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Original Article

Efficacy of zoledronic acid combined with radiotherapy on cervical cancer patients with bone metastasis and its influence on immune function and inflammatory factors

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Abstract: Objective: To investigate the clinical efficacy of zoledronic acid combined with radiotherapy on cervical cancer patients with bone metastasis and its effect on immune function and inflammatory factors. Methods: A total of 120 cervical cancer patients with bone metastasis were involved in this study, and the patients were divided into an observation group and a control group according to a random number table, with 60 cases in each group. The observation group was treated with zoledronic acid combined with radiotherapy, and the control group was treated with pamidronate disodium glucose injection combined with radiotherapy. Clinical efficacy, adverse reactions, immune function status and concentration of inflammatory factors were compared between the two groups. Results: The clinical effective rate of the observation group (57/60, 95.00%) was higher than that of control group (40/60, 66.67%, P=0.001). After 6 courses of treatment, compared with control group, the ratios of CD3+, CD4+ and CD4+/CD8+ T cells in peripheral blood of patients in observation group were higher, while the ratio of CD8+ was lower (all P<0.001). Moreover, the levels of Treg, Th17 and NK cells in peripheral blood of patients in observation group were all higher than those in the control group (all P<0.001). After one course of treatment, the levels of C-reactive protein, interleukin-6 and tumor necrosis factor-α were decreased in different degrees in the two groups, while in observation group, each indicator was decreased more significantly (P=0.000, 0.012, 0.023). Compared with the control group, the total incidence of adverse bone events was lower in the observation group (P<0.05), and the total incidence of adverse reactions was slightly lower in the observation group (P>0.05). Conclusion: Compared with pamidronate disodium, zoledronic acid combined with radiotherapy on cervical cancer patients with bone metastasis had a significant clinical effect, with no increase in adverse reactions, and could reduce immunosuppression and the inflammatory response.

Keywords: Zoledronic acid, cervical cancer, bone metastasis, immune function

Introduction

Cervical cancer has a high incidence in human cancers, with a high degree of malignancy. Bone is a common metastatic site after cervical cancer surgery, with bone destruction, severe bone pain, pathological fracture, limb function limitations and immunodeficiency caused by bone metastasis seriously affecting patients' quality of life and brings a heavy burden to society and families. Therefore, improving patients' immune function, clinical efficacy and quality of life has become the focus of research [1, 2]. At present, radiotherapy combined with bisphosphonate (BP) drug is commonly used in the treatment of cervical cancer with bone metastasis. Bisphosphonates (BPs) can specifically bind to hydroxyapatite in bone, inhibit osteoclast activity, and thus inhibit bone resorption, which are used in the treatment of osteoporosis, scleromalacia, hypercalcemia and bone pain caused by malignant bone metastasis. Pamidronate disodium, as a second generation BP, has been used for many years in clinical practice, and its efficacy has been affirmed. Zoledronic acid, as a new generation of BP drug, and it plays a strong role in the treatment of pain caused by osteolytic bone

metastasis of malignant tumors [3]. At present, how zoledronic acid affects the immune function of cervical cancer patients with bone metastasis is still unclear. Therefore, this study aimed to observe the application effect of zoledronic acid in cervical cancer patients with bone metastasis, and compare it with pamidronate disodium, hoping to provide a basis for clinical use.

Materials and methods

General information

This study was a randomized controlled study. A total of 120 cervical cancer patients with bone metastasis admitted to The Third Affiliated Hospital of Qiqihar Medical University from January 2016 to August 2018 were involved in this study. The patients were divided into an observation group and a control group according to the random number table method, with 60 cases in each group. Inclusion criteria: (1) All patients were pathologically confirmed with cervical cancer, and did not receive radiotherapy and chemotherapy or BP drug treatment before admission; (2) Patients with definite bone metastasis by auxiliary examination; (3) Patients without obvious radiotherapy contraindications; (4) Patients without mental disorders. Exclusion criteria: patients with heart, liver and kidney damage. The study was approved by the Ethics Committee of The Third Affiliated Hospital of Qiqihar Medical University, and all patients signed the informed consent.

Treatment methods

All patients received intensity modulated radiation therapy 5 times a week at a dose of 2 Gy for 4 weeks, with a total dose of 40 Gy. The control group was given 250 mL intravenous infusion of pamidronate disodium glucose injection (Nanjing zhengdaqing Pharmaceutical Co., Ltd., China) 5 d before radiotherapy, once a month. The observation group, was given 4 mg zoledronic acid (Yangzi River Pharmaceutical Group, China) which was added to 100 mL normal saline for intravenous drip 5 d before radiotherapy, for more than 15 min, once a month. Patients in the two groups received one course of treatment a month, with a total of 6 courses. Clinical efficacy, serum levels of immune function indicators (CD3, CD4, CD8, Th17 cells, Treg cells, NK cells), adverse bone events and adverse reactions were compared before treatment and after 6 courses of treatment. The levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in serum were compared before treatment, at 1 month after treatment and after 6 courses of treatment.

Outcome measures

Main outcome measures: (1) Evaluation criteria of curative effect of bone metastases: Complete remission (CR): The examination indicates no tumors in the bone for more than 4 weeks. Partial remission (PR): The examination shows that the area of bone destruction decreases, the density decreases or calcification appears for at least 4 weeks. Stable degree (SD): The examination shows that there is no expansion of tumor area in the bone for more than 4 weeks. Progress degree (PD): There is expansion in bone area and new focus occurred [4]. Effective rate = (CR + PR)/total number * 100%. (2) Detection of CD3, CD4 and CD8 levels in peripheral blood by flow cytometry: In the morning, 2 mL of venous blood was extracted and centrifuged at 3,000 r/min for 20 min to separate the serum, and the serum was stored in a freezer at -70°C. Lymphocytes were isolated with Ficoll lymphocyte separation solution, and 10 μL of CD3-FITC, CD4-PE and CD8-APC fluorescent monoclonal antibodies (1:500, Sigma company, USA) were added into the PR tube, and incubated at room temperature for 30 min, centrifuged, then aspirated the supernatant, suspended cells with PBS, and detected by FACSVerse flow cytometry (BD company, USA). (3) Detection of Th17, Treg and NK cells levels in peripheral blood by flow cytometry: In the morning, 2 mL of venous blood from the elbow was extracted and centrifuged at 3,000 r/min for 20 min to separate the serum, and the serum was stored in a freezer at -70°C. Lymphocytes were isolated with Ficoll lymphocyte separation solution, and CD4-FITC, CD25-FITC (Treg cells), IL-17, Foxp3 (Th17 cells), CD16-FITC, CD56-FITC (NK cells) antibodies (1:300, Sigma company, USA) were added into the PR tube, incubated at room temperature for 30min, and detected by FACSVerse flow cytometry (BD company, USA).

Secondary outcome measures: (1) Detection of serum CRP, IL-6 and TNF-α levels: A total of 5

Table 1. Comparison of general information ($\bar{x}$ ± sd, n, %)

Indicators	Observation group (n=60)	Control group (n=60)	t/χ^2	P
Age (year)	57.6±9.7	58.2±9.5	1.032	0.134
BMI (kg/m^2)	25.6±2.6	24.9±2.1	1.077	0.128
Single/multiple (n)	42/18	37/23	1.754	0.089
Histological type (n)			0.986	0.174
Squamous cell carcinoma	52	51		
Adenocarcinoma	8	9		
Differentiation type (n)			1.845	0.081
Low	29	31		
High	31	29		
FIGO staging (n)			0.509	0.113
3	11	7		
4	49	53		
Location (n)			0.627	0.081
Pelvis	21	20		
Flat bone	8	9		
Long bones of limbs	6	7		
Spine	25	24		
Metastasis of other parts (n)			0.588	0.087
Yes	24	23		
No	36	37		
Previous history of surgery (n)			0.572	0.114
Yes	16	15		
No	44	45		

Note: BMI: body mass index.

mL venous blood was extracted from the elbow, after centrifuging, serum was retained, then serum CRP, IL-6 and TNF-α levels were detected by ELISA. The operations strictly followed the instructions of the kit (Shanghai Bangyi Biotechnology Co., Ltd., China). (2) Zoledronic acid-related adverse reactions and adverse bone events: During the injection of zoledronic acid, the following adverse reactions were observed: whether there was fever, allergy and muscular soreness, routine blood work, liver and kidney function, and blood coagulation were recorded [5]. Adverse bone events such as fracture, spinal deformation, spinal cord compression, surgical treatment, hypercalcemia, and mandibular osteonecrosis were observed [5].

Statistical analysis

SASS 11.0 software was used to process the data of this study. The effective rate was expressed as %, using χ^2 test. The levels of immune and inflammatory factors were expressed by mean ± standard deviation ($\bar{x}$ ± sd). Paired sample t test was used for comparison before and after treatment within the same group, and independent sample t test was used for comparison between two groups. There was a significant difference at $P<0.05$.

Results

Comparison of general information

There was no significant difference in baseline data between the two groups ($P>0.05$), which were comparable. See **Table 1**.

Comparison of clinical efficacy

During the follow-up period, there was no death or loss to follow-up in both groups. The effective rate of observation group (57/60, 95.00%) was higher than that of control group (40/60, 66.67%), with a significant difference ($\chi^2=10.035$, $P=0.001$). See **Table 2**.

Table 2. Comparison of treatment effect (n, %)

Group	CR	PR	SD	PD	Effective rate
Observation group (n=60)	15	42	2	1	57 (95.00)
Control group (n=60)	10	30	17	3	40 (66.67)
χ^2		9.368			10.035
P		0.002			0.001

Note: CR: complete remission; PR: partial remission; SD: stable degree; PD: progress degree.

Levels of CD3+, CD4+ and CD8+ in peripheral blood

Before treatment, there was no difference in each indicator between the two groups. After 6 courses of treatment, there was no statistically significant difference in each indicator of the observation group compared with that of before treatment (all P>0.05), while there was a statistically significant difference in each indicator of the control group compared with that of before treatment (all P<0.01). After 6 courses of treatment, compared with control group, CD3+, CD4+ and CD4+/CD8+ in observation group were higher, while CD8+ was lower (all P<0.001). See **Table 3**.

Levels of Treg, Th17 and NK cells in peripheral blood

Before treatment, there was no difference in each indicator between the two groups. After 6 courses of treatment, there was no statistically significant difference in each indicator of the observation group compared with that of before treatment (all P>0.05), while there was statistically significant difference in each indicator of the control group compared with that of before treatment (all P<0.001). Moreover, after 6 courses of treatment, the levels of Treg, Th17 and NK cells in observation group were all higher than those in control group (all P<0.001). See **Table 4**.

Comparison of serum CRP, IL-6 and TNF-α levels before and after treatment

After treatment, CRP, IL-6 and TNF-α decreased in different degrees in the two groups, while each indicator in the observation group decreased significantly. After one month of treatment, the improvement of the observation group was more obvious than that of control group (t=10.361, 11.016, 9.614, P=0.000, 0.012, 0.023). After 6 months of follow-up, there was no statistically significant difference in CRP, IL-6 and TNF-α levels between the two groups (t=1.247, 0.981, 0.664, P=1.651, 2.325, 3.638). See **Figure 1**.

Comparison of adverse bone events and adverse reactions

Compared with control group (27/60, 45.00%), the total incidence of adverse bone events was lower in observation group (7/60, 11.67%, P<0.001). Compared with control group (15/60, 25.00%), the total incidence of adverse reactions was slightly lower in observation group (13/60, 21.67%, P>0.05). See **Tables 5**, **6**.

Discussion

Cervical cancer is a common human malignant tumor that affects the quality of life of women. Bone pain, dyskinesia and fracture are found in the patients with advanced bone metastasis. Despite the emergence of various therapeutic regimens and drugs in recent years, the effect is not good [6, 7]. Therefore, it is urgent to find a safe and effective drug.

Zoledronic acid is a kind of nitrogen-containing diphosphate recently developed. Zoledronic acid can induce apoptosis of tumor cells, prevent infiltration and invasion of tumor cells, inhibit angiogenesis, and then inhibit malignant biological behavior of the tumors [8-10]. Zoledronic acid can also prevent osteoclast proliferation and induce osteoclast apoptosis [11]. In addition, zoledronic acid can also inhibit the production of vascular endothelial growth factor and fibroblast factor in peripheral blood, prevent tumor cells from infiltrating into the bone, enhance the efficacy of chemotherapy drugs, and achieve the effect of inhibiting tumors and enhancing immune function [12]. Currently, zoledronic acid has been used in the chemoradiotherapy for a variety of tumors [13-16]. Zhang et al. showed that zoledronic acid combined with radiotherapy could significantly reduce the bone pain of cervical cancer patients with bone metastasis, improve the quality of life, and with good clinical effect [17]. In this study, the clinical efficacy of zoledronic acid and pamidronate disodium was observed, and the results showed that the total effective rate of the observation group was higher than

Table 3. Comparison of immune cell subsets before and after treatment ($\bar{x}$ ± sd)

Group	Time	CD3+ (%)	CD4+ (%)	CD8+ (%)	CD4+/CD8+ (%)
Observation group	Before treatment	56.26±4.38	33.46±6.13	23.31±6.09	1.61±0.21
	At 6 courses of treatment	59.14±7.74	34.51±6.53	22.21±5.43	1.71±0.32
	t	0.658	0.465	0.443	0.153
	P	0.106	0.114	0.118	0.235
Control group	Before treatment	56.41±5.29	33.49±6.09	23.46±7.03	1.63±0.44
	At 6 courses of treatment	42.87±9.31	24.33±5.63	33.17±9.73	1.34±0.51
	t	9.795	8.555	6.266	3.335
	P	<0.001	<0.001	<0.001	0.001
	$t_{\text{After treatment of two groups}}$	10.409	9.146	7.072	4.760
	$P_{\text{After treatment of two groups}}$	<0.001	<0.001	<0.001	<0.001

Table 4. Comparison of Th17, Treg and NK cells before and after treatment ($\bar{x}$ ± sd)

Group	Time	Treg cells (%)	Th17 cells (%)	NK cells (%)
Observation group	Before treatment	9.60±2.11	5.70±1.03	15.76±2.32
	At 6 courses of treatment	9.13±0.53	5.52±0.71	15.11±1.63
	t	1.025	1.011	1.135
	P	0.095	0.103	0.085
Control group	Before treatment	9.61±1.13	5.69±0.98	15.80±1.63
	At 6 courses of treatment	5.19±0.66	3.29±0.33	9.37±1.22
	t	26.839	19.792	22.458
	P	<0.001	<0.001	<0.001
	$t_{\text{After treatment of two groups}}$	25.392	20.614	22.181
	$P_{\text{After treatment of two groups}}$	<0.001	<0.001	<0.001

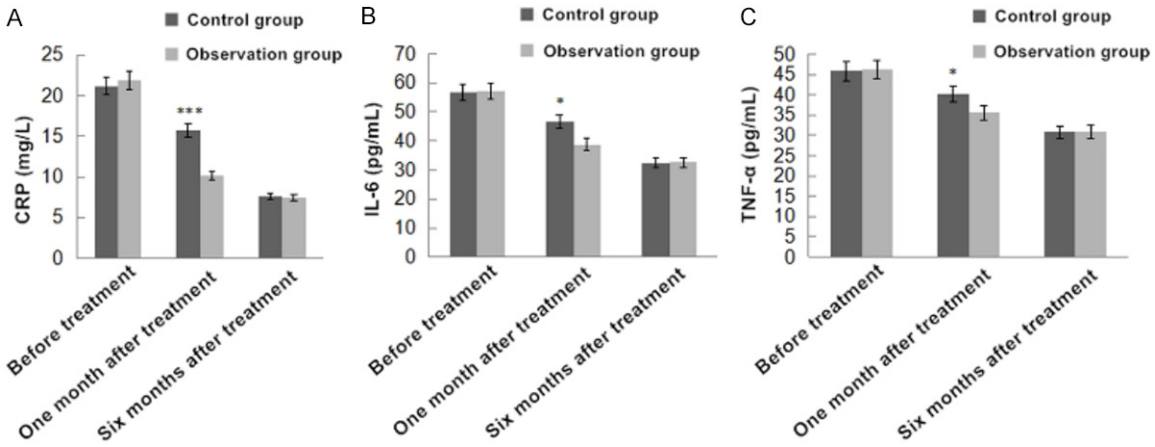

Figure 1. Comparison of serum CRP, IL-6 and TNF-α levels. A: Comparison of CRP level; B: Comparison of IL-6 level; C: Comparison of TNF-α level. Compared with observation group after one month of treatment, *P<0.05, ***P<0.001. CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α.

that of control group, which was basically consistent with other studies, suggesting that the third generation of zoledronic acid has more significant clinical efficacy, better effect and stronger function than the second generation of pamidronate disodium. The adverse reactions of zoledronic acid are manifested in the blood system, myalgia, and bone pain [10-13]. In this study, compared with control group, the total incidence of adverse bone events was

Table 5. The occurrence of adverse bone events (n, %)

Indicators	Observation group (n=60)	Control group (n=60)	χ^2	P
Bone radiotherapy	1	5	11.336	0.000
Spinal deformity	4	6	2.016	0.125
Spinal cord compression	1	4	9.964	0.000
Hypercalcemia	1	12	19.214	0.000
Fracture and surgery	0	0	0.653	0.235
Total incidence	7 (11.67)	27 (45.00)	13.264	<0.001

Table 6. The occurrence of adverse reactions (n, %)

Indicators	Observation group (n=60)	Control group (n=60)	χ^2	P
Fever	4	2	6.687	0.026
Muscle soreness	2	1	6.016	0.031
Bone marrow suppression	6	8	1.067	0.145
Abnormal liver function	1	4	16.354	0.000
Mandibular osteonecrosis	0	0	0.711	0.234
Total incidence	13 (21.67)	15 (25.00)	2.023	0.135

lower in the observation group. The total incidence of adverse events in the observation group was not statistically different from that in control group, suggesting that zoledronic acid did not significantly increase the adverse events brought by the drug itself while reducing the adverse bone events, and so the safety was guaranteed.

Radiotherapy and chemotherapy can not only kill tumor cells, but also lead to immune dysfunction and inhibit the production of immune cells. T cells include CD3, CD4 and CD8 cells, when the three kinds of cells are out of balance, immune dysfunction will occur in the human body [18, 19]. This study showed that compared with control group, CD3, CD4 and CD4/CD8 in the observation group were higher, but CD8 was lower, suggesting that zoledronic acid had little effect on patients' immune function. Treg/Th17 cells mainly mediate immune responses, while NK cells participate in the non-specific immune response [20, 21]. Th17 can also induce osteoblasts to produce receptor activator of NF-KB ligand (RANKL) by producing IL-17. RANKL and tumor-derived IL-1 and IL-6 stimulate the fusion of osteoclast precursors to form mature multinucleated osteoclasts. Treg can secrete anti-inflammatory factor IL-10, prevent the initial differentiation of Th17 and the secretion of IL-17, and maintain the balance of the Treg/Th17 subgroup [22]. In this study, it was found that the levels of Treg, Th17 and NK cells in the observation group were all higher than those in the control group, suggesting that zoledronic acid had little impact on the immune function of the patients, but the specific mechanism still needs further study.

Malignant tumor bone metastasis can release inflammatory factors such as TNF-α and IL-1β, induce osteoclast synthesis, further destroy bone tissue, and promote osteolytic cytokine synthesis. In this study, it was found that zoledronic acid could significantly reduce CRP, IL-6 and TNF-α levels in patients. We speculated that it may be related to the fact that zoledronic acid disrupted the Treg/Th17 balance and inhibited the release of inflammatory factors.

There were some limitations in this study. First, the sample size was small, and the relevant results need to be further verified. Secondly, the mechanism of the effect of zoledronic acid on immune function and inflammatory factors in patient needs to be further studied.

In conclusion, zoledronic acid combined with radiotherapy can improve the radiotherapy effect of cervical cancer patients with bone metastasis and reduce the inhibition of radiotherapy on immune function, which is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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