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RESEARCH

An Effective Therapy to Painful Bone Metastases: Cryoablation Combined with Zoledronic Acid

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Abstract Approximately half or more of patients diagnosed with late malignant tumors may suffer from metastatic bone pain, effective palliation of pain becomes an important part of comprehensive therapy for malignant tumors. In this study, we examined the efficacy and safety of the combined regimen of cryoablation and zoledronic acid in patients of bone metastatic pain. A total of 84 subjects were randomly divided into three groups, and underwent treatments of cryoablation plus zoledronic acid, cryoablation alone, zoledronic acid alone between June 2009 and March 2012. Patients responses had been assessed for a total of 6 months by using the Brief Pain Inventory (BPI)-Short Form. The results showed that the mean response of worst and average pain significantly dropped at week 2 (all $P<0.05$) in group with cryoablation treatment but at week 4 (all $P<0.05$) in group with zoledronic acid treatment. While between week 16 and week 24, zoledronic acid treatments showed more durable response to worst and average pain compared to cryoablation (all $P<0.05$). Cryoablation plus zoledronic acid regimen showed significant drop in worst and average pain between week 1 and week 4 compared to zoledronic acid alone (all $P<0.05$) and more durable effect on bone metastatic pain between week 12 and week 24 than cryoablation alone (all $P<0.05$). Additionally, no serious adverse effects and complication were observed by this combination use. In conclusion, cryoablation combined with zoledronic acid was safe and effective regimen and showed its superiority of fast response and durable effect on painful bone metastases.

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Abbreviations
BPI Brief pain inventory
KPS Physical performance status

Introduction

Bone metastasis is one of common complications in late malignant tumors, about 20~70 % patients with tumor ultimately have bone metastasis, mainly in lung cancer, breast cancer, prostate cancer and renal cancer [1–6]. Bone metastases may cause devastating clinical complications associated with dramatic reductions in quality of life, mobility, independence, as well as excruciating refractory pain [7]. Pain is the most common symptom of bone metastases and seriously influenced the life quality of the sufferers [8, 9], to palliate the pain becomes an important part of comprehensive therapy for malignant tumors, and plays important role in improvement of life quality for patients. Oncologists have explored multiple strategies for painful bone metastases include systemic therapies (chemotherapy, hormonal therapy, radiopharmaceuticals, and bisphosphonates), analgesics (opioids and nonsteroidal anti-inflammatory drugs), localized therapies (radiation, laser-induced interstitial thermotherapy, percutaneous radiofrequency ablation, and cryoablation) and surgical approaches [9, 10]. Each of these therapies has its merits and demerits in clinical application. up to now, there is no a quite satisfactory therapy to treat painful bone metastases. Cryoablation has showed a safe and effective method to treat bone metastatic lesion and pain in recent years [10–15]. Zoledronic acid, one of bisphosphonates, is a potent inhibitor of the bone resorption mediated by the osteoclasts, has been

confirmed to be an effective medicine in preventing the skeleton complications and in controlling the painful symptoms of bone metastases [16–20]. Cryoablation is a kind of physical therapy, while zoledronic acid belongs to pharmaceutical treatment, the mechanisms of the two regimens are not identical. In this study, we prospectively assessed the clinical safety and efficacy of simultaneous combination therapy with cryoablation and zoledronic acid in treatment of painful bone metastases.

Materials and Methods

Patients

A total of 84 cases of malignant tumor bone metastases with pain between June 2009 and March 2012 were recruited into this study. All patients enrolled were older than 18 years and singed informed consent. The study was approved by the ethical committees of the First Hospital of Lanzhou University. According to Brief Pain Inventory (BPI)-Short Form, patients with substantial pain as indicated by a score of 5 on a scale of 0–10 for the worst pain over the past 24 h were included in the study [10, 21].

Patients Inclusion Criteria

The patients enrolled should be in accordance with the criteria that was designated on the basis of previous literatures [10, 22]: (1) metastatic bone tumor was confirmed by histologic or cytologic proof and imaging (including the systemic CT and MRI and bone ECT) with middle to severe pain; (2) the life expectancy was greater than 6 months; (3) blood routine examination was normal, and serum calcium were higher than 2.00 mmol/L; (4) the functions of heart, liver, kidney and other important organs were basically normal; (5) physical performance status (KPS) was higher than 60.0 %; (6) subjects could tolerate preoperative and postoperative plain and enhanced CT scanning; (7) patients completed chemotherapy or radiation of metastatic lesions at least 3 weeks prior to enrollment; (8) pain resulting from no more than two sites of metastatic disease;.

Patients Exclusion Criteria

The subjects was excluded according to one of following criteria optimized on the basis of previous literatures [10, 22]: (1) patients diagnosed as primary bone cancer by pathology; (2) patients with impending fractures (3) The portions of lesions within 0.5 cm of the spinal cord, brain, aorta, inferior vena cava, bowel, or bladder; (4) unwilling to accept cryoablation or zoledronic acid therapy; (5) intolerant of targeted argon-helium cryoablation due to serious dysfunctions of vital organs including heart, liver and kidney etc.; (6) patients had received bisphosphonate treatment; (7) blood coagulation disorders; (8) serious hypocalcemia.

Pretreatment Patient Assessment

Prior to therapy with cryoablation, each patient was assessed with the BPI-Short Form [10, 21], which is a validated visual analog scale for assessment of patient pain, and use of analgesic medicine was recorded. The BPI questionnaire asks patients to rate their worst pain in 24 h, least pain in 24 h, and average pain with responses from 0 to 10 (0, no pain; 10, maximum pain intensity). Relief of pain through the use of pain treatments or medications is scored on a 0–100 % scale (0 %, no relief; 100 %, complete relief). Pain interference with activities of daily living was evaluated with questions concerning general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life on a 0–10 scale (0, no interference; 10, completely interferes). Each patient was asked to answer these questions with respect to the lesion that was to be treated.

Equipments and Techniques

Targeted argon-helium cryoablation minimally invasive operating system: argon-helium cryoablation system, cryoprobes with diameter 1.7, 2.4 and 3 mm (Endocare Cryocare System, USA.). Sixteen or 64 slice CT (Siemens, Germany).

Therapeutic Regimen

All of the patients were informed the relevant precautions and operational risk and signed informed consent. Preoperative plain CT scanning was taken to confirm tumor range and select freezing levels, and figure out the feeding angle and direction. Metal markers were used as guide to determine puncture point. The group A patients were given targeted argon-helium cryoablation one time and monthly administered with Zoledronic Acid Injection 4 mg melt in 0.9 % Sodium Chloride Injection 100 ml by intravenous drip more than 15 min, totally over six times. Group B patients were giver targeted argon-helium cryoablation to metastatic lesion for one time. Group C patients were given zoledronic acid 4 mg over six times.

Cryoablation Procedure

After routine sterile preparation, 0.2 % chloroprocaine was used to anesthetize puncture point. 5-11F cryoprobes were placed into sheath tube and inserted into metastatic lesions, feeding direction and depth were under the guide of plain CT scanning. A single cryoprobe was placed for lesions 3 cm or less in diameter. For larger lesions, two to five additional

cryoprobes were systematically placed with CT guidance. Cryoablation treatments were focused on the margin of the lesion involving bone to treat the soft-tissue–bone interface. Plain CT scanning was performed approximately every 2 min throughout the freezing portions of the cycle to monitor the growth of the ice ball. Each lesion was given three freeze-thaw-freeze cycles, 20 min each circle, after each freezing cycle, cryoprobes were warmed with active heating by using helium gas until the temperature reached >20 °C. The cryoprobes were then withdrawn.

Patient Assessment after Treatment and CT Imaging

Patients were evaluated for pain severity and influence of pain on activities of daily living by using the BPI-Short Form [10, 21]. The patients completed the BPI questionnaire in the day after the treatment. The BPI questionnaire was also completed 4 days after treatments, weekly during a telephone interview for the following 2 weeks, and every 2 weeks thereafter for a total of 6 months. The patients were not given a copy of the BPI, and no prior responses were available for review at subsequent interviews in order to ensure accuracy and minimize bias. Each patient was asked to answer these questions with respect to the lesion that was treated. Analgesic use was also recorded during each of these interviews. Each patient underwent contrast material–enhanced CT imaging of the treated region 4–6 weeks after the treatment. Mean patients responses for worst pain and mean patients responses for average pain was taken as primary endpoints, and mean score for interference of pain and average relief from pain was taken as secondary endpoints in this study.

Statistics Processing

Student's *t* test was used to assess the differences in age, KPS score, BPI of each two group, Chi-square test was used to assess the differences in gender, malignant hypercalcemia, pain medication and primary tumor location and type. Findings with $P<0.05$ were considered to indicate a statistically significant difference.

Results

Demographic Characteristics

Patients aged from 37 to 72 years old, among them, the male 44 cases, the female 40 cases, lung cancer in 30 cases, breast cancer in 22 cases, kidney cancer in 10 cases, prostate cancer in 7 cases, gastrointestinal cancer in 11 cases, nasopharyngeal carcinoma (NPC) in 4 cases. Patients were randomly divided into three groups according to therapeutic regimens: group A (28 cases, argon-helium cyroablation plus zoledronic acid), group B (28 cases, argon-helium cyroablation), group C (28 cases, zoledronic acid). Among the three groups in general: age, gender, KPS score, malignant hypercalcemia, pain medication and primary tumor location and type were balanced comparable (Table 1). The frequency of missing data was minimal. Two patients of group A died of primary tumors at week 19 and 22 respectively. Three patients of group B died of primary tumors at week 18, 20 and 21 respectively. Three patients of group C died of primary tumors at week 17, 20 and 23 respectively. And one patient of group C quitted the study at week 16 for renal dysfunction resulting from zoledronic acid.

Cryoablation Plus Zoledronic Acid Exerted Evident Analgesic Effect

The mean patient responses for worst pain were 8.12 of 10 in group A, 8.20 of 10 in group B, 7.91 of 10 in group C (Fig. 1a), there was no statistical difference in three groups prior to cryoablation or zoledronic acid treatment. It showed a gradual downward trend occurred in mean response for worst pain for most patients of three groups. At 2, 4 weeks after treatment, this mean response dropped more obviously in group A and B compared to group C (all $P<0.05$). Between week 6 and week 10, this mean responses were not statistically different among three group (all $P>0.05$). Between week 12 and week 24, this mean response dropped more distinctly in group A compared to group B and C (all $P<0.05$), then, between week 18 and week 24, this mean response of group C was slightly statistically higher than it of group B (all $P<0.05$).

The mean patient response for average pain were 7.12 of 10 in group A, 7.32 of 10 in group B, 7.05 of 10 in group C (Fig. 1b), there was no statistical difference of in three groups prior to cryoablation or zoledronic acid treatment. It showed a gradual downward trend occurred in mean response for average pain for most patients of three groups. At 1, 2 weeks after treatment, this mean responses were not statistically different among three group (all $P>0.05$). At week 4, the mean response of average pain of group A was lower than group B ($P=0.032$), and group B was lower than group C ($P=0.026$). Between week 8 and week 24, this mean response dropped more distinctly in group A compared to group B and C (all $P<0.01$). Between week 8 and week 24, this mean responses were not statistically different between group B and C (all $P>0.05$). Between week 18 and week 24, this mean response of group C was statistically higher than it of group B (all $P<0.05$).

The mean score for interference of pain were 5.83 of 10 in group A, 6.12 of 10 in group B, 5.76 of 10 in group C (Fig. 1c), there was no statistical difference of in three groups prior to cryoablation or zoledronic acid treatment. Between week 2 and week 12 after treatment, this mean score was continuously dropped in group A (all $P<0.05$). Between week 2 and week

Table 1 Demographic and clinical characteristics of patients

Characteristic		Group A *N*=28	Group B *N*=28	Group C *N*=28	*P*
Age		51.8±9.31	54.8±10.52	56.6±11.33	0.514[a]
Sex	Male (n)	15	15	14	0.757[b]
	Female (n)	13	13	14	
KPS score		70±1.1	70±1.3	70±0.9	0.900[a]
Pain medication (n)		15	14	15	0.766[b]
Malignant Hypercalcaemia		13	12	11	0.625[b]
Previous radiotherapy		4	6	5	0.784[b]
Mean number of the bone metastases		1.32±0.469	1.43±0.514	1.39±0.487	0.727[a]
Mean lesions size (cm)					
Craniocaudal		5.8±2.9	6.0±3.1	5.6±2.8	0.682[a]
Left		4.6±1.9	4.7±2.3	4.9±1.8	0.724[a]
Anteroposterior		5.2±2.7	5.3±2.5	5.4±3.0	0.716[a]
Primary tumor location and type (n)					
Non-small cell lung cancer		10	9	11	0.856[b]
Breast cancer		7	8	7	0.940[b]
Renal cell cancer		4	3	3	0.893[b]
Prostate adenocarcinoma		2	3	2	0.860[b]
Colorectal carcinoma		2	2	1	0.808[b]
Hepatocellular caricinoma		2	1	2	0.794[b]
Gastric adenocarcinoma		0	1	0	0.329[b]
Nasopharyngeal carcinoma		1	1	2	0.769[b]
Metastatic lesions localization (n)					
Rib		12	14	11	0.713[b]
Chest wall		6	7	5	0.809[b]
Thoracic vertebra		4	5	5	0.864[b]
Lumbar vertebra		5	5	6	0.926[b]
Clavicle		3	3	2	0.866[b]
Sacrum		2	3	2	0.860[b]
Ilium		2	1	3	0.570[b]
Acetabulum		2	2	3	0.860[b]
Scapula		1	1	2	0.769[b]
Type of the lesions (n)					
Osteolytic		21	23	21	0.762[b]
Osteoplastic		11	12	15	0.535[b]
Mixed		5	6	3	0.534[b]

a denotes P values from Student's *t* test, b denotes P values from Chi-square test

8, the mean score of group A was significantly lower than it of group C (all $P<0.05$), and slightly but not statistically lower than it of group B (all $P>0.05$). Between week 12 and week 24, the mean score in group A was significantly lower than group B and C (all $P<0.05$). Between week 4 and week 8, the mean score of group B was lower than it of group C (all $P<0.05$), but after week 10, there was no significant difference between group B and C ($P>0.05$).

The average relief from pain were 42 % in group A, 40 % in group B, 39 % in group C (Fig. 1d), there was no statistical difference of in three groups prior to cryoablation or zoledronic acid treatment. It showed a gradual improving trend of pain relief occurred for most patients. Between week 2 and week 4 after treatment, the average relief was significantly improved in group A and B, compared to group C (all $P<0.05$). Between week 6 and week 24, the average relief was significantly improved in group A compared to group B and C (all $P<0.05$), after week 6, there was no significant difference in improvement of pain relief between group B and C (all $P>0.05$), and after week 12, the improvement of average relief of group C was statistically better than group B (all $P<0.05$).

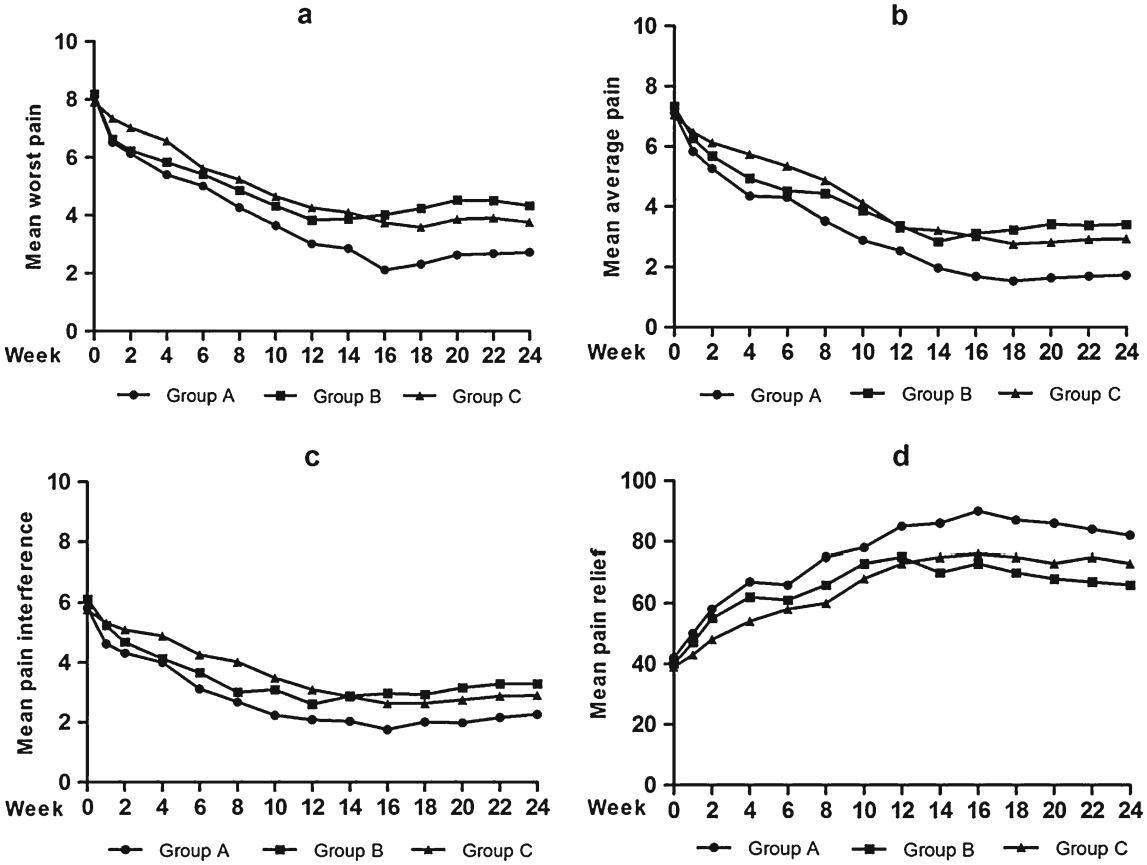

Fig. 1 BPI measured for patients of three groups prior to and after treatments, week 0 is response prior to treatment, weekly recorded for 2 weeks following treatments, and every 2 weeks thereafter for a total of 6 months. **a** Mean patients responses for worst pain; **b** mean patients responses for average pain; **c** mean score for interference of pain; **d** average relief from pain

Adverse Effect and Complication

Main adverse effect and complication of the two therapeutic regimens include frostbite, fever, muscle pain, hypercalcemia, hypocalcemia, dysfunction of kidney, pathological fracture and so on. The total incidence of adverse effect and complication were 92.9, 89.2 and 50 % in group A, B and C respectively (Table 2). The adverse effect and complications were thought mainly from argon-helium cryoablation, so they were significantly higher in group A and B than group C (all $P<0.05$). Most adverse effect and complication were relatively mild, and almost alleviated after short-term treatment. Except for one case of renal dysfunction resulting from zoledronic Acid, there was no severe adverse effect and complication occurred in subjects.

Discussion

Treatments for painful bone metastases may not only diminish pain, but may also improve quality of life and independence/mobility, and reduce skeletal morbidity, potential pathologic fractures, spinal cord compression, and other skeletal related events [9]. Cryoablation and zoledronic acid have each been

Table 2 Main adverse effects and complication

	Fever	Muscle pain	Hypercalcemia	Hypocalcemia	Renal dysfunction	Frostbite	Pathological fracture	Total
Group A	16	4	2	0	0	1	3	26(92.9 %)*
Group B	15	3	2	0	0	0	5	25(89.2 %)*
Group C	5	3	0	3	1	0	2	14(50.0 %)

*denotes $P<0.05$ compare to group C

confirmed to be effective therapy for bone metastatic lesion and pain, however, the mechanisms underlying their pain-killing effects are different from each other. Cryoablation exerts effect by direct and fast extermination to the metastatic lesion, while zoledronic acid acts by restraining maturation and function of osteoclast and inhibiting tumor cell proliferation and infiltration in bone matrix. To our knowledge, there is no reports on comparison and combination of cryoablation and zoledronic acid in treatment of bone metastatic pain. In order to compare the effect of cyroablation and zoledronic acid and confirm whether they could exert synergic effect on painful bone metastasis, this study was designed and performed.

Cryoablation Exerted Fast Response for Bone Metastatic Pain

Argon-helium cyroablation have been applied to treatment for bone metastatic pain in recent years, and proved to be safe and effective [10–15]. Based on its unique advantage, direct and fast freezing damage to metastatic lesion, cyroablation could not only mitigate the pain but exterminate the tumors with a little injury and less complications, non-toxic side effects [10]. Farrar et al. showed that cryoablation resulted in substantial pain reduction with a 43 % mean reduction in worst pain at 4 weeks which was considered to be clinically important [23]. In this study, 28 cases of patients (group B) received percutaneous cyroablation therapy, pain was significant alleviated in 23 cases, only 5 patients showed weak response, the results was consistent with previous reports [10–15]. Furthermore, compared to therapy of zoledronic acid (group C), cryoablation showed its superiority of fast response after treatment, in group B, the mean worst pain significantly alleviate at week 2 (P=0.034) in group B but at week 4 (P=0.016) in group C, the mean average pain significantly alleviate at week 4 (P=0.033) in group B but at week 6 (P=0.014) in group C, the mean score for interference significantly dropped at week 2 (P=0.015) in group B but at week 4 (P=0.019) in group C, the average relief significantly improved at week 2 (P=0.023) in group B but at week 4 (P=0.012) in group C.

Zoledronic Acid Exerted Durable Effect on Bone Metastatic Pain

Zoledronic acid is the most widely used bisphos-phonate to treat cancer-induced bone disease [16–20]. The mechanisms of zoledronic acid in the treatment of malignant tumor bone metastases include [24–27]: (1) inhibiting maturation, gathering and function of osteoclast; (2) to reduce the production of the cytokine (such as IL-6); (3) inhibiting tumor cell proliferation and adhesion, infiltration in bone matrix; (4) antiangiogenic effect. Many of reports showed that zoledronic acid has strong effect on bone metastatic pain with durable analgesic property, mild adverse reactions [16–20, 28]. The present results were consistent with previous reports: the BPI of patients administered only with zoledronic acid showed that from week 16 to week 24 after treatments, the recipients had longer mean response to worst and average pain and more durable dropped mean score for interference and improved average relief from pain compared to cryoablation only (all P<0.05). Meanwhile, zoledronic acid had merits of lower complication (42.9 versus 71.4 %) and relatively simple administration process (intravenously versus percutaneously) compared to Cryoablation.

Cryoablation Plus Zoledronic Acid Exerted Fast Response and Durable Effect on Bone Metastatic Pain

Patients of group A were treated with Cryoablation combined with zoledronic acid showed satisfactory effect on bone metastatic pain, from BPI results, this therapeutic regimen showed mean response of worst pain dropped at week 2 (P=0.032) and lasted to week 24, mean response of average pain dropped at week 2 (P=0.027) and lasted to week 24, mean score of interference for pain dropped at week 4 (P=0.016) and lasted to week 24, the average relief significantly improved at week 4 (P=0.011) and lasted to week 24. So, cryoablation combined with zoledronic acid made joint contribution to the clinical benefits: fast response and durable effect on bone metastatic pain..

In conclusion, in this study, cryoablation plus zoledronic acid exerted significantly fast response and durable effect on bone metastatic pain, which was better than cryoablation or zoledronic acid alone, for this combination remedies the demerits of both therapies. Additionally, no serious adverse effects and complication were observed by this combination, it suggests this combined treatment would be an acceptable therapeutic option for patients with bone metastatic pain. However, further large-scale studies are necessary to confirm these results because of the small sample size of this study.

Conflict of interest None. All authors have no conflicts of interest or financial ties to disclose.

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