Original Article

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

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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 discusses on 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.

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Expert group of oncologist meet in the update in oncology-X-2017 to discuss on available strategies of adjuvant Bone-Modifying Agents in breast cancer patients.

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer out of these we are discus about adjuvant Bone-Modifying Agents in this chapter. While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.[13,14] The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologist, radiation oncologist, surgical oncologist, molecular oncologist and radiologist are present in the update in oncology-X-2017 was taken into consideration by the expert panel. The expert group was chaired by Dr. Vineet Talwar whereas the discussions were moderated by Dr. Madhu Chandakar and Dr. Anubha Bharatuar. The core expert group consists Dr. Sameer Khatri, Dr. Vikas Goswami, Dr. Ramesh Sarin, Dr. Shaheenah Dawood and Dr. Rajeev Iyenger. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations.

The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use adjuvant Bone-Modifying Agents in breast cancer patients.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.[15-17] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their ersonal experiences, make

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comments and record dissent while voting for the consensus statements. Total of five broad question categories were part of the expert group discussions [Tables 1-6].

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.[18] 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.[26,27] 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]

Table 1: Question categories addressed by the update in oncology-X-2017

Broad question title
Case 1-38 year old premenopausal lady diagnosed with infiltrating duct carcinoma left breast. She undergoes modified radical mastectomy. HPE results - T2N1M0. ER positive, PR positive, HER 2/neu negative. She needs adjuvant chemotherapy followed by hormonal therapy. She is on LHRH agonists and exemestane?
Question 1 - Will you give bone modifying agents along with hormonal therapy to all such cases?
Question 2 - Patient is not given bone modifying agents, however, after 1 year, BMD shows osteopenia, will you now give bone modifying agent?
Question 3 - Will you give bone modifying agent to a premenopausal woman who is on tamoxifen alone (no LHRH agonist)?
Question 4 - Do you believe that zolendronic acid and other oral bisphosphonates have similar efficacy in adjuvant setting?
Question 5 - Do you believe that denosumab will replace bisphosphonates in adjuvant setting?

ER=Estrogen receptor, PR=Progesterone receptor, LHRH=Luteinizing hormone releasing hormone, BMD=Bone mineral density, HER 2=Human epidermal growth factor receptor 2

Table 2: Question 1 - Will you give bone modifying agents along with hormonal therapy to all such cases?

Options (%)	Yes	No
Percentage of polled oncologists	66.7	33.3

Expert group consensus: Bone modifying agents along with hormonal therapy should be given in all such cases - except where it is contraindicated

Table 3: Question 2 - Patient is not given bone modifying agents, however, after 1 year, bone mineral density shows osteopenia, will you now give bone modifying agent?

Options (%)	Yes	No
Percentage of polled oncologists	81.8	18.2

Expert group consensus: Bone modifying agents should be introduced if osteopenia is detected on follow up - unless it is contraindicated

Table 4: Question 3 - Will you give bone modifying agent to a premenopausal woman who is on tamoxifen alone (no luteinizing hormone releasing hormone agonist)?

Options (%)	Yes	No
Percentage of polled oncologists	25	75

Expert group consensus: Bone modifying agent should not be given to a premenopausal woman who is on tamoxifen alone

Table 5: Question 4 - Do you believe that zolendronic acid and other oral bisphosphonates have similar efficacy in adjuvant setting?

Options (%)	Yes	No
Percentage of polled oncologists	46	54

Expert group consensus: Zolendronic acid and other oral bisphosphonates have similar efficacy in the adjuvant setting as well

Table 6: Question 5 - Do you believe that denosumab will replace bisphosphonates in adjuvant setting?

Options (%)	Yes	No
Percentage of polled oncologists	14.3	85.7

Expert group consensus: Denosumab is currently not recommended to replace bisphosphonates in the adjuvant setting

In premenopausal women bone density loss averages 8% in the first year of treatment with premature ovarian suppression.[29] In contrast bone loss during natural menopause is typically 1% per year.[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.[30] 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 fi rst antiestrogen therapy used for treating breast cancer and is a mixed estrogen agonist/antagonist.[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.[32] AIs, which have a role in treating postmenopausal women with breast cancer, cause bone resorption and a higher fracture risk compared to tamoxifen.[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 profi le, 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.[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.[36] Bone resorption releases factors that subsequently promote tumor growth and propagate a " vicious cycle " of tumor expansion and bone destruction.[36] Bone-modifying agents like BPs and denosumab have the potential to break this cycle and prevent bone loss.[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.[36,38,39] Although clodronate is a relatively weak bisphosphonate compared with the intravenous BPs that were developed subsequently,[40] the effects of clodronate were sufficient to suggest that not only there was 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.[8,41,42]

Pilot and phase II studies in women with early-stage, highrisk 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.[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,[8] the ZOledronic acid and FemarA Synergy Trial (ZO-FAST),[46] and the Does Adjuvant Zoledronic acid redUce recurrence in stage II/III breast cancer? (AZURE) trial.[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.[46,48] The DTCs in particular may seed future cancer recurrence in and outside bone,[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.[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 osteoclastmediated bone resorption and the formation of new bone by osteoblasts.[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.[50] Moreover, zoledronic acid has been shown to not only prevent bone loss,[7,42,51,52] but also to improve DFS and reduce DTC levels during adjuvant therapy for breast cancer.[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.

Take Home Message

1	Bone modifying agents along with hormonal therapy should be given in all such cases – except where it is contraindicated
2	Bone modifying agents should be introduced if osteopenia is detected on follow up – unless it is contraindicated
3	Bone modifying agent should not be given to a premenopausal woman who is on tamoxifen alone
4	Zolendronic acid and other oral bisphosphonates also have similar efficacy in the adjuvant setting
5	Denosumab is currently not recommended to replace bisphosphonates in the adjuvant setting

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Conflicts of interest

There are no conflicts of interest.

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