CORRELATIONS BETWEEN BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW

PhD THESIS ABSTRACT

Scientific Coordinator
Prof. Univ. Dr. POPESCU Eugenia

PhD Student
CIOFU Mihai Liviu

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Key words: osteonecrosis, bisphosphonates, Cone Beam CT, PRP, Oral Health Impact Profile, treatment strategies

This PhD thesis contains 103 figures and 73 tables. The research included 312 references.

The abstract of the thesis contains a limited number of tables and figures. The summary and the number of figures and tables are the same with the ones from the thesis.
6. MOTIVATIONS AND OBJECTIVES OF THE STUDY

Osteonecrosis of the jaws related to medication is a serious adverse event that occurs mostly among patients receiving antiresorptive and antiangiogenic treatment administered intravenously for the treatment of bone metastases from various forms of cancer, and also for other diseases that cause bone fragility.

There are two theories about the pathophysiological mechanism of MRONJ. The first theory, *inside-out*, refers to the emergence of bone necrosis as a result of the inhibitory effect of bisphosphonates on osteoclasts. The second theory, *outside-in*, suggests that destruction of the mucosal barrier leads to local infections, and subsequently to bone necrosis (Fliefel R et al, 2015).


The strict limitations of Retroalveolar X-ray and Orthopantomography in the diagnosis of MRONJ have imposed the use of CBCT, which, by using low doses of radiation provides a good analysis of the bone structure.

At present there is no standard protocol for the treatment of osteonecrosis. AAOMS and Marx RE (2011) stand for the symptomatic and conservative treatment, namely for delaying the surgery treatment as much as possible. On the other hand, Van den Wyngaert (2009) and Scoletta (2010) concluded that non-invasive treatment leads to healing in 50% of the cases. Carlson, Basile (2009) or Otto et al (2010) argue that surgery approach is the only curative treatment.

The use of growth factors is considered a therapeutic option as well because it gets a light acceleration in the tissular healing process, by stimulating the angiogenesis and migration of stem cells, which are specifically differentiated (Badro et al, 2006). Good results have also been obtained from the use of laser therapy, teriparatide or fluorescence-guided bone resection.

The key factors for achieving a therapeutic success have not been identified yet. There are many authors who acknowledge and explain differently the significance of therapeutic success. Ruggiero and Drew argue that it is essential to maintain an optimal level of the patient’s quality of life, by controlling pain and infection. Vescovi et al (2012) stated that one can talk about therapeutic success if only the MRONJ transition goes from a late stage to a lower one. Getting mucosal healing is the main purpose of the treatment, having the role to prevent secondary infection. The treatment success is achieved when mucosal integrity is maintained and the radiological signs of local healing remain the same one year after the surgical intervention (Fliefel R et al, 2015).

Osteonecrosis management is still a controversial subject. It seems that conservative and minimally invasive treatment is useful in early stages and the radical surgery in advanced stages. For treatment-refractory osteonecrosis, it is recommended the surgical approach combined with adjuvant therapy (growth factors, ozone therapy, photodynamic therapy), but these methods are not sufficiently scientifically documented.

The PhD-study objectives are as follows:
- ascertaining the epidemiological peculiarities of the bisphosphonate-related osteonecrosis of the jaws;
- importance of CBCT in the diagnosis and planning of surgery intervention based on the clinical stage;
- clinical and therapeutic features of osteonecrosis at the level of maxilla and mandible;
- assessment of adjunctive therapy outcomes, represented by PRP in the surgical treatment of osteonecrosis of the jaws;
- highlighting the impact on the quality of life of the patients suffering from osteonecrosis of the jaws induced by the antiresorptive and antiangiogenic treatment.

7. CLINICO-EPIDEMILOGICAL STUDY OF THE OSTEO NECROSIS OF THE JAWS (ONJ) RELATED TO ANTIRESORPTIVE AND ANTIANGIOGENIC THERAPY

7.1 THE PURPOSE OF THE STUDY

The purpose of the study is to ascertain the epidemiological peculiarities of the antiresorptive-related osteonecrosis of the jaws for the population living in Moldova area and to research the prevalence of bone metastases and/or osteoporosis among patients.

7.2 MATERIAL AND METHOD

The Retrospective Cohort Study (also called a historic cohort study) is performed for a group of 62 patients hospitalized in the Clinic of Oral and Maxillo-Facial Surgery, at the Hospital “St. Spiridon” Iași, starting from January 2009 to June 2015.

*The Inclusion Criterion* for participation in the study is as follows:
- diagnosis certainty proved by clinical and laboratory parameters (imaging, bacteriological and anatomo-pathological investigations).

*The Exclusion Criterion* for participation in the study is as follows:
- patients under bisphosphonate therapy who did not develop osteonecrosis of the jaw, either spontaneously or following oral surgical maneuvers.

7.3 OUTCOMES

*Gender distribution* emphasizes higher percentage of female patients (67.7%), the sex ratio being of 2/1.

In terms of the studied cases, the structure of the lot based on the epidemiological characteristics (Table 7.III) has the following features: predominance of MRONJ disease in women - 67.7%; higher frequency of cases after age 60 (72.6%); predominantly in patients coming from urban areas (58.1%).

Depending on the overall condition, the most common disease is breast cancer - 22 cases (35.5%), then the prostate cancer - 13 cases (21%), and one case of bone metastases, with undefined starting point (Fig. 7.7).

The descriptive analysis based on the epidemiological characteristics and per types of locations of the osteonecrosis has revealed the following:
- out of these 20 patients with osteonecrosis located on mandible: 75% are women, 80% are aged 60 years, and 55% are from rural areas;
- referring to the patients with osteonecrosis located on maxilla, namely a number of 35 persons: 65% of them are female, 71.4% are aged over 60, and 65.7% of them have urban origin;
- with reference to the patients with osteonecrosis located both on maxilla and mandible, namely a number of 7 persons: female patients are prevailing (57.1%), they are aged over 60 (57.1%), and they have urban origin (57.1%).
Table 7.III: Profile of MRONJ Patient

<table>
<thead>
<tr>
<th>Lot Features</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>67.7</td>
</tr>
<tr>
<td>Aged over 60</td>
<td>72.6</td>
</tr>
<tr>
<td>Urban Origin</td>
<td>58.1</td>
</tr>
</tbody>
</table>

The share of the cases with stage II osteonecrosis is 65.6%. Out of these patients, 70% have the lesion located on mandible, while for 61.9% of the patients with stage III osteonecrosis the lesion is located on maxilla (chi-square = 12.63, df = 2, p = 0.002) (Table 7.VI).

Thus, in terms of the epidemiological characteristics, the patients with stage II osteonecrosis have been predominantly female (65%), being aged over 60 (67.5%) and having urban origin (55%), facts that are slightly higher for the patients with stage III osteonecrosis: 71.4% female, 81% aged over 60, 61.9% urban origin (p>0.05).

The onset of the disease is post-extraction in 77.4% of the patients.

All the patients in the study have been treated with bisphosphonates. The vast majority have received treatment with acidum zoledronicum (72.6%). With a frequency of 11.3%, it has also been administrated acidum alendronicum and ibandronicum in 9.7% of the cases. Combinations with other bisphosphonates are rarely used.

Table 7.VI: Structure of the lot depending on location and staging of osteonecrosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Stage II (n=40)</th>
<th>Stage III (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Maxilla</td>
<td>7</td>
<td>17.5%</td>
</tr>
<tr>
<td>Mandible</td>
<td>28</td>
<td>70.0%</td>
</tr>
<tr>
<td>Both</td>
<td>5</td>
<td>12.5%</td>
</tr>
</tbody>
</table>
The therapy with acidum zoledronicum has been used in average for over a period of 2.6 years while the therapies with acidum alendronicum and acidum ibandronicum have been administered for more than 3 - 4 years (3.50 and 4.67 years, respectively) with variations of 1 to 9 years.

7.4 DISCUSSIONS

Medication-related osteonecrosis of the jaws is a relatively new clinical entity, being considered a serious adverse event occurred after antiresorptive and/or antiangiogenic therapy (Ruggiero SL et al, 2014).

The outcomes support the findings of the literature that emphasize the predisposition of mandibular bone to being more frequently affected than the maxilla (Bamias et al, 2011 Ruggiero SL et al, 2004). In the study group it is revealed that the frequency of mandible MRONJ (56.5%) is higher than maxilla MRONJ, and most patients came to a medical examination in stage II (65.6%), and with postextractional onset in 70% of cases. In 61.9% of stage III patients, the location of the disease is in the maxilla.

Occurrence of osteonecrosis is closely related to dose, duration and type of bisphosphonate therapy. All the patients included in the study group have been treated with bisphosphonates. Most of them have received intravenous therapy with zoledronic acidum (72.6%). With a frequency of 11.3%, it has also been administrated acidum alendronicum and ibandronicum in 9.7% of the cases.

Intravenous antiresorptive therapy is most often involved in osteonecrosis (Hinchy NV et al, 2013 Marx RE et al, 2007, Bamias et al, 2006). The patients in our study group received intravenous antiresorptive therapy in 80.64% of the cases, the result being similar to the one obtained by Fliefel et al (Fliefel R et al, 2015). The risk of osteonecrosis occurrence increases at a rate commensurate with the duration of zoledronic acid therapy; the effect is cumulative from one therapeutic session to another, starting from 6.7% after 20 sessions of treatment to 31.7% after 30 sessions (Calvo-Villas JM et al, 2006).

It is also worth noting that patients taking oral antiresorptive therapy have a higher risk of developing osteonecrosis, especially if the duration of therapy is more than 4 years (Ruggiero SL et al, 2014).

7.5 CONCLUSIONS

- MRONJ epidemiology is closely related to the epidemiology of underlying diseases.
- The number of patients diagnosed with MRONJ receiving intravenous antiresorptive therapy is higher than of those who undergo treatment per os.
- Zoledronic acid is the most used antiresorptive.
- The vast majority of patients have lesions classified in stages 2 and 3 of disease, stage 2 being most frequent.
- The location is predominantly the mandible, the most frequent onset is postextractionally, and the most affected are females. When the location is in the maxilla, the most frequent is stage 3 of the disease.
- Spontaneous onset is correlated with a longer duration of antiresorptive therapy.
8. THE ROLE OF CBCT (CONE BEAM COMPUTED TOMOGRAPHY) IN THE DIAGNOSIS AND TREATMENT OF THE OSTEONECROSIS OF THE JAWS (ONJ) RELATED TO ANTIRESORPTIVE AND ANTIANGIOGENIC THERAPY

8.1 INTRODUCTION

Introducing the imaging of cone beam computed tomography (CBCT) in the field of oral and maxillofacial surgery has opened new horizons for the use of three-dimensional imaging (3D) as one of the most relevant method of diagnosis and surgical treatment planning. Using retroalveolar or panoramic radiographs as the single method of investigation in cases of complex treatments involving careful examination is now nothing more than history.

8.2 THE PURPOSE OF THE STUDY

The purpose of the study is to highlight the CBCT's role, as current state-of-the-art radiological exploration in the diagnosis and treatment of bisphosphonate-related osteonecrosis of the jaws but also to correlate certain imaging aspects with the stage of the disease.

8.3 MATERIAL AND METHOD

Selection of patients

There are studied a total of 30 patients diagnosed with bisphosphonates-related osteonecrosis of the jaws, hospitalized in the Clinic of Oral and Maxillo-Facial Surgery, at the Hospital “St. Spiridon” Iași, between January 2009 and June 2015.

CBCT examination

It is used the CBCT equipment PlanmecaPromax 3D Mid (Planmeca OY, Helsinki, Finland). Scanning is performed by selecting a FOV of 40x40 mm and the following exposure parameters: 90 kV, 12 mA, 13.8 seconds, 0.4 x 0.4 x 0.4 mm voxel size.

8.4 OUTCOMES

There are 30 patients participating in the study, with a mean age of 63.40 years (standard deviation s = 8.45). Differentiated based on the gender variable, the study group comprises 12 male and 18 female subjects, aged between 46 and 78 years. Most of the patients have a history of treatment with zoledronate injection. After applying the crosstabs technique of SPSS and following the calculation of $\chi^2$ test it is found that there are significant statistical differences at the threshold of $p \leq 0.05$ regarding the bisphosphonate variable based on the gender variable [$\chi^2 (2) = 13.333, p = 0.001 <0.05$] (Table 8.I).

The onset of the disease is mainly postextractional (Table 8.II), and based on the staging of osteonecrosis according to AAOMS recommendations, the study group comprises only 4 cases in stage 1, 13 cases in stage 2 and 13 cases in stage 3. The most common clinical aspect is represented by the presence of denuded bone in 17 cases, intraoral fistula in 5 cases and oroantral fistula in 8 cases.

The general therapy consists of antibiotics with penicillin and/or clindamycin derivatives. The surgical treatment has been performed depending on the stage of the disease
Correlations Between Bisphosphonates Treatment And Osteonecrosis Of The Jaws

and it implies debridement, sequestrectomy, partial bone resection (marginal alveolar), mandibular segmental bone resection, radical excision of the sinus, resection of infra or mesostructure of the jaws.

Table 8.I: Frequencies and Percentages for Cross Tabulation of Gender and Bisphosphonates variables

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>SEX</th>
<th>Count</th>
<th>Expected Count</th>
<th>% within SEX</th>
<th>Adjusted Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>zoledronate</td>
<td>masculin</td>
<td>12</td>
<td>7.2</td>
<td>100.0%</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>feminin</td>
<td>6</td>
<td>10.8</td>
<td>100.0%</td>
<td>-3.7</td>
</tr>
<tr>
<td>ibandronate</td>
<td>masculin</td>
<td>0</td>
<td>2.8</td>
<td>0.0%</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>feminin</td>
<td>7</td>
<td>4.2</td>
<td>100.0%</td>
<td>2.5</td>
</tr>
<tr>
<td>alendronate</td>
<td>masculin</td>
<td>0</td>
<td>2.0</td>
<td>0.0%</td>
<td>-2.0</td>
</tr>
<tr>
<td></td>
<td>feminin</td>
<td>5</td>
<td>3.0</td>
<td>100.0%</td>
<td>2.0</td>
</tr>
<tr>
<td>Total</td>
<td>masculin</td>
<td>12</td>
<td>12</td>
<td>100.0%</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>feminin</td>
<td>18</td>
<td>18</td>
<td>100.0%</td>
<td>4.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>30</td>
<td>30</td>
<td>100.0%</td>
<td>5.6</td>
</tr>
</tbody>
</table>

After thoroughly analysing the frequency of radiological signs found in osteonecrosis, it has been ascertained the following:
- out of the total of thirty (30) patients investigated, twelve (12) of them have showed osteosclerosis in the CBCT examination, predominantly located in the mandible;
- trabecular osteolysis is found in all the cases;
- eighteen (18) patients have cortical discontinuity;
- presence of bone seizure is noted in sixteen (16) patients;
- all those twelve (12) patients with osteonecrosis located in the maxilla bone reveal signs of sinusal inflammation, while eight (8) of them reveal the presence of oroantral fistula;
- ten (10) patients have periosteal reaction.

Table 8.IV: Frequency Ratio and Percentages for Cross Tabulation of MRONJ stage and periosteal reaction variables

<table>
<thead>
<tr>
<th>Reacție periostală</th>
<th>stadiul MRONJ</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
<td>2.00</td>
</tr>
<tr>
<td>nu</td>
<td>Count</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Expected Count</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>% within stadiul MRONJ</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Adjusted Residual</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Expected Count</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>% within stadiul MRONJ</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

After applying crosstabs technique in SPSS and calculating $\chi^2$ test it is revealed that there are statistically significant differences at a threshold of $p \leq 0.05$ regarding the periosteal reaction variable contingent on MRONJ stage variable [$\chi^2 (2) = 19.615$, $p = 0.000 <0.05$]. It
thus appears that in the stages I or II no periosteal reaction exists, and in stage III there are significantly more patients with periosteal reaction.

**Case 1, stage 3**

Patient (L.A.) aged 75 years is hospitalized in the Clinic of Maxillofacial Surgery Iași having at the level of the right maxilla an edentulous space 13-17, on an area of 3 cm, white gray denuded bone, with atonic surrounding mucous membrane. She is diagnosed in the left breast with T4N2M1 breast cancer (bone and lung metastases) 18 months before coming to our ward.

The patient has attended six courses of chemotherapy (Taxotere and Doxorubicin), making intravenous perfusions with zoledronic acid prior to the time of presentation in the clinic. Four months before hospitalization she has noticed the presence of the bone exposed in the oral cavity, unilateral purulent rhinorrhea (right side) and feeling of tension in the right cheek, accentuated by bending the head. The surgical intervention has been delayed, making the following recommendations: long-term antibiotics (penicillin V), oral rinses with chlorhexidine and interruption with the approval oncologist of the bisphosphonate therapy.

**CBCT Result:**

The native examination analyzed in the axial, coronal and sagittal plane has highlighted as follows:

- an area of osteonecrosis in the edentulous space from the level of the right maxilla lateral region (from 13 to 17), with the presence of bone attachments, having dimensions of 12/8mm (CC/T) and 16/6,8mm (CC/T) respectively, which causes oral-sinus communication associated with right maxillary chronic sinusitis, with sclerosis of the sinusal edges and extension of inflammation in the mucosal lining of the right ethmoid cells, with the narrowing of the right sinusal ostia (Fig.8.1).
- discontinuity of the right nasal fossa roof and lateral wall, in relation with the bone sequestrum and associated bone resorption.

![Fig.8.1 CBCT Aspect – coronal reconstruction](image)

**8.5 DISCUSSIONS**

Frequently, osteonecrosis of the jaws related to antiresorptive and antiangiogenic medication is diagnosed in an advanced stage when clinical symptoms appear, represented by the exposure of a bony area in the oral cavity. This is due to the absence of clear criteria of clinical and radiological diagnosis. Some authors claim that occurrence of osteonecrosis can be detected in the early stages by analyzing bone mineral density that seems to be very often increased in the vicinity of the necrosis (Y Takaishi et al, 2010).
Computed tomography (spiral or cone-beam) is superior to conventional radiography because it provides a three-dimensional image. Thus, the following elements can be assessed: maxillary and mandibular cortical bone, presence of periosteal reaction or bone sequestrum, the ratio between the area of osteolysis and adjacent anatomical structures (Stockmann P et al, 2010, Bianchi SD et al, 2007).


In the study conducted by Wilde F et al, the cortical erosion and osteolysis of trabecular bone are described as being the most common signs seen in MRONJ upon the CBCT examination. Also, the osteosclerosis was distributed irregularly in all stages, with a downward trend of the frequency towards early stages (Wilde F et al, 2012).

Similar to this study, our outcomes indicate the trabecular bone lysis as being a predominant radiological sign appearing in the CBCT examination of all patients, osteosclerosis being more frequent in stage 2 and less frequent in stages 1 and 3. Note that, for the cases with the location of the disease on mandible, our study group has revealed significantly more patients with osteosclerosis.

8.6 CONCLUSIONS

CBCT examination provides more information regarding the extension of bone lesions from osteonecrosis than conventional radiographs, being useful both for diagnosis and surgical treatment planning.

It is a fast imaging technique with low costs and a low radiation dose compared with conventional CT, providing tridimensional images of a good clarity that enable the analysis of bony structure.

Due to the possibility of detecting osteonecrosis in subclinical stage, CBCT may be used as a disease expansion prevention method.

Osteonecrosis of the jaws related to antiresorptive medication presents a wide variety of imaging, starting from osteosclerosis, focal or diffuse osteolysis, cortical erosion and destruction, and ending with periosteal reaction. Among these signs, only the periosteal reaction has been associated with the advanced stages of the disease.

Further studies are needed to determine the specificity of certain imagistic aspects in different stages of the osteonecrosis.

Also, in the management protocol of osteonecrosis related to antiresorptive medication should be included radiological monitoring of the patient.

9. CLINICAL AND THERAPEUTIC FEATURES OF OSTEO NECROSIS

9.1 CLINICAL AND THERAPEUTIC FEATURES OF THE OSTEO NECROSIS OF THE MAXILLA BONE

9.1.1 INTRODUCTION

Although recent studies show an incidence of osteonecrosis related to resorptive medications at a ratio of 8-12% (Bamias et al, 2005), the frequency of the disease is uncertain (P Maurer et al, 2011) and the mandibular bone is affected more frequently than the maxillary bone (Bamias et al, 2011 Ruggiero SL et al, 2004).
Correlations Between Bisphosphonates Treatment And Osteonecrosis Of The Jaws

Antiresorptive-related osteonecrosis of the jaws is a disease with multifactorial etiology that responds differently to treatment, which only makes the therapeutic management process more difficult (P Maurer et al, 2011).

9.1.2 THE PURPOSE OF THE STUDY

The purpose of the study is to assess the immediate or late postoperative result of different surgical approaches that have been used in the treatment of osteonecrosis of the jaws.

9.1.3 MATERIAL AND METHOD

There are studied a total of 62 patients diagnosed with bisphosphonates-related osteonecrosis of the jaws, hospitalized between January 2009 and June 2015 in the Clinic of Oral and Maxillo-Facial Surgery, at the Hospital “St. Spiridon” Iași. Out of these, a number of 20 patients show maxillary MRONJ.

9.1.4 OUTCOMES

There are 20 patients participating in the study, with a mean age of 63.85 years (standard deviation s = 11.47), 75% of them being women.

The antiresorptive therapy has been administered for osteoporosis or various forms of neoplasia (Table 9.I). The most common disease is breast cancer with bone metastases (55.5%), and 80% of the patients have a history of chemotherapy while 10% of them have a history of corticosteroid therapy.

Table 9.I: Patients’ Basic Diseases

<table>
<thead>
<tr>
<th>neoplazia</th>
<th>cale de administrare</th>
<th>Crosstabulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>noneplazie</td>
<td>iv</td>
<td>po</td>
</tr>
<tr>
<td>Expected Count</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>% within cale de administrare</td>
<td>.0%</td>
<td>80.0%</td>
</tr>
<tr>
<td>Adjusted Residual</td>
<td>-3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>c. prostată cu MTS osoase</td>
<td>Count</td>
<td>4</td>
</tr>
<tr>
<td>Expected Count</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>% within cale de administrare</td>
<td>26.7%</td>
<td></td>
</tr>
<tr>
<td>Adjusted Residual</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>c. san cu MTS osoase</td>
<td>Count</td>
<td>6</td>
</tr>
<tr>
<td>Expected Count</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>% within cale de administrare</td>
<td>66.7%</td>
<td></td>
</tr>
<tr>
<td>Adjusted Residual</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>melion multiplu</td>
<td>Count</td>
<td>1</td>
</tr>
<tr>
<td>Expected Count</td>
<td>.8</td>
<td></td>
</tr>
<tr>
<td>% within cale de administrare</td>
<td>6.7%</td>
<td></td>
</tr>
<tr>
<td>Adjusted Residual</td>
<td>.6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>15</td>
</tr>
<tr>
<td>Expected Count</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>% within cale de administrare</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

*localizare osteonecroza = maxilar

In our study group, Zoledronate is found to be the most commonly used antiresorptive. Ibandronate has been used in four cases, Risedronate and Alendronate in one case and in 2 cases, respectively.

The most common route of bisphosphonate administration is intravenously (15 cases, namely 75%). Antiresorptive treatment duration averaged to 30.24 months.
The onset of the disease is mostly postextractional (85%), rarely spontaneously (15%). Six of the patients in stage 3 have showed acute sinusal symptoms, and four of them showed oroantral fistula, all with a history of zoledronate therapy for a period of minimum 6 months.

The patients came to medical examination in stage 2 (seven cases) and stage 3 (thirteen cases) of the disease. Out of the patients in stage 3, a number of ten patients have received antiresorptive therapy administered intravenously. We have found that: stage 2 is more significantly present in men while stage 3 in women ($\chi^2 (1) = 5.934, p = 0.015 < 0.05$) (Table 9.III). We have also found that stage 2 is more common in patients living in rural areas, while stage 3 is more common in patients living in urban areas.

Table 9.III: Study Group Structure depending on Gender and MRONJ Stage

<table>
<thead>
<tr>
<th></th>
<th>STADIUL</th>
<th>Count</th>
<th>Expected Count</th>
<th>% within STADIUL</th>
<th>Adjusted Residual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>masculin</td>
<td></td>
<td>4</td>
<td>1.8</td>
<td>57.1%</td>
<td>2.4</td>
</tr>
<tr>
<td>feminin</td>
<td></td>
<td>3</td>
<td>5.3</td>
<td>42.9%</td>
<td>-2.4</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>7</td>
<td>7.0</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

|       | 3.00    |       |                |                  |                  |
| masculin |       | 1     | 3.3            | 7.7%             | -2.4             |
| feminin |       | 12    | 9.8            | 92.3%            |                  |
| total |       | 13    | 13.0           | 100.0%           |                  |

Table 9.III a.

Imaging evaluations of the patients is made by Orthopantomography or CBCT.
Surgery treatment is performed depending on the staging.
All the patients received antibiotics (penicillin derivatives or clindamycin) in combination with Chlorhexidine-based oral antiseptics 0.12%.
In stage 3, it has been performed sequestrectomy, radical excision of the sinus and immediate plasty of oroantral communication with vestibular flap, or bone resections. In Stage 2, it has been performed debridement of necrotic bone tissue.

9.1.5 DISCUSSIONS

Because osteonecrosis is located mainly on the mandibular bone and due to the fact the maxillary bone is affected only in one third of the cases, there are few studies that have investigated the manifestations of osteonecrosis of the maxilla (Mast G et al, 2012 Estillo CL et al, 2008, Stockmann P et al, 2010 Filleul O et al, 2010). This difference in distribution of the osteonecrosis in terms of location can be attributed to the following causes: richest vasculature of the maxilla, differences in bony architecture between maxilla and mandible or embryologic factors (desma ossification of mandible) (Allen MR, Burr DB, 2009 Ruggiero SL et al, 2006).

The study group is comprised of 20 patients diagnosed with MRONJ, out of which 75% are women, 80% of them are aged over 60 years, and 55% of them are living in rural areas. Thirteen (13) patients came in stage 3 of the disease.

Maxilla bone is affected by osteonecrosis less often than the mandibular bone (Bamias et al, 2005, Marx RE et al, 2005). According to the literature, osteonecrosis of the maxilla bone occurs more frequently in patients with various forms of cancer receiving intravenous antiresorptive treatment and rarely in patients with osteoporosis (Fedele S et al, 2009 Thumbigere-Math V et al, 2009). Some forms of malignancy may be associated with an
increased risk for osteonecrosis due to paraneoplastic syndrome that occurs after specific treatment of the underlying disease, and which directly affects patient immunity (Thumbigere-Math V et al, 2009). Some studies have described a relation between appearance of MRONJ and existence of arterial hypertension, diabetes, vascular diseases and tobacco (Assouline-Dayan Y et al, 2002 Gebara SN et al, 2009). In our study, the majority of patients have had at least one of these risk factors.

It is noteworthy that patients have come in our clinic in advanced stages, most commonly in stage 3 (65%) than in stage 2.

In the study performed by Mast G et al on a study group of 53 patients diagnosed with bisphosphonates-related osteonecrosis of the maxilla, 43.6% of them have showed acute sinusal symptomatology while 35.8% of them have presented oroantral fistula (Mast G et al, 2012). In our study, 30% of the patients present sinusal symptomatology and 20% of them oroantral fistula. The differences may be caused by the fact that our study group includes a smaller number of cases.

9.6 CONCLUSIONS

As far as the maxilla bone is concerned, stage 3 osteonecrosis is more common than stage 2 osteonecrosis.

Sinusal damage is a common complication of osteonecrosis of the jaw. Therefore, we consider that further investigations are useful and mandatory, namely, we refer especially to 3D imaging, which besides specifying the extent of the bone lesion it can also assess the impairment of the maxillary sinus. The setting of diagnosis and treatment plan is always done by a close multidisciplinary collaboration (surgeon, oncologist, endocrinologist, radiologist, etc.).

Oral cavity control (by clinical examination and orthopantomography) and restoring of the periodontal optimal healthy condition before starting bisphosphonate therapy is the proper conduct which effectively reduces the probability of occurring osteonecrosis of the jaws.

9.2 CLINICAL AND THERAPEUTIC FEATURES OF THE OSTEONECROSIS OF THE MANDIBLE BONE

9.2.1 INTRODUCTION

Therapeutic possibilities for the antiresorptive-related osteonecrosis of the maxillar bones are various.

Although the new 2014 AAOMS recommendations support conservative approach of osteonecrosis, its rate of success places between 20% (Marxs RE et al, 2005, Hoff AO et al 2008) and 50% (Badr et al 2008), being significantly lower than the therapeutic success (over 85%) obtained by the surgical therapy.

9.2.2 THE PURPOSE OF THE STUDY

The purpose of the study is to evaluate the outcomes and the surgical therapy efficiency when osteonecrosis is located on the mandibular bone.

9.2.3 MATERIAL AND METHOD

There are studied a total of 62 patients diagnosed with bisphosphonates-related osteonecrosis of the jaws, hospitalized between January 2009 and June 2015 in the Clinic of
Correlations Between Bisphosphonates Treatment And Osteonecrosis Of The Jaws

Oral and Maxillo-Facial Surgery, at the Hospital “St. Spiridon” Iași. Out of these, a number of 35 patients show mandible MRONJ.

9.2.4 OUTCOMES

There are 35 patients participating in the study, twenty-three of them being female and twelve of them male, with a mean age of 66.46 years (standard deviation s = 9.60).

The antiresorptive therapy is represented by bisphosphonates for different forms of malignant neoplasms (85.7%) and/or osteoporosis (22.9%) (Table 9.VI.). In terms of the route of administration, thirty (30) patients have received intravenous therapy.

Table 9.VI: Neoplasia-based Distribution of Patients

<table>
<thead>
<tr>
<th>Neoplasia</th>
<th>Frequency</th>
<th>Percent</th>
<th>Valid Percent</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fara neoplazie</td>
<td>5</td>
<td>14.3</td>
<td>14.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Pulmonar cu MTS ososase</td>
<td>2</td>
<td>5.7</td>
<td>5.7</td>
<td>20.0</td>
</tr>
<tr>
<td>Prostata cu MTS ososase</td>
<td>7</td>
<td>20.0</td>
<td>20.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Put cu MTS ososase</td>
<td>11</td>
<td>31.4</td>
<td>31.4</td>
<td>71.4</td>
</tr>
<tr>
<td>Renal cu MTS ososase</td>
<td>1</td>
<td>2.9</td>
<td>2.9</td>
<td>74.3</td>
</tr>
<tr>
<td>Ovarian cu MTS ososase</td>
<td>2</td>
<td>5.7</td>
<td>5.7</td>
<td>80.0</td>
</tr>
<tr>
<td>Gastric cu MTS ososase</td>
<td>1</td>
<td>2.9</td>
<td>2.9</td>
<td>82.9</td>
</tr>
<tr>
<td>Mielon multiplu</td>
<td>5</td>
<td>14.3</td>
<td>14.3</td>
<td>97.1</td>
</tr>
<tr>
<td>MTS ososase</td>
<td>1</td>
<td>2.9</td>
<td>2.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

The surgical therapy has been performed based on the staging (Table 5.II), and it has been recommended by AAOMS (Ruggiero SL et al 2014).

All the patients received antibiotics (penicillin derivatives or clindamycin) in combination with Chlorhexidine-based oral antiseptics 0.12%.

The surgical therapy has involved the following procedures: bone resection – five (5) patients, marginal alveolar resection – four (4) patients, segmental resection – one (1) patient, debridement and sequestrectomy for the remaining thirty (30) patients. Particular attention has been paid to surgical smoothing of the bone edges and to the margino-edge closure of the wound. The bony defect has been covered with a vestibular flap sutured in two (2) planes.

The most common type of bisphosphonate prescribed is Zoledronate in 85.7% of the cases, followed by Iblandronate in 8.6% of the cases and Alendronate in 5.7% of the cases.

At the same time, 85.7% of the patients have a history of chemotherapy and 8.6% of them a history of corticosteroid therapy.

The duration of bisphosphonate therapy is significantly higher when bisphosphonates are administered orally.

Disease Staging has been done according to 2014 AAOMS recommendations. 28 patients included in the study group were presented in stage 2 (Table 9.XI), 1 stage 1 and stage 3 June. Twenty-eight (28) patients included in the study group came to medical examination in stage 2 (Tabel 9.XI), one (1) patient in stage 1 and six (6) patients in stage 3.

Clinical Observations

Clinical Case 1 - Stage 2

Female patient aged 69, known with arterial hypertension under control by administration of medication and diabetes mellitus type 2, is hospitalized in the Clinic of
Maxillofacial Surgery Iași presenting fistula holes in the alveolar ridge in straight line with the teeth 33, 34, 35. Under the protection of antibiotics and in an atraumatic manner, the following procedures are performed: teeth extractions (32, 33, 34, and 35), sequestrectomy and debridement of necrotic tissue up to the healthy bone.

Fig.9.13 Clinical Aspect

Sharp bone edges are smoothen and closure of the wound is achieved through a vestibular flap sutured in two (2) planes. The postoperative evolution is favorable, yielding local healing to one year after surgery intervention (Fig.9.18).

Fig.9.18 Late Postsurgery Aspect – one year from the surgical intervention

9.2.5 DISCUSSIONS

The study group includes 35 patients: 65% women, 71.4% aged over 60 years, and 65.7% living in urban areas. The main diseases requiring antiresorptive therapy are breast and prostate carcinoma.

Similarly to Boonyapakorn et al’s study, which reveals that 77% of the patients suffer from osteonecrosis installed after tooth extraction, in our study, the postextractional onset is found in a ratio of 71.4%.

The duration of bisphosphonate therapy is described as an important risk factor for osteonecrosis. There are studies that have reported an average duration of 39 months for the antiresorptive therapy (Bamias et al, 2005, Badr et al, 2006, Dimopoulus MA et al, 2006). Also, Mucke et al reports an average duration of 36 months for zoledronate therapy (Mucke T et al, 2009). Our study outcome regarding zoledronate therapy duration shows lower values (29.2 months).

For the patients in our study, we used the technique proposed by Triaca et al and modified by Voss et al. After removing the necrotic bone and rounding off the sharp edges we performed the primary closure of the wound by a suture in two planes: the first one is represented by the periosteum of the vestibular flap, which is sutured to the oral submucosa.
with absorbable wires, and the second is represented by the suture of the margino-edge of the vestibular flap to the oral mucosa (PJ Voss et al, 2012 Fig.9.23).

9.2.6 CONCLUSIONS

The most common trigger of osteonecrosis is tooth extraction performed during antiresorptive therapy, especially with zoledronate.

Anatomical risk factors represented by the presence of mandibular torus, bone exostoses or sharp milohidioniana ridge, which are normally covered by a thin and friable mucosa, can also contribute to osteonecrosis.

Spontaneous onset of the disease is associated with a longer duration of the antiresorptive therapy. Also, stage 2 is more frequent than stage 3 in the mandible.

The success of surgical treatment depends, on the one hand, on entire removal of the necrotic tissue, and on the other hand, on a complete margino-edge closure of the wound.

10. STUDY REGARDING THE ROLE OF USING PRP (PLATELET-RICH PLASMA) TO THE SUCCESS OF SURGICAL TREATMENT OF OSTEONECROSIS OF THE JAWS RELATED TO ANTIRESORPTIVE AND ANTIANGIOGENIC MEDICATION

10.1 INTRODUCTION

The therapy objectives for the patients diagnosed with osteonecrosis are as follows: eliminating pain, infection control and limiting the progression/occurrence of osteonecrosis areas. Therapeutic possibilities vary based on the disease staging and they include the use of oral antiseptics solutions, antibiotics, debridement or resection of the affected bone fragment.

10.2 THE PURPOSE OF THE STUDY

The purpose of the study is to evaluate the result of using adjuvant therapy, namely PRP injecting, within the surgical therapy set for osteonecrosis.

10.3 MATERIAL AND METHOD

The study group comprises twelve (12) patients diagnosed with osteonecrosis of the jaws related to antiresorptive medication.

10.4 OUTCOMES

The group of study comprises twelve (12) patients aged 46-80 years, predominantly male. Eleven (11) patients received zoledronate therapy for various forms of cancer.

In the group of study, three (3) patients are diagnosed with osteonecrosis related to antiresorptive medication with maxillary and mandibular location. 50% of the patients, predominantly male, have come in our clinic in an advanced stage of the disease (stage 3), and for three (3) of them the location of the disease is only on mandible.

All the patients have taken antibiotics, mainly penicillin derivatives.

The surgical therapy has been performed according to the new 2014 AAOMS recommendations, meaning: debridement, sequestrectomy, partial bone resection. In addition,
Correlations Between Bisphosphonates Treatment And Osteonecrosis Of The Jaws

PRP is applied in all the cases, by injection in the post-operative wound. Two (2) of the cases have undergone radical excision of the sinus. Bone resection is performed in three (3) cases, two (2) of them having mandibular location.

Clinical Observations

Clinical Case 1 - Stage 3

Patient P.F. aged 46, known with insulin-dependent diabetes, is hospitalized in the Clinic of Maxillofacial Surgery Iași showing swelling in the right maseterine region and limitation of mouth opening amplitude. The intraoral exam is found necrotic bone exposed in the oral cavity at the level of 46-48 edentulous space, with swollen and congested adjacent mucosa. Onset of the symptoms is closely related to a dental extraction (tooth 46) performed by a dentist during the antiresorptive therapy four months ago.

The surgical therapy involved sequestrectomy (Fig.10.12), debridement, postsurgical wound injected with PRP (Fig.10.15), and covering of the defect with a vestibular flap sutured in two (2) planes.
10.5 DISCUSSIONS

The use of platelet rich plasma in combination with the surgery therapy has been described by several authors (Addornato MC et al, 2007, Lee CY et al, 2007, Curi MM et al, 2007). They noted a decrease by half of the time needed to healing and tissue regeneration and also a decrease in the need for analgesic medication use.

Uses in oral and maxillofacial surgery are vast, including various marrow ablation procedures, mandibular reconstruction, and treatment of labio-maxillo-palatine clefts. PRP is being used successfully in periodontal surgery to treat infrabony defects but also in implantology (Albanese et al, 2013). Recently, use of PRP has been proposed for management of osteonecrosis of the jaws related to antiresorptive therapy.

Positive results have also been achieved by Mozzi et al and Coviello et al, who emphasize that surgical therapy used in combination with PRP offers promising results for the osteonecrosis refractory to conservative treatment (Mozzi M et al, 2012 Coviello V et al, 2012).

Our group of study comprises twelve (12) patients who have received surgical therapy in combination with PRP injection. Local healing is achieved in all the cases, without subsequent appearance of inflammatory phenomena. The drawback of this study is the impossibility of pursuing on long-term the postoperative outcomes due to the severity of the underlying disease.

10.6 CONCLUSIONS

Joining the local application of PRP with the surgery therapy proves to be beneficial in the treatment MRONJ. Since it has not been set an effective standard treatment yet, this combination may be considered a therapeutic option, given the fact that it has yielded satisfactory results.

The major advantage of this method is that being not the synthesis compounds but the body’s own cells the ones that are responsible for tissue repair and regeneration, then, the intolerance and allergy risk is nonexistent.

Given that the literature cites a few cases where the PRP has been used in the treatment of MRONJ, further studies are needed to assess the efficacy of the therapy.

11. STUDY REGARDING THE INFLUENCE OF OSTEOENEOSIS OF THE JAWS RELATED TO ANTIRESORPTIVE THERAPY ON THE QUALITY OF LIFE

11.1 INTRODUCTION

One of the instruments for assessing the quality of life associated with oral health is Oral Health Impact Profile (OHIP), which is a multidimensional structure that reflects the comfort during mastication, during sleep, involvement in social interactions, self-esteem and satisfaction regarding the level of oral health.

Oral Health Impact Profile is a well validated tool to measure OHQoL, which detects dysfunction, discomfort and disability attributed to oral conditions based on WHO (World Health Organization) model “disease-impairments-disabilities-handicaps”.

19
11.2 THE PURPOSE OF THE STUDY

The purpose of the study is to highlighting the impact of osteonecrosis of the jaws related to antiresorptive and antiangiogenic medication on the quality of life of the patients included in our study.

11.2 MATERIAL AND METHOD

The current study has been approved by the University of Medicine and Pharmacy “Grigore T. Popa” Iași, getting the informed consent from all the participants.

The group of study is consisted of 62 patients, out of which: 67.7% are females; 53.2% are aged over 65 years.

The Exclusion Criteria are as follows: 1) presence of mental or psychological disorders; 2) need of antibiotics in the last 6 months; 3) presence of removable dentures; 4) presence of oral symptomatic lesions, other than those in MRONJ.

In order to measure the impact of osteonecrosis of the jaws on the quality of life it is used the Oral Health Impact Profile index (OHIP-14), which is a tool for measuring the own perception containing fourteen (14) questions divided into seven (7) areas of interest: functional limitation, physical pain, psychological discomfort, physical disability, psychological difficulties, social barriers and social handicap.

11.3 OUTCOMES

In terms of our study, it is noted that 40.3% of the interviewed subjects have never had problems of words pronunciation caused by oral cavity diseases, while 37.1% of them have very rarely had. However, it should be noted that 6.4% of the subjects have pretty often and very often had such problems.

The percentage distributions per gender and groups of age of the responses to OHIP-1 are homogeneous. In terms of words pronunciation problems caused by oral cavity diseases, it is revealed that: 10% of the men have pretty often had such problems while 21.4% of the women occasionally (Chi-square = 4.79, df = 4, p = 0.310). Per groups of age, it is revealed as follows: 17.2% of the patients aged less than 65 years and 15.2% of those aged over 65 years have occasionally had difficulties of pronunciation (Chi-Square=1,81; df=4; p=0,772) (Tabel 11.III).

<table>
<thead>
<tr>
<th>OHIP-1</th>
<th>Male</th>
<th>Female</th>
<th>&lt; 65 years</th>
<th>65+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>never</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>40.0%</td>
<td>17</td>
<td>40.5%</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>37.9%</td>
<td>14</td>
<td>42.4%</td>
</tr>
<tr>
<td>very rarely</td>
<td>14</td>
<td>33.3%</td>
<td>10</td>
<td>34.5%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>17.2%</td>
<td>5</td>
<td>15.2%</td>
</tr>
<tr>
<td>occasionally</td>
<td>9</td>
<td>21.4%</td>
<td>5</td>
<td>17.2%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6.9%</td>
<td>1</td>
<td>3.4%</td>
</tr>
<tr>
<td>pretty often</td>
<td>1</td>
<td>2.4%</td>
<td>1</td>
<td>3.4%</td>
</tr>
<tr>
<td>very often</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Regarding taste damage due to oral cavity diseases it is emphasized the following: it occurs occasionally in 40.3% of the subjects and pretty often in 12.9% of them; approximately ¼ (21%) of the subjects have never noted this problem in their mouth (Fig.11.3).
11.4 DISCUSSIONS

Antiresorptive medication is mainly used to treat osteoporosis and bone metastases. One of the adverse effects of antiresorptive medication use is occurrence of osteonecrosis at the level of maxillary bones. Occurrence of osteonecrosis at the level of maxillary or mandible bones means a significant deterioration in the quality of life of a patient.

Being a relatively new disease, the studies regarding influence of maxillary osteonecrosis on the quality of life are small in number. Most of the responses like “pretty often” or “very often” have been obtained from questions concerning the presence of pain, discomfort during feeding, the state of tension and difficulty in appropriate feeding due to oral cavity problems, and at last but not least, concerning the presence of a state of irritability. 60% of patients have a high degree of clinical impairment due to localized to the oral cavity without recording significant differences between the sexes, age groups. 60% of the patients have a high degree of impairment due to the clinical manifestations localized in the oral cavity, without recording significant differences between gender and groups of age.

Treatment of advanced osteonecrosis often involves bone resections more or less flat. Damage that results can cause facial asymmetry and disharmony, negatively influencing the stomatognathic system functions (chewing, swallowing, phonation, breathing and physiognomy). Similarly, in patients who have received surgical therapy for oral cancer may occur various degrees of malnutrition that have a direct negative impact on the overall health condition.

11.5 CONCLUSIONS

Osteonecrosis of the jaws can negatively affect the patient's quality of life, both by the presence of symptoms and following the extensive surgery therapy. For this reason, therapeutic conduct should be carefully chosen and assessed in the context of the patient's general health condition.

12. GENERAL CONCLUSIONS

Osteonecrosis of the jaws is a rare disease that occurs most frequently as a consequence of antiresorptive and antiangiogenic therapy with long term intravenous administration (an average of 29 months).

The diagnosis is determined by a thorough case history, rigorous clinical examination correlated with brain imaging. To this end, CBCT is a valuable assessment method (having a
low-dose of irradiation), allowing 3D reconstructions that are useful to the clinician both for determining lesion extension and establishing the surgery protocol.

Oral surgery interventions are the main trigger factors involved in MRONJ pathogenesis.

Surgical therapy, associated with oral antibiotics and antiseptics, varies depending on the clinical stage and location (on maxilla or mandible), including: debridement, sequestrectomy, partial or segmental bone resection, radical excision of the sinus. Interdisciplinary approach is mandatory in the therapeutic management and it includes the following specialties: oncology, radiology, radiotherapy, endocrinology or rheumatology.

Especially helpful in wound healing is the PRP – an autologous product that is rich in growth factors, easy to be collected, processed and applied.

The quality of life in patients with osteonecrosis is adversely affected in the context of the underlying disease and oral symptoms, and implicitly in the context of more or less extensively surgical therapy.

In the process of the disease prevention, an important role plays the treating physician who has prescribed the therapy with antiresorptive and antiangiogenic medication, and who should direct the patient to dental physician for oral drainage and rehabilitation before starting the general therapy.

It is desirable that, in patients under bisphosphonates therapy, the oral surgical interventions be carried out under protection of antibiotics, with a correct closure of the bone wound using mucoperiosteal flap.

Constant and careful monitoring of these patients, informing and educational activities towards side effects of this therapy are crucial factors in improving the quality of life.

13. ELEMENTS OF ORIGINALITY AND PERSPECTIVES

The paper makes a depth study in a topical pathology, rare and recently reported in the literature, but with severe implications on the quality of life in patients under chronic antiresorptive and antiangiogenic therapy.

The clinico-epidemiological study of MRONJ patients, diagnosed and treated in the Clinic of Oral and Maxillo-Facial Surgery Iași, is the only study of this kind conducted for the population living in Moldova area.

Using advanced sectional imaging techniques we have evaluated the type and extension of the lesions through CBCT scan, with 3D reconstruction, a method that is far less irradiating compared with other imaging investigations.

Observing current AAOMS therapeutic protocols, we have found how important PRP value is in the process of accelerating the postoperative wound healing, although the study group is limited to a small number of people.

Assessing the quality of life for MRONJ patients using OHIP-14 method is the only study in the country for this pathology.

Publishing the results of these studies will be of great help to all the clinicians involved in the therapeutic management of this category of patients.
SELECTIVE BIBLIOGRAPHY


Correlations Between Bisphosphonates Treatment And Osteonecrosis Of The Jaws


