Review

Skeletal morbidity in lung cancer patients with bone metastases: Demonstrating the need for early diagnosis and treatment with bisphosphonates

Corey Langer a, *, Vera Hirsh b

a Hematology-Oncology Division, University of Pennsylvania, 3400 Civic Center Blvd., 2 Perelman Center for Advanced Medicine, Philadelphia, PA 19104, USA
b Departments of Medicine and Oncology, McGill University Health Centre, Royal Victoria Hospital Room A2.04, 687 Pine Avenue West, Montreal, QC, Canada H3A 1A1

1. Introduction

Novel therapies are yielding improved survival for patients with advanced lung cancer [1,2]. However, the efficacy of promising new agents in treating metastatic disease in one of the most common metastatic sites—the skeleton—is unknown and may be undetermined by the complex interplay between tumor and bone in the osseous microenvironment. Historically, 30–40% of patients with advanced lung cancer have developed bone metastases [3], and the number of patients with advanced lung cancer is expected to increase with the application of newer and more sensitive screening/imaging technologies for metastatic disease [4,5]. Moreover, with the introduction of new therapeutic modalities, median survival for patients with advanced lung cancer has increased from approximately 6 months [6] to 12 months [2], thereby extending the disease course and potentially increasing the risk of painful and debilitating complications from bone metastases. Advanced lung cancer is often symptomatic, and patients’ quality of life (QOL) typically decreases during disease progression [7]. Skeletal morbidity from bone metastases can add substantially to the overall burden of disease and loss of functional independence for patients with lung cancer [8]. Moreover, malignant bone disease has historically been considered less sensitive to cytotoxic therapies compared with pulmonary, nodal, or soft-tissue metastases.

During their lifetimes, most patients with bone metastases from lung cancer experience skeletal-related events (SRE), including pathologic fractures, the requirement for palliative radiotherapy or surgery to bone, spinal cord compression, and, less frequently, hypercalcemia of malignancy (HCM) [9,10]. Skeletal-related events can occur regardless of the radiographic appearance of bone lesions (e.g., osteolytic or osteoblastic) [10–12]; both types of lesions are associated with increased levels of bone destruction by osteoclasts [12–14]. In a recent clinical trial, most patients with bone metastases from non-small cell lung cancer (NSCLC) experienced an SRE within the first 5 months on study [15]; however, bone lesions may be overlooked and often are not diagnosed until they manifest as bone pain or an SRE [4]. Notably, the consequences of SREs (e.g., bone pain, loss of mobility) may persist throughout the lifetime of the patient. Therefore, detection and treatment of bone metastases before the onset of SREs could conceivably help
preserve patients’ QOL and functional independence, and could contribute to maintaining patients’ performance status and thus allow further chemotherapy or targeted lung cancer therapies.

Bisphosphonates are inhibitors of osteoclast-mediated osteolysis and have demonstrated utility in preventing SREs in patients with bone metastases [10,16]. Zoledronic acid (Zometa®; Novartis Pharma AG, Basel, Switzerland, and Novartis Pharmaceuticals Corporation, East Hanover, NJ) significantly delays the onset of SREs and reduces the ongoing risk of skeletal morbidity and further SREs in patients with bone metastases from breast cancer, prostate cancer, lung cancer, and a broad range of solid tumors [15,17–19]. Zoledronic acid is the only bisphosphonate approved for the treatment of bone metastases secondary to solid tumors other than breast cancer.

The treatment landscape for lung cancer is evolving and may progress in a similar way to that for breast cancer. Historically, treatments for patients with advanced breast cancer have not been curative, but have resulted in relatively long survival compared with patients with other advanced solid tumors. In patients with bone metastases from breast cancer, bisphosphonates have become an integral component of therapy to delay the onset of pathologic fractures and other SREs, with the goal of reducing painful complications and preserving the capacity to independently perform daily activities [20]. Improved survival with newer therapies has also been achieved in patients with hormone-refractory prostate cancer, and recent guidelines recommend the use of zoledronic acid to prevent SREs from bone metastases [21]. With the success of newer therapies in extending survival although not curing patients with advanced lung cancer, the need to focus on ancillary issues such as bone metastases and their sequelae is heightened.

2. Malignant bone disease causes substantial morbidity

2.1. Pathophysiology of bone metastases

In addition to the vast surface area of the skeleton, the bone microenvironment has characteristics that make it especially conducive to the development of metastatic lesions, such as the release of osteolytic factors from the bone matrix during osteoclast-mediated osteolysis [22]. The interplay between tumor and bone promotes tumor growth, undermines skeletal integrity, and can result in bone pain and structural failure. In osteolytic lesions, factors secreted by tumor cells induce osteoclast recruitment and activation, leading to increased osteolysis [23]. Elevated levels of osteolysis decrease bone integrity, can cause bone pain, and may overwhelm serum homeostasis by the release of minerals from the bone matrix, resulting in HCM [3]. Bone resorption also releases growth factors that stimulate tumor growth and increase secretion of osteoclast-stimulating factors [11]. In contrast, tumor cells in osteoblastic lesions secrete factors that stimulate osteoblasts, the cells responsible for the generation of new bone tissue (osteogenesis). Levels of osteolysis are enhanced in response to increased osteogenesis and other stimuli, releasing growth factors from the bone matrix [23]. Therefore, although bone destruction may be more apparent for osteolytic bone lesions, osteoblastic lesions also contain a strong osteogenic component that can decrease bone integrity [10,11]. Furthermore, aberrant new bone formation in osteoblastic lesions produces new bone tissue that is malformed and does not contribute to the overall bone strength [11,16].

2.2. Screening and detection of bone metastases

Without the appropriate diagnostic tests, bone metastases can be easily overlooked in the NSCLC setting. Bone metastases are typically detectable via bone scans before they reach an advanced stage, but many oncologists do not order bone scans in patients who do not report bone pain or other symptoms of bone lesion progression or do not have other signs of bone involvement such as elevated bone-specific alkaline phosphatase (BALP) levels [10,24]. In a recent investigation, whole-body bone scanning was performed on 60 patients whose initial evaluation indicated that they had operable (nonmetastatic) NSCLC [4]. Of the 11 patients who had pain or laboratory values consistent with early bone lesions, bone metastases were confirmed in 3 (27.3%) patients. Moreover, among the other 49 patients, bone metastases were detected in 8 (16.3%) patients, although no clinical symptoms of bone metastases had been reported. In addition to the lost opportunity for early treatment of the bone lesions, the incorrect staging of these patients could result in suboptimal treatment decisions including the implementation of major surgery or aggressive chemoradiation therapy in patients with no hope of curative outcome.

Current American Society of Clinical Oncology (ASCO) guidelines suggest that bone scans can be performed on patients with NSCLC with abnormal clinical evaluations [25]. Imaging may be performed on patients with advanced disease at presentation, especially if patients are symptomatic (e.g., have bone pain or fractures). Suspicious lesions identified on bone scans generally warrant further investigation using X-ray, computed tomography, magnetic resonance imaging, metabolic-labeling positron emission tomography (PET), or biopsy [4,25–27]. Recently, PET scanning for the evaluation and accurate staging of NSCLC, including stage IV disease, has been recognized as a valuable tool by the National Comprehensive Cancer Network [28]. In fact, fluorine-18 deoxyglucose (FDG)-PET scans for the detection of bone metastases in NSCLC have been shown to have a higher specificity compared with bone scans (approximately 90% versus approximately 70%, respectively) [29,30] and a much lower rate of false negatives (6% versus 39%, respectively) [31]. The sensitivity of FDG-PET and bone scans for the detection of bone metastases from NSCLC was comparable after appropriate follow-up imaging [29,30].

2.3. Clinical and pharmacoeconomic implications of bone metastases

Insight into the burden of disease from bone metastases can be gained from the placebo-controlled arms of recent trials with bisphosphonates. In large-scale clinical trials of approximately 2 years’ duration in patients with bone metastases, on-study SREs occurred in the majority of patients, and most patients experienced multiple SREs per year, depending on the primary malignancy (Fig. 1) [15,32–35]. Among patients with bone metastases from NSCLC,
most patients in the placebo group experienced an SRE during the first 5 months on study, which was a shorter time period than the median survival in this group [6]. These data are consistent with later evaluations by Delea et al. [36,37], in which patients with NSCLC were found to survive a median of approximately 4 months after experiencing their first SRE. Therefore, the underlying pathophysiology of bone metastases results in skeletal morbidity regardless of the primary histology, and SREs from bone metastases have time to develop even in patients with aggressive malignancies and shorter survival.

Malignant bone disease is one of the most frequent causes of chronic cancer-associated pain, which is common in patients with advanced cancer and has been associated with compromised QOL [24,38,39]. Skeletal-related events add to the burden of disease. In addition to being acutely painful, SREs such as pathologic fractures and spinal cord compression can permanently impair patient mobility and functional independence. Furthermore, pathologic fractures have been associated with decreased survival in multiple tumor types [40], although these analyses have not been performed for the NSCLC setting specifically. Each type of SRE has been associated with decreases in QOL. In a retrospective analysis of a large-scale clinical trial in men with bone metastases from prostate cancer who experienced an SRE on study (n = 248), there were clinically relevant and statistically significant decreases in physical, functional, and emotional well-being after an SRE occurred [41]. Therefore, delaying the onset of SREs and reducing the ongoing risk of SREs could provide meaningful benefits to patients with bone metastases from NSCLC. For example, good performance status is an essential eligibility criterion before offering further treatments to patients with advanced NSCLC, and preventing SREs can help prevent performance status deterioration.

In addition to their effects on patients’ well being, QOL, and performance status, SREs are associated with increased healthcare costs. In a retrospective analysis using a database, 534 patients with bone metastases from NSCLC were identified, of whom 295 had medical claims associated with SREs [37]. The estimated lifetime cost per patient with bone metastases directly related to SREs was approximately $12,000 (US dollars, based on 2004 costs) [37]. However, when the analysis was not limited to the costs directly related to the acute management of an SRE (e.g., radiation to bone or treatment for a pathologic fracture or HCM), medical costs were an average of $27,982 higher per patient with SREs compared with patients who did not experience SREs (p < 0.001) [42], perhaps reflecting increased need for additional supportive care or subsequent interventions after the onset of skeletal morbidity. Therefore, prevention of SREs in patients with NSCLC could have a substantial economic impact [38].

3. Bisphosphonates: inhibitors of osteoclast-mediated osteolysis

Bisphosphonates are pyrophosphate analogues that are deposited at sites of bone remodeling, bind to bone mineral surfaces, and are ingested by osteoclasts, wherein they inhibit osteolysis [43]. Early bisphosphonates (e.g., etidronate, clodronate) demonstrated efficacy for the treatment of HCM and provided the rationale for the use of bisphosphonates to reduce skeletal morbidity associated with bone metastases, but these agents are weak and have limited utility in the oncology setting [43]. Successive generations of bisphosphonates, each with increasing clinical utility, have since been developed [44]. The introduction of a nitrogen group to the bisphosphonate backbone resulted in considerably increased potency and a different cellular target than the earlier-generation bisphosphonates: farnesyl diphosphate synthase, a key enzyme in the mevalonate pathway. By inhibiting this pathway, nitrogen-containing bisphosphonates inhibit protein prenylation and Ras signaling in osteoclasts, thereby inducing apoptosis [45].

In animal model systems of human cancers including multiple myeloma, breast cancer, and prostate cancer, bisphosphonates reduced the number and size of bone lesions, skeletal disease burden, and levels of biochemical markers of bone resorption [43,45]. Of these agents, the new-generation bisphosphonate zoledronic acid has demonstrated the greatest activity in preclinical assays in human cancer cell lines and animal models of tumor-associated osteolysis. In 2 models of osteolast-mediated bone resorption, zoledronic acid consistently achieved the greatest antiresorptive efficacy among bisphosphonates tested [46,47]. In a preclinical model assessing farnesyl diphosphate synthase activity, zoledronic acid produced near-complete inhibition of farnesyl diphosphate synthase activity at a concentration of 0.1 μM, which was 5- to 40-fold lower than the concentrations required for other bisphosphonates (e.g., risedronate, ibandronate, alendronate, pamidronate) [43].

4. Zoledronic acid can reduce skeletal morbidity in patients with lung cancer and other solid tumors

Bisphosphonates have been used for more than a decade for the treatment of HCM and, more recently, to prevent skeletal complications in patients with bone lesions from multiple myeloma or breast cancer. However, it was not until the introduction of zoledronic acid in 2002 that the benefits of bisphosphonate therapy could be extended to patients with other solid tumors including hormone-refractory prostate cancer and NSCLC. Regulatory approval in the United States for zoledronic acid in patients with any solid tumor was based on results from a phase III, randomized, placebo-controlled trial, in which patients (n = 773) with bone metastases from solid tumors other than breast or prostate cancer received zoledronic acid (4 mg or 8 mg) or placebo via 15-min infusion every 3 weeks for up to 21 months [15]. Among the 507 patients randomized to the 4 mg zoledronic acid or placebo groups of this trial, 249 had NSCLC and 36 had small cell lung cancer. In the overall trial population, zoledronic acid significantly reduced the proportion of patients who experienced at least 1 SRE (including HCM; 39% versus 48% with placebo; p = 0.039) and reduced the proportion of patients who experienced each type of SRE (Fig. 2) [15]. Moreover, zoledronic acid significantly decreased the annual incidence of SREs (1.74 per year versus 2.71 per year for placebo; p = 0.012) and significantly delayed the median time to first SRE compared with placebo (236 days versus 155 days, respectively; p = 0.009) [15]. A multiple event analysis using a robust Andersen–Gill model was also performed for the overall population. This analysis takes into account not only the number of SREs but also the timing between the SREs, thereby providing a sensitive comparison of the ongoing risk of SREs between 2 treatment groups. Zoledronic acid reduced the risk of SREs by 31% versus placebo in the overall trial population (relative risk [RR] = 0.693; p = 0.003).

Many patients with lung cancer might not be diagnosed until after the onset of SREs. However, pre-existing skeletal morbidity does not preclude the benefits of subsequent therapy. Indeed, patients who have already experienced an SRE are at especially high risk for subsequent events. For example, in an exploratory analysis of the zoledronic acid phase III trial in patients with NSCLC and other solid tumors, patients with a history of SREs before study entry had a 41% increased risk of experiencing an on-study SRE compared with patients with no history of prior SREs (p = 0.036) [19]. In patients with a prior SRE, zoledronic acid produced a significant 31% reduction in the risk of developing an on-study SRE compared with placebo in a robust Andersen–Gill multiple event analysis (p = 0.009), and significantly reduced the skeletal morbid-
ity rate (1.96 versus 2.81 events per year for placebo; \( p = 0.030 \)) [19]. Furthermore, zoledronic acid significantly prolonged the median time to first SRE on study by approximately 4 months compared with placebo in this prior-SRE cohort (215 versus 106 days, respectively; \( p = 0.011 \)) [19]. Benefits were also seen in the subset of patients who had not experienced a prior SRE, although that group lacked the statistical power to achieve statistical significance in these endpoints. This study suggests that zoledronic acid is effective in patients at high risk for skeletal complications and provides benefits after the onset of SREs.

### 4.1. Established tolerability profile of zoledronic acid

The most commonly reported adverse events for zoledronic acid and placebo during the trial were bone pain (51% and 61%, respectively), nausea (49% and 36%, respectively), and dyspnea (45% and 30%, respectively) [15]. Grade 3 or 4 serum creatinine increases were observed in 1.8% of patients in each of the groups receiving placebo or 4 mg zoledronic acid via 15-min infusion. There were no significant differences in serious adverse events between groups. In the NSCLC stratum, zoledronic acid had an overall safety profile generally comparable with that of placebo. The most commonly reported adverse events for zoledronic acid and placebo during the trial were bone pain (48% and 58%, respectively), nausea (47% and 32%, respectively), and dyspnea (45% and 30%, respectively) [48]. The 10% difference in the incidence of bone pain favoring the zoledronic acid group may reflect either effects from the SRE reduction or an analgesic effect. There were no apparent differences in analgesic score between groups, and no significantly lower incidence of palliative radiotherapy to bone in the 4 mg zoledronic acid group versus placebo [6]. There were no grade 4 increases in serum creatinine reported in the NSCLC stratum.

Since the regulatory approval of zoledronic acid, monitoring of renal function and oral health during bisphosphonate therapy is now recommended to avoid uncommon but potentially serious adverse events [49,50]. Because all intravenous bisphosphonates are cleared by the kidneys, renal function and hydration status should be determined before each infusion to ensure renal safety. Infrequently, patients with normal renal function may experience dose- and infusion-rate-dependent effects on renal function; however, patients with impaired renal function are at greater risk. Therefore, a reduced starting dose scale for zoledronic acid is recommended for patients with impaired renal function [51].

Osteonecrosis of the jaw (ONJ) has been reported as an uncommon event in patients receiving complex treatment regimens that may include bisphosphonates and is characterized by exposed bone in the maxillofacial area with no evidence of healing after 6 weeks of appropriate dental care in the absence of metastatic disease in or radiation to the jaw [50]. Although the true incidence of ONJ is not known, reports using the limited data obtained from retrospective analyses and reviews of medical records databases suggest that the frequency of ONJ in patients with malignant bone disease may be between 0.7% and 12.6% [52–54]. This wide range in ONJ frequency is likely due to several inherent limitations of these studies, such as variability in preventive dental measures before and during bisphosphonate therapy, lack of a standard definition of ONJ at the time of these studies, variations in the duration of bisphosphonate treatment, and geographic differences. Preventive dental measures have been identified that can significantly reduce the incidence of ONJ during bisphosphonate therapy, including preventive dentistry, regular dental check-ups, and good oral hygiene [50,55–57]. In addition, a recent pilot study in patients with active ONJ lesions found that local application of a medical ozone oil suspension led to complete ONJ resolution [58].

### 4.2. Analysis of biochemical markers of bone metabolism

Additional insight into the contribution of bone metastases to the overall disease burden in patients with NSCLC can be obtained through the use of biochemical markers of bone metabolism, including peptides released from the bone matrix during osteolysis or enzymes that are secreted during osteogenesis. In a subset of patients with NSCLC or other solid tumors in the placebo group (n = 238), urinary levels of the bone resorption marker N-telopeptide of type I collagen (NTX) and the serum bone formation marker BALP were assessed approximately every 3 months [59]. High NTX levels (\( \geq 100 \) nmol/mmol creatinine) at baseline were associated with an increased risk of first SRE (RR = 1.85; \( p = 0.026 \)) and bone disease progression (RR = 1.76; \( p = 0.029 \)) compared with patients with low NTX levels (\(<100 \) nmol/mmol creatinine) (Fig. 3) [59]. Moreover, compared with patients with low NTX levels, patients with high NTX levels had a more than 3-fold increased risk of death (RR = 3.03; \( p < 0.001 \)) and a 5-month reduction in median survival (3.2 versus 8.2 months for patients with low baseline NTX levels) [59]. Patients with high baseline BALP levels (\( \geq 146 \) IU/L) also had statistically significant increases in risk of disease progression (RR = 1.77; \( p = 0.005 \)) and death (RR = 1.53; \( p = 0.003 \)) compared with patients with low BALP levels (\(<146 \) IU/L) [59].

Zoledronic acid dramatically suppresses biochemical markers of bone resorption in patients with bone metastases. In a prospective study measuring levels of bone markers in patients with newly diagnosed bone metastases receiving zoledronic acid every 3–4...
weeks (n = 71), zoledronic acid significantly reduced NTX levels at first (55 days) and second (115 days) treatment evaluations (mean reductions of 43% and 45%, respectively), and the levels remained suppressed throughout the study [60]. This reduction correlated with a lower rate of bone disease progression compared with patients whose NTX levels increased (18.8% versus 66.7%, respectively; p = 0.001) [60]. These results are consistent with data from a recent exploratory analysis of the zoledronic acid phase III clinical trial database [61] in which zoledronic acid was found to reduce mean urinary NTX levels within 3 months in patients with bone metastases from NSCLC and other solid tumors who had bone marker assessments (n = 204) [62]. Zoledronic acid also significantly reduced the RR of death by 35% versus placebo (RR = 0.650; p = 0.024) among patients with NSCLC and high baseline NTX levels (NTX ≥ 64 nmol/mmol creatinine; n = 144) [63]. Differences in survival between the zoledronic acid and placebo groups did not reach statistical significance in the normal baseline NTX subset, consistent with the lower risks of SREs and death that have been reported statistically in the normal baseline NTX subset, consistent with the lower risks of SREs and death that have been reported statistically [59,63]. This benefit could result from reduced osteolysis, resulting in less release of growth factors from the bone matrix; reduced SRE rate; or possibly also from direct antitumor effects.

5. Investigational studies of bisphosphonate therapy

In addition to reducing the risk of SREs, bisphosphonate therapy may have additional benefits including bone metastasis prevention and antitumor effects, especially in combination with chemotherapy agents.

There is an expanding database of preclinical evidence to suggest that bisphosphonates can inhibit proliferation and induce apoptosis in a broad range of human cancer cell lines [43,64]. In vitro, zoledronic acid inhibits the growth of cell lines derived from human primary tumors, including 12 small cell lung cancer cell lines, in which it potently inhibited growth with 50% inhibitory concentration (IC50) values ranging from 13 to 30 nM [65]. Similar effects on cellular viability and proliferation were observed in 16 NSCLC cell lines, with IC50 values ranging from approximately 2–25 μM [66]. Moreover, 10 μM zoledronic acid blocked motility in 3 of these cell lines that were highly motile. Zoledronic acid also exerts antitumor synergy with chemotherapy agents in the A549 lung cancer cell line [67]. In combination with cisplatin, zoledronic acid 100 μM significantly enhanced cytotoxicity up to 70% (p = 0.007) compared with cisplatin alone. Zoledronic acid in combination with paclitaxel produced synergistic inhibition of cellular proliferation compared with either agent alone [68].

In a murine lung cancer cell line, zoledronic acid inhibited the growth of these tumors, and mice that were treated with zoledronic acid (1 μg/kg/week) survived significantly longer compared with untreated mice (p < 0.05) [69]. In a murine model of lung metastases from osteosarcomas, mice treated with zoledronic acid (0.1 mg/kg either 2 or 5 times per week) did not develop lung metastases and had significantly longer survival compared with untreated mice (p = 0.036) [70].

Multiple effects may contribute to the antitumor activity of zoledronic acid that has been reported in preclinical models [71]. For example, in addition to direct antitumor effects and their effects on blocking the cycle of malignant osteolysis in bone lesions, nitrogen-containing bisphosphonates appear to have immunomodulatory properties, especially with regard to γδ T cells, a subset of T cells that plays a role in immunosurveillance for malignancies. In an in vitro model, zoledronic acid induced maturation and up-regulated co-stimulatory surface receptor expression (e.g., CD40, CD80, CD83) on peripheral γδ T cells [72]. In addition, bisphosphonates have been shown to activate the cytolytic activity of γδ T cells and, therefore, may enhance the antitumor immune response [73].

One recent randomized phase II study in patients with NSCLC (n = 150) evaluated the efficacy and safety of docetaxel (75 mg/m²) plus carboplatin (AUC 6) with (n = 100) or without (n = 50) zoledronic acid (4 mg) every 3 weeks for 6 cycles, followed by an additional 6 month follow-up for a total of 12 months [74]. Analyses indicate that after completion of the treatment phase, there were no significant between-group differences in disease progression, time to progression, and disease progression in bone. Compared with the chemotherapy-alone group, however, the median overall survival time in the zoledronic acid group was slightly longer during the treatment phase (266 days versus 206 days for no zoledronic acid). Overall, the combination of zoledronic acid plus chemotherapy was well tolerated, and although there were more AEs related to study medications in the zoledronic acid group (41.8% versus 28.8%), a large proportion of the between-group difference resulted from a higher incidence of nausea in the zoledronic acid group (16.3% versus 5.7%). Unfortunately, this study was not powered to detect differences in the primary and secondary endpoints, and a substantial proportion of patients in both groups discontinued treatment because of disease progression after 3 cycles. Although this is the first randomized study to evaluate the effects of zoledronic acid plus chemotherapy on disease progression and survival in patients.
with NSCLC, several limitations hinder the interpretation of outcomes, including the lack of sufficient power, high discontinuation rate, and short duration of zoledronic acid treatment, among others.

Zoledronic acid has demonstrated efficacy not only in preventing cancer treatment-associated bone loss, but also in prolonging disease-free and recurrence-free survival when combined with adjuvant endocrine therapy versus endocrine therapy alone in women with early stage breast cancer [75,76]. These data provide the rationale for similar studies to investigate the ability of zoledronic acid to delay disease progression in patients with NSCLC. Accordingly, ongoing studies in patients with NSCLC are evaluating the efficacy of zoledronic acid in the adjuvant setting for prevention of bone metastases and in other exploratory studies for antitumor activity. In the adjuvant setting, an open-label trial (G2419; n = 436) has completed enrollment and will randomize patients to either zoledronic acid 4 mg every 3–4 weeks or no bisphosphonate treatment for up to 2 years [77]. Patients in the no-bisphosphonate treatment group who develop bone metastases during the trial will be switched to zoledronic acid 4 mg. The primary endpoint will evaluate disease progression (e.g., in bone). The anticipated completion of this trial is in the last quarter of 2009. An open-label antitumor trial (Z-PACT) in patients with stage IIIIB or stage IV NSCLC and without bone metastases has completed enrollment [78]. Patients are receiving chemotherapy and are randomized to either zoledronic acid 4 mg or no bisphosphonate treatment for up to 6 cycles or until disease progression. Patients in the zoledronic acid group who respond to treatment will be further randomized to zoledronic acid 4 mg monthly or no bisphosphonate treatment for up to 12 months. The primary endpoint is the proportion of patients with no disease progression. This trial has been completed and results are eagerly awaited.

6. Conclusions

Skeletal morbidity can contribute heavily to the burden of disease in patients with bone metastases from various cancers, including NSCLC. Skeletal-related events can result from both osteolytic and osteoblastic lesions. Although disease in bone may not contribute heavily to the overall tumor burden from lung cancer, the skeletal disease burden can result in severe morbidity that can influence patient QOL and independence. Extended patient survival with newer chemotherapy and biologic agents may result in increased incidence of SREs in the NSCLC setting. As such, early identification of bone metastases and management of SREs have become increasingly crucial for maintaining QOL, thereby containing healthcare costs throughout the continuum of care. Early treatment may especially help maintain patients’ performance status, which is an important predictive factor for survival, and enable patients to be eligible for subsequent lines of therapy with the newer targeted agents [19].

Zoledronic acid is the only bisphosphonate that has been shown to significantly reduce the risk of skeletal morbidity in patients with bone metastases from NSCLC. In addition, an exploratory analysis suggests that zoledronic acid may improve survival benefit in NSCLC patients with high levels of biochemical markers of bone resorption, possibly by preventing life-limiting SREs or by blocking the release of growth factors from the bone matrix. Clinical trials of zoledronic acid for the prevention of bone metastases in patients with locally advanced NSCLC are ongoing, and the role of bisphosphonate therapy in the lung cancer setting will continue to evolve. The identification of risk factors for skeletal metastases in patients with NSCLC is needed to optimize screening and implement early treatment to prevent or delay the onset of potentially debilitating SREs.

Conflicts of interest statement

Corey Langer, MD, has received payment/honoraria from Novartis for consultation, speaking engagements, and service on advisory boards. Vera Hirsh, MD, reports no financial or other conflicts of interest relevant to this manuscript.

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References

[16] Lipton A. Pathophysiology of bone metastases: how this knowledge may lead to therapeutic intervention. [Support Oncol 2004;2:205–13 [discussion follows]].
[17] ROSEN LS, GORDON D, KAMINSKI M, ET AL. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast car-


