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Research Article
Curative Effects of Zoledronic Acid Combined with Calcitonin on the Treatment of Bone Metastasis and Osteoporosis in Lung Cancer

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Abstract

Background and Objective: The role of calcitonin on cancers complicated with bone metastasis has not been reported. This study aimed to evaluate the clinical efficacy of zoledronic acid combined with calcitonin for bone metastasis and osteoporosis in patients with lung cancer. **Materials and Methods:** Total of 100 patients with lung cancer complicated with bone metastasis and osteoporosis were randomly and equally divided into the control group (conventional analgesic (non-opioids→mild-opioids→strong opioids), calcium and 1,25-Dihydroxycholecalciferol) and the observational group (additional zoledronic acid combined with calcitonin therapy). Then, the life quality, bone pain, activity ability, metastatic lesion, serum biochemical indicators of bone metabolism and bone mineral density (BMD) of hip joint, as well as the adverse reactions and skeletal-related events (SREs) were recorded in both two groups. The effectiveness of treatment as ordered categorical variable was measured using Mann-Whitney U method. All the data of serum indicators were expressed as the mean±SD and analyzed using paired t-test for the comparison before and after treatment. Independent samples t-test was used for the comparison between the two groups. Chi-square test was used for the comparison of incidence of adverse reactions and SREs. **Results:** The significant improvement of life quality, bone pain, activity ability, serum biochemical indicators of bone metabolism and BMD of hip joint were observed in the observational group compared with the control group ($p<0.01$). Bone metastatic lesions were significantly reduced by this combined therapy compared with conventional therapy ($p<0.05$). The incidences of adverse reactions and SREs in the observational group were significantly lower than that in the control group (6.0 vs. 24.0% and 4.0 vs. 22.0%, $p<0.05$), respectively. **Conclusion:** The application of zoledronic acid combined with calcitonin was significantly more effective for bone metastasis and osteoporosis in patients with lung cancer, compared with conventional therapy.

Key words: Zoledronic acid, calcitonin, bone metastasis, skeletal-related events, bone metabolism, bone mineral density

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Lung cancer is the most common malignant tumor[1]. The metastasis of lung cancer is common due to delayed diagnosis and treatment[2]. Bone is a common site of cancer metastasis in patients with lung cancer and there are more than 30% of patients with lung cancer complicated by bone metastasis[3]. Bone metastasis usually leads to pain, fracture, spinal compression, paraplegia and hypercalcinemia[4]. These complications lower the life quality of patients and lead to a series of skeletal-related events (SREs)[4]. The two year survival rate of lung cancer patients with bone metastasis is less than 30% and the median survival time is generally less than 12 months[5]. Although chemotherapy, molecular targeted therapy, radiotherapy, surgery, analgesia, bisphosphonate therapy have been widely used in lung cancer patients complicated with bone metastasis, current clinical treatment effect of bone metastasis is still limited. Therefore, effective therapeutic methods for bone metastasis of lung cancer are urgently needed.

Currently, the pharmacological intervention of bisphosphonates has been considered as the current standard treatment of cancer patients with bone metastases[6]. Zoledronic acid, as a new and potent bisphosphonate, has been widely used in the treatment of patients with osteoporosis or mixed bone metastases/lesions[7]. Several studies have demonstrated that zoledronic acid can reduce the risk of SREs in the treatment of cancers complicated with bone metastasis[8-10]. However, due to several unsatisfied effects and side effects of zoledronic acid, the combined treatments of zoledronic acid with other drugs such as dasatinib[11], denosumab[12], or erlotinib[13] are used for the treatment of cancers complicated with bone metastasis. Notably, it has been reported that calcitonin, also named as salmon calcitonin, inhibits the activity of parathyroid hormone and the growth of tumor cell, thus inducing cell apoptosis[14]. The application of calcitonin in the treatment of osteoporotic fractures also reported to significantly reduce the bone mass loss and relieve pain 1 week after the treatment[15,16]. The above studies indicate the potential role of calcitonin in bone metastasis. However, as mentioned above, few studies have investigated the role of calcitonin on cancers complicated with bone metastasis. In addition, the combined treatment of zoledronic acid and calcitonin in lung cancer patients with bone metastases has also not been reported.

Therefore, a hypothesis is provided that the combined treatment of zoledronic acid and calcitonin may have the good curative effects for lung cancer patients with bone metastases. In the present study, patients with lung cancer complicated with bone metastasis and osteoporosis were treated with zoledronic acid combined with calcitonin and the curative effects were observed and analyzed, aimed to search for a novel effective therapeutic method for bone metastasis of lung cancer.

MATERIALS AND METHODS

Patients: From December, 2011-December, 2013, a total of 100 patients with lung cancer complicated with bone metastasis and osteoporosis at the First Hospital of Jilin University were enrolled in this study. The inclusion criteria were as follows: (i) Patients were all over 50 years old, (ii) Patients were diagnosed as bone metastases by magnetic resonance imaging (MRI, using 3.0 T MR scanner, Philips Achieva, Best, Netherlands), computed tomography (CT, using Discovery CT 750 High Definition, GE Healthcare, Milwaukee, WI, USA) and other imageological diagnostic tools, (iii) The sites of bone metastases included spine, limbs, ribs and skull, (iv) All patients had moderate spontaneous whole-body bone pain or weight-bearing bone pain in accordance with the diagnostic criteria in Primary Osteoporosis Treatment Guidelines (2011)[17]. T-Score of bone mineral density (BMD) in waist or hip was less than 2.5 based on the formula: T-Score = (detected value - peak value)/standard deviation of normal adult BMD. Exclusion criteria included: (i) Patients who have received radiotherapy or chemotherapy 1 month before, (ii) Patients who have received the treatment of bisphosphonate, (iii) The expected survival time of patients was less than 3 months, (iv) Patients had severe heart, liver and kidney dysfunction, (v) Patients were unable to do self-assessment of pain, (vi) Patients were allergic to the drug in this study. All patients signed an informed consent form and the study has been approved by the Ethics Committee of the First Hospital of Jilin University (Changchun, China).

Patients treatment: This was a prospective randomized controlled trials. The patients were randomly divided into the observational group and the control group with 50 patients in each group. All the patients were treated with conventional radiotherapy and chemotherapy and received three-step analgesic ladder (non-opioids→mild-opioids→strong opioids) to reduce cancer pain in accordance with World Health Organization (WHO)[18]. Meanwhile, tablets with calcium carbonate and vitamin D (Caltrate, one tablet contains calcium 600 mg and cholecalciferol 37.5 μg, administered with one tablet for one time daily, Wyeth Consumer Healthcare, Madison, NJ, USA) and tablets with calcitriol (Rocaltrol, one tablet contains 1,25-Dihydroxycholecalciferol 0.25 μg,

administered with one tablet for 2 times daily, Hoffman La Roche, Switzerland) were orally taken. In addition, the patients in the observational group were treated with zoledronic acid combined with calcitonin. No additional treatment was performed in the control group. Zoledronic acid injection (Zometa injection, 5 mg zoledronic acid dissolved in 100 mL normal saline, Novartis Pharmaceuticals, Switzerland) with the amount of 100 mL was administered by intravenous infusion once each 4th week. Calcitonin injection (Miacalcic® solution for Injection, contains salmon calcitonin 50 IU dissolved in 1 mL normal saline, Novartis Pharmaceuticals, Switzerland, administered with 50 IU once daily) was intramuscularly or subcutaneously injected in the 1st week. In the 2nd week, calcitonin injection was given 50 IU every other day. From the 3rd to the 12th week, subcutaneous injection of calcitonin was given 50 IU once a week. The patients in the control group and observational group were treated for 3 consecutive months.

Observed indicators and evaluation criteria: The changes of the life quality, bone pain, activity abilities as well as the curative effects on the bone metastatic lesion of the patients in the 2 groups were evaluated and compared in this study. The evaluation criteria of improvement in life quality were as follows: "markedly effective" was defined as the increase of Karnofsky score >20, "improved" was defined as the increase of Karnofsky score >10 and "ineffective" was defined as the increase of Karnofsky score $\leq$10[19].

The evaluation of pain improvement was based on the verbal rating scale (VRS) score[20]. After the treatment, the decrease of VRS score >2 was considered as "markedly effective", the decrease of VRS = 1 was considered as "improved" and no change of VRS score was regarded as "ineffective".

The improvement of activity abilities was evaluated according to the self-report scales (SRS)[21]: "markedly effective" was defined as the increase of SRS score $\geq$2, "improved" was defined as the increase of SRS score = 1 and no change of SRS score was considered as "ineffective".

The bone metastatic lesion was assessed based on the following criteria: "Progressive disease (PD)" was defined as the increase of bone metastases or the appearance of new lesions, "no change (NC)" was defined as no changes in volume and number of lesions, "partial remission (PR)" was defined as the reduction of osteolytic lesions, calcification or density decreases for at least 4 weeks, "complete remission (CR)" was defined as complete disappearance of all bone metastases based on radiographic examination for at least 4 weeks.

The serum levels of type I collagen cross-linked N-telopeptides (uNTX), bone sialo protein (BSP), bone gla protein (BGP), collagen carboxy-terminal peptide (CTX) and Ca^{2+} in the two groups were detected before and after treatment using enzyme linked immunosorbent assay (ELISA) kit (Cusabio Biotechnology Company, China). Hip BMD was measured using bone density measuring instrument (DiscoveryWi11, Hologic Inc., Madison, WI, USA). Adverse reactions, including fever, muscular pain, nausea, vomiting and liver and kidney dysfunction, were observed during the treatment according to WHO toxicity grading standards. The incidences of SREs such as fractures and spinal cord compression were detected by emission computed tomography (ECT, using GEMG D670, GE Healthcare), MRI, CT and X-ray (diagnostic X-ray equipment, MRAD-A50S/70, Toshiba Medical Systems Corporation, Nasu, Japan).

Statistical analysis: Statistical analysis of all data in this study was conducted using SPSS13.0 statistical software package (SPSS Inc., Chicago, IL, USA). The probability level used is $p<0.05$. The effectiveness of treatment as ordered categorical variable was measured using Mann-Whitney U method. All the data of serum indicators were normally distributed and expressed as the Mean±SD. Paired t-test was used for the comparison before and after treatment. Independent samples t-test was used for the comparison between the two groups. Chi-square test was used for the comparison of incidence of adverse reactions and SREs.

RESULTS

Clinical efficacy: All patients completed the treatment and follow-up. As shown in Table 1, there was no statistically significant difference between the two groups in baseline data of patients, including age, gender, BMD, Karnofsky score and distribution of metastatic lesions of patients. The improvements of the life quality, bone pain, activity ability as well as the reduction of bone metastatic lesion of the patients

Table 1: Characteristics of patients in control and observational group

Groups	Observational group (n = 50)	Control group (n = 50)
Gender (male/female)	31/19	33/17
Median age (rang, year)	68.23 (50-85)	71.45 (50-89)
Metastatic lesions distribution (n)		
Vertebra	15	14
Rib	13	14
Pelvis	8	9
Skull	5	4
Bones of the extremities	9	9
Karnofsky score (Mean±SD)	31.37±11.26	32.26±10.35

in the observation group were significantly better than those in the control group (p<0.05) (Table 2).

Serum indicators and BMD: Before treatment, there was no significant difference in serum indicators, including NTX, BSP, Ca^{2+}, BGP and CTX, as well as hip joint BMD between the control and observation groups. After treatment, serum indicators and hip joint BMD were significantly improved (p<0.05). The serum indicators of bone metabolism and the hip joint BMD of the patients in the observational group were significantly improved compared to the control group (p<0.05) (Table 3).

Table 2: Clinical outcomes in control and observational group

Groups	Observational group (n = 50)	Control group (n = 50)	p-value
Improvement of life quality			<0.01
Ineffective	4	22	
Improved	11	13	
Markedly effective	35	15	
Metastatic lesion			<0.05
Complete remission	4	0	
Partial remission	16	10	
No change	20	16	
Progressive disease	10	24	
Pain improvement			<0.01
Ineffective	4	12	
Improved	10	16	
Markedly effective	36	22	
Activity abilities			<0.01
Ineffective	3	10	
Improved	13	15	
Markedly effective	34	25	

p-value of <0.05 or 0.01 presents the significant difference between the 2 groups using chi-square test

Adverse reactions and SREs: The incidence of adverse events in the observational group was obviously higher than that in the control group (p<0.05). The incidences of fever, liver and kidney dysfunction in the observational group were significantly lower than those in the control group (p<0.05), respectively. In addition, the incidence of SREs of patients in the observational group was also significantly lower than that in the control group (p<0.01) (Table 4). The incidence of spinal cord compression in the observation group was significant lower than that in the control group (p<0.05), while there was no statistical difference in the incidence of fractures (Table 4).

DISCUSSION

Bone metastasis is one of the main parts of the lung transfer[3]. The median survival time is prolonged due to the development of the new technology in the clinical treatment of advanced lung cancer. However, the incidences of SERs such as pathologic fractures, spinal cord compression caused by osteoporosis continued to rise, thereby affecting the life quality of patients[22]. Chemotherapy, tyrosine kinase inhibitor therapy and bisphosphonate therapy have an good effect on the prognosis of patients with bone metastasis of lung cancer[23].

Table 3: Serum biochemical indexes of bone metabolism and bone mineral density (BMD) of patients before and after treatment

	Observational group (n = 50)[a]		Control group (n = 50)[a]	
Groups	Before treatment	After treatment	Before treatment	After treatment
NTX (mmol L^{-1})	27.04±8.63	14.150±6.94[b,c]	27.210±9.23	21.130±7.06[b]
BSP (mmol L^{-1})	38.71±7. 86	23.260±5[b,c]	37.750±8.18	34.870±8.25[b]
Ca^{2+} (mmol L^{-1})	2.62±0.69	1.910±0[b,c]	2.590±0.73	2.290±0.51[b]
BGP (ng mL^{-1})	15.22±3.08	25.020±3.85[b,c]	15.310±3.13	19.770±3.23[b]
CTX (ng mL^{-1})	0.56±0.26	0.310±0.19[b,c]	0.540±0.25	0.420±0.23[b]
Hip joint BMD (g cm^{-2})	0.73±0.04	1.442±0.034[b,c]	0.729±0.035	0.962±0.033[b]

uNTX-urinary type I collagen cross-linked N-telopeptides, BSP - bone sialoprotein, BGP - bone gla protein, CTX -collagen carboxy-terminal peptide, [a]Mean±SD, Statistically significant difference at p<0.05 compared with: [b]Level before treatment, paired t-test, [c]control group, independent samples t-test

Table 4: Adverse reactions and incidences of skeletal related events during treatment in control and observational group

Groups	Observational group (n = 50)	Control group (n = 50)	p-value
Adverse reactions (%)	3 (6.0%)	12 (24.0%)	<0.05
Nausea	2 (4.0%)	6 (12.0%)	>0.05
Fever	1 (2.0%)	7 (14.0%)	<0.05
Liver and kidney dysfunction	1 (2.0%)	3 (6.0%)	<0.05
Skeletal related events (%)	2 (4.0%)	11 (22.0%)	<0.01
Fracture	1 (2.0%)	4 (8.0%)	>0.05
Spinal cord compression	1 (2.0%)	7 (14.0%)	<0.05

p-value<0.05 or 0.01 presents significant difference between the 2 groups using chi-square test

This study showed that the improvements of the life qualities, bone pains, activity abilities and the curative effects on the bone metastatic lesion of the patients in the observation group were obviously improved compared with the control group. In addition, the improved serum indicators and increased hip joint BMD of patients in the observation group were also found in this study. It had been reported in 14 randomized controlled studies including a total of 1184 cases of patients that zoledronic acid combined with chemotherapy might improve the effective rate of pain management and reduce the incidences of short-term SREs[24], which was similar to this study. In addition, previous study has shown that serum calcitonin may be a good indicator for early diagnosis of bone metastases in lung cancer patients[25]. Miacalcic combined with radiotherapy also exhibited satisfying curative effect in patients with bone metastases[26]. The mechanism of the combination use of zoledronic acid and miacalcic might be that zoledronic acid was able to quickly inhibit the markers of bone resorption and it had a lower incidence of severe adverse reactions[27]. Besides, miacalcic could inhibit osteoclast activity, stimulate the formation of osteoblast and protect the sclerotin from further damage[28]. Miacalicin affected neurotransmission of pain by directly acting on the specific receptor in the pain sensation district of the central nervous system and inhibited the release of pain inducing factors such as acetic acid, citric acid and lysosomal to have a analgesia effect[29]. In this study, also found that zoledronic acid combined with miacalcic significantly $p<0.05$ reduced the incidences of adverse reactions and SREs. All these results suggested the obvious clinical effects of zoledronic acid combined with miacalcic in the treatment of the patients with lung cancer complicated with bone metastasis.

Furthermore, some limitations of this study should be concerned. First, this study just assessed the efficacy of zoledronic acid combined with calcitonin, the comparison between zoledronic acid alone and zoledronic acid combined with calcitonin should be concerned in the further studies. Secondly, some confounding factors such as different pathological type of lung cancer were not considered in this study, which may influence the results. Thirdly, long-term clinical outcomes should be further investigated by follow-up.

CONCLUSION

In this study, zoledronic acid combined with calcitonin had significantly better efficacy in improving bone density, quality of life and activity, alleviating pain symptoms, as well as reducing bone metastatic lesions and incidences of SREs or adverse reaction for the patients with lung cancer complicated with bone metastasis and osteoporosis, compared with the conventional treatment. The results of this study supported the clinical application of zoledronic acid combined with calcitonin.

SIGNIFICANCE STATEMENTS

This study discovers the possible curative effects of zoledronic acid combined with calcitonin that can be beneficial for the treatment of lung cancer patients with bone metastases. This study will help the researcher to uncover a novel effective therapeutic method for bone metastasis of lung cancer that many researchers were not able to explore. Thus, the combined treatment of zoledronic acid and calcitonin, as a new therapeutic method, may be arrived at for lung cancer patients with bone metastases.

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