

Impact of bisphosphonate therapy on quality of life and costs of care in patients with metastatic bone disease

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ABSTRACT

Bone metastases are a common complication of advanced breast, lung and prostate cancer, as well as being virtually ubiquitous among patients with myeloma. Metastases can cause a number of skeletal-related events (SREs), such as fractures and vertebral compression, which can compromise the patient's mobility, independence and quality of life. Bisphosphonates are medicines with a high affinity for mineralised bone; they inhibit osteoclast-mediated bone resorption, and have been shown to limit or prevent SREs associated with metastatic bone disease (MBD). We reviewed the current literature on the prevalence and impact of bone metastases to characterise the economic repercussions and quality of life (QoL) consequences of SREs and assess the evidence supporting the efficacy of bisphosphonates, their impact on QoL and their cost-effectiveness in preventing and delaying SREs. As few as 30% of those with lung cancer, and as many as 100% of those with multiple myeloma reportedly develop SREs. The longer the patients survive after the diagnosis of cancer, the more likely they are to develop SREs. Of the 39 clinical studies we reviewed, 36 found that bisphosphonate therapy limits or prevents SREs in cancer patients, and recommend bisphosphonate treatment in conjunction with the usual antineoplastic therapy for cancer patients who develop symptomatic MBD. However, there remains some debate regarding which of the bisphosphonates is most beneficial, cost-effectiveness of bisphosphonate therapy, and whether or not to treat cancer patients prophylactically before the development of bone metastases, with the hope of delaying incidents of SREs and preventing subsequent SREs.

KEYWORDS

Metastatic bone disease (MBD), bisphosphonate, skeletal-related event (SRE)

INTRODUCTION

Malignant metastases to the bone are common in patients with breast, lung and prostate cancer, and occur in nearly all patients diagnosed with multiple myeloma. Patients with bone metastases can experience significant skeletal morbidity such as severe bone pain, pathological fractures and surgical interventions to stabilise the fractures, spinal cord compression, and radiation therapy for bone pain or for treatment or prevention of fractures. These clinical consequences or complications of MBD are often called

SREs (Table 1). SREs reduce the quality of life (QoL) for cancer patients and pose a burden on healthcare systems through increased resource utilisation [1, 2].

The contemporary treatment for MBD and associated SREs includes palliative radiotherapy, surgery, analgesics and bisphosphonates. Severe bone pain is the most common SRE and usually requires treatment with analgesics and radiation therapy [3]. During the past few years, numerous clinical trials have shown that bisphosphonate therapy is also effective in reducing bone pain due to metastases, and can reduce the incidence of new SREs, or at least delay their occurrence (Table 2). Bisphosphonates are bone-sparing drugs that act by specifically inhibiting osteoclast-mediated bone resorption thereby preventing bone loss [4]. They prevent bone resorption at sites of bone remodelling and thus help in reducing the incidence of hypercalcaemia of malignancy, bone pain and fractures. By preventing bone resorption and its consequences, bisphosphonates also reduce the need for radiation therapy, surgery and analgesics. Bisphosphonate preparations are available for both oral and intravenous (IV) administration. While oral ingestion might otherwise be considered preferable, this route of administration is associated with gastrointestinal side effects that can be quite uncomfortable. In addition, proper absorption of the oral formulation requires the patient to

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Table 1: Incidence of SREs in patients with malignancies

Primary tumour	Incidence of malignancy: US (estimates for 2007) ^a	Incidence of malignancy: global (estimates for 2002) ^b	Estimated percentage of patients experiencing SREs ^c	Calculated global incidence of SREs	Median survival of patients with bone metastases ^c
Breast	180,510	1,150,000	65-75	747,500-862,500	24 months
Prostate	218,890	679,000	65-75	441,350-509,250	40 months
Lung	213,380	1,350,000	30-40	405,000-540,000	<6 months
Myeloma	19,900	86,000	95-100	81,700-86,000	20 months

Key: ^a: data from American Cancer Society, 2007 [63]; ^b: data from Parkin et al., 2002 [64]; ^c: data from Coleman, 1997 [3]

Table 2: Efficacy of bisphosphonates in the prevention of SREs

Reference	Agents tested	Time to first SRE (respectively)	Study duration
Primary tumour: breast			
[27]	Placebo Oral ibandronate 20 mg Oral ibandronate 50 mg	48 weeks 76 weeks 54 weeks (<i>P</i> = NS)	96 weeks
[28]	Placebo Oral ibandronate 50 mg	64.9 weeks 90.3 weeks (<i>P</i> = NS)	96 weeks
[29]	Placebo IV ibandronate 2 mg IV ibandronate 6 mg	33.1 weeks 44.6 weeks (<i>P</i> = NS) 50.6 weeks (<i>P</i> = 0.018)	24 months
[15]	Placebo Pamidronate 90 mg	7.0 months 13.1 months (<i>P</i> = 0.005)	12 months
[34]	Zoledronic acid 4 mg Pamidronate 90 mg	310 days 174 days (<i>P</i> = 0.013)	12 months
[42]	Placebo Zoledronic acid 4 mg	12 months Median not reached (<i>P</i> = 0.007)	12 months
Primary tumour: prostate			
[9]	Placebo Zoledronic acid 4 mg	321 days 488 days (<i>P</i> = 0.009) 363 days	24 months
Primary tumour: lung			
[30]	Placebo Zoledronic acid 4 mg	155 days 236 days (<i>P</i> = 0.009) 219 days	21 months

Key: NS: not significant

fast, both before and after taking the medicine, and remain upright for a period of time after ingestion. As a result, it has been suggested that patient compliance can be higher with IV bisphosphonates than with oral formulations [5].

Though a number of bisphosphonates exist, the latest generation – and the most widely prescribed – comprises ibandronic acid, pamidronate, zoledronic acid and clodronate. In patients with MBD, these drugs are prescribed to relieve bone pain, treat hypercalcaemia of malignancy, delay and reduce SREs, and thereby improve QoL [4, 6-8]. SREs typically are recurrent over the course of the disease in patients with bone metastases [9]. Bisphosphonate treatment is therefore typically recommended until there is evidence of substantial decline in the patient's health [10]. Clearly, however, bisphosphonate therapy is beneficial for prolonging the period of time the patient is free of SREs.

Despite evidence suggesting positive effects on patient outcomes, the economic benefits of bisphosphonate therapy for patients with cancer remain the source of some debate [1, 4, 6, 11]. This article reviews the current literature on the prevalence and impact of bone metastases in breast, prostate and lung cancer, and multiple myeloma. It discusses the economic repercussions and the impact of SREs on QoL, and reviews the evidence supporting the efficacy of bisphosphonates, their impact on QoL and their cost-effectiveness in preventing and delaying SREs in patients with MBD.

METHODS

A literature search of the PubMed database was conducted for English language articles published between 2000 and 2006 [12]. References were primarily identified using the following search terms: “metastatic bone AND bisphosphonate,” “metastatic bone AND bisphosphonate AND quality of life,” “metastatic bone AND quality of life,” “SRE AND cost,” and “metastatic bone AND cost.” Other publications warranting review were identified from reference citations from the publications identified in these PubMed searches.

RESULTS AND DISCUSSION

Impact of SREs on patients' QoL

SREs are a major cause of morbidity and impairment of QoL for patients with cancer. It has been estimated that 65% to 75% of patients with breast and prostate cancer, 30% to 40% of patients with lung cancer, and 95% to 100% of those with multiple myeloma will experience at least one SRE (Table 1). The actual number of patients requiring treatment for SREs is difficult to estimate because of differences in survival rates and the fact that some patients will experience multiple SREs in a 12-month period [13]. Of all the SREs experienced by patients with MBD, pain is the most common. Bone pain affects two-thirds to three-quarters of symptomatic myeloma, breast, and prostate cancer patients with MBD [14]. Studies in patients with breast cancer found that almost half of patients with MBD experienced severe and/or frequent pain that worsened over time and that such pain was accompanied by declining QoL scores [15-17]. Similarly, patients with prostate cancer and MBD with associated SREs have significantly lower QoL scores compared with the general population, experience pronounced pain and fatigue, and have a general deterioration in their physical and emotional well-being [2, 18].

Economic impact of SREs

Direct costs for lifetime treatment of SREs have been estimated in European and US studies and range from approximately Euros 6,490 to Euros 9,080 (July 2008) [1, 19-22], with the highest costs incurred in breast cancer patients [19] and the lowest costs in prostate cancer patients [20, 21]. Patients experiencing SREs incur higher overall treatment costs than cancer patients without metastatic disease. Such costs include hospital expenses for the management of hypercalcaemia of malignancy, bone surgery and radiotherapy. Patients with SREs also require more outpatient clinic visits, adverse-event management, and use of long-term care resources than cancer patients without SREs [1, 23, 24]. They need more medicines such as antibiotics, haematopoietic factors, anti-emetics

and analgesics. Among the types of services rendered for SRE-related care in the US, hospitalisation accounts for 62% of the estimated total costs, followed by clinic visits (23%), outpatient visits (12%) and miscellaneous costs (3%), such as nursing, pain management and emergency room visits [1]. In the US, most SRE-related costs are incurred within the first two months of the first SRE-related insurance claim [1]. Radiotherapy can account for as much as 60% to 70% of the estimated total costs of treatment of SREs, and this appears to be the case in both Europe and the US [1, 21]. Bone surgery accounts for 21% and fracture management for 15% of the estimated costs [1].

Effect of bisphosphonates on SREs

Bisphosphonate therapy begun early after the diagnosis of cancer can be the most cost-effective way to prevent SREs [1]. While bisphosphonates have not yet been proven to provide a survival advantage to patients with MBD, these drugs can prevent or delay the occurrence of SREs [4, 13, 25]. Several large, phase III clinical studies have demonstrated that prolonged administration of bisphosphonates can delay the time to appearance of SREs by 30% to 40% (Table 2) [26]. In breast cancer patients, oral and IV ibandronic acid, pamidronate and zoledronic acid reduced the proportion of patients with at least one SRE and delayed the occurrence of the first SRE, compared to placebo [14, 27-29]. In prostate and lung cancer patients, zoledronic acid reduced the percentage of patients experiencing at least one SRE and significantly extended the time to first new SRE ($P = 0.009$), compared to placebo (Table 2) [9, 30]. In patients with multiple myeloma, oral clodronate treatment reduced the percentage of patients with new vertebral and non-vertebral fractures, compared to placebo [31, 32]. A Finnish study found that, compared with standard treatment alone, patients with multiple myeloma who also received clodronate experienced a 50% reduction in the rate of progression of osteolytic bone lesions [33]. Treatment with clodronate also prevented the progression of the number of fractures compared to the placebo group. Rosen et al. compared zoledronic acid (4 mg) with pamidronate (90 mg) in patients with metastatic breast disease and found that in patients with at least one osteolytic lesion, the median time to an SRE was significantly longer in the group receiving zoledronic acid than pamidronate (310 days versus 174 days, $P = 0.013$) [34]. Zoledronic acid has also been used to prevent SREs in patients with prostate, lung and other solid cancers, as well as in patients afflicted by multiple myeloma [35-38].

In a recent Cochrane Database review of nine randomised clinical trials of 2,189 women with breast cancer and clinically evident bone metastases, bisphosphonates were

found to reduce the risk of developing an SRE by 17% [25]. Among the nine clinical trials, the risk reduction varied substantially for the available bisphosphonate formulations. The largest risk reduction was 41% and was seen with zoledronic acid therapy at a dose of 4 mg IV. Pamidronate 90 mg IV led to a 33% risk reduction, and ibandronate and clodronate were associated with risk reductions of 18% or less for developing SREs.

Effect of bisphosphonates on QoL

By delaying or preventing SREs, bisphosphonates can be shown to improve a patient's QoL (Table 3). In one placebo-controlled study, ibandronate treatment of patients with MBD led to significant improvement

in QoL as manifested by decreased bone-pain scores and decreased analgesic use [29]. In two randomised, placebo-controlled 96-week studies comparing oral ibandronate with placebo, treatment significantly reduced bone-pain scores, an effect that was sustained until the end of the studies ($P = 0.001$) [39]. Investigators measured QoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–C30 (EORTC QLQ-C30) to demonstrate that patients receiving ibandronate had lower decreases in QoL than patients receiving placebo ($P = 0.032$).

Pamidronate was also shown to improve brief pain inventory (BPI) scores and Eastern Cooperative Oncology

Table 3: Clinical trials investigating the impact of bisphosphonate therapy on quality of life

Reference	Number of patients	Primary malignancy	Bisphosphonate	Duration of study	Effect on quality of life ^a
[29]	466	Breast	Ibandronate	104 wks	<ul style="list-style-type: none"> • Decrease in bone pain • Decrease in analgesic use
[39]	564	Breast	Ibandronate	96 wks	<ul style="list-style-type: none"> • Decrease in bone pain scores • Improvement in EORTC QLQ-C30 scores
[15]	380	Breast	Pamidronate	52 wks	<ul style="list-style-type: none"> • Improved pain scores • Improved ECOG performance scores
[40]	404	Breast	Pamidronate	104 wks	<ul style="list-style-type: none"> • Increased time to progression of pain • Improved WHO Scale performance status
[14]	638	Breast, prostate or multiple myeloma	Zoledronic acid	18-24 wks	<ul style="list-style-type: none"> • Decreased pain on visual analog scale • Improvement in emotional and physical functioning components of FACT-G • No significant change in overall (FACT-G) scores
[42]	228	Breast	Zoledronic acid	52 wks	<ul style="list-style-type: none"> • Improvement in BPI scores
[43]	101	Breast	Zoledronic acid	38 wks	<ul style="list-style-type: none"> • Improvement in BPI scores • Improvement in global health status in the physical, emotional, and social functioning domains
[17]	1124	Breast	Zoledronic acid or pamidronate	52 wks	<ul style="list-style-type: none"> • Improvement in the physical, functional and emotional scales of the HR-QoL instrument
[44]	378	Prostate	Pamidronate	27 wks	<ul style="list-style-type: none"> • No sustained differences in pain relief, analgesic use or mobility
[46]	27	Prostate	Clodronate	12 wks	<ul style="list-style-type: none"> • No sustained pain relief
[45]	209	Prostate	Clodronate	88 wks	<ul style="list-style-type: none"> • No significant improvement in PPI or the Prostate Cancer-Specific Quality-of-Life Instrument scales
[47]	422	Prostate	Zoledronic acid	104 wks	<ul style="list-style-type: none"> • Improvement in BPI Scores

Key: ^a: unless otherwise specified, all differences are significant ($P < 0.05$); BPI: brief pain inventory; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FACT-G = Functional Assessment of Cancer Therapy—General; HR-QoL = Health-Related Quality of Life; PPI = present pain intensity

Group (ECOG) performance scores compared with placebo ($P = 0.03$) in a 12-month study of patients with breast cancer and MBD [15]. Hultborn et al. found that in women with advanced breast cancer and MBD, those receiving pamidronate had a significantly increased time to progression of pain ($P < 0.01$), significantly fewer SREs ($P < 0.01$) and better performance status (WHO scale) ($P < 0.05$) compared to placebo [40].

Others have evaluated the benefits of zoledronic acid on QoL. In an open-label study of zoledronic acid (4 mg intravenously every three to four weeks) in patients with MBD from breast or prostate cancer or multiple myeloma, treatment was associated with decreased pain (visual analog scores) compared with baseline, and no significant change in overall QoL scores, as assessed using the functional assessment of cancer therapy-general (FACT-G) scale [41] over the 18- to 24-week course of the study [14]. However, significant improvements were observed for all the components of the FACT-G that measured changes in emotional and physical functioning ($P < 0.05$). Kohno et al. conducted a multicentre, randomised, double-blind, placebo-controlled study of zoledronic acid in 228 women with bone metastases from breast cancer [42]. Patients were evaluated for pain using the BPI and for the development of SREs every four weeks for one year. At one year after initiation of the trial, the patients treated with zoledronic acid had 39% fewer SREs than those in the placebo group, and these differences were statistically significant. BPI composite pain scores were significantly lower in the zoledronic acid group than in the placebo group at every follow-up visit from four weeks to the end of the study. In another placebo-controlled study of patients with breast cancer and bone metastases, zoledronic acid treatment was found to improve BPI scores and global health status in physical, emotional and social functioning domains ($P = 0.013$, 0.005 and 0.043 , respectively) [43]. Yet another clinical trial found that women with breast cancer who were treated with either zoledronic acid ($n = 737$) or pamidronate ($n = 387$) experienced gradual improvement in overall physical, functional, and emotional well-being during the one-year study as measured by the health-related QoL (HR-QoL) instrument [17]. This study was designed to investigate the impact of bisphosphonate therapy on QoL in these patients, but not the relative efficacy of zoledronic acid versus pamidronate.

In contrast, a randomised, placebo-controlled study of pamidronate in metastatic prostate cancer found no sustained differences in self-reported pain measurements, analgesic use, proportion of patients with an SRE, or mobility after nine and 27 weeks of treatment [44].

Moreover, clodronate resulted in no or only short-lived pain relief and/or improvement in performance status and QoL in two studies of prostate cancer patients [45, 46]. Zoledronic acid may be more efficacious in patients with metastatic prostate cancer. Treatment with zoledronic acid was shown to result in a significant reduction in the mean composite score of the BPI when measured at several time points during a 24-month placebo-controlled trial of patients with metastatic prostate cancer [47]. As a result of these and other clinical studies, zoledronic acid is the only bisphosphonate indicated for the prevention of skeletal complications in patients with hormone-refractory prostate cancer and renal cell cancer (see Table 4 for a comparative listing of the clinical implications of these studies [48-50]).

Cost of bisphosphonate therapy

Because there are several different bisphosphonates, with various formulations, recommended dosing regimens and routes of administration, there is considerable variability in the cost of bisphosphonate treatment, depending on which drug is used. The costs of pamidronate treatment in patients with advanced breast cancer were measured over a 12-month period and compared with the costs of treating 25 patients who received a placebo infusion, using an outcomes decision-analytic model [51]. Costs for patients receiving pamidronate were found to be 44% higher than for those who received placebo (Euros 5,820 versus Euros 4,050, respectively). A Swiss study measured all the direct costs of treatment for patients having terminal osteolytic bone disease associated with pain and receiving pamidronate (60 mg or 90 mg intravenously every three weeks for a maximum of six cycles) [52]. After six treatments, patients were followed up for an additional six months. Average monthly costs amounted to Euros 1,290 (± 410) and Euros 1,050 (± 430) during the treatment and follow-up phases, respectively. In a US study considering the SRE-related costs in breast cancer patients, US Medicare total net cost was approximately Euros 11,750 per pamidronate-treated patient, compared with Euros 5,930 for placebo-treated patient [11]. A 2001 micro-costing analysis of zoledronic acid versus pamidronate found that, although faster infusion of zoledronic acid led to more efficient use of hospital infusion facilities, the direct healthcare costs per patient were similar (Euros 475 and Euros 506, respectively) [53]. The availability of resources gained per year from the administration of the drugs at the infusion centre was 1.8 chairs per day and 426 chairs per 240-workday year in favour of zoledronic acid compared with pamidronate. Romanus et al. calculated the direct medical costs for treatment with oral clodronate and IV pamidronate in patients with breast cancer

Table 4: Bisphosphonate meta-analysis conclusions^a

Drug	Implications for clinical practice
IV zoledronic acid (4 mg every 3-4 weeks)	<ul style="list-style-type: none"> • Acts as effectively as IV pamidronate on SRE rate, delays SREs and alleviates bone pain equally well • Approved for treatment of osteolytic lesions in breast cancer, prostate cancer, lung cancer and other solid tumours; also for treatment of HCM • Can be given in one 15-minute infusion
IV pamidronate (90 mg every 3-4 weeks)	<ul style="list-style-type: none"> • Used with standard antineoplastic therapy to <ul style="list-style-type: none"> ◦ reduce bone pain and incidence and rate of SREs ◦ delay SREs in breast cancer patients with bone metastases • Approved for treatment of osteolytic lesions in breast cancer or multiple myeloma patients; also for treatment of HCM • Given as one four-hour infusion
IV ibandronate (2-6 mg or 6 mg every 3-4 weeks)	<ul style="list-style-type: none"> • Approved in EU for treatment of HCM and bone metastases in breast cancer patients, but not approved for any indication in US • Given as 2-6 mg in one two-hour infusion for HCM or 6 mg in one one-hour infusion for reducing new SREs and delaying SREs • Has not yet been compared head to head with pamidronate or zoledronic acid in patients with bone metastases
Oral clodronate (1600 mg taken daily)	<ul style="list-style-type: none"> • Used with standard antineoplastic therapy to <ul style="list-style-type: none"> ◦ reduce bone pain and incidence and rate of SREs ◦ delay SREs in breast cancer patients with bone metastases
Oral ibandronate (50 mg taken daily)	<ul style="list-style-type: none"> • Approved in EU, but not in US, for prevention of SREs in breast cancer patients

Key: ^a: data from Lipton, 2005[37]; HCM: hypercalcaemia; SRE: skeletal-related event

and bone metastases [54]. The study found that the mean management costs for patients from diagnosis to death (or to last follow-up) was Euros 31,430 for IV pamidronate (n = 18) and Euros 32,000 for oral clodronate (n = 34). Despite the different drug administration methods, there was no significant difference between the observed mean costs of treatment with these drugs. This may be because the assessment done by the investigators was based on total costs of treatment in a routine care setting. Inpatient and terminal care were the major cost drivers for these patients, accounting for 70% of overall costs.

Cost-effectiveness of bisphosphonate therapy

Many of the costs related to cancer care are due to SREs. Since bisphosphonates have been shown to limit or prevent SREs, meaningful cost-effective studies must consider costs associated with specific types of SREs, as well as indirect costs of SREs, in addition to quality-of-life issues and drug compliance. Costs associated with specific types of SREs can be difficult to resolve because clinical studies evaluating the safety and efficacy of SREs typically do not differentiate between types of SREs experienced by patients. Because hospitalisation and bone surgery dominate the costs of treating MBD, a more specific record of the prevention and delay of SREs with

bisphosphonate therapy would be helpful [25]. It is possible that one particular bisphosphonate has advantages over another for preventing or reducing pain but not for preventing bone fractures. These efficacy questions may never be conclusively resolved in the medical literature, so economic models using non-specific skeletal morbidity rates may be flawed. Indirect costs of SREs, such as income loss for patients still able to work as well as income loss for family and friends who must transport the patient to and from medical appointments, have not yet been studied in great detail.

It is difficult to put a value on palliative therapies such as bisphosphonates that reduce patient pain or improve QoL issues such as the patients' ability to function emotionally and physically. Preserving QoL must be the priority and therapeutic imperative. In order to evaluate the course of disease and the consequences of non-compliance, economic studies should ideally track the costs of patients who discontinue bisphosphonate therapy, possibly against physician recommendations, and are at greater risk for MBD and associated SREs.

Recently, Botteman and Foley completed a literature review to determine the cost-effectiveness of bisphosphonates

versus no treatment, and the relative cost-effectiveness of several different bisphosphonates in patients with breast cancer and bone metastases [55]. Twelve studies were identified that described the cost of bisphosphonate therapy versus no treatment. Eight of the studies also included data about QoL and were amenable to true cost-effectiveness analyses. The authors found that bisphosphonates were cost-effective for the prevention of SREs compared with no treatment. Key variables were drug costs and assumed QoL gains from non-SRE bone pain reduction. No firm consensus emerged on the most cost-effective bisphosphonate. A study by Guest and colleagues did claim that pamidronate might be more cost-effective than zoledronic acid, but the conclusions of that study were based on unrealistically low estimates of the costs of SRE treatment [56]. When data from that study were re-analysed using more reasonable estimates of the costs of SREs, pamidronate therapy appeared to be slightly less cost-effective than zoledronic acid [55]. Thus, the results of some of these studies could reflect differences in cost and effectiveness assumptions used across different analyses.

Several studies have expressed the effects of bisphosphonates on QoL in terms of quality-adjusted life years (QALYs) [57]. QALY values are usually reported as between 0 to 1 – one year of perfect health has a value of 1, and death a value of 0. Thus, if a treatment causes no drop in QALY but extends a patient's life with a QALY value of 0.5 by three years, the QALY gain is 1.5. QALY analysis has been applied to a study of pamidronate treatment in patients with advanced breast cancer, where, over a 12-month period the direct costs for 25 patients were measured and compared with 25 control patients using an outcomes decision-analytic model [51]. When treatment preferences were incorporated into the model, the results of the decision model revealed an incremental pamidronate cost of Euros 12,200 per QALY gained. Sensitivity analyses suggest that the cost of bone surgery greatly influenced the increase in QALY because of pamidronate treatment. De Cock et al. used a global economic model adapted to the UK National Health Service to compare cost-effectiveness of oral ibandronate with IV pamidronate or zoledronic acid in patients with breast cancer [58]. According to this analysis, oral ibandronate was the most economical option, with a QALY score 0.02 higher than those for IV zoledronic acid and IV pamidronate. These results have been disputed on several grounds, including inappropriate assumptions regarding renal side effects with zoledronic acid [59]. Additionally, in the absence of comparative efficacy and safety data from clinical trials, the authors of this study used unsubstantiated "expert clinician opinion" to support its conclusions [24]. Further

confounding the De Cock studies is the assumption that compliance with oral bisphosphonate regimens was similar to compliance with IV therapies. Most studies suggest that compliance is better with IV regimens, which avoid the adverse gastrointestinal side effects and need for fasting associated with oral bisphosphonate therapy [5, 60]. Botteman et al. examined the cost and QALY associated with several commonly used bisphosphonates in patients with breast cancer and MBD [61]. Compared with no therapy, all bisphosphonates provided cost savings or were otherwise cost-effective (costs were \leq Euros 7,770). In contrast with the findings of De Cock et al., this study found, through a literature-based decision-analytic model, that zoledronic acid was more cost-effective than all the other bisphosphonates. Moreover, IV bisphosphonates can be safely administered at home, thereby avoiding hospital costs, costs of travel to and from the hospital, and the discomfort such travel can cause. In a study of 107 cancer patients treated with zoledronic acid, 97 chose to receive home treatments [62]. Based on a 22-item satisfaction questionnaire, the home-treated patients were very satisfied with the quality of care they received and described a significant decrease in pain that was not because of an increase in the use of analgesics.

A recent meta-analysis of randomised clinical trials examining bisphosphonate treatment in patients with breast cancer supports the findings of Botteman [25]. Among the oral and IV bisphosphonates examined, zoledronic acid was the most effective at reducing the risk of SREs, and toxicity associated with any of the bisphosphonates was mild and infrequent. The authors noted that renal toxicity with zoledronic acid was dose and infusion-time dependent and was minimised with 4-mg dosing and an infusion time of more than 15 minutes.

CONCLUSION

Bone metastases and the associated SREs exact a great toll on both patients' well-being and healthcare economic resources. Bisphosphonates have been shown to prevent or delay SREs and relieve pain in patients with bone metastases, and to improve patients' QoL. Bisphosphonate therapy is associated with substantial costs, though estimates of specific costs vary widely. The economic value of improved QoL and/or maintained patient functioning has not been widely tested and should be considered in future evaluations. Preliminary studies suggest that bisphosphonate therapy can be cost-effective by reducing the incidence of and time to development of SREs. This cost-effectiveness is in part because of indirect cost savings from an improved QoL and preserved physical and emotional function.

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