines provides predictable outcomes and in our series surgical treatment success rate was 89.7%. We would like to suggest that, in selected BRONJ cases that do not suffer from repetitive acute infections, operations could be postponed providing the oncologist agrees not to administer bisphosphonates. This approach can allow spontaneous sequester formation minimizing tissue loss and surgical trauma.

A thorough communication with the oncologist and dental examination is imperative in the management of BRONJ patients, and ideally dental treatment should be completed before starting bisphosphonates.

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