J Oral Pathol Med (2005) 34: 120–3

www.blackwellmunksgaard.com/jopm

CASE REPORT

Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases

J. V. Bagan[1], J. Murillo[1], Y. Jimenez[1], R. Poveda[1], M. A. Milian[1], J. M. Sanchis[1], F. J. Silvestre[2], C. Scully[3]

[1]*Department of Stomatology, Oral Medicine, University General Hospital, Valencia University, Valencia, Spain;* [2]*Department of Stomatology, University Peset Hospital, Valencia, Spain;* [3]*International Centres for Excellence in Dentistry, and Eastman Dental Institute for Oral Health Care Sciences, University College London, London, UK*

BACKGROUND: We present a series of 10 patients with osteonecrosis of the jaws (ONJ) that appeared following cancer chemotherapy.

MATERIAL AND METHODS: Of the 10 cases with ONJ, six had bone metastases from breast cancers and the other four had multiple myeloma. We analysed the location of bone metastases, as well as the characteristics of the ONJ, and the drugs with which they had been treated for their bone metastases.

RESULTS: Of the 10 patients, all had ONJ in the mandible; 50% also had maxillary involvement. The average number of areas of painful exposed was 2.1 per patient (range 1–5). In seven patients a tooth extraction preceded the onset of ONJ. Two patients developed oroantral communications and another a cutaneous fistula to the neck with suppuration. In all the 10 patients the histopatholological diagnosis was of chronic osteomyelitis without evidence of metastatic disease to the jaws. All the patients had received treatment for their malignant bone disease with bisphosphonates. These were the only drugs that all patients had received.

CONCLUSION: ONJ appears to have a relationship with the use of bisphosphonates.

J Oral Pathol Med (2005) **34**: 120–3

Keywords: bisphosphonates; cancer; chemotherapy; jaws; osteonecrosis

Introduction

Osteonecrosis of the jaws (ONJ) is an important complication in patients following radiotherapy to the head and neck (1). Such osteoradionecrosis most commonly affects the body of the mandible, and around 50% of cases follow tooth extraction (2). Chronic osteomyelitis arises, with areas of bone necrosis. The condition is debilitating and difficult to treat.

Osteonecrosis of the jaws can also be induced by fungal infections, trauma, herpes zoster and necrotizing sialometaplasia (3) and some chemicals and drugs. It has also recently been recognized that ONJ can sometimes arise in relation to cancer chemotherapy (4–6), particularly in relation to the use of bisphophonates (4, 5).

We present ten cases of jaw necrosis in patients with cancer chemotherapy, demonstrating the possible relationship with drugs used to treat the effects of bone metastases.

Patients and methods

The group consisted of 10 adult patients who presented with jaw osteonecrosis and had previously been diagnosed and treated for non-oral malignant neoplasms: six had breast cancer (BC) and four had multiple myeloma (MM). All ten patients had had bone scans and radiographs demonstrating malignant disease in bones apart from the jaws: all six patients with BC developed bony metastases and all four patients with MM had generalized bone lesions.

We documented the locations of the bone metastases, as well as the characteristics of the jaw osteonecrosis, including pain and other symptoms, locations of the lesions, number of areas with osteonecrosis, relation with previous dental extractions, oroantral communications and fistulas, and the histopathologic findings in biopsies from the affected jaw bones as well as the drugs used for treatment of the bone metastases. In all our patients we took a representative biopsy from an area of the jaw bones selected from the radiographic changes, plus a specimen of the overlying mucosa. All cases had had bone scintigraphy and radiography before oral biopsy, (always at least an orthopantograph and a CT scan of the jaws). The radiographs were repeated in all cases 6 months later. In no case (at 6 months) did we

Correspondence: Jose V. Bagan, Hospital General Universitario, Servicio de Estomatología, Avda/Tres Cruces s/n, 46014- Valencia, Spain. E-mail: bagan@uv.es
Accepted for publication July 6, 2004

find any radiographic changes suggestive of malignancy. Also, in all cases the histological study showed signs of osteonecrosis and never signs of malignancy.

In all cases the patients, at the beginning, were treated with antibiotics, long-term or intermittent courses (amoxicillin/potassium clavulanate and, in the case of penicillin allergy, clindamycin) at least for 15 days, repeated as necessary, with periodic minor debridement of bone necrosis. In two cases we had to resect affected areas of the jaws when the response to above mentioned treatment was inadequate.

Results

All six patients with bone metastases from BCs were female, with an average age of 59.5 years (range 45–80). The most frequent bone metastases in these six cases were in the spine (five cases, 86.8%), although some had lesions in other sites such as ribs, skull, sacrum, femur and hips. All these six patients were on treatment with bisphosphonates (Table 1).

The four patients with myeloma were two males and two females, also had lesions in their spines and were on treatment with bisphosphonates. Most patients were also on hormone antagonists and/or cytotoxic chemotherapy.

Osteonecrosis of the jaws appeared most frequently in the mandible, affecting the mandible in all cases, sometimes with maxillary involvement (Fig. 1a,b), and was associated with pain in all, and sometimes with several independent avascular exposed bone areas in the same patient, being triggered in seven of cases (70%) by previous dental extractions. Two patients developed oroantral communications and cutaneous fistula to the neck with suppuration. In all cases, the bone necrosis was histologically diagnosed as a chronic osteomyelitis without containing detectable metastases to the jaws (Table 2).

Discussion

That cancer chemotherapy can be associated with jaw necrosis has only relatively recently been recognized (4–10) (Table 3). Marx (6) described 36 cases of painful bone exposure in the mandible, maxilla or both, diagnosed as ONJ. Those patients had received treatments for hypercalcaemia. Wang (4) published a report of three patients with metastatic breast carcinoma who developed ONJ, two in the maxilla and one in the mandible. Finally, Migliorati (5) also described five cases with ONJ, all of them in the mandible. The patients described by these previous authors (4–6), had received medication with different drugs, but all of them had in common that they had taken bisphosphonates.

In the present report of 10 patients with malignant disease and ONJ, all patients had received the bisphosphonates, pamidronate or zoledronic acid. Interestingly, we and others, have previously recognized another bisphosphonate, alendronate, as causing mouth ulceration (11, 12).

Table 1 Malignant disease, detectable extra-oral bone involvement and drugs used, in the 10 patients who developed jaw osteonecrosis

						Drugs used			
Case	*Age*	*Gender*	*Primary malignancy*	*Spine metastases*	*Other detectable bony metastases*	*Bisphosphonates*	*Cytotoxics*	*Hormone antagonists*	*Others*
1	62	Female	Breast cancer	+	Ribs, skull	Pamidronate Zoledronic acid	Cyclophosphamide Methotrexate 5-fluorouracil	Tamoxifen Letrozole Exemestane	–
2	74	Female	Breast cancer	+	–	Pamidronate Zoledronic acid	Docetaxel	Tamoxifen Letrozole Exemestane	–
3	80	Female	Multiple myeloma	+	–	Zoledronic acid	5-fluorouracil Adriamycin Cyclophosphamide	Tamoxifen	Dexametasone
4	62	Female	Breast cancer	+	Sacrum, fémur	Zoledronic acid	5-fluorouracil Adriamycin Cyclophosphamide	Tamoxifen	–
5	67	Female	Multiple myeloma	+	–	Pamidronate	Busulfan Melphalan Cyclophosphamide	–	Interferon Dexametasone Thalidomide
6	50	Female	Breast cancer	–	Hip	Pamidronate	5-fluorouracil Adriamycin Cyclophosphamide	Tamoxifen Anastrozol	–
7	45	Female	Breast cancer	+	Hip	Pamidronate	5-fluorouracil Adriamycin Cyclophosphamide	Tamoxifen	–
8	36	Female	Breast cancer	+	Hip, fémur, ribs	Pamidronate	Adriamycin Docetaxel	–	–
9	67	Male	Multiple Myeloma	+	–	Pamidronate Zoledronic acid	5-fluorouracil Adriamycin Cyclophosphamide	Megestrol	Dexametasone Thalidomide
10	53	Male	Multiple Myeloma	+	–	Pamidronate Zoledronic acid	5-fluorouracil Adriamycin Cyclophosphamide	–	Dexametasone

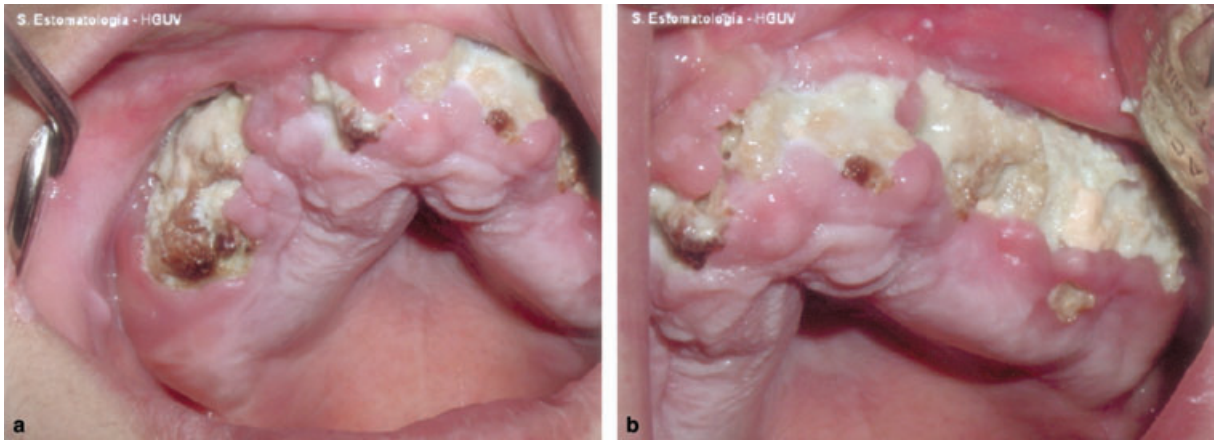

Figure 1 (a,b): Case 8. Extensive bone necrosis exposure in maxila.

Table 2 Oral history and manifestations in the 10 patients with jaw osteonecrosis

Case	*History of preceding tooth extraction*	*Jaw pain*	*Other features*	*Locations*		*Number of sites showing exposed jaw bone*	*Oroantral fistula present*	*Histopathology of affected bone showing chronic osteomyelitis*
				Mandible	*Maxilla*			
1	+	+	–	+	+	5	–	+
2	–	+	–	+	–	1	–	+
3	+	+	–	+	–	1	–	+
4	+	+	–	+	–	2	–	+
5	+	+	Suppuration	+	+	2	+	+
6	–	+	Suppuration	+	–	1	–	+
7	+	+	–	+	+	2	–	+
8	+	+	Suppuration	+	+	3	+	+
9	+	+	–	+	+	3	–	+
10	–	+	–	+	–	1	–	+
Total (%)	7 (70)	10 (100)	3 (30)	10 (100)	5 (50)		2 (20)	10 (100)

Of the other drugs that had been taken by our present 10 patients we emphasize that in six cases (60%) tamoxifen, a non-steroidal anti-oestrogenic agent with combined partial-oestrogen-agonist activity, effective in the treatment of metastatic BC, had been used. However, we have been unable to find any published information on ONJ in relation to tamoxifen. The same comment applies to the cytotoxic drugs such as cyclophosphamide (eight cases, 80%), 5-fluorouracil (seven cases, 70%), and adriamycin (seven cases, 70%). The frequency of use of other drugs in our patients was lower: dexametasone in four cases (40%), thalidomide, letrazole, exemestane and docetaxel, two (25%) in each case; and finally anastrazol, methotrexate, busulfan, melphalan, and interferon (all were used only in one case).

Bisphosphonates inhibit osteoclastic action, and also have an antiangiogenesis effect and are thus helpful in managing hypercalcaemia of malignancy and metastatic bone disease (13, 14). Marx (5) and Migliorati (6) suggested that bisphosphonates could be directly responsible for the ONJ in their patients. On the contrary, Tarassoff and Csermak (15) noted that pamidronate and zoledronic acid have been used in nearly 2.5 million patients worldwide with only rare instances of ONJ. Perhaps of most interest is that bisphosphonates such as alendronate have been used for the treatment of osteonecrosis of other aetiology (16, 17).

Osteonecrosis of the jaws or avascular bone necrosis related to cancer chemotherapy, can appear in both jaws, although in our cases the lesions predominated in the mandible. Marx (6) suggested that the jaws are the only bones exposed to the external environment, via the gingival crevice and, in a high percentage of cases, osteonecrosis is triggered by tooth extractions. He found that 77.7% of cases appeared after dental extractions. A similar percentage of our 10 cases occurred after dental extractions (70%), but in the other three cases we did not have any evidence of any previous significant trauma. Another aetiological and contributing factor may be the particular vascularization of the mandible. The arteries of the mandible are mainly end arteries, which is claimed to be one of the reason why radiotherapy causes necrosis.

What appears to happens in these patients is that, after a tooth extraction, the jaw bone is exposed to the oral flora and incapable to heal, becoming infected and producing pain, and being very difficult to treat, so that

Table 3 Cancer chemotherapy related jaw osteonecrosis reported in the literature

Author (year)	*Number of patients*	*Primary lesions*	*Drugs used for bone metastases: number of cases (percentage)*	*Location ONJ (% cases)*	*Number related to tooth extractions (%)*
Marx (2003) (6)	36	18 MM 17 breast cancer 1 osteoporosis	24 (66.6) with Pamidronate 6 (16.6) Zoledronate 6 (16.6) Pamidronate and Zoledronate	Mandible 29 (80.5) Maxilla 5 (14) Both 2 (5.5)	28 (77.7)
Wang (2003) (4)	3	3 breast cancer	3 (100) Pamidronate 2 (66.6) Anastrozole 2 (66.6) Docetaxel 2 (66.6) Dexamethasone 1 (33.3) Paclitaxel 1 (33.3) Dolasetron 1 (33.3) Tamoxifen	Mandible 1 (33.3) Maxilla 2 (66.6)	2 (66.6)
Migliorati (2003) (5)	5	Not specified	All taking Pamidronate or Zaledronic acid (not specified)	Mandible 5 (100)	2
Bagan et al. (2004), present study	10	4 MM 6 breast cancer	8 (80) Pamidronate 6 (60) Tamoxifen 8 (80) Cyclophosphamide 6 (60) Zoledronic acid 7 (70) 5-fluoruracil 7 (70) Adriamycin 4 (40) Dexametasone 2 (20) Thalidomide 2 (20) Letrazole 2 (20) Exemestane 2 (20) Docetaxel 1 (10) Anastrazol 1 (10) Megestrol 1 (10) Methotrexate 1 (10) Busulfan 1 (10) Melphalan 1 (10) Interferon	Mandible 5 (50) Maxilla and mandible 5 (50)	7 (70)

MM, Multiple myeloma.

the patients periodically need regional debridement and control of infections with antibiotics (5).

References

1. Vissink A, Burlage FR, Spijkervet FK, Jansma J, Coppes RP. Prevention and treatment of the consequences of head and neck radiotherapy. *Crit Rev Oral Biol Med* 2003; **14**: 213–25.
2. Reuther T, Schuster T, Mende U, Kubler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients – a report of a thirty year retrospective review. *Int J Oral Maxillofac Surg* 2003; **32**: 289–95.
3. Pogrel MA, Miller CE. A case of maxillary necrosis. *J Oral Maxillofac Surg* 2003; **61**: 489–93.
4. Wang J, Goodger NM, Pogrel MA. Osteonecrosis of the jaws associated with cancer chemotherapy. *J Oral Maxillofac Surg* 2003; **61**: 1104–7.
5. Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003; **21**: 4253–4.
6. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003; **61**: 1115–7.
7. Rosenberg TJ, Ruggiero S. Osteonecrosis of the jaws associated with the use of bisphosphonates. *J Oral Maxillofac Surg* 2003; **61**: 60.
8. Pogrel MA. Bisphosphonates and bone necrosis. *J Oral Maxillofac Surg* 2004; **62**: 391–2.
9. Assael LA. New foundations in understanding osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2004; **62**: 125–6.
10. Ruggiero SL, Merotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. *J Oral Maxillofac Surg* 2004; **62**: 527–34.
11. Gonzalez-Moles MA, Bagan-Sebastian JV. Alendronate-related oral mucosa ulcerations. *J Oral Pathol Med* 2000; **29**: 514–8.
12. Demerjian N, Bolla G, Spreux A. Severe oral ulcerations induced by alendronate. *Clin Rheumatol* 1999; **18**: 349–50.
13. Fournier P, Boissier S, Filleur S, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res* 2002; **62**: 6538–44.
14. Wood J, Bonjean K, Ruetz S, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther* 2002; **302**: 1055–61.
15. Tarassoff P, Csermak K. Avascular necrosis of the jaws: risk factors in metastatic cancer patients. *J Oral Maxillofac Surg* 2003; **61**: 1238–9.
16. Agarwala S, Sule A, Pai BU, Joshi VR. Alendronate in the treatment of avascular necrosis of the hip. *Rheumatology (Oxford)* 2002; **41**: 346–7.
17. Astrand J, Aspenberg P. Systemic alendronate prevents resorption of necrotic bone during revascularization. A bone chamber study in rats. *BMC Musculoskelet Disord* 2002; **3**: 19.