Recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates

José Bagán 1, Juan Blade 2, Jose Manuel Cozar 3, Manuel Constela 4, Ramón García Sanz 5, Francisco Gómez Veiga 6, Juan José Lahuerta 7, Ana Lluch 8, Bartomeu Massuti 9, Juan Morote 10, Jesús F. San Miguel 11, Eduardo Solsona 12

(1) Stomatology Professor, Valencia School of Medicine, and Head of the Stomatology Service in the Valencia General Hospital
(2) Senior Consultant in Hematology, Barcelona Clinical Hospital
(3) Urology Registrar, Urology Service, Granada “Virgen de las Nieves” Hospital
(4) Head of the Medical Oncology Service in the Pontevedra “Montecelo” Hospital
(5) Hematology Registrar, Hematology Service, Salamanca University Hospital
(6) Urology Service Registrar, A Coruña “Juan Canalejo” Hospital
(7) Head of the Hematology Service, Madrid “Doce de Octubre” University Hospital
(8) Oncology Professor, Hematology and Medical Oncology Service, Valencia Clinical University Hospital
(9) Head of the Medical Oncology Service, Alicante General Hospital
(10) Head of the Urology Service, Barcelona “Valle Hebrón” Hospital
(11) Head of the Hematology Service, Salamanca Clinical University Hospital
(12) Head of the Urology Service, Valencia Institute of Oncology (IVO)

Correspondence:
Dr. José Bagán
E-mail: Jose.V.Bagan@uv.es

INTRODUCTION

In the last few years, cases of osteonecrosis of the jaw (ONJ) have been detected in cancer patients taking bisphosphonates as part of their treatment. The publications and cases notified to date mention that the majority of the patients were on antineoplastic treatment (chemotherapy, steroids treatment, or radiotherapy for head and neck tumors), and they were administered bisphosphonates concomitantly for the treatment of cancer and its related symptoms, indicating, most of such reports, the appearance of ONJ following dental procedures.

Both prevention, as well as diagnosis and treatment of the ONJ and other oral complications caused by cancer, should be dealt with in an interdisciplinary way, based on the clinical evaluation made by the physician who establishes the treatment, as well as by the physician responsible for the treatment of the ONJ, according to the possible benefit and potential risks of such treatment.

It is important that all physicians involved are sufficiently informed about the disease, its symptoms, and the treatments of cancer patients who take bisphosphonates, as well as about the most suitable treatment; a good communication among them is also important.

Various bibliographic references, guides, and recommendations exist on the prevention, diagnosis, and treatment of the ONJ; although due to its low incidence and recent appearance, it is an issue still unknown to the majority of the physicians. Information available for a better understanding of the pathology and the treatment of patients with osteonecrosis of the jaw, as well as its adaptation to the Spanish healthcare setting is limited. A panel of Spanish experts representing the specialties of Medical Oncology, Hematology, Urology, and Stomatology, has recently held a meeting to debate on and identify the risk factors associated with the osteonecrosis of the jaw, as well as to develop some clinical guidelines on the prevention, early diagnosis, management, and interdisciplinary treatment of such pathology, in patients with advanced malignancies with bone affection, treated with bisphosphonates.

The experts panel developed various documents to facilitate the physicians’ orientation in the treatment of their patients.

1. Recommendations document for cancer patients treated with bisphosphonates, including the following aspects:
   a. Consensus on the definition of the ONJ.
   b. Preventive measures.
   c. Action plan in case of ONJ suspicion.
   d. ONJ treatment.
   e. Recommendations on the use of bisphosphonates in patients with malignancies.
1. A patient who is or has been taking bisphosphonates due to suffering a malignancy.
2. Presence of one or various ulcers in the mucosa of the alveolar processes, with exposure of the maxillary or mandibular bone.
3. The lesion is produced either spontaneously or, most often, after a dental surgery or procedure (especially dental extractions).
4. The bone observed at the bottom of the ulceration looks like a necrotic bone.
5. Absence of cicatrisation during a minimum six-week period; on the contrary, in most cases, the lesion progresses, causing bone exposure expansion and pain increase.

IN CASE OF A CLINICAL SUSPICION OF ONJ
Refer patients to the hospital where they are treated of their neoplastic problem, in order to confirm the ONJ diagnosis and establish a suitable treatment.

1. PREVENTIVE MEASURES TO BE TAKEN BY THE ODONTOLOGIST OR STOMATOLOGIST, OR BOTH, FOR PATIENTS TREATED WITH BISPHOSPHONATES WITHOUT ONJ
1.A. BEFORE INITIATING BISPHOSPHONATES TREATMENT
All patients with concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids), who are going to begin a treatment with bisphosphonates, should consider being examined by their Odontologist / Stomatologist, before initiating the treatment; the physician should take into account the following recommendations:
- It is very important to detect possible infection sources in the patient, both already existing, as well as potential ones and, if any, to eliminate them before initiating bisphosphonates treatment.
- Those teeth that, due to periodontal pathologies, is not quite clear that could be subsequently maintained, should be extracted before the commencement of the bisphosphonates treatment.

The specialist treating the patient’s cancer should bear in mind the following recommendations:
- To inform patients and their families about the necessary buccal care.
- To inform patients that they notify the specialist treating their cancer of the appearance of any buccal problems or any odontological procedures (including dental extraction). In this case, the patient should be referred to the odontologist / stomatologist, who will proceed in accordance with the recommendations.

1.B. DURING BISPHOSPHONATES TREATMENT
During bisphosphonates treatment, it is recommended that the patient visits an odontologist / stomatologist, at least once a year, to detect and, if any, to treat caries and periodontal diseases at an early stage. To this end, it is recommended to:
- Explore teeth to detect and treat caries. It is advisable to proceed to obturations and endodontics, avoiding any “dental extractions” due to caries during bisphosphonates treatment.
- Explore the periodontal area and, subsequently, eliminate plaque and periodontal pouches, to avoid the need of a teeth extraction in the future due to this kind of problems.
- Avoid friction lesions (chronic traumatisms), paying special attention to prostheses.

1.C. IN CASE OF EXTRACTION DURING BISPHOSPHONATES TREATMENT
In case of a patient treated with bisphosphonates, it has been already mentioned that, whenever possible, “dental extractions” should be avoided, although if it is absolutely necessary to perform an extraction the following recommendations should be taken into account:
- Perform the extraction in the less traumatic way possible. Residues of large alveolar bone defects should be avoided, and, of course, the possibility of conducting an alveolus suture to facilitate subsequent cicatrisation should be evaluated.
- Administering oral amoxicillin / clavulanic acid (875 mg / 125 mg three times a day) or clindamycin (300 mg / 3-4 times a day) two days prior to the extraction, and during ten days after the extraction.
- Following the extraction, the patient should rinse with 0.12% chlorhexidine, twice a day for 15 days.
- Reviewing the evolution of the procedure by the stomatologist.
- The possibility to temporarily suspend the bisphosphonates treatment (2-3 months prior to the procedure, and until the lesion cicatrisation has been confirmed), is up to the physician, since there is no evidence of the benefit of such interruption and lesions without osteonecrosis.

2. ACTION PLAN IN CASE OF A CANCER PATIENT WITH A SUSPICION OF OSTEONECROSIS OF THE JAW (ONJ)
The above-mentioned recommendations should be follo-
wed for areas without osteonecrosis, with regards to dental plaque, caries and periodontal pathology.

2.A. DIAGNOSIS OF THE OSTEONECROSIS AREA (S).
A.1. Clinical diagnosis
- Presence of one or various ulcers in the mucosa of the alveolar processes, with exposure of the maxillary or mandibular bone.
- The bone observed at the bottom of the ulceration looks like a necrotic bone.
- Absence of cicatrisation during a minimum six-week period; on the contrary, in most cases, the lesion progresses, thus bone exposure expands and pain increases.
A.2. Diagnosis based on complementary tests 12.506.
- Request an orthopantograph.
- Request a CAT scan, which will determine and evaluate the ONJ expansion in conjunction with what is clinically observed inside the mouth. Special attention shall be paid to the possible existence of osteolysis areas, attributable to the basal disease.
- Make a microbiological culture and antibiogram of the exposed bone.
- In case of doubts in the differential diagnosis between ONJ and affection due to basal disease, a bone biopsy shall be used, given that it is the definite test.

2.B. TREATMENT OF PATIENTS WITH ONJ.
For the treatment of the OSTEONECROSIS area(s) a distinction shall be made between two situations in terms of the expansion of the lesion:
B.1. Patients with small ONJ areas.
A "conservative treatment" shall be initiated. Based on the microbiological analysis, establish a treatment for 10-15 days with the appropriate antibiotic, in parallel with chlorhexidine rinses (once every 12 hours for a month). In case of a normal flora, it is recommended to use 875 / 125 mg of amoxicillin / clavulanic acid or clindamycin.
- The healthcare professional should carry out irrigation of the exposed necrotic bed.
with 0.12% chlorhexidine - once every 72 hours for four weeks. After one month, the patient should be reevaluated; two possibilities exist:
a. If an improvement is confirmed the patient should continue with the 0.12% chlorhexidine rinses for another month of follow-up, both for the patient’s daily applications and the professional’s application every 72 hours.
b. In case there is not a good response to the conservative treatment, the said treatment shall be maintained for another month. If, this period has elapsed but there is still no improvement, then the regimen stipulated in section B.2 should be followed.
B.2. Patients with large ONJ areas and patients who have not evolved satisfactorily following a conservative treatment.
- Plan a surgical procedure to remove the area of the necrotic bone (the expansion and magnitude of the surgical procedure will depend on the size of the ONJ).
- In case of ONJ presence, bisphosphonates treatment shall be suspended, being up to the physician to reintroduce it in case of an active bone disease, evaluating the risk / benefit ratio. Corticoids withdrawal should also be evaluated, in case they had been administered as a maintenance therapy.

2.C. PHARMACOVIGILANCE INFORMATION
It is recommended to physicians to notify any ONJ suspicion to the Pharmacovigilance Center of the corresponding Autonomous Community.
In case this happens during the treatment with Areidia® or Zometa®, Novartis Pharmaceuticals, S.A. can also be notified: by tel. +34 900 35 30 36 or fax +34 93 306 44 12.

3. CANCER AND BONE LESION
Bone remodeling in adults is an active process and, normally, osteoclasts activity is equal to that of osteoblasts. Nevertheless, in situations of alteration of the bone metabolism, like in malignant bone metastases and multiple myeloma, an increase of the osteoclastic activity causes bone resorption.
Bone metastases are a common cause of morbidity in patients with many types of cancer and they can cause pain, hypercalcemia, pathologic fractures, and spinal cord compression. They are quite frequent in patients with breast, prostate or lung cancer. Hypercalcemia, associated with malignancies, represents around 45% of the total hypercalcemia cases.
It is the most frequent potentially mortal metabolic complication among malignancies.

3.A. ADVANCED BREAST CANCER.
Breast cancer is the most common malignancy in the female sex and it is the main mortality cause due to cancer in European women. The bone is the most frequent site for metastases in breast cancer patients. Almost 80% of the patients deceased due to a breast malignancy present bone dissemination, while this is also the most common site of disease recurrence, following a primary treatment against breast cancer.
Breast cancer expansion to bones can lead to significant morbidity in patients suffering from it. Events related to the complications secondary to the bone disease progression include: pain appearance, hypercalcemia, risk of bone fractures, risk of appearance of a medullary compression syndrome, and the need for radiotherapy administration. All this could limit patients’ mobility and, in short, reduce their quality of life.
Breast cancer treatment is palliative, and its main objective is to achieve the improvement of the patient’s symptoms and of her quality of life. Systemic treatment with chemotherapy or hormone therapy could accomplish this, although the introduction of bisphosphonates, in the last few years, has offered a greater confidence to this end. Lytic metastasis of breast cancer are the result of an increased activity of osteoclasts reabsorption. Such process is mediated by various molecules, among which the following: tumor necrosis factor beta (TNF-
The development of treatments with osteoclast inhibitors, like bisphosphonates, offer a new dimension to the control of the symptoms and the prevention of skeletal complications. Bisphosphonates, especially third generation ones, like zoledronic acid, are potent osteoclast inhibitors (they delay maturation and induce the apoptosis of the osteoclasts with evident clinical effects), and they have allowed to improve patients’ symptoms, to reduce the risk of pathological fractures, or the need for antalgic radiotherapy. On the other hand, various in vitro studies suggest that bisphosphonates have an antitumor effect and this way they be in synergy with chemotherapy. Such effect has been used as a basis in the design of bisphosphonates studies as an adjuvant treatment for breast cancer, to avoid or delay the appearance of bone metastases.

3.B. MULTIPLE MYELOMA
Multiple Myeloma (MM), is a malignancy derived from B-lymphoid cells in the last stage of maturation (plasma cells, PC) that, from a clinical point of view, is characterized by the triad of anemia, bone lesion, and renal insufficiency; while from a biological point of view, it is characterized by the presence of either a serum or urine monoclonal component or both, and medullary plasmacytic infiltration. It is the second most frequent malignant hemopathy, with an incidence of 56 new cases for every million of inhabitants per year. The presence of bone lesions is a typical finding in MM patients, and they are visible through conventional X-rays in 80% of the cases, which can reach 96%, if they techniques like NMR or PET are used. Bone lesions are produced due to an imbalance between bone resorption and formation in two phases. In early stages, there is an increase in resorption due to the osteoclast activation, secondary to the RANK / RANK-L hyperactivity. At first, the destructive increase is compensated for with an increase in the bone formation, although, during the tumor clone growth, DKK1 gets synthesized: a factor inhibiting osteoblasts. This causes a loss of a net bone mass, and another triad appears: bone pain, fractures, and hypercalcemia. This mechanism of bone lesion generation constitutes the basis for the use of bisphosphonates inhibiting bone resorption and thus contributing to the re-equilibration of the bone metabolism, improving patients’ bone lesion.

3.C. BISPHOSPHONATES AND PROSTATE CANCER
The clinical evolution of the bone metastases in prostate cancer is relatively long, with the appearance of skeletal complications for various years. Such skeletal complications include pain, fractures, hypercalcemia, and spinal squeezing, actively influencing in patients’ quality of life. It is known that the main treatments administered to patients with advanced cancer include radiotherapy, systemic hormone therapies and cytotoxic treatments. Nevertheless, the use of bisphosphonates represents a new strategy as an additional treatment for the reduction of skeletal symptoms and complications.

Androgenic deprivation or Androgen Blocking (AB) is the standard treatment for disseminated prostate cancer. Nevertheless, currently, it also forms part of the high risk localized prostate cancer treatment, and it is the first or second line rescue treatment after low or medium risk localized prostate cancer radical treatment fails. Currently, it is estimated that a patient diagnosed with prostate has a 60% chance to receive AB throughout his life. Precedents of skeletal fractures are an independent predictive factor of minor survival rates in patients with prostate cancer subjected to an AB; moreover, it suggests deterioration of the quality of life from the moment of the fracture. Prostate cancer patients run a higher risk of bone fracture, as a consequence of the bone fragility secondary to the metastases or the bone mass loss secondary to the AB with LH-RH analogues to the testosterone serum levels similar to those of surgical castration) or both.

Incidence of skeletal osteoporotic fractures, as well as the increase in the relative risk of suffering them is relevant to AB; their duration or the number of LHRH analogues doses administered, or both. Various clinical studies carried out with zoledronic acid have offered evidence on the clinical usefulness of this bisphosphonate, in patients with advanced prostate subjected to an AB, basing its efficacy on the results obtained and published on:
1. Avoiding and significantly delaying (vs. placebo) skeletal-related events (SRE) in patients with bone metastases.
2. Relieving pain and improving patient’s mobility at rest and in motion.
3. Preventing bone mass loss and treating osteoporosis.

Calcium and vitamin D supplements have been normally used in combination with bisphosphonates and in the control groups of the clinical trials. Their individual use can prevent the bone mass loss in patients subjected to an AB. Moreover, it has been observed that inadequate calcium ingestion has been associated with the presence of osteoporosis in prostate cancer patients, either subjected to an AB or not.

4. BISPHOSPHONATES
Bisphosphonates constitute a group of compounds and their structure is based on that of pyrophosphate: a compound that regulated precipitation and extraction of minerals from the bone, albeit they are sensitive to phosphatase hydrolysis. Bisphosphonates change the structure through a phosphorus-carbon-phosphorus axis, which is very stable and resists enzyme hydrolysis, which thus allows a strong bond to the bone. Bisphosphonates, thanks to their capacity to inhibit osteoclastic activity, are the standard treatment for tumor-related hypercalcemia, and they have been proven to reduce bone pain, improve quality of life, delay skeletal events, and decrease their number.

ZOLEDRONIC ACID.
Description: zoledronic acid is the active ingredient of Zometa®. It is an IV administered aminobisphosphonate. Zometa® has been marketed since August 2002.
Action: zolendronic acid is rapidly bound to the bone, inhibiting osteoclastic activity, and thus improving bone resorption. Its selective bone action is based on its great affinity for bones at remodeling phase. Obviously, zolendronic acid inhibits bone resorption without affecting bone formation, mineralization or mechanical properties.

Indications:

- Prevention of skeletal complications associated to the myeloma bone lesion (pathological fractures, medullary compression, need to use bone irradiation or surgery, and tumor-induced hypercalcemia), in patients with advanced malignancies with bone affectation.
- Treatment of tumor-induced hypercalcemia (TIH).

Dosing and administration: the recommended dose for the prevention of events related to the skeleton in multiple myeloma 4 mg of Zometa®, administered as a 15-minute IV perfusion every four weeks.

Recommendations included in the technical file: patients with cancer should be subjected to a dental revision before initiating treatment with intravenous bisphosphonates. Avoid dental procedures while on treatment with bisphosphonates, since in patients who might develop an ONJ during the bisphosphonates treatment, dental surgery could exacerbate this situation. In case a patient needs a dental procedure, there are no data available suggesting that the interruption of the treatment with bisphosphonates reduces the risk of osteonecrosis of the jaw.

5. GENERAL RECOMMENDATIONS ON THE USE OF BISPHOSPHONATES IN PATIENTS WITH MALIGNANCIESTS

- Currently, there is evidence of the usefulness of the administration of bisphosphonates for a two-year period. As of that moment, international experts’ recommendations are controversial, especially because there is no scientific evidence on their unlimited administration in en patients with an inactive or plateau phase of the disease.
- Some groups advocate that, after two years of treatment, it could be continued with an administration regimen of every three to four months. Nevertheless, such regimen has not yet been proved by scientific evidence.
- In case of recurrence in patients who have taken bisphosphonates for two years but then their treatment has been interrupted, it shall be necessary to consider the reintroduction of the drug, especially if there is bone symptomatology or alterations in calcium metabolism.

REFERENCES


This Consensus has been endorsed by the scientific groups represented by the members of the Experts Group.

E340