



# Bone-targeted Agents Used in Breast Cancer Patients with Bone Metastases

Bařak OYAN

Department of Internal Medicine, Section of Medical Oncology, Acibadem University, Acibadem Altunizade Hospital, Istanbul-Turkey

## Introduction

Bone is the most common site of metastases in breast cancer. Bone metastasis develops in 73% of the patients with metastatic breast cancer.[1] Bone metastases cause skeletal complications in 68% of the patients with breast cancer including, pathological fractures in 52%, need for radiotherapy in 43%, surgery requirement in 11%, and spinal cord compression in 3% of patients.[2] Skeletal-related events (SRE) develop early in the course of the disease. The median time to first SRE is 7 months in breast cancer patients with bone metastases.[2]

Bisphosphonates effectively reduce skeletal complications. On comparing pamidronate for up to 2 years with placebo in breast cancer patients with at least one lytic bone metastasis, the former was observed to reduce the rate of SREs from 68% to 53%.[2] Zoledronic acid reduced SRE risk by an additional 20% compared to pamidronate.[3] On comparing oral ibandronate with zoledronic acid, the former failed to achieve non-inferiority in reducing the risk of SRE.[4]

Denosumab is a monoclonal antibody against RANKL and inhibits bone resorption. Denosumab has been evaluated for SRE prevention in three large, international, randomized, double-blind phase III trials in patients with bone metastases. In all these trials, patients in the control arm received zoledronic acid. One of these trials was specific to patients with breast cancer.[5] Patients were randomized to denosumab 120 mg subcutaneous (SC) and placebo intravenous (IV) every four weeks or zoledronic acid 4 mg IV and placebo SC Q4W. Denosumab was superior to zoledronic acid in delaying time to first and subsequent SREs.

The adherence to guidelines for bone health in cancer is suboptimal. Despite the proven efficacy of bone-

targeted agents in bone metastases of solid malignancies, including breast cancer, 20-50% of the patients with bone metastases do not receive any of these agents to prevent SREs.[6-8]

Recommendations for the use of bone-targeted agents in breast cancer patients with bone metastases as per the European Society for Medical Oncology practice guidelines are as follows:[9]

- All breast cancer patients with bone metastases, even when asymptomatic, should receive zoledronate or denosumab.
- Zoledronic acid and denosumab are both effective. The choice of the agent depends on the efficacy, patient's preferences, renal functions, and cost.
- Denosumab is superior to zoledronic acid in terms of efficacy. Also, it is administered as an SC injection, while zoledronic acid is administered as an IV infusion.
- Three monthly dosing intervals of zoledronic acid are non-inferior to monthly dosing and have become a standard approach in patients with breast cancer.[10,11] The less frequent dosing regimen of zoledronic acid can be more preferable for some patients. Denosumab is administered every four weeks. Currently, it is not recommended to extend intervals.
- Denosumab is the agent of choice for patients with impaired renal functions.
- Oral ibandronate is an alternative for patients who desire to receive oral therapy.
- Treatment with bone-targeted agents should be continued as long as it is beneficial for the patient. However, selected patients with oligometastatic disease can discontinue therapy if they have a low risk

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Dr. Bařak OYAN  
Acibadem Üniversitesi,  
Acibadem Altunizade Hastanesi,  
İç Hastalıkları Anabilim Dalı,  
Tıbbi Onkoloji Bölümü,  
Istanbul-Turkey  
E-mail: basak.uluc@acibadem.com

of bone complications or when there is a long period of disease remission.

- All patients should have a dental evaluation before initiation of bisphosphonates and denosumab. All invasive dental procedures should be completed before initiating bone-targeted agents to prevent jaw osteonecrosis.
- Vitamin D supplementation with adequate calcium intake is recommended.
- Renal functions should be monitored in patients receiving zoledronic acid.

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