

Bisphosphonate-related osteonecrosis of the jaw: the Florence experience

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Summary

Aims. Bisphosphonates (BPs) are important therapeutic drugs in multiple myeloma and cancers with bone metastases. Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) has been described as a potential side effect of the last generation BPs. The Authors evaluated clinical features, preventing measures and treatment strategies.

Patients and methods. The Authors retrospectively analyzed 19 patients affected by malignant cancer in endovenous treatment with BPs. Fourteen patients were treated with zoledronate, 1 with pamidronate and 4 with both drugs for breast cancer (9 patients), multiple myeloma (6 patients), prostatic cancer (3 patients) and colon cancer (1 patient).

Results. The length of therapy was 5-36 months before osteonecrosis was observed; in 15 patients BRONJ involved the mandible, in 2 the maxilla and in 2 both jaws. The trigger factors were tooth extractions, inadequate removable total denture, basic and advanced surgery, root canal treatment. Ten patients received non-surgical treatment, 7 patients minor surgical procedures and 2 patients a partial maxillectomy. Healing was achieved in all maxillary localization, and in one mandibular localization with partial maxillectomy.

Conclusions. Prevention is the best important phase in the management of this pathology. Risk factors are the type of bisphosphonate and the length of exposure, while dental surgical procedures are trigger factors. Conservative treatment seems to be the best way to control BRONJ, but bone resection and soft tissue closure have to be performed when the lesion is refractory to conservative approach.

KEY WORDS: bisphosphonates, osteonecrosis of the jaw, BRONJ.

Introduction

Bisphosphonates stand as an important group of drugs for the treatment of metabolic and oncologic pathologies involving the skeletal system.

Bisphosphonates act by inhibiting osteoclastic bone resorption. The most common drugs utilized in the prevention and therapy of osteoporosis are: alendronate, risendronate, ibandronate.

Pamidronate and zoledronate are utilized in the prophylaxis of bone complications and in the hypercalcemia associated to multiple myeloma and to metastatic bone disease due to breast and prostatic cancer (1-3).

All these chemical substances are characterized by a high power and selectivity. Nowadays, literature is demonstrating the correlation between chronic bisphosphonate assumption and jaw's osteonecrosis onset (4-19).

Aims

The purposes of this report are: to describe Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) clinical aspects and to describe possible preventing measures and treatment strategies of BRONJ.

Background

First reports on BRONJ were published in 2003 (4). Since then, a study with 63 cases published by Ruggiero (6), one with 119 cases by Marx (20), one with 10 cases by Bagan (21) along with some case reports and case series provide more information on BRONJ features (22-26).

In the literature BRONJ's incidence ranges from 0.01% with oral administration to 0.8-12% with intravenous injection (12).

One of the main BRONJ risk factors is the bisphosphonate therapy length with a high risk of complications in patients treated for more than 12 months (10, 27).

From 1998 to 2004 Research on Adverse Drugs Events and Reports identified 561 cases of ONJ in patients with cancer treated with zoledronate (28). In the position paper of the American Academy of Oral and Maxillofacial Pathology 368 cases were published from 2004 to 2006 (11).

Nowadays every year 300.000 oncologic patients are treated with zoledronic acid in Italy and from 2003 to 2005 zoledronic acid prescriptions have been increased by 18% (29). These epidemiologic data show the importance in evaluating bisphosphonate associated morbidity.

In accordance with the American Association of Oral and Maxillofacial Surgery (12) and with the majority of the Authors (11, 13) the main risk factors for BRONJ development are:

- drugs related (administration way and length of therapy);
- local risk factors (basic or advanced oral surgery with bone injury; oral hygiene; smoke; alcohol; local anatomy; inadequate removable total denture; oral pathologies; infection and/or ischemic susceptible factors such as diabetes; high dose steroid treatment; radiant therapy; anemia; blood clot disease; etc.);
- demographic and systemic factors (age; race; neoplastic pathology; associated therapies).

Patients and methods

From February 2004 to September 2006 19 patients with bisphosphonate endovenous treatment and with BRONJ came to the Oral Surgery Department of the Florence University Hospital (18, 19). The mean age was 66.4 ± 11.7 years.

In 14 patients the used bisphosphonate was zoledronate, in 1 patient pamidronate and in 4 patients both drug were administered. The mean interval administration was 12 months (minimum 5 months, maximum 36).

In 9 patients (47,4%) the oncologic disease was breast cancer; in 6 patients (31,5%) it was myeloma; in 3 (15,8%) it was prostatic cancer; and in 1 (5%) patient it was colon cancer. All the patients were chosen following strict diagnostic criteria. The most frequent symptoms in the early stage were: spontaneous pain, swelling, odontogenic abscesses, oral fistula, bone exposure due to mucous ulcer, post-extraction alveolitis, and local lymphadenopathy.

The trigger factors were considered to be tooth extractions, local concussion (inadequate removable total denture, edentulous ridges), root canal treatment, basic and advanced surgery. In some cases it was not possible to identify a trigger factor.

Pre-existing inflammatory lesions and other pharmacological treatments appeared to worsen the development of the disease. The treatment of this lesion is extremely difficult and prolonged. There are no data to support any therapeutic choice: surgery often worsens the pathology.

Surgical curettage to achieve mechanical debridement is indicated in patients with no complications. Chemical debridement is carried out with antiseptic irrigations and with iodine gauze. Re-infection prevention is improved by local ointment use and 0.12% chlorhexidine daily rinses.

Surgical procedures to achieve a mechanical debridement of necrotic tissue, broad spectrum antibiotic treatment for a long period, and local antibiotic use are useful before clinical lesion changes with bone exposure and small bone sequestra.

More invasive surgical treatments (such as deeper curettage, sequestrectomies, large resections and vascularized bone grafts) are indicated after clinical changes characterized by clinical symptoms (pain, fever), oral or extra oral fistula, necrotic tissue, pathologic fractures and ineffective antibiotic treatment.

The necrotic tissue curettage, sequestrectomy, sliding flap procedure (in two cases with oro-antral communication), and peduncle vascularized bone graft (in case with fracture) (Fig. 1) were the surgical treatments used in order to stop osteonecrotic lesion progress.

Metastatic foci were not shown by histological examination both in the lesion core and in the neighbouring bone tissue.

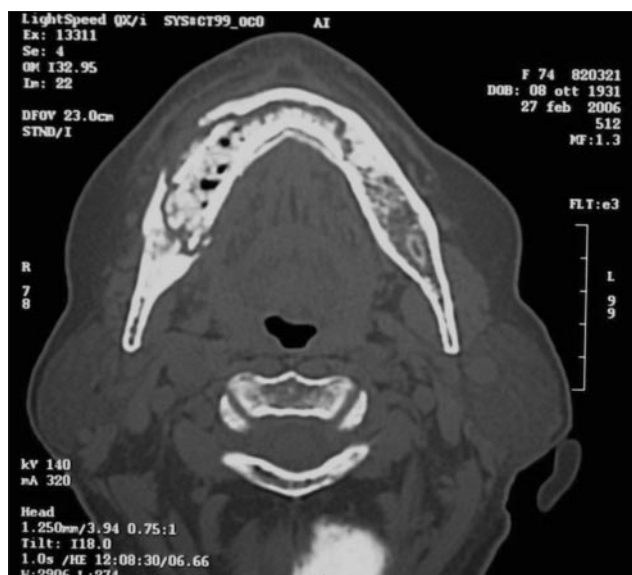


Figure 1 - CT scan: bone necrosis with pathologic fracture.

Macroscopic healthy bone samples showed cortical necrosis with well preserved lamellar bone. Furthermore, empty osteocytic lacunae were detected and midullary bone tissue appeared necrotic.

Results

In most of the cases complete healing was not observed, although therapeutic protocol was strictly applied (18, 19). All cases of maxillary location reached complete healing.

On the contrary we observed only symptoms of improvement when the location was mandibular, probably for the reduced regenerative capacity at this site (Table I).

Following American Association of Oral and Maxillofacial Surgery (12) staging and treatment criteria, two different clinical courses have been identified:

- 1) early clinical course, where small bone sequestrum can be assessed (Fig. 2);
- 2) late clinical course, where large necrotic areas worsened by suppurative phlogosis can be detected (Fig. 3).

Table I - Results of the study.

Outcome	Localization	n°	Treatment	Prognosis
Healing	Upper jaw	2	Minor surgery	Follow up 1 year
	Lower jaw	1	Bone resection and vascularized bone graft	Follow up 6 months
Prolonged controlled phase	Lower jaw	9	Mouth rinse, strict clinical follow up, no surgery/minor surgery	?
Large necrosis phase and complications	Lower jaw	5	Bad clinical condition, not recommended surgery	inauspicious
Death	Lower jaw	1	Bone resection and vascularized bone graft	
	Upper and lower jaw	1	Mouth rinse, strict clinical follow up, no surgery/minor surgery	



Figure 2 - Panoramic radiograph demonstrating a bone sequestrum area.



Figure 3 - Large necrotic areas with suppurative phlogosis.

Discussion

Up to 2002 BRONJ incidence was lower than 1 out of 10.000 treated patients (4, 5). The use of the last generation bisphosphonates (i.e. zoledronate) increased the incidence of BRONJ up to an endemic behavior (6-9). All patients observed had bisphosphonate endovenous treatment with administration intervals of 30 days. Our data, in agreement with what published, showed a higher incidence in patients treated with zoledronate (Zometa) and pamidronate (Aredia). On the other hand these kind of lesions were seldom detected in patients treated with aledronate (Fosamax) and risedronate (Actonel). Clinical pictures varied from the more frequent limited osteonecrosis areas with or without suppurative phlogosis to the larger os-



Figure 4 - Submental region: extra-oral fistula.

teonecrotic areas with suppurative phlogosis, jaw fractures and extra-oral fistulae (Fig. 4).

The role of bisphosphonates in the onset of the lesion is confirmed by the time elapsed between drug assumption and lesion development, that seems to be around 18 months for zoledronate and 6 year for pamidronate (10), even though the lesion can onset even after 5 months of treatment (9-14, 30).

All the patients of our study underwent a drug treatment longer than 6 months. For many Authors long periods of drug treatment is a risk factor (as chemotherapeutic treatment, myeloma, renal failure, hypoproteinemia, steroid therapy, anemia, blood clot disease, infections, etc.) (8, 11-14, 31-34).

Patients under chemotherapeutic and corticosteroid treatment and patients who underwent radiant therapy presented larger tissue necrosis and refractoriness to our therapeutic protocol. In our study osteonecrotic lesions preferential location was in the lower jaw. This location seems to be explained by anatomic local factors such as terminal vascularization and by a lower quantity of trabecular bone in the mandible than in the upper jaw (35).

Actually even spontaneous lesions (incidence 22-30%) (14, 36) are due to microinjuries; these lesions are more frequent in the lingual posterior areas of the lower jaw. Indeed in this region mucosa is very thin and there are higher trauma due to removable denture and higher masticatory forces (4, 20, 31).

In the majority of cases the clinical picture evolved in two phases: in the first phase small multiple bone sequestra are dominant with a good therapeutic response; the following phase is characterized by a large suppurative necrotic area in which pharmacologic treatment becomes inefficient.

We have seen a clinical change after which the conservative treatment led to poor results and in these cases a more invasive treatment should be indicated (Fig. 5).

Hellstein et al. (7) suggest the surgical treatment only when infection cannot be controlled but large bone resections should always be avoided (4, 9, 11, 37).

According to Ruggiero et al. (38-40) the clinician should adopt different treatment protocols on the basis of patient's characteristic lesions.

In order to trace guidelines American Association of Oral and Maxillofacial Surgery (12) suggested four staging categories (risk category and stage 1, 2, 3) for the patient who underwent endovenous or oral bisphosphonate treatments (38).

The interruption of bisphosphonate assumption is one of the most difficult decision and should be taken in agreement with the oncologist. According to Migliorati et al. (9) the discontinuation of bisphosphonate treatment is mandatory, even though there is no immediate clinical improvement.

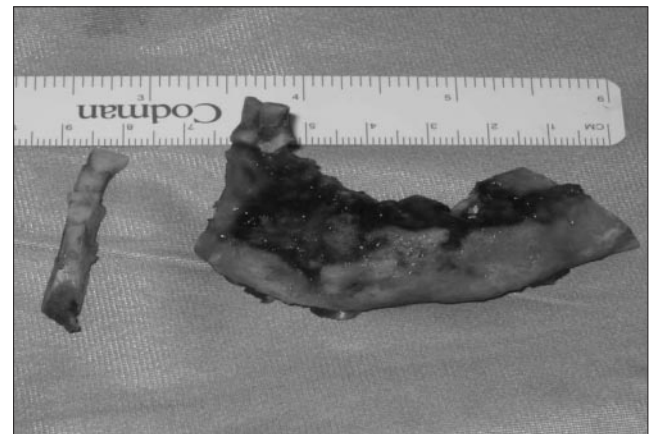


Figure 5 - Emimandibulectomy.

Robinson (31) contraindicates any surgical treatment when the patient is taking bisphosphonates, as the implant treatment is doomed to failure in patient with bisphosphonate treatment. In an experimental study Narai (41) assessed a dangerous torque during implant placement.

In a patient treated with zoledronate reaching our observation for an exposed bone in the implant area with a wide bone necrotic area developed after implant surgery. This patient was treated with broad spectrum antibiotics for a long period of time (Fig. 6).

One should not generalize on bisphosphonate morbidity, as there are some molecules as clodronate, that can improve implant stability and osteointegration (42).

Hyperbaric treatment is considered by many Authors with no effect (9, 43). In our experience patients treated with antibiotic and hyperbaric chamber showed a good soft tissue regeneration (18), making possible to conclude that hyperbaric treatment represents a good aid in soft tissue management (44, 45).



Figure 6 - Failure of implant therapy with large bone osteonecrotic area.

Conclusions

After numerous reports published in the last four years about the adverse effects of bisphosphonates on bone health, many Organizations [Novartis (14), American Academy of Oral Medicine (13), American Academy of Oral and Maxillofacial Pathology (11), and American Association of Oral and Maxillofacial Surgeons (12)] elaborated the precautionary measure guidelines on diagnosis and treatment of BRONJ in oncologic patients treated with endovenous bisphosphonates (46).

We added more information about prevention and treatment strategies. Prevention is of primary importance in patients who need bisphosphonate treatment (11-14, 47-50). It is, therefore, necessary:

- a) close dialogue between dentist, oral pathologist, oncologist and physician;
- b) patients must be informed of these complications in order to do not underestimate some early symptoms;
- c) general detailed anamnesis;
- d) specific oral anamnesis (facial pain, swelling and chewing impairment, oral mucosa status and progressive oral surgery treatment);
- e) evaluation of all systemic and local risk factors;

- f) informed consensus;
- g) strumental evaluation: panoramic X-ray and TC. Patients should take a panoramic X-ray for compromised tooth extractions. A TC-99mT can help in detecting possible lesions and "increased uptake areas" or "cold spots". Cold spots could stand for cavitary necrosis;
- h) all dental procedures should be completed (48);
- i) do not wear inadequate total removable denture;
- j) strict hygiene control.

Treatment strategies are based on BRONJ staging. The treatment objectives for patients with BRONJ are to eliminate pain, control infections of the soft and hard tissues and minimize the progression or occurrence of bone necrosis (12).

According to our clinical experience, there is not a clear correlation between tooth extraction and BRONJ onset. A clinical picture showing dental suffering represent a suspected osteonecrotic area. Leaving these lesions untreated means to promote a quicker and heavier osteonecrotic lesion expansion (swelling, abscesses, mucous/cutaneous fistulae).

In these patients therapeutic choices must be guided by the lesion clinical features, applying a conservative protocols in the early stage and resective surgery in the late stage of the pathology.

Bisphosphonate drugs should be administered only to the most severe oncologic cases: patients with normal calcemic pictures or with stable bone metastatic disease have not be treated.

However, bisphosphonates represent a therapeutic possibility irreplaceable for many patients affected by neoplastic pathologies. Bisphosphonate morbidity appears in a limited group of patients. It becomes therefore essential to genetically identify a subclass of patients at risk of osteonecrosis.

Our group is researching a possible genetic profile implicated in the development of BRONJ also searching for genetic markers, useful to detect pharmacogenetic differences before the start of treatment.

Clinical research about this pathology requires a multicentric study. A common data base collecting all epidemiologic and clinical data is essential to reach a deeper knowledge on the management of BRONJ patient.

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