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Medication-related osteonecrosis of the jaw in oncological patients with skeletal metastases: conservative treatment is effective up to stage 2

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Abstract

There is currently no widespread strategy for treating medication-related osteonecrosis of the jaw (MRONJ), so our aim was to evaluate retrospectively the outcome of a minimally invasive treatment protocol for patients with both MRONJ and cancer. We designed a retrospective cohort study of patients with cancer who had been diagnosed with MRONJ after treatment with denosumab or bisphosphonates given intravenously. Primary outcome measures were improvement in the clinical stage of MRONJ and the time course to its resolution. Secondary outcome measures included the incidence of risk factors and patterns of treatment. Seventy-nine patients with 109 lesions were enrolled, and their characteristics, presentation of the lesions, complications, and relations to previous oral interventions were recorded. Treatment depended on the stage of disease, and included conservative medical, and minimally-invasive surgical, procedures. There was complete healing and resolution of disease in 38/57 stage 1 lesions, 30/47 stage 2 lesions, and 3/5 stage 3 lesions. The symptoms improved in 16/47 stage 2 lesions, and 2/5 stage 3 lesions. Fifteen of the stage 1 lesions, and one of the stage 2 lesions, failed to respond. Despite the possibility of an aggressive approach to the treatment of MRONJ, conservative treatment remains the first line of defence as regression is obvious, with evidence of no evolution to a higher stage. In our experience surgical intervention is recommended in persistent stage 3 MRONJ that has failed to respond to conservative treatment.

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Keywords: MRONJ; osteonecrosis; risk factors; treatment; bisphosphonates; denosumab

Introduction

In 2003 Marx reported the first cases of what has become known as medication-related osteonecrosis of the jaw (MRONJ).¹ Initially, osteonecrosis was reported only after treatment with bisphosphonates and referred to as bisphosphonate-related osteonecrosis of the jaw (BRONJ). As other antiresorptive agents (for example, monoclonal anti-

bodies such as denosumab) seemed to lead to the same outcome – it was soon referred to as antiresorptive-related osteonecrosis of the jaw (ARONJ).² Since 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) has recommended the use of the term “medication-related osteonecrosis of the jaw” (MRONJ). The change is justified to accommodate the growing number of cases of osteonecrosis that are associated with other antiresorptive and antiangiogenic treatments in patients who have not used bisphosphonates previously.³

Current treatments of patients with skeletal metastases vary depending on the stage and severity of MRONJ, from conservative approaches (including long-term antibiotics,

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Table 1

Patients' characteristics (data are number, except where otherwise stated).

	Female (n = 40)	Male (n = 39)	Total (n = 79)
Mean (SD) age (years)	67 (12)	72 (10)	70 (11)
Smokers	5	6	11
First signs and symptom of MRONJ:			
Exposed bony lesions only	30	29	59
Exposed bony lesions accompanied by pain	3	2	5
Pain only	5	7	12
Intraoral fistula	1	1	2
Extraoral fistula	1	0	1
Site of carcinoma:			
Breast	27	0	27
Prostate	0	21	21
Multiple myeloma	10	10	20
Renal cell	2	4	6
Lung	1	2	3
Bladder	0	1	1
Stomach	0	1	1
Medication used:			
Denosumab (Xgeva [®])	22	21	43
Zoledronate acid IV (Zometa [®])	19	16	35
Pamidronate acid IV (Aredia [®])	0	1	1

chlorhexidine and iso-Betadine[®] mouth rinses, sequestrectomy, hyperbaric oxygen, and extensive use of leucocyte- and platelet-rich fibrin) to radical surgical techniques that may involve resection of the jaw with or without osseous free-flap reconstructions.⁴

Management of MRONJ continues to be controversial, however. Conservative medical, and minimally-invasive surgical, treatments give good results during the early stages of the disease. More extensive surgical treatment should be reserved for the advanced stages, although more recently some authors have promoted early extensive surgical intervention.^{5–9} Most reports, though, have expressed reservations about the surgical treatment. Some authors have reported worsening of symptoms, pathological fractures, or even loss of parts of the jaw after surgical intervention.^{10–11} Conservative medical treatments or minimally-invasive surgical treatments remain the most common methods used for the management of MRONJ.^{10–12}

The main goals of treatment for patients with cancer who present with MRONJ should be prioritisation and support of continued oncological treatment (mainly because such treatment outweighs the risk, incidence, or evolution of MRONJ lesions), and preservation of quality of life by controlling infection, pain, and the progression of bony necrosis.² Evolution under different treatments is evaluated clinically, and defined as complete healing of the lesion or transition to a less severe stage (according to the AAOMS classification).

Although the incidence and risk factors associated with MRONJ are well established, at present we have limited information about how it should be managed in routine clinical practice, or about the resolution rates after such treatment. Time of exposure, number of treatments, duration of treat-

ment, and cumulative dose of antiresorptive drugs have been shown to increase the risk of its development.^{13–14} Our main aim in this study was to evaluate the efficacy of conservative medical treatment and minimally-invasive surgical treatment of MRONJ.

Patients and methods

We initially included all patients with skeletal metastases who presented with clinically diagnosed MRONJ, recorded at the University Hospitals Leuven, Belgium, between 2014 and 2016. We excluded patients who were treated for osteoporosis or osteopenia, or who were treated with oral bisphosphonates. Patients who were given both bisphosphonates and denosumab intravenously throughout their treatment were also excluded.

All patients had radiographic documentation of the lesions. Patients' characteristics, treatment, and follow-up data were recorded from their medical notes. The final group comprised 79 patients (with 109 lesions) who had developed MRONJ. We followed the accepted updated criteria by the AAOMS to establish the diagnosis.²

The following data were collected and divided into patient-related information such as age, sex, whether they smoked, main disease and type of treatment (Table 1); and lesion-related data such as site, number, size, and stage of lesions, and treatment given (Table 2). The patient's first complaint, relation to previous dental extractions, present signs and symptoms of MRONJ, presence of severe complications, and type of treatment given were also recorded.

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