Prevention of bisphosphonates-induced osteonecrosis

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Summary

The osteonecrosis of the jaw is a new emergent disease, secondary to prolonged use of bisphosphonates. Bisphosphonates are a class of drug used in prevention and cure of bone diseases such as malignancy or bone metabolic diseases. In this article, we have tried to summarize, for patients taking IV or oral bisphosphonates-therapy, the most important informations on the pathogenesis and the risk factors in osteonecrosis of the jaw with particular attention about the preventive policies.

KEY WORDS: osteonecrosis of the jaw, bisphosphonates.

Background

In the last four years an increasing number of case reports, letters to editors and reviews have (1-6) described the osteonecrosis of the jaw (ONJ) in patients treated with bisphosphonates (BIS). The objective of this paper is to focus practical guidelines and recommendations about ONJ prevention.
Bisphosphonates are used to prevent or to treat osteoporosis, Paget's disease of bone and other metabolic bone diseases (7-9). In patients affected by multiple myeloma and metastatic bone cancer, BIS are strategic drugs to treat severe hypercalcemia, pain and skeletal events (fractures, spinal cord compressions) (10, 12). The most recent nitrogen-containing bisphosphonates or aminobisphosphonates have greater potency and better selectivity of action. Zoledronic acid and pamidronate have been using intravenous in neoplastic diseases, while oral alendronate, residronate and ibandronate have been using in rheumatologic patients. These drugs are powerful inhibitors of bone resorption. This effect gives rise to the blocking osteoclastic activity due to the cell apoptosis (11), and by inducing osteoblasts to cause an osteoclast-inhibiting factor (13). Moreover, BIS may induce a tumor cell apoptosis and also antiangiogenetic effect (14, 15).

ONJ related to BIS is also named BRONJ, BRON, BON, avascular necrosis (1, 16, 17).
ONJ is clinically characterized by an area of yellow-white exposed bone, persisting for more than 8 weeks, associated with current or previous treatment with BIS and without history of radiation therapy of the jaw (16). The ONJ could also present as non healing extraction socket, gingival swelling or purulent discharge. Often patient may remain asymptomatic until sites become infected (4, 18).
At the moment, ONJ's treatment is a great challenge and many problems remain unsolved. A lot of reports have shown a negligible response to the different attempt of treatment (surgical therapy, local or systemic antimicrobial therapy and hyperbaric therapy). However it seems clear that the primary goal, in the treatment of the ONJ, is to eliminate pain, controlling secondary infections of the soft and hard tissues and minimize the progression or occurrence of bone necrosis (4, 5).

Pathogenesis and risk factors

In the management of ONJ is essential to evaluate the risk factors for developing effective preventive measures.
Since the first paper published in 2003 (1), a lot of reports have contributed to clarify our understanding on the pathogenesis of the ONJ induced by BIS. From those works have been elaborated the requirement for the preventive strategy.

Pathogenetic hypothesis: The mechanisms by which BIS may cause ONJ are not completely explained.
The inhibition of osteoclast-mediated resorption of bone seems to be a possible pathogenetic mechanism. The suppression of bone remodelling and an increase of the mineralization, lead to formation of brittle bone (19, 20). The inhibition of bone remodelling could produce an accumulation of microfractures in the jaw as effect of the daily mastication. In addition, to the anti-angiogenetic effect of BIS it could reduce blood flow and cause osseous hypoxia (5). Moreover, the concomitant compromised vascular supply associated with superinfectious of hard and soft tissues may play an important part to cause ONJ.
Recently, a new hypotesis has been proposed by Ardine and Berruti. It is common knowledge that patients with cancer presented, during only first month of treatment with BIS, an increase of the PTH levels. In Berruti's study, patients with metastatic breast cancer developing ONJ, have a clear persistence of relative hypocalcemia and secondary hyperparathyroidism at the time preceding this event. Subsequently obstaculated bone repair may contribute to genesis of ONJ (21).

Risk factors
The most important predisposing factors are:
a) the type of BIS, the total dose and lenght of treatment. The risk is substantially higher in patients taking zoledronic acid than pamidronate, because the former is much potent and with a longer half-life. Durie et al., reported an incidence of ONJ 10% of the patients receiving zoledronic acid, compared with 4% receiving pamidronate, at 36 months censure of data (22). Bamias et al., described an increased inci-

dence of ONJ correlated with – increasing – the number of the BIS infusions and with the exposition (23, 24);
b) recent dental surgical procedures are present in 60% of all cases, respect to the cases of spontaneous osteonecrosis (4, 25, 27);
c) patient older age and sex female are more frequently associated to ONJ (25, 26) in myeloma;
d) the highest incidence of ONJ seemed in myeloma patients (10%), respect to breast cancer (3%) and prostate cancer (7%) (23) (Table I).

There are others conditions usually related to osteonecrosis, which are considered as furter risk factors and therefore evalutated and scheduled. In brief they could be indicate as general or local risk. However, further study are required to determine their importance.

Table I - Predisposing factors to ONJ.

– Type, total dose and length of treatment with bisphosphonates
– Prior history of dental procedures or oral infections
– Older age
– Female sex
– Type of malignancy

ONJ: osteonecrosis of the jaw.

General risk factors are: neoplasia, chemotherapy, corticosteroids, diabetes, smoking, overindulgence in alcohol, old age, female sex, anemia, coagulopathies (16, 18). In multiple myeloma doesn't appear to be an additional risk of ONJ in association to the treatment with thalidomide or corticosteroid (22, 23, 28).
Only Zervas and colleagues described an increased risk of ONJ 2-4 fold in patients treated with thalidomide (29).
At this moment, further studies are necessary to evaluate the potential relationship between ONJ BIS associated in patients taking others anti-angiogenetic drugs – such as Bortezomib – or aromatase inhibitors used in adjuvant cancer therapy.

Local risk factors are: locoregional radiotherapy, dental procedures, poor oral hygiene, dental or periodontal infections, local trauma and edentoulus region (16, 30).

Guidelines for prevention

Considering that, at the moment, many questions on ONJ remaining open it doesn't seem easy to provide definitive recommendations on the more useful preventive strategies. To make easier, it could try dividing the patients into two groups, those treated with intravenous BIS for malignancy and those taking oral BIS for osteoporosis and other rheumatologic diseases.

Intravenous BIS (Table II) – Those patients have high risk of ONJ. The incidence of ONJ raising 6-11% in myeloma and 3-6% in neoplastic disease (22, 23, 28).
On June 2004, a panel of expert, developed a series of recommendations for the diagnosis prevention and treatment of the ONJ associated to the BIS in cancer patients (30). This "white paper" was distribuited during ASCO meeting and subsequently was submitted a two reviews on January and December 2006 respectively (18, 31).
Initially the recommendations developed by the panel were applied to specific two subsets of patients with neoplastic diseases. The former (group 1) involved patients before beginning BIS therapy. The latter (group 2) regarded patients already taking

Table II - Guidelines for patients taking intravenous Bisphosphonates.

– Perform dental clinical evaluation and panoramic jaw radiograph
– Remove abscesses and other high risk infection sites
– Avoid tooth extraction and dental implants
– Prefer conservative therapy (eg. endodontic therapy)
– Check removable dentures
– Maximize good oral hygiene
– Show to patients the signs, symptoms, and clinical feactures of ONJ
– Provide regulary scheduled hard and soft oral tissue assessments
– Develop a close collaboration between patient,oncologist,dentist and oral surgeon

BIS drugs. Also Woo et colleagues have divided patients in two similar group. In the first group, are added patients who have less than 3 months of drug therapy while in the second group the patients with more than 3 months of therapy (6). In an other paper Ruggiero described a common pathway, with few differences between patients which haven't urgency to begin therapy and patients during therapy (31). It would like to submit every patient to oral evaluation and to a jaw X-ray, to detect incidental dental and periodontal disease (4). Oral x-ray is conventionally used as a first step to detect a characteristic imaging features of osteonecrosis. Subsequently when ONJ is suspected a CT scan is useful to display ostheolytic lesions with the involvement of cortical bone whereas MRI is very important to determine the lesion extension in soft tissues.
PET and 99Tc – MPD 3 – phase bone scan scintigraphy are described such as very sensitive investigation to detect subclinical osteonecrosis (32, 33).
In case of documented problems is suggested to remove abscesses and cure all sites that seemed at high risk of infection. Patients should be instructed to avoid any aggressive dental procedure and to prefer conservative dental therapy (endodontic therapy) if possible. Only if metastatic disease is suspected, tissue biopsies are performed, associated with microbial cultures (6, 31).
The teeth with a poor prognosis should be extract prior to starting BIS-therapy and it is important to allow a complete tissues healing. Several authors (16, 34) have recommended in patients, taking therapy, to suspend BIS, from 1 to 3 months before the invasive dental procedure and resuming when oral healing is complete. The stop of the BIS therapy is fundamental to remove the antiangiogenic effect upon the soft tissues around the periosteum of the jaw; in this way could be better the mechanism of tissue repair (6, 31). Modification or cessation of BIS therapy should be done in the consultation with the treating physician and the patient.
Those patients should not be considered as candidates for dental implants.
Periodic examination of full dentures is recommended. The patients should be educated about the importance of maintaining good oral hygiene, without soft tissue injuries, and a prompt surveillance of dental care. Patients must be informed about ONJ, including an explanation of its signs, symptoms and clinical features. Prophylactic antibiotic therapy before of the non invasive dental care is not required but is recommended for all invasive dental procedure and in patients with risk of bacteremia (venous central cateter carrier). It is important to perform twice year a professional dental cleanig. A brief visual

evaluation by oncologist at every follow-up visit. The frequency of checks should be every 3 or 4 months, depending on the concomitant risk factors.
A close collaboration among patient, oncologist/haematologist, dentist and oral surgeon is fundamental for the prevention of ONJ and for a quick identification of the problems. Recently, in multiple myeloma Lacy and colleagues recommended to discontinue BIS after 2 years of therapy, in the patients in remissions or plateau phases, and to reduce the frequency of BIS therapy every 3 months in patients with active disease. Moreover for newly diagnosed patients the use of pamidronate instead of zoledronic acid is suggested (34).

Oral BIS: (Table III) Oral BIS are used in osteopenia, in osteoporosis related to menopause, inflammatory bowel disease, primary biliary cirrhosis, steroid therapy, Paget's bone disease, osteogenesis imperfecta of childhood and other rheumatologic diseases (7-9, 16, 17). These patients have a potential, but very low risk of ONJ. Among patients who have received oral therapy for osteoporosis 50 cases of ONJ have been reported (6) and 5 cases in Paget's disease of bone (17).
In patients taking alendronate the incidence of ONJ has been estimated to occur in approximately 0,7/100000 persons/year exposure. Few cases was described in patients treated with ibandronate (12 cases) and residronate (1 case) (17). Up to day, the estimate of incidence of osteonecrosis is based on incomplete data and prospective studies are needed.
Oral BIS have a minor bio-availability for the incorporation into the bone matrix and this may account for the low number of cases of ONJ (36, 37).
Though patients treated with oral BIS have a low risk of ONJ, it is necessary to be aware about the necessity of a prevention programme. For this reason would be useful before to start oral BIS-therapy that the physician collect a brief history for systemic or local risk factors and also submits to oral evaluation all patients.
Afterwards, periodic control of oral care should be scheduled, to reduce dental and periodontal infections. Each patient must be addressed in developing oral care. The risk and benefit profile for each patient should be considered before and during therapy (38).
Initially patients taking oral BIS have the same preventive like the patients who must start BIS- IV therapy (6).
In 2006 a panel of expert developed clinical guidelines for the prevention and dental management of patients receiving oral BIS (16, 17). As pictured from this study, the risk of developing ONJ with oral BIS is increased if the therapy exceeded three years or when it is associated with steroids or in elderly patients (16).
In these guidelines patients are divided in three groups.
Group 1: individuals who take oral therapy for less than three years and haven't any further clinical risk factors.
Group 2: individuals who take oral therapy for less three years and had also taken corticosteroids concomitantly.
Group 3 patients who take therapy for more than three years with or without concomitant steroids.

Table III - Guidelines for patients taking oral Bisphosphonates.

– Perform oral evaluation
– Collect a history for risk factors
– Encourage good oral hygiene
– Provide regular dental care, to avoid infections
– Prefer conservative therapy
– Discourage implants
– Offer an alternative theraphy in osteoporosis, or "drug holidays"

In patients of group 1, routine dental treatment and surgical jaw procedures should be not modified. In both group 2 and 3 the endodontic therapy is preferred to tooth extraction and invasive periodontal procedures. If the disease situation for which the BIS therapy is assumed is getting well, the authors of the paper encourage the discontinuation of the oral therapy for at least three months before oral surgery.They suggest to start again BIS therapy only when osseous healing has occurred. Patients with implants are regulary monitored to avoid peri-implantitis. Before the placement of implants, dentist and patient should be discuss the risks and benefit of the treatment. In any case it would be better obtaining a written consent from the patient. Patients in BIS therapy for post-menopausal osteoporosis should be considered for an alternative therapy: estrogens, raloxifene, strontium ranelate, teriparatide or clodronate. Clodronate is BIS of first-generation that doesn't seem associated to ONJ (39, 40). In patients treated with oral BIS for five or more years, a "drug holiday", a discontinuation of BIS therapy until one year have been recommended. These recommendations are based on the hypotesis that this procedure may mitigate the risk of ONJ.

Conclusions

ONJ is a serious complication of long-term BIS therapy. These drugs are effective in the treatment of hypercalcemia, osteolytic lesion in myeloma, bone metastatic cancer and to prevent and cure osteoporosis and other metabolic bone diseases. Many questions are yet unanswered. Prospective and retrospective case-control studies are also needed to determine which additional risk factors may predispose the patients to the development of ONJ. Let's hope that in the future might be created a national registry to allow systematic study of cases of ONJ. In that prospective, the basic research should have the aim to better explain pathophisiology of ONJ and should be made easier to determine the best approach to perform a tailored pathway in patients treated with BIS.

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