Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline
Introduction

• In women, breast cancer is the most common cancer, accounting for approximately 25% of all cancers.

• 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.

• Where benefit exists, the value of adjuvant bone-targeted therapy tends to be in women with a “low estrogen environment,” either through menopause or suppression of ovarian function.

• To develop recommendations for the use of bisphosphonates and other bone-modifying agents as adjuvant therapy for patients with breast cancer, the Program in Evidence-Based Care (PEBC) of Cancer Care Ontario (CCO) and ASCO’s Clinical Practice Guidelines Committee (CPGC) established a joint guideline panel.
ASCO and CCO Guideline Development Methodology

The Program in Evidence-Based Care (PEBC) of CCO practice guidelines development cycle and the ASCO guideline development methods include:

• A systematic review
• Interpretation of evidence
• Drafting of recommendation
• Internal review by content and methodology experts
• External review by clinicians and other stakeholders.

The full guideline methodology supplement can be found at:
www.asco.org/breast-cancer-adjuvant-bisphosphonates-guideline
Clinical Questions

1. Does administration of bisphosphonates or other bone-modifying agents as adjuvant treatment in patients with breast cancer reduce metastasis and/or recurrence and improve survival?

2. Does effectiveness depend on patient or disease characteristics, especially age or menopausal status (either natural or induced menopause)?

3. Do effectiveness and adverse effects differ according to which bisphosphonate or bone-modifying agent is used?

4. What doses, duration of administration, and route (intravenous or oral) are optimal?
Target Population and Audience

Target Population
Patients with early or locally advanced (nonmetastatic) breast cancer.

Target Audience
Medical oncologists and other clinicians involved in postsurgical (adjuvant) treatment of patients with breast cancer.
Summary of Recommendations

**Recommendation 1**

- It is recommended that administration of bisphosphonates as adjuvant therapy be considered for postmenopausal patients with breast cancer (including patients premenopausal before treatment who have menopause induced by ovarian suppression) deemed candidates for adjuvant systemic therapy.

- The final decision of whether or not to administer bisphosphonates should be made during consultation between the patient and oncologist, taking into account patient and disease characteristics, including risk of recurrence, and weighing the potential benefits and risks (adverse effects).

**Qualifying Statements for Recommendation 1**

- While the EBCTCG meta-analysis found benefit for bisphosphonates in all subgroups of postmenopausal patients, the absolute benefit was small. For patients with cancers assessed as having low risk of recurrence, the use of bisphosphonates may not result in clinically meaningful effect.
Summary of Recommendations

- Considerations in deeming patients at high enough recurrence risk to receive adjuvant systemic therapy may also apply in deciding on bisphosphonate use. The majority of patients (83%) in the meta-analysis had also received adjuvant chemotherapy. Standard clinical and pathologic risk factors and recognized clinical tools may be used, where applicable, to estimate risk of recurrence and mortality.\(^2,3\)

- Risk factors for ONJ and renal impairment should be assessed.

- Patients should receive all other recommended breast cancer treatment, including surgery, radiation, and/or systemic therapy (see, for example, the CCO guideline on systemic therapy in early breast cancer).\(^2\)

- There is no information to guide the use of bone-modifying agents for patients receiving systemic adjuvant therapy for completely resected local recurrence.
Summary of Recommendations

Recommendation 2

• Zoledronic acid and clodronate are the recommended bisphosphonates for adjuvant therapy in breast cancer.

• There is a need for more information comparing different agents and schedules, and it is recommended that such trials be conducted to establish the utility and optimal administration of other bisphosphonates for adjuvant therapy.

Qualifying Statements for Recommendation 2

• Preliminary data from the SWOG S0307 trial⁴,⁵ suggest that clodronate, ibandronate, and zoledronic acid may provide similar DFS and OS benefit. However, as these data have, to date, only been published in abstract form, no definitive recommendations regarding ibandronate can yet be made. Full publication of the SWOG S0307 trial and results of the TEAM Iib (BOOG 2006-04) trial⁶ may support adjuvant ibandronate use. There is a large difference in ibandronate dosage between these trials (50 mg/d) and that used in treating osteoporosis (150 mg/mo orally or 3 mg every 3 months intravenously). This dosage difference should be considered in future comparisons.
Summary of Recommendations

- Clodronate has not been studied specifically in patients receiving AIs.

- While the direct evidence from adjuvant trials is considered sufficient only for zoledronic acid and clodronate, others have hypothesized that any agent proven to reduce the risk of fragility fractures in at-risk populations (eg, patients with postmenopausal or drug-induced osteoporosis) may be effective as adjuvant therapy for breast cancer. Given orally for osteoporosis treatment, alendronate has been used daily or weekly, while risedronate and ibandronate have been used daily, weekly, or monthly. Ibandronate has also been used intravenously. Less frequent administration, compared with clodronate, may make these preferable to patients if shown to be of adjuvant benefit. Further trials with adequate power and primary outcomes of DFS and OS are required to determine the optimal agent and dosing schedule.

- Different adverse effect profiles, frequency and route of administration, cost, and regulatory approval may influence selection.

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Summary of Recommendations

**Recommendation 3**

- While results for adjuvant denosumab look promising, data are insufficient at this time to make any recommendation regarding its use in the adjuvant setting.

- It is recommended that studies directly comparing denosumab with bisphosphonates and evaluating administration schedules be conducted.

**Qualifying Statements for Recommendation 3**

- While the ABCSG-18 trial studied denosumab use in postmenopausal women with hormone receptor–positive breast cancer receiving AIs and found clear fracture reduction benefit, DFS results have only been reported as a conference presentation or abstract. As survival data have, to date, only been published in abstract form, no definitive recommendations can yet be made. Results are promising but limited compared with the body of evidence for bisphosphonates. Further results of the ABCSG-18 and D-CARE trials may provide stronger evidence for adjuvant denosumab use.
Summary of Recommendations

**Recommendation 4**
- For patients who will receive adjuvant bisphosphonates, zoledronic acid at 4 mg intravenously over 15 min (or longer) every 6 months for 3 to 5 years or clodronate orally at 1,600 mg/d for 2 to 3 years are recommended. Different durations may be considered.

- More research is recommended comparing different bone-modifying agents, doses, dosing intervals, and durations.

**Qualifying Statements for Recommendation 4**
- In jurisdictions where the recommendation cannot be followed due to availability, similar doses and schedules of zoledronic acid or clodronate are considered reasonable.

- The optimal dose and schedule of administration of zoledronic acid and clodronate have not been determined; however, the recommended doses and schedules have been found effective in many of the adjuvant breast cancer trials and result in fewer or less severe adverse effects than regimens used in patients with metastatic disease (ie, 4 mg zoledronic acid every 3 to 4 weeks).

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Summary of Recommendations

- The optimal duration of adjuvant bone-targeted agents has not been determined; the recommendations reflect durations found effective in the EBCTCG meta-analysis and other trials included in the literature review. It is unclear whether there is benefit to longer-term administration, although studies indicate that the benefit of bisphosphonates continues after administration is stopped due to the persistence of the drug within the bone. There are concerns about adverse effects such as atypical bone fractures based on reports from the osteoporosis literature, and some osteoporosis recommendations allow a treatment holiday from bisphosphonates after 3 to 5 years for patients with a lower risk of fracture.\textsuperscript{12,13}

- Administration of clodronate for > 3 years or zoledronic acid for > 5 years has not been evaluated in adjuvant trials, and, therefore, a recommendation of longer duration is not supported at this time. This limitation in the evidence may be especially relevant to patients receiving long-term endocrine therapy, as the recent CCO guideline on systemic treatment\textsuperscript{2} includes recommendations for endocrine therapy for up to 10 years based primarily on results from the ATLAS, aTTom, and MA.17 trials.

- The optimal timing to start bisphosphonates after diagnosis of breast cancer is unclear; however, most of the clinical trials started soon after surgery or chemotherapy.
Summary of Recommendations

Recommendation 5
• For purposes of adjuvant bisphosphonate use, the definition of menopause should include both natural menopause (at least 12 months of amenorrhea prior to initiation of chemotherapy or endocrine therapy) and menopause induced by ovarian ablation or suppression (but not the cessation of menses due to chemotherapy alone). In women age ≤ 60 years with a previous hysterectomy and ovaries left in place, luteinizing hormone, follicle-stimulating hormone, and serum estradiol should be in the postmenopausal range and measured prior to initiation of any systemic therapy to receive adjuvant bisphosphonates.

Qualifying Statements for Recommendation 5
• As indicated in the recent CCO guideline on systemic therapy in early breast cancer, assessing menopausal status is difficult in patients age ≤ 60 years who experience amenorrhea secondary to chemotherapy or tamoxifen. Cessation of menses does not necessarily denote the absence of ovarian function, and premenopausal estradiol levels can be found in patients with transient chemotherapy-induced amenorrhea. In addition, hormone levels and the absence of menses are unreliable indicators of menopause during treatment with tamoxifen.
Some publications have suggested that patients experiencing chemotherapy-induced amenorrhea are at high risk for adverse bone effects and may be candidates for bone-modifying agents. Evidence is insufficient to address use of these agents as adjuvant treatment in this population.

**Recommendation 6**

- A dental assessment is recommended, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to starting treatment, if possible. Patients should be informed of the risk of developing ONJ, especially with tooth extractions and other invasive dental procedures. Patients should inform their dental practitioner of their treatment. Patients with suspected osteonecrosis of the jaw (ONJ) should be referred to a dental practitioner with expertise in treating this condition. Recent guidelines or position papers by groups such as the International Task Force on Osteonecrosis of the Jaw, the American Association of Oral and Maxillofacial Surgeons, and the American Dental Association should be consulted.

- Patients should have serum calcium measured prior to starting treatment. Patients receiving intravenous bisphosphonates (zoledronic acid) should be monitored for renal function prior to starting this treatment, and for serum calcium and increase in serum creatinine throughout the treatment period.
Summary of Recommendations

• Calcium and vitamin D supplementation is recommended unless otherwise contraindicated. Oral bisphosphonates and calcium should not be taken concurrently; several monographs suggest an interval of at least 2 hours to allow for maximum absorption.

• Symptoms such as ocular pain or loss of vision may be due to serious inflammatory conditions such as uveitis or scleritis and should be promptly evaluated by an ophthalmologist.

Qualifying Statements for Recommendation 6

• The risk of ONJ increases with frequency, dose, and duration of bisphosphonate administration. Risk can be reduced with appropriate screening prior to treatment and modification of dental care. Risk of ONJ when bisphosphonates are administered is lower than for patients receiving higher doses or more frequent administration as is used for cancers with bone metastasis.

• Some organizations advise dental assessment and care prior to any cancer treatment, preferably as soon as possible after diagnosis to allow time for dental procedures and adequate healing prior to treatment.16-20
Summary of Recommendations

- The CCO formulary monograph for zoledronic acid recommends comprehensive dental evaluation of both hard and soft tissues before starting bisphosphonate treatment; undergo invasive dental procedures, if needed, before starting bisphosphonate treatment.”25(p6) US FDA prescribing information for zoledronic acid indicates that “cancer patients should maintain good oral hygiene and should have a dental examination with preventative dentistry prior to treatment with bisphosphonates.”26(p5),27(p2)

- It is unclear whether bone-modifying therapy should be withheld if invasive dental treatment is required. Some have hypothesized that withholding bone-modifying therapy may allow for better bone healing and suggested stopping treatment 2 months prior to oral surgery and delaying restarting until osseous healing has occurred. The alternative view is that a short break in bisphosphonate administration will have no effect as bone effects of bisphosphonates are maintained for years after treatment stops.

- Hypocalcemia is a known adverse effect of bisphosphonate treatment, especially with the higher doses and more frequent administration given to patients with metastatic cancer. It is relatively rare (< 1%) at lower doses in patients without pre-existing conditions such as renal insufficiency and who have adequate vitamin D status and calcium intake.

- There is conflicting evidence as to whether inflammatory eye conditions are directly caused by bisphosphonates or in conjunction with some underlying inflammatory disease process28; however, if not treated promptly, these conditions may lead to blindness. Discontinuation of bisphosphonates may be necessary.29
Limitations of the Research and Future Research

There is an urgent need for trials that directly compare different bone-modifying agents and different doses, schedules, and durations of therapy.

The authors also suggest the following trials be conducted:

• Comparison of single zoledronic acid infusion versus zoledronic acid every 6 months for seven infusions.

• Denosumab versus zoledronic acid every 6 months for seven infusions.

• Denosumab versus clodronate.

• Zoledronic acid versus denosumab: once versus every 6 months versus yearly for 2 or 5 years.

• Risedronate or alendronate (standard osteoporosis treatment) versus denosumab versus zoledronic acid.
Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/breast-cancer-adjuvant-bisphosphonates-guideline

Patient information is available at www.cancer.net
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