Osteonecrosis of the Mandible Associated with Bisphosphonate Treatment

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This study analyzes 35 patients with bisphosphonate-related osteonecrosis of the mandible (BRONJ) diagnosed and treated in the Oral and Maxillofacial Surgery Clinic of St. Spiridon Hospital Iasi. The inclusion criteria were in line with the recommendations of the American Association of Oral and Maxillofacial Surgery (AAOMS). The analysis included the underlying disease, the type of bisphosphonate and the route of administration, the duration of treatment as well as the osteonecrosis triggering factor. Surgery was consistent with the condition of the disease, ranging from debridement and sequestrectomy to alveolar marginal and even segmental bone resections. The results of the study were similar with the data from the literature suggesting that the condition is more common in the lower jaw compared to the upper jaw, and the main risk factors are dental extraction and intravenous bisphosphonate administration.

Keywords: bisphosphonates, osteonecrosis, mandible

Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) is defined as a condition that has the following characteristics: exposed bone in the maxillofacial region (or which may be evidenced by an intra or extraoral fistula) that persists for more than 8 weeks, current or previous treatment with antiresorbtive or antiangiogenic agentst, no history of radiation therapy to the jaws [1]. Basically, this new definition with its criteria mainly refers to osteonecrosis induced by bisphosphonates but also to other substances with antiresorptive action such as denosumab or antiangiogenic medication. The clinical reality and studies published in the literature converge towards an increasing incidence of patients with this disabling and unpredictable evolutionary pathology, with a high degree of morbidity, mainly due to the administration of bisphosphonates over prolonged time. Oral bisphosphonates are frequently used in the treatment of osteoporosis and osteopenia and less used in the treatment of Paget's disease or osteogenesis imperfecta [2,3].

Intravenous bisphosphonates are used for the treatment of bone metastasis, primary bone osteolythic pathologies (multiple myeloma, Paget's disease), secondary hypercalcaemia of neoplastic disease or skeletal related events. Antiangiogenic medication is used mainly in the treatment of gastrointestinal, renal and neuro-endocrine malignancies [4]. The RANKL inhibitor (denosumab) is an antiresorptive agent used to treat osteoporosis or to relieve symptoms of bone metastatic disease [5, 6]. Generally, bisphosphonates are well tolerated, but some adverse effects are also reported: renal toxicity, atrial fibrillation, skin and inflammatory ocular reactions, musculoskeletal pain, gastrointestinal irritation, atypical femoral fractures, and last but not least osteonecrosis of the jaw [7-12]. The therapeutic action and toxicity of bisphosphonates are determined by their effect on osteoclasts.

In terms of structure and mechanism of action, bisphosphonates are synthetic analogs of pyrophosphate and they contain a phosphate-carbon-phosphate structure with two side chains, R1 and R2, attached to the carbon atom (fig. 1). The R1 chain gives this chemical compound an increased affinity for circulating calcium, without having any antiresorptive effect. The R2 chain provides the antiresorptive potency and the duration of action of bisphosphonates, determining their efficiency [13].

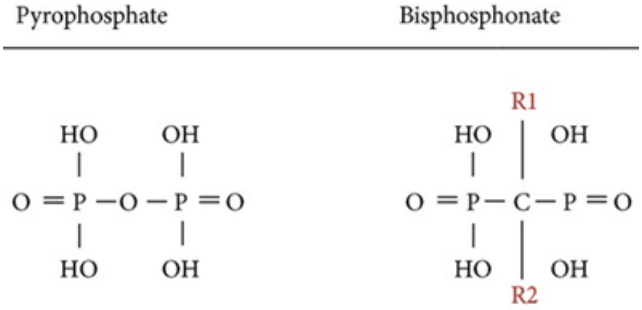

Fig.1 Chemical structure of pyrophosphate and bisphosphonate

After the mechanism of action, bisphosphonates are divided into three classes. Those in generation I (Clodronat, Etidronate) do not contain nitrogen in their molecule and are intracellularly metabolised by condensation with adrenosine triphosphate. Accumulation of metabolites within the osteoclast inhibits its function by inducing apoptosis. 2nd and 3rd generation bisphosphonates (Pamidronat, Alendronate, Ibandronate, Zoledronat) interfere with other metabolic reactions by inhibiting the precursor of proteins involved in intracellular signaling processes [7]. In vitro, bisphosphonates containing nitrogen in their molecule inhibit osteoblast proliferation by having a direct and proapoptotic cytostatic action on tumor cells, a synergistic cytostatic effect with other anti-tumor drugs and due to their anti-adhesion / anti-invasive action [14].

Although there is a large volume of publications on this pathology reported by Marx since 2003, the pathophysiology of the disease remains unclear [15, 16]. There are currently two theories. The first one, called *inside-out,* considers that the mechanism by which bisphosphonate can induce osteonecrosis of the jaws is suppression of

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bone turnover (by reducing osteoclast activity and inducing apoptosis in osteoclasts), inhibition of neoangiogenesis and local infection with mucosal involvement and bone exposure [17, 18]. The second theory, *inside-in,* focuses on the toxic action of bisphosphonate on the soft tissue and the mucosa, which cracks, thus permitting the microbial invasion and penetration into the bone, with the consecutive installation of the osteonecrosis of the jaws [19].

If pathophysiology is still controversial, local factors associated with bisphosphonate-induced osteonecrosis of jaws are well-known. Experimental and clinical studies have shown that the main factor is dental extraction, followed by periodontal diseases, decubital lesions in total prosthesis carriers and local infection [1, 20, 21]. Rarely, injuries can occur spontaneously in the absence of any local risk factor.

Experimental part

A total of 62 patients, diagnosed with osteonecrosis of the jaw associated with bisphosphonate treatment, admitted between 2009-2015, were treated in the Oral and Maxillofacial Surgery Clinic, St. Spiridon Hospital, Iasi. Of these, a total of 35 patients presented BRONJ with mandibular localisation.

Both inclusion and staging criteria were established according to the latest AAOMS recommendations [1].

Statistical analysis of the data was performed using the SPSS (Statistical Package for Social Sciences) program for Windows, version 20.0. The statistical tests used were:

- independent square chi test for non-parametric data to compare frequencies between two samples;
- *t* test for independent samples for parametric data.

Results and discussions

The study group consisted of 35 patients, 23 of them female and 12 male, with an average age of 66.46 years (standard deviation s = 9.60).

Antiresorbtive treatment consisted in bisphosphonates for various forms of malignant neoplasia (85.7%) and / or osteoporosis (22.9%) (table 1). Regarding the route of administration, 30 patients followed intravenous therapy.

The most common type of used bisphosphonate was zoledronate in 85.7% of cases, followed by ibandronate in 8.6% of cases and alendronate in 5.7% of cases.

85.7% of patients had previous chemotherapy and 8.6% corticosteroid therapy.

The duration of bisphosphonate treatment was significantly higher when bisphosphonates were administered orally (table 2).

In the case of malignant neoplasms, the duration of antiresorbtive therapy was 29.60 months, significantly lower ($t(33) = 4.195$, $p = 0.000 < 0.05$) than in osteoporosis patients (table 3).

Osteonecrosis was present after dental extractions in 71.4% of cases. The duration of treatment was significantly higher in patients who had a spontaneous onset of osteonecrosis (table 4) and lower (29.76 months) following tooth extraction.

The staging of the disease was performed according to AAOMS 2014 recommendations (table 5).

Twenty-eight patients enrolled in the study group were in stage 2 (table 6), 1 in Stage 1 and 6 in Stage 3.

Surgical treatment was performed according to staging system (table 7), also recommended by AAOMS [1].

All patients received antibiotherapy (penicillin derivatives or clindamycin), in combination with 0.12% chlorhexidine oral antiseptics.

Table 1

DISTRIBUTION OF PATIENTS ACCORDING TO NEOPLASIA

	Frequency	Percent	Valid percent	Cumulative percent
Without neoplasia	5	14.3	14.3	14.3
Pulmonary cancer with bone MTS	2	5.7	5.7	20
Prostate cancer with bone MTS	7	20	20	40
Breast cancer with bone MTS	11	31.4	31.4	71.4
Renal cancer with bone MTS	1	2.9	2.9	74.3
Ovarian cancer with bone MTS	2	5.7	5.7	80
Gastric cancer with bone MTS	1	2.9	2.9	82.9
Multiple Mieloma	5	14.3	14.3	97.1
Bone MTS with unclear emerging point	1	2.9	2.9	100
Total	35	100	100	

MTS-metastasis

Variable	Mean value of treatment duration (months)	t Test results
Administration route		t (33) = 4.742 p = 0.000
IV	29.20	
PO	67.20	

IV-intravenous, PO-orally

Table 2

RESULTS OF THE t TEST IN CASE OF TREATMENT DURATION, ACCORDING t THE ADMINISTRATION ROUTE

Variable	Mean value of treatment duration (months)	t Test results
Neoplasia		t (33) = 4.195 p = 0.000
Yes	29.60	
No	64.80	

Table 3

AVERAGE DURATION OF ANTI-RESORPTIVE THERAPY BASED ON THE PRESENCE OF NEOPLASIA

Variable	Mean value of treatment duration (months)	t Test results
Onset		t (33) = 1.998 p = 0.050
Spontaneous	44.73	
Post-extractional	30.00	

Table 4
THE MEAN DURATION OF ANTIRESORBENT TREATMENT BASED ON THE ONSET OF OSTEONECROSIS OF THE JAW

Table 5
OSTEONECROSIS STAGING

Stage	0	1	2	3
Clinical aspects	- Absence of exposed necrotic bone -specific non-specific: dental pain, sinus pain, dental mobility, periapical / periodontal fistula in the absence of endodontic or periodontal pathology	- Exposed necrotic bone or the presence of an intraoral fistula without signs of local infection	- Exposed necrotic bone or intraoral fistula with clear signs of infection	- Exposed necrotic bone or intraoral fistula with clear signs of infection, plus at least one of the following: - Exceeding the limit of the alveolar process -pathological bone fracture - Extraoral fistula - oro-antral or oro-nasal communication
RX aspects	-resorbtion of the alveolar bone - changes in the trabecular bone pattern by increasing its density -osteosclerosis - narrowing / disappearing of the desmodontal space	- the same changes encountered in stage 0, placed at the alveolar bone	- the same changes encountered in stage 0, placed at the alveolar bone	- the osteolysis area exceeds the limits of the alveolar process

Stage	Frequency	Percent	Valid percent	Cumulative percent
1	1	2.9	2.9	2.9
2	28	80	80	82.9
3	6	17.1	17.1	100
Total	35	100	100	

Table 6
STRUCTURE OF THE STUDY GROUP ACCORDING TO THE STAGE OF MAXILLARY OSTEONECROSIS

Risk patients	No treatment indications
Stage 0	Pain therapy, antibiotic therapy
Stage 1	Oral antiseptic, periodic control at every 3 months
Stage 2	Antibiotic, pain killers, oral antiseptic, debridement
Stage 3	Antibiotic, pain killers, oral antiseptic, debridement, sequestrectomy and/or apicectomy

Table 7
THERAPEUTIC STRATEGIES ACCORDING TO MAXILLARY OSTEONECROSIS STAGING

Five patients underwent bone resection, marginal alveolar resection (4 cases) and segmental resection (1 case); the rest has followed debridement and sequestrectomy. Particular attention was paid to the smoothing of the bone margins and to the closure of the wound. Bone defect was covered with a 2 layer sutured vestibular flap.

The exclusive localisation of BRONJ in the oral cavity and in particular in the maxillary bones is explained by the fact that they are subjected to micro-traumatisms following the exertion of the masticatory forces, to which is added the alveolar bone turnover rate that is 10 times higher than in long bones [22]. A possible explanation for the higher frequency of BRONJ in the mandible may be the antiangiogenic effect of antiresorbtive treatment under conditions of a lower, end-to-end vascularization of this bone compared to the upper jaw. [23].

The results obtained in the study (56.5%) support the conclusions of the literature on this preferred location [24, 25]. Most of the patients included in the statistical analysis were female (65%), aged over 65, and the primary condition for which antiresorptive therapy was prescribed was breast cancer with bone metastases. In men predominated prostate cancer.

Similar to the study conducted by Boonyapakom et al., in which 77% of patients had osteonecrosis following tooth extraction, in our study 71% of the patients developed the disease following dental extraction [26]. The duration of bisphosphonate therapy, its type and the route of administration are considered important risk factors for BRONJ. There have been studies that reported an average duration of 39-month of antiresorption therapy [25, 27, 28]. Mucke also reported an average duration of 36-month of zoledronate treatment [29]. 30 patients from our study that undergone intravenous bisphosphonates (zoledronate) for bone metastases had a lower mean duration of treatment (29.2 months). This anti-resorbtive agent is associated with a 9.5-fold greater risk than other types of bisphosphonates

in BRONJ [30]. Intravenous antiresorptive therapy is most commonly involved in disease onsetting [25, 31, 4]. 80.64% of our patients had a history of intravenous bisphosphonate treatment similar to Fliefel's study [32].

With regard to surgical and / or medical treatment, this was made according to the stage of the disease in consensus with the AOOMS 2014 recommendations. Along with the general antibiotic treatment and local use with oral antiseptics based on chlorhexidine, the actual surgical treatment comprised the entire range of interventions, ranging from debridement and sequestrectomy to partial or even segmental resections of the mandible. Immediate postoperative outcomes were satisfactory and uncomplicated in the vast majority of cases, but the severity of underlying conditions had prevented long-term postoperative monitoring for many patients [33]. Even in publications from 2003 to date the treatment of this lesions remains controversial. Hoff reported a healing rate of 23% following conservative treatment [34]. Lazarovici obtained a local healing in 82% of cases after superficial curretage of the necrotic bone [35]. There are several studies demonstrating the therapeutic success rate in the surgical approach ranging between 85-100% [36-38]. These authors support the idea of removing necrotic bone to healthy tissue and the primary closure of the wound.

Conclusions

With all of the scientific evidence achieved so far, BRONJ is a clinical entity poorly known, particularly in terms of disease pathogenicity. It is certain that BRONJ is a multifactorial condition in which the type of bisphosphonate, the duration of treatment, the route of administration and the dose play a decisive role in the onset of the disease. The only measure to avoid the occurrence of osteonecrosis lesions is to restore the optimal dental-periodontal health condition before initiating bisphosphonate therapy.

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