ACP
AMERICAN COLLEGE OF PROSTHODONTISTS®

Bisphosphonate Therapy for Skeletal Malignancies and Metastases: Impact on Jaw Bones and Prosthodontic Concerns

Arvind Tripathi, MDS,[1] Saumya Pandey, MDS,[2] Saumyendra V. Singh, MDS,[3] Naresh Kumar Sharma, MDS,[4] & Ronauk Singh, BDS[5]

[1] Professor and Head, Prosthodontics Department, Saraswati Dental College & Hospital, Lucknow, India
[2] Senior Lecturer, Prosthodontics Department, Saraswati Dental College & Hospital, Lucknow, India
[3] Assistant Professor, Prosthodontics Department, Dental Faculty, CSM Medical University, Lucknow, India
[4] Professor, Oral and Maxillofacial Surgery Department, Saraswati Dental College & Hospital, Lucknow, India
[5] Postgraduate Resident, Prosthodontics Department, Saraswati Dental College & Hospital, Lucknow, India

Keywords
RANK ligand; osteoprotegerin; BRONJ; bisphosphonates.

Correspondence
Saumyendra V. Singh, 2/273 Viram Khand, Gomtinagar, Lucknow, UP, India. Pin: 226010. E-mail: saumyendravsingh@rediffmail.com

Accepted October 7, 2010

doi: 10.1111/j.1532-849X.2011.00738.x

Abstract

Healthy jawbones ensure better tooth anchorage and the ability to masticate and maintain metabolism. This is achieved by a delicate balance between bone formation and resorption in response to functional demands. An imbalance in the expression of receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) and osteoprotegerin (OPG) or osteoclastogenesis inhibitory factor (OCIF) is believed to be the underlying mechanism of osteolysis in metastases, multiple myelomas, and cancer therapy-induced bone loss in patients. Considered mainly as bone-specific agents to treat postmenopausal osteoporosis, bisphosphonates, in combination with certain chemotherapeutic agents have proved to be effective in prevention of tumor formation and metastatic osteolysis in bone tissue. Osteonecrosis of the jaws associated with them has, however, been of grave concern to the prosthodontist, as it predisposes patients to a bone-deficient basal seat for dental prostheses. This manuscript reviews available information over the past 13 years on possible mechanisms of bone loss, bisphosphonate-induced osteonecrosis of jaw bones, and prosthodontic concerns.

The relationship between integrity of jawbones and efficient masticatory function is beyond argument. When metastases occur in the jaws from cancers of the breast, prostate, or lung or from multiple myeloma, accelerated bone resorption leading to early tooth loss and poor prosthodontic prognosis takes place. This breakdown of bone architecture is grossly similar to osteoporotic changes. Key factors in bone remodeling include the receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL), which stimulates bone resorption, and the soluble decoy receptor osteoprotegerin (OPG) or osteoclastogenesis inhibitory factor (OCIF), which inhibits bone resorption by preventing RANK-RANKL interaction.[1-5] The ratio between these two factors regulates osteoclast differentiation, function, and survival. RANKL overwhelming the effects of OPG is believed to be the underlying mechanism in bone loss associated with metastases from solid tumors and multiple myeloma.[6,7]

Bone tumors also produce parathyroid hormone related protein (PTHrP), a known stimulator of osteoclastic bone resorption, and a major mediator of the osteolytic processes. Transforming growth factor beta (TGFβ), which is abundant in bone matrix and is released cyclically as a consequence of osteoclastic bone resorption, stimulates PTHrP production by tumor cells.[8] Eck et al reported the role of matrix metalloproteinase-1 (MMP-1) in metastatic bone osteolysis via mechanisms involving matrix degradation, angiogenesis, and osteoclast activation.[9] Fili et al demonstrated that the increased RANKL:OPG ratio in metastatic bone disease leads to successful colonization and subsequent invasive growth of cancer cells in bone. Also, cathepsin K (a lysosomal cysteine protease expressed by the osteoclasts during the process of metastatic bone resorption) is supposed to be responsible for the degradation of organic bone matrix and is therefore a potential target for therapeutic intervention.[10]

Bisphosphonates

Bisphosphonates, characterized by the P-C-P bond, are analogues of pyrophosphates (P-O-P) and are resistant to chemical and enzymatic hydrolysis. Bisphosphonates bind strongly to hydroxyapatite crystals and inhibit their formation and

dissolution. In vivo, this physicochemical action leads in some instances to inhibition of normal calcification, though the main effect is to inhibit bone resorption. The serum half life of this group of drugs is very short compared to their half life in bone, which in turn depends on the turnover rate of the skeleton. Twenty to fifty percent of a given dose is taken up by the skeleton, and the rest is excreted in urine.

Bisphosphonates, apart from being potent inhibitors of bone resorption, also act by inducing osteoclast apoptosis. Thus, they prevent the development of cancer-induced bone loss, though they have been considered mainly as bone-specific agents to treat primary estrogen-deficiency osteoporosis.[11] When the third-generation nitrogen-containing bisphosphonate, Zoledronic acid, is administered in combination with certain chemotherapeutic agents, the combination is more efficient, compared to other bisphosphonates, for treating skeletal metastases and hypercalcaemia of malignancy (both of which cause considerable morbidity).[11-15] Other bisphosphonates currently in use are Alendronate, Palmidronate, Etidronate, and Clopidronate. The mechanism of action is induction of osteoclast apoptosis through inhibition of the mevalonate pathway.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Since the first report by Marx in 2003, the peculiar presentation of osteonecrosis of the jaws associated with bisphosphonate therapy (particularly, intravenous) has been confirmed by several research groups.[16-19] This is of concern to the prosthodontist, as it predisposes patients to a bone-deficient basal seat for all dental prostheses. Marx cautioned against the use of bone grafts at such deficient sites, as there is a programmed cell death of osteoclasts with poor modeling and regenerative potential, accompanied by the possibility of activation of cancer.[20]

Allen and Burr presented the possible pathogenesis of BRONJ to be a bisphosphonate-induced remodeling suppression, to allow accumulation of nonviable osteocytes as a necrotic mass under the overlying mucosa.[21,22] The antiangiogenic effects of bisphosphonates are believed to contribute to postintervention poor healing. Pazianas et al reported predeliction factors, such as age more than 60 years, female sex, and previous invasive dental treatment, for BRONJ. Surgical removal of these avascular, necrotic masses produces deficient areas in the foundation for dentures and implants. Further, BRONJ may go undetected until the overlying mucosa has dehisced under masticatory loads of a recently provided prosthesis.[23]

In the quest to avoid such adverse reactions, newer classes of anti-resorptive drugs for skeletal metastases/malignancies are being developed with limited success. These include Selective Estrogen Receptor Modulators ([SERM] Ospemifene, Lasofoxifene, Bazedoxifene, Arzoxifene), Odanacatib, Denosumab, Strontium Ranelate, Glucagon-like peptide 2, Teriparatide, recombinant PTH, antibodies (sclerostin, dickkopf-1), calcium-sensing receptor antagonists, and an activin receptor fusion antagonist.[24-40] The current approach is to develop drugs specifically targeting tumor cells in bone, since skeletal metastases are more resistant to therapy and serve as a site for secondary spread of tumor cells. Gene therapy and immunotherapy are also being developed to improve treatment with reduced side effects.[41]

The prosthodontic concern

The prosthodontist not only records the history of the prospective prosthodontic patient pertaining to malignancy or metastases and relevant medication, but also cautions the patient on the prosthetic treatment concerns of bisphosphonates where applicable. In malignancies, the accelerated loss of trabecular and cortical bone leads to reduced quality and quantity of the ridge, making it more vulnerable to functional loading transmitted through the prosthesis.

If a removable prosthesis is planned, forces on the basal seat should be reduced with minimal pressure impressions and functional placement of the borders to provide the "snowshoe effect," reducing the force per unit area while providing retention and stability. Preprosthetic surgery could ensure removal of bony spikes and spicules, which act as foci of stress concentration in specific conditions, under the denture in function. Gross bony defects created by scalloping to remove necrotic bone mass (in case of BRONJ) must be evaluated prior to impression-making.

Preliminary impressions in such cases may be made in irreversible hydrocolloid and definitive impressions in light-body silicones in a pressure-less fashion. For less-stress transference to the remnant bone and reduction of undesirable horizontal forces, acrylic cuspless/monoplane teeth are indicated. Decreasing the occlusal table and reducing vertical overlap of prosthetic teeth within functional limits may also be advocated. Heat-cured soft liner materials could be used to line the intaglio surface of dentures to dissipate and distribute forces by their cushioning effect, and to improve patient compliance and treatment prognosis.

Finally, after prosthodontic treatment, the patient should be recalled at intervals of at least 2 to 3 months to monitor health of the denture-bearing tissues, clinically and radiographically. Advice on keeping the prostheses out of the mouth for at least 12 hours daily should be given. Caution should be taken to avoid fixed prosthesis/implant treatment until the patient is in remission, and/or bisphosphonate therapy has been suitably concluded to prevent an osteonecrotic reaction.

References

1. Simonet WS, Lacey DL, Dunstan CR, et al: Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997;89:309-319
2. Tsuda E, Goto M, Mochizuki S, et al: Isolation of a novel cytokine from human fibroblasts that specifically inhibits osteoclastogenesis. Biochem Biophys Res Commun 1997;234:137-142
3. Lacey DL, Timms E, Tan HL, et al: Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93:165-176
4. Yasuda H, Shima N, Nakagawa N, et al: Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. Proc Natl Acad Sci USA 1998;95:3597-3602

5. Katagiri T, Takahashi N: Regulatory mechanisms of osteoblast and osteoclast differentiation. Oral Dis 2002;8:147-159
6. Dougall WC, Chaisson M: The RANK/RANKL/OPG triad in cancer-induced bone diseases. Cancer Metastasis Rev 2006;25:541-549
7. Murthy RK, Morrow PK, Theriault RL: Bone biology and the role of the RANK ligand pathway. Oncology(Williston Park) 2009;23:9-15
8. Guise TA: Molecular mechanism of osteolytic bone metastases. Cancer 2000;88:2892-2898
9. Eck SM, Hoopes PJ, Petrella BL, et al: Matrix metalloproteinase-1 promotes breast cancer angiogenesis and osteolysis in a novel in vivo model. Breast Cancer Res Treat 2009;116:79-90
10. Fili S, Kalarki M, Schallar B: Mechanism of bone metastasis: the role of osteoprotegerin and of the host-tissue microenvironment-related factors. Cancer Let 2009;283:10-19
11. Holen I, Coleman RE: Bisphosphonates as treatment of bone metastases. Curr Pharm Des 2010;16:1262-1271
12. Fleisch H: Bisphosphonates: pharmacology and use in treatment of tumor-induced hypercalcaemia and metastatic bone disease. Drugs 1991;42:919-946
13. Mundy GR: Bisphosphonates as anti-cancer drugs. Drugs 1999;8:2009-2015
14. Barni S, Mandala M, Cazzaniga M, et al: Bisphosphonates and metastatic bone disease. Ann Oncol 2006;17:ii91–ii95
15. Neville-Webbe H, Coleman RE: The use of Zoledronic acid in the management of metastatic bone disease and hypercalcaemia. Palliat Med 2003;17:539-553
16. Estefanía FR, Ponte FR, Aguirre UJM: Bisphosphonates and oral pathology II. Osteonecrosis of the jaws: review of the literature before 2005. Med Oral Pathol Oral Cir Buccal 2006;11:456-461
17. Gevorgyan A, Enepekides DJ: Bisphosphonate-induced necrosis of the jaws: a reconstructive nightmare. Curr Opin Otolaryngol Head Neck Surg 2008;16:325-330
18. Sambrook PN, Ebeling P: Osteonecrosis of the jaw. Curr Rheumatol Rep 2008;10:97-101
19. Rizzoli R, Burlet N, Cahall D, et al: Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. Bone 2008;42:841-847
20. Marx RE: Reconstruction of jaw defects caused by bisphosphonate induced osteonecrosis of jaws. J Oral Maxillofac Surg 2009;67:207-219
21. Allen MR, Burr DB: The pathogenesis of bisphosphonate related osteonecrosis of the jaw: so many hypotheses so few data. J Oral Maxillofac Surg 2009;67:61-70
22. Allen M, Burr D: Mandible matrix necrosis in beagle dogs after 3 years of daily oral bisphosphonate treatment. J Oral Maxillofac Surg 2008;66:987-994
23. Pazianas M, Miller F, Blumental WA, et al: A review of literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. Clin Ther 2007;29:1548-1558
24. Singh MM: Centchroman, a selective estrogen receptor modulator, as contraceptive, and in the management of hormone-related clinical disorders. Med Res Rev 2001;21:302-347
25. Gennari L, Merlotti D, Nuti R: Selective estrogen receptor modulator (SERM) for the treatment of osteoporosis in postmenopausal women: focus on Lasofoxifene. Clin Interv Aging 2010;5:19-29
26. Deutertre M, Smith CL: Molecular mechanisms of selective estrogen receptor modulator (SERM) action. J Pharmacol Exp Ther 2000;295:431-437
27. Gennari L, Merlotti D, Valleggi F, et al: Selective estrogen receptor modulators for postmenopausal osteoporosis: current state of development. Drugs Aging 2007;2495:361-379
28. Clarke BL, Khosla S: New selective estrogen and androgen receptor modulators. Curr Opin Rheumatol 2009;21:374-379
29. Maeda T, Ke HZ, Simmons H, et al: Lasofoxifene, a next generation estrogen receptor modulator: preclinical studies. Clin Calcium 2004;14:85-93
30. Cummings SR, Ensrud K, Delmas PD, et al: PEARL study investigators: lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med 2010;362: 590-599
31. Lewiecki EM: Denosumab update. Curr Opin Rheumatol 2009;21:369-373
32. Iguchi H: Molecular mechanism and potential targets for bone metastasis. Gan To Kagaku Ryoho 2007;34:1-10
33. Ellis GK, Bone HG, Chlebowski R, et al: Effect of Denosumab on bone mineral density in women receiving adjuvant aromatic inhibitors for non-metastatic breast cancer: subgroup analysis of a phase 3 study. Breast Cancer Res Treat 2009;118:81-87
34. Santini D, Fratto ME, Vincenzi B, et al: Denosumab: an era of target therapies in bone metastatic diseases. Curr Cancer Drug Targets 2009;9:834-842
35. O'Donnell S, Cranny A, Wells GA, et al: Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database Syst Rev 2006;3:CD005326
36. Blake GM, Fogelman I: Strontium ranelate: a novel treatment for postmenopausal osteoporosis: a review of safety and efficiency. Clin Interv Aging 2006;1:367-375
37. Deal C: Potential new drug targets for osteoporosis. Nat Clin Pract Rheumatol 2009;5:174-181
38. Deal C: Future therapeutic targets in osteoporosis. Curr Opin Rheumatol 2009;21:380-385.
39. Ettinger B, San Martin J, Gauss G, et al: Differential effects of Teriparatide on bone mineral density (BMD) after treatment with Raloxifene or Alendronate. J Bone Miner Res 2004;19:745-751
40. Maurya R, Singh G, Yadav DK, et al: Osteogenic activity of constituents from Butea monosperma. Bioorg Med Chem Lett 2008;19:610-613
41. Bagi CM: Targeting of the therapeutic agents to bone to treat metastatic cancer. Adv Drug Deliv Rev 2005;57:995-1010