

Metastatic bone pain: treatment options with an emphasis on bisphosphonates

Roger von Moos · Florian Strasser · Silke Gillessen ·
Kathrin Zaugg

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Abstract

Introduction One of the key targets for metastatic cancer cells is the skeleton. Once metastatic cells are established within the bone matrix, skeletal integrity becomes increasingly compromised. Bone lesions lead to various complications, including bone pain, fractures and spinal cord compression.

Mechanisms of bone pain Bone pain is debilitating and affects quality of life of the patient. In addition, it increases the use of health care resources. Many patients with metastatic bone disease experience substantial bone pain despite state-of-the-art systemic analgesic treatment. Incident pain is the predominant pain syndrome.

Treatment options for bone pain Typically, this syndrome requires moderate baseline analgesia with increased on-demand doses. Other techniques for treating bone pain, including radiation therapy, neuraxial application of analgesics, nerve blocks and local stabilisation procedures, should be considered. In addition, therapy with bisphosphonates targeting bone-specific pain is an important strategy. This review discusses the various management options for bone pain arising from metastatic bone disease.

Keywords Metastatic bone disease · Skeletal-related events · Bone pain · Bisphosphonates · Analgesic

R. von Moos (✉)
Medical Oncology, Kantonsspital Graubünden,
Loestrasse 170,
Chur 7000, Switzerland
e-mail: roger.vonmoos@kssg.ch

F. Strasser
Palliative Medicine Section Oncology,
Department of Internal Medicine, Kantonsspital,
Rorschacherstrasse 95,
9007 St. Gallen, Switzerland
e-mail: Florian.Strasser@kssg.ch

K. Zaugg
Department of Radiation Oncology, University Hospital,
Rämistrasse 100,
8091 Zurich, Switzerland
e-mail: kathrin.zaugg@usz.ch

S. Gillessen
Oncology–Haematology, Kantonsspital,
Rorschacherstrasse 95,
9007 St. Gallen, Switzerland
e-mail: silke.gillessen@kssg.ch

Introduction

Bone metastases are frequent and often very painful consequences of advanced cancer. The incidence of bone metastases varies according to the primary tumour type and can reach 95% in patients with certain cancers (Tables 1 and 2) [16, 22]. In addition to pain, the main complications of bone metastases are pathological fractures, spinal cord compression and hypercalcaemia. In addition to rapid treatment of these complications, maintenance of skeletal integrity is a long-term goal for these patients.

Many patients with metastatic bone disease (MBD) experience bone pain that is often severe and debilitating and require additional physician consultations and inpatient treatment for this symptom [42, 61, 84]. Treatment options for MBD must consider pain palliation, both acute and long term. Research suggests that >20% of patients are resistant to current systemic pain treatment [12, 43, 100]. This review discusses the different treatment options that have been shown to be effective in reducing bone pain in patients with MBD.

Table 1 Incidence of skeletal-related events in various tumour types [16, 22]

Primary tumour origin	Incidence (%)
Multiple myeloma	70–95
Breast	65–75
Prostate	65–75
Lung	30–40

Overview of bone lesions

Even after skeletal growth is complete, bone remains metabolically active and continues to remodel throughout adulthood (annual turnover 5–10%) [27]. Bone remodelling requires coordination between bone resorption by osteoclasts and generation of new bone tissue by osteoblasts. Metastatic tumour cells disrupt the balance between osteoblast and osteoclast activity by paracrine secretion of activating factors (i.e. endothelin-1 and parathyroid hormone-related protein) [45]. For several primary tumours, osteolytic lesions are the most common manifestation of secondary disease and result in excessive bone resorption. Osteolytic bone metastases can be associated with bone pain, skeletal fractures, spinal cord compression (with associated neurological symptoms), hypercalcaemia and bone marrow carcinosis.

Dysregulated osteoblast activity results in surplus bone. However, this new bone is of poor quality and fractures easily. Osteoblasts can also upregulate osteoclast activity, which leads to the apparent paradox of bone resorption also increasing as a result of osteoblastic metastasis. Treatment options for osteoblastic lesions should additionally include therapy, such as the bisphosphonates, that targets osteoclasts [7, 34, 74, 80].

Cross-talk exists between invasive malignant cells and osteoclasts. This communication promotes osteoclast recruitment and upregulates their activity. Furthermore, destruction of the bone matrix leads to the release of growth factors that induce tumour cell proliferation [34, 74]. This two-way communication leads to increased tumour burden and skeletal destruction and is commonly called the “vicious circle.”

Detecting and monitoring bone metastases

Several imaging modalities are available to detect bone metastases: plain radiography, skeletal scintigraphy (mainly with technetium), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography and single photon emission CT. Radionuclide bone scans are particularly suited to screen for and to determine the

extent of suspected bone metastases derived from the majority of solid tumours; however, they are not sensitive to all tumours (e.g. multiple myeloma and renal cell carcinoma) or bone marrow involvement. Conventional radiography is generally able to determine the fracture risk at the relevant sites. Typically, initial detection of bone metastases is made using skeletal scintigraphy and confirmed using radiography [32]. Research results in high-risk prostate cancer patients suggest that whole-body MRI is more sensitive at detecting bone metastases than sequential scintigraphy and radiographs [48]; however, MRI is not easily accessible everywhere and is costly. Images providing higher specificity of bone lesions can be obtained using MRI and CT.

One of the current recommendations is to assess metastases thereafter every 2–6 months [32]. However, there is no consensus about the validity of the different imaging techniques. Using CT or MRI, it may be possible to visualise a response as soon as 2 months after treatment start. In comparison, responses do not typically become evident using conventional radiography before 3–6 months.

Bone metastases cause upregulation in bone remodeling. The rate of skeletal turnover can be assessed using several serum and/or urine levels of biomarkers (indicating bone formation or bone resorption) [66]. Two subgroups of biomarkers are defined: substances released by osteoblasts and osteoclasts and markers that indicate the formation–breakdown of collagen.

The most commonly used assays for bone formation are serum tests of bone-specific alkaline phosphatase, osteocalcin and procollagen peptides, which are proteins produced by osteoblasts and released into the bloodstream during bone formation [66]. Bone resorption markers typically measure the breakdown products of collagen, the major protein of bone. These include pyridinoline, deoxypyridinoline, N-telopeptides (NTX) and C-telopeptides of type I collagen cross-links. Measurement of bone turnover biomarkers provides supportive information as to the extent of metastases to bone [66].

Mechanisms of bone pain

Although significant advances are being made in cancer diagnosis and treatment, the mechanisms of bone pain in

Table 2 Frequency of common complications arising from bone lesions in metastatic bone disease [16, 22]

Complication	Frequency (%)
Bone pain	50–90
Pathological fractures	10–40
Hypercalcaemia	10–20

patients with MBD are poorly understood. In addition to tumour-directed osteoclast-mediated osteolysis and tumour-induced nerve injury, neurochemical and cellular characteristics derived from experimental animal models of bone cancer pain are uniquely different to inflammatory or neuropathic pain [30]. A reorganisation of the central dorsal horn of the spinal cord and nociceptor peripheral sensitisation demonstrated in experimental cancer models the release of substance P, a neurotransmitter synthesised by nociceptors, which in turn activates the neurokinin-1 receptor that is expressed by a subset of spinal cord neurons [30, 83]. In addition, astrocyte hypertrophy, which is associated with decreased expression of glutamate reuptake transporters, increases extracellular levels of excitatory neurotransmitter glutamate and leads to excitotoxicity within the central nervous system [83].

Expression of glial fibrillary acidic protein, an astrocyte-specific cellular protein found in the supporting glial cells of the spinal cord, increases in bone cancer pain [30]. This further increases transmission of nociceptive information, leading to the amplification of the non-noxious input that is perceived as a noxious stimulus. Understanding novel mechanisms of bone pain arising from animal models potentially could change the management of pain associated with MBD; further research is needed.

Treatment options for bone pain from MBD

Once bone metastases have been diagnosed and evaluated, the clinical focus is on effective treatment of skeletal complications, including bone pain. Several strategies have been shown to relieve bone pain in patients with MBD.

Conventional anti-cancer therapy

A common approach to treating bone metastases is to continue therapy targeted against the primary tumour using systemic therapy (i.e. chemotherapy, endocrine therapy or immunotherapy). The ideal systemic therapy will target malignant cells, regardless of where they have migrated within the body, including the skeleton. Treatment with systemic therapy has the potential to reduce tumour burden and bone pain. This approach is not always successful but should be combined with other more focused palliative pain treatment, such as radiotherapy.

Radiotherapy and radionuclide therapy

Radiotherapy is an effective treatment of local metastatic bone pain. Some degree of pain relief occurs in 80–90% of patients within 4 weeks. Complete and long-lasting pain relief is seen in approximately 50% of patients [3, 39, 54].

Although palliative doses of radiation are less than those used during a curative course of radiotherapy, a high number of tumour cells are eradicated. Tumour shrinkage will induce osteoblastic repair, leading to partial recovery of bone integrity. External beam irradiation results in ossification in 65–85% of osteolytic metastases [69]. This counters the common misconception that radiation treatment results in a decrease in ossification.

Some patients experience pain relief within 24 h of receiving radiotherapy. Furthermore, this effect can be achieved with a single dose of only 4 Gy. This rapid response is described before tumour shrinkage occurs and supports the hypothesis that this is not the only mechanism of analgesic effect of radiation therapy. Additional pathways responsible for this early response may include altered activity by inflammatory cells, upregulated osteoclast precursor cell activity and inhibition of release of chemical pain mediators [16, 69].

Several randomised studies have compared single fractions versus multiple fractions of radiotherapy [31, 33, 39, 59, 61, 64, 89, 92, 94].

Meta-analysis of single-fraction radiotherapy versus multifraction radiotherapy for metastatic bone relief and prevention of bone complications showed no difference between the two schedules [90, 99]. A study using meta-analysis for single and multifraction radiotherapy to approximate the outcome of treatment on pain response demonstrated that overall pain response rates were 60% and 59% and complete pain response rates were 34% and 32%, respectively [90]. However, patients treated by single-fraction radiotherapy had a higher re-treatment rate and a two to threefold increase of pathological fracture compared to those treated with a multifractionated schedule (e.g. 5×4 or 10×3 Gy) [33, 90]. The drawbacks to radiotherapy include depression of the immune response, anaemia and tumour flare, which may limit its use [89].

A recent small-scale study provided evidence that a combination of a bisphosphonate (standard-dose ibandronate 6 mg) with local radiotherapy worked synergistically. A significant decrease in pain scores was achieved (32/45 patients had a complete pain response, i.e. a pain score of zero) with an overall improvement in performance status [94]. In another study, 35 patients with prostate or breast cancer and suffering from painful bone metastases were treated with zoledronic acid and radiotherapy (30–40 Gy over 3–4 weeks using conventional dose fractionation). Intensity of bone metabolism was indicated by measuring levels of the markers of bone resorption procollagen-I-propeptide and β -crosslaps before and during therapy. Where high initial values (procollagen-I-propeptide $> 190 \mu\text{g/L}$ or β -crosslaps $> 0.5 \mu\text{g/L}$) were measured, complete analgesia was achieved through therapy [96].

Patients with disseminated painful metastases can receive radionuclide treatment (single injection). These compounds accumulate in regions of bone with high metabolic activity, especially in metastatic foci where active bone formation is occurring. Pain relief begins 1–4 weeks after the start of treatment and typically continues for up to 18 months. Repeat doses are possible. Currently, strontium-89 and samarium-153 are approved for use in Europe and the US, and two rhenium isotopes (186 and 188) are under investigation. A recent Cochrane review compared results of four trials ($n = 325$ patients) and concluded that there was only weak evidence for a small effect of radioisotopes on pain control (1–6 months) [75]. However, a smaller-scale study of 79 patients reported effective pain palliation with strontium-89, samarium-153, rhenium-186 and rhenium-188 [49].

Radium-223 (^{223}Ra) is a new bone-seeking treatment for patients with bone metastases from hormone-refractory prostate cancer and was recently evaluated in a phase II study of 33 patients [65]. The results showed an overall safety profile comparable to conventional isotopes but with less haematologic toxicity: heavily pretreated patients with bone marrow insufficiency and patients with tumour bone marrow infiltration are at risk of relevant haematotoxicity with the use of radionuclides; caution should be exercised with patients receiving concomitant myelosuppressive chemotherapy. Larger-scale studies are needed to investigate the value of radium-223 on skeletal-related events (SREs) and bone pain in patients with MBD. Haematological tolerability would be particularly beneficial where repeat treatment is required to control bone pain effectively.

Systemic and epidural analgesia

In general, when treating metastatic bone pain, the World Health Organisation (WHO) three-step analgesic ladder can be followed [18]. For mild pain, anti-inflammatory adjuvant analgesics (i.e. paracetamol or acetylsalicylate) are good initial options. Most patients will also require non-steroidal anti-inflammatory drugs, but their use is frequently contraindicated in these patients due to renal impairment.

Many patients will advance to opioid treatment. Patients taking opioids for background pain may also require additional doses (an additional 10–16%) to counter incident pain. Although not currently considered as standard practice, increasing evidence suggests that combination therapy with several opioids may be of value [88]. Management of opioid-related side effects (cognitive impairment, nausea and constipation) should be started prophylactically [55, 85]. Barriers to opiate treatment also include patient concerns, such as the possibility of addiction, additional side effects and the fear that if pain progresses there are no further palliative options.

The dose of opioids required for palliation of movement-related pain is generally high and may be accompanied by significant side effects (sedation, somnolence, depression, cognitive impairment, respiratory depression and constipation) [19, 72]. For localised bone pain in the distal spine that is refractory to systemic palliative therapy, epidural application of analgesics (i.e. local anaesthetics, opioids and others) is an important option to consider. This technique is especially useful in patients who have slow progressive tumours and few, but difficult to treat, bone metastases.

Evaluation of pain management should include patient-reported outcomes (visual analogue scale [VAS], Brief Pain Inventory [BPI]) [62]. Pain syndrome(s) must be characterised by localisation, deteriorating and improving factors, associated symptoms and their impact on the patient's life. Neurological examination can detect neuropathic pain. For patients with advanced cancer, the risk factors for refractory pain need to be assessed (neuropathic pain, incident pain, psychosocial–spiritual distress and cognitive impairment) [26, 84].

For the treatment of neuropathic pain, systemic opioid treatment is usually efficacious in a majority of patients. Adjuvant analgesics, namely anti-epileptics (pregabalin) and tricyclic anti-depressive agents, also have proven effects for treatment of neuropathic pain, although limited evidence supports their value in cancer patients [20, 25].

Surgery

Often used in conjunction with or prior to other therapy to prevent bone fracture, successful surgical intervention also can reduce bone pain. Conventional techniques for stabilising osteolytic lesions include impregnated acrylic-based bone cements [47], salvage surgery to remove the cancerous area and replace with a prosthesis or bone transplant and surgical insertion of rods and plates. Support frames or surgical fusion of vertebrae can prevent spinal cord compression [51], and laminectomy is also beneficial to increase space around and relieve pressure on the spinal nerves. More recent advances in spinal surgery for metastatic lesions are vertebroplasty and kyphoplasty, both minimally invasive procedures where injections of a cement-like material are made directly into the fractured bone, typically the vertebra. Kyphoplasty includes an additional step to restore bone height and reduce deformity: prior to injection, a balloon is inserted and gently inflated inside the fractured vertebrae [21, 70, 71]. Vertebroplasty and kyphoplasty are very effective at stabilising fractures and providing immediate bone pain relief, with reduced requirement for analgesics and some restoration of mobility in many patients [1, 11, 21, 70, 71]. Clinically asymptomatic cement leakage from the vertebrae is a complication

but occurs in the minority of patients treated [71]. These approaches provide mechanical stability to an affected bone; however, biocompatible cement technology is a developing area. To aid in the strengthening of local bone, bisphosphonates have been incorporated into some of these cements [35]. Although this technology is in its infancy, this treatment shows promising effects.

Rationale of targeting bone pain with bisphosphonates

The bisphosphonates are a broad group of compounds, each with a complex pharmacological profile [5, 53]. A key effect of bisphosphonates is to inhibit osteoclast activity, thereby reducing osteolytic destruction of bone and MBD-related complications [30]. Bisphosphonates (e.g. clodronate, ibandronate, pamidronate and zoledronic acid) are the current standard of care for MBD. Inhibiting bone resorption, mechanical stabilisation and increasing the pH of the bone tumour microenvironment, resulting in a decrease of acid-sensing ion channel stimulation, are proposed mechanisms for reducing bone pain using bisphosphonates [30].

The current recommendation is that bisphosphonate therapy is initiated at first diagnosis of bone lesions and should remain ongoing [38] because the clinical benefits of bisphosphonate-based therapy in reducing pathological SREs are well documented [6, 15, 50, 93]. Bisphosphonates also reduce metastatic bone pain and thereby improve quality of life (QoL) [5, 67, 98], with regular dosing typically suppressing pain after 8–12 weeks. A systematic review [98] concluded that further data were necessary to recommend bisphosphonates as first-line therapy for metastasis-related bone pain, even though evidence supported bisphosphonate effectiveness in providing some pain relief. Since that time, several investigations of bone pain relief with bisphosphonates have been undertaken, typically as a secondary end point of large-scale clinical trials or in smaller studies of investigational doses.

Standard-dose bisphosphonate therapy for bone pain

Although usually measured as a secondary end point in phase III clinical trials of bisphosphonates, bone pain is often the first manifestation of metastatic disease and negatively impacts QoL and mobility of patients. To date, the efficacy of aminobisphosphonates to reduce bone pain is better than for non-aminobisphosphonates (clodronate), suggesting that this class of compounds should be preferred in patients reporting a high pain score. Table 3 summarises randomised, controlled or large-scale prospective studies that have examined the effect of standard recommended

doses of bisphosphonates on metastatic bone pain by primary tumour type.

Prostate cancer

In a pooled analysis of two studies investigating palliation of bone pain in metastatic prostate cancer, pamidronate did not achieve a significant difference versus placebo [86]. In another study, zoledronic acid was compared with placebo and bone pain was defined as a secondary end point. Patients requiring strong opiate analgesics were excluded. The core phase study (15 months) was completed by 147 patients; 133 patients entered the extension phase of 9 months. The pain increase in the group with zoledronic acid was significantly lower at 3, 9, 21 and 24 months [81, 82]. In two smaller placebo-controlled studies of prostate cancer, zoledronic acid also reduced metastatic bone pain [29, 97]. Fulfaro et al. [28] reported that zoledronic acid significantly reduced VAS scores by approximately 50% ($P < 0.0005$) by 1 month. More recently, results from Weinfurt et al. [97] suggest that zoledronic acid reduced bone pain by a clinically meaningful degree (>2 points on the BPI). The analgesic effects of zoledronic acid were particularly notable as more pain-relieving radiotherapy and surgery interventions were received by the control group.

Breast cancer

Although evidence for a reduction in bone pain has been reported for oral clodronate, other trials have reported no palliation of bone pain with this bisphosphonate [40, 46, 91]. This result may reflect that the data were derived from patient populations with different baseline characteristics.

In a combined analysis of two phase III studies, 90 mg pamidronate led to a significantly less increase in pain after 24 months versus placebo [52]. In a small comparative trial, pamidronate improved pain scores more than oral clodronate over 3 months of treatment [41]. In a placebo-controlled registration study in breast cancer patients, zoledronic acid reduced the bone pain index (approximately -0.8 relative to baseline) throughout the whole study from weeks 4–52 [44]. These results are supported by a recently published study on patients with progressive bone metastases who were pretreated with oral clodronate or intravenous pamidronate. After a switch to intravenous zoledronic acid, a relevant palliative benefit in sense of pain reduction was demonstrated, especially in patients with a significant drop in urinary bone markers (uNTX) after the switch, where a large decrease in the worst bone pain was recorded [13]. In phase III trials of patients with breast cancer and bone metastases, oral and intravenous formulations of ibandronate reduced bone pain below baseline for up to 2 years. In comparison, bone pain gradually increased

Table 3 Studies evaluating relief from metastatic bone pain with recommended bisphosphonate doses for MBD

Primary cancer type/ number of patients	Study design	Drug/dose	Results	Reference
Prostate cancer 378 patients	Double-blind, placebo-controlled (pooled analysis of two trials)	Pamidronate 90 mg IV every 3 weeks for 27 weeks	No pain reduction with pamidronate	Small et al. 2003 [86]
643 patients	Double-blind, placebo- controlled trial	Zoledronic acid 4 mg IV every 3 weeks for 15 months	Bone pain and analgesic use increased	Saad et al. 2002 [81]
20 patients	Placebo-controlled trial	Zoledronic acid 4 mg IV every 3 weeks for 6 months	Bone pain significantly reduced after 1 month ($P=0.007$) and 3 months ($P=0.011$)	Weinfurt et al. 2006 [97]
209 patients	Randomised, double-blind controlled trial	Clodronate 1,500 mg IV or placebo every 3 weeks, in combination with mitoxantrone 12 mg/m ² IV every 3 weeks and prednisone 5 mg orally bid	No significant pain reduction with clodronate	Ernst et al. 2003 [26]
55 patients	Randomised trial	Placebo or clodronate 300 mg IV for 3 days, followed by oral clodronate 3,200 mg for 4 weeks.	No significant differences were found between the treatment arm and the controls	Strang et al. 1997 [87]
Breast cancer 144 patients	Double-blind, placebo- controlled trial	Clodronate 1,600 mg/day oral for 1 year	Reduced pain and analgesic use versus placebo ($P=0.01$ and 0.02 , respectively)	Tubiana- Hulin et al. 2001 [91]
754 patients	Double-blind, placebo- controlled trial (pooled analysis of two trials)	Pamidronate 90 mg IV every 3–4 weeks, for up to 2 years	Final bone pain scores increased after 2 years but less than placebo ($P=0.007$). Analgesic use increased	Lipton et al. 2000 [52]
51 patients	Randomised trial versus oral clodronate	Pamidronate 90 mg IV monthly for 4 months	Improved pain scores compared with clodronate after 3 and 4 months	Jagdev et al. 2001 [41]
227 patients	Randomised, placebo- controlled study	Zoledronic acid 4 mg IV every 4 weeks for 12 months	Reduction in bone pain score ($P=$ 0.0004); analgesic scores not different	Kohno et al. 2005 [44]
31 patients	Phase II trial	Zoledronic acid 4 mg IV every 4 weeks for 3 months (second line after pamidronate or clodronate)	By week 8, significant improvements in pain control ($P<0.001$)	Clemons et al. 2006 [13]
466 patients	Multicentre, double-blind, placebo- controlled trial	Ibandronate 6 mg IV every 3 weeks for 2 years	Bone pain reduced below baseline for 2 years ($P<0.001$ versus placebo)	Diel et al. 2004 [23]
564 patients	Multicentre, double-blind, placebo- controlled trial	Ibandronate 50 mg/day oral for 2 years	Bone pain reduced below baseline for 2 years ($P=0.001$ versus placebo); analgesic use was significantly reduced ($P=0.019$)	Body et al. 2004 [8]
30 patients	Phase II trial	Ibandronate 50 mg/day oral (second line after pamidronate or clodronate)	Bone pain significantly reduced after 12 weeks ($P=0.028$)	Clemons et al. 2008 [14]
Myeloma 392 patients	Double-blind, placebo- controlled	Pamidronate 90 mg IV every 4 weeks for 9 months	Pain scores decreased from baseline, only significant at 7 months ($P\leq$ 0.05)	Berenson et al. 1996 [4]

Table 3 (continued)

Primary cancer type/ number of patients	Study design	Drug/dose	Results	Reference
Various neoplasms 55 patients with breast, lung, prostate or other tumours or multiple myeloma	Double-blind, placebo- controlled trial	Clodronate 1,600 mg/day oral for 1 year	Reduced pain ($P=0.03$)	Robertson et al. 1995 [73]
1,648 multiple myeloma and breast cancer	Double-blind versus pamidronate 90 mg every 3– 4 weeks	Zoledronic acid 4 mg IV every 3–4 weeks for 13 months	Bone pain below baseline for 13 months; analgesic use unchanged	Rosen et al. 2007 [78]
773 lung and other solid tumours	Multicentre, double-blind, placebo- controlled trial	Zoledronic acid 4 mg IV every 3 weeks for 9 months	Bone pain increased from baseline	Rosen et al. [76]
604 various primary cancers	Multicentre, prospective single-arm study	Zoledronic 4 mg IV every 3–4 weeks	Bone pain and analgesic scores reduced after 36 weeks ($P<$ 0.0001)	Rosen et al. 2003 [77]

through the study period with placebo [8, 23]. Oral ibandronate was associated with significantly lower use of analgesics compared with placebo ($P = 0.019$) and both formulations improved QoL ($P < 0.05$). As shown with zoledronic acid, switching patients with MBD and breast cancer from oral clodronate or intravenous pamidronate to oral ibandronate led to rapid and significant improvements in metastatic bone pain scores in a phase II study [14].

Multiple myeloma and mixed primary tumour studies

Relief from bone pain in patients with multiple myeloma has been demonstrated with recommended doses of clodronate, pamidronate and zoledronic acid (Table 3) [4, 73, 78]. Ibandronate has also been shown to reduce bone pain in these patients, using a non-standard 2-mg intravenous dose [60]. Other studies have shown that zoledronic acid can relieve metastatic bone pain from various primary tumour types, though some results show that pain increases over time [76, 77].

When selecting bisphosphonate therapy for pain relief, possible side effects should be considered. Patients with MBD typically receive multiple therapies. Additionally, renal impairment is also an issue in elderly patients and patients with multiple myeloma. Depending on the primary tumour, patients with MBD may survive for several years, so the impact that adverse events have on QoL should therefore be minimised. Hypocalcaemia is a common event that can be controlled with dietary calcium and vitamin D. Renal toxicity is reported following high doses and rapid administration of intravenous pamidronate and zoledronic acid and is thought to be caused by damage to the renal

tubules [9, 56, 57]. In a phase III clinical trial, decline in renal function was reported in 10.7% of patients receiving intravenous zoledronic acid for bone metastases from multiple myeloma or breast cancer, and some patients receiving zoledronic acid or pamidronate have progressed to renal failure requiring dialysis [2, 10, 56, 102]. However, ibandronate does not seem to have the same effect on renal function, with an incidence of adverse events similar to placebo in phase III trials of patients with breast cancer and bone metastases for up to 4years of treatment [68].

Osteonecrosis of the jaw (ONJ) is another serious side effect associated with aminobisphosphonate, and diagnosis requires the presence of exposed bone for at least 6weeks [58, 63, 79]. Main symptoms include oral mucosal ulcerations, soft tissue infection and pain. The pathogenesis of ONJ is not fully understood yet, although it has been suggested to result from bisphosphonate interference with bone remodelling or anti-angiogenic effects. Current evidence suggests that the incidence of ONJ is related to duration of exposure and the type of bisphosphonate used [24, 101]. For this reason, the benefit of long-term use of bisphosphonates has to be weighed carefully against the risk of ONJ occurrence. Further studies are required to determine the relative incidence of this condition with the different bisphosphonates.

Loading-dose bisphosphonate therapy for bone pain

Evidence suggests that standard-dose bisphosphonates reduce metastatic bone pain to a greater or lesser degree depending on the drug used, primary tumour burden and

bone pain. It is likely to take at least 4–12 weeks after start of bisphosphonate therapy before a significant decline in bone pain is recorded. In addition to standard recommended doses, several studies have evaluated the analgesic potential of intensive bisphosphonate therapy for the relief of metastatic bone pain. Results to date have been promising. For example, an early trial in prostate cancer patients where intravenous clodronate was administered as a loading dose (300mg/day for 8 days) followed by standard high-dose oral clodronate 1,600mg/day demonstrated palliation of pain [36]. Mean pain score significantly declined ($P < 0.001$) in 64/85 patients, and 22% became pain free without the need for additional analgesics. The first analgesic effects of clodronate were seen on day 4 of parenteral therapy. Because of severe side effects and poor tolerance, this regimen was discontinued. High doses of intravenous pamidronate were also found to be beneficial in symptomatic relief for patients with MBD [17]. A single 120-mg, 2-h infusion of pamidronate was administered to 86 patients with progressive bone metastases from breast, prostate or other carcinoma in two separate studies. Both studies showed approximately 25% reduction in the overall pain score based upon a questionnaire and WHO performance status. The authors also found that clinical benefit was greatest for patients with slowly progressive disease and only modest increases in the rate of bone resorption.

More intensive dosing schedules for bisphosphonates have been limited (e.g. due to low bioavailability with oral formulations and renal toxicity with intravenous therapy). However, recent reports have suggested that intensive bisphosphonate treatment is possible for some intravenous formulations that can then be followed by long-term standard therapy. Phase II studies demonstrate that ibandronate has a marked analgesic effect in patients with moderate to severe metastatic bone pain from various tumour types, including bladder, prostate and kidney cancer, when administered as 6-mg infusions on three consecutive days. Bone pain scores were significantly reduced within days (compared with the 4–12 weeks with standard dose; 6mg infused every 3–4 weeks), and many patients were pain free at the end of study [37, 95].

Conclusion

Metastatic bone pain is a debilitating problem for patients with advanced cancer. A variety of treatment options to reduce bone pain are available to physicians, although choosing and prescribing a suitable treatment for each individual is not always easy. Fortunately, not only can several therapies be used sequentially without reducing the efficacy of future treatment, they can also be used concomitantly. Recent advances in surgical techniques for

painful vertebral compression and the potential to combine such approaches with other interventions, such as radiotherapy, are improving available options for patients. Treatment schedules designed to specifically provide relief from bone pain in addition to other SREs provide promise for future therapeutic algorithms for patients with bone metastases.

Unfortunately, many patients with MBD still experience bone pain despite recommended doses of opioids (according to the WHO analgesic ladder), highlighting the need for improved symptom management. Bisphosphonate therapy, which targets the underlying skeletal metastases to improve bone integrity, has proved particularly successful in patients with moderate to severe bone pain and has reduced the need for analgesic consumption and palliative radiotherapy in clinical trials. Skeletal-related efficacy and safety profiles (renal toxicity, hypocalcaemia and ONJ) should be considered, especially during long-term use of bisphosphonates. Another question remains as to which dosing schedule is the best for bisphosphonates intended for bone pain relief. Standard dosing provides long-term reductions in bone pain for up to 2 years but takes several weeks to become maximal. Rapid relief of bone pain with loading-dose bisphosphonates may represent an additional treatment option for patients with MBD. There are not enough data yet from large clinical trials, but this approach seems to be effective and well tolerated and may be particularly beneficial for patients who are receiving standard analgesia but still have treatment-resistant (breakthrough) pain and pain on movement, but further research is required.

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