Clinical aspects of bisphosphonate-associated oral osteonecrosis in patients with multiple myeloma

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Summary

Background. **Bisphosphonates are drugs which act on bone metabolism. They act on osteoclastic activity and inhibit neoangiogenesis. In the bisphosphonate class the most clinically used molecules are pamidronate and zolendronate. They represent "the gold standard" and are used in multiple myeloma treatment, solid tumors with bone metastases, and prevention of pathological fractures.**
In recent years it has been supposed that bisphosphonates may lead to jaws osteonecrosis, expecially after dentistry procedures such as dental extractions, implant surgery and periodontics interventions.
Our work aim is to delineate clinical aspects of patients' lesions come to our observation for jaws osteonecrosis. These belonged to a patients' group treated by bisphosphonates for multiple myeloma, osteoporosis, hyperparathyroidism, Paget's disease.
Patients and methods. **We examinated clinical data of 9 patients (8 females, 1 male), with jaws osteonecrotic lesions and treated by bisphosphonates, for a mean time of 42 months. Six of the 9 patients were treated for multiple myeloma. In 4 cases osteonecrotic were located on superior maxillary, in 5 ones on jaw. Clinically exposed bone area was infected, with radiated and burning pain, and antibiotic therapy was necessary.**
Results. **Most clinically represented lesion was an area of ulcerated mucosa with not vital exposed bone. Flogosis was typical in area surrounding the necrosis. Neither bleeding nor pain could be appreciated in the exposed bone area. Painful lesions make more difficult oral hygiene, with frequent onset of local parodontosis. At radiographic exams typical illness marks are not corresponded instead. A standardized protocol for jaws osteonecrosis doesn't exist. In our clinical trial we performed several clinical plans, with different results. The suspension of bisphosphonate therapy does not appear to hasten recovery of the osteonecrosis. Despite antibiotic therapy, resective surgery, osteoplastics and hyperbaric oxygen therapy most of the lesions did not respond well to therapy.**
Discussion. **Although bisphosponates use started about 30 years ago, first osteonecrotic lesions were described in 2003 (Max and Stern). The pathogenesis is correlated to the modifications of vascularization induced from such drugs, but would compete even factors as masticatory stress, iatrogenic procedures, local bacterial position, association with other drugs and some systemic pathologies. Surgical treatment may lead to not predictable results and recurrences. Antibiotic therapy reduces the inflammation and the pain, but did not assure healing; therapies with disinfectant and irrigantes have not produced results; in our clinic the hyperbaric oxygen therapy has gotten good results toward in the comparisons of the inflammation and in the improvement of the course-operating after sequestrotomy.**
Conclusions. **Bisphosphonates are essential drugs in the treatment of several diseases other than osteoporosis. But considering the impact on the quality of life of the patients on which rise up osteonecrosis of the maxillary, it is necessary to perform odontostomatologic visit before the therapy, and to evaluated the relationship between benefit of the treatment and the risk of such lesions.**

KEY WORDS: osteonecrosis, bisphosphonates, osteoporosis, multiple myeloma.

Introduction

Bisphosphonates are non-metabolised pyrophosphonates analogues that are absorbed on the durapatite crystals of the bone matrix slowing down both growth speed and break-up by strongly inhibiting osteoclast activity (1).
Their clinical use dates back to 30 years ago (2), and in the years they have been mainly used in onco-haematology for the treatment of patients suffering from severe malignancies with bone metastasis such as lung, breast and prostate cancer, in hypercalcemia of malignancy, in the treatment of multiple myeloma and they are also prescribed in the osteoporosis and Paget's disease (3-6).
Several bisphosphonate molecules are on the market but the most widely used in the clinical setting are pamidronate and zolendronate (7).
Bisphosphonates act on osteoclasts blocking their function in several ways: inhibiting the osteoclast formation from monocytes (8), reducing the osteoclasts' life cycle (9), inhibiting osteoclastic activity on the bone surface (10).
At a molecular level, bisphosphonates are deemed to modulate osteoclast function interacting with a surface cell receptor or with an intracellular enzyme (11). Considering that they are not metabolised and have a strong binding affinity with osteoclasts, they produce their death (osteoclasts apoptosis) (12).
In addition to the anti-reabsorption effect on the bone, an anti-angiogenetic effect on animals has been recently described (13). Bisphosphonates can inhibit the endothelial cell function both *in vivo* and *in vitro* (14). The cells treated with bisphosphonates have shown a decreased proliferation, an increased apoptosis and a reduced capillary vessels formation (15, 16).

As to negative side effects, treatment with bisphosphonates produced flu-like symptoms, fatigue, gastrointestinal disorders, anaemia, dyspnoea and oedemas (7). Oral and oesophageal mucosal ulcerations were also observed (7, 17, 18).
In 2003, following the clinical observations by Marx and Stern (19) in patients suffering from myeloma, a possible implication of bisphosphonates in the development of maxillary osteonecrosis was postulated. Afterwards, this hypothesis was also supported by several Authors who highlighted a strong correlation between intra-oral bone necrosis and bisphosphonates treatment, in particular after tooth avulsion or other oral cavity surgery (20-23).
Hence, the aim of this article is to describe the clinical aspects of the osteo-necrotic lesions in a group of patients suffering from myeloma and treated with bisphosphonates. Furthermore, the possible pathogenetic mechanisms will be also dealt with because the authors are convinced that these lesions are a possible complication of bisphosphonates treatment.

Patients and methods

We analysed the clinical data of 9 patients demanding treatment for maxillary bone necrosis of unknown origin, sent to us by the Haematology department of the "San Giacomo" Hospital of Rome. The 9 patients belong to a group of 54 patients (41F, 13M) who were under bisphosphonate treatment for multiple myeloma, osteoporosis, hyperparathyroidism and Paget's disease (Table I).

Table I - Group of analysed patients.

Diagnosis	Patient's number	
Asymptomatic myeloma	4	(3F, 1M)
Symptomatic myeloma	36	(28F, 8M)
Osteoporosis	8	(6F, 2M)
Hyperparathyroidism	4	(4F)
Paget's disease	2	(2M)
Total	54	(41F, 13M)

Table II shows the clinical data of the 9 patients with maxillary osteonecrosis associated with bisphosphonate treatment. The group included 8 females and 1 male, with average age 71 years (range 89-59) and affected for multiple myeloma (6 cases), chronic leukemia (1 case), osteoporosis (1 case) and Waldenstrom's disease with osteoporosis (1 case). Average bisphosphonates treatment duration was 42 months (range 18-75). Oral manifestations were of upper maxillary osteonecrosis areas in 4 cases and mandibular lesions in 5 cases. All patients were under observation because of the presence of an infection in the exposed areas, with stinging and diffused pain that demanded systemic antibiotic treatment.

Table II - Demographics of 9 patients with bisphosphonates-associated oral cavity osteonecrosis.

Patient n.	Sex	Age	Systemic disease	Bisphosphonates therapy (months)	Oral manifestations (type/location)	Therapy
1	F	81	Multiple myeloma-k	Pamidronate (2) Zolendronate (27)	Osteonecrosis, infection/ mandible postextraction	Antibiotics, Rinses, Analgesics
2	F	58	Waldenstrom's disease and severe osteoporosis	Pamidronate (59) Zolendronate (27)	Osteonecrosis, infection/ maxilla	Sequestrectomy, Hyperbaric oxigen therapy, Antibiotics
3	M	84	Multiple myeloma IgG-$_{lamba}$	Zolendronate (18)	Osteonecrosis, infection/ maxilla postextraction	Sequestrectomy, Antibiotics
4	F	59	Multiple myeloma IgA-k	Pamidronate (75)	Osteonecrosis, infection/ mandible postextraction	Sequestrectomy, Hyperbaric oxigen therapy, Antibiotics
5	F	67	Multiple myeloma IgG-k	Pamidronate (13) Zolendronate (34)	Osteonecrosis, infection/ mandible postextraction	Sequestrectomy, Hyperbaric oxigen therapy, Antibiotics
6	F	70	Multiple myeloma IgG-k	Pamidronate (53) Zolendronate (27)	Osteonecrosis, infection/ maxilla	Antibiotics, Rinses
7	F	72	Severe osteoporosis with chronic lymphatic leukemia	Pamidronate (26) Zolendronate (20)	Osteonecrosis, infection/ mandible postextraction	Sequestrectomy, Hyperbaric oxigen therapy, Antibiotics
8	F	71	Severe osteoporosis	Pamidronate (3) Zolendronate (47)	Osteonecrosis/mandible	Antibiotics, Rinses
9	F	78	Multiple myeloma IgG-k	Pamidronate (20) Zolendronate (29)	Osteonecrosis, infection/ maxilla	Hyperbaric oxigen therapy, Antibiotics

Results

Clinical aspects

The most common clinical aspect of the lesions was mucosal ulceration with a non-vital bone exposure (Figs. 1, 2 and 3). In 1 case, we observed a mucosal fistula with a mild serosanguineous exudation. The exposed bone was yellowish/whitish whereas the surrounding mucosa was often irritated and painful if touched (Fig. 4). On the other hand, the exposed bone did not cause any pain and did not bleed. The clinical situation showed all the features of avascular bone necrosis. Bone lesions showed a quite regular surface that in the following became irregular as a consequence of bone microtraumatisms during chewing. In 1 case, the above mentioned irregularity produced ulcerations of the tongue edge touching the bone surface (Fig. 5). In 4 cases, bone exposed areas involved the upper maxillary at the crest and on the palate and in 5 cases the mandible on the postero-lingual and crest areas. When bone necrosis was close to the teeth, a deterioration of the local hygiene conditions was observed, with initial damage to the soft tissue with subsequent increased tooth mobility and loss. Case history revealed a previous intervention of the oral cavity, in particular tooth avulsions, insertion or removal of implants with subsequent incomplete healing of the surgical site and osteonecrosis of the post-avulsion

Figure 3 - Nonhealing alveolus with bone necrosis after the extraction of tooth 15.

Figure 1 - Exposed necrotic alveolar bone after tooth 31 extraction.

Figure 4 - Bone necrosis and secondary infection near palatal root of tooth 26.

Figure 5 - Exposed necrotic bone on the posterior left lingual side of the

Table III - Disease and events associated with osteonecrosis (any bone).

Disease or etiologic factor	Subcategories
Alcohol abuse	Cirrhosis; Pancreatitis
Arthritis	Subchondral cyst; Subchondral marrow edema
Atmospheric pressure variations	Caisson's disease; Deep-sea divers disease
Blood dyscrasias	Disseminated intravascular coagulation (DIC); Leukemia; Sickle cell anemia
Cancer	Chemotherapy for cancer; Cancer-induced hypercoagulation; Lymphoma; Metastatic intraosseus carcinoma; Radiation therapy for cancer
Chronic inactivity	Bedridden; Full body cast; Paraplegic
Corticosteroids	Hypercortisolism; Inflammatory bowel disease; Lupus erythematosus; Transplants
Estrogen	Birth control pills; Estrogen replacement therapy; Fertility drugs; Pregnancy; Prostate chemotherapy; Transient ischemic osteoporosis
Gaucher's disease	
Hemodialysis	
Hypercoagulable state, local	Acute infection/inflammation; Chronic infection/inflammation; Increased intramedullary pressures
Hypercoagulability	Antiphospholipid antibody syndrome; Factor V gene mutation hyperhomocysteinemia; Homozygosity for MTHFR or CBS*; Protein C deficiency; Protein S deficiency
Hyperlipidemia & embolic fat	Diabetes mellitus; Dysbaric phenomena; Fracture of bone; Hemoglobinopathies; Osteomyelitis acute
Hypertension	
Hypothyroidism	
Inflammation intraosseous	Bacterial and viral infection; Trauma (mild or severe); Autoimmunity/ hypersensitivity
Hypersensitivity reactions	Allograft organ rejection; Anaphylactic shock; Immunoglobulin therapy
Lupus erythematosus	With corticosteroid therapy; Without corticosteroid therapy
Neurodamage	Brain injury/surgery
Osteoporosis	Regional or generalized
Starvation	Anorexia nervosa
Storage diseases	Gaucher's disease
Tobacco use	Tobacco smoking
Vascular occlusive disease	Atherosclerosis
Vasculitis	
Vasoconstriction	Local anestesia (with vasoconstrictor); Raynaud's phenomenon; Tobacco use

* MTHFR: *methylene tetrahydrofolate reductase*; CBS: *cystathionine beta-synthetase.*

fault.

Depending of the clinical situation of osteonecrosis, radiographic evaluation and computerized tomography did not show any radiographic signs of the disease (Figs. 6, 7).

The absence of the radiographic signs of the disease was probably due to the early development of the lesions contrarily to osteomyelitis where an active bone resorption or sequestration were observed.

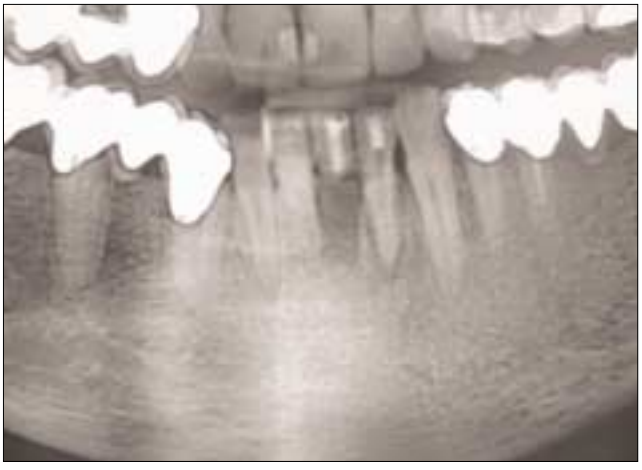

Figure 6 - Radiographic view of the area of tooth 31 without sequestra-

Figure 7 - Panoramic radiograph of the mandible following extraction of tooth 46. The image shows the mottled bone in the not healing extraction sites.

Treatment

Treatment of patients with bisphosphonates-associated osteonecrosis was difficult and was based on the different clinical situations. Even tough we do not have any scientific data to support a protocol for the treatment of patients with osteonecrosis treated with bisphosphonates, we are following the recommendations issued by the Expert Committee in June 2004 (24). Our study showed a high variability of responses. Despite discontinuation of bisphosphonate treatment at the osteonecrosis diagnosis, none patient showed any improvement.

The most common therapeutical approach consisted in the administration of systemic antibiotics (metronidazole 250x3 mg and moxifloxacine 400 mg/die) combined to a local clorexidine

therapy followed by surgical toilette of the necrotic area or removal of the bone sequestrum.
Aggressive bone surgery was performed on three patients to remove necrotic bone tissue and to enhance healing starting from the vital bone edges.
Nevertheless in one patient produced a deterioration of the bone damage with deepening of the necrosis and clinical aggravation (Fig. 8).
Hence, patients should be informed as to the risks of surgery and of the possible complications implying a deterioration of the lesions.
In the other cases, osteoplasty produced an improvement consisting mainly of the decrease of adverse effects of the mucosal traumatisms.
Hyperbaric oxygen therapy (thirty sessions) performed on 4 patients produced a clinical improvement of lesion infection and a reduction of lesion-related pain but did not produce a restitutio

Figure 8 - Exposed area in the left mandible after sequestrectomy with deepening of the necrosis and no healing.

ad integrum.

Discussion

The observation of the clinical cases described above could suggest that the origin of osteonecrosis has to be associated to pamidronate and zolendronate-induced insufficient vascularity. Hence, the onset of the lesions could be considered as a complication of bisphosphonate treatment as it has been shown by the literature (20-23).
In 2003 Marx and Stern (19) were the first to describe osteonecrosis in patients suffering from multiple myeloma and treated with bisphosphonates, even though this medication had been used for more than thirty years.
No osteonecrotic lesions had been observed in the clinical trials for these drugs and this leads us to infer that other factors could contribute to the onset of lesions. The selective onset of maxillary lesions could be associated with an ecosystem of the oral cavity that can highly colonize any open wound (post-avulsion sites).
Maxillary osteonecrosis is probably due to the inability of an hypodynamic and hypovascular bone to support an increased healing demand with bone remodelling following physiological distress (chewing), iatrogenic traumas (tooth avulsions, implant surgery, periodontal operations) and tooth infections in an environment such as the oral cavity that is continuously exposed to traumas and to a strong bacterial action. Other factors could be concomitant medications with anti-angiogenic properties (such as glucocorticoids, talidomide, chemotherapeutic drugs), diabetes mellitus, maxillary irradiation, peripheral vascular disorders and clinical conditions associated with the development of osteonecrosis in any points (25).
The management of patients with bisphosphonate-associated maxillary osteonecrosis is particularly complicated. The surgical ablation of the necrotic bone cannot fully control the disease because of the difficulties in obtaining surgical edges with a vascularised bone or because of relapses that could expose an even larger osteonecrotic area. For this reason, resection surgery should be performed on symptomatic patients only. Antibiotics treatment administered to control the infections in exposed areas gives positive results reducing tissue inflammation and relieving pain. However, antibiotics cannot lead to a complete healing of lesions. Topic treatment with disinfectant-based mouth wash has not shown any efficacy. In our experience, hyperbaric oxygen therapy seems to give positive results on controlling inflammation of exposed areas and on improving the post-surgery course in patients that have undergone sequestrotomy. None of the treated patients has shown a dehiscence of surgical wounds.
Today, bisphosphonates are the standard treatment for patients suffering from multiple myeloma and neoplasia with bone metastasis and they give excellent results in preventing pathologic bone fractures. Nevertheless, the onset of the abovementioned complications produced a deterioration of the quality of life and led to discontinuation of treatment. Furthermore, bisphosphonates are used for treating osteoporosis: hence their use must be carefully monitored. In most cases, the diagnosis is made by the oral surgeon because the oncologist often underestimates or misunderstands this complication. Hence, the medical community as a whole should become fully aware of this risk.

Conclusions

So, likewise the patients demanding radiation therapy for the heads and the neck, all patients eligible for bisphosphonate treatment should undergo a dental check up in order to detect any possible dental condition before starting therapy. As for the patients already treated, we strongly recommend dentists to collect an accurate anamnesis in order to single out not only pre-existent conditions but also the type of treatment that the patient has followed before performing any kind of oral surgery.

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