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What do patients with metastatic bone pain need?

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ABSTRACT

Bone pain is a considerable problem for patients with bone metastases from various primary tumors. In this introduction to the Supplement, various data on metastatic bone pain are summarized and available treatment options are briefly introduced.

Bone metastases are common among patients with advanced cancer, particularly breast, prostate, or lung cancer, and almost all patients with multiple myeloma have bone lesions.[1] Patients with metastatic bone disease develop a variety of complications, including pathological fractures, hypercalcemia, and spinal cord compression, with metastatic bone pain (MBP) the most frequent complication. Skeletal metastases are the principal cause of pain in cancer patients, and the degree of pain is often disproportionate to the size or degree of bone involvement.[2,3] In a study of patients with breast cancer and bone metastases, 80% of patients had MBP.[4] In a study of patients referred to a multidisciplinary clinic for bone metastases, 78% reported severe or intolerable pain in the previous 24 h (brief pain inventory score 7–10), and 79% rated their average pain as moderate to severe (brief pain inventory score 4–10).[5] These data demonstrate that MBP is an important clinical problem in oncology.

MBP results in a considerable disease burden and substantially impaired quality of life. Patients with MBP have significantly reduced mobility or can be bedridden and are therefore often dependent on family or caregivers. In addition, patients require increased levels of therapy, which is often associated with frequent hospital visits. Studies have demonstrated that cancer pain detrimentally affects work, relationships, sleep, mood, and enjoyment of life.[6,7]

The most debilitating aspects of MBP are caused by breakthrough pain, defined as transient exacerbations of pain that occur in addition to otherwise stable persistent pain.[8,9] Although patients with MBP often suffer from a continuous level of background pain (ongoing pain), this is normally well controlled with standard analgesia. Breakthrough pain is characterized by changing frequency, unpredictability, and high severity, making it difficult for physicians to treat and for patients to cope with. In different surveys, between 40% and 65% of patients with chronic cancer pain also experienced breakthrough pain.[10–12] Studies have not been performed specifically in patients with bone metastases, although the incidence of breakthrough pain may be higher in this group than among patients with other causes of cancer pain. Breakthrough pain is most often induced by movement, such as walking, sitting, standing, coughing, touching, or turning in bed (incident pain). It can also be spontaneous, however, without any identifiable precipitating event.[9]

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Because of the variable nature of the condition, MBP is difficult for patients to describe and is subsequently often underreported.[13] At early disease stages, MBP may be attributed to other conditions, such as arthritis, muscle pains, or "old age". As the disease progresses, patients often limit their daily activities to minimize or avoid severe breakthrough pain experienced during movement. As a result, reported pain levels may not reflect the extent to which MBP is affecting patients' lives or how severe the pain would be if a patient attempted a normal level of daily activity. In addition, patients are often reluctant to discuss the details of their pain with their physicians.[13] These problems of communication may lead to a delay in the provision of effective palliative care. When physicians are selecting treatment, comprehensive patient assessments are required, including evaluations of worst pain experienced in the last 24 h and level of patient mobility.

MBP is often underdiagnosed and undertreated. In two surveys comprising 900 clinicians treating metastatic bone disease in Europe and North America, approximately one quarter of patients were reported to be experiencing uncontrolled MBP despite optimal analgesic treatment.[14,15] A separate survey found that 40% of radiation oncologists thought that pain relief in their own practice was fair or poor, and 83% believed that most cancer patients with pain were undermedicated.[16] In two other studies, 42% and 51% of patients with cancer were not receiving adequate pain management.[6,17] These data illustrate that there is scope for more effective therapies for palliating MBP.

Various treatment options for MBP are available, although all standard therapies are associated with drawbacks or side effects. Opioid analgesics are the mainstay for managing moderate to severe cancer pain. However, the high doses of opioids required to control breakthrough pain are associated with an unacceptable level of side effects, which may include constipation, nausea, drowsiness, and cognitive impairment.[18,19] Nonsteroidal anti-inflammatory drugs are also recommended in World Health Organization guidelines for cancer pain, although there is no clear evidence that these agents have efficacy in MBP.[2,20] In addition, prolonged use of nonsteroidal anti-inflammatory drugs is associated with renal or gastrointestinal toxicity. Radiotherapy is an effective treatment for MBP, with most patients deriving some benefit.[21–24] However, side effects such as nausea, vomiting, diarrhea, or myelosuppression can result from irradiation of adjacent healthy tissues and patients may also experience a transient increase in pain.[3] Radiopharmaceuticals have palliative effects in MBP, although hematologic toxicity is a concern with these agents.[25,26] In addition, there are practical difficulties associated with radiopharmaceutical administration, and questions remain regarding optimal dosing schedules and choice of agent. Orthopedic surgery is useful for stabilization of tumor-associated fractures, particularly in the spine.[2] Patients receiving hormone therapy or chemotherapy may also experience decreases in bone pain. Unfortunately, all treatments become less effective as disease progresses, and patients with multiple bone lesions present additional management difficulties.

Bisphosphonates, such as ibandronate, are a standard of care for patients with metastatic bone disease.[27] This class of agents inhibits the increased bone-resorbing activity of osteoclasts induced by bone metastases, which is the main cause of complications in metastatic bone disease.[28] Increasing evidence suggests that bisphosphonates are useful for treating MBP.[29] Palliative effects may vary between agents, although this has not been widely studied in clinical trials.[30] An optimal bisphosphonate treatment would deliver both rapid and long-term MBP relief as well as effectively preventing skeletal complications. A range of studies demonstrate that ibandronate has these attributes, and in particular, has proven efficacy for reducing skeletal-related events.[31,32] Pamidronate, clodronate, and zoledronic acid have also demonstrated efficacy for preventing skeletal-related events in patients with metastatic bone disease.[27,33] Because patients with advanced cancer have a substantial disease burden and may be receiving therapies with significant side effects, a favorable safety and tolerability profile is as important as efficacy when choosing a bisphosphonate. Ibandronate has an excellent safety and tolerability profile, particularly with respect to renal safety.[34]

This supplement is based on a symposium, titled "Optimizing outcomes: experience with Bondronat® in metastatic bone pain", held during the eighth workshop on "Bisphosphonates: from the laboratory to the patient" in Davos, Switzerland, on 23 March 2006. The supplement focuses on the science behind MBP, and on efficacy and safety data for ibandronate. In the first article, Patrick Mantyh summarizes preclinical experiments that have provided an insight into the mechanisms that drive MBP. Next, Andreas Kurth reviews clinical efficacy data for intravenous and oral ibandronate in MBP, including intensive loading-dose treatment that provides rapid MBP relief. Finally, Roger von Moos discusses clinical data illustrating the excellent safety and tolerability profile of ibandronate, including its superior renal safety.

Conflict of interest statement

The author has received honoraria within the last 3 years from AstraZeneca, Novartis, Pfizer, Roche, and Schering, and has served as a consultant for Amgen, Novartis, Roche, and Schering.

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