Antitumor Activity of Bisphosphonates

Matthew R. Smith
Massachusetts General Hospital, Boston, Massachusetts

Introduction
Bone metastases are a major cause of morbidity for patients with many types of cancer including multiple myeloma, breast cancer, prostate cancer, and other solid tumors. The clinical complications of bone metastases include pain, fracture, spinal cord compression, and hypercalcemia of malignancy. Although there are important differences in the biology of bone metastases from different cancer types, osteoclast activation is the major mechanism for all tumor-mediated bone destruction.

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and play an important role in the supportive care of patients with bone metastases. Several bisphosphonates (clodronate, pamidronate, and zoledronic acid) improve clinical outcomes for patients with multiple myeloma and metastatic breast cancer. Zoledronic acid decreases the risk of skeletal complications for patients with prostate cancer and other solid tumors including lung cancer and renal cell carcinoma.

Bisphosphonates inhibit osteoclast-mediated bone resorption by several mechanisms. Etidronate and clodronate are metabolized into cytotoxic analogues of ATP. More potent nitrogen-containing bisphosphonates (risendonate, pamidronate, and zoledronic acid) inhibit farnesyl diphosphate synthase, a key enzyme in the mevalonate pathway, and decrease prenylation and enzymatic activity.

Bisphosphonates inhibit osteoclast-mediated bone resorption of essential GTP-binding proteins. Bisphosphonates also inhibit invasion through extracellular matrices. The relative ability of various bisphosphonates to inhibit proliferation and promote apoptosis (5–2000 μM) was relatively resistant to bisphosphonate concentrations similar to the peak plasma concentrations from clinical studies.

Adhesion and Invasion
Bisphosphonates inhibited adhesion of breast and prostate cancer cells to mineralized and unmineralized matrices in vitro. Bisphosphonates also inhibited invasion through extracellular matrices. The relative ability of various bisphosphonates to inhibit tumor cell adhesion and invasion parallels their antiresorptive potency. Some of these activities are observed at very low bisphosphonate concentrations (10^-12 to 10^-6 M), suggesting that inhibition of adhesion and invasion are among the most potent biological effects of bisphosphonates. Maximum inhibition of adhesion and invasion was achieved at bisphosphonate concentrations similar to the peak plasma concentrations from clinical studies.

Angiogenesis
Zoledronic acid inhibited the proliferation of human umbilical vein endothelial cells in vitro. In rodents, zoledronic inhibited basic fibroblast growth factor-induced angiogenesis and testosterone-induced revascularization of the ventral prostate gland. Zoledronic acid also inhibited tumor-induced angiogenesis in a mouse myeloma model.

Proliferation/Survival
Several in vitro studies have shown that bisphosphonates inhibit proliferation and promoted apoptosis of myeloma, breast, and prostate cancer cell lines in a concentration-dependent and time-dependent manner. The concentrations necessary to inhibit proliferation and promote apoptosis (5–2000 μM) exceeded the peak plasma concentrations from clinical studies, although these concentrations may be achieved locally in bone. Zoledronic acid had synergistic effects with standard anticancer drugs in multiple myeloma, breast cancer, and prostate cancer cell lines.

Do these antitumor properties contribute to the clinical efficacy of bisphosphonates in cancer patients? Some studies suggest that bisphosphonates have clinically important antitumor activity (4). Clodronate and pamidronate confer a survival advantage to certain groups of patients with multiple myeloma. Similar data have been reported for pamidronate in women with metastatic breast cancer. Some but not all studies suggest that adjuvant clodronate prevents metastases and improves survival in women with breast cancer. These clinical observations and preclinical evidence of antitumor activity provide a compelling basis to further study the antineoplastic efficacy of bisphosphonates in cancer patients. All marketed bisphosphonates have been developed based on their antiresorptive potency. The characterization of antitumor properties distinct from osteoclast inhibition raises the possibility that future drug development may identify new compounds with enhanced antitumor activity and greater clinical efficacy.
References


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