Practical consensus recommendaton for adjuvant bone-modifying agents in breast cancer

A. Bharatuar, M. Kar, S. Khattri, V. Goswami, R. Sarin, S. Dawood, R. Iyenger, M. Ganvir, Purvish M. Parikh, S. Aggarwal, Vineet Talwar

Abstract
Bone-modifying therapy is a primary research interest in breast cancer. Several features contribute to the importance of the bone environment in the management of breast cancer. Firstly, bone metastases represent the most common site of breast cancer metastases and secondly, the emergence of cancer treatment-induced bone loss (CTIBL) among breast cancer survivors and patients is of increasing concern. In the adjuvant setting, bisphosphonates can be given to prevent and treat tumor therapy-induced bone loss in premenopausal and postmenopausal women and, owing to their beneficial effect on bone turnover, have also been evaluated for prevention of bone metastases occurrence. Expert oncologists discuss the update on the approaches of Bone-modifying Agents and its treatment options. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at this practical consensus recommendations for the benefit of community oncologists.

Key words: Denosumab, hormonal therapy, osteopenia, tamoxifen, zolendronic acid

Introduction
Breast cancer is the most common cancer among females on all continents and the most rapidly increasing.[1] Early detection and advances in systemic therapy have improved clinical outcomes.[2] Women with both early breast cancer (EBC) and metastatic breast cancer (MBC) are surviving longer.[3] Many women in both populations have increased bone fragility either from treatment-induced bone loss or secondary to bony metastases. There already exists substantial data to support a role for bone-conserving therapy in patients with EBC to prevent treatment related bone loss.[4-9] Despite improvements in long-term outcomes for early breast cancer, recurrence and death rates are still significant. Bone remains the most common site of breast cancer recurrence. The pivotal effects of the interaction between the tumor and its microenvironment have been recognized for more than 100 years through the so-called seed and soil hypothesis.[10]

In advanced breast cancer, bone-modifying agents are important adjuncts to care in patients with metastatic bone disease. Skeletal-related complications of MBC include pathologic fractures, pain, spinal cord compression, and hypercalcemia of malignancy. One metastases occur in most women with advanced breast cancer. The destruction of bone in these lesions results from osteoclast-induced bone resorption that may be stimulated by osteoclast-activating factors released by tumor cells.[11,12] Cytotoxic chemotherapy or hormone therapy is the preferred treatment for symptomatic bone disease, but progressive skeletal destruction ultimately leads to increased pain, immobility, and deterioration in the quality of life.
Bone is the most frequent target of metastatic breast cancer, and although bone metastases are not life threatening, some of the complications (spinal cord compression, hypercalcemia) can be.[19] More important, bone metastases and their complications can be substantially disabling, require multiple interventions, and are costly to the patient and the health care system.

The bone microenvironment provides a supportive niche for cancer cell survival and tumor growth.[19,20] Breast cancer cells have a natural predilection for metastasizing to the skeleton. Indeed, approximately 70% of patients with advanced breast cancer will develop bone metastases, and bone is the first site of metastasis in 30–40% of patients with relapsed disease.[21] The release of bone-derived growth factors and cytokines into the microenvironment can attract cancer cells to the bone surface and facilitate their growth and propagation.[22] In turn, many cancer cells secrete factors that can increase rates of bone resorption.[22]

The dependence of metastasis on the link between cancer stem cells (the ‘seeds’) and the microenvironment (the ‘soil’) was first hypothesized by Stephen Paget more than a century ago, and this ‘seed and soil’ hypothesis has become especially meaningful to oncologists as our understanding of cancer–bone interactions has developed in recent years.[23] Indeed, the bone marrow is now also recognized as a sanctuary for harboring cancer ‘seeds’ for subsequent relapse in bone and other sites.[19,20]

Bisphosphonates (BPs) are the current standard of care for the prevention and treatment of malignant bone disease.[24,25] BPs naturally bind to mineralized surfaces such as bone and inhibit osteoclast-mediated bone resorption. The second-generation nitrogen-containing BPs (N-BPs) (eg, zoledronic acid, pamidronate) have been proven more effective at reducing SREs compared with the first-generation BP compounds (eg, clodronate).[25] Ibandronate and zoledronic acid followed, with clinical trials demonstrating that the latter was significantly more effective than earlier generation bisphosphonates for control of bone metastases and reduction of skeletal-related events.[16,22] Bisphosphonates were shown to be more effective and/or easier to use than previously existing agents (calcitonin, mithramycin) or newer agents with established activity (gallium nitrate). Over a short period of time, bisphosphonates became part of the standard of care for metastatic cancers, and clinical trials were initiated to determine their contribution to curative treatment of primary malignancies. It is clear that the addition of bisphosphonates to multidisciplinary treatment strategies has dramatically altered the clinical course of bone metastases.

Patients with EBC often develop bone loss secondary to cancer treatment itself, while in MBC metastases cause bone fragility and associated complications. Three mechanisms of bone loss due to cancer treatment have been identified. The first is as a result of estrogen deprivation therapies. Second, chemotherapies and supportive drugs, such as steroids, affect bone density directly or do so indirectly by the induction of premature ovarian failure.

Therapeutic ovarian ablation, whether medically or surgically induced, also results in premature menopause with consequent bone loss. In postmenopausal women there is on average a 2.6% loss of bone density in the first year of breast cancer treatment when treated with an aromatase inhibitor (AI).[28]
In premenopausal women bone density loss averages 8% in the first year of treatment with premature ovarian suppression.\footnote{29} In contrast bone loss during natural menopause is typically 1% per year.\footnote{28} To date, no study has correlated bone loss in EBC with adverse clinical outcomes although indirect evidence shows that osteoporotic women with breast cancer have a higher incidence of fractures and mortality compared to age-matched controls.\footnote{19} Endocrine therapies may interfere with estrogen signaling (e.g. tamoxifen) or inhibit estrogen production (e.g. AIs); both of which may precipitate bone loss depending on a woman’s menopausal status. Tamoxifen was the first antiestrogen therapy used for treating breast cancer and is a mixed estrogen agonist/antagonist.\footnote{31} Tamoxifen effects on bone are dependent on the ambient estrogen concentrations; tamoxifen causes bone loss in premenopausal women, but is bone protective in postmenopausal women.\footnote{32} AIs, which have a role in treating postmenopausal women with breast cancer, cause bone resorption and a higher fracture risk compared to tamoxifen.\footnote{33,34}

However, since AIs significantly reduce the risk of breast cancer recurrence in postmenopausal women at five years compared to tamoxifen, and overall have a more favorable side effect profile, AIs are preferred for adjuvant treatment among postmenopausal patients. Within the class, the impact of different AIs on bone density is still being studied. Recent data suggest that the steroidal AI exemestane may result in less BMD loss and potentially reduced fracture risk compared to the non-steroidal AIs, anastrozole and letrozole.\footnote{35} Cytotoxic chemotherapy is the only standard adjuvant treatment option for women with hormone receptor negative breast cancer and is also used in women with high-risk hormone receptor positive disease. Hemotherapy treatment causes bone loss by directly damaging bone architecture or inducing early menopause in premenopausal women, and/or through concomitant steroid use. In MBC, tumor cells can affect bone by secreting growth factors that stimulate bone resorption.\footnote{36} Bone resorption releases factors that subsequently promote tumor growth and propagate a “vicious cycle” of tumor expansion and bone destruction.\footnote{36} Bone-modifying agents like BPs and denosumab have the potential to break this cycle and prevent bone loss.\footnote{37}

**Anticancer effects of bisphosphonates in breast cancer**

The earliest clinical studies used oral clodronate to test the potential efficacy of bone modifying agents in preventing bone metastasis in early-stage (stages I–III) breast cancer.\footnote{36,38,39} Although clodronate is a relatively weak bisphosphonate compared with the intravenous BPs that were developed subsequently,\footnote{40} the effects of clodronate were sufficient to suggest that not only was there the potential to prevent bone metastases but that other effects on the disease course might be possible, thereby laying the groundwork for further clinical investigations. Subsequently, several large clinical trials have investigated the potential of adjuvant zoledronic acid to prevent recurrence of breast cancer.\footnote{8,41,42}

Pilot and phase II studies in women with early-stage, high-risk breast cancer have reported that monthly zoledronic acid, in combination with standard anticancer therapy, can effectively increase DTC clearance and reduce DTC number and persistence in bone marrow compared with standard therapy alone.\footnote{43-45} These zoledronic acid-mediated reductions in DTC persistence might be one of the mechanisms underlying the observed clinical benefits in studies such as the Austrian Breast and Colorectal Study Group (ABCSG)-12 trial,\footnote{33,34} the ZOledronic acid and FemarA Synergy Trial (ZO-FAST),\footnote{46} and the Does Adjuvant Zoledronic acid redUce recurrence in stage II/III breast cancer? (AZURE) trial.\footnote{47}

**Bone-modifying agents for preventing disease recurrence**

The seed and soil hypothesis provides a useful theoretical framework for evaluating breast cancer recurrence in women with early stage disease. The distribution of metastases does not appear to be random; rather, the soil of the bone microenvironment actually may promote cancer cell survival and tumor growth. Cancer cells often can be detected as disseminated tumor cells (DTCs) in the bone marrow or as circulating tumor cells (CTCs) in the blood of patients with breast cancer. Both DTCs and CTCs have been correlated with increased risks of disease recurrence and poor clinical outcomes.\footnote{46,48} The DTCs in particular may seed future cancer recurrence in and outside bone,\footnote{49} and the specialized cellular interactions and signaling pathways in the bone marrow niche may inadvertently protect dormant DTCs from the cytotoxic and proapoptotic effects of systemic anticancer therapies.\footnote{19,20}

Bone remodeling is controlled by a variety of local and systemic factors, and is characterized by coupled and balanced osteolysis followed by osteogenesis. Tumor cells destroy the balance between osteoclast-mediated bone resorption and the formation of new bone by osteoblasts.\footnote{22} As with all BPs, preferentially targets bone and is a key component of care for women with bone metastases from breast cancer. Zoledronic acid (in conjunction with standard anticancer therapy) is indicated for preventing skeletal-related events in patients with bone metastases from a variety of solid tumors and osteolytic lesions from multiple myeloma.\footnote{50} Moreover, zoledronic acid has been shown to not only prevent bone loss,\footnote{7,42,51,52} but also to improve DFS and reduce DTC levels during adjuvant therapy for breast cancer.\footnote{53-56}

**Conclusion**

In conclusion, our experts recommended the routine use of Bone-modifying agent therapy for patients with breast cancer with evidence of bone metastases. Current standards of care for cancer bone pain management should be applied at the onset of pain, in concert with the initiation of bone modifying agent therapy. There is insufficient evidence to demonstrate greater efficacy of one bone-modifying agent over another. Experts also support the use of zoledronic acid as adjuvant therapy in unselected patients with early-stage breast cancer. Further investigation into the possible interaction between zoledronic acid and reproductive hormones is required. For postmenopausal women, the use of bisphosphonates remains appropriate for the prevention of treatment-induced bone loss and osteoporosis and might have beneficial effects on disease outcomes. The optimum schedule, duration, and type of bisphosphonate therapy remain unknown. Data for adjuvant denosumab look promising but are currently insufficient to make any recommendation.
Bone modifying agents should be introduced if osteopenia is detected on follow up – unless it is contraindicated. Bone modifying agent should not be given to a premenopausal woman who is on tamoxifen alone. Zoledronic acid and other oral bisphosphonates also have similar efficacy in the adjuvant setting. Denosumab is currently not recommended to replace bisphosphonates in the adjuvant setting.

**References**

1. American Cancer Society. Global Cancer Facts and Figures 2nd ed. Atlanta: American Cancer Society; 2011.
2. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2006 Incidence and Mortality Web-Based Report. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2010.
3. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. CA Cancer J Clin 2011;61:409-18.
4. Brufsky AM. Cancer treatment-induced bone loss: Pathophysiology and clinical perspectives. Oncologist 2008;13:187-95.
5. Brufsky AM, Bosserman LD, Caradonna RR, Haley BB, Jones CM, Moore HC, et al. Zoledronic acid effectively prevents aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST study 36-month follow-up results. Clin Breast Cancer 2009;9:77-85.
6. Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, et al. Breast cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2009;7:122-92.
7. Grant M, Mileritsch B, Luschin-Ebengreuth G, Kässmann H, Pfsangwer-Sölkner JC, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 2008;9:840-9.
8. Grant M, Mileritsch B, Schippinger W, Luschin-Ebengreuth G, Pöbstberger S, Menzel C, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360:679-91.
9. Higgins MJ, Park BH. Expanding role of bisphosphonates in the management of early breast cancer. Expert Rev Anticancer Ther 2009;9:1051-4.
10. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889;133:571-3.
11. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889;133:571-3.
12. Rodman JD. Pathology of metastatic tumors in bone. Clin Orthop Relat Res 1970;72:8-32.
13. Coleman RE, Rubens RD. Bone metastases and breast cancer. Cancer Treat Rev 1985;12:251-70.
14. National Cancer Registry Programme, Indian Council of Medical Research. Leading Sites of Cancer. In, Consolidated Report of Population Based Cancer Registries 2001-2004, Incidence and Distribution of Cancer. Bangalore: Coordinating Unit, National Cancer Registry Programme (ICMR); 2006. p. 8-30.
15. Badwe RA, Gangawal S, Mitra I, Desai PB. Clinico-pathological features and prognosis of breast cancer in different religious communities in India. Indian J Cancer 1990;27:220-8.
16. Altekruse SF, Kosary CL, Krapcho M, editors. SEER Cancer Statistics Review 1973-2007. SEER Cancer Statistics Review. National Cancer Institute.
17. National Cancer Registry Program. Ten Year Consolidated Report of the Hospital Based Cancer Registries, 1984–1993, An Assessment of the Burden and Care of Cancer Patients. New Delhi: Indian Council of Medical Research; 2001.
18. Aggarwal G, Pradep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. World J Surg 2007;31:1031-40.
19. Coleman RE. Metastatic bone disease: Clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27:165-76.
20. Meads MB, Hazlehurt LA, Dalton WS. The bone marrow microenvironment as a tumor sanctuary and contributor to drug resistance. Clin Cancer Res 2008;14:2519-26.
21. Shiozawa Y, Havens AM, Pienta KJ, Taichman RS. The bone marrow niche: Habitat to hematopoietic and mesenchymal stem cells, and unwitting host to molecular parasites. Leukemia 2008;22:941-50.
22. Coleman RE. Adjuvant bisphosphonates in breast cancer: Are we witnessing the emergence of a new therapeutic strategy? Eur J Cancer 2009;45:1909-15.
23. Mundy GR. Metastasis to bone: Causes, consequences and therapeutic opportunities. Nat Rev Cancer 2002;2:584-93.
24. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889;133:571-3.
25. Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, et al. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. J Clin Oncol 2007;25:2464-72.
26. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, et al. Guidance on the use of bisphosphonates in solid tumours: Recommendations of an international expert panel. Ann Oncol 2008;19:420-32.
27. Coleman RE. Bisphosphonates: Clinical experience. Oncologist 2004;9 Suppl 4:14-27.
28. Rosen LS, Gordon DH, Dugan W Jr., Major P, Eisenberg PD, Provencher L, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004;104:36-43.
29. Hadji P. Aromatase inhibitor-associated bone loss in breast cancer patients is distinct from postmenopausal osteoporosis. Crit Rev Oncol Hemtol 2009;69:73-82.
30. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol 2001;19:3306-11.
31. Colleoni M, O’Neill A, Thürlimann B, Vertanen T, et al. Identifying breast cancer patients at high risk for bone metastases. J Clin Oncol 2000;18:3925-35.
32. Lenning PE. Endocrine therapy and bone loss in breast cancer: Time to close in the RANK (L)? J Clin Oncol 2008;26:4859-61.
33. Perez EA, Josse RG, Pritzak KL, Ingle JN, Mantino S, Findlay BP, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: A companion study to NCIC CTG MA.17. J Clin Oncol 2006;24:3629-35.
34. Lluch A, Dieu-Mazauric E, Leiguarda R, Llorca P, Kulkarni P, Ferrer J, et al. Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. J Clin Oncol 2005;23:5126-37.
35. Hershman DL, Cheung AM, Chapman JW, Ingle JN, Ahmed F, Hu H, et al. Effects of Adjuvant Exemestane Versus Anastrozole on Bone Mineral Density: Two-Year Results of the NCIC CTG MA.27 Bone Companion Study. Presented at the 2011 ASCO Annual Meeting. Chicago, IL, 3–7 June, 2011.
36. Forman MN. Denosumab: Second chapter in controlling bone metastases or a new book? J Clin Oncol 2010;28:5127-31.
37. Rodman GD. Mechanisms of bone metastasis. N Engl J Med 2004;350:1655-64.
38. Diel IJ, Jaschke A, Solomayer EF, Bastert G, Sohn C, et al. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: A long-term follow-up. Ann Oncol 2008;19:2007-11.
39. Saarto T, Blomqvist C, Virkkunen P, Elomaa I. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. J Clin Oncol 2008;26:3220-7.
40. Powles T, Paterson S, Kanis JA, McCloskey E, Ashley S, Tidy A, et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. J Clin Oncol 2002;20:3219-24.
41. Green JR. Bisphosphonates: Preclinical review. Oncologist 2004;9 Suppl 4:3-13.
42. Eidtmann H, de Boer R, Bundred N, Llobrart-Cussac A, Davidson N, Neven P, et al. Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZOL-FAST study. Ann Oncol 2010;21:2188-94.
43. Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinhshaw R, Keane M, et al. Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med 2011;365:1396-405.
44. Aft R, Naughton M, Trinkaus K, Watson M, Ylagan L, Chavez-MacGregor M, et al. Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: An open label, randomised, phase 2 trial. Lancet Oncol 2010;11:421-8.

45. Rack B, Jückstock J, Genss EM, Schoberth A, Schindlbeck C, Strobl B, et al. Effect of zoledronate on persisting isolated tumour cells in patients with early breast cancer. Anticancer Res 2010;30:1807-13.

46. Solomayer EF, Gebauer G, Hirnle P, Janni W, Lück HJ, Becker S, et al. Influence of zoledronic acid on disseminated tumor cells in primary breast cancer patients. Ann Oncol 2012;23:2271-7.

47. Bidard FC, Kirova YM, Vincent-Salomon A, Alran S, de Rycke Y, Sigal-Zafrani B, et al. Disseminated tumor cells and the risk of locoregional recurrence in nonmetastatic breast cancer. Ann Oncol 2009;20:1836-41.

48. Cristofanilli M, Hayes DF, Budd GT, Ellis MJ, Stopeck A, Reuben JM, et al. Circulating tumor cells: A novel prognostic factor for newly diagnosed metastatic breast cancer. J Clin Oncol 2005;23:1420-30.

49. Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, et al. Tumor self-seeding by circulating cancer cells. Cell 2009;139:1315-26.

50. Ibrahim A, Scher N, Williams G, Sridhara R, Li N, Chen G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clin Cancer Res 2003;9:2394-9.

51. Hershman DL, McMahon DJ, Crew KD, Cremers S, Irani D, Cucchiara G, et al. Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 2008;26:4739-45.

52. Shapiro CL, Halabi S, Gibson G. Effect of Zoledronic Acid (ZA) on Bone Mineral Density (BMD) in Premenopausal Women Who Develop Ovarian Failure (OF) Due to Adjuvant Chemotherapy (AdC): First Results from CALBG Trial 79809 (Oral Presentation). Presented at: 44th Annual Meeting of the American Society of Clinical Oncology. Chicago, IL, USA; 30 May–03 June, 2008.

53. Rack B, Schindlbeck C, Strobl B, Sommer H, Friese K, Janni W, et al. Efficacy of zoledronate in treating persisting isolated tumour cells in bone marrow in patients with breast cancer. A phase II pilot study. Dtsch Med Wochenschr 2008;133:285-9.

54. Greenberg S, Park JW, Melisko ME. Effect of adjuvant zoledronic acid (ZOL) on disseminated tumor cells (DTC) in the bone marrow (BM) of women with early-stage breast cancer (ESBC): Updated results (abstract). J Clin Oncol 2010;28 15 Suppl: 114s.

55. Gnant M, Mlineritsch B, Schippering W. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360:679-91.

56. Solomayer E, Gebauer G, Hirnle P. Influence of zoledronic acid on disseminated tumor cells (DTC) in primary breast cancer patients (abstract). Cancer Res 2009;69 Suppl 2:S170-1.