Medication related osteonecrosis of the jaws (MRONJ): Diagnosis and treatment

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Treatment of pathologic fractures of the mandible in stage III MRONJ- an observational study

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ABSTRACT

INTRODUCTION

The treatment of pathologic fractures in stage III MRONJ remains challenging. The treatment in literature is controversial varying from extensive and aggressive surgery with resections and musculocutaneous free flap reconstruction to conservative treatment with only mouth rinses and/or antimicrobial treatment. The purpose of this study was to analyse the results of the treatment protocol in the Leiden University Medical Center in the Netherlands.

METHODS

Between 2003 and 2017 15 consecutive patients were seen with pathologic fractures in stage III MRONJ. Patient characteristics and treatment were studied.

RESULTS

7 patients were dentate and were all surgically treated according to protocol and 3 were additionally intermaxillary fixated. 8 patients were edentulous of whom 6 were surgically treated: 2 with osteosynthesis and the rest were instructed a soft diet post-operatively for several weeks. One patient showed healing in a later stage and was not treated. Two patients were treated with antimicrobial treatment and a soft diet.

11 patients (73%) showed complete healing of the fracture or a pseudarthrosis and were free of complaints and were able to function.

CONCLUSION

These results show that a relative simple (surgical and/or antimicrobial) approach combined with intermaxillary fixation on occasion can lead to consolidation and/or a pseudarthrosis with a remaining and acceptable function of the jaw.

INTRODUCTION

The treatment of medication related osteonecrosis of the jaws (MRONJ) can be very challenging. MRONJ is defined as exposed bone in the maxillofacial region for more than 8 weeks, with a previous use of anti-resorptive medication like bisphosphonates or denosumab and no history of radiation therapy or obvious metastatic disease to the jaws. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has written a Position Paper[1,2] with an additional staging of MRONJ (table 1).

The stages 0, I and II can be shortly described as respectively: 0- aspecific complaints or clinical and radiological signs without apparent osteonecrosis; I- exposed bone without signs of inflammation (foetor, pus, swelling or hypoesthesia); II- exposed bone with signs of inflammation. The AAOMS suggests to treat these first stages only with symptomatic conservative treatment with chlorhexidine mouthrinse and antibiotics and maybe a very limited local debridement.

Symptoms in stage III are as described in stage II, but extending beyond the region of the alveolar process and/ or involvement of the inferior border of the mandible or the maxillary sinus, cutaneous fistulas, and pathological fractures. The advised treatment strategies in stage III disease are mouthrinses and/or antibiotics and, depending on the symptoms, surgical debridement or resection for longer-term palliation.

In the literature there is still an ongoing debate on the treatment in stage III MRONJ with involvement of the inferior border with or without pathologic fractures. Some authors[2-5] suggest a conservative treatment for as long as possible, whereas other authors[6-19] suggest an aggressive approach with resections and reconstructions of the jaw with for example a free vascularized osseocuteanous flap of the fibula.

In these medically compromised stage III patients this aggressive approach may not be desirable or possible. Especially for the elderly patients with comorbidities or with (end stage) metastasized disease, major surgery with resection and reconstruction may not be the treatment of choice. However, many patients have pain and a decreased intake, leading to a lower quality of life. Therefore, refraining from treatment is not an option either. In our clinic promising results were seen with a previous reported and relative simple approach[20-22]. The purpose of this study was to analyse this treatment strategy and its follow-up for patients with stage III MRONJ of the mandible with a pathologic fracture.

METHODS

In a cohort of 150 consecutive patients, referred from other clinics, and presenting with stage II/ III MRONJ, treatment and follow-up were studied. Patients were seen between January 2003 and January 2017 in the department of Oral & Maxillofacial Surgery of the Leiden University Medical Center. At presentation, the clinical features, medical and dental history, bisphosphonate use, and the use of other medications were noted.

The inclusion criteria for this study was a MRONJ diagnosis according to the criteria stated by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[2]. As previously mentioned this means a recent use of bisphosphonates or denosumab, the presence of exposed or necrotic bone in the oral cavity for more than 8 weeks, and no history of radiation therapy to the jaws.

Only patients with a stage III MRONJ with severe osteonecrosis and involvement of the inferior border of the mandible and a pathological fracture were included in this present study.

The primary outcome in this study was to observe the result of treatment for stage III MRONJ with pathological fracture of the mandible. Healing of the bone and mucosa were observed. Healing of the bone was classified as healed or a pseudarthrosis. A pseudarthrosis was defined as a fibrous healing of the fracture without evident mobility of the fracture and with an acceptable function of the mandible.

Healing of the mucosa was defined as a closed or open mucosa in case of dehiscences or fistulas.

The follow-up was done on a regular base the first weeks, then after every month, until at least 12 months. During follow-up the main focus was on pain, on the mucosa, and whether dehiscence or recurrence of the exposed bone had developed.

At presentation, panoramic radiographs were taken of all the patients to localize the lesion, and to gain a first impression of the lesion. A computed tomography (CT) scan (predominantly cone beam CT) was used to determine the extent of the defect. The clinical features and the radiological findings, together, defined the stage of MRONJ, based on the AAOMS classification[2]

Table I: Classification Stages MRONJ and recommendations by Ruggiero et al., 2014 (AAOMS)

MRONJ stage	Description	Treatment strategies
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment Patient education
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	Systemic therapies including pain medications and antibiotics
Stage I	No symptomatic lesions or bone exposure in the absence of signs of infection	Topical antiseptic therapy Follow-up
Stage II	Bone exposure with pain, infection, and swelling in the area of the lesion	Oral antibiotics, antibacterial mouth rinse, pain control Superficial debridement to relieve soft tissue irritation
Stage III	Bone exposure, pain, inflammation, maxillary sinus involvement, cutaneous fistulas, and pathological fractures	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement and resection for longer term palliation of infection and pain

(Table 1). Osteolysis in large parts of the jaws beyond the alveolar process and inferior alveolar canal or pathologic fractures were categorized as stage III.

The patients underwent surgical intervention under general anaesthesia as reported before[20-22]. Surgery was performed by senior surgeons. The surgical approach consisted of the removal of sequestra, thorough surgical removal and saucerization of the non-vital bone until reaching the bleeding bone margins. In the case of dentate patients intermaxillary fixation was applied with arch bars (fig. A-E). The defect was closed primarily in layers. This meant closing the periosteum as close to the bone as possible with mattress sutures, leaving no or as little dead-space as possible when closing the overlying mucosa in layers.

During the surgery culture samples were collected, and the resected bone was submitted for histopathological analysis.

The surgical treatment was supplemented by the administration of the antibiotics, penicillin G and metronidazole, intravenously for 1 week, and amoxicillin and metronidazole, orally for 3 weeks.

Panoramic radiographs were taken immediately after surgery, and every 3–6 months, for up to 1 year after the surgery, in order to monitor the condition of the bone margins and the healing of the bone. After 1 year, an annual radiographic follow-up was considered sufficient.

Overlying dentures were not allowed during the first 12 weeks in order to avoid pressure and damage to the mucosa, which could lead to dehiscence of the wound. The patients were instructed to maintain a liquid diet postoperatively for at least 2 weeks, and were otherwise permitted a soft diet after that period.

RESULTS

Fifteen patients could be included in this observational study. The patients were followed for a mean of 24,3 months (6 to 50 months). Two patients could not be followed longer than 6 months because these patients died of metastatic disease.

Fractures

Twelve patients were surgically treated. In 7 cases there was a fracture before or noticed during surgery. In 5 cases there was a spontaneous fracture after surgery.

In the remaining 3 cases the patients presented with pain and a pathological fracture in an edentulous mandible. The fractures showed signs of healing in a later stage, and therefor received no additional surgical treatment.

Patient characteristics (table 2)

The clinical features are listed in Table 2. The ages of the female (53.3%; n = 8) and the male (46.7%; n = 7) patients varied from 47–85 years, with a mean of 71.8 years.

Oral bisphosphonates had been used in 9 cases, with a minimum of 24 months and a maximum of 120 months (mean = 72.1). Intravenous bisphosphonates had been used in 3 cases, with a minimum of 6 months and a maximum of 30 months (mean = 18 months). In 8 patients, steroids, such as prednisone, or methotrexate were used as co-medication.

Table II: Clinical features

Gender		
	Female	8
	Male	7
Indication		
	Osteoporosis	11
	Multiple Myeloma	1
	Prostate Cancer	2
	Breast cancer	1
	Other	-
Intravenous use bisphosphonates		3
	Zoledronic acid	2
	Pamidronic acid	1
Oral use bisphosphonates		11
	Alendronic acid	10
	Risedronic acid	1
Subcutaneous use Denosumab		
	Xgeva	1
	Prolia	-
Co-medication		8
	None	8
	Steroids	7
	Immunosuppressants	2
	Cytostatics	2
	Combination	4

Dentate

There were 7 dentate patients of whom 5 patients had osteoporosis and oral medication use and 2 patients had metastasized cancer and intravenous use of medication.

Edentulous

There were 8 edentulous patients of whom 6 patients had osteoporosis with oral medication use. Two patients had cancer of whom one patient used xgeva and one patient used intravenous bisphosphonates.

Surgical outcome (table 3)

Dentate

7 patients were dentate and were all surgically treated according to protocol and the three patients with a pre-operative fracture were intermaxillary fixated for 6-8 weeks (fig 1). The remaining four patients developed the fracture after initial surgery, due to loss of vertical height of the mandible. These patients were instructed a soft diet. Four patients healed with a closed mucosa. Three patients had a pseudarthrosis, two with closed mucosa and one with a small mucosal dehiscence, but free of pain. No further treatment was installed.

Two of the three patients with a pseudarthrosis had intravenous use of bisphosphonates with a mean of 18 months and one patient had oral use of bisphosphonates of 24 months duration.

Edentulous

8 patients were edentulous and 5 patients were surgically treated. four presented with a fracture and 1 developed a fracture after surgery. Two patients were treated with osteosynthesis (one

Table III: Treatment results

Patient	Indication	Duration	Dentate	Treatment	IMF	Healing bone	Closed mucosa	Co-med
1	OP	24	+	seq+ab	-	+	+	+
2	OP	24	+	seq+ab	-	pseud	-	+
3	OP	59	+	seq+ab	+	+	+	+
4	OP	120	+	seq+ab	-	+	+	-
5	Canc	30	+	seq+ab	+	pseud	-	-
6	Canc	6	+	seq+ab	+	pseud	+	-
7	OP	40	+	seq+ab	-	+	+	+
8	Canc	24	-	seq+ab	-	pseud	+	-
9	OP	84	-	seq+ab	-	pseud	+	-
10	OP	36	-	seq+ab	champy	pseud	-	-
11	Canc	12	-	seq+ab	reconstr	pseud	+	-
12	OP	120	-	seq+ab	-	+	+	+
13	OP	120	-	ab	-	+	+	-
14	OP	120	-	ab	-	+	+	+
15	OP	46	-	-	-	+	+	-

OP= osteoporosis with oral use of bisphosphonates
Canc=cancer with monthly treatment with intravenous bisphosphonates or subcutaneous xgeva (denosumab)
Duration in months
IMF: intermaxillary fixation
Pseud= pseudarthrosis
Ab= antibiotics
Seq= sequestrectomy under general anaesthesia
Co-med= co-medication such as immunosuppressants, steroids or cytostatics
Champy= one patient was treated with champy miniplates
Reconstr= one patient was treated with a reconstruction plate

2.0 4 hole champy plate and one reconstruction plate). All patients were instructed a soft diet post-operatively for several weeks.

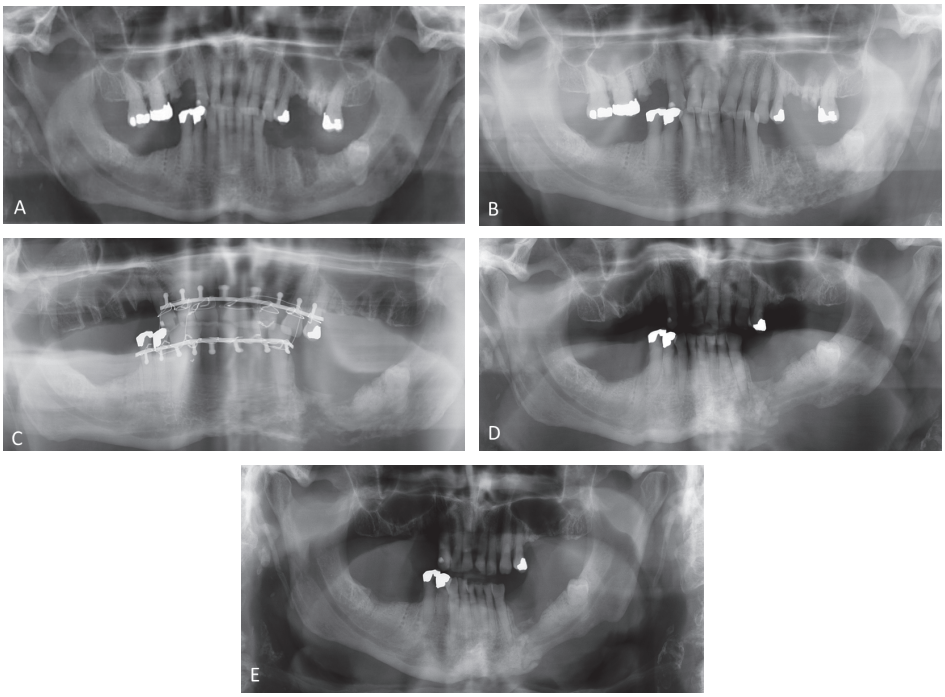
Two of the four patients with a pseudarthrosis had an oral use of bisphosphonates with a mean of 60 months, one patient had intravenous use of bisphosphonates of 12 months and the last patient had xgeva use of 24 months.

Of the 15 patients, 11 patients (73%) showed complete healing or a pseudarthrosis of the fracture and were free of complaints. 4 patients had a remaining dehiscence or fistula, but without discharge and pain.

Ten patients had an uneventful follow-up. The panoramic radiographs taken during follow-up showed healing of the bone (fig 1), without further progression of the disease. 1 received a soft diet only, 2 antibiotics only and 7 underwent a sequestrectomy.

Five patients had a sequestrectomy with persistent complaints. One healed after a second surgery. Another showed an persistent fistula without further complaints.

Figure 1: Illustrations



A: Panoramic radiograph after removal 36 at start of complaints: except empty alveolus no signs of lysis
B: severe lysis visible after a few months. Lysis beyond mandible canal and into inferior border of mandible
C: after surgery with IMF: wisdom tooth not involved in necrosis and left in place to not further compromise healing and cause possible fracture
D: Fracture and healing visible after 6 months
E: after 24 months evident healing, with no palpable mobility

Three had three surgical interventions. These patients remained with a small dehiscence, but died of their primary disease within six months after their last intervention.

DISCUSSION

In this study fifteen patients with stage III MRONJ and a pathologic fracture of the mandible were treated without extensive surgery. Patients were treated with a limited sequestrectomy in combination with intravenous antibiotics or with antibiotics and a soft diet.

In total 11 patients (73%) showed complete healing or a pseudarthrosis of the fracture and were free of pain. Four patients had a remaining dehiscence, but with no pus discharge and no further complaints.

Our results show that with a relatively simple surgical approach healing and functional improvement can be achieved. In the medically compromised patients the gain of this relative less aggressive surgical treatment is high compared to the mutilating and very invasive resection and reconstruction procedure. Removal of sequesters, assessment of vital bone margins and primary closure is essential in the treatment.

Applied intermaxillary fixation with arch bars demonstrates good results in dentate patients. A good healing of the bone was seen in half of the patients, the other half remained with a pseudarthrosis but with an acceptable function.

In edentulous patients, especially with atrophied mandibles, curation was more difficult to reach. In the patients with post-operative fractures after surgery a soft diet was sufficient. Two patients with a preoperative fracture were treated first with one 2.0 4-hole champy plate. The usual treatment with 2 champy plates was not possible due to loss of vertical height of the mandible leaving room for only one plate.

Not unexpectedly these patients developed a dehiscence on top of the plate, due to a compromised healing as a consequence of the extensive inflammation in the soft tissues and the bone and infection of the plate. Surprisingly these dehiscences were a few millimetres and sometimes only a fistula to the plate. Subsequently the plate was removed. A pseudarthrosis was achieved in these patients. These patients were free of pain complaints and one was able to function with an overdenture.

Some patients had no denture, but were satisfied with the ability to have a liquid or soft diet without having pain or any other complaints.

Three patients presented with a fracture, but very few clinical symptoms and the CBCT scan showed sequestra, but also signs of healing of the fracture. In these cases the patients had already started with antibiotics elsewhere and we decided to continue this treatment unless the symptoms would deteriorate. In that case a surgery would be planned. But improvement was seen in these patients and no further surgery was necessary. Subsequently these patients healed and developed a pseudarthrosis. This conservative treatment is not the first choice of

treatment, because not surgically removing necrotic bone often leads to deterioration of the disease. However it was estimated that the progression of the healing process at first presentation could be awaited.

For the indication of the anti-resorptive medication or the duration of this medication no relation was found with the outcomes. Cancer patients may seem to have a lesser surgical outcome –pseudarthrosis- than the osteoporosis patients, but the number of patients is limited. Besides this, there is a functional and complaint free situation in an often medically compromised patient.

In addition although long term anti-resorptive medication is associated with more morbidity and therapy resistant disease, the four healed edentulous patients had a very long mean use of oral bisphosphonates of 101,5 months. This may suggest that the duration is less of influence than expected. In this limited number of patients it is difficult to draw conclusions. Therefor in our study no association could be found between indication and duration of anti-resorptive therapy and the outcome.

Patients with co-medication seemed not to have a lesser outcome than the ones without. Statistical analysis was not performed in this limited group of patients.

Pathologic fractures in stage III MRONJ of the mandible can be difficult to treat. In the literature there is no consensus on treatment of these patients. So far conservative treatment with mouth rinses and/or antibiotics have been proven ineffective. The majority of authors including the AAOMS promote resection of the jaw with reconstruction with free vascularized osseocutaneous flaps[2,6-11,13-18]. These surgeries may lead to serious comorbidities in an already medically compromised population, next to the fact that in the oncologic patient the donor site should be free of bone metastases. The arguments against these major surgical procedures are clear[9].

Reasons not to perform regular sequestrectomy are the fear to damage the bone causing or increasing the necrosis. Or the possibility that due to the bisphosphonates there will be problems with the union of the bony margins[8,12,19,23].

The use of reconstruction plates is also mentioned in literature[24,25]. An extra-orally approach leading to more (surgical) risks for the already medically compromised patient, potential contamination of the intra-oral defect and the need for removal often due to infection of the plate can make the use of these plates less favourable.

To our knowledge there are no other reports on the treatment of stage III MRONJ with pathological fractures.

Given the fact that the treatment of pathologic fractures with MRONJ is still challenging, this treatment shows promising results. In medically compromised patients these less invasive but thorough early surgical interventions should be considered as alternative to major surgeries with resection and reconstruction.

CONCLUSION

This study shows that a relatively simple (surgical and/or antimicrobial) approach combined with intermaxillary fixation in individual cases can lead to consolidation and/or a pseudarthrosis with a remaining and acceptable function of the jaw in 11 from the 15 patients (73%).

The results show that performing aggressive surgery like the use of reconstruction plates or a resection of the jaw with the additional morbidity in a medical compromised population is not always necessary. Further research is mandatory.

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