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Original Article

Zoledronic acid directly suppresses cell proliferation and induces apoptosis in highly tumorigenic prostate and breast cancers

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Abstract

Background: Bisphosphonates (BPs) were designed for the prevention of skeletal-related events secondary to bone metastases. The purpose of this study was to show that zoledronic acid (ZA) directly eradicates highly tumorigenic and potentially metastatic cancer cells. **Materials and Methods:** Human prostate and breast highly tumorigenic (PC3, MCF 7) and low- or non-tumorigenic (LNCaP, MCF 10a) cell lines, respectively, were exposed to different concentrations of ZA (0–10 μM). Reverse transcriptase double quantitative polymerase chain reaction was used for quantitative gene expression analysis. Apoptosis and cell proliferation were determined using microscopic observation and MTS assays. Western blot was used to confirm the translational effects of apoptotic genes on protein expression. **Results:** Human prostate and breast highly tumorigenic (PC3, MCF 7) and low- or non-tumorigenic (LNCaP, MCF 10a) cell lines, respectively, showed multiple genes demonstrating differential expressions, including TRAF, TRADD, BCL2, CASPASES and IAP families. Increasing ZA concentrations showed a greater concentration–time response on cell proliferation and apoptosis in the highly tumorigenic cells. These results were confirmed by both reversing and enhancing the effect of ZA on cell proliferation with caspase 3, 7 or survivin siRNA, respectively. Pro-apoptotic proteins bax and caspase 2, 3, 7 and 9 were up-regulated, while the anti-apoptotic proteins bcl2, birc3 and survivin were down-regulated only in the highly tumorigenic cells. **Conclusions:** This explains the ability of ZA to inhibit bony metastasis in highly tumorigenic cells compared with the low- or non-tumorigenic cells through a significant decrease in cell proliferation and increase in apoptosis through gene-regulated and translational-mediated down-regulation of survivin coupled with the inhibition of caspase 3 or 7. This has significant implications toward understanding the pharmacophysiology of BPs in metastasis and supports the clinically observed effect of BPs when administered adjunctively with anticancer drugs such as cyclophosphamide/methotrexate/5-fluorouracil, epirubicin in combination with cyclophosphamide or docetaxel, and doxorubicin.

Keywords: Apoptosis, bisphosphonate, cancer, metastasis, zoledronic acid

BACKGROUND

In the United States, prostate cancer is the most common cancer in men (aside from skin cancer) and is the second leading cause of cancer-related deaths in the United States. About one in six men (192,280 in the US in 2009) will be diagnosed with prostate cancer during their lifetime, with 27,360 dying of their disease; therefore, comprising 10% of