

# Clinical effect of intravenous infusion of zoledronic acid combined with oral medication of cinobufagin in the treatment of metastatic bone tumors

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**Abstract:** Aim of the study was to observe and analyze the clinical effect of intravenous infusion of zoledronic acid combined with oral medication of cinobufagin in treating metastatic bone tumors. The 120 patients who have been treated in the hospital for metastatic bone tumor from June 2014 to June 2017 were selected as research objects. They were randomly divided into research group and control group, each containing 60. The research group was treated with intravenous infusion of zoledronic acid combined with oral medication of cinobufagin. In the control group, only zoledronic acid intravenous infusion was administered. The overall treatment effect of the two groups was observed. The pain of two groups was evaluated using numerical rating scale (NRS). The results showed that compared with the control group, the research group achieved better clinical effect and had a higher quality of life, and the intergroup difference was of statistical significance,  $P < 0.05$ . There was no difference in rate of adverse reactions between the two groups,  $P > 0.05$ , without statistical significance. The combined therapy of intravenous infusion of zoledronic acid and oral medication of cinobufagin can obtain better therapeutic effect in treating metastatic bone tumors.

**Keywords:** Zoledronic acid, intravenous drip, cinobufagin, metastatic tumor of bone, therapeutic effect.

## INTRODUCTION

The common site for malignant tumor metastasis is bone. Problems of metastatic bone tumors can cause severe bone disease and various complications such as pathological fractures, pain and spinal cord compression, which poses a serious impact on patients' quality of life, even threatening life safety (Guo *et al.*, 2017; Shou *et al.*, 2017; Shareef and Akhtar 2018). At present, the main goal in the treatment of metastatic bone tumors is to minimize pain and improve quality of life.

Metastatic bone tumors (fig. 1), malignant tumors that originate in organs or tissues outside the bone, metastasize in the bone through the blood circulation or the lymphatic system (fig. 2), while continuing the growth at the same time. The treatment of this disease is mainly to use bisphosphonate drugs, but often have poor effects in analgesia. This study is to observe and analyze the clinical efficacy and safety of intravenous infusion of zoledronic acid combined with oral medication of cinobufagin in treating metastatic bone tumors.



**Fig. 1:** Metastatic bone tumors



**Fig. 2:** Lymphatic system

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## MATERIALS AND METHODS

The 120 cases diagnosed as metastatic bone tumors in our hospital were selected as study subjects. The time range was from June 2014 to June 2017. This paper has a rigorous structure, and the conclusion has been approved by relevant ethics and relevant departments. The patient's inclusion criteria were: Pathological examination confirmed malignant tumors. At the same time, X-ray, CT and MRI scans and bone scans clearly identified bone metastases. The patient had undergone surgical treatment or radiotherapy and chemotherapy, with relatively stable condition during the study period. Meanwhile, chemotherapy, radiotherapy and surgery were not used in the past 4 weeks (Zhu *et al.*, 2017; Zhang *et al.*, 2014; Raza *et al.*, 2017). There was a significant pain in the bone metastatic lesion. The survival time was expected to be over half a year. Exclusion criteria were: those who did not have organ dysfunction such as heart, liver, or kidney; persons with a history of drug allergy; those with unclear verbal expression and inability to make autonomous judgment; persons with mental disorders. Both patients and their family members have signed formal informed consent. The patients were divided into research group and control group, each with 60 cases. Where, the research group had 32 males and 28 females, ranging in age from 38 to 80 years, with an average of (56.9±3.2) years. The primary tumors were: prostate cancer, breast cancer, lung cancer, kidney cancer, thyroid cancer, esophageal cancer, colon cancer, respectively 10, 15, 8, 8, 11, 6, 2 cases. The sites of metastasis were: spine, ribs, pelvis and limb bone, 28, 19, 10 and 3 cases respectively. The control group had 30 males and 30 females, ranging in age from 36 to 78 years, with an average of (57.6±3.6) years. The primary tumors were: prostate cancer, breast cancer, lung cancer, kidney cancer, thyroid cancer, esophageal cancer, colon cancer, respectively, 12, 14, 10, 6, 6, 8 and 4 cases. The sites of metastases were: spine, ribs, pelvis and limb bone, 26, 18, 14 and 2 cases respectively. Comparison of relevant data of the two groups shows comparability,  $P>0.05$ . This study was approved by ethics committee of our hospital.

For patients in the control group, only the usual conventional zoledronic acid injections were administered, i.e., 4mg of zoledronic acid injection (produced by Chiatai Tianqing Pharmaceutical Group Co., Ltd., SFDA approval No.H20041346) was added in 100 mL normal saline, intravenous drip was performed for one hour, and treatment was performed once a month. On this basis, the research group was treated with cinobufagin capsule. The patients were instructed to take cinobufagin capsules (manufactured by Shaanxi Dongtai Pharmaceutical Co., Ltd., SFDA approval No.Z20050846) orally, 500mg each time for three times a day. The treatment lasted three consecutive months.

### *Observation indicators*

The treatment efficacy and safety of the research group and the control group were evaluated. X-ray, MRI and bone scans were observed at 1 month, 2 months and 3 months after the treatment. The criteria for bone metastases evaluation in the recent evaluation criteria of solid tumors in the WHO were strictly observed, and the patient's treatment efficiency was counted. Where, the original lesions' calcification or disappearance and restoration of the bone imaging for more than 4 weeks are the standard for markedly treatment. If the osteolytic lesion is partially shrunk or calcified, the density of osteogenic lesions decreases, and the maintenance time of this state lasts more than 4 weeks, treatment is the effective. If there is no significant change from the lesion before the treatment, and this state has maintained for more than 8 weeks, the treatment is invalid. If the original lesion is enlarged after treatment or new lesions appear, the disease progresses. In addition, before and after treatment, numerical rating scale (NRS) was used to evaluate the patient's pain status, and Karnofsky functional status scoring criteria was followed to evaluate the patient's quality of life.

## STATISTICAL ANALYSIS

The statistical analysis software used was SPSS 21.0. Where, the measurement data were expressed as mean ± average ( $\bar{x}\pm s$ ), and t was used for comparison between groups; the count data was expressed using natural numbers (n) and percentages (%), and  $\chi^2$  was used for comparison between groups. When  $P<0.05$ , there is statistical value.

## RESULTS

### *Comparison of treatment effects between the two groups*

As shown in table 1, the overall treatment effectiveness of the two groups is compared. The results show that compared with the control group, the research group enjoys more significant treatment advantage,  $P<0.05$ , with statistical significance.

### *Comparison of pain NRS scores between the two groups*

As shown in table 2, the NRS pain scores of the patients are statistically analyzed. Compared with the control group, the pain improvement of the research group is relatively more obvious, and there is a significant difference between the groups,  $P<0.05$ , statistically significant.

### *Comparison of quality of life scores between the two groups*

As shown in table 3, in comparison of the quality of life scores before and after treatment in the two groups, the

improvement of the quality of life in the research group is more significant,  $P < 0.05$ , with statistical significance.

#### Comparison of incidence of adverse reactions in the two groups

As shown in table 4, the incidence of adverse reactions is compared between the two groups. The results show no significant difference between the two groups,  $P > 0.05$ , no statistical significance. Also, all the adverse reactions are mild. After effective treatment was taken, the patients recovered.

## DISCUSSION

Metastatic bone tumors usually occur in patients with breast cancer, lung cancer, thyroid cancer and kidney cancer. Most cases of advanced malignant tumors can cause bone metastases. Bone metastases must be treated with appropriate treatments (Li et al., 2014; Chuanlei et al., 2018) to greatly improve the symptoms. Application of surgery and radiotherapy is a treatment for localized lesions. Indications are very strict and long-term application is not allowed. Drug therapy is a well-recognized treatment that can improve clinical symptoms.

As a typical bisphosphonate drug, drug treatment such as zoledronic acid can obtain good efficiency (Jones et al., 2014; Mushtaq et al., 2017). Zoledronic acid can effectively inhibit the activity of osteoclasts, reduce the abnormal serum calcium levels, and significantly reduce bone-related adverse events caused by tumor bone metastases to fight tumors. In addition, inhibition of osteoclast activity reduces inflammatory response to bone metastases and ultimately reduces pain.

Relevant literatures show that Traditional Chinese medicine has unique advantages in the treatment of metastatic bone tumors. Cinobufagin as a kind of TCM is an effective drug, of which the constituents include bufalin, cinobufagin venom toad and cinobufagin venom, which can exert anti-cancer and analgesic effects (Xu et al., 2017; Gong 2017; Maryam et al., 2017). Cinobufagin can inhibit the proliferation of tumor cells through immune regulation, induce apoptosis in cells, and differentiate tumor cells at the same time, thereby avoiding the formation of tumor vessels (Wroblewska 2015; Abdel 2016; Kanwal et al., 2018). The combination of zoledronic acid intravenous injection and cinobufagin capsule in treatment of metastatic bone tumors achieves better therapeutic effect.

**Table 1:** Comparison of overall treatment effect between the two groups [n(%)]

Group	Case number	Markedly	Effective	Invalid	Progression	Total effective rate
Research group	60	30	14	10	6	44(73.33)
Control group	60	20	8	16	16	28(46.67)
$X^2$						12.59
P						<0.05

**Table 2:** Comparison of pain NRS scores between the two groups ( $\bar{x} \pm s$ )

Group	Case number	Pre-treatment pain NRS score	Pain NRS score after 3 months of treatment
Research group	60	6.08±0.40	1.68±0.55
Control group	60	6.12±0.45	4.39±0.60
t		0.11	8.31
P		>0.05	<0.05

**Table 3:** Comparison of quality of life scores between the two groups ( $\bar{x} \pm s$ )

Group	Case number	Pre-treatment quality of life score	Quality of life score after 3 months of treatment
Research group	60	70.53±0.42	84.30±0.60
Control group	60	71.29±0.68	78.05±0.58
t		0.35	12.19
P		>0.05	<0.05

**Table 4:** Comparison of incidence of adverse reactions in the two groups [n(%)]

Group	Fever	Nausea and vomiting	Diarrhea	Muscle soreness	Incidence of adverse reactions
Research group (n=60)	3	4	2	3	12(20.00)
Control group (n=60)	2	3	2	4	11(18.33)
$X^2$					1.20
P					>0.05

The pain of two groups was evaluated using numerical rating scale (NRS). The results showed that compared with the control group, the research group achieved better clinical effect and had a higher quality of life, and the intergroup difference was of statistical significance,  $P < 0.05$ . There was no difference in rate of adverse reactions between the two groups,  $P > 0.05$ , without statistical significance. This indicates that the combined therapy of intravenous infusion of zoledronic acid and oral medication of cinobufagin can obtain better therapeutic effect in treating metastatic bone tumors. Considering limited sample size of this paper, future researches on large sample size are needed to validate the results.

## CONCLUSION

In summary, better results can be obtained for the treatment of metastatic bone tumors by intravenous infusion of zoledronic acid combined with oral administration of cinobufagin capsule. It can improve the treatment effectiveness, and actively improve the quality of life. Also, it features mild adverse reactions and good safety.

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