Activity and safety of a prolonged daily schedule of zoledronic acid in a patient with bone metastases from urothelial carcinoma

It has recently been shown that, in a mouse model, frequent administration of bisphosphonates inhibits skeletal tumor growth [1]. We report here the activity and toxicity of zoledronic acid administered at a prolonged daily schedule in a patient with metastatic bone disease.

A 69-year-old woman presented to our unit in October 2006 with hematuria and severe bone pain leading to bed rest for most of the day. A high-grade (G3) papillary urothelial carcinoma of the bladder was diagnosed with multiple lytic lesions involving the left scapula, left ribs and right ribs, left pelvis and left lower limb.

High doses morphine were administered via a peridural catheter (300 mg every week). This treatment was not efficacious in controlling pain during movement, so the patient was bedridden for most of the day. Due to the poor condition of the patient, systemic chemotherapy was not indicated. Zoledronic acid was prescribed at the dose of 4 mg on day 1 every 21 days plus calcium and vitamin D supplementation. This prescription, however, was misinterpreted and zoledronic acid was administered at 4 mg every day for 21 consecutive days. When on the 21st day the patient was visited by the oncology staff, the general condition appeared improved. Bone pain was dramatically reduced allowing the removal of the spinal device and was effectively controlled by transdermal fentanyl 100 mcg every 3 days. The patient walked with crutches. During zoledronate therapy, a modest asymptomatic hypocalcemia was observed (2.17 mmol/l), while creatinine was always within the normal range. Zoledronic acid was discontinued and a high dose of vitamin D (300 000 UI i.m.) was administered to prevent late onset of hypocalcemia. The patient was discharged from hospital and ambulatory chemotherapy administration with gemcitabine (1000 mg/m² on days 1 and 8 every 21) was introduced. The first radiological evaluation after 3 months revealed a complete osteoblastic reaction of most of target bone lesions (Figure 1) and pain was completely controlled. In July 2007, the bone pain worsened again and a progressive disease was observed both in the bladder and in bone. The patient general condition progressively worsened and death occurred in November 2007, 13 months from the diagnosis. During this time period, the patient was also monitored by oral surgeons and no clinical and radiological signs of jaw osteonecrosis was observed.

There were already reports of improved bone pain and lytic lesions with bisphosphonates administered at conventional doses. Daily doses of zoledronic acid, however, were extremely rapid in controlling bone pain in our patient leading to an early mobilization. The pain control was durable. The metronomic schedule adopted may have facilitated the prolonged exposure of bone marrow to the drug, enabling a direct effect on tumor cells in bone, a synergistic activity with gemcitabine [2] and antiangiogenetic effects [3]. Despite of the safety profile of
zoledronic acid in this case, such a schedule should not be recommended due to the risk of renal toxicity. The efficacy of frequent administration of bisphosphonates deserves to be explored in randomized clinical trial.

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Figure 1. Treatment activity on target bone lesions. Computed tomography scan at baseline conditions (A) demonstrated an osteolytic lesions of left pelvis, with pathological soft tissue, that showed a complete recalcification after 3 months (B).