

Mechanisms of, and Adjuvants for, Bone Pain

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KEYWORDS

- Metastatic • Bone • Pain • NGF • Bisphosphonate • RANKL inhibitor • Kyphoplasty
- Vertebroplasty

KEY POINTS

- Bone metastasis is a heterogeneous compilation of diseases that require a multidisciplinary approach to personalize treatment to the patient's individual needs.
- Metastatic bone pain is caused by several mechanisms, including osteoclast activation within the tumor microenvironment, inflammatory factors at the tumor-nociceptor interface, mechanical nerve damage, and neuroplastic changes.
- Several adjuvant therapies are available to alleviate metastatic bone pain, including nonsteroidal analgesics, bisphosphonates, RANKL inhibitors, surgery, kyphoplasty, vertebroplasty, and radiofrequency ablation.

INTRODUCTION

Each year, approximately 400,000 people in the United States are diagnosed with metastatic bone cancer.¹ Bone is the third most common site of metastases, after the lung and the liver.² As cancer screening and treatments improve and patients experience longer life expectancies, they are at increasing odds of developing bone metastases, which may lead to chronic pain, pathologic fractures, and spinal cord compression.

Approximately 30% to 50% of all patients who have cancer will experience moderate to severe pain; of those with advanced or metastatic disease, as many as 75% to 95% of patients will report severe pain.³⁻⁵ Complications from bone metastasis appear an average of 7 months after the patient first reports bone pain.⁶ Chronic cancer-induced bone pain (CIBP) negatively affects a patient's quality of life, increases

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patient morbidity, and decreases overall functional status. The current paradigm in managing metastatic bone disease focuses on preventing CIBP, pathologic fractures, and spinal cord compression, which are collectively known as skeletal-related events (SREs).

Bone metastasis is actually a heterogeneous collection of diseases made up of various primary cancers occurring in various sites of metastases and with baseline functional statuses. Accordingly, metastatic bone pain requires a multidisciplinary approach to personalize treatment to the patient's individual needs and performance status.

This article discusses the mechanisms of metastatic bone pain and the many adjuvant treatment options available to alleviate it.

BONE METASTASES

Cancers of the lung, breast, and prostate cause approximately 80% of all bone metastases. As many as 70% of all patients who have breast or prostate cancer develop skeletal metastases as compared with only 20% to 30% of patients with gastrointestinal cancers.⁷

Cancer commonly metastasizes to bone because of the high blood flow and concentration of immobilized cellular growth factors residing in the red marrow. Metastatic disease most commonly deposits in the axial skeleton, such as the vertebral column and pelvis, or in the medullary portions of the appendicular skeleton, such as the proximal femur.^{8,9}

Bone metastases are frequently asymptomatic and incidentally found on initial staging evaluation. For symptomatic patients, pain is the most common and earliest manifestation of bone metastases. (See Regina M. Fink and Jeannine M. Brants' article, "[Complex Cancer Pain Assessment](#)," in this issue.)

Metastatic bone pain has a gradual onset that worsens over time and typically increases in intensity at night. The pain may be described as somatic (musculoskeletal) or neuropathic but commonly presents with mixed aspects of each. The intensity or nature of the pain cannot be predicted by tumor size, location, or histology, and the pain is often disproportionate to the degree of bone involvement.³

As the disease progresses, patients may begin to experience breakthrough pain. Breakthrough pain is an acute and unpredictable flare of pain not controlled with long-acting pain medications. It may occur spontaneously or be reproducible with nonnoxious movements and/or mechanical weightbearing of the involved bone. Breakthrough pain is often difficult to manage owing to its rapid, striking onset and it frequently results in the decline of a patient's functional status.^{10,11}

MECHANISMS OF PAIN PERCEPTION

Pain is the cognitive perception of potentially harmful environmental stimuli. It requires the synchronization of complex processes, including the (1) detection of an environmental stimuli that is (2) converted to an electrochemical signal and (3) transmitted along the nervous system, where it is (4) cognitively perceived as an unpleasant sensation.

Primary afferent sensory neurons are the pathways on which sensory information is received and transmitted. These sensory neurons provide innervation throughout every organ of the body, except for the brain. The cell bodies of the primary afferent sensory neurons that innervate the body and the face reside in the dorsal root and the trigeminal ganglia, respectively. The nerve fibers of these sensory neurons are divided into 2 main categories: myelinated A fibers and unmyelinated C fibers, each

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