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REVIEW OF JAW OSTEONECROSIS IN PATIENTS TREATED WITH BISPHOSPHONATE

SUMMARY

This article presents a small series of the patients with osteonecrosis of the jaws (OJ), recently treated with bisphosphonate (BP).

The OJ is a significant complication revealed recently as a consequence of the treatment with BP.

From 2003, the cases of OJ in relation to intravenous administration of BP have been published, particularly in the patients with advanced cancer and bone metastases. Also, there have been mentioned the cases of OJ with oral intake of BP.

Low incidence and lack of information as well as its recent detection results in the fact that the OJ is still an unknown issue, although these patients are seen relatively frequently and many patients with OJ appear in medical/dental offices.

Key words: **osteonecrosis of the jaws, bisphosphonate, osteoporosis, bone metastases, prevention**

INTRODUCTION

All the BPs have the common chemical structure where one atom of the carbon is attached to two groups of phosphate (Ph-C-Ph) producing negative electronic charge, which explains its affinity towards bone tissue.

Bisphosphonate (BP) is a synthetic analogue of natural inorganic pyrophosphate that possesses high affinity towards calcium. This characteristic causes deposition of BP in the mineralized bone matrix during a long period of time (1).

The potency of this action derives from the chains laterally bonded to the common nucleus; these chains are nitrogenised, which impulses major BP activity (2).

The mechanism of action, although not yet completely revealed, is based on BP fixation and apposition in the hydroxylapatite, avoiding osteoclastic reabsortion without intervening in the bone formation and mineralization (3). The antiosteoclastic effect of BP is achieved initially by stopping the differentiation of haematopoetic stem cells, as well as inducing apoptosis (programmed cell death) of mature osteoclasts (2).

Some of BPs, particularly those of the last generation and more potent that incorporate nitrogen in their molecules show an inhibitory effect on tumour cells proliferation as well as in angiogenesis (3, 4).

Induced by the tumour cells that control stimulating liberation factors, releasing of bone calcium is stopped (3). All this can contribute to the inhibition of bone reabsortion and stimulate an increment of the bone mass (1).

The intravenously administered BPs are used basically in the treatment of oncologic patients, including malignant hypercalcemia, bone metastasis

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from the breast, prostate or lung cancer, and also in the therapy of litic lesions of the multiple myeloma (5-9).

Those are the goals of prevention and reduction of skeletal complications, such as severe pain, pathologic fractures or compression of the spine medulla (10).

Although the increase in the oncologic patients has not been demonstrated, there is a huge impact on improving the quality of life particularly in the patients with advanced stage of cancer of the skeletal system (11). In August 2007, the FDA (Food and Drug Administration) approved the use of zoledronic acid (Aclasta ®), as a yearly monodosis for postmenopausal osteoporosis (12, 13).

The orally used BP has a very low absorption rate, no more than 1%, or even less if consumed in fasting. The average life of BP in plasma is almost one hour, while 20% of the orally absorbed BP is incorporated in the jaw bones. The average bone life of BP is superior to 10 years and it is eliminated from the body metabolized through the urinary tract (2). Apart from the aetiology, BP together with calcium and vitamin D play a fundamental role in the osteoporosis and osteopenia treatment. Furthermore, BP is used for less frequent conditions such as Paget's disease and imperfect infantile odontogenesis (11).

They are indicated only for the treatment of osteoporosis (14, 15) with eventual history of inflammatory intestinal or primary billiary cirrhosis, use of other medicaments, basically steroids (16), or as a consequence of menopause.

The presence of BP is associated with multiple risk factors such as diagnosis of cancer, concomitant treatments (chemotherapy, irradiation of the head and neck tumours, and corticoids) as well as with multiple situations of co-morbidity (anemias,coagulopathies, infections and pre-existence of oral disease) (17). It seems that OJ is caused by a combination of deficiencies of vascularisation as well as remodelation and regeneration of bone. Thus, the medicaments used to decrease the bony destruction provoked by tumour cells in fact produce the bone problems in some patients (3).

MATERIAL AND METHODS

We conducted the study comprising 30 patients who received BP and were referred to our clinic, between February 2006 and September 2007, suspected on OJ.

As including criteria (established by AAOMS – American Association of Oral & Maxillofacial Surgery) (18) we adopted:

1. Current or previous treatment with BP.
2. Jaw bone exposed for at least 8 weeks, and,
3. No irradiation history of the jaws.

The patients affected with cancer of the jaws were excluded.

RESULTS

The majority of cases were oncologic patients receiving antineoplasic treatment (80%), most of them with cycles of intermittent steroid involvement (53, 3%). Totally, there were 24 females (80%) and 6 males (20%), with mean age of 62 years (41-84).

From these 30 cases, four (13.3%) had the diagnosis of osteoporosis, two (6.6%) had rheumatoid arthritis, while other patients presented with breast cancer, twelve of them (40%) multiple myeloma (13.3%) and prostate cancer (13.3%). Further two cases (6.6%) had coexistent multiple myeloma and prostate cancer. In eighteen (60%) cases zoledronic acid (Zometa®) was used as BP; in six cases (20%) sodium alendronate (Fosfamax®) was administered; in four cases (13.3%) bi-sodium pamidronate was used (Aredia®) which was previously substituted by zoledronic acid; in two cases (6,6%) the treatment with zoledronic acid was replaced by ibandronic acid (Bondronat®).

The average time of intravenous BP treatment was 31.2 months (14-65), while oral administration of BP was 89 months (32-176). In one case, the total time of treatment was 29 months (13 orally and 16 intravenous). Average doses of zoledronic acid were 93.7 mg (14-65), while alendronate treatment average was 26.350mg (8963-51.332). The quantity in milligrams for patients treated with pamidronate prior to zoledronic acid was 1955mg (1180-2690) and 143 mg (138-142), respectively.

The time passed from the beginning of treatment with BP until the appearance of OJ in the cases where there was no evidence of any dental treatment was 23 months (16-30). In all of these cases, the BP used was zoledronic acid and all the treatments were completed within the following 13 months, except one which was suspended immediately.

Most frequently, the localization was in the mandible (22 cases or 73.3%) in its posterior lingual region, while in two cases, the maxilla was affected. Other 8 cases (26.6%) were isolated in the maxilla. In 28 cases OJ was unilateral (93.3%), while two cases were bilateral in maxilla (6.6%).

In 18 patients (60%) where DXA was performed (dual x-ray apsortiometry), the alterations in bone density were found in the spine and hip along with osteopenia in 12 patients as well as osteoporosis in another 6 patients. In 12 cases (40%), diabetes mellitus type II was diagnosed previously.

Fourteen patients (46.6%) were smokers consuming 16 cigarettes a day on average (5-37) during the mean time of 27 years (12-32).

The beginning of OJ is in manifested with pain in 18 (60%) patients, inflammation in 6 (20%) patients, while 6 of them (20%) had the jaw bone exposed.

The most common symptoms found in our series were: bone exposure (100%), halitosis (73.3%), pus (60%), pain (53.3%), tooth sensibility (53.3%), bone loss (46.6%), nutritional difficulties (46, 6%) and disturbances in the mandible (46.6%).

In our series, we found 6 cases with fistula submental (20%) and 6 cases (20%) with fistula oral-nasal and sinusitis maxillaries.

The most common finding was an ulcerated mucosa, with exposed bone and suppuration due to the overinfection of the area (60%). Biopsy was performed in 10 cases (33.3%); the histology result always indicated the presence of tissue with inflammatory signs, chronic or acute non-specific, and no evidence of malignancy nor the presence of microorganisms compatible with Actinomyces.

Orthopantomographic radiography was performed in all cases and basically showed osteolysis associated with OJ. Bone scintigraphy was done in 22 cases (73.3%) and was very unspecific, capturing not only the pathology compatible with OJ. CT was performed in 12 cases (40%) to obtain a better evaluation of bone destruction or affectation of the maxillary sinus.

Treatment approach was conservative with continuous cycles of systemic oral antibiotherapy, 0.12% chlorhexidine for mouth rinsing in all cases. The most utilized antibiotic was Amoxicillie/ clavulanic acid (80%). In one case (6.66%), sequestrectomy was performed with mucosal flap, but in two years sequestrectomy and partial ostectomy of alveolar process of mandible were necessary again, and, actually, the bone was exposed again.

In 6 patients (20%) which presented submental fistula, the local cures were realized with physiologic solution, ciprofloxacin and one hydro gel (Nu-Gel®), resulting in fistula disappearance, improving a clinical presentation and less problems in alimentation in 2-3 weeks of treatment.

In total: three patients (20%) exhibited significant clinical improvement, decrease in their oral lesions and stopped taking their initial treatment; 18 patients (60%) continued with the symptoms, with occasional improvement related to the cycles of treatment; six patients died from their basic disease.

DISCUSSION

In 2003/04, for the first time, maxillofacial surgeons (19, 20) reported about the patients treated intravenously with BP that presented with bone exposure in the mouth, condition that did not cicatrize. Currently, there are more and more cases published in reviews and journals, congresses etc. in which an important relation between OJ and BP is presented (21-25).

The true incidence of OJ has been unknown yet. The studies and reports on it are very limited and are not quite demonstrable. The cumulative estimation of OJ incidence varies from 0.8-12 % (26, 27) in cases of intravenous BP to 0.7/100.000 patients treated by BP orally (dates on alordenate) (11). This incidence is probably higher when more sophisticated devices are employed during the examination and follow-up of cases.

The Spanish Consensus of Experts (2006) considered different criteria of diagnosis for OJ associated with BP (28, 29):

1. Patients who are or have been treated with BP intravenously.
2. Presence of one or more ulcerated lesions in the mucosa of alveolar ridge with exposure of the mandibular or maxillary bone. Also, the pain and fistula cases may be present.
3. The exposed bone has a necrotizing aspect, and
4. Absence of mucosa cicatrisation during 6 weeks at least.

These criteria are focused on the previous diagnosis of neoplasia. However, as there were the cases developed in non-neoplastic patients, we decided to apply the criteria of AAOMS for our study which included the cases of general BP treatment, not only IV treatment with BP for neoplasic patients.

The mechanism of BP action is still unknown completely. Basically, BP is a selective inhibitor of osteoclastic action in bone remodelation cycle.

Because of this anti re-absorptive action, BP reduces the bone remodelation and, due to a so-called accelerated secondary mineralization, produces a rapid and detectable increase of mineral density of bone (12). It seems that it also acts on osteoblasts, decreasing apoptosis and stimulating secretion of the inhibitors of osteoclasts recruitment (30). The anti-angiogenic effect was described due to inhibitory effect on endothelial cells decreasing their proliferation and inducing their apoptisis (4).

It is still difficult to explain that its inhibitory action on bone reabsortion and its use for skeletal complications prevention is related to OJ. Possible explanation might be that the jaw bones are exposed to greater act of remodelation, and that are in closer contact with septic ambient which exists in the mouth (22). However, in order to establish a firm relation

between BP and OJ, more investigations, controlled clinical tests, randomized, prospective and double blind (with $p < 0.05\%$) studies are requested (17).

In our study, the age ranged from 41 to 82 years, which is very similar to other studies (25, 27, 31). The feminine gender was affected up to 80%, which differs from other studies (25, 31, 32).

Although the vast majority of cases are associated with intravenous administration of BP, particularly zoledronic acid, which in our study was applied in 80% of cases, there were cases described in literature as well as in our study (20%) of OJ related to oral use of BP such as alendronate, ibandronate or risendronate (20).

The basic disease most frequently was breast cancer (40%), which coincides with other studies (22, 25).

Regarding the time of BP application, we concluded that the risk for OJ with venous treatment begins to be evident after 12-14 months of treatment and significantly increases after 36 months (17, 30). Accordingly, the Mayo Clinic recommends the limitation of BP use in multiple myeloma no more than two years in stabilized patients and decreasing it every three months for the patients more seriously affected (9).

With oral BP it is necessary to apply much higher doses, because its biodisponsibility is very poor. The risk increases after three years of treatment and a decent posture should be no more than five years of treatment (25), continuing with general measures for the patient (balanced diet, no smoking, moderate gymnastics, calcium and vitamin D supplements). In addition, the treatment can be switched from one schedule of intermittent administration to other type of treatment if there are risks of pathological fractures (25).

The most frequent localization is the mandible (73, 3%) and the major affectation of jaws indicates that OJ develops from the vicinity of periodontal ligament of teeth which induces infection propagation through damaged tooth or periodontal disease.

Factors, as thickness of mucosa which covers the jaws and makes it vulnerable to various traumatisms, can provoke ulcerated lesions, resulting in the bone exposure, its infection and avascularisation.

Very important facts for the development of OJ in our study were previous extractions of teeth (66.6%); other series show 33% (22), up to 86% (20). Nevertheless, there are cases of spontaneous appearance of OJ, particularly in our study (33, 4%). Because of this, the treatment of these patients is difficult, while the initial radiography might show negative result in these cases (22). Also, the standardized protocols of treatment were established depending on every single case, its evolution and medical team responsible.

The pharmacology treatment is based on antibiotics and application of 0.12%-0.2 % chlorhexidine for mouth rinsing.

The surgical approach is not quite effective in eradication of necrotic bone, so that the surgery involves the sequecuetretomy, partial maxillectomy and mandibulectomy even being very difficult to obtain surgical margins that are well- vascularised (19, 20, 25).

Up to now, the first goal of treatment has been to control secondary infections and pain, prevent extension of the lesion and new areas of necrosis; also, the patient should be advised about the importance of mouth and teeth hygiene, cleansing the prosthesis and going to the dentist for systemic controls.

The hyperbaric oxygen therapy has not been effective to stop this process (16, 17, 19, 27, 32), although it has been published that pain disappeared in some cases with the use of hyperbaric oxygen along with antibiotics (14).

The BPs are not metabolized so they can be present in the bone for a long time, sometime years after suspension of them. This is the reason why the suspension of BP does not seem to accelerate the recuperation of OJ (1,17,19), although in our study an improvement in three cases associated with oral intake of BP (20%) was noted, 5-6 months after discontinuation of BP.

If the patient has to initiate the treatment with BP, the physician, who prescribes BP, should send the patient to his dentist for further clinical and radiological exploration of the oral cavity and eventual diagnosis of any pathological process present, as well as the dental treatment that the patient should undertake and finally to be scheduled for periodical follow-up.

The decision of venous BP suspension in oncological patients having OJ should be brought by oncologist consensed in collaboration with maxillofacial surgeon (17).

The treatment being too complex, our principal goal is the prevention of disease and thorough information to the patient.

If the patient needs an invasive surgical approach (extractions, periodontal surgery, torus elimination etc.), some authors (17, 18, 19, 20) recommend a delay of BP treatment for at least one month and realize the same under antibiotic prophylaxis with penicillin and 0.12% chlorhexidine (in case of allergy, use azitromicin, metronidazol and quinolone).

If the patient is already under BP treatment, he/she should necessarily be remitted for a validation of mouth and teeth and realization of the treatment,

which means the most conservative approach, avoiding, if possible, teeth extractions, and surgical procedures (19, 30).

If the surgery is necessary, the antibiotic prophylaxis and chlorhexidine must be employed. Certainly, always make previous consent information in a written form, and specify that the patient was completely informed of possible complications.

The AAOMS recommends that the patients being under less than 3 years oral treatment with BP and without other concomitant factors, such as a long-term treatment with corticoids, do not need a change or delay in oral surgery treatment. Otherwise, (if they consume steroids more than 3 years) suspension of BP before and after the surgery should be reconsidered, although it has not been proven if thus OJ could be avoided (4,18). In our series, out of three patients with OJ associated with oral BP intake, only one had corticoid backing treatment and he presented OJ after 32 months associated with tooth extraction with antibiotic prophylaxis.

Any unnecessary treatment should be avoided, particularly are the dental implants contra-indicated (3, 19, 30-36) as well as procedures related to dental aesthetics (17).

Some authors (19, 30, 34) consider that in cases of irreparable teeth, it is better to perform endodontics with crown amputation than extraction of tooth.

The problem might be the economy (33, 35) of the patients for conservative treatment, in the case of which extraction should not be performed because of OJ risk (patients with profound caries, root rests, pain or impossibility to restore or renew prosthesis, or in the patients with very prolonged medical treatment).

It is convenient to check and adjust adequately the dental prosthesis, put it out during the night and motivate the patient to undertake adequate measures of mouth hygiene and alimentation, as well as to programme periodical checking of oral cavity (17, 30-39).

CONCLUSION

The best way to prevent and avoid OJ appearance is one thorough and deep tooth check-up as well as the application of all preventive methods for the patients under BP treatment. If the patient is already under BP treatment, he should be informed about the importance of maintaining mouth, dental and prosthesis hygiene, scheduled check-ups and visits to the dentist if acute pain or exposed bones appear.

If the patients under BP treatment are not affected with OJ, extraction should be done or surgery that is absolutely necessary; they always must be covered by antibiotic prophylaxis and chlorhexidine.

It is very important to personalize every patient and evaluate the type of BP treatment (venous or oral), time and doses of intake, basic pathology and accompanying diseases.

Further research of multiple interactions existing in the genesis of this complication will enlighten the exact etiologic and pathogenetic mechanisms involved in it. In addition, this will clarify some questions, such as what the real incidence of this complication is, so that diagnostic, preventive and therapeutic guidelines could be established.

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PRIKAZ OSTEONEKROZE VILICE KOD BOLESNIKA LEČENIH BISFOSFONATOM

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SAŽETAK

Članak prikazuje malu grupu bolesnika sa osteonekrozom vilice (OJ) koji su nedavno lečeni bisfosfonatom (BP).

OJ je značajna komplikacija nedavno otkrivena kao posledica lečenja bisfosfonatom.

Od 2003. godine objavljeni su radovi na temu osteonekroze vilice u kojima je prikazana veza sa BP, naročito kod bolesnika sa kancerom u odmakloj fazi i metastazama kostiju. Takođe, pominju se i slučajevi osteonekroze vilice kod oralnog unosa BP.

Mala incidenca i manjak informacija kao i skorašnje otkriće rezultiraju činjenicom da je osteonekroza još uvek neistražena tema, premda se ovi bolesnici često javljaju u medicinskim i stomatološkim ordinacijama.

Ključne reči: **osteonekroza vilice, bisfosfonat, osteoporoza, metastaze kostiju, prevencija**