Routine Use of Pamidronate in NSCLC Patients with Bone Metastasis: Results from a Retrospective Analysis

GILBERT SPIZZO*, ANDREAS SEEBER* and MANFRED MITTERER

Department of Oncology and Haematology, Franz Tappeiner Hospital, 39012 Merano, Italy

Abstract. *Background: No data on the tolerability and effects of pamidronate in non-small cell lung cancer patients with bone metastasis are available. We performed a retrospective analysis to evaluate the routine use of pamidronate in these patients. Patients and Methods: One hundred and four patients with NSCLC were treated at our Day Hospital between May 2003 and February 2009. Forty-one (39.5%) presented with bone metastasis during the course of the disease. Thirty (73.2%) of these patients received pamidronate at a dose of 90 mg every four weeks. Results: The occurrence of bone metastasis was associated with a poor overall survival, but patients treated with pamidronate had a significantly better median overall survival than untreated patients (15.4 months vs. 2.1 months; p<0.001). Pamidronate was well tolerated and only grade 1 or 2 toxicities were registered. Conclusion: The diagnosis of bone metastasis and the consequent routine administration of pamidronate have an impact on survival of NSCLC patients; this drug is a good candidate for routine use in haemato-oncological centres.*

Lung cancer is one of the most common malignancies worldwide with a high mortality rate (1). The majority of lung tumors are classified as non-small cell lung cancer (NSCLC), which includes adenocarcinoma, squamous cell carcinoma, large cell carcinoma and other non-small cell histologies. The major risk factor for developing NSCLC is cigarette smoking, accounting for approximately 80-90% of all NSCLC cases (2). Most patients diagnosed with NSCLC have advanced disease at clinical presentation. Distant metastasis from NSCLC is frequent, and the most involved sites are bone, liver, adrenal gland and brain.

Bone metastases are detectable by conventional radiography, computer tomography, positron-emission tomography (PET) or bone scan and are frequently symptomatic. Twenty percent of NSCLC patients have bone metastasis on presentation (3) and a significant proportion of patients develop metastasis during follow-up. Bone metastasis is associated with skeletal related events (SRE) which include hypercalcemia (4), bone pain, bone fractures with surgery requirement, spinal cord compression and need for radiation therapy (5). These SRE can impair quality of life and may even be responsible for a shortened survival.

The preferential seeding and growth of tumour cells in the bone is purportedly due to both tumour cell factors and stromal components of the bone. Recently, an interaction of nuclear factor kappa B ligand (RANKL) in bone with the receptor activator of nuclear factor kappa B (RANK) on tumour cells has been reported (6). Monoclonal antibodies such as denosumab which block RANKL have shown promising effects in patients with bone metastasis (7).

Osteoclasts are the most important bone resorbing cells and are of monocyte macrophage origin (8). Osteoblastic bone resorption can be inhibited by the use of bisphosphonates, which reduce the adherence of osteoclasts to the bony surface, resulting in reduced bone resorption (9). Two different classes of bisphosphonates are known: the simple bisphosphonates and the aminobisphosphonates. The aminobisphosphonates such as zoledronic acid, pamidronate and ibandronate are more potent than simple bisphosphonates (*e.g.* clodronate) and thus represent the treatment of choice in patients with bone metastasis. ASCO guidelines recommend the routine use of pamidronate or zoledronic acid in patients with bone metastasis from breast cancer (10). The use of zoledronic acid is also recommended in prostate cancer patients with bone metastasis (11). Zoledronic acid seems to have one of the most potent *in vitro* and *in vivo* activities (12). However, adverse events appear to be more frequent with this drug. In fact, osteonecrosis of the jaw has been reported in 20% of patients after 3 years of zoledronic acid treatment compared to 7% of patients treated with pamidronate (13). Thus, long-term use of pamidronate appears to be safer than that of zoledronic acid.

*Both authors contributed equally to this work.

Correspondence to: Manfred Mitterer, Department of Oncology and Haematology, Franz Tappeiner Hospital, Via Rossini 5, 39012 Merano, Italy. Tel: +39 0473263280, Fax: 00390473 263292, e-mail: Manfred.Mitterer@asbmeran-o.it

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Data regarding the use of bisphosphonates in NSCLC patients with bone metastasis are scarce and consensus regarding their use is lacking. Zoledronic acid has been shown to reduce skeletal-related events and time to the first event in a randomized double-blind trial (14). However, no survival benefit was shown for these patients (15). No data are available on the use of pamidronate in NSCLC patients with bone metastasis. The purpose of this retrospective study was to determine the tolerability and the effect of routine pamidronate use in patients with bone metastasis from NSCLC.

Patients and Methods

Patients. From May 2003 to February 2009, 104 patients with NSCLC entered our Day Hospital. Seventy-four (71.2%) were men and 30 (28.8%) women. Median age at diagnosis was 65.3 years (range 37 to 88). Most patients presented with advanced-stage disease. Seventy-three (70.2%) and 17 (16.3%) patients had stage IV and stage IIIB disease, respectively. Fourteen (13.6%) patients had stage IA to IIIA disease. Only 11 patients (10.6%) were surgically treated with curative intent. Most frequent histological subtypes were adenocarcinoma (58 patients; 55.8%), squamous cell carcinoma (14 patients; 13.5%) and adenosquamous carcinoma (7 patients; 6.7%). The routine use of pamidronate in patients with bone metastasis (n=41) from NSCLC was introduced at the beginning of 2005 after publication of positive data by Hirsh *et al*. in NSCLC patients (16).

Documentation of data. All clinical relevant data were documented using the electronic medical record software ONCOnet® that was developed in collaboration with EDP Progetti S.r.l. in Bolzano (www.edp-progetti.it). The project was started in May 2003 with the intent to support the work of specialized personnel in haemato-oncological centres. The primary goal was to computerize both medical and administrative practical steps referable to the management of these patients, to reduce time consuming administrative workload and favouring the devotion to the patients' clinical and psychological problems. To favour interdisciplinary work, NSCLC-specific databases were created for medical doctors, nurses, psycho-oncological personnel and palliative care-givers. Patients' history and physical examination results are recorded on the first day when the patient enters the Day Hospital. The ONCOnet® questionnaires for history and physical examinations were disease and treatment specific. The name and personal data records of the patient for first-time entry to the Day Hospital for a hemato-oncological visit is retreived by the ONCOnet® software from the central regional residence office by telematic data transfer. Blood examinations are automatically imported by the ONCOnet® software from the central laboratory. The death of patients is registered automatically from the regional residence office. This retrospective evaluation of the data of NSCLC patients was approved by the local Ethics Committee on April 24th 2009.

Bisphosphonate label use in Italy. The aminobisphosphonates zoledronic acid and pamidronate received approval for use in patients with predominant lytic bone metastasis of various origin in 1998. Ibandronate has approval for treatment of patients with bone metastasis from breast cancer. Clodronate is a first-generation bisphosphonate with approval for treatment of bone metastasis from tumours of various origin.

Statistics. Statistical analysis was performed with the SPSS software program for Windows™ (IBM, Chicago, USA). The primary end point in our study was overall survival (OS). Thus, survival curves were calculated according to the method of Kaplan and Meier using survival data generated by the ONCOnet® software. *P*-values were evaluated using the log-rank test for censored survival data. Follow-up time was censored if the patient was alive at the last visit. χ^2 Test was performed to directly test association of pamidronate treatment with clinicopathological features. The median follow-up time of censored patients was 21 months. The median OS of all patients was 13.4 months. To calculate survival of patients with bone metastasis, the survival period was evaluated from the time of first clinical evidence of bone metastasis to death or censoring date.

Results

Diagnosis of bone metastasis is associated with poor prognosis and SREs. The OS of all patients at our Day Hospital was poor. The median OS was 13.4 months and only 14% of patients were alive after 5 years of follow-up (Figure 1). Forty-one patients (39.4%) presented with bone metastasis or developed bone metastasis during their clinical course. SREs were registered in 12 patients: radiotherapy to bone was performed in 8 patients (19.5%) and 2 patients (4,8%) had episodes of hypercalcaemia. As compared to OS of patients without bone metastasis, these patients had a significantly shorter survival (Figure 2). The median survival of patients with bone metastasis was 8.1 months after diagnosis of bone metastasis; no such patient reached a survival of more than 3 years.

The use of pamidronate is associated with a prolonged survival. The characteristics of patients with bone metastasis are summarized in Table I. Eleven NSCLC patients (26.8%) with bone metastasis were not treated with bisphosphonates. Thirty patients (73.2%) received a median of 5 courses of pamidronate infusions (range 1 to 28) with 90 mg pamidronate every 4 weeks. Patients that received pamidronate infusions had a significant better OS as compared to patients without treatment (Figure 3). Patients with and without treatment had a median survival time of 15.4 and 2.1 months, respectively. The median survival of patients without bone metastasis and patients with bone metastasis but pamidronate treatment was nearly the same (15.1 and 15.4 months, respectively). Stage, age and histological subtype were not significantly different between those treated with pamidronate and those not. A trend towards there being a significant difference in chemotherapy treatment was observed (Table I).

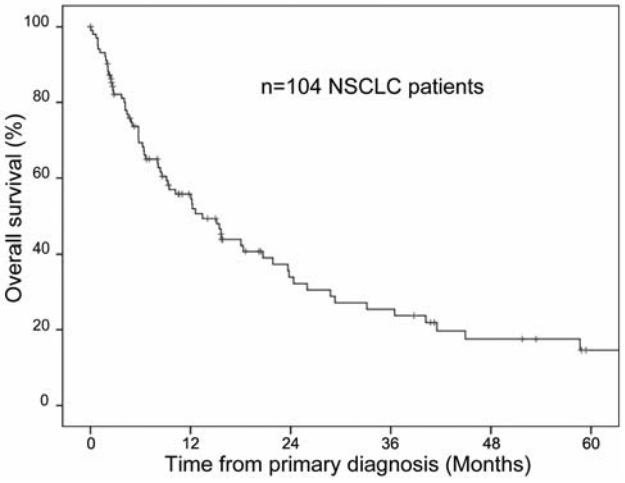

Figure 1. *Overall survival of 104 patients with NSCLC diagnosed at the Department of Oncology and Haematology of the Merano Hospital.*

Table I. *Clinicopathologic characteristics of patients with bone metastasis with or without pamidronate treatment.*

		Pamidronate treatment				
	Total patients (n)	No		Yes		
		n=11	%	n=30	%	*p*-Value*
Gender						
Male	30	9	82	21	70	0.45
Female	11	2	18	9	30	
Age at diagnosis						
<65 years	20	7	64	13	43	0.25
>65 years	21	4	36	17	57	
Histological subtype						
Adenocarcinoma	26	7	64	19	63	0.82
Squamous cell carcinoma	5	2	18	3	10	
Other	9	2	18	7	23	
Not evaluable	1	0	0	1	3	
Chemotherapy						
No	5	3	27	2	7	0.07
Yes	36	8	73	28	93	
UICC stage at primary diagnosis						
III	5	1	9	4	13	0.71
IV	36	10	91	26	87	

*χ^2 test.

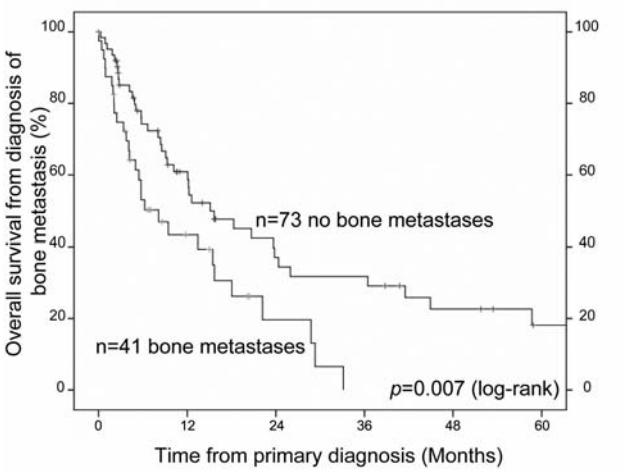

Figure 2. *Overall survival of patients with (n=41) and without (n=73) bone metastasis. The overall survival of patients without bone metastasis is calculated from the time of primary diagnosis to death or to censoring event. Survival of patients with bone metastasis is calculated from the time of first diagnosis of bone metastasis to death or censoring event.*

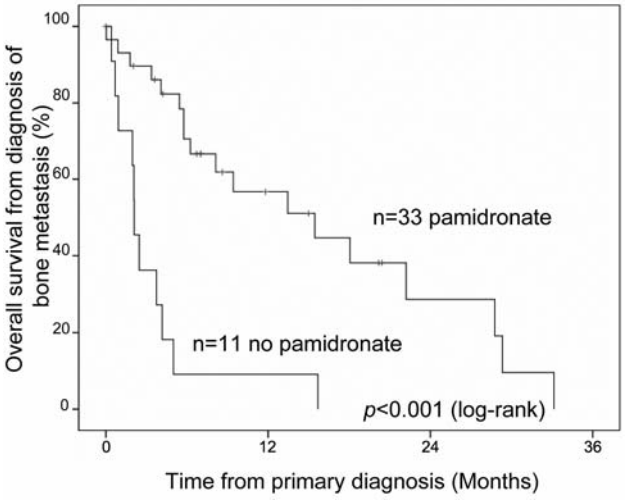

Figure 3. *Overall survival of patients with and without pamidronate treatment.*

Tolerability of pamidronate. Pamidronate infusions were well tolerated. Side-effect-specific anamnesis was carried out after each pamidronate infusion. In three patients (10%), fatigue was reported as the most frequent event. Muscle rigidity was reported in two patients (6.6%), and nausea, myalgia, arthralgia and bone pain in only one patient (3.3%), respectively. All side-effects were grade 1-2 according to WHO classification. In four cases (13.3%), an increase of creatinine level (grade 1-2) during pamidronate therapy was observed. Since no other reasons for creatinine increase in these patients were found, this side-effect was attributed to pamidronate treatment. However, after increasing the amount of parenteral fluid administration, creatinine levels stabilized and no patient had to interrupt treatment. In two patients (6.6%), a hypercalcemia (grade 1-2) was observed as the first sign of tumour-related bone destruction. The calcium values normalized after initiation of pamidronate treatment. No osteonecrosis of the jaw was observed.

Cost-effectivenes of pamidronate treatment in NSCLC patients with bone metastasis. Our base-case cost-effectiveness analysis for Italy showed cost savings for pamidronate therapy compared to zoledronic acid. In Italy, public offering costs per patient per year (13 infusions) in October 2009 were €3487.38 for pamidronate (90 mg Pamidronato D.HIK®) and €5112.12 for zoledronic acid (4 mg Zometa®). The economical impact of bisphosphonate infusions in haemato-oncological centres is considerable. The use of zoledronic acid and pamidronate in patients with haemato-oncological malignancies accounts for approximately 12% of the total drug budget of our Day Hospital. The use of the generic form of pamidronate can significantly reduce these costs.

Discussion

Patients with bone metastasis from NSCLC are at risk for developing skeletal-related events that can negatively influence quality of life and reduce life expectancy (17). The introduction of bisphosphonates has become a mainstay of treatment of metastatic bone disease in most oncological diseases (18), as they delay the onset and reduce the risk of skeletal-related events. Furthermore, palliation and control of bone pain favours the preservation of quality of life. First convincing data on the benefit of bisphosphonate use in patients with lung cancer were reported at the end of 2004 (16). In patients that received zoledronic acid, the risk of SREs and the mean skeletal morbidity rate was reduced dramatically. Time to first SRE was significantly prolonged in patients with or without prior SREs. This exploratory analysis demonstrates that zoledronic acid reduces skeletal morbidity regardless of SRE history. However, guidelines regarding the use of bisphosphonates are not available for patients with lung cancer, and their routine use in NSCLC patients is not universally accepted as standard treatment in oncological centres (19).

ASCO guidelines for treatment of bone metastasis are available for breast cancer patients (10) and multiple myeloma (20). Meta-analyses have been performed for different tumour entities (21) and for prostate cancer (22). At least in patients with breast cancer and multiple myeloma, the consensus statement accepted zoledronic acid and pamidronate as equally effective treatment options and both are recommended for metastatic bone disease.

The economic costs of SREs in patients with bone metastasis from NSCLC are considerable. Intravenous bisphosphonates, which have been shown to prevent these events, may reduce this burden (23). However, the routine use of these drugs in all patients with bone metastasis has a substantial impact on the budget of haemato-oncological treatment centres. Because of the convenient economical profile of pamidronate and the therapeutic equivalence between the two most commonly used amino-bisphosphonates (namely zoledronic acid and pamidronate), we decided to introduce pamidronate as treatment of choice. Following the publication of the data by Hirsh and colleagues (16), the routine use of bisphosphonates in NSCLC patients with bone metastasis was introduced at the oncologic Day Hospital in Merano at the beginning of 2005. Patients with bone metastasis from NSCLC before this period were not routinely treated with bisphosphonates.

Intriguingly, in recent years, new insights into a potential antineoplastic effect of bisphosphonates have been revealed. Bisphosphonates have shown anticancer activity against different cell lines *in vitro*. The effectiveness of nitrogen-containing bisphosphonates (such as pamidronate or zoledronic acid) at inhibiting proliferation and increasing apoptosis of tumour cells has been demonstrated for the most frequent tumour entities such as breast (24) and prostate cancer (25). Bisphosphonates appear to slow tumour growth and prolong survival in lung cancer mouse models (26). Zoledronic acid has been shown to have anti-angiogenic effects by reducing circulating vascular endothelial growth factor levels in cancer patients (27). Similarly, pamidronate treatment of nude mice inoculated with hepatocellular carcinoma cells was shown to significantly reduce tumour growth by promoting their apoptosis *in vivo* (28). Thus, beyond their antiresorptive activity, bisphosphonates appear to have anti-neoplastic effects. Recent data on the use of bisphosphonates in breast cancer cancer patients confirm this hypothesis (29). In our study, NSCLC patients with bone metastasis that received pamidronate treatment had a similar median overall survival to patients without bone metastasis, and survival was superior to that of untreated patients. Our data may be flawed by pitfalls resulting from retrospective evaluation of unbalanced groups, which may in part be responsible for this result. Of note, we observed a trend for a more frequent use of chemotherapy in patients treated with pamidronate, suggesting a selection of patients with a probably better performance status. Furthermore, this is a monocentric study evaluating a small patient sample, which limits clinical conclusions. However, we propose that pamidronate treatment may contribute significantly to the optimal therapeutic management of these patients, and merits further evaluation in prospective clinical trials.

In summary, these data confirm that the diagnosis of bone metastasis in patients with NSCLC and subsequent treatment with bisphosphonates has a significant impact on survival of these patients. Pamidronate appears to be well tolerated and to be a safe and cost-effective alternative to zoledronic acid. Future randomized trials comparing different bisphosphonates in NSCLC patients with bone metastasis are clearly warranted to define the best treatment option for these patients.

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