case report

OSTEONECROSIS CAUSED BY BISPHOSPHONATES: A CLINICAL CASE

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SUMMARY

Osteonecrosis caused by Bisphosphonates: a clinical case

The osteonecrosis of the maxillares caused by bisphosphonates (OMB) either wrongly known or not reconised in earlier times became nowadays very important among the dentists and maxillo-facials surgeons because of the potential serious consequences that might bring in the oral cave of the patients, who are suffering already for their base condition. The goal of our work was to verify if a deep treatment and an attentive observation with a close follow-up can bring to the resolution of serious cases of osteneсrosis of the maxillares by bisphosphonantes. Although without a statistic value our case report put the basis for a chance to execute wider casistic studies.

Key words: osteonecrosis, bisphosphonates.

RIASSUNTO

Osteonecrosi da Bifosfonati: presentazione di un caso clinico

L'osteonecrosi dei mascellari da bifosfonati (OMB) dapprima misconosciuta o non riconosciuta è divenuta attualmente di preminente importanza tra i clinici odontoiatri e maxillo-facciali per le potenziali gravi conseguenze che può avere nel cavo orale dei pazienti, spesso già seriamente sofferenti per la loro condizione di base. L'obiettivo del nostro lavoro è stato quello di verificare se un approfondito trattamento ed un'osservazione scrupolosa con un serrato follow-up possono portare alla risoluzione di casi anche gravi di osteonecrosi dei mascellari da bifosfonati. Pur non avendo valore statistico il nostro case report pone le basi della possibilità di eseguire studi casisitici più ampi.

Parole chiave: osteonecrosi, bifosfonati.

Introduction

The bisphosphonates represent an important class of drugs, which are useful for the treatment of metabolic and oncologic pathology involving the apparatus of the skeleton. Their mechanism of action is based on the capability of blocking the bones reabsorption mediated from the osteoclasts. Commonly these molecules are incorporated inside the osteoclasts determining a serious functional alteration to the cellular apoptpsis. The most common bisphosphonates used in therapy are: alendronate, risendronate, ibandronate, zolendronate and pamidronate. The first three are used for the prevention and the treatment of the osteoporosis and are taken per mouth whereas pamidronate and zoledronate have an essential role in the prevention of the bony complications and in the treatment of severe hypercalcemia associated to multiple myeloma or to bony metastasis followed to mammary or prostatic carcinoma and are generally taken intravenous.

Since 2003, the year when the first case of osteonecrosis associated to the use of bisphosphonates appeared (1), it's now happening more often to notice a similar collateral effect as a consequence of bony traumatisms, like a simple dental extraction, in patients treated with these kind of drugs. The osteonecrosis can be linked to a wide variety of local and systemic factors like emoglobino-pathologies, presence of antibodies anti cardiolipin and defects of fibrinolytic, gas embolisms, alcoholism, systemic erythematous lupus and corticosteroid therapies, capable of compromise the vascularization of the bone. Before then, described for the first time by Marx and Stern in 2002, the osteonecrosis of the maxillaries caused by bisphosphonates was defined as a condition that involves the presence of bony exposition in

mandibular or maxillary site, which persists from more than 8 weeks in a patient which took or is taking bisphosphonates and with negative anamnesis for radiotherapy of maxillaries. The same illness was probably observed more than 100 hundreds years ago as "industrial occupational" illness, called chemical osteonecrosis by phosphor or "phossy jaw". As reported, the miners of the factories producing matches in USA and UK developed persistent bony exposition just in the oral cave, linked to the time they were spending in the miners and factories (22).
Consequently for this class of drugs it became necessary to do an accurate pharmacological anamnesis (present, past or future), in order to reduce the most the risk of post-traumatic osteonecrosis of maxillaries, doing at the same time a preventive action which can avoid a such dramatic possibility.

Clinical and epidemiological aspects

In the 70-80% of the cases, the osteonecrosis of the maxillaries caused by bisphosphonates is manifesting with a missed healing or with a late process of healing of the maxilla or the mandible after a dental extraction or after any other kind of oral surgery (2). The early steps of the pathology consists of the missing of symptoms and absence of radiological alterationsi; in this phase the pain can be caused by some infections of the portions of the bone that is exposed. In the 25-40% of the cases, the osteonecrosis of the maxilliares happens on his own without any correlation to particular traumas (3). In these cases the first and most common symptoms is manifested with a bad sensation in the mouth with pareshesia and soreness. It happens then a gradual alteration of the oral mucosa with a formation of persistent ulcers. In this phase it can be manifested a strong pain caused by infection of the portion of the bone which is necrotised inducted by the oral bacterial flora. Since these symptoms arrive before the proper osteonecrosis, their identification is essential to the goals of the prevention. Normally, the mandible and the maxilla are the only bones involved in the osteonecrosis caused by bisphosphates; in the 70% of cases the effect is manifesting principally in the mandible, at the level of the region of the molars, whereas in the 30% of the cases the osteonecrosis is manifested in the posterior maxillaries region; just in very few cases the alterations involves both the bones (4). The involving of the maxilla represents a noticeable difference between the osteonecrosis cuased by bisphosphonates and the osteoradionecrosis, a form of osteonecrosis which is secondary at radiotherapy for the treatment of the carcinoma in the head and the neck. In the 95% of the cases this form of osteonecrosis involves just the mandible (5).
It is not still clarified who are the patients which are the most on a risk for the osteonecrosis of the maxilla. Till now, the complication was observed principally in the patients with tumors treated with bisphosphonates intravenous. The cancer and the use of the chemiotherapies for systemic way are in fact considered the most important co-morbose conditions. There were reported some cases of patients which have manifested osteonecrosis not linked to cancer; among these, 19 manifested osteoporosis (17 were treated with alendronate, 1 with risedronate and 1 with alendronate and zoledronate) and 9 were affected from Paget disease (4 were treated with alendronate, 4 with pamidronate and 1 with pamidronate and alendronate).
Anyway, it is with any probability a bad valuation of what is the real importance of this complication in patients treated with bishosphonates taken by mouth. In fact, in a recent review made by the American Dental Association, the cases of osteonecrosis associated at the oral use of bisphosphonates on a worldwide level resulted 170 for the alendronate, 12 for the risedronate and 1 for the ibandronate.
For what it concerns about the patients treated with bisphosphonates taken by mouth the two factors which add more risk for the development of osteonecrosis are the following: the duration of the treatment and the association at the same time with corticosteroids and in particular with the prednisone (19).
In relation to the type of dental procedures, in 60% of cases of osteonecrosis is manifesting after dental extractions (6). Cases of osteonecrosis were noticed on holders of removable incongruous prosthesis, of traumas on bony exostosis, after the surgeon procedures for the insertion of the implants (7). There were even some cases of post-endodontics osteonecrosis (8).

Patogenetic mechanism

In the past, the bisphosphonates were called diphosphonates: the modification of the terms sometimes caused confusion. The bisphosphonates are linked to the complex pyrophosphates, which were used as anti-tartar agents in the toothpastes and as osteospecific radionuclides in bone scintigraphy with medium of contrast.
The affinity for the sites of the active bone change is clear by looking the increment of the uptake on the plates of *coltura,* in the neoplastic localisations, in the bone grafts and in the scintographies of normal bones of the superior maxillaries and of the mandible. The pyrophosphates are easily degraded with a process of hydrolysis and then eliminated. Because of a substitution with an atom of carbon of the atom of oxygen in the principal axes of the molecule, the bisphosphonates are totally resistant to the hydrolytic scission, which is followed by their increment in the bone tissue and their extremely long half-life. Moreover, the substitution of the lateral chain of nitrogen on the central atom of carbon increments the power and probably the toxicity. Till now, it is known that just the bisohosphonates including nitrogen can cause the osteonecrosis of the maxillaries. The main biological action of all the bisphosphonates is the inhibition of the reabsorption and of the turnover and renovation of the bone tissue, which naturally reduce the silky levels of calcium. The anti-osteoclastic and anti-reabsorption action is made by the effect of inhibition on the osteoclastics, of which the bisphosphonates cause in fact the irreversible cells death. After the taking one of the oral bisphosphonates with less toxicity by vein or by mouth, the drug links quickly to the mineral crystals of the whole bone tissue. After several doses it fill the bone matrix. During the normal bone remodelling the osteoclastics reabsorb the mineralised bone tissue and the bisphosphonate is introduced into the cell; the effect of the drug is similar of the isoprenoid diphosphates lipids. This isoprenoid lipids are essential for the enzymes which have a preventive function to the apoptosis of the osteoclastis. On the microscope you can observe that the osteoclastics lose their usual *orletto*, they disappear from the bone surface and they have a necrosis. Without the bone reabsorption and the release of the proteins inducing the osteogenesis, the fix bone is not removed and the new osteoid substance is not created. The old bone, then, remains present ahead of its programmed vitality. Since the osteocyte is not an immortal cell, it will have a necrosis leaving there a not vital bone. The function of the osteocyte is not the bone neo-formation (which is function of the osteoblasta instead), but the acting like a *meccanocettore* in order to maintain the mineral matrix of the existent bone. So, if the osteocyte doesn't provide the control of the normal bone remodelling, a more than enough production of mineral matrix is created, which is a factor that contributes to the osteonecrosis caused by bisphosphonates since this last ones are toxic for the osteoclasts and stop the bone turnover, represent a perfect example of paradox biological situation and with no way out. The increment of the bosphosphonates in the bone, in particular in the maxillaries bones, is not reversible for their toxic effect on the osteoclasts, which goes up with every dose. So, the bone toxicity of the bisphosphonates depends from both the dose that is taken and the duration of the therapy.
The bisphosphonates prevent the bone reabsorption through the inibition of the osteoclastic activity which happens with the involvment of different mechanisms (9-10-11-12).
Inibition of the development of the osteoclasts by monocytes.
Increment of the apoptosis of osteoclasts.
Prevention of the development of the osteoclasts and their using from the bone marrow precursors.
Stimulation of the factor of inibition of the osteoclasts.
Reduction of the osteoclastic activity through an effect on the cell cytoskeleton.
Recently some anti-angiogenetic characteristics were described for these drugs (13). The result is a deep suppression of the bone turnover and, with the time passing by, reduction or stopping of the bone remodelling. The bone which becomes fragile will be incapable to repair the physiological microfractures which are caused every day in the maxilla or the mandible by the strength the chewing acts are made with. Dixon and Coll. (21) documented the ve-

locity of the bone remodelling in different sites and they found that the alveolar crest is remodelled with a velocity which is 10 times superior than the one of the tibia, 5 times superior to the one of the mandible at the level of the mandible canal and 3.5 superior to the one of the mandible in the correspondence of the inferior border. As result, the alveolar bones of the maxillaries have a much elevated uptake of bisphosphates which are concentrated in this point very quickly and in a good quantity. This study demonstrated as well that the maintaining of the alveolar bone structure depends more than any other corporeal bone of the adult skeleton from the processes osteoclastic of reabsorption-rimodelling and renovation. The particular collocation of the osteonecrosis inducted from bisphosphonates in the oral cavity can be attributed to the exposition of these bone structures to the environment through the gum sulcus, which can facilitate the infection of the bone and the progression to osteomyelitis. The particular conformation of the oral cavity allows to explain why a wide number of cases are associated to dental extractions or to other invasive procedures, which are situations in which the risk for infection and the necessity of reparations and remodelling of the bone are major.

Prevention - Therapy

The evaluation of the risk starts from a good anamnesi, the next level would coincide with the effectuation of a scrupulous clinical exam and the analysis of radiographic exams. In this specific case, particular attention has to be dedicated to the observation of the molar elements that might present previous signs of toxicity for the bone tissue, like the spread sclerosis of the alveolar bone, of the *strong lamina* and the opening of the area of the periodontal link. An evident mobility to the dental elements not secondary to the reabsorption of the alveolar bone and deep algici synthoms without evident odontogenic link might be dependent to a meaningful action of toxicity of the bisphosphonate. A third modality for the evaluation of the risk consists of the dosage of the sierologic mark of the bone changing CTX, which results approximately linked to the systemic *soppressione* of the renovation of the bone tissue depending from the action of the bisphosphonate. The inferior values at 100 pg/mL can be associated to a high risk of osteonecrosis of the maxillaries. The General Congress of the Osteoporosis of the HIN arrived to the conclusion that the marker of the bone turnover can't substitute the exams finalised to the evaluation of the mineral bone density BMD (20). Before starting the therapy with bisphosphonates or, when it's not possible, at the maximum within the first 3 months at the start of the treatment, it should be made a screening of the mouth and evaluated the presence of factors of local or systemic risks. So it will be opportune to take all the elements out with uncertain prognosis, to solve all the problems of infective nature through oral igene appointments, rooth scailing associated or not to the use of antiseptic solutions. So it will be opportune paying the maximum attention to the situations that can configure a trauma (control and eventual corrections of removable incongruous prosthesis, extraction of teeth which are partially included) using protocols usually applied on patients which are going to have radiotherapy on head-neck area or a transplantation of bone marrow. In case the therapy with bisphosphonates is started from more than 3 months, it is advised to not proceed by extractions, swapping tem with canalar therapies and eventual "coronations" or "decoronations" of the compromised elements. Where it's necessary execute some extraction, it has to be limit the bone trauma to its maximum putting at the same time an antibody therapy with wide spectrum for a long time (es. Amoxicilline per mouth, 2-3 gr per day for 21 days) associated with clorexidina 0,12%, twice per day. In the extreme case in which the osteonecrosis is already there, the therapeutic approach can be represented with the taking off of the portions of necrotic bones (modest *sequestrectomie* and surgeon curettage) associated to irrigations with antiseptic or antibody solutions. These steps are accompanied with a long systemic antibody therapy (monotherapy es.: amoxicillina or therapy combined adding tetracycline or metronidazole). Nowadays the iperbaric therapy, instead, didn't offer good results, like it happens instead in the cases of osteonecrosis of radiotherapy, because the patophisiological mechanisms at the base of the two

illnesses are completely different. A strategy finalised to the reduction of the incidence of osteonecrosis caused by bisphosphonates consists of the adoption, by the patient, of a regime of intermittent treatment of the drug which is indicated for the therapeutic needs of the patient and that includes an often follow-up. It was an evident result that the actual indication of the utilisation of bisphosphonates is based on quantitative evaluations with BMD at the level of the femur, basin and lumbar vertebrate bodies; but the effect of the bisphosphonates in the districts of maxillaries bones, since it's more than in the district of reference, the result is that the same maxillaries receive a relative extra-dosage of the drug. In other words a therapeutic dose which is indicated for femur, basin, vertebrates and long bones would be actually toxic for the maxillaries. With the suspension of the therapy, there can be as well cases of healing and important improvement of the conditions of bone exposition, indicating the fact that the population of the precursors of the osteoclasts of the bone marrow can generally regenerate. The removing operations of detritus of osteonecrotic areas, have been successful in cases where there was a suspension of the treatment from 6 months to one year.

Clinical case

The case was represented by a 60 years old, no-smoker, African woman affected by serious osteoporosis in pharmacologic treatment with alendronate per mouth. The objective exam was putting in evidence on the level of the III quadrant an important dehiscence of the mandible alveolar mucosa with areas of bone exposition associated to pain and pyrosis (Figs. 1, 2).
After ulterior radiographic exams (Figs. 3 and 4) and considering the pharmacologic anamnesis positive to the bisphosphonates it was clear the conclusion of a diagnosis of osteonecrosis of the maxillaries. So, following the pharmacologic protocol coded by Marx and Stern in 2002 it was put under antibody prophylaxis and, with the patient in "therapeutic holiday from the drug", under a attentive surgery curettage of the area of the necrosis (Figs. 6-8) and to the parallel avulsion of the dental elements involved in the pathological process (Fig. 10).
After a follow up of about 6 months (Figs. 12-14) here was the total healing of the tissues, this result encouraged our studies to wider cases statistics.

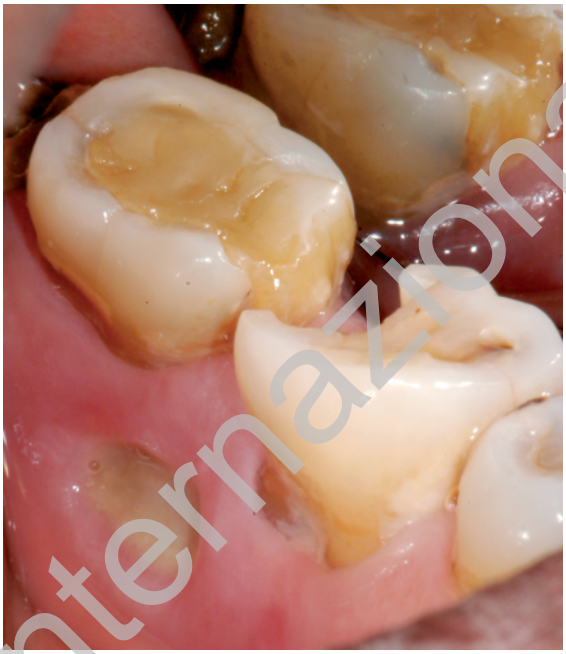

Figure 1
Intra-oral view of the osteonecrosis area.

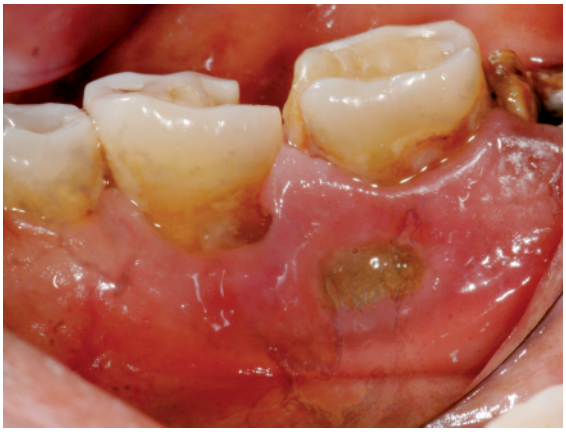

Figure 2
Intra-oral view of the osteonecrosis area.

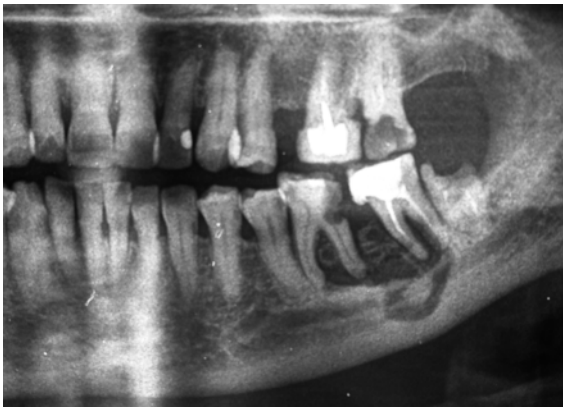

Figure 3
Initial Rx panoramic.

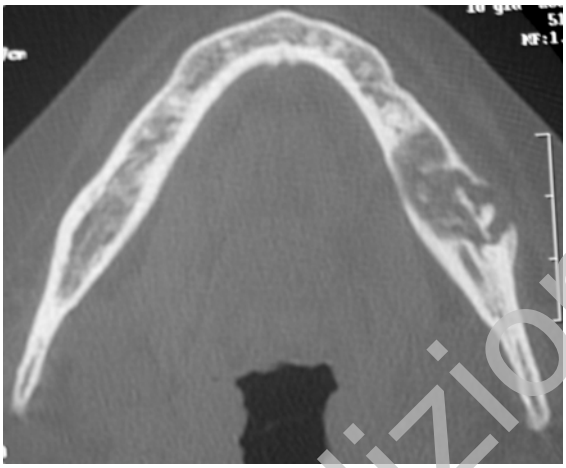

Figure 4
4TC Dentascan.

Conclusions

Apparently, the long term bioavailability (14) (it is calculated that its permanence could arrive till 12 years after its suspension) and the sistemic absorpion of the aminobisphosphonates (15) makes useless the suspension of their treatment in patients who are clearly affected by osteonecrosis of the maxilla. But it was suggested that, in patients who need to have an oral surgery and, waiting for a protocol of universal work, the suspension of the therapy with bisphosphonates, when it's possible, is thought useful

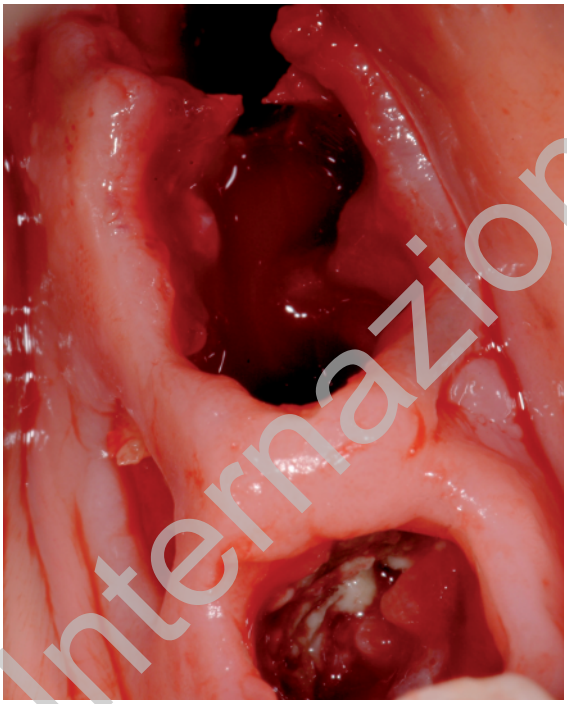

Figure 5
5 Intra-oral view after teeth extraction.

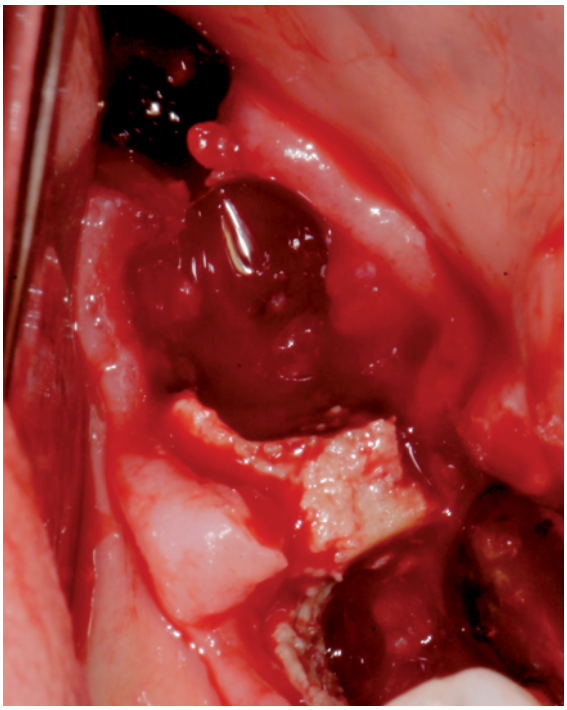

Figure 6
Is possible to see in the post-extraction sites portions of bone in necrosis.

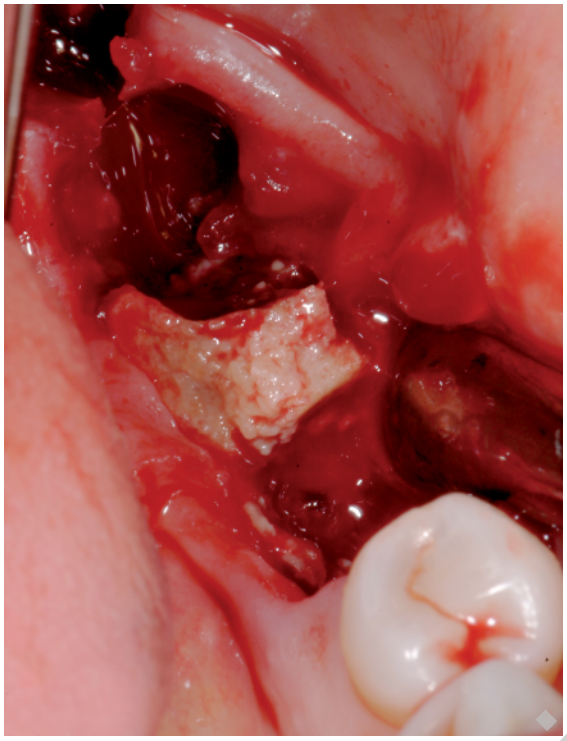

Figure 7
With more blowups we can see that the bone necrosis interests also the lingual bone cortical.

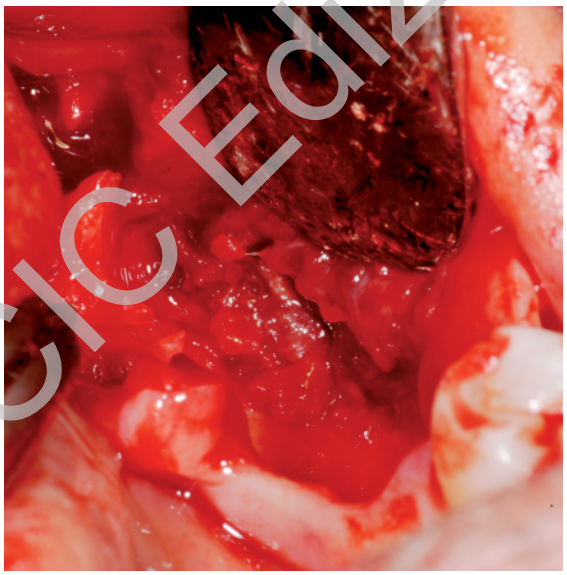

Figure 8
Post extraction sites after surgical curettage.

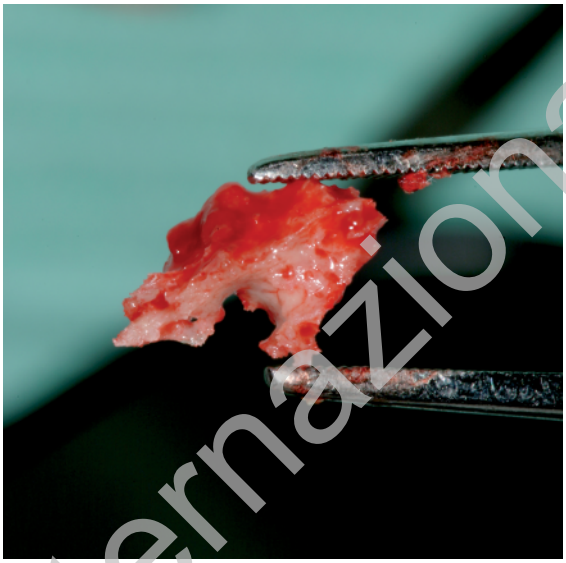

Figure 9
Portion of bone in necrosis we can see the roof of the mandibolar tunnel.

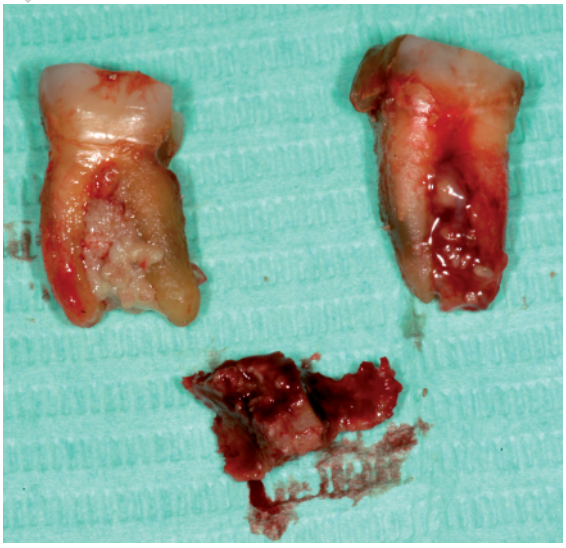

Figure 10
Teeth after extraction. Is possible to see bone chips joined with the roots.

but not an absolute need (16-17-18). In conclusion the prevention of the osteonecrosis with bisphosphonates per mouth needs a strict collaboration between the doctor and the dentists who are taking care of the treatment of the patient. This preventive pro-

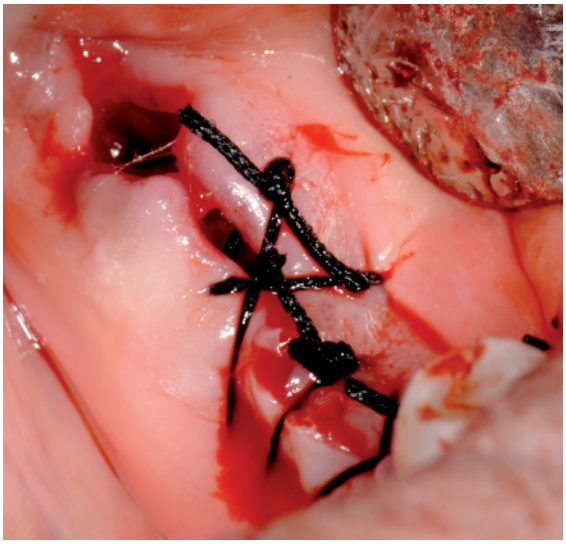

Figure 11
Suture of the hut with healing for second intention.

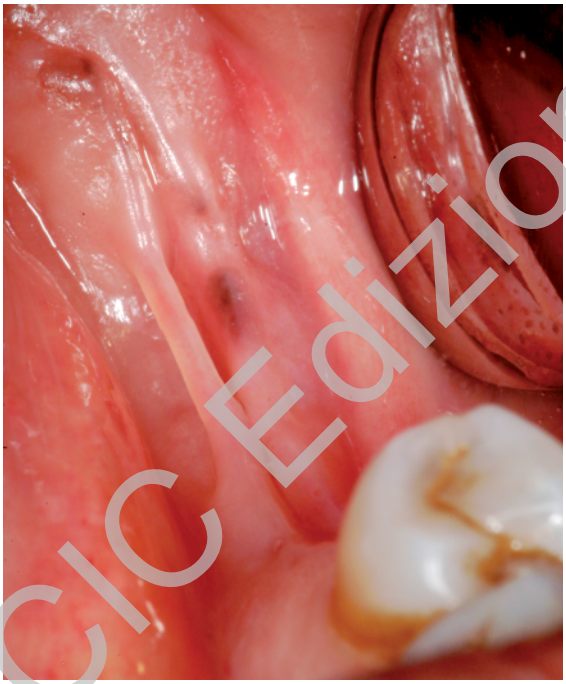

Figure 12
Intra-oral view of the state of healing after one month.

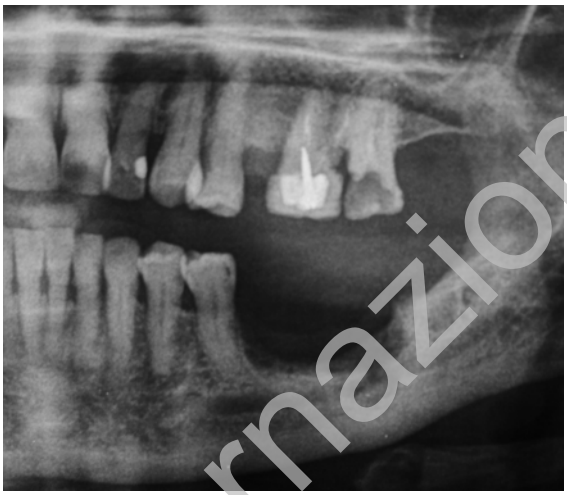

Figure 13
Rx panoramic of control after one year.

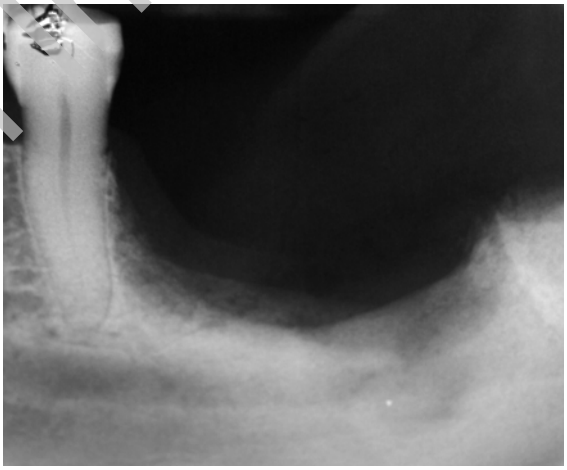

Figure 14
Rx of control after 6 months. We can see the perfect healing of the bony woven.

tocol starts with the indication, from the doctor, of the absuntion of bisphosphonate for the treatments of cases of osteopenia, osteoporosis or other conditions which present the same indication. It would be better that the same doctor sent the patient for an odontostomatologyc evaluation before starting the cicle of the assumption of the drug. The dentistry should then proceed to the execution of a clinical and total radiographic exam of the oral cave in order to write a plan of treatment with the finality of limiting the need of making invasive movements. In the case of an oncologic patient, the doctor could postpone of two months the assumption of the bisphosphonates per veins in order to allow the dentist the

reduction and/or the elimination of evident factors of risk. Since these drugs taken by mouth are scarcely absorbed on an intestinal level, they take place on a bone level with a major slowness than the similar ones taken by vein. The consequence is the fact that the risk of presenting bone exposition is not relevant before three years of continous therapy passed and the dental treatment plan would be then more flexible.

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