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Original Article

On the horizon: Can bisphosphonates prevent bone metastases?

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Abstract

Skeletal complications of bone metastases increase the risk of death and undermine patients' functional independence and quality of life. Although bisphosphonates are integral in the treatment regimen of patients with metastatic bone disease and have demonstrated efficacy in delaying the onset and reducing the incidence of skeletal-related events, there is great interest in developing treatments to prevent metastasis to bone. Emerging evidence indicates that the potential benefits of bisphosphonate therapy extend beyond the treatment of metastatic bone lesions. Data from preclinical studies suggest that bisphosphonates may have antitumour activity and may prevent bone metastasis. The mechanisms of these antitumour effects are currently under investigation and may include induction of apoptosis, inhibition of tumour cell invasion and angiogenesis, and tumour growth reduction. Therefore, patients with early-stage disease may benefit from early bisphosphonate therapy, before bone metastasis develops, and investigations are ongoing to determine the clinical utility of bisphosphonates in this setting.

Keywords: Antitumour; Bisphosphonates; Bone metastases; Skeletal-related events

Introduction

Bone metastases are a major source of skeletal morbidity in the form of skeletal-related events (SREs) including pathologic fractures, spinal cord compression, severe bone pain requiring strong analgesics or palliative radiotherapy, surgery to bone, and hypercalcaemia of malignancy (HCM).[1,2] These events can dramatically erode a patient's sense of well-being and significantly undermine functional independence and quality of life. In addition, treatment of SREs can result in an economic burden on families and the healthcare system. Therefore, there is great interest in developing treatments to prevent metastasis to bone, and bisphosphonates are under investigation in this setting.

Bisphosphonates are inhibitors of osteoclast-mediated bone resorption. The current indications for bisphosphonates include the treatment of metabolic disorders of bone metabolism (e.g., osteoporosis and Paget's disease), the treatment of HCM, and the prevention of SREs from malignant bone disease. Clinical trials also confirm that bisphosphonates, and zoledronic acid in particular, can prevent bone loss from cancer treatment.[3] There is also emerging evidence that the benefits of bisphosphonate therapy in the oncology setting are more extensive. For example, data from preclinical studies demonstrate that bisphosphonates may have antitumour activity, as evidenced in vitro by reduced proliferation rates of tumour cell lines and in vivo by slower bone lesion progression in animal models.[4,5] The mechanisms responsible for these antitumour effects are currently under investigation. It is likely that the multiple effects of bisphosphonates on cancer cells, as summarised herein, may be beneficial for patients with early-stage disease.

Preclinical evidence for antitumour effects of bisphosphonates

There is a strong rationale from preclinical assessments and preliminary clinical data to support the hypothesis that bisphosphonates may affect the course of cancer progression, especially with regard to the development of bone metastases. In addition to their inhibitory effects on

Abbreviations: FGF, fibroblast growth factor; FPP, farnesyl diphosphate; HCM, hypercalcaemia of malignancy; MMP, matrix metalloproteinases; NSCLC, non-small cell lung cancer; SREs, skeletal-related events; VEGF, vascular endothelial growth factor

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osteoclast-mediated osteolysis, bisphosphonates can also exert direct and indirect effects on osteoblasts, macrophages, and cancer cells.[6] In preclinical assays and model systems, the more active nitrogen-containing bisphosphonates have been found to exert anticancer effects and inhibit multiple steps necessary for metastasis to bone.[7] For example, zoledronic acid induces apoptosis in human breast and prostate cancer cell lines and exerts synergistic antitumour effects with both anthracyclines and taxanes.[8,9] Clinically relevant concentration of doxorubicin and zoledronic acid-induced sequence- and dose-dependent apoptosis of breast and prostate cancer cell lines, whereas the replacement of zoledronic acid with a non-nitrogen-containing bisphosphonate did not increase levels of apoptosis (Fig. 1).[8] Similar sequential effects of paclitaxel and zoledronic acid have also been observed in breast cancer cells.[9] Furthermore, in mouse model systems of breast cancer, zoledronic acid not only delayed the development of metastatic lesions in the bone and viscera (Fig. 2),[10] but also had synergistic effects in combination with doxorubicin for suppressing tumour growth and vascularisation.[11]

Nitrogen-containing bisphosphonates have also been shown to reduce tumour-induced osteolysis and disease progression in bone in mouse models of human cancers such as multiple myeloma, breast cancer, and prostate cancer.[5,12–14] Furthermore, the use of radiographic, histologic, and histomorphometric techniques in various models has demonstrated that nitrogen-containing bisphosphonates can inhibit the formation or progression of bone metastases and/or reduce skeletal tumour burden independent of the timing of bisphosphonate administration.[4] In these models, bisphosphonates were effective when administered at the time of tumour cell inoculation as well as after bone metastases were already established, suggesting that they may play a role in both the prevention and treatment of bone metastases.

Inhibition of new blood vessel formation

In animal model systems, bisphosphonates have been shown to inhibit cancer-associated increases in angiogenesis,[15–21] an important early step in tumour growth and metastasis.[22] In mice, bisphosphonate treatment reduced the microvessel density of osteolytic lesions from multiple myeloma bone disease,[12] and zoledronic acid was found to potently inhibit fibroblast growth factor (FGF)-induced angiogenesis.[19] The FGF family of proteins has been reported to play a role in the development of the mammary gland and to act as oncogenic factors during the development of breast cancer.[23] The effects of bisphosphonates on angiogenesis may be clinically meaningful because in recent pilot studies in patients with advanced tumours metastatic to bone, both pamidronate and zoledronic acid were found to lower serum levels of vascular endothelial growth factor (VEGF).[24,25] Similarly, in a pilot study of patients with metastatic bone disease ($N=26$) who were treated with 4 weekly doses of 1 mg zoledronic acid followed by standard doses (4 mg every 28 days), basal levels of VEGF were significantly decreased after 7 days of treatment ($P=0.038$).[26] This reduction in circulating VEGF levels persisted throughout the entire 84-day study ($P<0.01$ for all time points) and demonstrated the potential and persistent antiangiogenic properties of zoledronic acid.[26] Moreover, in a recent study in women with bone metastases secondary to breast cancer, zoledronic acid lowered serum VEGF levels in most treated patients, and reductions in VEGF levels correlated with prolonged times

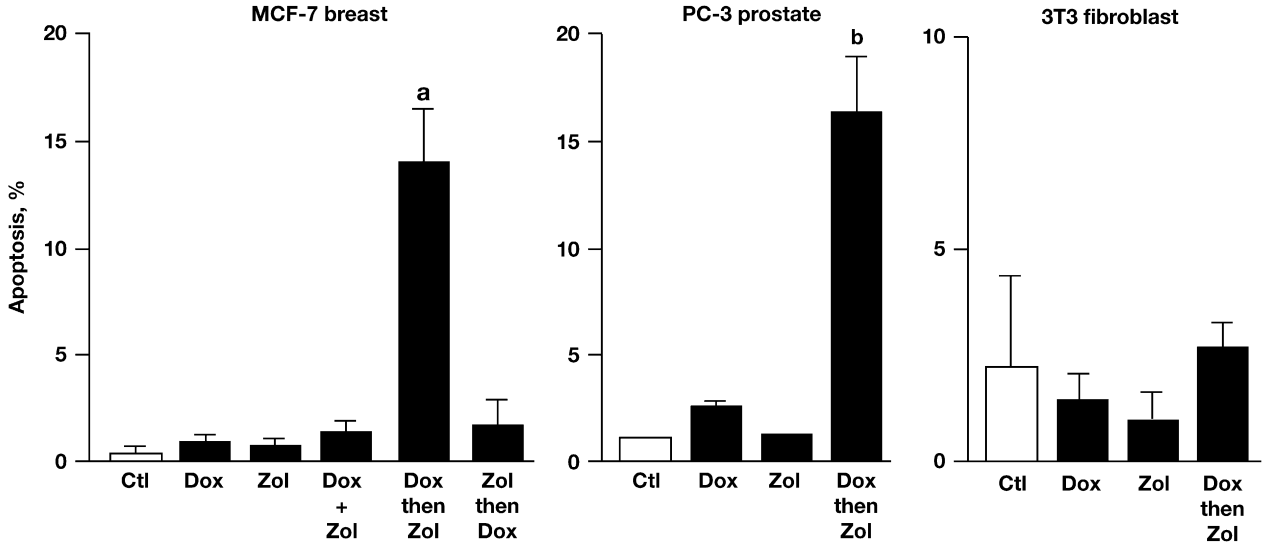

Fig. 1. Sequential treatment of human cancer cells with doxorubicin and zoledronic acid enhances apoptosis. MCF-7 (breast), PC-3 (prostate), and 3T3 (murine fibroblastic) cells were treated with doxorubicin (0.05 μM for 24 h) and then zoledronic acid (25 μM [MCF-7 or 1 μM [PC-3 and 3T3] for 1 h), maintained in fresh medium for 48 h, and percent apoptotic cells determined. Dox = doxorubicin; Zol = zoledronic acid; Ctl = control. [a] $P = 0.004$ and [b] $P \leqslant 0.03$ for doxorubicin then zoledronic acid compared with drugs alone. Adapted with permission from Neville-Webbe et al.[8]