Bisphosphonate Use in Patients with Lung Cancer and Bone Metastases

Recommendations of a European Expert Panel

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Introduction: Bisphosphonates (BPs) are effective in preventing, reducing the incidence, and delaying the onset of skeletal-related events in patients with bone metastases in a variety of solid tumors, including lung cancer. The purpose of this article is to review the current evidence for the use of BPs in lung cancer and to provide specific European recommendations to support the clinical practice of using BPs to treat patients with lung cancer with bone metastases.

Methods: An expert panel of European clinical oncologists and lung cancer specialists convened for two face-to-face meetings designed to review available evidence on the efficacy of BPs in lung cancer and to develop recommendations based on published literature and clinical practice experiences.

Results: The panel recommends screening patients with lung cancer for bone metastases at the initial staging of disease to assess symptomatic bone metastases and screen for asymptomatic bone metastases and to allow accurate monitoring of bone disease progression and initiate bone-specific therapy. Bone assessment should be based on positron emission tomography (if available) or bone scan. BPs should be added to the treatment of patients with lung cancer (with non-small cell lung cancer or small cell lung cancer) who develop bone metastases. In such patients, BPs must be considered part of metastatic lung cancer treatment to prevent and delay the occurrence of further bone metastases and skeletal-related events and to relieve pain where present. BP treatment should continue for as long as it is practically feasible in the absence of any significant adverse effects.

Key Words: Bisphosphonates, Lung cancer, Bone metastases, Skeletal-related events, Recommendations.

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Many patients with advanced cancer develop bone metastases during the course of their disease, and these are often associated with significant morbidity. The majority of bone metastases arise from primary tumors of the breast, lung, or prostate. Approximately 30 to 40% of patients with advanced non-small cell lung cancer (NSCLC) develop bone metastases.[1] The median survival time of these patients is less than 1 year. The high mortality is predominantly due to the difficulties in the early diagnosis of bone metastases and the high-metastatic potential of lung cancer.

Malignant cells secrete factors, including interleukin (IL)-1, IL-6, receptor activator of NF-kappaB (RANK) ligand, parathyroid hormone-related protein, and macrophage inflammatory protein-1-alpha (MIP-1α), that disturb the coupling of the normal bone metabolism, leading to an increase in bone resorption.[2] As a consequence, bone metastases from lung cancer are primarily osteolytic and result in bone lesions that undermine the structural integrity of the skeleton and may cause bone pain and also skeletal-related events (SREs) that include pathologic fractures, the need for surgery or radiotherapy, spinal cord or nerve root compression, and hypercalcemia of malignancy[3,4] (Figure 1).

A retrospective review of 435 patients with NSCLC revealed an incidence of 24% for bone metastases; the majority of bone metastases (66%) were detected at the time of initial staging.[5] In a recent retrospective study of 259 patients with NSCLC, 70 (30.4%) were found to have bone metastases during their clinical course. Among them, 46 patients (65.7%) had bone metastases at the time of initial diagnosis and 35 (50%) suffered from SREs. Thirty-one percent of the patients with SREs already had them at the time of initial staging, whereas 69% of this

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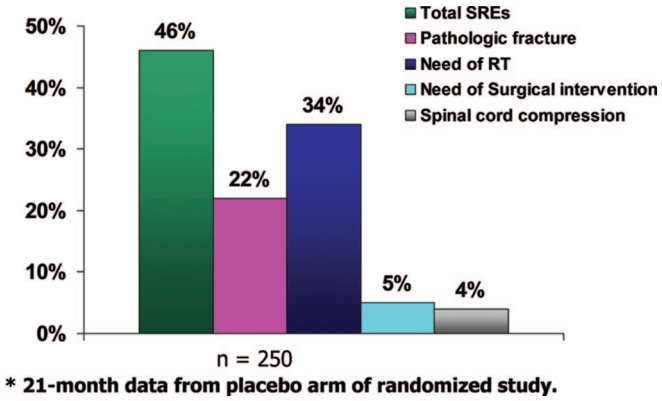

FIGURE 1. Graph of data from Rosen et al.[76] describing the total percentage of patients experiencing skeletal-related events (SREs; green). Also indicated is the percentage of patients suffering pathologic fracture (pink), requiring radiotherapy (dark blue), undergoing surgical intervention (light blue), or experiencing spinal cord compression (gray).

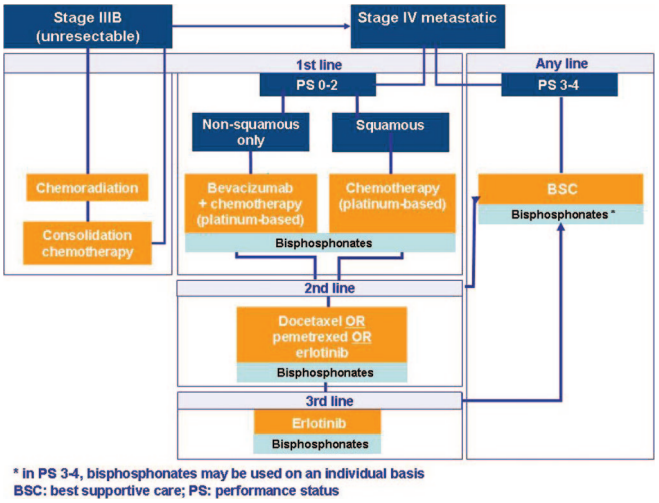

FIGURE 2. Treatment algorithm for advanced non-small cell lung cancer (NSCLC). The treatment scheme was developed by the authors based on current treatment recommendations and their own clinical experience. Patients in performance status 0 to 2 should undergo chemotherapy as 1st line treatment. Chemotherapy should be supported by the use of bisphosphonates. Also for 2nd and 3rd line therapy, a combination of chemotherapeutics or the tyrosine kinase inhibitor erlotinib with bisphosphonates is recommended. In the performance status 3 to 4, patients with lung cancer may be treated with bisphosphonates on an individual basis.

patient cohort developed SREs due to recurrence of their disease after treatment.[6] Bone pain is the most common symptom resulting from bone metastases in patients with lung cancer and occurs in around 80% of patients.[7]

Patients with bone metastases arising from lung cancer can experience up to four SREs per year, with the risk of developing subsequent SREs increasing after the first event.[8–14] In addition, patients with metastatic bone disease from lung cancer who developed SREs had a 50% shorter survival, when compared with patients who did not develop SREs.[15]

Most of the patients who suffer from SREs need radiation therapy or surgical interventions. These events often lead to rapid deterioration in quality of life (QoL) could eventually hamper adherence to therapy and significantly increase the overall costs of health care.

In recent years, the median survival of stage IV patients with lung cancer has increased[16–18] due to the use of better staging tools and the introduction of new therapeutic agents available in different lines of treatment (Figure 2). As patient life expectancy has increased, there has been a corresponding increase in patients presenting with bone metastases.

In the absence of any specific data on survival of patients with lung cancer with bone as the only metastatic site, it may be possible to extrapolate evidence from other solid tumors showing longer survival of patients with metastases in bone only, when compared with patients with liver and brain metastases.[19,20]

METHODS

An expert panel of European clinical oncologists and lung cancer specialists convened for two face-to-face meetings designed to review available evidence on the efficacy of bisphosphonates (BPs) in lung cancer and to develop recommendations based on published literature and clinical practice experiences. The initial draft that was created from minutes of an advisory panel meeting was critically revised during a second face-to-face meeting of the European experts and additionally edited in multiple revision rounds by all authors, until consensus was reached. The authors were selected as a panel of expert clinicians from across the European Union, each contributing specific information regarding BP management of patients with lung cancer, in a joint effort to produce recommendations reflecting the treatment options across the entire European Union.

BONE METASTASES AND QOL

SREs are associated with a loss of mobility, independence and social functioning, and a decrease in QoL. The Functional Assessment of Cancer Treatment-General analysis found a significant reduction in physical, functional, and emotional well being in prostate cancer patients who experienced an SRE, when compared with those who did not.[21,22] Assessing QoL changes due to SREs is currently based on tools for other cancers.[23,24] A specific tool for measuring the QoL in patients with advanced lung cancer and bone metastases should be developed and validated.

BP TREATMENT OF BONE METASTASES

The treatment of bone metastases usually involves symptomatic support (analgesics and surgery), medical anticancer treatment (chemotherapy and radiotherapy), and BPs to manage symptoms and maintain bone integrity.[25,7] Treatment with BPs has been shown to be effective in reducing the incidence and delaying the onset of SREs in patients with bone metastases in a variety of solid tumors, including NSCLC.[9–11,26–29] BPs bind to bone at sites of active bone metabolism and inhibit osteoclast-mediated bone resorption.[30]

BPs are synthetic analogs of inorganic pyrophosphate[31] but stable and resistant to hydrolysis by blood phosphatases.[32] Because of their affinity for Ca^{2+}, they bind quickly and specifically to hydroxyapatite, particularly in areas of osteoclastic resorption. They accumulate in the resorption space under osteoclasts, exposing them to elevated BP concentrations.[33,34]

Nonamino BPs such as etidronate and clodronate are metabolized to cytotoxic adenosine triphosphate analogs inducing osteoclast cell death.[35–37] Conversely, amino-BPs such as ibandronate, risedronate, pamidronate, and zoledronic (ZOL) acid are much more potent in vitro than nonamino compounds[30] and act by inhibiting farnesyl pyrophosphate synthase, an enzyme of the mevalonate pathway. ZOL acid is the BP with the highest relative inhibitory potency in vivo and in vitro known to date. The inhibition of the farnesyl pyrophosphate synthase disrupts the formation of farnesyl diphosphate and geranylgeranyl diphosphate[38–40] molecules, which are involved in prenylation, a posttranslational protein modification resulting in attachment to the cell membrane[41] (Figure 3). This localizes proteins in appropriate cell regions and mediates their biologic activity. Proteins involved include the small GTPases, Ras, Rac, and Rho, which play key roles in regulating osteoclast function and events in bone resorption.[42] Farnesyl pyrophosphate synthase inhibition ultimately leads to osteoclast apoptosis.

Among the BPs currently available, only ZOL has demonstrated a delay in the onset and a reduction in the incidence of SREs, when compared with placebo, and sustained and significant reduction of bone-related pain in patients with lung cancer with bone metastases.[9,29] In a double-blind, placebo-controlled, 21-month trial, 773 patients with bone metastases from solid tumors, including patients with lung cancer (244 with NSCLC and 38 with small cell lung cancer [SCLC]) were given 4 mg ZOL every 3 weeks. ZOL reduced the risk of developing the SRE at 21 months by 31% (hazard ratio [HR] = 0.693, $p = 0.003$).[9,29] Treatment with IV ZOL 4 mg every 3 to 4 weeks also delayed the onset of SREs, extending the time to first SRE by nearly 3 months relative to placebo (236 versus 155 days; $p = 0.009$) (Figures 4 and 5).

These findings are further supported by a retrospective study of 2539 patients with lung cancer with bone metastases (2174 nontreated and 365 treated with ZOL) as reported by Hatoum et al.[43] This study used data derived from a claims database of 80 health plans across the United States between 2002 and 2006. They found that in patients with lung cancer treated with intravenous (IV) ZOL 4 mg every 3 to 4 weeks,

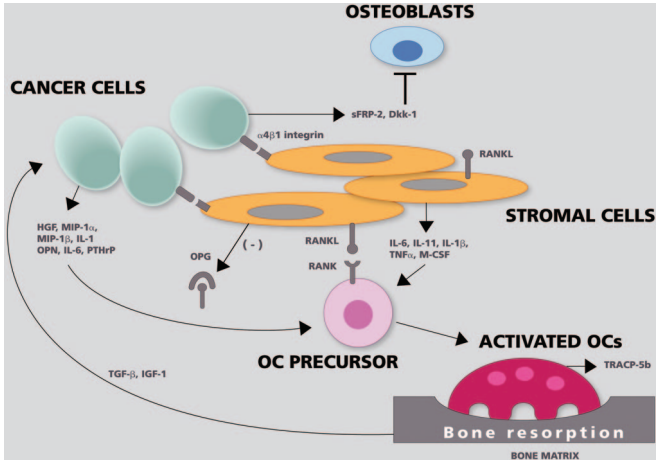

FIGURE 3. Cellular mechanisms of osteoclast-mediated bone resorption: cancer cells produce factors that stimulate both osteoclast and osteoblast activity. Overproduction of cytokines with osteoclast activation function results from interaction between cancer cells and stromal cells. Interleukin (IL)-6, IL-11, IL-1β, tumor necrosis factor (TNF)α, and macrophage colony-stimulating factor (M-CSF) are produced predominantly by stromal cells, whereas hepatocyte growth factor (HGF), macrophage inflammatory protein (MIP)-1α, MIP-1β, IL-1, osteopontin (OPN), IL-6, and parathyroid hormone-related protein are primarily produced by myeloma cells. Receptor activator of NF-kappaB (RANK) ligand (RANKL), a potent activator of osteoclasts, is expressed and secreted by stimulated stromal cells. RANKL binds to RANK on the surface of precursor and mature osteoclasts, activating bone resorption. When the ratio of RANKL/osteoprotegerin (OPG) is skewed in favor of RANKL, the normal regulatory effect of OPG is bypassed. This results in increased osteoclastogenesis and osteoclast function. The disruption of this RANK/RANKL/OPG axis is regarded as the main cause of the progression of bone metastases.

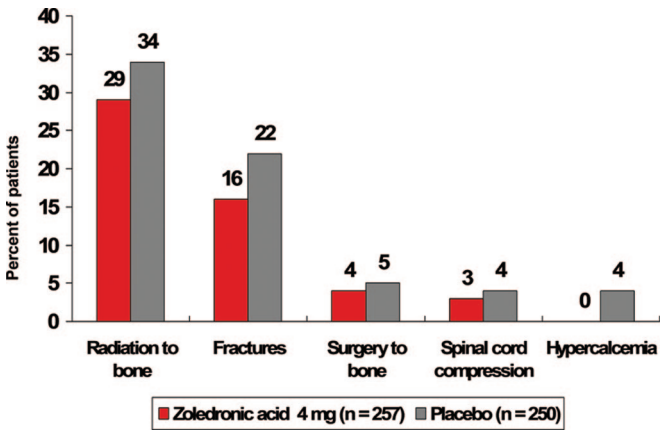

FIGURE 4. Graph based on data from Rosen et al.[76] shows that zoledronic acid reduced the proportion of patients with a skeletal-related events (SRE) across all types of SRE.

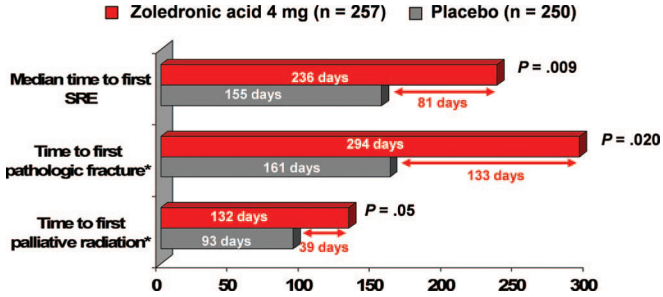

FIGURE 5. Graph of data from Rosen et al. demonstrates that zoledronic acid increased the median time to the first skeletal-related event (SRE).[29]

the risk of SREs was reduced by 30 to 40% (odds ratio [OR] = 0.727; 95% CI = 0.594–0.890) and the time from diagnosis to the first bone complication was increased by 85% (log regression model, 95% CI= 60.6–114.2%).

CURRENT GUIDELINES FOR BP USE IN LUNG CANCER SETTINGS ACROSS EUROPE

Most recent American and European treatment guidelines only address BP use in other cancer types, such as breast cancer[44] or multiple myeloma.[25,45,46] Although the National Comprehensive Cancer Network practice guidelines for 2008 do mention BP treatment for patients with lung cancer, it is only recommended for alleviation of diffuse bone pain, as part of general supportive care for all cancer patients.[47]

No European guidelines currently exist addressing BP use for patients with lung cancer with respect to the prevention or delay of SREs. Nevertheless, an international panel of experts, examining the results presented by Rosen et al.[9,29] (Figure 2), recommended that patients with lung cancer with bone metastases and a reasonable chance of benefiting (e.g., expected survival times and performance status) should be considered for ZOL treatment.[48] A separate group of international experts, looking at the same disease setting, further recommended screening for bone metastases at the initial diagnosis and staging, to allow more timely and effective treatment of bone metastases with bone-targeting therapy.[49]

EXPERT RECOMMENDATIONS FOR BP USE IN THE LUNG CANCER SETTING

In response to the variations that exist across Europe regarding the role of BPs in the treatment of lung cancer, a panel of European experts met to examine the current evidence and to agree on specific treatment recommendations for clinicians treating patients with lung cancer with bone metastases (Table 1).

TABLE 1. Summary of the Expert Panel Recommendations on the BP Use in Patients with Lung Cancer

Diagnosis of bone metastases	Patients with lung cancer should be investigated for bone metastases at the initial staging of disease to assess symptomatic and to screen for asymptomatic bone metastases, to allow accurate monitoring of progression of bone disease, and to initiate bone-specific therapy
	Bone assessment of patients with lung cancer should ideally be based on PET scan. If not available, bone scan should be used
Use of BP therapy	In patients with lung cancer (NSCLC and SCLC) diagnosed with bone metastases, bisphosphonate treatment must be considered part of the treatment to prevent and delay the occurrence of further bone metastases and SREs and to relieve pain, where present
Initiation of BP therapy	In patients with lung cancer (NSCLC and SCLC) who develop bone metastases during the course of their disease, bisphosphonates should be added to their treatment. A comprehensive dental examination before the start of treatment is recommended
Duration of BP therapy	Bisphosphonate treatment in patients with lung cancer should be continued for as long as it is practically feasible in the absence of any significant adverse effects
Combination with other therapies	Combination of bisphosphonates and chemotherapy is generally well tolerated, based on the published safety precautions, and may have synergistic effects
Final recommendations	Based on the currently available data, there is consensus to recommend ZOL acid for the therapy of patients with lung cancer with bone metastases

BP, bisphosphonates; PET, positron emission tomography; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ZOL, zoledronic.

DETECTION AND MONITORING OF BONE METASTASES IN PATIENTS WITH LUNG CANCER

Because of the morbidity associated with SREs, diagnosis and early treatment of bone metastases are vital to maintain the patients' QoL and functional independence. Current recommendations by ESMO advise that bone scans should only be performed during the staging of lung cancer in those patients who present with bone pain or clinical characteristics consistent with the existence of bone metastases.[50] Nevertheless, bone metastases may be asymptomatic in the early stage, and waiting until patients develop bone pain may result in underdiagnosis of bone metastases that could result in a lost treatment opportunity in this setting. Failure to detect bone metastases may lead to an inconsistent or incomplete staging and also result in less effective treatment strategies.[49,51] Patients with asymptomatic bone metastases may have an increased benefit from BP therapy, when compared with those with symptomatic bone metastases, as demonstrated in a study of prostate cancer patients.[14]

Analysis of the incidence of bone metastases in patients with NSCLC using bone scans over a period of 15 years has yielded different results, ranging from 8 to 34%.[7] Nevertheless, after the development of more sensitive positron emission tomography (PET) technology, the incidence of bone metastases was more accurately estimated at 24% and 30% in American and Japanese populations, respectively.[5–7] Higher sensitivity for detecting bone metastases is also provided by whole body magnetic resonance imaging. To monitor patients for the development of bone metastases, a convenient, radi-

ation-free, and easy to repeat method is essential. Research on such methods should be encouraged.

The expert panel strongly recommends screening of patients with NSCLC for bone metastases at the initial staging of disease, to detect asymptomatic bone metastases and allow accurate tracking of disease progression. Although PET scans were considered distinctly superior to bone scans in the detection of bone metastases, access to the appropriate diagnostic tools may currently be limited for some clinicians. Therefore, it is advised that every patient diagnosed with lung cancer should have a bone scan at initial staging, unless they have already received a PET scan.

INITIATION OF BP TREATMENT

Findings of a recent study suggest that initiation of BP treatment for bone metastases in NSCLC, early in the course of the disease, is the optimal treatment strategy.[15] Indeed, initiation of BP treatment before the onset of SREs has also been found to be the most effective strategy in the treatment of bone metastases in other solid tumor settings, such as breast and prostate cancer.[52,53] Therefore, BPs should ideally be used as part of first-line therapy, alongside other treatment strategies, to delay or prevent progression of bone disease and SREs, and to relieve pain, where present (Figure 2).

Although, at the current time, there are in vitro data addressing the positive interactions that may occur between BPs and other first-line drugs, the expert panel reached a consensus for concomitant BP use in this setting. Preliminary evidence available with ZOL suggests that this may even lead to improved treatment outcomes similar to those in other solid tumors.[54] In a subset of the Adjuvant Zoledronic Acid to Reduce Recurrence clinical trial in breast cancer patients, ZOL combined with neoadjuvant chemotherapy achieved a significantly greater shrinkage of the primary tumor than chemotherapy alone.[54] Although BP therapy should be considered an option in all patients with advanced lung cancer, the panel recommends that BP treatment decisions for patients with poor Eastern Cooperative Oncology Group performance status (3–4) should be taken on an individual basis, addressing primarily palliative endpoints.

DURATION OF TREATMENT WITH BPS

In the absence of available data regarding the optimal duration of BP treatment for bone metastases in patients with lung cancer, the panel advises that BP treatment during first- and second-line therapy should be continued for as long as it proves feasible. Progression of bone disease or the occurrence of an SRE alone should not necessarily trigger discontinuation of BP therapy, because this might influence the occurrence of subsequent SREs.[13,55]

SELECTION OF PATIENTS FOR BP THERAPY

With the emergence of more effective NSCLC treatments, a subgroup of patients with advanced lung cancer and bone metastases will survive for more than a year after diagnosis and could potentially benefit from BP treatment. Therefore, it is strongly advised to start patients on BP treatment before the emergence of symptoms of bone metastases to reduce the number or delay the occurrence and/or progression of SREs. In addition to the existing data on prognostic factors or predictive markers,[56] research should be encouraged to identify a patient subgroup with better outcome based on clinical and biologic characteristics.

Bone markers may provide a powerful laboratory tool for monitoring patients with bone metastases and could possibly be used to select for this long-lived subgroup of patients. A retrospective analysis conducted by Hirsh et al.[15] revealed a statistically significant correlation between ZOL treatment and increased survival versus placebo in patients with NSCLC with high-baseline amino-terminal crosslinking telopeptide of collagen levels (Figure 6). Nevertheless, such markers will need to be prospectively validated before implementation, and therefore at this stage the panel does not recommend the use of bone markers in the clinical routine treatment of patients with lung cancer with bone metastases.

Based on the only published studies,[9,29] which included patients with SCLC with bone metastases, the panel suggests that these patients should be treated following the same recommendations as patients with NSCLC.

SELECTION OF BPS

Currently, ZOL has the best data in lung cancer, both in vitro and in the clinical setting. Other BPs are being explored in phase II studies for use in lung cancer. The panel strongly recommends ZOL (4 mg IV/3–4 weeks) for the therapy for patients with lung cancer with bone metastases in the absence of randomized clinical trial data with other BPs.

QOL AND PHARMACOECONOMIC CONSIDERATIONS IN BP TREATMENT

SREs lead to a loss of functional capacity, an increase in emergency care, days of hospitalization, and increased need for external medical services and further indirect social costs. This typically results in significantly increased treatment costs[57] (Figure 7).

Several recent studies have investigated the economic value of treatment with ZOL, when compared with placebo in patients with lung cancer with bone metastases in the United Kingdom, France, and Germany.[58–60] In each case, treatment with ZOL was found to improve QoL and provide a clear economic benefit. For example, the use of ZOL was associated with a reduction in SRE costs per person of €2486 in Germany and €1652 in the United Kingdom.[59]

Therefore, it is strongly recommended that, both for the QoL of the patient and for overall cost savings, the long-term cost of BP treatment should be considered by health care systems when defining the therapeutic strategy in this clinical setting.

SAFETY OF BPS IN PATIENTS WITH LUNG CANCER

Being almost entirely cleared by the kidneys, IV BPs have been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, preexisting renal impairment, concomitant use of other nephrotoxic drugs, and the lack of adherence to the

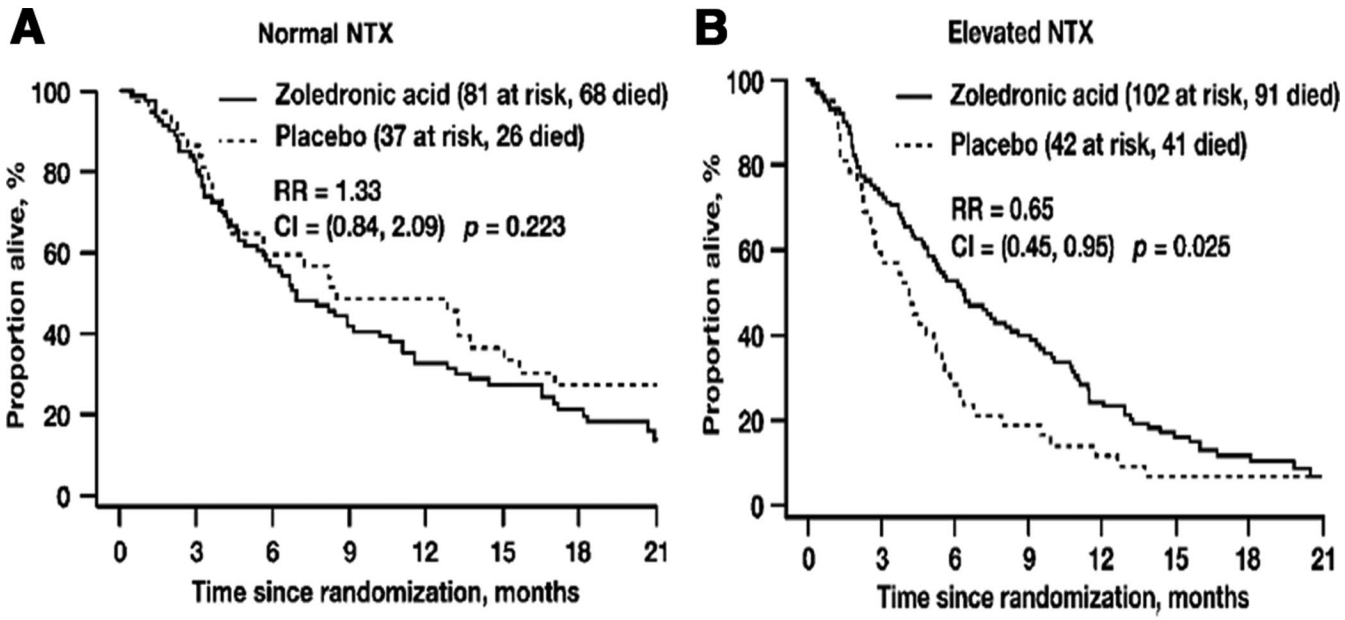

FIGURE 6. Survival patterns of patients with non-small cell lung cancer (NSCLC) based on NTX levels at baseline. Graphs are adapted with permission from *J Thorac Oncol* Copyright 2008.[15] NTX, amino-terminal crosslinking telopeptide of collagen.

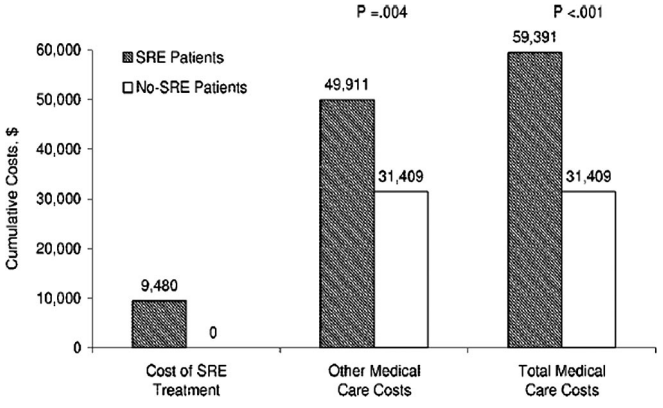

FIGURE 7. Kaplan Meier estimated cumulative costs of skeletal-related event (SRE)- and non SRE-related care. Graphs are adapted with permission from *J Thorac Oncol* Copyright 2006.[57]

recommended infusion time. The product label for ZOL acid, i.e., the only BP licensed in Europe for the treatment of bone metastases in patients with lung cancer, recommends to assess the serum creatinine and creatinine clearance before starting treatment and monthly before each dose. Dose adjustment is recommended in patients with mild to moderate renal impairment, whereas ZOL acid is not recommended in patients with severe renal impairment. Although osteonecrosis of the jaw (ONJ) is rare in patients with cancer-induced bone disease and is usually associated with dental trauma or suboptimal dental hygiene,[61,62] a dental examination by a qualified dentist should be performed before initiation of BP treatment in patients with lung cancer, to avoid any occurrence of ONJ.[62] Recent studies on ONJ during BP treatment showed that preventive measures and oral health care can reduce the incidence by almost threefold.[63] In addition, antibiotic prophylaxis may prevent ONJ occurrence after dental procedures.[62] Ripamonti et al.[62] observed a reduction from 3.2 to 1.3% when comparing pre- and postimplementation of a preventative measures program. So far, there have been no reports of ONJ in patients with lung cancer.

FUTURE DIRECTIONS FOR BP USE

Recent evidence, both in vitro and from some early clinical studies, has shown that ZOL may have additional therapeutic activities beyond the reduction in the risk of SREs or pain relief.[64] Preclinical tests have shown that ZOL can impede tumor growth, both in the bone and overall.[65] This may be due to several additional effects reported for some BPs (particularly ZOL) on tumor migration, adhesion, and invasion across membranes,[66] or their antiangiogenesis or immunomodulatory activities.[67–72] Interestingly, a study examining the in vitro and in vivo effect of ZOL on a murine lung cancer cell line, which simulates NSCLC, found that the drug had an antiproliferative effect in vivo, arresting cells at the S/G2/M phase of the cell cycle.[73] Further, ZOL-treated mice in this study were found to have slower tumor growth and a significantly longer lifespan than those who did not receive treatment.

The antitumor effect of BP treatment has already been observed at a clinical level in a number of other malignancies. In a subset analysis of patients with renal cell carcinoma, ZOL was found to delay disease progression, when compared with placebo.[74] Most notably, a study by Gnant et al.[64] of premenopausal women with endocrine-positive breast cancer found that the addition of ZOL to adjuvant endocrine therapy significantly prolonged the disease-free and recurrence-free survival periods, when compared with adjuvant endocrine therapy alone (disease-free survival increased by 36%, HR = 0.64; $p = 0.01$; relapse-free survival increased by 35%,

HR = 0.65, $p = 0.015$). Evidence of increased tumor shrinkage from the Adjuvant Zoledronic Acid to Reduce Recurrence trial[54] and data from the ZO-FAST trial in breast cancer support a clinically relevant antitumor activity of ZOL.[75] The available evidence suggests that ZOL may also act by directly affecting tumor progression, possibly in synergy with other therapeutic treatments.[52,54]

Currently, a large, phase III, international randomized prospective trial is underway examining the efficacy of ZOL in delaying or preventing bone metastases in patients with successfully treated stage III NSCLC.

SUMMARY OF PANEL RECOMMENDATIONS

- Patients with lung cancer should be investigated for bone metastases at the initial staging of disease to assess symptomatic and to screen for asymptomatic bone metastases, to allow accurate monitoring of progression of bone disease, and to initiate bone-specific therapy.
- Bone assessment of patients with lung cancer should ideally be based on PET scan. If not available, bone scan should be used.
- In patients with lung cancer (NSCLC and SCLC) diagnosed with bone metastases, BP treatment must be considered part of the treatment to prevent and delay the occurrence of further bone metastases and SREs and to relieve pain where present. BP treatment in patients with lung cancer should be continued for as long as it is practically feasible in the absence of any significant adverse effects.
- In patients with lung cancer (NSCLC and SCLC) who develop bone metastases during the course of their disease, BPs should be added to their treatment. A comprehensive dental examination before the start of treatment is recommended.
- Combination of BPs and chemotherapy is generally well tolerated, based on the published safety precautions, and may have synergistic effects.
- Based on the currently available data, there is consensus to recommend ZOL for the therapy for patients with lung cancer with bone metastases.

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