symposium article

Annals of Oncology 18 (Supplement 6): vi168–vi172, 2007
doi:10.1093/annonc/mdm250

Bisphosphonate-related osteonecrosis of the jaw (BRONJ): run dental management designs and issues in diagnosis

G. Campisi[1]*, O. Di Fede[1], A. Musciotto[1], A. Lo Casto[1], L. Lo Muzio[2], F. Fulfaro[3], G. Badalamenti[3], A. Russo[3] & N. Gebbia[3]

[1]Section of Oral Medicine, Department of Oral Sciences, Università di Palermo, Palermo; [2]Department of surgical Sciences, University of Foggia, Foggia; [3]Section of Medical Oncology, Department of Surgery and Oncology, Universitá di Palermo, Palermo, Italy

Recently, jawbone osteonecrosis has been largely reported as a potential adverse effect of bisphosphonate (BP) administration. Because of the peculiar pharmacokinetic and pharmacodynamic features of the BF (mainly for i.v. administration), their efficacy and large use, some major issues have to be taken into account extendedly both by oncologists and by dentists: 1) therapeutic dental protocol for patients with diagnosis of bisphosphonate-related osteonecrosis of the jaw (BRONJ); 2) dental strategies for patients in former or current i.v. BF treatment and in absence of BRONJ signs; 3) strategies for patients before i.v. BF treatment. Clinical features and guidelines for the management of this condition have been investigated and reported, sometimes with unclear indications; hence, on the basis of the literature and our clinical experience, major end points of this paper are providing our run protocols for the issues above described and, finally, focusing on a crucial, but not extensively investigated point: the early and correct diagnosis of BRONJ versus metastatic jaw lesions in cancer patients.

Key words: bisphosphonates, metastatic bone disease

introduction

Osteonecrosis of the jaws has been recently recognized as a potential complication of BF treatment [1–12], mainly by i.v. regimen, for malignancy-associated hypercalcemia and prevention of bone fractures in patients with metastatic bone disease or multiple myeloma [13–15]. With regard to the social impact and limitedly to the underestimated cumulative incidence, as taken from retrospective studies among patients receiving i.v. BF, it has been calculated a range from 0.8% to 12% [8, 16]. Pathogenetic mechanisms of this condition are not completely understood and management of affected patients is mostly on the basis of the clinical guidelines drawn from expert opinions and case series analysis [17, 18]. Among amino-bisphosphonates, pamidronate and zoledronate have shown the most consistent effects for the treatment of bone metastases in cancer, with zoledronate being more potent *in vitro* than pamidronate [19]. Amino-bisphosphonates inhibit osteoclasts at different stages, binding selectively to hydroxyapatite and accumulating in sites of active bone remodeling. Once BF are stored in bone, their release is dependent on the rate of bone remodeling [20]. In addition, amino-bisphosphonates have antiangiogenic properties both *in vitro* and *in vivo*. Clinically, these lesions appear as nonhealing-exposed bone areas, which can be accompanied by fistulization, purulent discharge and pain. The current nomenclature for bisphosphonate-related osteonecrosis of jawbone (BRONJ) lesions reflects the prevailing hypothesis that such a condition is a form of osteonecrosis. The need for a higher level of scientific evidence has been already underlined [3]. In fact, the pathogenesis of jawbone disease in patients receiving BF is largely unknown and the biological mechanisms by which BF are responsible for bone remodeling and angiogenesis impairment in human jaws are still uncertain.

Risk factors for BRONJ occurrence are usually grouped in three great categories: (i) drug-related risk factors, (ii) local risk factors, and (iii) demographic/systemic risk factors as extensively reported [16–21]; furthermore, other factors have been recently thought to be linked, such as corticosteroids, thalidomide, diabetes, smoking, alcohol use, poor oral hygiene and chemotherapeutic agents [22–27] (Table 1).

Because of the proven benefits of i.v. BF, their high BF half-life [28–30] and the considerable number of prescriptions, some major issues have to be taken into account extendedly both by oncologists and by dentists: (1) therapeutic dental protocol for patients with diagnosis of BRONJ, (2) dental strategies for patients in former or current i.v. BF treatment and in absence of BRONJ signs, and (3) strategies for patients before i.v. BF treatment. On the basis of the literature as providing sometimes unclear indications and our clinical experience, major end points of this paper are providing our protocols for the issues above described and, finally, focusing on a crucial, but not extensively investigated point: the early

*Correspondence to: G. Campisi, Department of Oral Sciences, University of Palermo, Palermo, Italy. E-mail: giuca1@inwind.it

Table 1. Risk factors for the development of BRONJ

Drug-related risk factors
Potency of the bisphosphonate (zoledronate > pamidronate > alendronate > clodronate)
Way of administration (i.v. > oral)
Duration of therapy
Local risk factors
Dentoalveolar surgery (e.g. extractions, dental implant placement, periodontal surgery involving osseous injury, periapical surgery)
Trauma to the jaw bones
Poor oral hygiene
Periodontal disease
Inflammatory dental disease (e.g. periodontal abscesses, dental abscesses)
Palatal and lingual tori, bony exostoses, mylohyoid ridge
Trauma from poorly fitting dentures
Alcohol and tobacco abuse
History of osteonecrosis/osteomyelitis of the jaws
History of head and neck radiotherapy (?)[1]
Demographic and systemic risk factors
Elderly (>65 years)
Gender: female > male (?)
Caucasian race (?)
Chronic corticosteroid therapy
Chemotherapy
Estrogenic therapy
Alcohol and cigarettes abuse
Cancer diagnosis (increased risk for multiple myeloma > breast cancer > prostate cancer > other cancers)
Osteopenia/osteoporosis diagnosis concurrent with cancer diagnosis
Malnutrition
Diabetes
Acquired or induced immunodeficiency
Anemia and thalassemia
Coagulopathies, blood dyscrasias and vascular disorders
Hyperlipemia
Connective tissue diseases
Gaucher's disease
Systemic lupus erythematous
Hypothyroidism

[1]AAOMS (American Association of Oral and Maxillofacial Surgeons), in the ''Position Paper on BRONJ'', asserts that patients may be considered to have BRONJ only if they have no history of radiation therapy to the jaws.

and correct diagnosis of BRONJ versus metastatic jaw lesions in cancer patients.

As follows, some schemes are provided about the issues 1, 2 and 3, respectively.

Issue 1: dental management of patients under treatment (or with history of treatment) with BF presence of clinical BRONJ lesions

1. Thorough oral examination

- Signs

  -Grade of bony exposure
  -Oral/skin fistulas
  -Local or general swellings of the soft intraoral tissues
  -Degree of dental mobility

Symptoms

  -Pain
  -Aesthesia/dysesthesia (e.g. numbness, feeling of a 'heavy jaw')

2. Appraisal of BRONJ

- Periodic clinical follow-up (1–2 months)
- X-ray of jaws every 4–6 months
- Computed tomography dental scan every 6 months
- Staging (early versus late)

3. Special investigations

- Microbiological cultures should be collected to identify bacterial or mycological pathogens with potential to cause secondary infections
- Halitosis evaluation (e.g. by Halimeter®, OralChroma®)

4. Nonsurgery therapy

- Achievement and/or maintenance of optimal periodontal and dental health
- To avoid procedures that involve direct osseous injury to prevent other bony exposures
- To avoid the use of vasoconstrictor associated with local anesthetics
- To eliminate sharp edges of dental crowns, inadequate dental prosthesis, inadequate conservative restorative treatments to prevent other bony exposures. To settle if required.
- To examine patients with full or partial dentures for areas of mucosal trauma, especially along the lingual flange region (i.e. mylohyoid ridge) and where palatal and lingual tori and bone exostoses can be present.
- To make stable teeth with grade 1 or 2 of dental mobility
- To make conservative restorative and prosthesis treatments
- To make acrylic stents or individual trays to cover areas of exposed bone, to protect adjacent soft tissue, to improve comfort and to maintain therapeutic agents *in situ*
- In case of necessary tooth extraction (see Table 2)

5. Achievement and/or maintenance of a good oral hygiene

- Over-gingival scaling
- Instruction to oral self-hygiene
- Prescription of antiseptic rinses, such as chlorhexidine 0.12% without alcohol (three times/day)
- Local application of fluorine
- Motivation of patients regarding the importance of good dental hygiene

6. Patient education and reassurance about BRONJ

- Delivery of informative papers (e.g. letter to dentistry, information for the patients)
- Instruction to avoid every elective dental or surgical procedures involving osseous injury during the treatment

Table 2. Pharmacological therapy

Antibacterial	Initial dose	Maintenance dose
FIRST RATE		
Penicillin	500 mg 3-4 times/ die for 10 days	500 mg every 12 h
Amoxicillin	500 mg 3-4 times/ die for 10 days	500 mg every 12 h
IN CASE OF PENICILLIN ALLERGY		
Clindamicin	150-300 mg 4 times/die	
Erythromicin	100 mg 4 times/die	
Azithromycin	400 mg 4 times/die	
NON-RESPONSIVE PATIENTS OR IN CASE OF SEVERE SIMPTOMATOLOGY (IN ADDITION TO THE PREVIOUS ONE)		
Metronidazole	250-500 mg 3 times/ die for 14 days	
IN CASE OF SEVERE INFECTION		
Ampicillin	1 gr 4 times/die	
Clavulanic acid	500 mg 4 times/die	
Metronidazole	500 mg 3 times/die	
IN CASE OF PENICILLIN ALLERGY		
Ciprofloxacine +	500 mg 2 times/die	
Metronidazole	500 mg 3 times/die	
Erythromicin +	400 mg 3 times/die	
Metronidazole	500 mg 3 times/die	
Antifungal (when required)		
On the basis of susceptibility test		
Antiviral (when required)		
Acyclovir	400 mg 2 times/die	
Valacyclovir	500 mg-2 gr 2 times/die	

with BF and at least 5 years after the cessation of bisphosphonate therapy
- Education to periodic clinical and radiographic follow-up, with frequency depending on seriousness of BRONJ

7. Pharmacological therapy

- Broad-spectrum antibiotic therapy before antibiotic assay according to the regimens described in Table 2
- Antifungals, if required, should be prescribed
- If patient refers pain, systemic analgesics should be prescribed in order to mitigate symptoms

8. Surgery therapy in case of exposed/necrotic bone

- Debridement and/or sequestrectomy less traumatic as possible, also by means of piezosurgery [31–38]
- To avoid the use of vasoconstrictor associated with local anesthetics
- Resection of the affected bony tissue, less traumatic as possible, also by means of piezosurgery [31–38]
- Partial, marginal or segmental resection, eventually followed by a reconstructive therapeutic phase

9. Alternative therapy in case of exposed/necrotic bone

- Low-level laser therapy using He-Ne or diode laser.

Issue 2: dental management of patients under treatment (or with history of treatment) with i.v. and oral BF (for oral BF duration of therapy >3 years)—no clinical lesions

1. Early diagnosis of 'early stage' BRONJ

- Compilation of 'case history paper'
- Clinical follow-up (every 3–4 months)
- X-ray of jaws every 6 months
- Prescription of computed tomography dental scan when X-ray is doubtful
- Prescription of bony scintigraphy to evaluate the early bone involvement
- In case of necessary tooth extraction (see Table 3)

2. Thorough oral examination

- Signs

  -Bony exposure
  -Dental forcations exposure
  -Oral/cutaneous fistulas
  -Local or general swellings of the soft intraoral tissues
  -Mobility of teeth that were stable in the preceding inspection
  -Sudden change in the health of periodontal or mucosal tissues

Symptoms

  -Undiagnosed oral pain
  -Dysesthesias (e.g. numbness, feeling of a 'heavy jaw')

3. Achievement and/or maintenance of optimal periodontal and dental health

- To avoid procedures that involve direct osseous
- To avoid the use of vasoconstrictor associated with local anesthetics
- To eliminate the local risk factors (e.g. sharp edges of dental crowns, inadequate dental prosthesis, inadequate conservative restorative treatments)
- To examine patients with full or partial dentures for areas of mucosal trauma, especially along the lingual flange region (i.e. mylohyoid ridge) and where palatal and lingual tori and bony exostoses are represented. To settle if required.
- To make stable teeth with grade 1 or 2 of dental mobility
- To make conservative restorative and prosthesis treatments. Nonrestorable teeth may be treated by removal of the crown and endodontic treatment of the remaining roots. No surgical treatment is indicated.

Table 3. Protocol in case of not postponed tooth extractions in patients receiving IV BF

Discontinuation of BF from 1 to 3 months before and after dento-alveolar surgery, till a complete healing of tissue[1]
Broad-spectrum antibiotic therapy 5 days before and 20 days after tooth extraction, until a complete healing of treated tissues occurs, in combination with topical applications of chlorexidine gluconate
LLLT both during intra-surgical phase and 1 week after surgical treatment. Five topical applications for 1 minute should be performed. At least three periodic meetings are necessary. The LLLT improve tissue regeneration and decrease the bacterial colonization in the site of surgical procedure.

[1]Currently, there is no published evidence to support or oppose discontinuation therapy of BF (both IV and *per os*) before required dentoalveolar surgery. However, the removal of the anti-angiogenic effects of the drug on the soft tissues and periosteum may play an important role in a better vascularization and a more rapid healing after surgical treatment.

4. Achievement and/or maintenance of a good oral hygiene

- Over-gingival scaling
- Instruction to oral self-hygiene
- Prescription of antiseptic rinses, such as chlorhexidine 0.12%
- Local application of fluorine
- Motivation for the importance of good dental hygiene

5. Patient education and reassurance about BRONJ

- Delivery of informative papers (e.g. letter to dentistry, information for the patients)
- Information against every elective dental or surgical procedures involving osseous injury
- Instruction to report every early symptom or clinical sign (e.g. pain, swelling)
- Education to clinical and X-ray follow-up, with frequency depending on the number of concomitant risk factors and general dental health

Issue 3: dental management of patients before treatment with BF

1. Thorough examination of hard and soft intraoral tissues
2. X-ray of jaws to evaluate the general oral status
3. Achievement of optimal periodontal and dental health

- Extraction of teeth with partial inclusion (only mucosal inclusion, not bone inclusion) and of teeth with a poor prognosis (e.g. teeth with serious periodontal disease, nonrestorable teeth or unsalvageable with prosthesis)
- Extraction, in the children, of deciduous teeth with a certain grade of mobility
- Etiological periodontal therapy and stabilization of teeth with grade 1 or 2 of dental mobility
- Endodontic treatment of teeth with chronic periodontal lesions
- Conservative restorative and prosthesis treatments, when necessary
- Patients with full or partial dentures should be examined for areas of mucosal trauma, especially along the lingual flange region
- Elimination of local risk factors (e.g. sharp edges of dental crowns, inadequate dental prosthesis, inadequate conservative restorative treatments)

4. Achievement of a good oral hygiene

- Scaling and root planning
- Instruction to oral self-hygiene
- Prescription of antiseptic rinses, such as chlorhexidine 0.12%
- Local application of fluorine
- Motivation of patients regarding the importance of good dental hygiene

5. Valuation of risks/benefits to delay the BF therapy

- Initiation of bisphosphonate therapy should be delayed until periodontal and dental health is optimized. In order to get clinical and radiographic healing, all invasive dental procedures should be completed at least 3–4 weeks before starting BF therapy
- Collaboration among treating physician, oncologist, dentist and other specialists involved in the care of the patient.

6. Patient education and reassurance about BRONJ

- Delivery of informative papers (e.g. letter to dentistry, information for the patients)
- Instructions to avoid every elective dental or surgical procedures involving osseous injury during the treatment with BF and at least 5 years after the cessation of bisphosphonate therapy
- Instructions to report every early symptom or clinical sign (e.g. pain, swelling)
- Education to periodic clinical and radiographic follow-up, with frequency depending on the number of concomitant risk factors and general dental health.

Issue 4: diagnosis of BRONJ vs metastatic jaw lesions in cancer patients

It appears that one of the issues requiring to be further addressed are challenges in suspecting and diagnosing metastatic jaw lesions in cancer patients affected by BRONJ due to overlapping clinical and/or radiological appearance. In fact, considering the nature of tumors that generally affect patients requiring bisphosphonates administration and developing jaw osteonecrosis, the occurrence of jawbone metastases is an expectable event. Thus, in a correct diagnostic process it should be always kept in mind, suspected and excluded. This is

particularly true at the time of BRONJ onset, when this clinical condition can be correctly diagnosed ruling out metastatic infiltration from the underlying malignancy. However, clinical picture cannot provide any useful parameter; imaging techniques lack specificity and radiologic appearance of BRONJ can be quite variable ranging from osteolytic to osteosclerotic changes, so its differentiation from a metastasis may be very difficult. The only way to accurately identify and exclude metastatic lesions remains histopathological evaluation; it requires biopsy execution, but if we consider when and where carry out to a biopsy many issues remain unsolved. Surgical procedures may lead to worsening or progression of the disease, so, according to current clinical guidelines it is advised a conservative approach and it is recommended that biopsies of the exposed bone should be carried out only whenever metastatic bone disease is suspected. However, we have neither clinical nor radiological signs suggestive of cancer infiltration, thus a strict application of current guidelines might restrict biopsy execution limiting the possibility to rule out jaw metastasis; consequently, the relevance to the patient prognosis of such a differential diagnosis underlines the current contradiction and the need for revising clinical guidelines regarding both biopsy schedule and site selection. Under the latter point of view, the exposed portion of the diseased jawbone could appear as the most convenient site since current guidelines recommend reduction of traumas to soft tissues. However, it is mainly constituted by necrotic tissue, so for the results to be reliable it might be better shifting toward margins of exposed bone. Unfortunately, by now, we have no answer and clinical behavior remains case sensitive on the basis of personal judgment.

references

1. Treister N, Woo SB. Images in clinical medicine. Bisphosphonate-associated osteonecrosis of the jaw. N Engl J Med 2006; 355: 2348.
2. Rubegni P, Fimiani M. Images in clinical medicine. Bisphosphonate-associated contact stomatitis. N Engl J Med 2006; 355: e25.
3. Bilezikian JP. Osteonecrosis of the jaw—do bisphosphonates pose a risk? N Engl J Med 2006; 355: 2278–2281.
4. Woo SB, Hande K, Richardson PG. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005; 353: 99–102; discussion 199–102.
5. Rendina D, De Filippo G, Mossetti G. Paget's disease and bisphosphonates. N Engl J Med 2005; 353: 2616–2618; author reply 2616–2618.
6. Maerevoet M, Martin C, Duck L. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005; 353: 99–102; discussion 199–102.
7. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005; 353: 99–102; discussion 199–102.
8. Walter C, Grotz KA, Kunkel M, Al-Nawas B. Prevalence of bisphosphonate associated osteonecrosis of the jaw within the field of osteonecrosis. Support Care Cancer 2007; 15: 197–202.
9. Urade M. [Bisphosphonates and osteonecrosis of the jaws]. Clin Calcium 2007; 17: 241–248.
10. Sykes DL. Osteonecrosis of the jaw. Dent Today 2007; 26: 16.
11. Sala A, Mattano LA Jr, Barr RD. Osteonecrosis in children and adolescents with cancer—an adverse effect of systemic therapy. Eur J Cancer 2007; 43: 683–689.
12. Russell RG. Bisphosphonates: mode of action and pharmacology. Pediatrics 2007; 119 (Suppl 2): S150–S162.
13. Yamada K, Kohno N. [Efficacy of bisphosphonates for bone pain control]. Nippon Rinsho 2007; 65: 152–156.
14. Weitzman R, Sauter N, Eriksen EF et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients-May 2006. Crit Rev Oncol Hematol 2007.
15. Reid IR. Bisphosphonates. Skeletal Radiol 2007.
16. American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007; 65: 369–376.
17. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006; 102: 433–441.
18. Woo TC, Joseph DJ, Wilkinson R. Serious ocular complications of zoledronate. Clin Oncol (R Coll Radiol) 2006; 18: 545–546.
19. Body JJ, Coleman R, Clezardin P et al. International society of geriatric oncology (SIOG) clinical practice recommendations for the use of bisphosphonates in elderly patients. Eur J Cancer 2007.
20. Stepensky D, Kleinberg L, Hoffman A. Bone as an effect compartment: models for uptake and release of drugs. Clin Pharmacokinet 2003; 42: 863–881.
21. American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007; 65: 369–376.
22. Zervas K, Verrou E, Teleioudis Z et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. Br J Haematol 2006; 134: 620–623.
23. Badros A, Weikel D, Salama A et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol 2006; 24: 945–952.
24. Tosi P, Zamagni E, Cangini D et al. Osteonecrosis of the jaws in newly diagnosed multiple myeloma patients treated with zoledronic acid and thalidomide-dexamethasone. Blood 2006; 108: 3951–3952.
25. Bernardeschi P, Dentico P, Rossi S et al. Low-dose thalidomide plus monthly high-dose oral dexamethasone (Thali-Dexa): results, prognostic factors and side effects in eight patients previously treated with multiple myeloma. J Exp Clin Cancer Res 2003; 22: 129–133.
26. Kumar L, Vikram P, Kochupillai V. Recent advances in the mangement of multiple myeloma. Natl Med J India 2006; 19: 80–89.
27. Ural AU, Avcu F. Bisphosphonates may potentiate effects of thalidomide-dexamethasone combination in advanced multiple myeloma. Am J Hematol 2006; 81: 385–386; author reply 386.
28. Li EC, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. Clin Ther 2003; 25: 2669–2708.
29. Pentikainen PJ, Elomaa I, Nurmi AK, Karkkainen S. Pharmacokinetics of clodronate in patients with metastatic breast cancer. Int J Clin Pharmacol Ther Toxicol 1989; 27: 222–228.
30. Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with advanced cancer. Drugs 2004; 64: 1197–1211.
31. Su YC. [Development and clinical application of ultrasonic osteotomy in dentistry.]. Shanghai Kou Qiang Yi Xue 2007; 16: 1–7.
32. Beziat JL, Vercellotti T, Gleizal A. [What is Piezosurgery((R))? Two-years experience in craniomaxillofacial surgery.]. Rev Stomatol Chir Maxillofac 2007.
33. Gleizal A, Bera JC, Lavandier B, Beziat JL. Piezoelectric osteotomy: a new technique for bone surgery-advantages in craniofacial surgery. Childs Nerv Syst 2007.
34. Garg AK. Using the Piezosurgery device: basics and possibilities. Dent Implantol Update 2007; 18: 1–4.
35. Schlee M, Steigmann M, Bratu E, Garg AK. Piezosurgery: basics and possibilities. Implant Dent 2006; 15: 334–340.
36. Hoigne DJ, Stubinger S, Von Kaenel O et al. Piezoelectric osteotomy in hand surgery: first experiences with a new technique. BMC Musculoskelet Disord 2006; 7: 36.
37. Kotrikova B, Wirtz R, Krempien R et al. Piezosurgery—a new safe technique in cranial osteoplasty? Int J Oral Maxillofac Surg 2006; 35: 461–465.
38. Vercellotti T, Nevins ML, Kim DM et al. Osseous response following resective therapy with piezosurgery. Int J Periodontics Restorative Dent 2005; 25: 543–549.