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# Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain

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Review

# Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain

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**Abstract** Metastatic bone disease in patients with advanced cancer is frequently associated with skeletal complications. These can be debilitating, causing pain, impaired functioning and decreased quality of life, as well as reduced survival. This review considers how the management of metastatic bone pain might be optimised, to limit the considerable burden it can impose on affected patients. Cancer-related pain is notoriously under-reported and under-treated, despite the availability of many therapeutic options. Non-opioid and opioid analgesics can be used; the latter are typically administered with radiotherapy, which forms the current standard of care for patients with metastatic bone pain. Surgery is appropriate for certain complicated cases of metastatic bone disease, and other options such as radiopharmaceuticals may provide additional relief. Treatments collectively referred to as bone-targeted agents (BTAs; bisphosphonates and denosumab) can offer further pain reduction. Initiation of therapy with BTAs is recommended for all patients with metastatic bone disease because these agents delay not only the onset of skeletal-related events but also the onset of bone pain. With evidence also emerging for pain control properties of new anticancer agents, the potential to individualise care for these patients is increased further. Optimisation of care depends on physicians' thorough appreciation of the complementary benefits that might be achieved with the

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various agents, as well as their limitations. Appropriate anti-tumour treatment combined with early initiation of BTAs and adequate analgesia plays a key role in the holistic approach to cancer pain management and may minimise the debilitating effects of metastatic bone pain.
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## 1. Introduction

Managing patients with cancer requires a multidisciplinary approach, especially when the cancer has metastasised to bone. Bone metastases frequently cause complications known as skeletal-related events (SREs), which are associated with significant morbidity [1], impaired mobility and social functioning [2], reduced quality of life (QoL) [2], increased resource utilisation [3–7] and reduced survival [1,8]. Bone metastases are particularly common in advanced breast, prostate or lung cancer [9]; indeed, metastatic bone disease is evident *post mortem* in approximately 40–70% of these patients [1]. Renal cell carcinoma also metastasises to bone, and multiple myeloma invariably spreads to multiple sites within the bone [10,11]. Here, we review metastatic bone pain, its impact on patients, and how management can optimise QoL; implications for clinical practice are summarised in Table 1.

## 2. Incidence of metastatic bone pain

Approximately two-thirds of individuals with metastatic cancer experience pain, which is moderate to severe in almost half of the cases [12,13]. Often, this pain originates from primary cancers that have metastasised to bone. For example, 81.4% of patients with metastatic cancer reported bone pain, compared with only 23.3%, 10.9%, 7.8% and 0.8% of the same patients reporting pain that was deemed pleuritic, neural, visceral or attributable to headache, respectively [14]. Indeed, in bisphosphonate and denosumab studies in patients with bone metastases, significant pain was reported at study entry: mean Brief Pain Inventory (BPI) bone pain scores were 2.0–4.5 [15–18], mean BPI (Short Form; BPI-SF) worst pain scores were 4.1–6.3 [18–20], 21–24% of patients reported moderate bone pain (BPI-SF score 5–6) and 23–35% reported severe bone pain (BPI-SF score 7–10) [19–22].

## 3. Aetiology of metastatic bone pain

Metastatic bone pain is complex, originating via inflammatory and neuropathic pathways. Tumours may contain numerous inflammatory cells, and both inflammatory cells and tumour cells secrete various pain-mediating chemicals that activate sensory nerve endings in the bone. Increased osteoclast activity can destroy these endings and acidify the environment, causing neuropathic pain and stimulation of pH-sensitive nerve endings. Furthermore, osteoclastic bone loss destabilises bone, causing pain via mechanosensitive receptors. Bone distension or nerve damage caused by invading tumours may generate constant pain at rest and elevate sensitivity to pain during movement [23–28]. Although periosteal infiltration is rare, periosteum stretching may also cause bone distension [29]. SREs, including pathologic fracture, radiation or surgery to bone, and spinal cord compression, may also cause bone pain [30].

## 4. Impact of bone metastases and SREs on pain and QoL

Patients with metastatic breast cancer experiencing on-study SREs reported increased pain, and pain interference with daily functioning, compared with those with no on-study SREs [31]. Meta-analyses also show that SREs in patients with metastatic cancer significantly increase the risk of pain progression and the need for strong opioids (Fig. 1) [32]. Furthermore, SRE-associated pain may persist despite strong opioid use, such that patients might not recover fully [32]. Cancer-related pain can markedly reduce QoL [33], negatively affecting mood, work, relationships, the ability to walk [34,35] and sleep [34,36]. Sleep disturbance can further perturb pain tolerance thresholds, potentially leading to a vicious cycle of pain [37].

### *4.1. Assessing metastatic bone pain and related impact on QoL*

There are many tools for evaluating metastatic bone pain and its impact on QoL [38] (Table 2). The value of routinely assessing patient-reported outcomes was demonstrated recently in patients with metastatic cancer [39]. One group reported their symptoms between clinic visits via a Symptom Tracking and Reporting system, which alerted nurses to severe or worsening symptoms. Treating physicians received symptom printouts at visits. Compared with the routine care group, more patients using Symptom Tracking and Reporting reported improved QoL and fewer reported worsening QoL; they were also less likely to visit the emergency room or to be hospitalised, more likely to survive 1

Table 1
Management of metastatic bone pain; implications for clinical practice.

| | Implications |
|---|---|
| Diagnosis | Metastatic bone pain can have a profoundly negative impact on patients' lives, yet it remains under-reported and under-treated despite the availability of numerous therapeutic agents, treatment guidelines, and assessment tools and questionnaires |
| Treatment with opioids and radiotherapy | Opioids and radiotherapy form the current standard of care, but may not be suitable for all the patients; indeed, some never achieve effective relief with these treatment modalities. Historic guidelines on opioid use may also not reflect current understanding of pain, and optimal relief may require different strategies at each disease stage and for different types of pain |
| Effect of BTAs | The pain-relieving effects of BTAs are well established, but a lack of clear guidance regarding which to use and for how long they may prevent optimal management in patients receiving these drugs. Even when guidance exists, such as to initiate BTAs as soon as bone metastases are diagnosed, it is not always followed in daily practice |
| Potential of new treatments | New therapies (such as radiopharmaceuticals, enzalutamide and abiraterone acetate) and combination therapies may offer additional rapid and effective pain relief |
| Monitoring pain | There is a clear need to: assess pain routinely and monitor for changes; tailor and select the most appropriate therapy; and identify and reduce barriers to initiating prompt treatment. Preliminary evidence suggests that remote patient symptom-tracking tools may prove particularly valuable for improving the speed, precision and patient-centricity of cancer care |
| Multidisciplinary management | The multidisciplinary team also plays an important role. For example, by taking the time to listen to patients' concerns about treatment and understanding their unique needs and goals, physicians will be able to tailor therapy according to the benefit–risk profiles of individual patients. |
| Holistic approach | The subjective and variable nature of patients' pain perception is potentially affected by elements of social, emotional and spiritual pain; these aspects should be considered when making assessments in clinical practice. |

Abbreviation: BTA, bone-targeted agent.

year, and had better quality-adjusted survival (all $p < 0.05$) [39]. These findings demonstrate the potential power of patient-reported outcome assessments to improve the precision and patient-centeredness of cancer care [40].

## 5. Therapeutic goals and treatment approaches to bone pain management

Appropriate pain management is vital for maintaining good QoL at any disease stage, and treatment must be individualised to each patient to be successful. Cancer-induced bone pain is multifactorial; hence, optimal pain relief may require different strategies for different disease stages and pain types. Background pain is a dull, continuous pain that increases with disease progression and can usually be managed well with traditional analgesics [23]. By contrast, breakthrough pain is a transient and severe exacerbation of pain that can be idiopathic or precipitated following specific actions [41], is intermittent, starts suddenly and lasts only briefly, and can therefore be very difficult to treat [23].

Therapeutic goals for pain management are distinct from those for preventing SREs. The immediate aim is to reduce pain at rest and during movement, whereas long-term goals focus on preventing pain progression and SREs. For patients with no bone pain, the goal should be to delay the onset of pain and SREs [32]. Together, these approaches should help to improve patients' QoL, allowing them to maintain normal life as much as possible.

The World Health Organization (WHO) guidelines for managing cancer-related pain recommend a three-step 'analgesic ladder' approach. Mild pain is addressed by the use of non-opioid analgesics. If pain persists or increases, mild opioids should be used, and if pain persists/increases further, strong opioids are recommended. All treatments should be given promptly and regularly [42,43].

In addition to opioids, the European Society for Medical Oncology (ESMO) recommends radiotherapy, bone-targeted agents (BTAs) (e.g. bisphosphonates and the RANK ligand inhibitor denosumab) and radiopharmaceuticals [44] to reduce pain associated with bone metastases [30]. Surgery may be appropriate in selected cases involving spinal cord compression or requiring bone stabilisation [44]. When conventional radiotherapy and chemotherapy prove inadequate (e.g. for spinal metastases, vertebral fractures and/or spinal instability [45]), percutaneous vertebroplasty may be an option. It improves pain and QoL when administered alone [46–48] or in combination with radiotherapy [49], transarterial embolisation [50] and $^{125}$I-seed implantation [45,51]. The National Institute for Health and Care Excellence therefore recommends considering vertebroplasty to alleviate pain and associated disability in such cases [52]. Other recent developments include thermoablation techniques, with microwave ablation and high-intensity focused ultrasound options for the palliative treatment of painful bone metastases [53].

Despite the many treatment options for managing cancer-related pain, under-treatment is common [54],

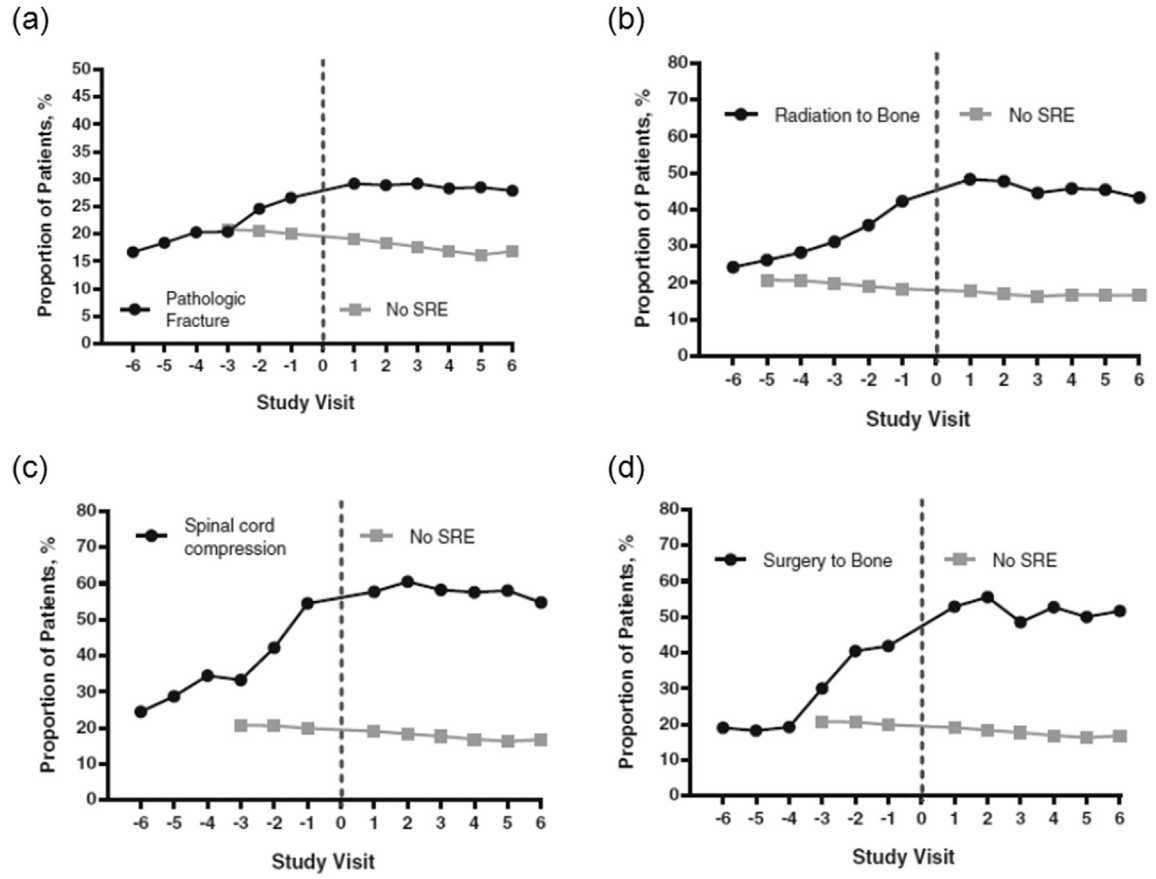


Fig. 1. Proportion of patients using strong opioids (AQA score $\geq 3$) before and after SREs. (a) Pathologic fracture, (b) radiation to bone, (c) spinal cord compression and (d) surgery to bone [32]. Study visit 6 is the visit at 6 months before the occurrence of the first on-study SRE. The dashed vertical line represents the occurrence of the first SRE. Study visit 1 is the first visit after the SRE. For patients with no SRE, data were not consistently available for months 6, 5 and 4. AQA, Analgesic Quantification Algorithm; SRE, skeletal-related event. Reproduced from von Moos R *et al*. Support Care Cancer, Pain and analgesic use associated with skeletal-related events in patients with advanced cancer and bone metastases. Vol. 24; p1327–37, Fig. 1 'Proportion of patients with moderate/severe pain and strong opioid use' with permission of Springer.

Table 2
Assessment measures for evaluating metastatic bone pain and the associated impact on QoL used frequently in interventional clinical studies.

| Pain-related assessment measures |
|---|
| Analgesic Quantification Algorithm [117] |
| Brief Pain Inventory [118] |
| Brief Pain Inventory-Short Form [119] |
| Numerical rating scales (various) [120] |
| Present Pain Intensity index from the McGill–Melzack Pain Questionnaire [121] |
| Rotterdam Symptom Checklist [122] |
| Verbal rating scales (various) [120] |
| Visual analogue scales (various) [120] |
| QoL-related assessment measures |
| Eastern Cooperative Oncology Group performance status [123] |
| European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [124] |
| 5-dimension EuroQol questionnaire [125] |
| Functional Assessment of Cancer Therapy—General [126] |
| Spitzer QoL Index [127] |

Abbreviation: QoL, quality of life.

which may be due to patient reluctance to report cancer-related pain [55]. Also, despite improvements in the quality of cancer pain management over the last two decades, approximately one-third of patients still do not receive appropriate pain medication [56]. The extent to which metastatic bone pain contributes to the burden of under-treated cancer pain is well established and underlies efforts to promote standardisation of bone pain assessment in trial settings [57]. The following sections summarise the key advantages and disadvantages of the main treatment options.

### 5.1. Opioids

Opioids form the cornerstone of cancer-based pain relief, but data are inconclusive regarding whether moderate pain should be treated with weak opioids (WHO step 2) or low-dose morphine (step 3). However, a recent study in adults with moderate cancer pain suggested low-dose morphine was more effective, with more patients achieving clinically meaningful and highly

meaningful reductions in pain intensity on low-dose morphine than on weak opioids ($p < 0.001$); adverse events (AEs) were similar between groups [58]. This suggests that the WHO analgesic ladder, first established in 1986, may need to be adapted.

Common opioid-associated AEs include nausea, vomiting and constipation, but these can generally be managed with dose adjustments and/or adjuvant antiemetics and laxatives [59]. Some opioids should be used with caution in patients with renal impairment, owing to the potential for accumulation of renally excreted metabolites [60]. Response to opioids for chronic cancer pain is variable, with many patients being non-responders or poor responders [61]. Patients may also be reluctant to take opioids [62]; thus, it is important that physicians take time to understand patients' concerns and provide necessary advice to patients and carers.

### 5.2. Radiotherapy

Together with opioids, radiotherapy is the treatment of choice for localised metastatic bone pain [30] and provides effective pain relief [63–65]. Evidence suggests that low-dose, short-course radiotherapy schedules may be as effective as high-dose, protracted programmes [63,66]. Other factors (e.g. frequency of hospital visits and treatment tolerability) must also be taken into account when considering the overall QoL of a patient receiving radiotherapy [67,68].

Approximately half of the patients receiving radiotherapy for pain experience benefits within 1–2 weeks, although a complete response may take several months, and some patients never obtain effective relief [30,66]. However, a systematic review of single-fraction conventional palliative radiotherapy found that higher doses produced statistically superior pain response rates [64] to lower doses, suggesting that some patients may benefit from increased doses. Potential drawbacks of radiotherapy include reports of 'pain flare', a temporary worsening of pain in the treated site [69], and it may not be ideal in patients who have widespread pain that is difficult to localise [30] (in such cases, systemic agents such as bisphosphonates can be effective alternatives [70]).

### 5.3. Radiopharmaceuticals

The β-emitting radiopharmaceuticals strontium-89 and samarium-153 lexidronam are approved for the treatment of metastatic bone pain and can provide complete reductions in pain with no increase in analgesic use for up to 6 months, although AEs are frequent [71] (including myelosuppression, pain flares, leukocytopenia and thrombocytopenia [71–73]). Radioisotopic pain relief typically starts 1–4 weeks after treatment initiation, and mean overall, complete and partial response rates with strontium-89 have been reported as 76%, 32% and 44%, respectively [72]. Compared with placebo, samarium-153 lexidronam improves pain scores and reduces analgesic use over 4-week periods [74,75].

In contrast to β-emitters, α-emitting radiopharmaceuticals have a short path length, which reduces myelosuppression [76]. The analgesic efficacy of radium-223 dichloride is being assessed in several tumour types, and it was recently approved for men with prostate cancer and bone metastases, but with no visceral metastases [77]. In such patients, radium-223 improved survival significantly compared with placebo (median, 14.9 versus 11.3 months, respectively; hazard ratio [HR], 0.70; $p < 0.001$), and prolonged time to first symptomatic skeletal event (median, 15.6 versus 9.8 months, respectively; HR, 0.66; $p < 0.001$) [77]. It also reduced the need for external beam radiotherapy for bone pain (HR, 0.67; $p = 0.00117$) [78] and more patients experienced clinically meaningful improvements in QoL (25% versus 16%, respectively; $p = 0.02$); there were also fewer AEs with radium-223 chloride than with placebo [77]. Of the 109 patients participating in the US expanded access programme and not receiving opioids at baseline, 42% achieved meaningful pain relief with radium-223 (28% had worse pain and 18% experienced no change) [79].

### 5.4. Bone-targeted agents

In metastatic cancers, the efficacy of bisphosphonates for reducing BPI scores, pain symptoms, analgesic use and radiation to bone has been well demonstrated (Table 3) [15,17,80–93]. Pamidronate may also delay time to pain progression [83] and clodronate may delay time to first regular use of analgesics [92]. In a single-centre study comparing clodronate and zoledronic acid in patients with metastatic prostate cancer, both agents provided pain relief, but zoledronic acid was significantly more effective [93]. There is some inconsistency, however, in the findings of various studies of bisphosphonates in this setting, and results also vary across cancer types [94,95].

The RANK ligand inhibitor denosumab has also demonstrated efficacy in relation to pain palliation. An integrated analysis of data from three phase 3 studies in patients with bone metastases showed that, compared with zoledronic acid (widely accepted to be the most effective bisphosphonate [30]), denosumab delayed the onset of moderate/severe pain by a median of 1.8 months (95% CI 0.76, 0.92; $p < 0.001$) and delayed median time to clinically meaningful increases in pain interference by 2.6 months (95% CI 0.75, 0.92; $p < 0.001$) [20]. Progression to strong opioid use was less common with denosumab than with zoledronic acid ($p < 0.05$), as was worsening of QoL ($p = 0.005$) [20].

These studies have typically been conducted against a background of as-needed opioid use. Thus, BTAs appear to provide an effective therapeutic option for reducing opioid-mediated pain relief. Studies of BTAs

Table 3
Key data from pivotal phase 3 trials of agents used to treat bone metastases, focussing on pain and quality of life outcomes.

| Study | Treatment groups | Primary tumour | Study duration | N | Efficacy: bone pain outcomes | Efficacy: QoL outcomes |
|---|---|---|---|---|---|---|
| Adami 1989 [92] | Clodronate (300 mg i.v. once daily) versus placebo | Prostate | 4 weeks | 13 | • Mean pain score was significantly lower in the clodronate group than in the placebo group at all time points to week 4 ($p < 0.01$)<br>• Mean analgesic consumption was significantly lower in the clodronate group than in the placebo group at all time points to week 4 ($p < 0.01$) | |
| Body 2004 [80] | Ibandronate (50 mg p.o. once daily) versus placebo | Breast | 96 weeks | 564 | • Sustained reductions were observed in bone pain score for ibandronate (−0.1) versus placebo (+0.2); $p = 0.001$ versus placebo at study end)<br>• Analgesic use increased in both groups, but the increase was significantly smaller in the ibandronate group than in the placebo group (0.60 versus 0.85 points, respectively; $p = 0.019$)<br>• The mean number of 12-week periods with events requiring radiotherapy to bone significantly reduced with ibandronate versus placebo (0.73 versus 0.98; $p < 0.001$) | • QoL (EORTC QLQ-C30) deteriorated in both groups; the decrease in QoL was significantly lower with ibandronate than with placebo (−8.3 versus −26.8 points, respectively; $p = 0.032$)<br>• On the individual functioning scales of the EORTC QLQ-C30, ibandronate significantly improved physical and role functioning versus placebo ($p \leq 0.05$) |
| Diel 2004 [81] | Ibandronate (2 mg or 6 mg i.v. every 3 or 4 weeks) versus placebo | Breast | 96 weeks | 466 | • Bone pain scores were increased at study end in the placebo (+0.19) and ibandronate 2 mg groups (+0.21), but were significantly reduced in the ibandronate 6 mg group (−0.28; $p < 0.001$ versus placebo)<br>• Mean absolute change in analgesic requirement was numerically lower in the ibandronate 6 mg group (0.51 points) than in the placebo group (0.90 points; $p > 0.05$)<br>• Pain was reduced significantly in the ibandronate 6 mg group ($p < 0.05$ versus placebo) | • Mean overall QoL scores decreased to a lesser extent over 96 weeks for patients receiving ibandronate 2 mg (−18.1) and 6 mg (−10.3) than for those receiving placebo (−45.4)<br>• Overall difference in functioning between the placebo and ibandronate treatment groups was statistically significant ($p = 0.005$)<br>• At study end, patients in the ibandronate 6 mg group showed significantly better functioning than those in the placebo group ($p = 0.004$), with significantly better scores on the domains of physical, emotional and social functioning, and in global health status ($p < 0.05$) |
| Hortobagyi 1996 [82] | Pamidronate (90 mg i.v. every 4 weeks) versus placebo | Breast | 12 cycles | 382 | • Bone pain decreased from baseline in the pamidronate group after 3, 6 and 9 cycles of treatment versus progressive worsening | • ECOG performance status scores and Spitzer QoL Index scores worsened from baseline to study end, with significantly greater worsening in ECOG performance |

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Table 3 (*continued*)

| Study | Treatment groups | Primary tumour | Study duration | N | Efficacy: bone pain outcomes | Efficacy: QoL outcomes |
|---|---|---|---|---|---|---|
| | | | | | in the placebo group. A similar pattern was observed for analgesic drug use<br>• Among patients with pain at baseline, significantly more individuals in the pamidronate group than in the placebo group had decreased pain scores at the last measurement (44% versus 32%; p = 0.03) | status scores in the placebo group than in the pamidronate group (p = 0.03) |
| Hultborn 1999 [83] | Pamidronate (60 mg i.v. every 4 weeks) versus placebo | Breast | 2 years | 404 | • Time to progression of pain was significantly delayed with pamidronate compared with placebo (p < 0.01)<br>• Patient self-assessment of pain according to visual analogue scales favoured pamidronate (not statistically significant)<br>• Consumption of opioid analgesics was numerically lower in the pamidronate group than in the placebo group (p = 0.14) | • The proportion of patients with a poor performance status was significantly lower in the pamidronate group than in the placebo group (p = 0.013) |
| Kohno 2005 [15] | Zoledronic acid (4 mg i.v. every 4 weeks) versus placebo | Breast | 1 year | 228 | • BPI score was significantly reduced from baseline at every time point from 4 to 52 weeks in the zoledronic acid group. Patients in the placebo group reported no change or an increase from baseline at each time point. No between group statistics were reported<br>• There were no clinically significant differences between treatment groups in analgesic scores | |
| Lipton 2000 [84] | Pamidronate (90 mg i.v. every 3–4 weeks) versus placebo | Breast | 2 years | 751 | • Mean pain scores and analgesic scores at the last study visit increased in both groups, but the increase was significantly lower in the pamidronate group than in the placebo group (p < 0.001)<br>• For patients with data at 2 years, those in the pamidronate group experienced a significant decrease in mean pain scores compared with an increase in the placebo group (p = 0.015)<br>• Of patients with pain at baseline (79% in each group), 40% in the pamidronate group and 52% in the placebo group experienced increased pain during the study (p = 0.003) | • ECOG performance status and QoL scores worsened from baseline to the last visit in both groups, although less so in the pamidronate group compared with the placebo group (difference versus baseline not significant for either) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Saad 2005 [85] | Zoledronic acid (4 mg i.v. every 3 weeks) versus placebo | Prostate | 9-month extension (following a 15-month core phase) | 422 | • BPI composite pain scores increased for both treatment groups over time, but were consistently lower in the zoledronic acid group than in the placebo group ($p < 0.05$ at 3, 9, 21 and 24 months)<br>• There was no statistically significant mean change from baseline analgesic score between treatment groups | |
| Saad 2010 [86] | Zoledronic acid (4 mg i.v. every 3 weeks) versus placebo | Prostate | 2 years | 422 | • Zoledronic acid significantly reduced mean BPI composite pain scores versus placebo at 3, 9, 21 and 24 months ($p \leq 0.03$ for each time point)<br>• Zoledronic acid produced significant reductions versus placebo in several components of the BPI composite, including interference with sleep, general activities, mood, walking and enjoyment of life ($p < 0.05$) | • No significant differences in performance status or QoL scores were observed between the treatment groups during the 24 months of follow-up |
| Saad 2002 [17] | Zoledronic acid (4 mg or 8 mg i.v. reduced to 4 mg i.v.; every 3 weeks) versus placebo | Prostate | 15 months | 643 | • The mean increase in pain score from baseline to 15 months was smaller for zoledronic acid 4 mg (+0.58; not significant) and 8 mg/4 mg (+0.43; $p = 0.026$) than for placebo (+0.88)<br>• Differences in analgesic scores between groups were not statistically significant | • There was no statistically significant difference between the groups in mean ECOG performance status scores, FACT-G QoL scores or EQ-5D scores |
| Saad 2004 [87] | Zoledronic acid (4 mg or 8 mg i.v. reduced to 4 mg i.v.; every 3 weeks) versus placebo | Prostate | 2 years (15-month core; 9-month extension) | 643 randomised to initial study, 186 continued into extension | • Mean increase from baseline in BPI score was significantly smaller with zoledronic acid 4 mg (+0.58; $p = 0.024$) or 8 mg/4 mg (+0.54; $p = 0.013$) than with placebo (+1.05) at 2 years<br>• There was no statistically significant difference between groups in mean change in analgesic score from baseline to 2 years | |
| Theriault 1999 [88] | Pamidronate (90 mg i.v. every 4 weeks) versus placebo | Breast | 24 cycles | 372 | • Skeletal morbidity for any radiation to bone and for radiation to bone for pain relief was significantly lower in the pamidronate group than in the placebo group at 6, 12, 18 and 24 cycles ($p = 0.012$, $p = 0.006$, $p = 0.025$ and $p = 0.011$, respectively)<br>• At the final measurement, bone pain scores had increased (worsened) significantly more in the placebo group than in the pamidronate group ($p = 0.007$) | • ECOG performance status and Spitzer QoL Index scores worsened from baseline in both treatment groups, with no statistically significant difference reported between the two groups |

(*continued on next page*)

Table 3 (*continued*)

| Study | Treatment groups | Primary tumour | Study duration | N | Efficacy: bone pain outcomes | Efficacy: QoL outcomes |
|---|---|---|---|---|---|---|
| | | | | | • Mean analgesic use at 12 cycles and at the final measurement increased significantly more from baseline in the placebo group than in the pamidronate group ($p = 0.001$ and $p < 0.001$, respectively) | |
| Tripathy 2004 [89] | Ibandronate (20 mg or 50 mg p.o. once daily) versus placebo | Breast | 96 weeks | 435 | • Bone pain scores (LOCF) increased from baseline to study end in the placebo group (+0.21), whereas there was a reduction in the ibandronate 20 mg group (−0.06; $p = 0.071$) and a slight increase of in the ibandronate 50 mg group (+0.03; $p = 0.201$)<br>• Changes from baseline in mean analgesic score were +0.96 for placebo, +0.43 for ibandronate 20 mg ($p = 0.006$ versus placebo) and +0.73 for ibandronate 50 mg ($p = 0.074$ versus placebo) | |
| Tubiana-Hulin 2001 [90] | Clodronate (1600 mg p.o. once daily) versus placebo | Breast | 1 year | 144 | • Patients treated with clodronate had significant reductions in pain intensity versus the placebo group ($p = 0.01$; measured using a visual analogue scale) and significantly fewer patients receiving clodronate required analgesics ($p = 0.02$) | |
| Weinfurt 2006 [91] | Zoledronic acid (4 mg or 8 mg i.v. reduced to 4 mg i.v.; every 3 weeks) versus placebo | Prostate | 60 weeks | 422 | • At all 11 assessment times, patients in the zoledronic acid group reported more favourable pain responses than those receiving placebo<br>• Over the duration of the trial, a typical patient receiving zoledronic acid had a 33% chance of a favourable response; a typical patient receiving placebo, who had a 25% chance of a favourable response ($p = 0.036$) | |

Abbreviations: BPI, Brief Pain Inventory; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EQ-5D, 5-dimension EuroQol questionnaire; FACT-G, Functional Assessment of Cancer Therapy—General; i.v., intravenous; LOCF, last observation carried forward; p.o., oral (per os); QoL, quality of life.

have not generally been designed to assess the speed of onset of pain relief, but significant separation in pain scores has occurred as early as 1 week or 4 weeks after initial treatment [15,92].

For patients with opioid-resistant bone pain, a loading-dose approach with ibandronate can provide rapid analgesic relief. Following early promising data [96,97], an observational study was conducted in patients with bone pain from newly diagnosed skeletal metastases [98]. Ibandronate (6 mg intravenous [i.v.] infusion on 3 consecutive days) significantly decreased pain intensity on days 3–5 and 5–7 (both $p < 0.01$), compared with day 0 [98]. The loading-dose technique has not yet been evaluated using zoledronic acid (restricted by the potential for renal toxicity) or denosumab.

## 6. Considerations for use of BTAs: applying guidelines in clinical practice

Clinical practice guidelines recommend using BTAs as soon as bone metastases are detected, and continuing use throughout the disease course [30]. In real-world settings, however, 19% of the patients with breast cancer and bone metastases did not receive a BTA until more than 3 months after bone metastases were detected [99], and for prostate cancer this proportion was even higher (28%) [100]. The main reasons for delaying treatment were a very recent diagnosis [99] and a perceived low risk of bone complications [100].

Palliative radiotherapy may suffice in patients with newly diagnosed bone metastases who have only a small number of non-lytic lesions in low-risk regions; however, there is no guidance regarding which patients may be considered low risk for SREs or bone pain. Moreover, data show that even patients with mild or no pain at treatment initiation can benefit from bone-targeted therapy [20].

ESMO guidelines for the management of metastatic bone pain are presented in Fig. 2 [44]. Based on their efficacy in delaying SREs, ESMO recommends BTAs in all patients with bone metastases, regardless of whether bone pain is present [30]. Early use of BTAs in patients with no pain or only mild pain can delay pain progression and improve QoL [19,101]. For patients already experiencing bone pain, BTAs may offer additional pain relief to that provided by opioids and radiotherapy. BTAs may be particularly effective for patients with widespread pain. The ESMO guidelines do not offer clear recommendations regarding selection of BTAs [30] but acknowledge the potential implications of the mechanism of action of denosumab. As a circulating antibody, denosumab may reach more sites in the bone than bisphosphonates, which have a strong affinity for hydroxyapatite and sites of active bone turnover, potentially reducing their distribution across the whole skeleton [30].

The optimal duration of BTA therapy is not completely defined by ESMO, but continuous treatment is recommended in patients with progression of underlying bone metastases, a recent SRE and/or elevated bone resorption markers [30]. In real-world practice, unplanned discontinuations may occur owing to hypocalcaemia, risk and presence of osteonecrosis of the jaw and primary tumour progression [99,100]. A considerable proportion of patients may also stop receiving BTAs owing to completion of planned treatment [99,100]; indeed, in a large patient chart survey, the most common reason for discontinuation was reaching the

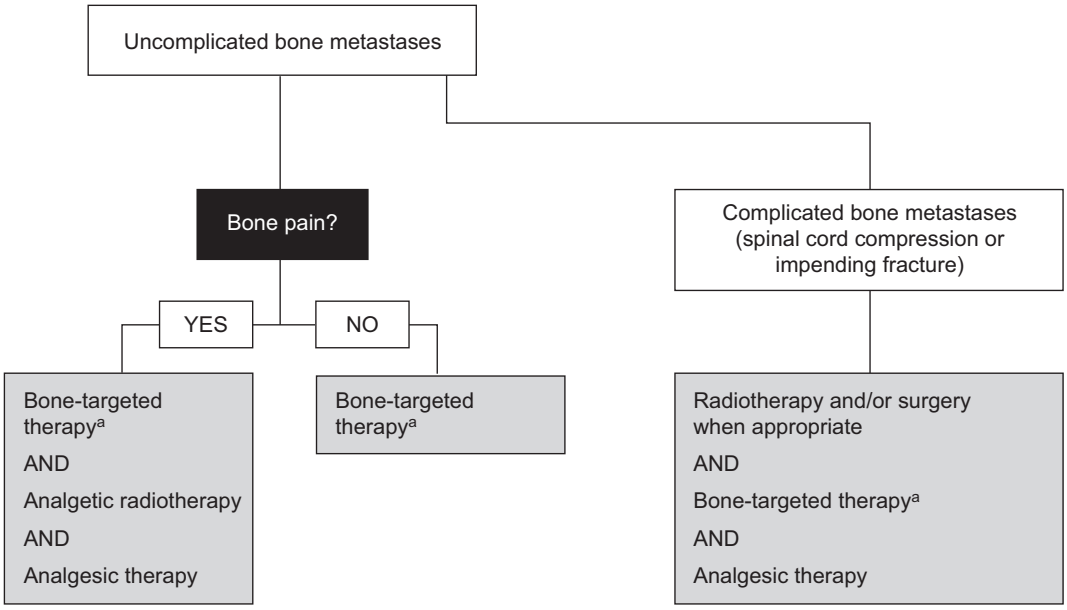


Fig. 2. European Society for Medical Oncology guidelines for the management of metastatic bone pain [44]. [a]Product-specific guidance should be adhered to with regards to calcium and vitamin D supplementation, as well as preventive dental screening.

end of planned treatment [102]. This implies that, despite the lack of guidance, physicians tend to determine treatment course length when prescribing BTAs. When evaluating the benefit–risk profile of long-term BTA therapy, the potential for SRE prevention, the patient's renal function and risk of osteonecrosis of the jaw should be taken into account.

To address concerns about prolonged monthly administration of bisphosphonates, several studies have examined, or are examining, the impact of reducing the dosing frequency from every 4 weeks to every 12 weeks [103–106]. Although the completed studies have confirmed the feasibility of a lower dosing frequency, suggesting the 12-week regimen may become a future standard of care, pain and QoL outcomes were not assessed in all studies. Thus, further trials are needed to confirm whether or not a reduced dosing frequency affects bone-pain-related outcomes.

## 7. Developments in metastatic bone pain therapy

### 7.1. Enzalutamide

Enzalutamide is an androgen-receptor inhibitor approved for patients with metastatic prostate cancer. In the large, phase 3 AFFIRM trial, enzalutamide significantly prolonged survival in individuals with metastatic castration-resistant prostate cancer (mCRPC) who had progressed following docetaxel treatment [107]. Enzalutamide also prolonged time to first SRE versus placebo (median, 16.7 versus 13.3 months, respectively; HR, 0.69; $p < 0.001$). Furthermore, fewer patients reported pain progression at week 13 (28% versus 39%, respectively; $p = 0.0018$) and more patients reported an overall improvement in QoL (42% versus 15%, respectively; $p < 0.0001$) [108]. However, no studies have compared the efficacy of enzalutamide against an active comparator.

Enzalutamide significantly improved overall survival and radiographic progression-free survival in men with chemotherapy-naive mCRPC in an interim analysis of the PREVAIL trial [109]. Compared with placebo, median time to QoL deterioration was significantly longer with enzalutamide, and significantly more patients reported clinically meaningful improvements in various measures of QoL (all $p < 0.0001$) [110]. At data cut-off, fewer patients receiving enzalutamide had experienced an SRE compared with those receiving placebo (32% versus 37%, respectively), and median time to first SRE was 31.1 and 31.3 months, respectively (HR, 0.72; $p < 0.0001$) [110].

### 7.2. Abiraterone acetate

Abiraterone acetate is an androgen synthesis inhibitor indicated for use in combination with prednisone in patients with mCRPC. In the phase 3 COU-AA-301 study in patients previously treated for mCRPC [111,112], prednisone plus abiraterone offered significant benefits over prednisone alone in terms of pain relief and delayed pain progression (both $p < 0.01$) [112]. In addition, 48% of patients reported significant improvements in QoL with abiraterone, compared with 32% in the prednisone arm ($p < 0.0001$) [111]. Similarly, in COU-AA-302 (treatment-naïve patients), abiraterone plus prednisone significantly delayed time to opiate use ($p < 0.001$) and time to pain progression ($p = 0.05$), and increased median time to functional status deterioration ($p = 0.003$), compared with prednisone alone [113].

### 7.3. Combination therapies

A *post hoc* analysis of the abiraterone COU-AA-302 study compared patient outcomes with or without concomitant BTA therapy [114]. Approximately one-third of all patients were receiving concomitant BTAs, with zoledronic acid prescribed the most often (93%), followed by denosumab (6%), then other BTAs (1%). BTAs added to abiraterone or prednisone promoted significant improvements to overall survival (risk reduction 25%; $p = 0.012$) and reduced the time to performance score deterioration (25%; $p < 0.001$) and time to opiate use (20%; $p = 0.036$) [114].

A number of analyses have also suggested a positive interaction between BTAs and radium-223, including the ALSYMPCA study, in which 41% of patients with mCRPC were receiving bisphosphonates at study entry [78]. There was a clear delay in development of symptomatic skeletal events with radium-223 plus bisphosphonates, compared with placebo (19.6 versus 10.2 months; HR, 0.49; $p = 0.00048$), but no significant effect in patients receiving radium-223 alone (11.8 versus 8.4 months; HR, 0.77; $p = 0.07$) [78]. *Post hoc* analyses of a prospective study of radium-223 in patients with metastatic prostate cancer showed that concomitant use of novel endocrine agents (abiraterone or enzalutamide) or denosumab prolonged overall survival compared with radium-223 alone [115]. These data have encouraged researchers to initiate investigations into the use of radium-223 combined with hormone therapy and denosumab in patients with stage IV metastatic breast cancer [116].

## 8. Conclusions

Metastatic bone pain has a marked negative impact on patients' QoL, and despite numerous therapeutic options, remains under-treated. Treatment should combine anti-tumour therapy with BTAs and analgesia. Owing to their demonstrated efficacy in improving pain, QoL and skeletal outcomes, BTAs should be initiated as soon as bone metastases are diagnosed, and treatment duration tailored to each patient's benefit–risk profile. As part of

a holistic approach to pain management, the complementary short- and long-term effects of these agents should be harnessed to help to optimise the quality of these patients' lives.

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## Conflict of interest

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