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Clinical Practice Guidelines - Breast Disease Site

Guideline Title:	Adjuvant Bisphosphonate Therapy in Primary Breast Cancer - **Summary**	**Date:**	**(O):** **(R):**	Jan 18, 2018
Tumor Group:	Breast Disease Site Group	**Page:**		1 of 7
Issuing Authority:	Dr. Jehan Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**		Aug 30, 2019
Adapted From:	Joint Cancer Care Ontario and American Society of Clinical Oncology "Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer" guideline, June 2017 (14).			

Target Population:

These recommendations apply to patients with early stage breast cancer who may benefit from bisphosphonate therapy in the adjuvant setting.

Recommendations:

The following recommendations of the Eastern Health Breast Disease Site Group apply to patients diagnosed with early stage (non-metastatic) breast cancer:

1. All women diagnosed with early-stage (stage I, II or III) lymph node-positive or high-risk lymph node-negative breast cancer, regardless of molecular biomarker profile, who lack ovarian function should be offered adjuvant bisphosphonate therapy. In the case of:
   - ***Premenopausal women*** – consider the use of adjuvant bisphosphonate treatment as a part of adjuvant systemic therapy for those who have menopause induced by ovarian ablation or suppression (NOT chemotherapy-induced menses cessation alone);
   - ***Postmenopausal women*** – consider the use of adjuvant bisphosphonate treatment as a part of adjuvant systemic therapy for those having natural menopause (at least 12 consecutive months of amenorrhea prior to initiation of chemotherapy or endocrine therapy);
2. High-risk lymph node-negative breast cancer includes any or a combination of these patient and tumor-related features which include;
   - patient age of less than 35 years of age
   - presence of disease with lymphovascular invasion
   - grade 3 histology
   - hormone receptor-negative
   - HER2 over-expression (HER2 positive), and/or
   - has obtained a "high risk" test score on Oncotype DX;

3. When menopausal status is in question, women ≤ 60 years should have serum luteinizing hormone (LH), follicle-stimulating hormone (FSH) and estradiol levels performed prior to initiation of adjuvant bisphosphonate treatment to help determine menopausal status;
4. For patients eligible for adjuvant bisphosphonate treatment, the recommended bisphosphonate is zoledronic acid 4mg IV over 15 minutes every six months for three to five years OR in the event, where a patient is intolerant to zoledronic acid then clodronate, orally 1600mg daily for two to three years, is an acceptable alternative;
5. All patients should be advised of the potential adverse events of bisphosphonate treatment including the risk of developing osteonecrosis of the jaw (ONJ). All patients being considered for adjuvant bisphosphonate treatment should have a dental assessment performed, where feasible, and any necessary dental or oral health issues addressed prior to commencement of adjuvant bisphosphonate treatment;
6. All patients being considered for adjuvant bisphosphonate treatment should undergo a serum calcium prior to commencement and monitored for renal function when receiving zoledronic acid;
7. All patients are advised to take calcium and vitamin D supplements unless contraindicated.

Supporting Evidence:

The use of aromatase inhibitors (AIs) in postmenopausal women and the suppression, or elimination of ovarian function in premenopausal women are extremely effective therapies to combat the recurrence of breast cancer by reducing the production of estradiol levels. However, the resulting decline in estrogen levels have been found to result in an increased rate of bone demineralization and resorption which in turn, increases the risk of low bone mass and osteoporosis-related fractures in patients receiving such treatments (1, 2). Bisphosphonates have been successfully established as bone modifying agents which act as anti-resorptive therapy preventing bone loss by inhibiting the osteoclast activity of the bone and promoting an increase in bone mineral density. There are multiple indications for bisphosphonates in the oncology setting including preventing or treating bone loss, reducing the risk of skeletal-related events in patients with metastatic bony disease, as well as the current indication of improving outcomes in women with early-stage breast cancer.

In 2015, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a meta-analysis of 26 clinical trials involving patients with early breast cancer who randomly received two to five years of either bisphosphonate or placebo treatment (3). The results suggested that there was an overall significant reduction in the 10-year risk of bone recurrence with the addition of adjuvant bisphosphonates compared to control (7.8% vs 9.0%) (4). The subgroup analysis found that bisphosphonate treatment had no effect on premenopausal women however, there were small but significant reductions in risk for the postmenopausal women in terms of recurrences, distant recurrences, bone recurrences, and breast cancer mortality. The risk for bone fractures was also reduced with a five-year fracture risk of 5.1% in the bisphosphonate arm compared to 6.3% in the control arm (4). A 2017 Cochrane review confirmed that the use of bisphosphonates was associated with a lower risk of bone metastases compared to placebo/no bisphosphonate (5). The results also confirmed that no survival benefit was found for premenopausal women. However, an OS and a disease-free survival (DFS) benefit was found for postmenopausal women with the addition of bisphosphonate treatment.

The Eastern Health Breast Disease Site Group (BDSG) has determined that there is sufficient evidence to support the use of adjuvant bisphosphonates in the treatment of post-menopausal women with early stage breast cancer going forward. Natural menopause is defined as at least 12 consecutive months of amenorrhea prior to the initiation of chemotherapy, and not due to chemotherapy-induced cessation of menses alone. Treatment-induced menopause is defined as amenorrhea brought on with the intentional use of pharmaceutical, surgical or radiation treatment to temporarily suppress or permanently remove/ablate ovarian function in pre-menopausal women. The BDSG considers both of these populations of women to be eligible for adjuvant bisphosphonate therapy in this province when their risk of breast cancer recurrence is high enough to warrant adjuvant systemic treatment as per the joint CCO/ASCO guideline (14). This risk category would include having disease features such as lymph node involvement or high-risk tumor features in the absence of lymph node spread. Medical oncologists may offer adjuvant bisphosphonate therapy to some patients with intermediate-risk, on a case-by-case basis, who despite being outside the eligibility criteria, may have a health history which deems this therapy appropriate.

Qualifying Statement:

At the present time it is unclear which pharmaceutical bisphosphonate agent is most suitable in the adjuvant setting. The joint CCO/ASCO guideline recommends either zoledronic acid intravenously or oral clodronate (14). However, the Eastern Health BDSG recommends that the zoledronic acid should be the drug of choice and in the event where the patient is intolerant to zoledronic acid, then clodronate is an acceptable alternative. This recommendation has been based on several factors which include:

- There is a large body of evidence to support the use of zoledronic acid in this clinical setting which has identified DFS and OS benefits while published studies investigating clodronate have mixed results (6-13);
- Clodronate has never been studied specifically in the patient population receiving AIs which comprise a large proportion of the post-menopausal breast cancer patients who would be eligible for adjuvant bisphosphonate treatment in this province (14); and
- There are substantial out-of-pocket cost of clodronate which will likely be prohibitive for many breast cancer patients and has been reported to be associated with poor treatment adherence (13).

Disclaimer

Contact Information:

For more information on this guideline, please contact Dr. Joy McCarthy MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-7436. For the complete guideline on this topic or for access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

Literature Support:

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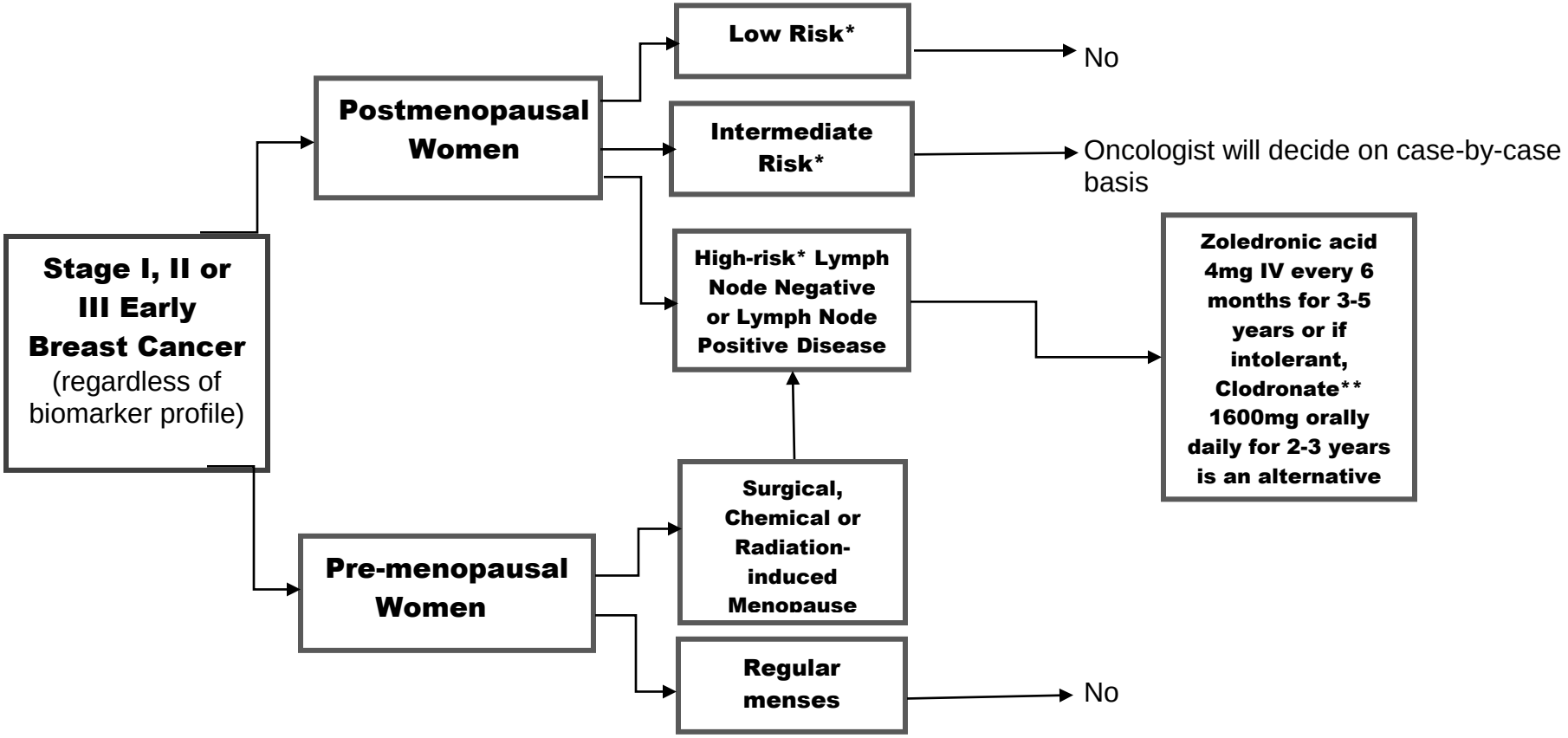
Appendix

Figure 1: Algorithm for Adjuvant Bisphosphonate Therapy



* See next page for definitions of risk categories
** Level of evidence is weaker for Clodronate

Figure 2: Risk Categories for Lymph Node Negative Breast Cancer*

Risk Category	Risk Factor
Adverse Prognostic Factors	• Age < 35 years • HER2 over-expression (HER2+) • Presence of lymphovascular invasion • Grade 3 • Hormone receptor negative disease • Oncotype DX** test score: “higher risk”
Lower Risk	• ≤ 2 cm, grade 1, with no other adverse prognostic factors • < 0.5 cm with any other feature • Oncotype DX** test score: “lower risk”
Intermediate Risk	• All other combination of factors that do not fit into either the low or high risk criteria • Oncotype DX** test score: “intermediate risk”
Higher Risk	• > 1 cm with any 2 or more adverse prognostic factors • > 2 cm with any 1 or more adverse prognostic factors • > 3 cm +/- adverse prognostic factors • Special considerations for HER2+ breast cancer • Oncotype DX** test score: “higher risk”

* Adopted from Alberta Health Services “Adjuvant systemic therapy for early stage (lymph node negative and lymph node positive) breast cancer” guideline, April 2018 (30).
** Can include any other approved genomic biomarker assay as well.