J Clin Periodontol 2005; 32: 1123–1128 doi: 10.1111/j.1600-051X.2005.00842.x

Journal of Clinical Periodontology

Osteonecrosis of the jaws in periodontal patients with a history of bisphosphonates treatment

G. Ficarra[1], F. Beninati[1], I. Rubino[1], A. Vannucchi[2], G. Longo[2], P. Tonelli[3] and G. Pini Prato[4]

[1]Reference Center for the Study of Oral Diseases; [2]Department of Hematology; [3]Department of Oral Surgery; [4]Department of Periodontology, University of Florence and Azienda Ospedaliera-Universitaria Careggi, Florence, Italy

Ficarra G, Beninati F, Rubino I, Vannucchi A, Longo G, Tonelli P, Pini Prato G. Osteonecrosis of the jaws in periodontal patients with a history of bisphosphonates treatment. J Clin Periodontol 2005; 32: 1123–1128. doi: 10.1111/j.1600-051X.2005.00842.x. © Blackwell Munksgaard, 2005.

Abstract

Background/Aim: Osteonecrosis of the jaws is being increasingly reported in patients with bone metastasis from a variety of solid tumours and disseminated multiple myeloma receiving intra-venous bisphosphonates. The signs and symptoms that may occur before the appearance of clinical evident osteonecrosis include changes in the health of periodontal tissues, non-healing mucosal ulcers, loose teeth and unexplained soft-tissue infection. A series of nine periodontally involving patients showing osteonecrosis of the jaws that appeared following the intra-venous use of bisphosphonates is reported.

Material and Methods: Nine consecutive patients with osteonecrosis of the jaws were prospectically studied. Patients' past medical histories and the drugs that they had received for their malignant disease were systematically documented. Clinical, histopathological and radiographic features and proposal for treatment modalities of osteonecrosis are also reported.

Results: Of the nine patients (six women and three men) observed, all had osteonecrosis in the mandible; two had maxillary involvement as well. All nine patients had a history of extraction of periodontally hopeless teeth preceding the onset of osteonecrosis. In two patients, the lesions also appeared in edentulous areas spontaneously. All the patients had received intra-venous bisphosphonates as treatment for their disseminated haematological neoplasms or metastatic bone disease. The duration of bisphosphonate therapy at presentation ranged from 10 to 70 months (median: 33 months).

Conclusions: Jaw osteonecrosis appears to be associated with the intra-venous use of bisphosphonates. Dental professionals should be aware of this potentially serious complication in periodontal patients receiving long-term treatment with bisphosphonates.

Key words: bisphosphonates; jaw osteonecrosis; osteomyelitis; periodontal patients

Accepted for publication 29 July 2005

Recent reports have described osteonecrosis of the jaw bones as a potentially serious complication that is suspected to be associated with intra-venous use of bisphosphonates. In 2003, after an alert initial observation by Wang et al. (2003) at the University of California San Francisco, Rosenberg & Ruggiero (2003), Marx (2003) and Migliorati (2003) have reported further findings in a new set of patients. The clinical aspects and behaviour of osteonecrosis in these patients showed a striking resemblance to osteoradionecrosis with exposed bone and sequestration non-responsive to conventional surgical management. All the initial observations have pointed to the potential role of the intra-venously administered bisphosphonates such as pamidronate and zoledronate. In June of 2004, in a detailed paper, Ruggiero et al. (2004) reported findings in 63 additional patients, of whom 56 had received intra-venous bisphosphonates for bone metastasis and seven had undergone chronic oral bisphosphonate treatment for osteoporosis. Recently, an editorial by Greenberg (2004) has further underlined the importance of this unrecognized destructive lesion, and alerted oncologists and dentists of its potential association with intra-venous use of bisphosphonates.

Bisphosphonates are indicated for the treatment of patients affected by multiple myeloma or bone metastasis from a

variety of malignant tumours (Berenson et al. 1996, Hortobagyi et al. 1996, Hillner et al. 2003). The American Society of Clinical Oncology has affirmed that intra-venous bisphosphonates, in conjunction with anticancer chemotherapy, represent the standard of care for the management of hypercalceamia of malignancy and metastatic osteolytic lesions associated with multiple myeloma and any solid tumour including breast, prostate and lung cancer (Berenson et al. 2002, Hillner et al. 2003). Bisphosphonates are also indicated in Paget's disease, osteogenesis imperfecta, idiopathic juvenile osteoporosis and severe steroid-induced osteoporosis (Brumsen et al. 1997, Glorieux et al. 1998, Devogelaer 2000).

Although the mechanism of action of these drugs, mainly based on a potent inhibitory effect on bone resorption, is not completely understood, there is proof that they block dissolution of hydroxyapatite and inhibit osteoclast function (Rodan & Fleisch, 1996). There is evidence that internalization of the drug in active osteoclasts disrupts the cytoskeleton and vesicular trafficking, leading to cessation of resorption and induction of apoptosis (Wood et al. 2002). These compounds also have antiangiogenic effects, being able to decrease endothelial cell proliferation (Fournier et al. 2002). At a molecular level, it has been shown that bisphosphonates influence osteoclast activity through the modulation of a cell surface receptor or an intra-cellular enzyme (Sahni et al. 1993).

Pamidronate (Aredia®, Novartis Pharmaceuticals, East Hanover, NJ, USA), a first-generation bisphosphonate, is administered intra-venously at a dose of 90 mg over a variable period of time (2–24 h) every 3–4 weeks. Zoledronate (or zoledronic acid) (Zometa®, Novartis Pharmaceuticals), a second-generation and most potent bisphosphonate, is administered every 4 weeks at a dose of 4 mg over a period of 15 min. (Brumsen et al. 1997, Glorieux et al. 1998, Devogelaer 2000). Preparations for oral use such as alendronate and risedronate are pharmacologically less potent and less effective for the treatment of bone metastasis and therefore they are used only in the treatment of osteoporosis.

The purpose of this case series is to report nine consecutive cases of osteonecrosis of the maxilla and mandible in patients with disseminated haematological neoplasms and metastatic bone diseases who were receiving intra-venous bisphosphonates therapy.

Material and Methods

The study consisted of nine consecutive patients with severe periodontal disease and tooth loss who had been diagnosed and treated for disseminated haematological neoplasms or metastatic bone diseases and presented with jaw osteonecrosis. All patients were observed and prospectively followed at the Reference Center for the Study of Oral Diseases or at the Department of Periodontology of the University of Florence. The patients were referred because of changes in the health of periodontal tissues, non-healing mucosal ulcers, loose teeth and unexplained soft-tissue infection. All nine patients had had bone scans and radiographs demonstrating bone metastasis in solid tumours and generalized bone lesions in haematological tumours.

The patients' past medical histories, drugs that they have received for their malignant disease as well as the symptoms, the anatomic locations and the number of areas with osteonecrosis, the relationship with previous extractions of periodontally involved teeth and the presence or absence of oroantral fistulas were systematically documented. The radiographic features and the histopathological findings in biopsies from the affected jaw bones were also reported. In seven patients, a biopsy from an area of the jaw lesion was taken. In two cases biopsy was not performed because of the patient's precarious conditions. In all cases, a panorex or a dental scan of the jaws was performed before oral biopsy.

At the initial diagnosis of jaw osteonecrosis, all the patients were treated with the same management protocol consisting of conservative debridement of bone sequestra, local irrigation with povidone–iodine and daily rinsing with 0.12% chlorhexidine mouthwash, oral nimesulide and prolonged antibiotic therapy with penicillin-type antibiotics. Conservative debridement consisted in a non-aggressive, superficial removal of bone sequestra. The dosages of amoxicillin/clavulanate potassium and nimesulide were two 1000 mg tablets every 12 h for 20–30 days and two 100 mg tablets per day after meals for 6–7 days, respectively. The treatment was then repeated in case of recurrence of pain and signs of infection. The patients were followed every 2 months.

Results

During the course of the past 13 months, nine consecutive patients who presented with jaw bone necrosis following the intra-venous use of pamidronate and/or zoledronate were observed (Tables 1 and 2). All the patients showed lesions on the mandible and two had lesions both on the maxilla and the mandible (Fig. 1a, b, c). In all the patients, a tooth extraction preceded the onset of osteonecrosis. The median time to diagnosis of jaw osteonecrosis since the first surgical manipulation consisting in tooth extraction was 7 months (range 3–12 months). In two patients with multiple lesions (patients 1 and 3), the lesions also appeared in edentulous areas spontaneously and in anatomically unrelated sites distant from those that followed tooth extractions (Fig. 2). In all cases, the exposed necrotic bone was infected, causing pain. Patients complained of other symptoms such as difficulty in eating, speaking, lower–lip paresthaesia and some showed clinical signs such as trismus, halitosis and recurrent abscesses. Chronic maxillary sinusitis secondary to bone necrosis and an oroantral fistula were evident in a patient with posterior maxillary involvement (patient 1). All affected patients had a history of one of the following malignant tumours: breast cancer (3), multiple myeloma (3), lung cancer (1), prostate cancer (1) and non-Hodgkin's lymphoma with bone involvement (1). All patients had radiographic or nuclear scan evidence of bone metastasis or disseminated disease. None of the patients had received radiation treatment to the area of the jaw bones. The duration of the bisphosphonates therapy at presentation with jaw osteonecrosis ranged from 10 to 70 months (median: 33 months). In seven patients in whom the biopsy was performed, the bone necrosis was histologically diagnosed as chronic osteomyelitis without evidence of detectable malignancy. All the specimens revealed areas of necrotic bone and fibrinous exudates accompanied by a polymorphonuclear leucocyte infiltrate (Fig. 3).

In all the patients, intra-venous bisphosphonate treatment was stopped once the diagnosis of jaw osteonecrosis was made. One patient died 3 months after the diagnosis of jaw osteonecrosis because of the progression of her metastatic bone disease. After several months of follow-up (see Table 2), we found

Table 1. Clinical features, primary tumour and anti-cancer drugs used in nine patients with jaw osteonecrosis

Case	Age/gender	Primary malignancy	Drugs used			
			bisphosphonate (duration in months)	cytotoxics	hormone antagonists	others
1	66/F	Breast cancer*	Zoledronate (16)	Cyclophosphamide Methotrexate 5-Fluorouracil		
2	50/F	Breast cancer*	Pamidronate (22) Zoledronate (20)	Cyclophosphamide Methotrexate 5-Fluorouracil		
3	69/F	Multiple myeloma*	Zoledronate (10)	Melphalan		Bone marrow transplantation Prednisone
4	60//M	Lung cancer*	Zoledronate (29)			
5	76/M	Multiple myeloma*	Zoledronate (44)	Melphalan		Prednisone
6	48/F	Breast cancer*	Zoledronate (33)	Cyclophosphamide Methotrexate 5-Fluorouracil Paclitaxel Vinorelbine	Exemestane Capecitabine Trastuzumab	
7	48/F	NHL*	Pamidronate (36) Zoledronate (34)	Chlorambucil Vincristine Cyclophosphamide		Prednisone
8	67/M	Prostate cancer*	Zoledronate (24)	Epirubicin	Antiandrogens	
9	70/F	Multiple myeloma*	Pamidronate (36) Zoledronate (24)	Melphalan		Prednisone

*All patients had documented metastatic/disseminated bone disease.
M, male; F, female.

Table 2. Additional clinical findings in nine patients with jaw osteonecrosis

Case	Locations		Number of sites showing exposed jaw bone	Histopathology: signs of bone necrosis and chronic osteomyelitis	Treatment	Bisphosphonate cessation after diagnosis of osteonecrosis	Follow-up (months)
	mandible	maxilla					
1	Yes	Yes	3	Yes	Debridement Cyclic oral antibiotics	Yes	13*†
2	Yes		1	–‡	Oral antibiotics	Yes	3§
3	Yes	Yes	3	Yes	Debridement Cyclic oral antibiotics	Yes	8*†
4	Yes		1	Yes	Debridement Cyclic oral antibiotics	Yes	8*†
5	Yes		1	–‡	Debridement Cyclic oral antibiotics	Yes	7*†¶
6	Yes		1	Yes	Debridement Cyclic oral antibiotics	Yes	6*†
7	Yes		3	Yes	Debridement Cyclic oral antibiotics	Yes	6*†¶
8	Yes		3	Yes	Debridement Cyclic oral antibiotics	Yes	4*†
9	Yes		1	Yes	Debridement Cyclic oral antibiotics	Yes	5*†

*Exposed necrotic bone areas still present.
†Resolution of both pain and local signs of infection.
‡Biopsy was not performed.
§The patient died because of progression of her metastatic bone disease.
¶Dimensional reduction of the necrotic area on panorex.

that the majority of our patients had experienced regression of both pain and signs of local infection, although areas of exposed bone persisted in all of them. Six patients declared that they had reached a ''pain-free'' state by the third month of continuous antibiotic treatment. In two patients, dimensional reduction of the necrotic bone areas was documented by panorex.

Discussion

Osteonecrosis of the jaw bones with intra-venous administration of bisphosphonates has been observed in several

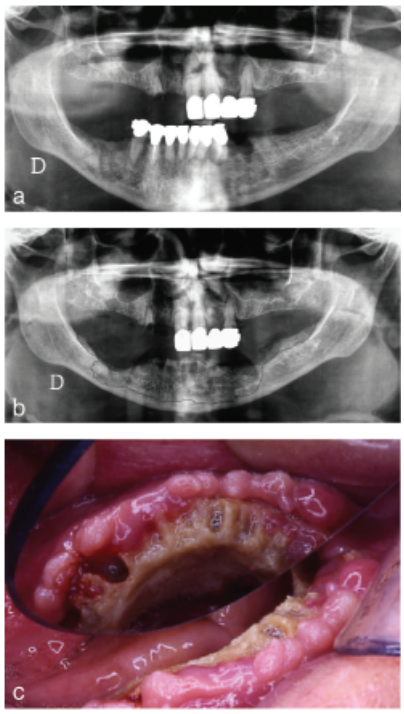


Fig 1. (Patient 2): (a) A panorex of the jaws shows periodontally hopeless teeth before extraction. (b) A panorex taken 4 months after multiple dental extractions reveals the presence of an extensive zone of bone necrosis involving the body of the mandible with large bone sequestra. The borders of the bone sequestra appear delineated by a fine dotted line. (c) Extensive osteonecrosis in the mandible with large sequestra.

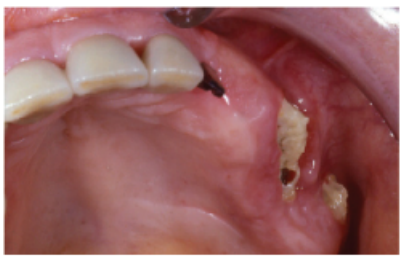


Fig. 2. (Patient 1): Osteonecrosis of the left maxilla that developed spontaneously in an edentulous area.

oral medicine and maxillofacial departments around the world (Lugassy et al. 2004, Bagan et al. 2005, Durie et al. 2005, Maerevoet et al. 2005, Melo & Obeid 2005, Migliorati et al. 2005, Vannucchi et al. 2005, Woo et al. 2005). Marx (2003) has called upon the clinicians' attention, stressing that this problem, because of the widespread use of bisphosphonates in cancer patients, will soon reach epidemic proportions. On a different *note*, Tarassoff & Csermak (2003) have criticized this

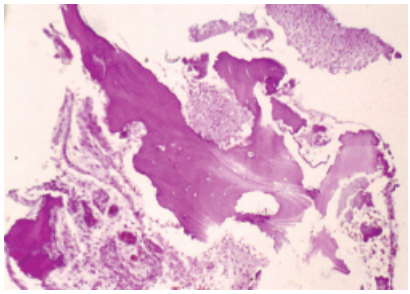


Fig. 3. Photomicrograph of biopsy tissue from a case of osteonecrosis demonstrates a polymorphonuclear leucocyte infiltrate with focal areas of fibrinous exudates. The bone is necrotic and shows focal surface erosion secondary to enzymatic digestion (H&E, × 25).

assertion by pointing out that the causal association remains uncertain as patients receiving intra-venous bisphosphonates are often taking multiple drugs including cancer chemotherapy and corticosteroids.

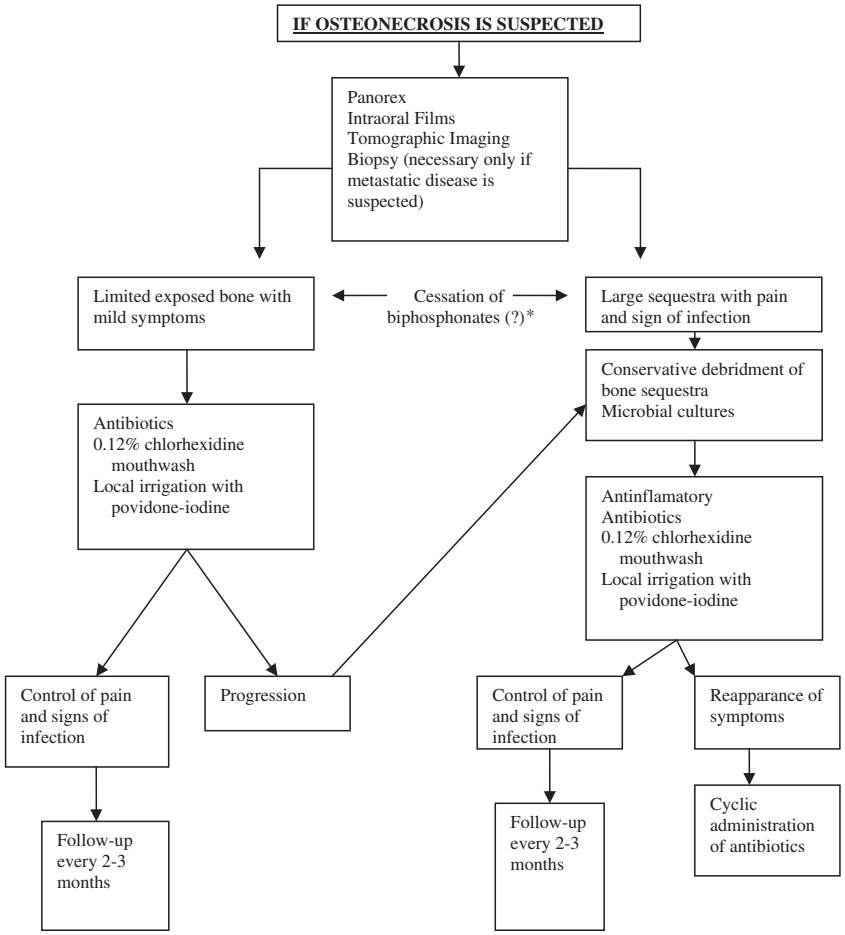
It is of historical interest to mention that osteonecrosis of the jaws was observed in the 19th and early 20th centuries in patients exposed to white phosphorus. At that time, the disease was called *phossy jaw* or *phosphorus necrosis*, and was mainly observed in people working in the matchmaking and fireworks factories or brass and war munitions industries (Miles 1972). Amazingly, clinical descriptions of phossy jaw lesions overlap with those reported today in cases of bisphosphonate osteonecrosis (Hellstein & Marek 2005).

Although the aetiological role of bisphosphonates remains to be elucidated, the alteration in bone metabolism together with surgical insult or prosthetic trauma appear to be key factors in the development of osteonecrosis. Tooth extraction as a precipitating event is a common observation in the previous reports (Marx 2003, Migliorati 2003, Rosenberg & Ruggiero 2003, Ruggiero et al. 2004, Migliorati et al. 2005, Vannucchi et al. 2005). However, lesions may also occur spontaneously in non-extractive sites. The phenomenon of spontaneous appearance of osteonecrosis may be explained by the fact that, once ''metabolically damaged'' by the treatment with the bisphosphonates, the entire skeleton remains susceptible even to minor causative factors such as prosthetic trauma (Ruggiero et al. 2004, Migliorati et al. 2005). Typical signs and symptoms are pain, soft-tissue swelling and infection, loosening of teeth and draining fistula. Some patients may present with atypical symptoms such as ''dull pain'', numbness, the feeling of ''bigger jaw'' or lower-lip paraesthesia. The signs and symptoms that may occur before the appearance of clinically evident osteonecrosis include changes in the health of periodontal tissues, non-healing mucosal ulcers, loose teeth and unexplained soft-tissue infection (Migliorati et al. 2005).

Osteonecrosis of the jaws can also be associated with a variety of aetiological factors such as radiation therapy, trauma, herpes zoster, HIV infection and fungal infections and pre-disposing conditions such as osteopetrosis, fibrous dysplasia, etc. (Lew & Waldvogel 2004, Ruggiero et al. 2004, Tolar et al. 2004). Therefore, it is important to consider co-morbid factors before indicting the bisphosphonate agents alone for the jaw lesions observed and encountered in these patients. Regarding the additional drugs that were taken by our patients, it is of relevance to note that we were unable to find any data in the literature to suggest a potential role of these drugs in the development of osteonecrosis.

At present, there is no definite treatment for this particular drug-induced necrosis of bone. Although it may seem reasonable and prudent to suggest that stopping the administration of intravenous bisphosphonates would improve the resolution rate of this condition, there is no proof to support such an indication for management (Migliorati et al. 2005). In fact, there is preliminary evidence that drug withdrawal does not lead to clinical improvement of bone necrosis (Ruggiero et al. 2004). This can be well explained by the fact that bisphosphonates avidly bind to bone mineral around active osteoclasts, resulting in very high levels in the resorption lacunae (Fournier et al. 2002). Because bisphosphonates are not metabolized, high concentrations are maintained within the bone for long periods of time (Rodan & Fleisch 1996).

Our patients were all treated using a conservative approach with the goal of preventing progression of lesions and limiting complications related to chronic infection. To achieve these goals, conservative debridement of bone sequestra, local irrigation with povidone–iodine and daily rinsing with 0.12% chlorhexidine mouthwash were considered. In particular, in all our patients we used the same treatment regimen consisting of oral administration of amoxicillin/clavula-



* To date there is no definitive proof which suggests that stopping the administration of intravenous bisphosphonates would improve the resolution rate of this condition.

Fig. 4. Management of biphosphonate osteonecrosis

nate potassium together with a short course of oral nimesulide. The treatment was then repeated in case of recurrence of pain and signs of infection.

Based on our experience, although limited because of the small number of patients, a management protocol that can be useful in order to limit complications of osteonecrosis is delineated in Fig. 4. Diagnosis of bisphosphonate osteonecrosis should be mainly based on clinical and radiographic criteria. Tissue biopsy is not always necessary and should be performed only if metastatic disease is suspected. Microbial cultures (aerobic and anaerobic) may provide identification of pathogens causing secondary infection. However, it is important to stress that cultures taken from an open sinus tract or exposed jaw bone may give misleading results because the isolates may include non-pathogenic microorganisms that are colonizing the site (Lew & Waldvogel 2004). The majority of patients with chronic bone exposure can be treated using a medical approach consisting of oral antibiotics, anti-inflammatories, local irrigation with povidone–iodine and 0.12% chlorehexidine mouthwash associated with conservative debridement. Aggressive surgical intervention (i.e. bone resection) appears counterproductive and often produces further exposed bone (Migliorati et al. 2005). Conservative debridement of bone sequestra is appropriate in patients with voluminous lesions in order to reduce the local infection process. The goal of surgery should be to eliminate dead bone that acts as foreign material (Lew & Waldvogel 2004). Regarding hyperbaric oxygen, some authors (Ruggiero et al. 2004) have considered it as not effective and, therefore, did not recommend it; other authors (Lugassy et al. 2004), instead, have found hyperbaric oxygen therapy to be of some use.

It is important to stress that a strict collaboration with the oncologists is mandatory in order to identify strategies to improve the care of this particular group of patients. It is anticipated that a better understanding of the role of bisphosphonates in the development of osteonecrosis will lead to improved prevention and perhaps treatment of bisphosphonates-associated jaws osteonecrosis. Until then, we recommend that measures be always taken to prevent osteonecrosis in those at risk. Such measures should include careful dental examination and mandatory extractions of candidate teeth with enough time allowed for healing in advance of the start of intra-venous bisphosphonate treatment. Also important is the adoption of preventive measures such as dental caries and periodontal disease control, avoiding dental implant placement and the use of soft liners on dentures. In patients with overt osteonecrosis, the cessation or interruption of bisphosphonates must be discussed with the oncologist and always weighted against the risk of skeletal complications or hypercalcaemia of malignancy.

References

Bagan, J. V., Murillo, J., Poveda, R., Milian, M. A., Sanchis, J. M., Silvestre, F. J. & Scully, C. (2005) Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. *Journal of Oral Pathology and Medicine* **34**, 120–123.

Berenson, J. R., Lichtenstein, A., Porter, L., Dimopoulos, M. A., Bordoni, R., George, S., Lipton, A., Keller, A., Ballester, O., Kovacs, M. J., Blacklock, H. A., Bell, R., Simene, J., Reitsma, D. J., Heffernan, M., Seaman, J. & Knight, R. D. (1996) Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *New England Journal of Medicine* **334**, 448–493.

Berenson, J. R., Hillner, B. E., Kyle, R. A., Lpton, A., Tee, G. C. & Biermann, J. S. (2002) American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *Journal of Clinical Oncology* **20**, 3719–3736.

Brumsen, C., Hamdy, N. A. & Papapoulos, S. E. (1997) Long-term effects of bisphosphonates on the growing skeleton: studies of young patients with severe osteoporosis. *Medicine* **76**, 266–283.

Devogelaer, P. (2000) Treatment of bone diseases with bisphosphonates, excluding osteoporosis. *Current Opinion in Rheumatology* **12**, 331–335.

Durie, B. G. M., Katz, M. & Crowley, J. (2005) Osteonecrosis of the jaw and bisphospho-

nates. *New England Journal of Medicine* **353**, 99–100 (letter).

Fournier, P., Boisser, S., Filleur, S., Guglielmi, J., Cabon, F., Colombel, M. & Clezardin, P. (2002) Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Research* **15**, 6538–6544.

Glorieux, F. H., Bishop, N. J., Plotkin, H., Chabot, G., Lanoue, G. & Travers, R. (1998) Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *New England Journal of Medicine* **339**, 947–952.

Greenberg, M. S. (2004) Intravenous bisphosphonates and osteonecrosis. *Oral Surgery Oral Medicine Oral Pathology* **98**, 259–260.

Hellstein, J. W. & Marek, C. L. (2005) Bisphosphonate osteochemonecrosis (bis-phossy jaw): is this phossy jaw of the 21st century? *Journal of Oral and Maxillofacial Surgery* **63**, 682–689.

Hillner, B. E., Ingle, J. N., Chlebowski, R. T., Gralow, J., Yee, G. C., Janjan, N. A., Cauley, J. A., Blumestein, B. A., Albain, K. S., Lipton, A. & Brown, S. (2003) American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *Journal of Clinical Oncology* **21**, 4042–4057.

Hortobagyi, G. N., Theriault, R. L., Porter, L., Blayney, D., Lipton, A., Sinoff, C., Wheeler, H., Simeone, J. F., Seaman, J. & Knight, R. D. (1996) Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastasis. Protocol 19 Aredia Breast Cancer Study Group. *New England Journal of Medicine* **335**, 1785–1791.

Lew, D. P. & Waldvogel, F. A. (2004) Osteomyelitis. *Lancet* **364**, 269–279.

Lugassy, G., Shaham, R., Nemets, A., Ben-Dor, D. & Nahlieli, O. (2004) Severe osteomyelitis of the jaw in long-term survivors of multiple myeloma: a new clinical entity. *American Journal of Medicine* **117**, 440–441.

Maerevoet, M., Martin, C. & Duck, L. (2005) Osteonecrosis of the jaw and bisphosphonates. *New England Journal of Medicine* **353**, 100–101 (letter).

Marx, R. E. (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *Journal of Oral and Maxillofacial Surgery* **61**, 1115–1117 (letter).

Melo, M. D. & Obeid, G. (2005) Osteonecrosis of the maxilla in a patient with a history of bisphosphonates therapy. *Journal of the Canadian Dental Association* **71**, 111–113.

Migliorati, C. A. (2003) Bisphosphonates and oral cavity avascular bone necrosis. *New England Journal of Medicine* **21**, 4253–4254 (letter).

Migliorati, C. A., Schubert, M. M., Peterson, D. E. & Seneda, L. M. (2005) Bisphosphonates-associated osteonecrosis of mandibular and maxillary bone. An emerging oral complication of supportive cancer therapy. *Cancer* **104**, 83–93.

Miles, A. E. (1972) Phosphorus necrosis of the jaw: ''phossy jaw''. *British Dental Journal* **133**, 203–206.

Rodan, G. A. & Fleisch, H. A. (1996) Bisphosphonates: mechanisms of action. *Journal of Clinical Investigation* **97**, 2692–2696.

Rosenberg, T. J. & Ruggiero, S. (2003) Osteonecrosis of the jaws associated with the use of bisphosphonates. *Journal of Oral and Maxillofacial Surgery* **61** (Suppl. 1), 60.

Ruggiero, S. L., Mehrotra, B., Rosenberg, T. J. & Engroff, S. L. (2004) Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *Journal of Oral and Maxillofacial Surgery* **62**, 527–534.

Sahni, M., Guenther, H. L., Fleisch, H., Collin, P. & Martin, T. J. (1993) Bisphosphonates act on rat bone resorption through the mediation of osteoblasts. *Journal of Clinical Investigation* **91**, 2004–2011.

Tarassoff, P. & Csermak, K. (2003) Avascular necrosis of the jaws. Risk factors in metastatic cancer patients. *Journal of Oral and Maxillofacial Surgery* **61**, 1238–1239 (letter).

Tolar, J., Teitelbaum, S. L. & Orchard, P. J. (2004) Osteopetrosis. *New England Journal of Medicine* **351**, 2839–2849.

Vannucchi, A. M., Ficarra, G., Antonioli, E. & Bosi, A. (2005) Osteonecrosis of the jaw associated with zoledronate therapy in a patient with multiple myeloma. *British Journal Haematology* **128**, 738.

Wang, J., Goodger, N. M. & Pogrel, M. A. (2003) Osteonecrosis of the jaws associated with cancer chemotherapy. *Journal of Oral and Maxillofacial Surgery* **61**, 1104–1107.

Woo, S.-B., Hande, K. & Richardson, P. G. (2005) Osteonecrosis of the jaw and bisphosphonates. *New England Journal of Medicine* **353**, 100 (letter).

Wood, J., Bonjean, K., Ruetz, S., Bellhcene, A., Devy, L., Foidart, J. M., Castronovo, V. & Green, J. R. (2002) Novel antiangiogenic effects of the bisphosphonates compound zoledronic acid. *Journal of Pharmacology Experimental Therapeutics* **302**, 1055–1061.

Address:
Giuseppe Ficarra
Reference Center for the Study of Oral Diseases
Institute of Odonto-Stomatology
Viale Morgagni 85
50134 Florence
Italy
E-mail: gificarr@tin.it

Clinical Relevance

Often, bisphosphonate - associated osteonecrosis is not recognized because the clinician is not aware of its existence. Subtle changes in the health of periodontal tissues and unexplained infection may precede the development of this devastating condition. We call the clinician's attention upon the clinical features and treatment modalities of this potential complication.

The mandible was the most affected bone. Pain, halitosis, difficulty in eating and speaking were common. Management consisted of conservative debridement of bone sequestra, local measures, oral nimesulide and antibiotic therapy. The majority of our patients experienced regression of pain.

Preventive measures such as careful dental examination and mandatory extractions of candidate teeth before treatment and dental caries and periodontal disease control should be taken.