



The Effectiveness of Bisphosphonate to Reduce Pain in Lung Cancer Patients with Bone Metastasis

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Abstract

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BACKGROUND: Bisphosphonates (BPs) are commonly used as supportive therapy to prevent skeletal-related events in lung cancer patients with bone metastasis, including severe bone pain, hypercalcemia, and pathological fractures.

AIM: The purpose of this study was to assess the effectiveness of bisphosphonate therapy to reduce pain in non-small cell lung cancer (NSCLC) patients with bone metastasis.

METHODS: This was a cross-sectional study carried on 38 patients diagnosed with lung cancer based on cytology or histopathology findings. Radiological examination such as thoracic CT scan, bone survey, and bone scan was performed to determine bone metastasis. Multimodality therapy is carried out for lung cancer palliative therapy including chemotherapy, radiotherapy, and bisphosphonate therapy (zoledronic acid and ibandronate) as supportive therapy to reducing cancer pain. The pain was assessed using the visual analog scale (VAS) determined by patients themselves. Statistical tests were performed by paired t-test, in which $p < 0.05$ was considered significant.

RESULTS: As many as 38 patients enrolled in this study consisting of 29 men (76.3%) and 9 women (23.7%). The subtype of adenocarcinoma was mostly found in 31 cases (81.58%) and seven cases (18.42%), which was squamous cell carcinoma. Cancer pain was found in all patients. The measurement of pain before treatment showed that most patients had VAS level of 7–10. After bisphosphonate therapy, the VAS level significantly decreased to 1–3 ($p < 0.01$).

CONCLUSION: Bisphosphonate therapy was proven to effectively decrease the severity level of cancer pain in lung cancer patients with bone metastasis.

Introduction

Bone metastasis occurs in many types of malignancy but most commonly found in breast, prostate, and lung cancer [1]. Studies have shown bone metastasis due to lung cancer occur in about 30.1% of all malignancies [2]. Bone metastasis is thought to develop through hematogenous spread of primary tumors, metastatic to bone skeletal disrupts homeostasis by disrupting the balance between osteoblastic bone formation and osteoclast-mediated bone destruction [3].

Lung cancer patients with bone metastasis always presented bone pain. Bone pain had been shown to decrease performance status, increase anxiety and depression, and eventually decrease quality of life. Finally, bone metastasis will result in decreasing survival and quality of life. Skeletal complications of bone metastasis, known as Skeletal-Related Events (SREs), include severe bone pain, hypercalcemia, and pathological fractures. Patients with SRE require radiation therapy or surgery [4]. Lung cancer patients

with bone metastasis will experience SRE each year and the risk to develop another SRE will eventually increase after the first SRE [5]. Lung cancer patients with SRE have 50% shorter survival compared with those without SRE [6].

The management of bone pain requires multimodality therapy, including analgesics, radiotherapy, and supportive therapy (bisphosphonates). Since the early 1990s, bisphosphonates have become a mainstay treatment of bone metastases from various cancers [7], [8], [9]. Bisphosphonate therapy is largely recommended to prevent and delay the occurrence of further bone metastases and to overcome severe pain in lung cancer patients [10].

Bisphosphonates are synthetic analogues of pyrophosphates that bind hydroxyapatite and later internalized by osteoclasts to stimulate osteoclast apoptosis [11]. Bisphosphonates such as zoledronate, ibandronate, pamidronate, and alendronate have shown to inhibit osteoclast-mediated bone resorption [12]. However, the efficacy and safety of bisphosphonate is still debated. To date, there has never been a study

to determine the role of bisphosphonates to decrease cancer pain. This study aimed to identify the role of bisphosphonate therapy in reducing pain in NSCLC patients with bone metastasis.

Materials and Methods

Subject

As many as 38 patients with diagnosed lung cancer in Adam Malik General Hospital, Medan, Indonesia enrolled in this study. Patients were all diagnosed based on cytology or histopathology findings. Patients with secondary lung cancer or patients with lung cancer that infiltrates the bone at the cancer site (confirmed by Radiologist) were excluded from this study. Bone metastases were determined by any specific findings on X-ray examination (Lumbar, Femur, and Skull), thoracic CT-scan, bone survey, bone scan, and magnetic resonance imaging (MRI). All patients received analgesics, radiation, and bisphosphonate administration.

Skeletal-related events (SRE)

SRE include secondary complications of bone metastasis and can occur in both osteolytic and osteoblastic lesions [13]. Skeletal-related events include pathological fractures, spinal cord compression, and severe pain requiring radiotherapy or surgery for bone lesions [13], [14]. SRE results in severe complications that reduce the quality of life.

Visual analog scale (VAS)

The severity of pain was assessed by the visual analog scale. All patients were asked to determine the level of pain they experienced before and after bisphosphonate treatment [15]. The VAS was then classified as:

VAS 0 = No pain

VAS 1–3= Mild pain

VAS 4–6 = Moderate pain

VAS 7–9 = Severe pain

VAS 10 = Extreme pain

Bisphosphonate therapy

All patients were given bisphosphonate therapy (either Ibandronate or zoledronic acid). Ibandronate 6 mg was administered intravenously for 1 h, while zoledronic acid 4 mg was administered intravenously for 15 min, given every 3–4 weeks [16].

Statistical analysis

The evaluation of VAS was conducted before and after bisphosphonate therapy. Statistical analysis was performed by paired t-test, in which $p < 0.05$ was considered significant.

Results

Of all participants, as many as 16 subjects (42.1%) were aged 60–69 years old, and only 1 patient aged below 40 years old. More than 75% of participants were male. Around 71% of patients were a heavy smoker and only nine patients were a non-smoker. The most commonly found lung cancer subtype was adenocarcinoma (81.5%) and squamous cell carcinoma (18.4%).

The SRE was frequently found in all participants. Bone pain was found in all patients (100%). Spinal cord compression was found in 20 patients (52.6%), and pathological fracture in nine patients (23.6%). The detailed characteristic of patients was listed in Table 1.

Table 1: General characteristics of participants

Characteristic	n	%
Age		
<40 years old	1	2.63
40–49 years old	9	23.68
50–59 years old	11	28.95
60–69 years old	16	42.11
>70 years old	1	2.63
Gender		
Male	29	76.32
Female	9	23.68
History of smoking		
Non smoker	9	23.68
Smoker	29	76.32
Brinkman-index		
Light smoker	0	0
Moderate smoker	2	5.26
Heavy smoker	27	71.06
Cancer subtype		
Adenocarcinoma	31	81.58
Squamous cell carcinoma	7	18.42
Bone pain		
With bone pain	38	100
Without bone pain	0	0
Bone radiation		
Yes	5	13.16
No	33	86.84
Spinal cord compression		
Yes	20	52.63
No	18	47.37
Pathological fracture		
Yes	9	23.68
No	29	76.32
Total	38	100

Table 2 showed the type of bisphosphonate therapy given to patients. Ibandronate 6 mg was given to 19 patients, while the rest got zoledronic acid 4 mg.

Assessment of pain

Table 3 describes the pain severity level before and after bisphosphonate therapy. Before treatment, more than 50% of patients experienced severe pain

Table 2: The type of bisphosphonate

Bisphosphonate	n	%
Ibandronate 6 mg	19	50
Zoledronic acid 4 mg	19	50
Total	38	100

(VAS 7–9) and one patient experienced extreme pain (VAS 10). There was no single patient who did not feel pain before treatment. After bisphosphonate therapy, there was a significant improvement in terms of bone pain. There was no more patient experienced severe nor extreme pain. More than 60% of patients had mild pain and about 40% of the patient experienced moderate pain.

Table 3: Assessment of VAS

VAS	Before bisphosphonate treatment		After bisphosphonate treatment	
	n	%	N	%
0	0	0	0	0
1–3	0	0	23	60.53
4–6	3	7.89	15	39.47
7–9	21	55.26	0	0
10	14	36.85	0	0
Total	38	100	38	100

Table 4 showed that there was a significant decrease in VAS level in patients with bone metastasis. Thus, bisphosphonate therapy can be effectively used to decrease the severity of bone pain.

Table 4: Statistical result

	Mean	SD	Delta	p-value
Before treatment	8.32	1.416	4.842 (CI: 4.406-5.278)	<0.001**
After treatment	3.47	1.033		

*Significant with paired t-test.

Discussion

The majority of lung cancer patients in this study was in the age range of 60–69 years old (42.1%). This study also found that lung cancer was mostly found in a smoker (76.3%) rather than in non-smoker (23.4%). It was in line with the result found by Soeroso *et al.* in 2018, in which 60% of lung cancer patients in Indonesia aged more than 60 years old [17]. Soeroso *et al.* also stated that smoking and nicotine dependence, measured by Fagerstrom Tolerance Questionnaire, were attributed to lung cancer, in which 65% of male with high level of nicotine dependence suffered from lung cancer [18].

It is estimated that 27% of deaths are caused by lung cancer. More than 57% of lung cancer case was found at an advanced stage, in which the 5-year survival rate was about only 4%. In cases of advanced lung cancer, bone (39%), brain (25%), liver (16%), and adrenal glands (13%) metastases need to be measured carefully [19]. Symptoms that require medical action are primary tumors, metastasis or paraneoplastic syndromes. Diagnosis can be very challenging in terms of clinical symptoms associated with distant metastases as the initial clinical manifestations found [19]. Soeroso

et al. also stated that the most rarely found metastasis is orbital metastasis, especially in adenocarcinoma subtype [20].

Malik *et al.* explained that the most common type of lung cancer is adenocarcinoma, and this may be explained by the habit of consuming “kretek” cigarettes [21]. Kretek cigarettes contain cloves, which make smokers inhale more deeply, and cigarette smoke will reach the small airways so that more carcinogens are exposed to the small airways [22]. Stellmann *et al.* added that the very high level of nitrosamine in the peripheral airway will change the normal cells into adenocarcinoma [23].

A study by Conen *et al.* in Switzerland found that 18.4% of patients with NSCLC underwent skeletal-related events (SRE), including 3.3% cases of pathological fracture, 10.9% cases of bone radiation, 2.2% cases of bone surgery, 1.2% cases of spinal cord compression, and 4.3% cases of hypercalcemia [24]. Likewise, in Asian countries such as Japan, the incidence of SRE in SCLC and NSCLC is about 18.2%, consisted of 4.7% pathological fractures, 15.7% bone radiation, 1.1% spinal cord compression, and 2.2% cases of hypercalcemia [25].

Pain is a distinctive sign experienced by all subjects in this study. Bone metastasis is a common cause of cancer-related pain, with metastatic cancer to bones in 60–84% of cases. This bone pain can result in decreased performance status, increased anxiety and depression, and eventually a decreased quality of life. Pain is described as dull, persistent pain, and increases with intensity over time. Pain episodes are intermittent which occurs spontaneously or during movement. Bone pain is the most common type of pain from cancer and significant problems are found both in clinical practice and in hospitals. Subjectively, patients can describe it as a deep sensation, which causes feelings of pain or burning, and accompanied by episodes of discomfort such as being pierced. This occurs because metastatic tumor cells penetrate the bone matrix and stimulate osteoclast activity and/or osteoblasts, causing osteolysis and the possibility of excessive bone formation around the site of tumor cell storage in the bones [26], [27].

Regarding the pain experienced by all lung cancer patients, the highest level of pain before being given supportive therapy with bisphosphonates was VAS 7–10 (92.11%). Interestingly, after bisphosphonate administration, all patients experienced a reduction in pain level to VAS 6. Bisphosphonates bind the bones in place of active bone metabolism and inhibit osteoclast bone resorption. Bisphosphonate therapy is given to lung cancer patients with bone metastasis which is a supportive therapy aimed at reducing pain, even though the patient has been given analgesic. Multimodality management of bone metastases is very necessary, such as analgesics, surgery, chemotherapy, radiotherapy, and bisphosphonate therapy to reduce the intensity of pain symptoms and to maintain bone

integrity. In addition, bisphosphonate therapy can delay the incidence of SRE in patients with bone metastases in various solid tumors, including NSCLC [10].

Conen *et al.* found that 10.9% of lung cancer patients underwent bone radiation [24]. Meanwhile, Cetin *et al.* found that bone radiation due to metastatic lung cancer to the bone is was about 67% [28]. In this study, only five people were given bone radiation besides being given chemotherapy and bisphosphonates. Radiation treatment is one way to deal with bone pain and eliminating or gradually reducing the need for opioids, especially for patients with opioids side effects. External administration of radiotherapy as one of the palliative therapies for bone pain provides excellent benefits. Radiotherapy is given in one to five fractions with 8 Gy beam strength and is considered sufficient to relieve pain [26]. Liu *et al.* also stated that bisphosphonate may be very helpful to relieve pain in those patients [29].

The limitation of this study was that the data was obtained from medical records and not by direct evaluation of the patient. However, information from this study may provide evidence of bisphosphonate benefit to reduce pain in lung cancer patients with bone metastasis. In conclusion, bisphosphonate therapy was proved to significantly reduce the severity level of pain in NSCLC patients with bone metastasis. Hence, we suggest considering bisphosphonate as additional therapy in every patient with NSCLC with bone metastases.

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