

# Zoledronic acid for the treatment of appendicular osteosarcoma in a dog

**A 10-year-old male intact Corso dog was referred for lameness and for a large neoplasm affecting the right foreleg. Physical examination of the patient revealed a 5 × 5 × 3 cm mass in the distal right foreleg. Histopathology was consistent with a diagnosis of appendicular osteosarcoma. The staging process found no evidence of metastasis. Because of the large size of the patient, the owners elected to treat their dog with antiresorptive therapy. The patient was treated with an infusion of zoledronic acid every 28 days. The tumour remained stable for 16 months and the lameness of the dog greatly improved. At that time, the patient returned for evaluation of a large rapidly growing prescapular mass. Biopsy confirmed lymph node metastasis and the dog was euthanased. Zoledronic acid showed remarkable palliation in our patient and possibly anti-tumour action and warrants further investigation.**

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## INTRODUCTION

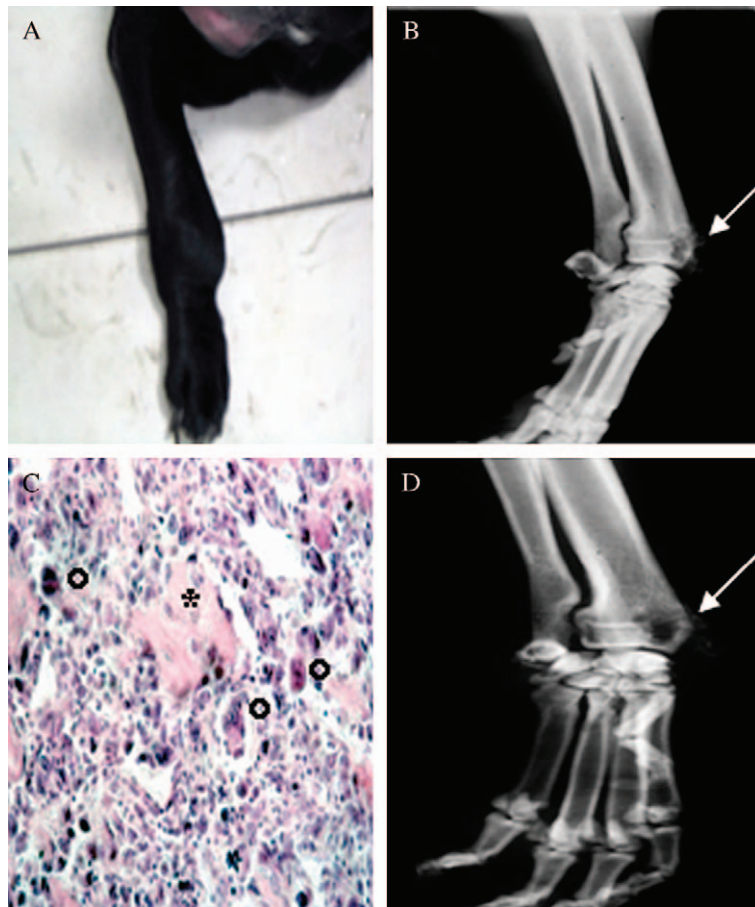
Canine osteosarcoma is the most common bone tumour in dogs and is associated with locally aggressive behaviour (Mueller and others 2007) and a high rate of metastatic spread (Porrello and others 2006). While standard treatment involves amputation and systemic chemotherapy (Spodnick and others 1992, Chun and others 2005), this may not be possible in large breed dogs, leading to the need for therapies aimed at increasing local tumour control (Ramirez and others 1999). The present report describes the use of zoledronic acid as palliation in a case of osteosarcoma. Bisphosphonates have been clearly demonstrated to provide significant benefits to human beings with bone metastases, decreasing skeletal complications and reducing bone pain. In patients with bone metastases from advanced breast cancer, several bisphosphonates have demonstrated significant clinical benefits. Four milligram zoledronic acid very three or four weeks has been shown to be significantly more effective than pamidronate in patients with breast cancer. In patients with other solid tumours (prostate, renal and non-small cell lung cancer), zoledronic

acid is the only bisphosphonate that has demonstrated significant clinical benefit (Santini and others 2006).

## CASE REPORT

A 10-year-old male intact Corso dog was referred for lameness and for a large mass affecting the right foreleg (Fig 1A). The owner reported that the tumour had grown significantly over the past month. On physical examination, the dog was bright, alert and responsive, well hydrated and in good body condition. A firm, painful, poorly circumscribed mass was present in the distal right foreleg measuring approximately 5 × 5 × 3 cm. Radiographs of the leg indicated bone lysis and remodelling in the distal radius, suggesting a primary bone neoplasia (Fig 1B). The dog was staged with a complete blood cell count, serum biochemical profile, urinalysis, chest radiographs (three projections), abdominal ultrasonography and bone biopsy. All tests were within reference limits and the imaging studies did not evidence metastatic spread. The dog was anaesthetised and the distal radius was biopsied with a 13 gauge Jamshidi needle. Grossly, the neoplasm consisted of multiple friable fragments. The samples were fixed in 10 per cent formalin for histological analysis. The dog was discharged on antibiotics (cephalexin 30 mg/kg bid for 10 days) and non-steroidal anti-inflammatory drug for pain control (carprofen 2.2 mg/kg bid for 10 days). Paraffin sections, 5 µm thick, were prepared and stained with haematoxylin and eosin and haematoxylin-Van Gieson staining. The histopathology was consistent with a diagnosis of high-grade osteosarcoma (Fig 1C).

Based on the advanced stage of the disease and the pathology report, several options were presented to the owner: amputation ± chemotherapy, palliative radiation therapy, immunotherapy with COX-2 inhibitors or palliative therapy with inhibitors of osteolytic activity (Spodnick and others 1992, Ramirez and others 1999, Tomlin and others 2000, Farese and others 2004, Kent and others 2004,



**FIG 1.** (A) The appearance of the right foreleg at presentation. (B) Radiographic appearance of the radial lesion (arrow) at presentation. (C) Microscopic appearance of the lesion, showing the production of osteoid by the tumour cells indicated by an asterisk (\*) and the presence of multinucleated cells indicated by a circle (○) (haematoxylin and eosin, original magnification  $\times 40$ ). (D) Radiographic appearance of the progressive radial lesion (arrow) at the last recheck

Chun and others 2005, Spugnini and others 2005, Fan and others 2007).

Because of underlying orthopaedic issues and owner reluctance to perform amputation, the owners elected to treat the dog with antiresorptive therapy using zoledronic acid. The single dose of zoledronic acid for dogs has been reported to be 0.25 mg/kg (de Lorimier and Fan 2005); however, the authors decided on the basis of data from human beings not to exceed the total dose of 4 mg (dog's weight: 60 kg) (Santini and others 2006).

The dog received 4 mg of zoledronic acid diluted in 100 ml of saline solution every 28 days in a slow intravenous infusion over 30 minutes. The dog had a complete blood cell count and a biochemical profile checked before each zoledronate infusion and a thorough oral examination and

jaw radiographs every six months to rule out bisphosphonate-induced bone necroses (Aguar Bujanda and others 2007, Wilkinson and others 2007).

The dog did not experience side effects from its therapy and after the second dose the lameness dramatically improved, with a complete restoration of the gait function after 45 days of treatment. The dog had limb radiographs taken every three months to monitor the status of the radius and chest radiographs taken to rule out metastatic spread. The dog had stable disease for 16 months but the limb lesion showed a 20 per cent circumferential increase over this period of time, also confirmed by radiographs (Fig 1D). At that time, the patient was referred for the sudden growth of a prescapular mass. The patient had a large right prescapular lesion (15 cm in diameter),

which had grown to this size over a 15 day period. A biopsy was performed confirming the diagnosis of metastatic spread to the regional lymph node. The owners elected not to pursue additional therapy.

## DISCUSSION

Osteosarcoma in dogs poses significant problems to veterinary oncologists because of its locally aggressive nature which results in pain, lameness, loss of function and ultimately, spontaneous fracture (Mueller and others 2007) in addition to its high metastatic potential (Porrello and others 2006), thus making it a valuable model for investigative therapies for local (Withrow and others 2004, Liptak and others 2006) and distant control (Khanna and others 2002, Vail and others 2002).

Bisphosphonates have also demonstrated anti-tumour activity in preclinical models and clinical evidence suggests that this class of drugs may slow the progression of bone lesions or prevent bone metastasis. In particular, there is scientific evidence, both in *in vitro* and in *in vivo* models, that zoledronic acid is able to induce tumour cell apoptosis in bone lesions, reduce tumour burden in bone, reduce the number of osteolytic lesions in tumour-bearing mice, prevent formation and progression of bone metastases in a variety of tumour models, including osteosarcoma (Ory and others 2005, Benassi and others 2007). Interestingly, this therapy was able to control the pain in our patient completely, despite the slow progression of the primary bone tumour. This could be ascribed to the remarkable efficacy of zoledronic acid in reducing the painful and burdensome skeletal-related morbidities as already described in human patients treated for skeletal metastases (Weinfurt and others 2006). The high tolerability of zoledronic therapy in our patient and the good response in terms of local control and improved quality of life suggest that bisphosphonates should be considered as an option for osteosarcoma palliation in heavy weight dogs, not only for the possible recalcification of the bone lesion, but also for its analgesic potential, and warrants further investigations.

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