JBUON 2021; 26(3): 830-836
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Zoledronic acid combined with chemotherapy in non-small cell lung cancer with bone metastasis

Jingnan Zhang[1], Lisha Yu[2], Jing Guan[2], Juan Zhang[2], Yunfang Pan[3], Mei Wang[4]

[1]Department of Pharmacy, Linyi Central Hospital, Linyi 276000, China. [2]Department of Traditional Chinese Medicine, Qingdao Eighth People's Hospital, Qingdao 266000, China. [3]Department of Pharmacy Intravenous Admixture, Weifang People's Hospital, Weifang 261000, China. [4]Cardiothoracic Surgery, PLA Rocket Force Characteristic Medical Center, Beijing 100088, China.

Summary

Purpose: *We aimed to investigate the efficacy and safety of zoledronic acid combined with chemotherapy in treating non-small cell lung cancer (NSCLC) with bone metastasis.*

Methods: *The clinical data of 148 NSCLC patients with bone metastasis were retrospectively analyzed. Among the patients, 74 were treated with zoledronic acid combined with chemotherapy (Zoledronic Acid group), while the remaining 74 received chemotherapy alone (Control group). The efficacy on bone metastasis, remission of bone pain, levels of bone metabolic markers before and after treatment, quality of life and incidence rate of adverse reactions were compared between the two groups. Besides, the patients were followed up, and their survival status was recorded.*

Results: *The efficacy was evaluated in all patients at 1 month after treatment. It was found that the overall response rate of bone metastasis was significantly higher in the Zoledronic Acid group than that in the Control group. After treatment, the ostealgia remission rate was markedly higher in the Zoledronic Acid group than that in the Control group. After treatment, the serum levels of alkaline phosphatase (AKP), Ca^{2+}, N-terminal telopeptide (NTx) and bone sialoprotein (BSP) declined notably in both groups in contrast with those before treatment, and they were prominently lower in the Zoledronic Acid group than those in the Control group after treatment. Moreover, after treatment, the Karnofski performance status (KPS) score was improved in both groups, and the Zoledronic Acid group had an evidently higher score than the Control group. The results of follow-up manifested that the 1-, 2- and 3-year overall survival (OS) rates in the Zoledronic Acid group and the Control group were 58.1% (43/74) vs. 43.2% (32/74), 40.5% (30/74) vs. 29.7% (22/74), and 24.3% (18/74) vs. 13.5% (10/74), respectively. Log-rank test revealed that the OS in the Zoledronic Acid group was significantly better than that in the Control group.*

Conclusion: *Zoledronic acid combined with chemotherapy is effective in the treatment of NSCLC with bone metastasis, which can markedly relieve bone pain, ameliorate the quality of life of patients, improve the long-term survival rate and reduce the incidence of SREs.*

Key words: *zoledronic acid, chemotherapy, NSCLC, bone metastasis, efficacy*

Introduction

Lung cancer remains one of the malignant tumors with the highest morbidity and mortality rates worldwide [1]. The incidence rate of bone metastasis in patients with stage IV non-small cell lung cancer (NSCLC) is 30-40%. Once a patient develops bone metastasis, the 5-year survival rate will be <5%, and the median overall survival (OS) will be <6 months [2,3]. The manifestation of NSCLC with bone metastasis is usually osteolytic destruction, and intractable bone pain can occur clinically. When the strength of the bone is weakened, pathological fractures will occur, and the

Corresponding author: Yunfang Pan, BM. Department of Pharmacy Intravenous Admixture, Weifang People's Hospital, 151 Guangwen Street, Kuiwen District, Weifang 261000, Shandong, China.
Tel: +86 013625365179, Email: zhuwenjuan11111@163.com
Received: 05/12/2020; Accepted: 28/01/2021

most common fracture sites are the vertebral bodies and the ribs. Vertebral body metastasis will also contribute to local depression or expansion, which will result in spinal cord compression and compression on the nerves. In addition, osteolytic bone metastasis can also induce hypercalcemia. Such a series of skeletal-related events (SREs) seriously affect the quality of life of patients to some extent, and have become important factors for the rapid death of lung cancer patients [4,5].

Currently, bisphosphonates, chemotherapy, immunotherapy, targeted therapy and three-step cancer analgesia are mainly used in the clinical treatment of lung cancer with bone metastasis [6]. Zoledronic acid, a new generation of bisphosphonates, can effectively relieve the pain caused by bone metastasis and reduce the incidence rate of SREs [7]. It has been pointed out in some studies that the binding of cytokines produced by target tissues to the specific receptors expressed in tumor tissues can facilitate the repair and metastasis of osteoclasts. Multiple studies have revealed that zoledronic acid is safe and effective in treating bone metastases from breast cancer, prostate cancer, lung cancer and so on [8-10].

The aim of the present study was to investigate the clinical efficacy and safety of zoledronic acid combined with chemotherapy in the treatment of advanced NSCLC patients with primary bone metastasis.

Methods

General data

A total of 148 advanced NSCLC patients with bone metastasis who were treated in our hospital from January 2016 to March 2017 were enrolled. The inclusion criteria involved: (1) patients with an age >18 years old, (2) those who were diagnosed as NSCLC by fiberoptic bronchoscopy, biopsy or cytology, (3) those with stage IV NSCLC with primary bone metastasis and pain symptoms, (4) those who were diagnosed with bone metastasis by a positive result in bone scan (bone metastasis was considered when there were radioactive concentration foci at the corresponding bone metastasis sites), with osteolytic or osteogenic lesions found by imaging data such as X-ray, computed tomography (CT) and magnetic resonance imaging (MRI), (5) those with a Karnofsky performance status (KPS) score ≥70 points, (6) those who received no radiotherapy, chemotherapy or other anti-tumor therapies within 4 weeks before enrollment, and (7) those with a life expectancy >3 months. The exclusion criteria were as follows: (1) patients allergic to the treatment in this study, (2) those with spinal destruction, paraplegia or pathological fractures, (3) those with severe heart, liver or kidney diseases or mental diseases, or (4) those with chronic or acute infectious diseases or autoimmune diseases.

According to the different treatment received, the patients were divided into the Zoledronic Acid group (treated with zoledronic acid combined with chemotherapy, n=74) and the Control group (treated with chemotherapy alone, n=74). Among the patients, there were 81 males and 61 females with an average age of

Table 1. Baseline characteristics of the studied patients

Characteristics	*Zoledronic acid group (n=74)*	*Control group (n=74)*	*p value*
Age (years)	61.42±10.13	62.06±10.08	0.701
Gender (Male/ Female)	49/25	44/30	0.496
Pathological type, n (%)			0.566
Squamous cell carcinoma	17 (23.0)	22 (29.7)	
Adenocarcinoma	54 (73.0)	48 (64.9)	
Others	3 (4.0)	4 (5.4)	
Bone metastasis, n (%)			0.509
Single	32 (43.2)	36 (48.6)	
Multiple	42 (56.8)	38 (51.4)	
Visceral metastases, n (%)			0.365
Yes	19 (25.7)	24 (32.4)	
No	55 (74.3)	50 (67.6)	
NRS score, n (%)			0.568
1-3 points	11 (14.9)	8 (10.8)	
4-6 points	30 (40.5)	27 (36.5)	
7-10 points	33 (44.6)	39 (52.7)	
KPS score, n (%)			0.219
80-90	7 (9.5)	12 (16.2)	
70-80	67 (90.5)	62 (83.8)	

NRS: numeric rating scales; KPS: Karnofsky performance status.

60.86±10.95 years. No statistically significant differences were observed in the baseline data between the two groups before treatment (p>0.05, Table 1).

This study was approved by the Ethics Committee of Linyi Central Hospital, and all patients enrolled were informed and signed the informed consent in accordance with the *Declaration of Helsinki.*

Treatment regimens

Patients in the Zoledronic Acid group received gemcitabine plus cisplatin (GP) chemotherapy. Specifically, gemcitabine (1000 mg/m^2) was intravenously infused for 30 min on d 1 and 8, and cisplatin (30 mg/m^2) intravenous infusion was administered on d 1-3. The treatment was administered for 3 consecutive weeks and then stopped for 1 week, with 4 weeks as a treatment cycle. Zoledronic acid (4 mg) + normal saline (100 mL) were intravenously infused for >15 min, once every 4 weeks.

Patients in the Control group were treated with GP chemotherapy. Specifically, gemcitabine (1000 mg/m^2) was intravenously infused for 30 min on d 1 and 8, and cisplatin (30 mg/m^2) intravenous infusion was administered on d 1-3. The treatment was conducted for 3 consecutive weeks and stopped for 1 week, with 4 weeks as a treatment cycle. Patients in both groups received a total of 2 cycles of treatment (4 weeks/cycle).

Observation indexes

The efficacy on bone metastasis was evaluated. Specifically, the intervention effect on bone metastasis was evaluated by imaging reexamination at 4 weeks after treatment in both groups. According to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, the efficacy was classified as follows: (1) Complete remission (CR): Disappearance of osteolytic lesions, which lasted for more than 4 weeks. (2) Partial remission (PR): The osteolytic lesions were reduced and calcified, or the density of osteogenic lesions was decreased, which lasted for over 4 weeks. (3) Stable disease (SD): There was no change in the lesions. (4) Progressive disease (PD): The lesions were enlarged or new lesions appeared. The overall remission rate was calculated according to the formula: Overall remission rate = (CR cases+ PR cases)/ total cases × 100%.

The remission of bone pain was evaluated using the numerical rating scale (NRS), and the degree of bone pain was divided into painless (0 points), mild pain (1-3 points), moderate pain (4-6 points) and severe pain (7-10 points). The evaluation criteria for remission of bone pain [11] were as follows: (1) CR: Disappearance of pain when the dosage of painkillers was constant or reduced, with an NRS score of 0 points. (2) PR: Pain was relieved when there was no increase in the dosage of painkiller, with an NRS score decreased by ≥2 points, or no aggravation of pain when the dosage of painkiller was decreased by ≥25%, with no increase in the NRS score. (3) PD: Aggravation of pain when the dosage of painkillers was constant, with an NRS score increased by ≥2 points, or the pain was not relieved when the dosage of painkillers was increased by ≥25%, with no change in the NRS score or NRS score increased by 1 point. (4) SD in all situations except those of CR, PR and PD. The remission rate of bone pain was calculated according to the formula: Bone pain remission rate = (CR cases + PR cases)/total cases × 100%.

The levels of bone metabolic markers were determined as follows: Before treatment and at 4 weeks after treatment, fasting elbow venous blood of patients was drawn, and the changes in the levels of serum bone alkaline phosphatase (AKP), Ca^{2+}, N-terminal telopeptide (NTx) and bone sialoprotein (BSP) were measured.

The incidence of adverse reactions in both groups was recorded according to the standards of common toxic reactions of the US National Cancer Institute, and the incidence rate of SREs was calculated in both groups. SREs included radiotherapy due to bone metastatic pain, vertebral compression deformation, spinal cord compression, surgical treatment, pathological fractures and hypercalcemia induced by bone metastasis.

The quality of life was evaluated by the KPS scale (0-100 points). The higher the score, the more obvious the improvement of patients' quality of life.

The survival status of the patients was followed up and recorded. The contents of follow-up included blood routine examinations, serum tumor markers, liver and kidney function, chest CT scan, X-ray, CT scan or MRI scan of bone metastatic lesions, and bone scan or PET-CT. The survival time of the patients was recorded, and those lost to follow-up were regarded as being deleted from the date of loss to follow-up. The OS refers to the period from enrollment to death (for any reason).

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was utilized for statistical analyses. The measurement data were expressed as mean ± standard deviation, and t-test was adopted for comparison between two groups. Comparison of clinical data was tested by x^2 test or Fisher's exact test. T-test was performed for the paired serological indexes within the group, and two-way analysis of variance (ANOVA) was applied for comparison between groups. Kaplan-Meier method and log-rank test were utilized for survival analysis. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of efficacy on bone metastasis between the two groups

The efficacy was evaluated in all patients at 1 month after treatment. In the Zoledronic Acid group, there were 12 cases of CR (16.2%), 40 cases of PR (54.1%), 9 cases of SD (12.2%) and 13 cases of PD (17.6%), with an overall response rate of 70.3% (52/74). In the Control group, there were 3 cases of CR (4.1%), 35 cases of PR (47.3%), 17 cases of SD (23.0%) and 19 cases of PD (25.7%), with an overall response rate of 51.4% (38/74). The Zoledronic Acid group had a markedly higher overall response rate than the Control group, with a statistically significant difference (p=0.018, Table 2).

Comparison of control effect on bone pain between the two groups

After treatment, there were 39 cases of bone pain CR (52.7%), 31 cases of PR (41.9%), 4 cases of SD (5.4%) and 0 cases of PD in the Zoledronic Acid group, with an ostealgia remission rate of 94.6% (70/74). In the Control group, there were 28 cases of CR (37.8%), 33 cases of PR (48.6%), 8 cases of SD (10.8%) and 5 cases of PD (6.8%), with an ostealgia remission rate of 82.4% (61/74). The Zoledronic Acid group had an obviously higher ostealgia remission rate than the Control group, with a statistically significant difference (p=0.020, Table 3).

Comparison of immunological indexes between the two groups before and after treatment

There were no significant differences in the serum levels of AKP, Ca^{2+}, NTx and BSP between the two groups before treatment (p>0.05). After treatment, the serum levels of AKP, Ca^{2+}, NTx and BSP declined prominently in both groups in contrast with those before treatment, and they were markedly lower in the Zoledronic Acid group than in the Control group after treatment (p<0.05, Table 4).

Table 2. Clinical effective rates of bone metastasis of patients in the two studied groups

Effective rates	*Zoledronic acid group (n=74) n (%)*	*Control group (n=74) n (%)*	*p value*
CR	12 (16.2)	3 (4.1)	
PR	40 (54.1)	35 (47.3)	
SD	9 (12.2)	17 (23.0)	
PD	13 (17.6)	19 (25.7)	
ORR	52 (70.3)	38 (51.4)	0.018

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate.

Table 3. Comparison of ostealgia remission rate of patients in the two studied groups

	Zoledronic acid group (n=74) n (%)	*Control group (n=74) n (%)*	*p value*
CR	39 (52.7)	28 (37.8)	
PR	31 (41.9)	33 (48.6)	
SD	4 (5.4)	8 (10.8)	
PD	0 (0)	5 (6.8)	
ORR	70 (94.6)	61 (82.4)	0.020

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: ostealgia remission rate.

Table 4. Comparison of bone metabolic markers of patients in the two studied groups

Metabolic markers	*Zoledronic acid group (n=74)*	*Control group (n=74)*	*p value*
AKP (U/L)			
Pretreatment	327.56±53.22	325.73±50.39	0.830
Posttreatment	126.67±33.64	178.95±31.45	0.001
Ca^{2+} (mmol/L)			
Pretreatment	2.81±0.19	2.76±0.23	0.152
Posttreatment	1.79±0.24	1.93±0.22	0.003
NTx (nmol/L)			
Pretreatment	28.54±15.17	27.73±14.53	0.741
Posttreatment	14.84±9.49	18.98±10.21	0.012
BSP (nmol/L)			
Pretreatment	41.26±11.58	40.77±16.93	0.638
Posttreatment	23.61±12.72	28.59±14.43	0.028

AKP: alkaline phosphatase; NTx: N- terminal telopeptide of type I collagen; BSP: bone sialoprotein.

Table 5. Comparison of adverse reactions of patients in the two studied groups

Parameters	*Zoledronic acid group (n=74)* *n (%)*	*Control group (n=74)* *n (%)*	*p value*
Bone marrow depression	31 (41.9)	28 (37.8)	0.663
Fever	5 (6.7)	3 (4.1)	0.467
Nausea and vomiting	41 (55.4)	36 (48.6)	0.411
Alopecia	33 (44.6)	30 (40.5)	0.618
Rash	8 (10.8)	14 (18.9)	0.166
Liver function damage	15 (20.3)	12 (16.2)	0.523
Renal function damage	19 (25.7)	16 (21.6)	0.562
SREs			
Ostealgia	18 (24.3)	25 (33.8)	0.205
Vertebral compression and deformation	5 (6.7)	4 (5.4)	0.731
Spinal cord compression	3 (4.1)	2 (2.7)	0.649
Pathological fracture	0 (0)	1 (1.4)	0.316
Hypercalcemia	2 (2.7)	9 (12.2)	0.028

SREs: skeletal related events.

Comparison of quality of life between the two groups after treatment

No statistically significant difference was observed in the KPS score between the Zoledronic Acid group and the Control group before treatment [(77.49±5.88) *vs.* (76.86 ±5.47) points, p>0.05]. After treatment, the KPS score was improved in both groups, and the Zoledronic Acid group had an obviously higher KPS score than the Control group [(86.08±5.61) *vs.* (83.94±5.32) points, p=0.019].

Comparison of adverse reactions

During treatment, the adverse reactions in both groups mainly included nausea and vomiting, bone marrow depression (degree I-II), fever, alopecia, rash, and liver and kidney function damage. There was no statistically significant difference in the incidence of treatment-related adverse reactions between the two groups (p>0.05). In the Zoledronic Acid group, the SREs included 18 cases of bone pain, 5 cases of vertebral compression and deformation, 3 cases of spinal cord compression and 2 cases of hypercalcemia. In the Control group, there were 25 cases of bone pain, 4 cases of vertebral compression deformation, 2 cases of spinal cord compression, 1 case of pathological fracture and 9 cases of hypercalcemia. There was no significant difference in the incidence rates of bone pain, vertebral compression deformation, spinal cord compression and pathological fracture between the two groups (p>0.05). The incidence rate of hypercalcemia in the Zoledronic Acid group was significantly lower than in the Control group (p=0.028, Table 5).

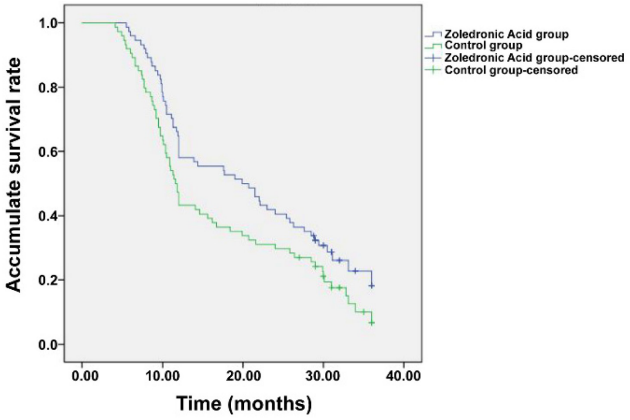

Figure 1. Kaplan-Meier survival curves of patients in the Zoledronic acid group and the Control group. The overall survival rate of patients in Zoledronic acid group was significantly higher than that of the Control group (p=0.033).

Follow-up results of patient survival

All the 148 patients were followed up until March 2020, with a follow-up period of 4-36 months. The 1-, 2- and 3-year OS rates in the Zoledronic Acid group and the Control group were 58.1% (43/74) *vs.* 43.2% (32/74), 40.5% (30/74) *vs.* 29.7% (22/74), and 24.3% (18/74) *vs.* 13.5% (10/74), respectively. Kaplan-Meier method was adopted to plot the survival curves (Figure 1). The results of log-rank test revealed that the OS in the Zoledronic Acid group was distinctly better than that in the Control group, with a statistically significant difference (p=0.033).

Discussion

Lung cancer is the most common malignant tumor with bone metastasis, and its incidence rate is up to 70%. Currently, the commonly used treatment for lung cancer with bone metastases includes chemotherapy, radiotherapy, and drug analgesia [12]. Chemotherapy has a certain efficacy on lung cancer with bone metastasis, and the response rate is about 40%. However, the efficacy of chemotherapy alone on pain and bone destruction induced by bone metastasis is not ideal [13]. Generally, it is difficult for most anticancer drugs to pass through the bone tissue barrier and reach the lesion sites to play a role. The damaged bone tissue recovers relatively slowly, and the adverse reactions triggered by long-term chemotherapy also influence the quality of life of patients. Radiotherapy alone is effective in treating localized lesions. However, it is not effective in the treatment of multiple metastatic lesions [14]. Osteophilic isotope internal-radiation therapy can reduce the destruction of osteolysis, has a certain therapeutic efficacy on bone pain, and can suppress the development of bone metastasis, but it is ineffective on extraosseous tissue [15].

Zoledronic acid, a third generation of bisphosphonates, can effectively repress the activity of osteoclasts, prevent bone resorption and accelerate the apoptosis of osteoclasts. Meanwhile, zoledronic acid can down-regulate the release of inflammatory factors and related bone stimulating factors in malignant tumors, and reduce the activity of osteoclasts, with fast action and long effect time [16]. In the past, chemotherapy or radiotherapy alone was effective in the control of localized bone metastasis from lung cancer, but the intervention effect on bone destruction and bone pain induced by chemotherapy or radiotherapy was not good. However, the treatment with zoledronic acid on the basis of radiotherapy or chemotherapy can optimize the control effect of bone pain and reduce the degree of bone destruction [17]. For advanced NSCLC, the overall response rate of platinum-based doublet regimen is 25-35%, the median time of disease progression is 4-6 months, the median OS is 8-10 months, and the 2-year survival rate is <20% [18]. The phase III randomized trial of Eastern Cooperative Oncology Group (ECOG) revealed that the median survival time of patients with advanced NSCLC undergoing paclitaxel combined with cisplatin is 9.9 months, and the 1-year survival rate is 38.9% [19]. The results of a phase III, randomized, international multicenter trial of the TAX326 study group manifested that the response rate of docetaxel combined with cisplatin is 32%, the median survival time is 11.3 months, and the 1- and 2-year survival rates are 46% and 21%, respectively [20]. The study of Satoh et al [21] demonstrated that the 2-year survival rate of advanced NSCLC is 12.8%. According to the studies of Giroux Leprieur et al [22], the 2-year survival rate of advanced NSCLC is 15.9%.

In this study, zoledronic acid combined with GP chemotherapy was adopted to treat the 74 lung cancer patients with bone metastasis. After treatment, the overall response rate of bone metastasis was 70.3%, and the bone pain remission rate was 94.6%. The patient quality of life (KPS score) was significantly improved, and the improvement was more significant in the Zoledronic Acid group than in the Control group ($p<0.05$), which was consistent with the results reported by most authors. The levels of serum Ca^{2+} and AKP in the Zoledronic Acid group declined continuously after treatment, and the Zoledronic Acid group had more significant decrease than the Control group ($p<0.05$). This is mainly because zoledronic acid can promote calcium deposition in bone, facilitating self-repair of bones, repressing the destruction of cancer cells in bone and bone resorption triggered by osteoclasts, and reducing the occurrence of hypercalcemia and other related complications induced by bone metastasis. NTx belongs to bone collagen, and type I bone collagen accounts for more than 90% of bone organic matter. Thus, NTx can be used as a specific index for the clinical diagnosis of bone tissue damage driven by osteoclasts [23]. BSP, the major protein of bone extracellular matrix, directly participates in cell adhesion and metastasis. It is an important index to judge the invasion of tumor cells [24]. In this study, the levels of NTx and BSP were markedly lower in the Zoledronic Acid group than in the Control group after treatment ($p<0.05$), suggesting that zoledronic acid + GP regimen can reduce the degree of bone tissue damage. It was found through safety analysis that the incidence rate of adverse reactions was comparable between the two groups, with no statistically significant difference ($p>0.05$). The Zoledronic Acid group had an obviously lower incidence rate of hypercalcemia than the Control group ($p=0.028$).

There were some limitations in this single-center retrospective study. The sample size was not large enough, the follow-up time was short, and the follow-up contents were not comprehensive enough. In the future, more rigorous and scientific prospective, randomized, multicenter, controlled trials with large samples need to be designed to verify the conclusions of this study.

Conclusions

Zoledronic acid combined with chemotherapy is remarkably effective in treating NSCLC with bone metastasis, which can distinctly relieve bone pain, ameliorate the quality of life, improve the long-term survival rate, and reduce the incidence of SREs.

Conflict of interests

The authors declare no conflict of interests.

References

1. Tsoukalas N, Kiakou M, Tsapakidis K et al. PD-1 and PD-L1 as immunotherapy targets and biomarkers in non-small cell lung cancer. JBUON 2019;24:883-8.
2. Zhang L, Gong Z. Clinical Characteristics and Prognostic Factors in Bone Metastases from Lung Cancer. Med Sci Monit 2017;23:4087-94.
3. Wang T, Li W, Li W, Liu L, Zhang H. MicroRNA-203 promotes the progression of non-small cell lung cancer via surviving. JBUON 2019;24:591-8.
4. Ulas A, Bilici A, Durnali A et al. Risk factors for skeletal-related events (SREs) and factors affecting SRE-free survival for nonsmall cell lung cancer patients with bone metastases. Tumour Biol 2016;37:1131-40.
5. Delea T, Langer C, McKiernan J et al. The cost of treatment of skeletal-related events in patients with bone metastases from lung cancer. Oncology 2004;67:390-6.
6. Bai SB, Liu DZ, Cheng Y et al. Osteoclasts and tumor cells dual targeting nanoparticle to treat bone metastases of lung cancer. Nanomedicine-Uk 2019;21:102054.
7. Song Z, Zhang Y. Zoledronic acid treatment in advanced non-small cell lung cancer patients with bone metastases. Med Oncol 2014;31:898.
8. Isla D, Afonso R, Bosch-Barrera J, Martinez N. Zoledronic acid in lung cancer with bone metastases: a review. Expert Rev Anticancer Ther 2013;13:421-6.
9. Vaishampayan UN, Tehrani OS, Lawhorn-Crews JM et al. A Pilot Trial Evaluating Zoledronic Acid Induced Changes in [(18)F]FMAU-Positron Emission Tomography Imaging of Bone Metastases in Prostate Cancer. Mol Imaging Biol 2017;19:810-6.
10. Lacerna L, Hohneker J. Zoledronic acid for the treatment of bone metastases in patients with breast cancer and other solid tumors. Semin Oncol 2003;30:150-60.
11. Di Staso M, Gravina GL, Zugaro L et al. Treatment of Solitary Painful Osseous Metastases with Radiotherapy, Cryoablation or Combined Therapy: Propensity Matching Analysis in 175 Patients. PLoS One 2015;10:e129021.
12. Jia F, Cheng X, Zeng H, Miao J, Hou M. Clinical research on stereotactic radiosurgery combined with epithermal growth factor tyrosine kinase inhibitors in the treatment of brain metastasis of non-small cell lung cancer. JBUON 2019;24:578-84.
13. Niu Y, Lin Y, Pang H, Shen W, Liu L, Zhang H. Risk factors for bone metastasis in patients with primary lung cancer: A systematic review. Medicine (Baltimore) 2019;98:e14084.
14. Sugiura H. Encounter of cancer cells with bone. Therapy for bone metastasis from lung cancer. Clin Calcium 2011;21:439-45.
15. Zhao F, Ding G, Huang W et al. FDG-PET Predicts Pain Response and Local Control in Palliative Radiotherapy With or Without Systemic Treatment in Patients With Bone Metastasis From Non-small-cell Lung Cancer. Clin Lung Cancer 2015;16:e111-e119.
16. Yu Z, Liu Y, Cui Y et al. Cost-effectiveness of standard utilization of zoledronic acid for bone metastases from advanced lung cancer in China. J Comp Eff Res 2019;8:487-95.
17. Nakahara Y, Hosomi Y, Shibuya M et al. Multicenter study of zoledronic acid administration in non-small-cell lung cancer patients with bone metastasis: Thoracic Oncology Research Group (TORG) 1017. Mol Clin Oncol 2019;11:349-53.
18. Souquet PJ, Chauvin F, Boissel JP et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. Lancet 1993;342:19-21.
19. Bonomi P, Kim K, Fairclough D et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000;18:623-31.
20. Fossella F, Pereira JR, von Pawel J et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-24.
21. Satoh H, Ishikawa H, Ohara G et al. Long-term survivors after chemotherapy in advanced non-small cell lung cancer. Anticancer Res 2007;27:4457-60.
22. Giroux LE, Lavole A, Ruppert AM et al. Factors associated with long-term survival of patients with advanced non-small cell lung cancer. Respirology 2012;17:134-42.
23. Zhao YY, Xue C, Hou X et al. Changes of bone resorption marker (NTX) in chemotherapy plus zoledronic acid versus chemotherapy alone for nasopharyngeal cancer patients with bone metastases. Eur J Cancer 2011;47:848-53.
24. Wei RJ, Li TY, Yang XC, Jia N, Yang XL, Song HB. Serum levels of PSA, ALP, ICTP, and BSP in prostate cancer patients and the significance of ROC curve in the diagnosis of prostate cancer bone metastases. Genet Mol Res 2016;15:gmr.15027707.