

# Bone-modifying agents for bone metastasis in patients with breast cancer

Lee Chun Park<sup>1</sup>, Eun Mi Lee<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Pohang St. Mary's Hospital, Pohang, Korea

<sup>2</sup>Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea

The bone is the most common location of breast cancer metastasis. Bone metastasis causes pain and skeletal-related events (SREs), and affects the quality of life and survival of breast cancer patients. Bone-modifying agents, including bisphosphonates and denosumab, reduce the risk of SREs in these patients. Among bisphosphonates, zoledronic acid is preferred due to its higher efficacy. Denosumab is marginally more effective than zoledronic acid in reducing the frequency of SREs. Patients with renal impairment should receive zoledronic acid with caution due to nephrotoxicity, and denosumab is an alternative option in these patients. Osteonecrosis of the jaw is a rare but severe complication of both zoledronic acid and denosumab, and all patients should undergo dental examinations before and during treatment. Although these drugs can reduce the risk of SREs in bone metastasis, no significant improvement in survival has been noted. This study reviews the effects and adverse events of bone-modifying agents for the treatment of bone metastasis from breast cancer.

**Keywords:** Bone neoplasm; Breast neoplasm; Diphosphonate; Denosumab

## Introduction

Worldwide, breast cancer is the most common diagnosed cancer and the leading cause of cancer in women [1]. The bone is the most typical metastatic location in breast cancer, with bone metastasis developing in up to 75% of metastatic breast cancer patients [2]. Bone metastases are a major cause of a variety of morbidities and cause skeletal-related events (SREs) such as pain, pathologic fracture, spinal cord compression, and hypocalcemia [3]. The prognosis is poor once SREs develop in patients with bone metastasis. In a population-based cohort study, the 5-year survival rate of metastatic breast cancer patients was 8.3%,

whereas that of patients with bone metastasis who developed SREs was 2.5% [4].

The management of patients with bone metastases aims to control symptoms, minimize the risk of SREs, stabilize the bone, and preserve and restore function [5]. Bone-modifying agents, bisphosphonates and denosumab, significantly reduce the risk of and delay SREs in patients with bone metastases from various cancer types, including breast cancer [6]. We here review the effects and adverse events of bone-modifying agents for the treatment of bone metastasis from breast cancer.

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**Corresponding Author:** Eun Mi Lee, MD

Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea  
Tel: +82-51-990-6107 Fax: +82-51-990-6107 E-mail: byule00@hanmail.net

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## Mechanism of bone metastasis from breast cancer

Normal bones are continually remodeled, with osteoclasts responsible for bone resorption and osteoblasts responsible for the deposition of new bone. Osteolytic and osteoblastic bone metastases are typically classified on the basis of the radiologic findings, primarily bone destruction or new bone deposition. Approximately 80% of bone metastasis from breast cancer presents as osteolytic lesions, and osteoclasts are mainly responsible for bone resorption of osteolytic metastases. Numerous substances produced by breast cancer cells can directly or indirectly cause the production of osteoclasts, and growth factors that are released from the bone matrix during osteoclast-mediated bone resorption promote tumor growth and bone destruction. Several factors, including parathyroid hormone-related peptide, receptor activator of nuclear factor-kappa B (RANK) and its ligand (RANKL), osteoprotegerin, transforming growth factor beta, and many other transcription factors, are implicated in this process. The RANKL/RANK system plays a particularly critical role in breast cancer development, both during initial tumorigenesis and secondary tumor formation [7-9].

## Bone-modifying agents

### Bisphosphonates

Bisphosphonates inhibit osteoclast activity and reduce bone resorption by inducing apoptosis in osteoclasts, which promotes mineralization. There are two types of bisphosphonates: non-nitrogen-containing and nitrogen-containing. Late-generation bisphosphonates (nitrogen-containing bisphosphonates including ibandronate, pamidronate, and zoledronic acid) exhibit a more potent osteoclast inhibitory effect than early-generation bisphosphonates (non-nitrogen-containing bisphosphonates including clodronate, and etidronate) [10,11].

Bisphosphonates prevent SRE, delay the time to SREs, relieve bone pain, and improve patients' quality of life (QOL). In a 2017 Cochrane review that analyzed the effects of bone-modifying agents for breast cancer treatment, bisphosphonates significantly reduced the absolute risk of SREs by 14% (risk ratios [RR], 0.86; 95% confidence interval [CI], 0.78-0.95) in breast cancer patients with bone metas-

tasis, compared with placebo/no bisphosphonate. Furthermore, bisphosphonates significantly delayed the median time to SRE and improved bone pain and QOL compared with placebo or no bisphosphonate; however, there was no significant effect in terms of overall survival [12].

Compared with other bisphosphonates, zoledronic acid is preferred owing to better efficacy, compared with other bisphosphonates [13]. The ZICE trial, which directly compared between ibandronate and zoledronic acid, found that zoledronic acid was more effective at preventing SRE in metastatic breast cancer patients [14]. Although pamidronate and zoledronic acid resulted in equivalent efficacy in preventing SREs in a phase 3 trial, long-term follow-up data indicated that zoledronic acid was more beneficial for breast cancer patients with bone metastasis [15,16].

### Denosumab

Denosumab, a fully human monoclonal anti-RANKL antibody, is another effective bone-modifying agent. The RANKL is a crucial component in the pathway for osteoclast formation and activation, and denosumab suppresses the RANKL/RANKL signaling-mediated bone resorption, decreasing bone turnover and leading to prevention of SREs in breast cancer [17,18]. Several randomized phase 3 clinical trials demonstrated denosumab was more effective than zoledronic acid in SRE prevention and pain reduction [19-22]. In a 2017 Cochrane review, denosumab reduced the risk of SRE compared with bisphosphonates by 22% (RR, 0.78; 95% CI, 0.72-0.85;  $p < 0.001$ ; three studies) in breast cancer patients with bone metastasis [12]. Patients receiving denosumab demonstrated greater clinical improvement in health-related QOL than those receiving bisphosphonates [23]. However, no significant difference was noted in terms of overall survival between patients receiving denosumab and bisphosphonate [12].

## Dose interval

The approved dose and schedule of administration for zoledronic acid and denosumab are 4 mg every 3 or 4 weeks and 120 mg every 4 weeks, respectively. Recently, there is increasing interest in the de-escalation of bone-modifying agents (every 12-week schedule) for bone metastasis treatment.

The Zoom and the Optimize 2 trials compared the effica-

cy and safety of every 4-week versus every 12-week schedules of zoledronic acid after 10–15 months of previous bisphosphonate treatment in breast cancer patients with bone metastasis and showed that every 12-week schedule was not inferior to every 4-week schedule in preventing SREs [24,25]. Moreover, in a randomized phase 3 trial, Himelstein et al. [26] reported that compared with every 4-week schedule, the use of zoledronic acid every 12-week schedule for patients with bone metastasis with on previous zoledronic acid did not increase the risk of SREs. A recent meta-analysis, which compared every 4-week and every 12-week dosing intervals of bone-modifying agents in patients with breast cancer, confirmed that the de-escalation of zoledronate is a reasonable option for breast cancer patients with bone metastases [27]

Conversely, data supporting the de-escalation of denosumab are limited [27]. Currently, the REDISE trial of denosumab 120 mg every 4 weeks versus 12 weeks for the treatment of bone metastasis from breast and prostate cancer is ongoing, and the results of this study will inform the benefit of the de-escalation of denosumab.

## Duration of treatment

There is no randomized clinical data on whether all patients with bone metastases should receive bone-modifying agents as soon as bone metastases are identified. A population-based cohort study in Denmark reported that breast cancer patients with bone metastases had a high incidence rate of SREs, especially in the first year after a diagnosis of bone metastases (38.5% at 1 year and 51.7% at 5 years) [28]. Additionally, other studies showed that the risk of symptomatic SREs was high in the first year after diagnosis of bone metastasis [19,29]. Therefore, the European Society for Medical Oncology (ESMO) 2020 guidelines recommend starting zoledronate or denosumab in all breast cancer patients with bone metastasis, whether they are symptomatic or not, at diagnosis of bone metastasis [30]. For patients starting bone-modifying agents, there is also no data on the optimal duration of treatment. According to a systemic review on the risk-benefit of bone-modifying agents for long-term duration in breast and prostate cancer, the risk of symptomatic SREs decreased with longer follow-up, while the risk of cumulative toxicities increased [6]. The ESMO 2020 guideline recommends that bone-modifying agents

should be considered throughout the course of the disease in absence of excessive toxicity [30].

## Adverse events of bone-modifying agents

Bone-modifying agents, bisphosphonate and denosumab, are associated with several adverse events including acute-phase reactions, hypocalcemia, nephrotoxicity, and osteonecrosis of the jaw (ONJ).

Acute-phase reactions are characterized by flu-like symptoms, including fever, chills, bone pain, headache, nausea, myalgias, and arthralgias [31]. In 15%–30% of patients who have not previously received bisphosphonates, intravenous (IV) administration of zoledronic acid and pamidronate can cause these reactions [19,21,31]. These symptoms generally occur in the first 3 days of treatment, resolve after a few days, and frequently do not recur with subsequent treatment. Acetaminophen or nonsteroidal anti-inflammatory drugs are effective in controlling symptoms [31].

Hypocalcemia is a common electrolyte abnormality associated with the use of bisphosphonates and denosumab. This is because these drugs inhibit the action of osteoclasts, which resorb bone and release calcium. In a combined analysis of randomized trials comparing denosumab and zoledronic acid, denosumab was associated with a higher incidence of hypocalcemia than zoledronic acid (16.0% vs. 7.2%), and serious hypocalcemia also occurred more frequently with denosumab (3% vs. 1%) [32]. Clinical features include lethargy, fatigue, general weakness, or tetany. Before initiating treatment, it is necessary to address preexisting hypocalcemia and potential vitamin D deficiency, and calcium and vitamin D supplementation is recommended for all patients unless there is a contraindication. Furthermore, serum calcium level monitoring is needed during treatment.

Nephrotoxicity is a well-known adverse event of IV bisphosphonates. Pamidronate and zoledronic acid are associated with renal insufficiency, and acute kidney injury has been reported more frequently with zoledronic acid [16,33]. Patterns of renal injury due to zoledronic acid and pamidronate include toxic acute tubular necrosis and collapsing focal segmental glomerulosclerosis, respectively [34]. Renal insufficiency is dependent on dose and infusion time and is mostly reversible following drug discontinuation but may be irreversible. In contrast, in a comparative trial, de-

nosumab showed a much lower nephrotoxicity than zoledronic acid; therefore, it may be beneficial for patients with preexisting renal insufficiency [19]. Renal function must be checked before initiating treatment of bisphosphonate, and close monitoring of renal function during treatment is needed. Bisphosphonate should be reduced or discontinued if creatinine level increases. For patients with underlying renal insufficiency, denosumab could be indicated.

ONJ is a relatively rare but potentially serious adverse effect of treatment with bisphosphonates or denosumab and pain, infection, and necrotic bone in the mandible or maxilla are usual symptoms of ONJ [31]. Although the pathogenesis of bone-modifying agent associated with ONJ remains not well understood, bone remodeling suppression, compromised angiogenesis, and infection are believed to be involved [35]. Denosumab has a slightly higher incidence of ONJ than bisphosphonates; however, a meta-analysis of several randomized trials comparing the safety and efficacy of denosumab and bisphosphonate showed that there was no difference in incidence of ONJ between the two groups [23]. The risk of ONJ increases with longer exposure duration, with a cumulative incidence of 0.7%–1.4% during the first year of treatment and increases to 2%–3.4% with continued treatment beyond 1 year [36]. Invasive dental procedures and poor oral hygiene are well-known risk factors for ONJ [31]. As this event is difficult to treat, strategies for preventing of ONJ is significant. All patients should undergo dental examination and complete any required invasive dental procedures before starting bone-modifying agents. A careful evaluation of patient's oral health is required during treatment of bone-modifying agent, and patients should maintain proper oral hygiene and avoid invasive dental procedures wherever possible.

## Conclusion

Bone-modifying agents, bisphosphonate and denosumab, are effective in reducing SREs in breast cancer patients with bone metastasis; however, survival benefit are controversial. These agents are associated with several adverse events, some of which could be irreversible (renal insufficiency) or could cause serious outcomes (ONJ); therefore, caution is required before and during treatment. Moreover, to reduce adverse events and to improve survival and SREs using these drugs, further studies are needed.

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### ORCID

Lee Chun Park, <https://orcid.org/0009-0002-7412-2003>

Eun Mi Lee, <https://orcid.org/0000-0002-0746-8883>

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