Antiresorptive Therapies for the Treatment of Malignant Osteolytic Bone Disease

Bhoomi Mehrotra, MD

KEYWORDS

• Antiresorptive therapy • Bisphosphonate
• Receptor activator of nuclear factor κB ligand (RANKL) inhibitor (denosumab) • Zoledronic acid
• Pamidronate • Malignant bone disease • Osteolytic bone disease

KEY POINTS

- Antiresorptive therapies, such as bisphosphonates and the receptor activator of nuclear factor κB ligand (RANKL) inhibitor (denosumab), are an established standard of care in the management of malignant osteolytic bone disease. They have been shown to improve the quality of life of patients with cancer who have advanced bony disease and to attenuate the negative effects of antiandrogens on bone health in patients with prostate cancer and the effects of aromatase inhibitors in the management of breast cancer.
- Bisphosphonates seem to have a role in improving survival in patients with multiple myeloma and may have a role in improving disease-free survival in the adjuvant therapy for hormone sensitive breast cancer.
- Current laboratory investigations to understand their mechanism of action and clinical studies to optimize their indications, dosage schedule, and duration of therapy are ongoing. These will help elucidate their evolving role in the management of patients with malignant disease.

INTRODUCTION

Oral bisphosphonate therapy has proven efficacy in the management of osteoporosis. Numerous more potent aminobisphosphonates, which are administered intravenously, such as pamidronate and zoledronic acid, are known to irreversibly bind to the bony matrix and make them resistant to the osteolytic activity of malignant cells. Initial clinical trials evaluated the role of aminobisphosphonates in inhibiting osteolytic activity and thereby controlling hypercalcemia of malignancy. Subsequent clinical trials evaluated the role of intravenous bisphosphonates in reducing pain related to skeletal lesions, delaying the time to skeletal-related events, reducing the incidence of compression fractures, reducing the need for orthopedic manipulations, reducing the need for radiation therapy, and improving the quality of life. Such trials initially focused on predominantly malignant diseases that led to osteolytic bony metastasis such as breast cancer, renal cell cancer, and multiple myeloma. Subsequent trials focused on malignant bone disease, even those of osteoblastic nature such as typically seen in metastatic prostate cancer. Zoledronic acid therapy was shown to be superior to pamidronate therapy in all malignant causes of bony disease except in multiple myeloma in which both agents were equally efficacious. Subsequent discovery

Department of Medicine, Cancer Institute at St. Francis Hospital, The Heart Center, 100 Port Washington Boulevard, Roslyn, NY 11576, USA
E-mail address: bhoomi.mehrotra@chsli.org

Oral Maxillofacial Surg Clin N Am 27 (2015) 561–566
http://dx.doi.org/10.1016/j.coms.2015.07.002
1042-3699/15/$ – see front matter

of receptor activator of nuclear factor κB ligand (RANKL) inhibitor (denosumab), which is a fully humanized antibody against RANKL that inhibits osteoclast function and consequent bone resorption has proven to be equally or more efficacious than aminobisphosphonates in the management of solid tumor-related metastatic bone disease. However, denosumab therapy is inferior to bisphosphonate therapy in the treatment of multiple myeloma-related bone disease.

Several trials have explored the role of antiresorptive therapy in the prevention of osteolytic bone disease during the natural history of a patient afflicted with advanced solid tumors. However, thus far, these data remain elusive. Bisphosphonate therapies have also been evaluated as adjuvant therapy in the management of early stage primary breast cancer. There are conflicting data regarding their role in impacting overall survival. However, there seems to be benefit from the addition of zoledronic acid to adjuvant endocrine therapy in premenopausal women with estrogen-responsive early breast cancer when evaluated for disease-free survival. In postmenopausal women, there seems to be a clear benefit in terms of disease-free survival of adjuvant bisphosphonates (oral or intravenous). In addition, adjuvant denosumab has been shown to abrogate aromatase inhibitor therapy-related adverse effects on the bone by significantly delaying the time to first clinical fracture.

Antiresorptive therapies have, therefore, become a standard part of the armamentarium of anticancer therapies as supportive and complementary agents in individuals with advanced disease. They are also now being evaluated in the adjuvant setting of oncologic managements and as preventative agents before the development of clinically symptomatic bony disease. This article focuses primarily on the 3 parenteral antiresorptive agents approved by the Food and Drug Administration (FDA) (**Table 1**) in the United States for the management of malignant bone disease: pamidronate, zoledronic acid, and denosumab.

PAMIDRONATE

Pamidronate disodium is an aminobisphosphonate that is indicated in the treatment of tumor-induced hypercalcemia, bone metastases, multiple myeloma, and Paget disease of the bone. It is a potent inhibitor of osteoclastic bone resorption in that it inhibits access of osteoclast precursors onto bone and their subsequent transformation into mature, resorbing osteoclasts.[1] It has a strong affinity for calcified tissues and it is almost exclusively eliminated by renal excretion.

Pamidronate disodium was initially evaluated in the treatment of cancer-related hypercalcemia. In a landmark trial by Gucalp and colleagues,[2] a single infusion of 60 mg of pamidronate was more effective than etidronate in the treatment of cancer-related hypercalcemia. After its role was proven in the management of hypercalcemia of malignancy, it was further evaluated in the management of bone metastases in several solid tumors and multiple myeloma. Berenson and colleagues[3] showed that monthly infusions of pamidronate provide significant protection against skeletal complications and improvement in the quality of life in subjects with stage III multiple myeloma. Subjects with stage III multiple myeloma and at least one lytic lesion received either placebo or 90 mg of pamidronate as a 4-hour intravenous infusion given every 4 weeks for 9 cycles in addition to antimyeloma therapy. Skeletal events

Table 1
Antiresorptive agents approved by the Food and Drug Administration in the United States

Agents	Oncologic Indications
Pamidronate	• Tumor-induced hypercalcemia • Predominantly lytic metastases from solid tumors and multiple myeloma
Zoledronic acid	• Hypercalcemia of malignancy • Patients with multiple myeloma and patients with documented bone metastases from solid tumors (in conjunction with standard antineoplastic therapy) • Patients with prostate cancer who have progressive disease after treatment with at least one hormonal therapy
Denosumab[a]	• Prevention of skeletal-related events in patients with bone metastases from solid tumors • Treatment of giant cell tumor of bone that is unresectable • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

[a] Denosumab is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.