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REVIEW ARTICLE

Impact of skeletal complications on patients' quality of life, mobility, and functional independence

Luis Costa · Xavier Badia · Edward Chow · Allan Lipton · Andrew Wardley

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Abstract
Introduction Skeletal-related events (SREs) from malignant bone disease cause considerable morbidity and can dramatically reduce patients' quality of life.
Discussion Pathologic fractures often require surgical intervention and palliative radiotherapy. Thus, patients suffer impaired mobility, loss of functional independence, and diminished health-related quality of life (HRQOL). Bisphosphonates can delay the onset and reduce the incidence of SREs and have become the standard of care for the treatment of malignant bone disease; however, minimal information on the effects of bisphosphonate treatment on HRQOL is available. Targeted HRQOL assessments for patients with malignant bone disease are currently under development and are discussed herein.

Keywords Bone metastases · Bone pain · Breast cancer · Prostate cancer · Zoledronic acid

L. Costa (✉)
Instituto de Medicina Molecular-Lisboa,
Servico de Oncologia, Hospital de Santa Maria,
Av Professor Egaz Moniz,
Lisbon 1649-039, Portugal
e-mail: luiscosta.p@netcabo.pt

X. Badia
Health Economics and Outcomes Research,
Doctor Ferran 25, 2°,
Barcelona 08034, Spain

E. Chow
Radiation Oncology,
Toronto-Sunnybrook Regional Cancer Centre,
2075 Bayview Ave.,
Toronto, ON M4N 3M5, Canada

A. Lipton
Milton S. Hershey Medical Center, Pennsylvania State University,
500 University Drive,
Hershey, PA 17033, USA

A. Wardley
Cancer Research Department of Medical Oncology,
Christie Hospital NHS Foundation Trust,
550 Wilmslow Road,
Manchester M20 4BX, UK

Introduction

Approximately 1.4 million new cancer cases and 560,000 deaths from cancer are expected in the United States in 2006 [43]. Bone is the most common distant site for tumor metastasis, and bone metastases are especially common in patients with breast or prostate cancer, accounting for an estimated 80% of all cases of metastatic bone disease [21]. Between 65% to 75% of patients with advanced breast cancer or prostate cancer and 30% to 40% of patients with advanced lung cancer experience bone metastases [20]. Metastatic bone lesions weaken the structural integrity of the bone, leading to an increase in the risk for skeletal-related events (SREs) such as pathologic fracture, spinal cord compression, hypercalcemia of malignancy, and severe bone pain requiring palliative radiotherapy or surgery to bone [21].

Among patients with bone metastases who were randomized to the placebo arm in clinical trials of pamidronate and zoledronic acid (bisphosphonates), approximately 50% to 70% of patients experienced at least one SRE during the 2-year study period (Fig. 1) [8, 48, 57, 58, 60]. The proportion of patients with an SRE ranged from 49% in patients with prostate cancer [60], to 68% of patients with breast cancer over 2 years of follow-up [48]. Moreover, patients with bone metastasis often experience multiple

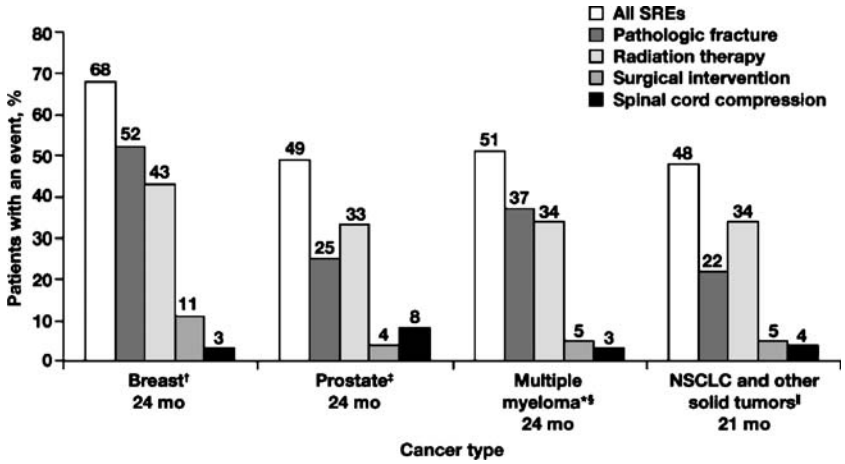

Fig. 1 Skeletal-related events (SREs) are prevalent in the absence of bisphosphonate therapy. Shown are the proportions of patients receiving placebo who experienced any SRE or a given class of SRE as observed in four different clinical studies. Each study examined bone metastases originating from a different primary tumor site (study length indicated). *NSCLC* Non-small cell lung cancer. *21-month data except for surgical intervention and spinal compression, for which only 9-month data are available; data from *dagger sign* Lipton et al. [48]; *double dagger* Saad et al [58]; *section sign* Berenson et al. [8]; and *parallel sign* Rosen et al [57]

SREs that typically occur at a more rapid rate following the initial event [22].

The available literature suggests that SREs are generally associated with decreases in health-related quality of life (HRQOL). Patients with breast cancer who experienced an SRE had worse HRQOL in physical and functional well-being compared with patients without a previous SRE [76]. Evidence from studies in men with prostate cancer suggests that pathologic fractures are associated with a significant decrease in functional well-being [77]. Patients with SREs were less able to perform basic functions of daily living, and patients experienced increased feelings of depression and anxiety [77]. However, clinical trial assessments to date have focused more on the frequency of SREs and less on other outcomes that are important to patients, such as their loss of mobility, functional independence, and HRQOL. The lack of focus on patient-reported outcomes for patients with metastatic bone disease is manifested in the lack of standardized methods to assess HRQOL issues for these patients. Consequently, there are limited data on the direct consequences of SREs on HRQOL.

In any context, HRQOL is challenging to quantify because assessment is subjective and multidimensional. In addition, HRQOL instruments have not been specifically tailored to the unique difficulties of patients with bone metastases. Although a number of methods to assess HRQOL are available (e.g., Spitzer QL-Index [64], European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 [EORTC QLQ-C30] [1], Functional Assessment of Cancer Therapy—General [FACT-G] scale [15], Brief Pain Inventory [BPI] [17], Visual Analogue Scale [VAS] [23], and the EQ-5D [31]), these instruments do not directly assess the unique combination of bone complications and pain that affects patients with malignant bone disease. To address this issue, the Bone Metastases Quality-of-Life questionnaire (BOMET-QoL) and the BM-22 module to the EORTC QLQ-C30 have recently been designed [2, 34, 66]. The BOMET-QoL was intended to be a simple, self-administered questionnaire for use in clinical research and to monitor patient HRQOL status including mobility and functional impairment. The primary focus of the EORTC QLQ-BM22 is clinical trial assessment [34].

This review briefly describes the most recent treatment options available for metastatic bone disease with a particular focus on bisphosphonates. Bisphosphonates offer the possibility of treating the underlying pathophysiology of malignant bone disease, thereby preventing and delaying SREs and controlling bone pain. The main focus of this review is the influence of skeletal complications on HRQOL, mobility, and functional independence of the patient. Information obtained from observational and controlled clinical trials will be discussed.

Treatment options

Supportive care for patients with bone metastases focuses on palliation of pain, preventing or delaying skeletal complications, and repairing or stabilizing the bone [47]. Analgesics can be administered to palliate the pain, and orthopedic surgery can repair or prevent pathologic fractures or spinal cord compression. Bone-directed therapies provide palliative as well as therapeutic benefits. For example, radiotherapy (both external-beam and radiopharmaceuticals) can treat existing bone lesions and palliate pain. Chemotherapy may delay disease progression, and slowing disease progression may delay the onset of bone

pain and SREs, but the latter has not been formally demonstrated in controlled clinical trials.

Bisphosphonates target the underlying cause of skeletal morbidity by binding to the bone surface and acting as potent inhibitors of osteoclast-mediated bone resorption. The current standard treatment for patients with bone lesions from advanced cancer is to initiate intravenous (IV) bisphosphonate therapy at the first signs of bone lesions [4, 7, 39]. In particular, the American Society of Clinical Oncology (ASCO) guidelines for breast cancer now suggest that zoledronic acid or pamidronate should be used concurrently with chemotherapy and/or hormonal therapy to prevent SREs, reduce bone pain, and improve patient HRQOL [39]. Although bisphosphonates have been shown to delay the onset of and prevent SREs, it has been a challenge to accurately quantify their palliative and HRQOL benefits, in part because of the underdevelopment of suitable metrics targeted to patients with bone metastases. In contrast with other therapies for treatment of metastatic bone disease, bisphosphonates have been shown in randomized, placebo-controlled trials to both reduce the occurrence and delay the onset of SREs [8, 48, 57, 60]. Additionally, bisphosphonates have been shown to prevent the increase in pain that accompanies the progression of malignant bone disease [48, 57].

Current assessment tools

The preservation of functional independence—specifically, the ability to remain mobile and maintain an independent life—is now recognized as a strong predictor of treatment outcomes [13]. It is therefore critical to examine the current tools used to assess functional status and to select the most appropriate metrics for patients with bone metastases. Among the most common instruments previously used in the field, the BPI [17], a general pain instrument with a scale of 1 to 10, includes some questions regarding functional independence such as the ability to walk and to perform work. The EORTC QLQ-C30 [1] and FACT-G [15] include subscales that focus on physical well-being and the ability to perform everyday tasks, yielding useful data.

Bone pain

Bone pain is the most frequent symptom of bone metastases in patients with advanced cancer, and effective pain management is critical to improving functional status and HRQOL [20]. Over the past few decades, systemic cytotoxic therapies have demonstrated improvements in pain and quality of life among patients with advanced cancers in many trials [3, 50, 63]. In a recent clinical trial in patients with advanced prostate cancer (N=674), mitoxantrone plus prednisone or docetaxel plus estramustine both palliated pain to a similar extent (24% and 21% of patients in each group, respectively) [9]. In another study, in patients with advanced solid tumors (N=146), chemotherapy produced pain relief compared with baseline based on questions from the EORTC QLQ-C30 [5]. It is unclear, however, whether patients can receive pain palliation with these agents in the absence of a clinical response or stable disease.

The International Bone Metastases Consensus Working Party has recommended the development of an HRQOL instrument for patients with bone metastases [16], and some trials have employed the EORTC QLQ-C30. In general, a tailored HRQOL assessment has not been widely used for this patient population. However, the effect of pain on HRQOL is well documented for patients with postmenopausal osteoporosis. In one study using an osteoporosis-specific HRQOL instrument, chronic pain was the most frequently reported undesirable consequence of osteoporotic disease (66% of women with fractures and 40% of women without fractures) [10]. These patients also reported impairment of physical ability and reduced social activity. In the community elderly population, 20% to 50% experience pain, and the increased incidence of unrelieved pain has been shown to correlate with a decrease in mobility and functional status [6]. Because pain assessment has been an endpoint in many clinical trials examining the use of bisphosphonates, the general correlation between incidence of pain and decrease in HRQOL suggests that bone pain metrics may be used as a surrogate for HRQOL in patients with bone metastases [24]. The most commonly used pain assessments in the bisphosphonate trials were the BPI and VAS. Summaries of the clinical data on the palliative effects of four widely used bisphosphonates are presented below.

Clodronate

A review of early placebo-controlled trials of oral clodronate suggested that this agent possesses a moderate analgesic effect at a dosage of 1,600 mg daily for bone lesions originating from a variety of primary tumors [32], but that increased dosages provided no additional pain control [28, 52]. For example, oral clodronate administered at 1,600 mg daily in combination with standard chemotherapy or hormonal therapy provided significant pain palliation (P=.01) and a reduction in the use of analgesics (P=.02) compared with placebo in 144 patients with breast cancer [70]. In a similar placebo-controlled trial in 209 patients with hormone-refractory prostate cancer, IV clodronate administered at 1,500 mg every 3 weeks did not significantly reduce pain intensity or analgesic consumption

[29]. Several uncontrolled trials of clodronate have also reported reductions from baseline pain scores [36, 38, 53, 56, 61]. Although open-label clinical trials assessing pain response must be interpreted with caution, these studies involving primarily prostate cancer patients suggest that clodronate may provide a palliative benefit [36, 38, 53, 56, 61]. However, in comparison with pamidronate 90 mg over a 3-month period in patients with malignant bone disease, clodronate was not as effective in reducing bone pain [42].

Ibandronate

The palliative effects of both IV and oral ibandronate have been examined in several clinical trials in patients with bone metastases from breast cancer [11, 12]. When ibandronate was administered orally (50 mg daily), patients reported reductions in bone pain scores below baseline; these benefits were maintained during the 96-week study period (P=.001 versus placebo by study end) [11]. Analgesic use increased in the ibandronate group but to a lesser extent than in the placebo group (P=.019) [11]. Additionally, in patients with breast cancer who had progressive bone disease or SREs despite clodronate or pamidronate treatment (N=30), oral ibandronate (50 mg daily) provided significant improvement in pain control versus baseline within 12 weeks (P=.028) [18]. Intravenous ibandronate (6 mg every 3 to 4 weeks) has also been shown to significantly reduce pain scores from baseline and compared with placebo [12]. Pain scores remained below baseline throughout the study in the 6-mg ibandronate arm [12]. In contrast, 2 mg IV ibandronate was not shown to be effective either in breast cancer or multiple myeloma [12, 51]. Placebo-controlled clinical trial results in patients with prostate cancer are not yet available. Smaller open-label trials, however, have shown that ibandronate provided significant levels of pain relief in combination with radiotherapy [71, 72] and in a variety of tumor types including breast, prostate, and lung [49, 71]. Pain response has also been evaluated with intensive ibandronate treatment (6 mg via 1-h infusion each day for 3 days) followed by treatment every 4 weeks in patients with bone metastases from prostate cancer or other urologic cancers [35, 37]. Within 3 days, more than 80% of all patients had at least a three-point reduction in their pain score based on a ten-point VAS. Moreover, an ongoing multicenter randomized trial of single-dose radiotherapy compared with ibandronate for localized pain from bone metastases (RIB trial) will evaluate pain changes at 4 weeks. This trial had enrolled 353 patients (78% with prostate cancer) as of April 2007 [14, 41]. Nevertheless, evidence of a palliative effect in placebo-controlled clinical trials has not been established in patients with bone metastases from tumor types other than breast.

Pamidronate

Pamidronate 90 mg administered every 3 to 4 weeks was shown to be effective for the palliation of bone pain in women with bone metastases from breast cancer in two similarly designed studies (N=382 and N=372) [40, 67]. Baseline bone pain scores increased in both studies; however, the increase was significantly less in the pamidronate groups compared with the placebo groups at 24 months (P=.043 [40] and P=.007 [67]). The data from these two studies were pooled to create a more robust assessment of pamidronate efficacy in breast cancer [48]. At study entry, approximately 79% of patients in each treatment group had pain. Of these patients, a significantly lower percentage in the pamidronate group (40%) experienced an increase in pain compared with the placebo group (52%; P=.003) at 24 months [48]. However, placebo-controlled studies in men with bone metastases from prostate cancer (N=138 and N=240) have shown that pamidronate 90 mg does not produce a sustained significant difference in bone pain scores or analgesic use [62].

Zoledronic acid

To date, randomized, placebo-controlled, clinical trials examining the therapeutic effects of zoledronic acid in patients with bone metastases from multiple tumor types have demonstrated significant reductions in pain [45, 59, 60]. In patients with breast cancer, pain scores decreased from baseline at all time points during a 12-month study, and the differences between treatment and placebo were significant at all time points after 2 weeks (P<.05) [45]. Moreover, in patients with breast cancer who had progressive bone disease or SREs despite clodronate or pamidronate treatment (N=31), zoledronic acid provided significant improvement in pain control versus baseline within 8 weeks (P<.001) [19]. In prostate cancer patients, zoledronic acid significantly reduced mean pain scores compared with placebo at 15, 18, 21, and 24 months [59, 60]. Among patients with pain at study entry, BPI scores declined below baseline and remained below baseline for more than 9 months in the zoledronic acid arm, compared with a steady increase in the placebo arm (Fig. 2) [26]. These data demonstrate the analgesic effect of zoledronic acid in this setting. Consistent and durable reductions in pain scores have also been observed in open-label, single-arm studies of zoledronic acid in patients with bone lesions from breast cancer, prostate cancer, or multiple myeloma [27, 33, 55, 65, 74, 75]. In one open-label study, patients with breast or prostate cancer receiving zoledronic acid experienced a statistically significant decrease in their level of bone pain at rest as well as a decrease in their incident pain [55]. Taken together, these findings suggest that zoledronic acid

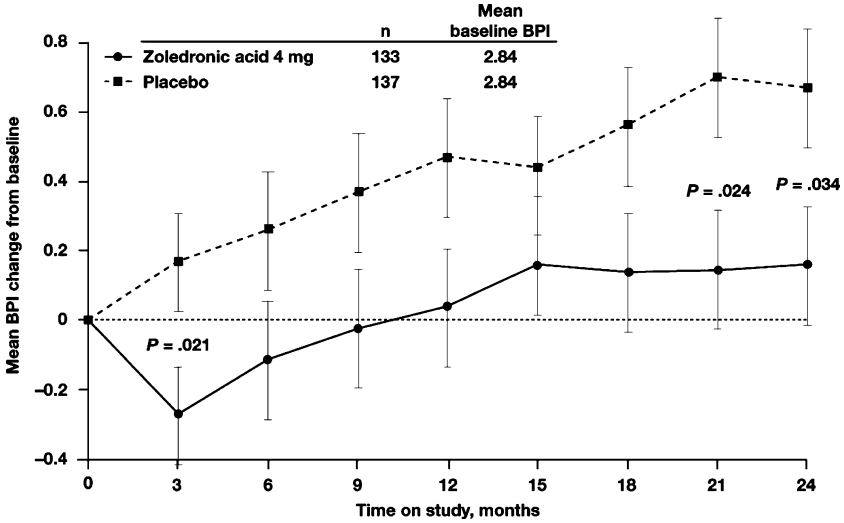

Fig. 2 Mean change from baseline composite Brief Pain Inventory (BPI) score in hormone-refractory prostate cancer patients with pain at baseline, by treatment group. Horizontal lines represent the standard error. Adapted with permission from Eastham et al. [26]

provides pain benefits for patients with bone metastases from a wide variety of tumor types including breast cancer, prostate cancer, lung cancer, and multiple myeloma.

Health-related quality of life

In general, clinical trials examining the benefits of bisphosphonates in the treatment of bone metastases have not directly assessed HRQOL or have not been able to establish significant treatment-related changes in HRQOL. However, Weinfurt et al. [77] were able to show that SREs are associated with decreases in HRQOL in their analysis of a large, phase III, placebo-controlled clinical trial of zoledronic acid in prostate cancer patients [59]. Their analysis compared patients' HRQOL status before their first SRE (the proper baseline) with their HRQOL scores after they experienced an SRE. When these investigators focused on patients for whom HRQOL data were available before the first SRE, and then compared the pre-SRE and post-SRE HRQOL scores, they demonstrated that SREs significantly affect HRQOL scores (Fig. 3) [44, 77]. The total FACT-G scores and FACT-G physical, functional, and emotional subscores were typically lower post-SRE compared with pre-SRE, and the mean scores were significantly lower for patients who experienced pathologic fracture or required radiation to bone. Therefore, interventions that reduce the occurrence of these SREs should improve HRQOL.

Wardley et al. recently conducted a study specifically designed to examine HRQOL issues [75]. The BPI and EORTC QLQ-C30 assessments were primary measures of the endpoint and were used to determine the potential benefits of zoledronic acid therapy in patients with bone metastases from breast cancer. The analysis of BPI scores revealed that zoledronic acid therapy improved scores from baseline for composite pain, worst pain, and average pain; zoledronic acid also significantly reduced the overall extent to which pain interfered with general activity or walking ($P \leq .05$; Fig. 4) [75]. The overall reductions from baseline pain were found to be significant for all subscales except composite pain. This study provides additional evidence that zoledronic acid had a positive effect on HRQOL. Significant improvements in global health and in physical, emotional, and social functioning, as assessed by the EORTC QLQ-C30, were also observed (Fig. 5) [75]. The observed improvements suggest that zoledronic acid may help to maintain mobility and functional independence.

Mobility and functional independence

Wardley et al. demonstrated that physical, emotional, and social functioning subscales of the EORTC QLQ-C30 significantly improved from baseline in patients with bone metastases treated with zoledronic acid ($P<.05$; Fig. 5) [75]. In a similar vein, Weinfurt et al. demonstrated that when the initial SRE experienced by a patient was radiation to bone or pathologic fracture, physical, functional, and emotional well-being subscales of the FACT-G were significantly reduced (Fig. 3) [44, 77]. Pamidronate 90 mg has been shown to ameliorate decreasing quality of life (Spitzer index) versus placebo in an analysis of two trials in metastatic breast cancer ($N=751$; $P=.088$) [48]. A smaller trial in patients with bone metastases from solid tumors ($N=52$) showed that pamidronate 120 mg significantly improved HRQOL from baseline (Rotterdam Symptom Checklist), primarily because of increases in the functional domain ($P<.05$) [73].

Intravenous ibandronate 6 mg has also shown significant improvements compared with placebo in the physical,

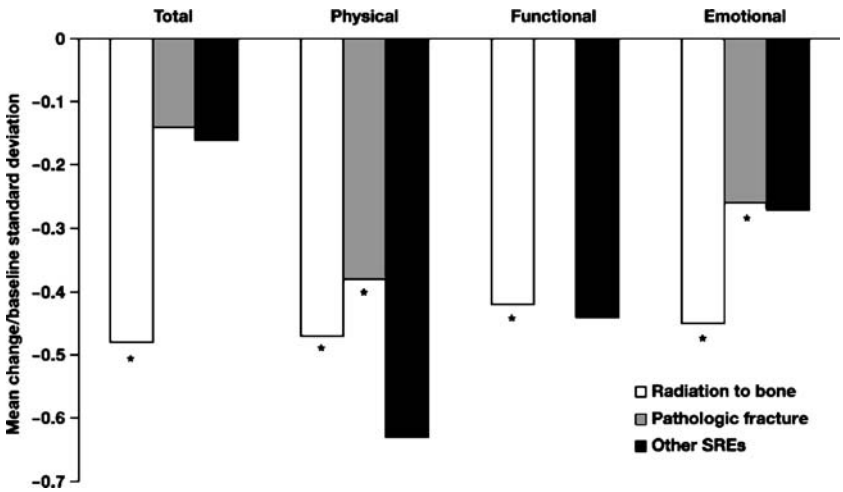

Fig. 3 Changes in Functional Assessment of Cancer Therapy-General (FACT-G) scores indicate that skeletal complications reduce health-related quality of life in patients with prostate cancer. The changes in FACT-G overall scores or subdomain scores per standard deviation unit are indicated for three categories of skeletal-related events (SREs). *asterisk* $P<.05$. Data from Weinfurt et al. [77]. Reprinted with permission from Elsevier from [44]

emotional, and social functioning subscales and the global health score of the EORTC QLQ-C30 ($P<.05$ for all) in patients with bone metastases from breast cancer ($N=466$) [25]. In a smaller open-label trial among patients with bone metastases from prostate cancer treated with IV ibandronate ($N=25$), the mean baseline Karnofsky index of 55% increased to 80%, although the time point for the improved index was not noted [35]. The investigators attributed the improvement in Karnofsky index to increased patient mobility. Although the benefits of oral ibandronate 50 mg daily did not reach significance in separate trials in patients with bone metastases from breast cancer, a combined analysis of the two trials ($N=564$) found significantly improved quality of life compared with placebo as measured by the EORTC QLQ-C30 ($P=.032$); however, deterioration was observed in both groups during the trials [11].

These studies and available data from elderly and osteoporotic populations suggest that fractures decrease mobility and functional independence [46, 68]. In addition, patients with bone metastases may potentially experience reduced survival, as has been already shown for patients with hip fractures [54, 69]. Given that bisphosphonates are known to reduce pain [75] and prevent fractures [57, 59], it is likely that treatment with bisphosphonates will have a positive effect on mobility and functional independence.

Emerging assessment tools

Analyses that more accurately capture the effect of bisphosphonates on HRQOL in patients with bone metastases based on existing methods have begun to emerge, and tailored methods to assess HRQOL in patients with bone

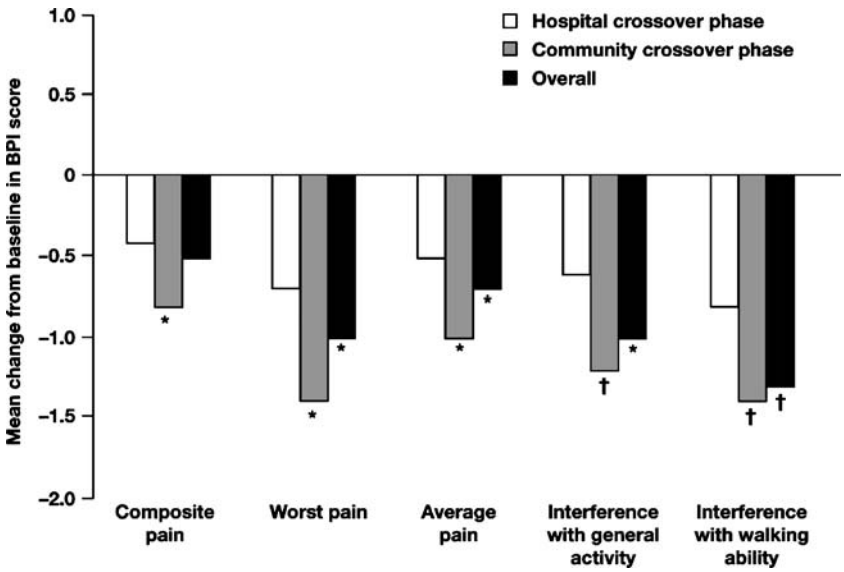

Fig. 4 Zoledronic acid significantly improved Brief Pain Inventory (BPI) pain scores, assessed at baseline, at the end of each cycle, and at the final visit (negative changes in BPI score indicate improvement). The histogram indicates mean change from baseline BPI scores as reported during the hospital crossover phase, community crossover phase, and overall score (score reported at final visit after nine infusions). *asterisk* $P<.05$; *dagger* $P<.005$ compared with baseline values. Reprinted by permission from Macmillan Publishers Ltd from [75], copyright 2005

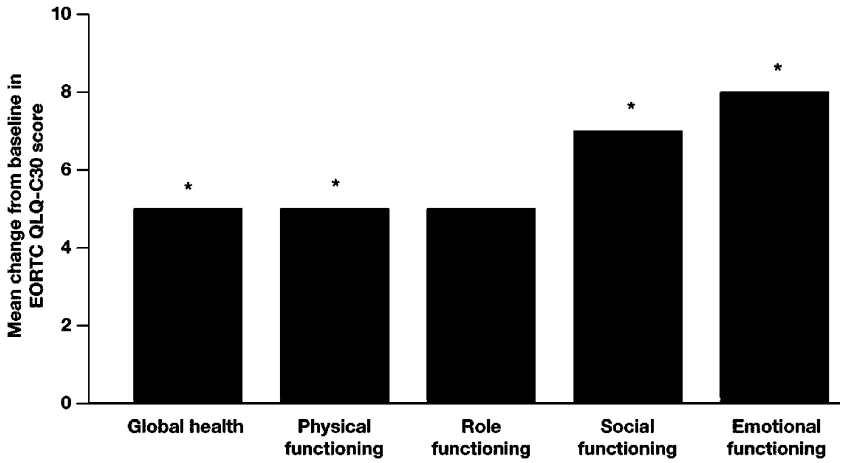

Fig. 5 Zoledronic acid significantly improved European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30) scores. Histogram indicates overall mean change from baseline quality-of-life scores as reported at the final visit after nine infusions. *asterisk* $P<.05$ compared with baseline values. Reprinted by permission from Macmillan Publishers Ltd from [75], copyright 2005

metastases are now being developed. The BOMET-QoL is the first bone metastases-specific assessment of HRQOL, and the validation study in patients with bone lesions from lung cancer, prostate cancer, breast cancer, or multiple myeloma has shown that statistically significant differences are not observed between key demographic groups (e.g., age, sex, and education) [66]. The BOMET-QoL scores correlated with the presence and duration of pain crises, with the Pain Management Index, and—to a certain extent—with Eastern Cooperative Oncology Group (ECOG) performance status. Furthermore, BOMET-QoL scores appear to be sensitive to changes in HRQOL status and ECOG performance status, but appear to be more sensitive to changes in the midline (Fig. 6) [66]. Scores from the BOMET-QoL assessment had good reliability as measured by internal consistency and test–retest criteria [66]. The final validated version, the BOMET-QoL-10, consists of 10 questions scored on a 5-point scale (Table 1) [2, 66]. For patients with bone metastases, BOMET-QoL-10 questions are intended to determine whether the patient experiences pain typical of the disease (intense, constant) and whether pain is localized to common metastatic sites [2, 66]. Questions designed to assess the more common dimensions of HRQOL are also included. For patients with bone metastases, the BOMET-QoL-10 assessment may prove to be more informative regarding mobility and functional independence compared with more traditional HRQOL assessments. The BOMET-QoL-10 takes approximately 5 min to administer and is suitable for use in clinical practice and in clinical trials. By focusing on the specific deficits of these patients, a more accurate picture of the effect of bisphosphonate therapies may be forthcoming.

A bone metastases-specific HRQOL module, the EORTC QLQ-BM22, is under development to supplement the EORTC QLQ-C30 [34], and consists of 22 questions on a four-point scale (Table 2). This assessment is designed primarily for use in clinical trials and has a somewhat different focus than the BOMET-QoL-10. Whereas the BOMET-QoL-10 is designed to assess pain and HRQOL deficits typical of metastatic bone disease, the EORTC

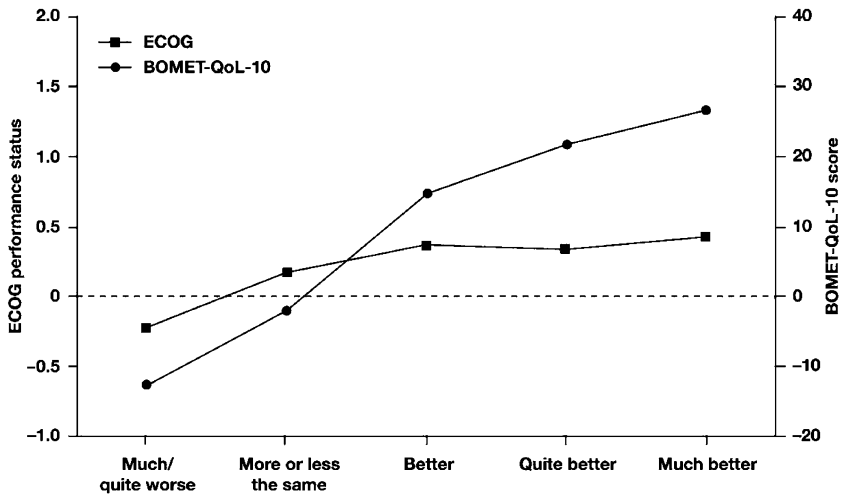

Fig. 6 Correlation of changes between the Bone Metastases Quality-of-Life questionnaire (BOMET-QoL)-10 score and Eastern Cooperative Oncology Group (ECOG) performance status. Changes were recorded over a 6-month period in patients with bone lesions from multiple myeloma, or breast, prostate, or lung cancer. Adapted with permission from [66]

Table 1 BOMET-Qol-10 questionnaire

BOMET-Qol-10 questionnaire (always = 0; never = 4)
1. I feel tired.
2. I find it difficult to get out of bed.
3. I have a feeling of general discomfort.
4. I feel depressed and feel like crying.
5. I have little interest in going out of the house.
6. I avoid doing activities with my family.
7. I feel pain in certain parts of my body, such as my back, legs, hips..., which affects my life.
8. I'm in constant pain, which affects my life.
9. I have an intense pain that constantly bothers me.
10. The pain prevents me from enjoying life like before.

Questions refer to patient experience during the previous week. Adapted with permission from [66].
BOMET-QoL Bone Metastases Quality-of-Life questionnaire.

QLQ-BM22 also assesses loss of mobility, side effects, and complications of treatment, as well as patient concerns regarding dependency. This effort is under the sponsorship of EORTC [30, 34] and has recently moved to phase III development to expand module validation to different countries and languages. A long-term goal of this development effort is to reduce the number of questions to create a more concise version of the instrument suitable for clinical practice and for clinical trials.

The EORTC QLQ-BM22 assessment and (to some degree) the BOMET-QoL-10 assessment address patients' ability to function independently in daily life. These more tailored assessments offer insight into the effects of SREs from bone metastases on patients' well-being apart from the effects of the primary disease.

Conclusions

Bisphosphonates are central to the treatment of patients with bone metastases; however, the true benefit of bisphosphonates in terms of HRQOL is not yet completely known. Most trials have focused on SREs and have not adequately assessed the HRQOL issues that are important to patients. For example, bone pain is an important component of HRQOL in patients with malignant bone disease and has been shown to correlate with functional status. Skeletal-related events also lead to a decline in the

Table 2 EORTC QLQ-BM22 questionnaire

Questions	Not at all	A little	Quite a bit	Very much
During the past week have you had pain in any of the following parts of your body:				
1. In your back?	1	2	3	4
2. In your leg(s) or hip(s)?	1	2	3	4
3. In your arm(s) or shoulder(s)?	1	2	3	4
4. In your chest or ribs?	1	2	3	4
5. In your buttock(s)?	1	2	3	4
During the past week:				
6. Have you had constant pain?	1	2	3	4
7. Have you had intermittent pain?	1	2	3	4
8. Have you had pain not relieved by pain medications?	1	2	3	4
9. Have you had pain while sitting or lying down?	1	2	3	4
10. Have you had pain when trying to stand up?	1	2	3	4
11. Have you had pain while walking?	1	2	3	4
12. Have you had pain with activities such as bending or climbing stairs?	1	2	3	4
13. Have you had pain with strenuous activity (e.g., exercise, lifting)?	1	2	3	4
14. Has pain interfered with your sleeping at night?	1	2	3	4
15. Have you had to modify your daily activities because of your illness?	1	2	3	4
16. Have you felt isolated from those close to you (e.g., family, friends)?	1	2	3	4
17. Have you been thinking about your illness?	1	2	3	4
18. Have you worried about loss of mobility because of your illness?	1	2	3	4
19. Have you worried about becoming dependent on others because of your illness?	1	2	3	4
20. Have you worried about your health in the future?	1	2	3	4
21. Have you felt hopeful your pain will get better?	1	2	3	4
22. Have you felt positive about your health?	1	2	3	4

Instructions: patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you. *EORTC QLQ* European Organisation for Research and Treatment of Cancer Quality of Life Core questionnaire. Adapted with permission from Drs. Edward Chow, Colin Johnson, and Andrew Bottomley (personal communication).

ability of patients to perform daily activities. Therefore, given that bisphosphonates decrease the occurrence of SREs and reduce bone pain, they should also decrease the negative effects of SREs and pain on patients' HRQOL. Recent data have begun to show the HRQOL benefits of bisphosphonates. Health-related quality-of-life instruments designed specifically for patients with bone metastases are needed to more accurately assess the true impact of malignant bone disease and to optimize patient care. Several such assessments are under development and are being integrated into clinical trials. It is of critical importance to educate those involved in community practice of the availability of tools and information they need to accurately diagnose and treat bone metastases. The ability to proactively address patient mobility, functional independence, and HRQOL concerns will lead to a higher standard of care in the future.

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