

Medication-related osteonecrosis of the jaws (MRONJ) and quality of life evaluation: a pilot study

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Abstract

Background. MRONJ (medication related osteonecrosis of the jaws) is a well-known side effect of certain drugs, which are used to influence bone metabolism for the cure of osteo-metabolic or cancer diseases.

The aim of this study is to assess the quality of life (QOL) under a physical and mental point of view in patients affected by MRONJ compared with the general population.

Methods. The study has been accomplished through the administration of the SF-12 questionnaire: 30 patients of the MRONJ group were evaluated.

Results. Significant differences based on the level of education and age of the subjects, on the location and finally on the stage of necrosis of the jaw have been identified.

In this pilot study the test sample shows how MRONJ can aggravate the conditions of patients, above all under a physical point of view.

Conclusions. Prevention of MRONJ and its symptoms as dysphagia, oral pain, immunological compromise and the need of frequent antibiotic therapies is a crucial part of modern oral pathology and dentistry, above all for oncologic patients who already have a general decrease of physical and mental activities, leading to a poor quality of life. *Clin Ter 2017; 168(4):e2523-257. doi: 10.7417/CT.2017.2015*

Key words: Bisphosphonates, osteonecrosis, quality of life

Introduction

From 2003 (1) to nowadays, the "osteonecrosis of the jaws" (ONJ) has been identified as a main side effect of antiresorptive therapies (bisphosphonates and denosumab) and antiangiogenic drugs (2, 3), used for the treatment of osteometabolic diseases or cancer bone metastases and for the prevention of their skeletal related events. In the beginning this particular necrosis was only associated with bisphosphonates exposure (so its definition was "BRONJ" (1)); since other medications (anti-RANKL/anti-resorptive and

antiangiogenic drugs) has been associated with the risk of developing ONJ, the definition changed in "MRONJ" (4).

MRONJ (medication related osteonecrosis of the jaws) can be clinically described as an exposed or probing non-healing bone lesion in the maxillofacial region that persists for more than 8 weeks, without history of radiation therapy to the jaws in patients exposed or currently under antiresorptive (bisphosphonates and/or denosumab) and/or antiangiogenic treatment (4).

Redness and mucosal swellings, purulent exudate sometimes with fistula formation can determine a further decrease of quality of life in these patients. Often the patients complain of bad taste and feeding difficulties, pain and discomfort in the mouth (1). MRONJ condition may progress to severe forms with involvement of the lower margin and fracture of the mandible, severe maxillary sinusitis, oroantral fistula, orbital abscess, extra-oral fistula, intractable pain and inability to eat, especially when it affects debilitated patients (1).

In 2012 a review of 671 publications reported a wide-ranging ONJ incidence from 0 to 27.5%, concerning patients exposed to intravenous N-BP (5), with a mean incidence of 7%.

A recent meta-analysis reports the mean incidence of ONJ associated with denosumab to be 1.7% (6-9). The studies in this meta-analysis reported similar incidence of N-BP-associated ONJ, which is definitely lower than previously reported: we can justify this changing starting from the adoption of risk-reduction dental strategies, but we cannot undervalue also the differences in study design.

The aim of the study is to define the quality of life (QOL) values of the patients affected by MRONJ of the "CROMa" (Coordination of Research on Osteonecrosis of the Jaws) project of "Sapienza" University of Rome by the use of SF-12 questionnaire and to compare those values with general population.

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Materials and methods

Population and Setting

The questionnaire, explained in the following section, was administered to patients recruited in the “CROMa” (Coordination of Research on Osteonecrosis of the Jaws) project of the Department of Oral and Maxillofacial Sciences of “Sapienza” University of Rome.

Participation in the study was voluntary.

The “CROMa” project

At Department of Oral and Maxillofacial Sciences of “Sapienza” University of Rome, in January 2007 a task-force of clinicians and researchers set up a Coordination of Research on Osteonecrosis of the Jaws (CROMa): a multidisciplinary expert group with thorough knowledge of basic and clinical bone biology as well as expertise and daily practice in the fields of preventive dentistry, oral pathology, operative dentistry, oral and maxillofacial surgery. The aim of CROMa is to prevent or treat established MRONJ and to give relevant informations and advices both to patients and to specialists prescribing therapies considered at risk of MRONJ. The task force joins several expertises (dentists, oral and maxillofacial surgeons, oral pathologists, oncologists and an expert in statistics) in order to provide a comprehensive patient-centered oral care delivery (10).

Questionnaire

The QOL of the MRONJ patients was evaluated with the SF-12 questionnaire: 12 questions about physical (PCS) and mental (MCS) status

A low PCS value indicates severe physical dysfunction and severe pain, fatigue, and negative assessment of the general health status; a low MCS value indicates frequent psychological distress and serious social-emotional problems.

The standard questionnaire has been integrated with questions regarding gender, age, present occupation, marital status and education level.

Data analysis

Frequency distributions were calculated and histograms of PCS and MCS levels were plotted. Moreover, differences between groups were tested using chi-square test for qualitative variables and Mann-Whitney and Kruskal Wallis tests for quantitative variables. Finally, a multiple linear regression analysis was conducted using PCS (Fig.1) and MCS (Fig.2) values as dependent variables. The multivariate models were performed using a stepwise approach (backward elimination procedure). The results are presented as beta values and p-values. The statistical significance was set at $p < 0.05$. The statistical analysis was carried out using SPSS for Windows, release 22.0 (Table 1).

Table 1. Sample characteristics

Variable	Frequency (%)
<i>Gender</i>	
Male	9 (30%)
Female	21 (70%)
<i>Educational Level</i>	
Low	21 (70%)
High	9 (30%)
<i>Marital Status</i>	
Married	18 (60%)
Others	12 (40%)
<i>Age</i>	
Over 60	25 (83%)
60 or less	5 (17%)
<i>Localization</i>	
Mandible	22 (73%)
Maxilla or Mandible&Maxilla	8 (27%)
<i>Bone Pathology</i>	
Osteo-Metabolic	12 (40%)
Cancer	18 (60%)
<i>Medication Administration</i>	
I.V.	16 (53,3%)
Oral	11 (36,7%)
I.M./S.C.	2 (6,7%)
Association	1 (3,3%)
<i>Medication Timing</i>	
Current	4 (13,3%)
Past	26 (86,7%)
<i>Active Principle</i>	
Zoledronic acid	16 (53,3%)
Risedronate	2 (6,7%)
Alendronate	7 (23,3%)
Denosumab	2 (6,7%)
Ibandronate	3 (10%)
<i>Duration of Therapy</i>	
< 3 years	8 (26,7%)
3+ years	8 (26,7%)
I.V. < 8 infusions	1 (3,3%)
I.V. 8+ infusions	13 (43,3%)
<i>Systemic Risk Factors</i>	
No	8 (26,7%)
1 or more	22 (73,3 %)
<i>Local Risk Factors</i>	
No	15 (50%)
1 or more	15 (50%)
<i>MRONJ stage</i>	
Stage 1	12 (40%)
Stage 2	13 (43,3%)
Stage 3	5 (16,7%)

Results

30 patients, 21 women and 9 men, aged between 44 and 87 years, were involved in this study; 12 of them have been exposed to medicaments at risk of MRONJ for osteometabolic diseases and 18 for cancer bone metastasis.

Our MRONJ patients reported relevant differences in PCS and MCS (Table 2). Significant differences for PCS have been found through the data analysis based on the level of education (primary / secondary / high / degree) and age of the subjects (41-50yy / 51-60yy / over 60), on

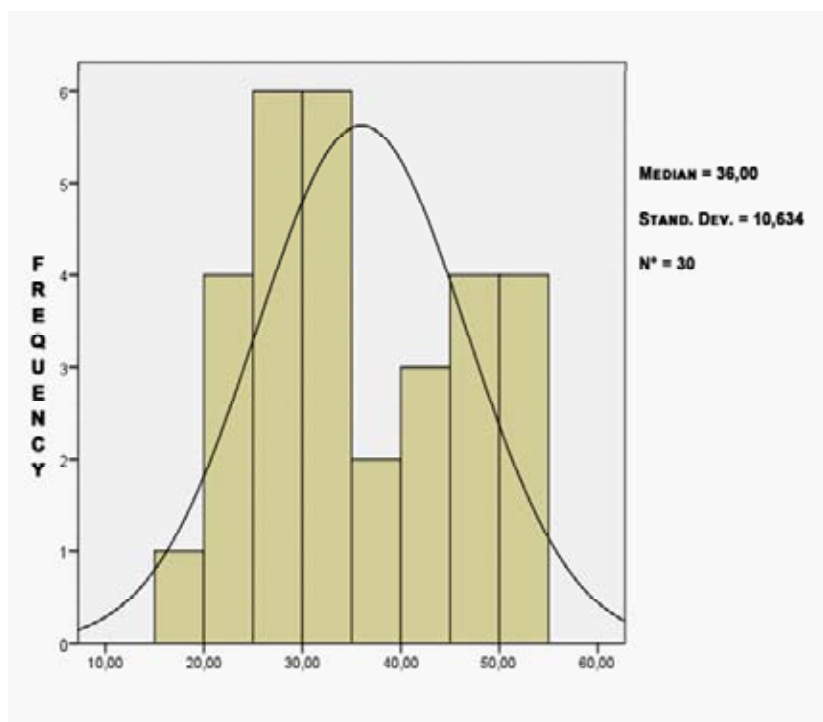


Fig. 1. PCS histogram (physical score values)

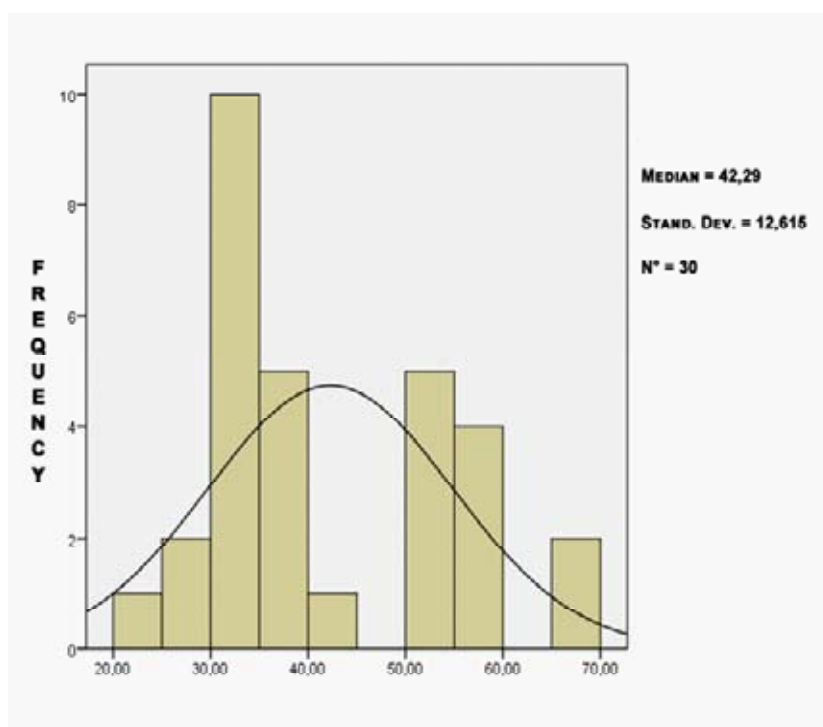


Fig. 2. MCS histogram (mental score values)

the location (mandible / maxilla / both) and on the stage of MRONJ (stage 1 / 2 / 3).

On the other hand, no statistically significant values in this study have been identified for gender (male/female), marital status (married / single / divorced / widow-widower), type of bone pathology (osteo-metabolic / cancer bone metastasis), route of administration (intravenous / oral / intramuscular-subcutaneous / association), therapy timing (current / past), active principle (zoledronic acid / risedronate

/ alendronate / denosumab / ibandronate), therapy duration, presence of systemic or local risk factors. The results of the multivariate analysis revealed that PCS values were influenced directly by the educational level ($\beta = 9.556$; $p = 0.007$) and mandibular localization ($\beta = 8.688$; $p = 0.016$) and indirectly by the MRONJ stage ($\beta = - 5.588$; $p = 0.013$). No variables were significantly associated to MCS at the multivariate analysis.

Table 2. Data analysis of PCS and MCS

Variable	PCS – median (min-max)	MCS – median (min-max)
MRONJ population	33,8623 (18,21 - 54,74)	35,8662 (24,88 – 66,65)
<i>Educational Level</i>		
Low	33,1 (18,2 – 54,7)	35,5 (30,8 – 66,6)
High	48,7 (29,8 – 54,2) *	40,4 (24,9 – 59,6)
<i>Marital Status</i>		
Married	29,6 (18,2 – 54,7)	37,7 (24,9 – 66,6)
Others	35,8 (22,6 – 52,1)	35,9 (25 – 59,6)
<i>Age</i>		
Over 60	27,8 (18,2 – 54,7) *	51,9 (35,5 – 54,7)
60 or less	34,6 (22,9 – 54,2)	34,9 (24,9 – 66,6)
<i>Localization</i>		
Mandible	36,6 (18,2 – 54,7) *	37,9 (24,9 – 66,6)
Maxilla or Mandible&Maxilla	27 (22,6 – 48,7)	35,2 (25 – 66,6)
<i>Bone Pathology</i>		
Osteo-Metabolic	31,5 (22,9 – 54,2)	37,9 (30,8 – 66,6)
Cancer	35,4 (18,2 – 54,7)	35,3 (24,9 – 59,6)
<i>Medication Administration</i>		
I.V.	36,6 (18,21 – 54,7)	35,3 (24,9 – 59,6)
Oral	29,8 (22,9 – 54,2)	39,8 (33,9 – 66,6)
I.M./S.C.	37 (32,9 – 41,1)	44,9 (30,8 – 59)
Association	29,9 (29,9 – 29,9)	36 (36 – 36)
<i>Medication Timing</i>		
Current	27,9 (22,6 – 47,3)	52,4 (34,9 – 59)
Past	34,6 (18,2 – 54,7)	35,6 (24,9 – 66,6)
<i>Active Principle</i>		
Zoledronic acid	36,6 (18,2 – 54,7)	35,3 (24,9 – 59,6)
Risedronate	42 (29,8 – 54,2)	47,9 (39,8 – 56)
Alendronate	27,8 (22,9 – 40,4)	35,5 (33,9 – 66,6)
Denosumab	37 (32,9 – 41,1)	44,9 (30,8 – 59)
Ibandronate	29,9 (22,9 – 47,4)	36 (34,9 – 52,1)
<i>Duration of Therapy</i>		
< 3 years	36,8 (22,9 – 54,7)	45,9 (25 – 66,6)
3+ years	29,9 (22,9 – 47,4)	35,4 (30,8 – 66,6)
I.V. < 8 infusions	36,1 (36,1 – 36,1)	40,4 (40,4 – 40,4)
I.V. 8+ infusions	34,7 (18,2 – 52,1)	34,8 (24,9 – 59,6)
<i>Systemic Risk Factors</i>		
No	33,1 (22,9 – 48,7)	35,2 (25 – 66,6)
1 or more	34,6 (18,2 – 54,7)	37,9 (24,9 – 59,6)
<i>Local Risk Factors</i>		
No	33,1 (18,2 – 54,7)	35,7 (24,9 – 66,6)
1 or more	34,6 (22,9 – 54,2)	36 (25 – 66,6)
<i>MRONJ stage</i>		
Stage 1	44,2 (22,9 – 54,7) *	35,8 (25 – 59)
Stage 2	33,1 (18,2 – 52,1)	34,9 (24,9 – 66,6)
Stage 3	29,8 (22,6 – 36,1)	39,7 (34,9 – 52,8)

* = P < 0.05;

Discussion

Medication related osteonecrosis of the jaw (MRONJ) is a debilitating condition often connected with pain which can affect the quality of life of cancer patients (11)

Prevention of MRONJ and its symptoms as dysphagia, oral pain, immunological compromise and the need of frequent antibiotic therapies is a crucial part of modern oral pathology and dentistry, above all for oncologic patients who already have a general decrease of physical and mental activities, leading to a poor quality of life.

Spreading the mindset of prevention in the whole health specialists community and intercepting early stages of MRONJ can avoid side effects and improve the conditions of our patients (12).

This study shows that MRONJ can be a further cause of QOL decrease in debilitated patients, mainly under a physical point of view. As expected, compared to general population values, the MRONJ patients present significantly lower values of PCS (33.86 vs 54.31 of the Italian general population) and MCS (35.87 vs 52.77 of the general population) (13).

In this sample, the variables that are associated with a different value of PCS are both socio-demographic (educational level and age) and clinical (mandibular localization and MRONJ stage).

Though it is a pilot study, the test sample shows how MRONJ can aggravate the health conditions of patients, above all in relation to concomitant diseases. Further studies with larger numbers of patients are needed to define more clearly and specifically the effect of cure and prevention of MRONJ in QOL improvement.

As other studies confirm, MRONJ often require combined therapeutic approaches to avoid local and systemic complications. Antibiotics, conservative debridement, low-level laser therapy (LLL), and photodynamic therapy (PDT) can be some of the main choices, also because the healing of MRONJ may be very slow (14).

There is no consensus yet about the clinical management of MRONJ. Successful treatment can be identified in a cure, with complete mucosal coverage and elimination of the disease, or in that which improves the quality of life without a cure (palliation) (15).

Our study has some limitations that need to be acknowledged. First of all the small sample size is not useful for arising general conclusions. Moreover, a control group composed by osteo-metabolic or cancer patients on BPs or Denosumab, but without MRONJ, could be the proper control group, but at the moment we only conducted a pilot study.

Author Contribution

All Authors equally contributed to this work

Competing financial interests statement

Authors declare no conflict of interest or financial support

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