Research Article

Incidence and consequences of bone metastases in lung cancer patients

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ABSTRACT

Background: Bone metastases (BM) are common in NSCLC patients. Despite some potential positive effects of bone-targeted therapies, their use in NSCLC is infrequent, which may relate to the overall poor prognosis of advanced lung cancer. We reviewed the literature to evaluate the incidence, consequences and use of bone-targeting agents in lung cancer patients with BM in both the trial and non-trial clinical setting.
Methods: Published prospective and retrospective papers investigating lung cancer and BM, in trial and non-trial settings, were identified and are discussed in this review.
Results: BM are common in patients with advanced lung cancer and often present symptomatically with pain and skeletal related events (SREs). Patients with high bone turnover marker levels, multiple BM, and history of pathological fractures have shorter overall survival. In randomized studies bone-targeted therapies reduced the risk of SREs and prolonged the time to first SRE. The use of bone-targeted agents may also be associated with a survival benefit.
Conclusion: BM are a common problem in advanced lung cancer. While the benefits of bone-targeted therapies have been demonstrated, their use is limited in non-trial populations. If better predictive markers of individual risk were available this might increase the appropriate use of bone-targeted agents.

1. Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide [1]. With modern cancer therapies, the 5 year survival rate for all lung cancer stages is around 16% [1], with a median overall survival of 9–13 months for advanced non-operable disease [2]. Bone is a common site of metastatic cancer spread in NSCLC patients (20–40%), comparable in frequency to liver (25–30%) and the contralateral lung (40–50%) [2–5]. The reported variability in sites of metastatic spread clearly differs between studies and is associated with whether data was obtained from imaging or autopsy series [6].

In patients who develop bone metastases, these are commonly diagnosed at the time of their initial work up for their metastatic disease (∼80%) [7], although others can develop skeletal metastases at any time during the disease course. The consequences of bone metastases include pain (∼80%) [3,6,8] and skeletal-related events (SRE's). SREs are defined as: pathological fractures; spinal cord or nerve root compression; the requirement for surgery or radiotherapy to bone; or hypercalcemia of malignancy. SREs occur in approximately half of lung cancer patients with bone metastasis [3,9,10]. Not surprisingly, these events negatively impact quality of life, performance status, and independent functioning. In addition, patients who experience one SRE are then at significant risk for developing additional SRE's and may possibly have a shorter survival [3,9]. It is not surprising therefore that the diagnosis of bone metastases and the occurrence of SREs frequently require therapeutic intervention, with an associated impact on increased health care costs [11,12].

The exact mechanism of bone breakdown is not fully understood in lung cancer. However, it is likely similar to what has been observed in bone metastases arising from other tumour types. Bone breakdown, or osteolysis, results from a disruption of the normal balance of bone resorption and formation controlled by opposing functions of the osteoclast and the osteoblast. As osteoclast activity is responsible for bone degradation, it has become an important target for drug intervention leading to the development of bisphosphonates and more recently the antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL), denosumab. A number of trials have shown that treatment with osteoclast inhibiting agents is associated with a reduction in both the risk of, and time to development of SREs [13–17].

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Bone-targeted therapies appear to be less commonly used in patients with bone metastases arising from lung cancer (6–50%) as compared with those from breast (80%) and prostate cancers(23%–70%) [3,7,18–20]. The reasons for this discrepancy are unknown, however may reflect the belief that patients with bone metastases from advanced lung cancer already have such a poor outcome that bone-targeted therapies are unlikely to significantly help as there is insufficient time for significant bone re-modelling. To further evaluate whether this is true we decided to review the literature in order to evaluate the frequency, consequences, and outcome of patients with lung cancer and bone metastases. We further examined literature describing the impact of bone-targeted therapy in both clinical trial and non-trial populations. This review could help determine whether or not the use of these agents may be warranted.

2. Methods

Searches were performed using Pubmed for articles published between 1977 and 2012 on prospective and retrospective studies related to lung cancer and bone metastasis. We initially identified papers that included the keywords non-small cell lung cancer and bone metastases. Using these initial search parameters, we identified 376 published articles and abstracts. Subsequent the further keywords: SRE, bisphosphonates, and denosumab were searched with non-small cell lung cancer to identify other relevant manuscripts. Further manuscripts were identified from reference lists of the primary papers.

Studies that were not specific to lung cancer, pre-clinical studies, other reviews and those not published in English were excluded.

In this review we discuss both prospective randomized trial data and 'non-trial' data, which is primarily comprised of retrospective series, retrospective analysis of prospective studies, insurance claim data and prospective observational data.

3. Results

In total, twenty nine articles matched the criteria for detailed review. Most of the literature was "non-trial" data that consisted of retrospective chart reviews, insurance claim data, retrospective analyses of prospective trials and 1 prospective observational study. "Trial" data included only two randomized, phase III (with additional long-term data on one of them) trial, one randomised phase II trial, two open label prospective and one single arm prospective studies.

3.1. Incidence and sites of bone metastases

The reported incidence of bone metastases in lung cancer was found to be quite variable and dependent on diagnostic tools, duration of follow up and the specific population studied. Earlier studies (1970s–1990s) using mainly X-ray and bone scans, reported an incidence of bone metastases in lung cancer patients ranging between 8–20% [4,21–24]. More recent data including that obtained from PET and CT scans has reported a higher incidence of bone metastases ranging from 20–40% [3,7,25–28]. In these patients, 40–80% had bone metastases detected at the time of initial staging for suspected advanced disease [1,3,4,7,9,29]. Bone only disease was relatively uncommon occurring in ∼1–7% of lung cancer patients with advanced disease [4,30] comparing to metastatic breast cancer were bone only involvement occurs in about 17–37% of patients [31]. In addition, multiple bone meta-static lesions were much more common (80%) than single sites of bone metastases (20%) [9,26]. The spine was reported to be the most common site of metastatic disease (40–50%), followed by ribs (20–27%) and pelvis (17–22%) [3,7,26]. With respect to the histological type of lung cancer, most studies did not include patients with small cell lung cancer (SCLC) and those that did rarely discussed them separately from NSCLC. Hence it remains uncertain whether the incidence of bone metastases differs between NSCLC and SCLC.

3.2. Consequences of bone metastases

The consequences of bone metastases can be broadly divided into reduced survival, SREs, and pain.

3.2.1. Overall survival

In breast cancer patients the presence of bone predominant metastases appears is associated with longer survival compared to the presence of visceral metastases [32]. In contrast, in lung cancer patients the presence of bone predominant metastases is not associated with longer survival [3] (Table 1). Indeed one small retrospective study suggested a reduced survival for patients with bone metastases compared to patients without bone metastases (8.1 months vs. 15.1 months, $p=0.007$) [27]. This however, could reflect the fact that bone only metastatic disease is relatively uncommon in advanced lung cancer patients, something quite distinct from advanced breast cancer.

One retrospective study that evaluated predictors of survival in lung cancer patients with bone metastases showed that the presence of multiple bone metastases or the occurrence of pathological fractures was associated with significantly shorter survival compared to patients with single metastases or no fracture

Table 1
Consequences of the occurrence bone metastases and SREs on survival.

Study	Overall survival without bone metastases	Overall survival with bone metastases	Overall survival with bone metastases and SRE	Refs.
Tsuya A et al., retrospective study	**7.9** months	**7.9** months	**6.2** months	[3]
Sugiura H et al., retrospective study	*n/a*	**7.2** months	*n/a*	[26]
Sekine I et al., retrospective study	*n/a*	**15** months	*n/a*	[28]
Sun JM et al., retrospective study	*n/a*	**12.7** months	**12.3** months	[7]
Spizzo G et al., retrospective study	**15** months	**8** months	*n/a*	[27]
Decroisette C et al., prospective, observation, multicenter study	*n/a*	**5.8** months	**5.3** months	[9]
Rosen LS et al., prospective, randomized, phase III study	*n/a*	**6** months	*n/a*	[13]
Delea TE et al., retrospective study	*n/a*	**2.5** months	**3.8** months	[12]

[26]. The same study also found that a performance status 0–1, presence of adenocarcinoma compared to the other types of lung cancer, receiving chemotherapy, or treatment with EGFR tyrosine kinase inhibitors (TKIs) were also associated with a more favourable prognosis (Table 2).

In order to assess impact of pathological fractures on survival in different cancer types a retrospective analysis using data from three large, phase III, placebo-controlled randomized studies evaluating the efficacy of zoledronic acid in multiple myeloma, breast, prostate, lung and other tumour types was conducted [33]. The analysis demonstrated that patients with metastatic breast, prostate cancer and multiple myeloma who had pathological fracture were at increased risk for death. However, in metastatic lung cancer patients there was no difference in survival between patients with and without pathological fractures. This could be explained by the short overall survival of advanced lung cancer patients (183 days in placebo group and 203 in zoledronic acid group, $p=0.623$ in this analysis) entered into this study.

A retrospective analysis assessing the prognostic significance of baseline bone turnover markers in NSCLC patients with bone metastases enroled into a prospective, phase III, randomized trial comparing efficacy of zoledronic acid to placebo was performed. In this study, high versus normal baseline urinary NTX (N-telopeptide of type I collagen) correlated with more than a twofold increased risk of bone lesion progression and death in the placebo group ($p=0.039$ and 0.001 respectively) [16]. This suggests a similar prognostic utility of NTX in bone metastatic lung cancer as has been reported in other tumour types [34].

3.2.2. SREs

3.2.2.1. Incidence of SREs in non-trial populations.
SREs have been used as a measure of the consequence of bone metastases and the benefits of bone-targeted therapies for over 20 years. In non-trial populations, between 30–60% of patients with bone metastases from lung cancer had at least one SRE and 30% of patients experienced multiple SREs through the course of their disease [3,7,9,10,27,28,35]. Both randomized and non-randomized data

Table 2
Predictor of survival in patients with bone metastasis of lung cancer [26].

Prognostic factors		Survival, months	p
Gender	Female ($n=41$)	13	0.02
	Male ($n=77$)	7.9	
Performance status	0-1 ($n=67$)	11.6	0.001
	2–4 ($n=51$)	7.1	
Type of NSCLC	Adenocarcinoma ($n=83$)	11.3	0.001
	Other ($n=35$)	5.8	
Number of bone metastases	Single ($n=19$)	14	0.02
	Multiple ($n=99$)	8.9	
Pathologic fracture	No ($n=103$)	10.2	0.04
	Yes ($n=15$)	6.4	
Chemotherapy	Yes ($n=67$)	11.4	0.0009
	No ($n=51$)	7.5	
EGFR TKI treatment	Yes ($n=14$)	17.8	0.0001
	No ($n=104$)	8.6	

Table 3
Distribution of skeletal related events (SRE) between patients with bone metastases in different studies.

Type of study	Pathological fractures (%)	Spinal cord compression (%)	Hypercalcemia	Need to surgery (%)	Need to radiotherapy (%)	Refs.	
Trial population	17	3	1%	4	26	ZA arm Patients with BM=523	[13]
	21	4	3%	5	32	Placebo arm Patients with BM=250	
Non-trial population	7.1	15.7	20.0%	0	34.3	[3] Retrospective study Patients with BM=70	
	16.4	6.7	9.2%	9.2	42	[9] Prospective study Patients with BM=554	
	13.1	12.2	0.8%	0.8	73.9	[7] Retrospective study Patients with BM=273	
	0	0	4.8%	0	19.5	[27] Retrospective study Patients with BM=41	
	1.3	1.3	4.2%	0.8	44	[28] Retrospective study Patients with BM=243	
	10.3	14.9	n/a	12.6	49.4	[25] Retrospective study Patients with BM=372	
	13	1.7	n/a	4.2	52	[26] Retrospective study Patients with BM=118	
	35	6	7%	14	68	[12] Retrospective study Patients with BM=534	
	18.3	10.7	0%	13.7	65.3	[35] Retrospective study Patients with BM=196	

have shown that the occurrence of a first SRE significantly increases the risk of subsequent SREs [13,36].

The most commonly reported SREs in bone metastatic lung cancer are radiotherapy (50–70%), pathologic fractures (7–35%), hypercalcemia (1–20%), spinal cord compression (1–15%) and surgery for bone metastases (0–9%) [3,7,26,28,35] (Table 3). The median time to first SRE was 8.9 months (95% CI, 6.1–11.7 months) in one retrospective study [7] ($n=273$ patients), while another reported that 31% of patients experienced their first SRE at time of initial diagnosis of bone metastases. ($n=70$) [3]. Sekine et al. reported that the first SRE occurred within 6 months of starting chemotherapy in 40.7% of cases ($n=243$ patients with bone metastases) [28]. An additional retrospective analysis of 2539 patients found the median time to first SRE was as short as 40 days [37].

In breast and prostate cancer metastatic to bone, the literature would suggest that patients with bone metastases who have an SRE have a worse median survival than those patients with bone metastases who do not have an SRE [33,38,39]. In contrast, the lung cancer literature suggests that the occurrence of an SRE in patients with bone metastases is not associated with a reduced survival [9,10,12] (Table 1). However, it is unclear whether this is simply a result of the generally reduced time of overall survival in lung cancer versus breast or prostate cancer or is a specific difference of the behaviour of the various tumour types in the bone.

3.2.2.2. Incidence of SREs in clinical trial populations.
Relatively few clinical trials have reported randomized data assessing the effect of bone-targeted therapies in lung cancer patients [13,17]. Of these, only one randomized study contained a placebo arm [13]. In this trial comparing the efficacy of zoledronic acid and placebo in metastatic bone disease from solid tumours, approximately half the enroled patients had metastatic lung cancer. During the study which included 9 and 21 month follow up data, the incidence of SREs was 44% and 46% respectively in the placebo group (for all types of solid tumors, 50% of which were lung cancer patients). Similar to the non-randomized population, radiotherapy was the most common SRE (32%) followed by pathological fractures (21%). However, spinal cord compression and hypercalcemia of malignancy were lower in these cohorts than in the non-trial populations. The average time to first on study SRE was 5 months [14] as compared to 1.5 to 8.9 months reported in non-trial settings [7,37].

3.2.2.3. Predictors of individual patient SRE risk.
In a retrospective study looking at predictors of SRE risk in lung cancer patients with bone metastases, it was found that patients with a history of smoking (5.2 months vs. 11.6 months, $P=0.004$), non-adenocarcinoma histology (3.1 months vs. 11.5 months, $P < 0.001$), and no EGFR TKI treatment (3.3 months vs. 11.8 months, $P < 0.001$) had significantly shorter median time to first SRE. These patients were at least twice as likely to have SRE on univariate analysis, however on multivariate analysis only ever smokers had statistically significant increased risk for SREs (odds ratio, 2.80; 95% CI, 1.32–6.00, $p=0.007$) [7]. Recently presented data supports a positive impact of EGFR activating mutation (either exon 19 deletion or L858R in exon 21) on outcome of patients with bone metastases secondary to lung cancer. The incidence of SRE was significantly lower (21% vs. 36%) and time to first SRE was longer (13 months vs. 6 months) in EGFR mutation positive patients treated with an EGFR TKI, compared with EGFR mutation negative patients mostly treated with platinum based chemotherapy [40].

A further retrospective study evaluated risk factors for SREs in metastatic lung cancer patients (with or without bone metastases) receiving first line palliative chemotherapy. This demonstrated that male sex, poor performance status and the presence of multiple bone metastases were associated with a shorter time-to-the first SRE and poor SRE-free survival [28].

3.2.3. Pain

Pain occurs in ~80% of lung cancer patients with bone metastases [3,9]. Usually multiple therapeutic interventions including localised therapies (radiotherapy and/or surgery) systemic therapy (chemotherapy, bisphosphonates), and analgesics are required to manage pain associated with bone metastases. There is limited data on the impact of EGFR inhibitors on bone pain [41,42]. Surprisingly there is relatively little data describing the degree of bone pain in the lung cancer literature, and the majority of published data is restricted to describing the incidence of bone pain and/or use of analgesics for pain. One Japanese retrospective study reported an 80% incidence of pain, 70% use of non-steroidal anti-inflammatory drugs (NSAIDs) and 70% use of opioids in lung cancer patients with bone metastasis. In a prospective observational French study, 89% of lung cancer patients with bone metastases required analgesic treatment, more than 70% of patients needed opioids, and 20% required NSAIDs for pain control [3,9,25].

One of the most common treatments for palliation of bone pain is radiation therapy, which can give pain relief in 65–100% of cases. Two meta-analyses from a variety of tumor types including lung cancer found the comparable efficacy of different doses and fractionations given for palliation of bone pain, however need for re-treatment was significantly higher in patients treated with a single fraction regimen [43,44]. Therefore single fraction radiotherapy is generally reserved for patients with poor performance status and a short life expectancy [45].

3.3. Bone-targeted therapies in lung cancer

3.3.1. Clinical trial data

Data regarding the use of bisphosphonates in NSCLC patients with bone metastases are surprisingly limited (Table 4). There is only one prospective randomised trial that evaluated the efficacy of zoledronic acid (in two different doses of 4 mg and 8 mg, given every 3 weeks, the 8 mg dose was subsequently reduced to 4 mg due to concerns over renal safety at the higher dose) versus placebo in lung cancer. This study enroled 773 patients with metastatic bone disease secondary to solid tumors (excluding breast and prostate cancer), and 378 patients had metastatic lung cancer. The primary endpoint was the proportion of patients with one or more SRE at 9 months and at 21 months. Zoledronic acid was shown to delay time to the first SRE (230 days vs. 163 days, $p=0.023$) and significantly reduced the risk of developing SREs as determined by multiple event analysis (HR=0.73, $p=0.017$) in all tumour types. Reduction in number of SREs (hypercalcemia of malignancy was excluded from analysis) did not reach statistical difference for the comparison of 4 mg zoledronic acid versus placebo (44% in placebo group vs. 38% in 4 mg zoledronic acid group, $p=0.127$), but the difference was significant for 4/8 mg zoledronic acid group compared to placebo (44% vs. 35%, $p=0.023$). When hypercalcemia of malignancy was added to the analysis the difference in SRE was significant in both groups (38% vs. 47%, $p=0.039$ in 4 mg zoledronic acid, 35% vs. 47% in 4/8 mg zoledronic acid, $p=0.006$) compared to placebo group. [13]. There was no significant difference in SRE outcomes between NSCLC and other solid tumors on subgroup analysis. It is interesting to note that the definition of SREs has also evolved over time. In all the initial bisphophonate trials hypercalcaemia of malignancy was classified as an SRE [46,47].

Table 4
Impact of bone-targeted agents on SREs.

Study	Type of tumour	Agents	SRE rate	Time to 1st SRE	Survival
Zoledronic acid vs. placebo in the treatment of skeletal metastases in patient with lung cancer and other solid tumors: a phase III, double-blind, randomized trial [13].	NSCLC 50%	ZA Placebo	36% 46%	236 days 155 days	189 183
Randomized, double-blind study of denosumab vs. zoledronic acid in the treatment of bone metastases in patient with advanced cancer (excluding breast and prostate cancer) or multiple myeloma [17].	NCSLC 40%	ZA Denosumab	n/a n/a	489 days 618 days	n/a Significant risk reduction of death in NSCLC (HR 0.79)

Indeed in the past the incidence of hypercalcaemia of malignancy was high enough to perform distinct clinical trials of bisphosphonates in this patient population [48] Over time as the incidence of hypercalcaemia has fallen with much wider use of bone-targeted agents early in disease presentation as has increased our knowledge around its aetiology and the pivotal role of PTHrP. Hypercalcaemia in lung cancer is also seen as a result of ectopic secretion of PTHrp in the absence of bone metastases [49].

Therefore in more recent trials some have classified hypercalcaemia as an SRE for analysis [50] while others have not or make a separate assessment [17,51,52].

Long term treatment and follow up of prospective randomized comparison zoledronic acid to placebo confirmed the efficacy of zoledronic acid in prolonging time to first on-study SRE (236 days vs. 155 days, $p=0.009$) and reduction of annual incidence of SRE (2.71 in placebo vs. 1.74 in zoledronic acid group, $p=0.012$) [14] in all types of cancer enroled in the trial. The retrospective analysis of this prospective study has shown that zoledronic acid reduced the risk of subsequent SREs by 31% in patients with previous events [15], as well as could reduce relative risk of death by 35% in patients with high baseline NTX levels at study entry [16]. However, no overall survival benefit was shown for the study population as a whole [14]. No prospective randomized phase 3 studies with any other bisphosphonate in comparison to placebo have been performed in lung cancer patients.

Several small trials have investigated the use of bisphosphonates in metastatic lung cancer; however their measured outcomes were mainly in terms of their impact on bone pain relief and their ability to decrease pain or analgesic use [53–56]. One open-label non-randomized study investigated 144 good performance status patients with lung cancer metastatic to bone, where 87 patients had pain so received zoledronic acid along with chemotherapy, whereas the 57 asymptomatic patients received only chemotherapy. Investigators found improved tumour response, prolonged time to progression ($p < 0.001$) and prolonged median survival ($p < 0.001$) in patients treated with zoledronic acid [57]. Conclusions from the statistical analysis of this paper should be interpreted with caution as it was a non-randomised study with clearly unbalanced arms. In contrast, data from a randomised, exploratory phase II study in 150 patients with inoperable stage III and/or stage IV NSCLC failed to show any difference in disease progression, time to progression and disease progression to bone when zoledronic acid was added to chemotherapy versus chemotherapy alone [58].

Recently published systematic review and meta-analysis investigating a role of bisphosphonates in patients with lung cancer and bone metastases found that patients treated with zoledronic acid in addition to chemotherapy had significantly fewer SREs (RR 0.81, 95% CI 0.67–0.97). Pain control was better in patients who received bisphosphonates in addition to chemotherapy or radiotherapy (RR 1.18, CI 1.0–1.4). There was a trend to increased overall survival but the difference did not reach statistical significance (mean 72 days, 95% CI 8.9–152.9) [59].

Recently, the RANKL inhibitor denosumab has been compared to zoledronic acid in a study that included 1776 patients with bone metastases from solid tumors and multiple myeloma, 40% of whom had metastatic lung cancer. In the whole study population denosumab was non-inferior to zoledronic acid in delaying time to first on-study SRE: 20 months for denosumab vs. 16 months for zoledronic acid (HR, 0.84; 95% CI, 0.71–0.98; $p=0.0007$). There was no difference in overall survival between the treatment groups when all tumour types were considered. Of note, a significant reduction of relative risk of death was found during a subset analysis of lung cancer patients; however, the authors interpreted this finding with caution, suggesting it may be associated with the heterogeneity of their study population [17]. Recently presented data from a post-hoc analysis of this randomised phase III trial has shown enhanced overall survival benefit in both adenocarcinoma (9.6 months for denosumab vs. 8.2 months for zoledronic acid, HR=0.80, 95% CI: 0.62–1.02; $p=0.0751$) and squamous cell carcinoma (8.6 months vs. 6.4 months, HR=0.68, 95% CI: 0.47–0.97; $p=0.0350$) in metastatic lung patients treated with denosumab compared to those treated with zoledronic acid [60].

3.3.2. Non-clinical trial data

Despite the reduction in SREs observed in clinical trials the uptake for use of these agents in the lung cancer population has been significantly lower than that seen in other populations such as breast and prostate cancers [3,7,9,18]. In the non-trial lung cancer setting bisphosphonates were used in only 6%–20% [3] of lung cancer patients with bone metastases and ∼10% of patients received bisphosphonates after the first occurrence of an SRE to prevent additional events [7,9]. In a more recent prospective observational French study, it was reported that only ∼50% of lung cancer patients were treated with bisphosphonates at any point during the course of their bone disease [9].

In another large retrospective study of 2539 lung cancer patients with bone metastases (data was derived from a claims database of 80 health plans across the US, from 2002–2006), 365/2539 (14%) lung cancer patients were treated with zoledronic acid. The treated patients tended to be younger and had lower co-morbidity. In these patients the risk of SREs was reduced by 30–40% (odds ratio [OR] 0.727; 95% CI, 0.594–0.890) and the time from diagnosis of bone metastases to the first bone complication was increased by 85% (log regression model, 95% CI, 60.6–114.2%) [37]. An additional retrospective claims-based analysis of 9874 lung cancer patients with bone metastases found that only 1090 patients (11%) were treated with zoledronic acid. In this treated population the relative risk of pathological fractures was reduced by 40% compared to the untreated population (p-0.005), although the authors do not state the actual percentages of patients with fracture in this analysis [61].

With respect to the impact of bisphosphonates on survival, a small retrospective analysis assessing the efficacy of pamidronate in lung cancer patients with bone metastases ($n=41$) demonstrated an

improvement in overall survival in pamidronate treated ($n=30$) versus not pamidronate treated patients ($n=11$) (15 months vs. 2 months respectively, $p < 0.001$), however this should be interpreted with caution because of the extremely low numbers in this study [27].

Comparing the data between trial and non-trial lung cancer populations, the results for incidence and consequences of bone metastases are comparable. They were also similar in terms of age and extent of disease, however, it is clear that the performance status of patients in clinical trial populations was higher than that seen in the non-trial setting [7,9,13,17,26].

4. Discussion

Retrospective, prospective, observational and clinical trial datasets have all shown that bone metastases in lung cancer patients are common and have important consequences for patients. Moreover, their disease is complicated by a high incidence of bone pain, SREs, impaired quality of life and a relatively short overall survival.

Due to the unfavourable prognosis and short overall survival in metastatic lung cancer patients, relatively little is known about the impact of bone targeted therapy in these patients. Most randomized trials which have evaluated these agents in lung cancer patients with bone metastasis, were not designed to specifically address the efficacy in lung cancer patients only, and included patients with different types of solid tumours. However, despite the results of some clinical trials suggesting that lung cancer patients with bone metastases could benefit from use of bone-targeted agents, it is evident that they are not frequently used in the non-trial setting, and when they are, their use appears to be restricted to younger patients or those with better baseline performance status.

There is clearly much more to learn regarding the use of bone-targeted agents in these patients. Although the data from clinical trial cohorts compared to the general lung cancer population are similar (particularly the incidence of SREs and survival) there are a few notable differences between the datasets, such as the performance status being slightly worse in the non-trial versus trial populations [62].

There is also increasing evidence regarding the role of EGFR TKIs, such as gefitinib and erlotinib, in the treatment of bone metastases. In a Japanese series of 127 NSCLC patients with bone metastases, of whom 50% had activating EGFR mutations, the time to SRE was significantly longer in mutation positive patients treated with EGFR TKI than mutation negative patients (13 vs. 6 months, $p < 0.05$) [40]. It would be interesting to investigate the impact on bone metastases in the numerous clinical trials that have randomized patients to chemotherapy versus erlotinib or gefitinib in EGFR mutation positive patients [63–66].

Finally, bone metastases and SREs contribute to the high economic burden of the treatment of patients with metastatic lung cancer [12]. The overall prognosis of metastatic lung cancer patients is poor, however, given the high incidence of symptomatic SREs, pain emerging in the first few months from diagnosis, and the costs associated with treatment of their SREs, it seems that these patients may significantly benefit from more routine use of bone-targeted agents. We do however need better predictive markers for the development of bone metastasis and SRE's in lung cancer patients to guide clinicians in the more appropriate use of bone targeted therapy for these patients. Some retrospective analyses suggest that high NTX levels, male sex, multiple bone metastases, and poor performance status may be predictors of SRE's, however these should be further validated in additional prospective cohorts.

In summary, it is evident that bone metastases are a significant cause of increased morbidity and reduced quality of life in lung cancer patients, thus new strategies are needed to enhance the use of bone-targeted agents in this population. This will be of increasing importance as the median survival of these patients increases as a result of other therapeutic advances.

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