JBUON 2019; 24(2): 826-831
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Therapeutic effects of adriamycin combined with high-intensity focused ultrasound on osteosarcoma

Chunqiu Wang

Department of Pharmacy, Luoyang Orthopedic Hospital of Henan Province. Luoyang, China.

Summary

Purpose: *To analyze the efficacy of adriamycin (ADM) combined with high-intensity focused ultrasound (HIFU) in patients with osteosarcoma.*

Methods: *A total of 72 patients with osteosarcoma were selected and divided into the control group (n=36) and the observation group (n=36). Patients in the control group were treated with ADM, while those in the observation group received HIFU in addition to ADM. The efficacy and adverse reactions in the observation and control group were compared.*

Results: *The response rate and disease control rate in the observation group were significantly higher than those in the control group (p<0.05). No significant difference was found in the survival rate at year 1 after treatment between the two groups, but the observation group had overtly higher survival rates at years 2 and 3 after treatment in comparison with the control group (p<0.05). There was no obvious difference in the incidence rate of adverse reactions between the observation and control group. After treatment, the levels of serum tumor necrosis factor-alpha (TNF-a), interleukin-2 (IL-2) and IL-8 in the observation group were clearly higher than those in the control group. Serum alkaline phosphatase (ALP) and creatinine (Cr) in the observation and control group showed no significant differences. Compared with the control group, ALP level was significantly decreased in the observation group (p<0.05). The limb function and psychological behavior after treatment in the observation group were significantly superior to those in the control group (p<0.05).*

Conclusions: *The application of ADM combined with HIFU is conducive to improving efficacy on osteosarcoma, prolonging survival and improving prognosis.*

Key words: *adriamycin, HIFU, osteosarcoma*

Introduction

Osteosarcoma, as the most common bone malignancy in clinical practice, has a high incidence rate in children and adolescents in particular, which is up to 5% based on relevant data [1]. For the treatment of osteosarcoma, surgery is usually adopted if there is no recurrence. However, osteosarcoma is difficult to be cured by surgery alone once metastasis occurs. In addition, it is easy to relapse after surgery, with poor prognosis [2].

As to chemotherapeutics for the treatment of osteosarcoma, adriamycin (ADM) is often used as first-line chemotherapy drug. Many clinical research data have shown that the combination of ADM and other chemotherapy drugs or other treatment methods is of great significance in improving the therapeutic effect [3]. Compared to other countries, the use of chemotherapy regimens for osteosarcoma is relatively late in China, so many current chemotherapy regimens are made based on foreign chemotherapy schemes [4]. However, some chemotherapy schemes are not applicable for patients in China in clinical practice due to individual

Correspondence to: Chunqiu Wang, BM. Department of Pharmacy, Luoyang Orthopedic Hospital of Henan Province, No. 82 Qiming South Rd, Luoyang, 471002 Henan, China.
Tel: +86 013703493838, E-mail: wangchunqiuluoyang@163.com
Received: 25/09/2018; Accepted: 07/10/2018

differences, so it is quite meaningful to consider some treatment regimens that are suitable for patients with osteosarcoma in China.

High-intensity focused ultrasound (HIFU) is a device developed in recent years and used for the treatment of malignant tumors, with independent intellectual property rights owned by China. It is a new non-innovative technology for external use [5]. HIFU is a high-end technology for the treatment of malignancies in addition to other therapeutic methods including surgery and chemoradiotherapy, with many advantages such as safety and precise treatment. However, there is no uniform conclusion on the evaluation of its efficacy [6]. Therefore, this study analyzed the efficacy of ADM combined with HIFU in osteosarcoma so as to further improve reference data.

Methods

General data

This study was approved by the ethics committee of Luoyang Orthopedic Hospital of Henan Province. Signed written informed consents were obtained from all participants before the study entry. A total of 72 patients definitely diagnosed with osteosarcoma in our hospital from March 2011 to March 2015 were enrolled. They were divided into control group (n=36) and observation group (n=36) according to the random number method. Among them, there were 47 males and 25 females, aged 10-65 (mean 29.1±4.7). All patients enrolled were diagnosed with osteosarcoma based on ultrasound, enhanced computed tomography (CT) and pathological examinations. Inclusion criteria: Patients without contraindications for chemoradiotherapy, at stage III according to Enneking surgical staging, without locally relevant recurrence, and with Karnofsky performance score (KPS) >70. Exclusion criteria: Patients with estimated survival time <3 months, severe infection, or severe cardiovascular and cerebrovascular diseases, pregnant or lactating patients, patients with mental disorders, or those complicated with other malignant tumors.

Therapeutic methods

All patients enrolled were treated with ADM (30mg/m^2, peripheral intravenous infusion on d1-d3), followed by two weeks of test. After that, the second course of treatment started, 3 weeks per treatment course, with 4 courses in total. Folic acid (400 μg/day) was taken orally before the administration of ADM for the entire course of treatment. One week before treatment intramuscular injection of vitamin B12 was given every 5 weeks. On day 1 before administration and the second day after administration, dexamethasone (3.75 mg) was taken orally. Patients in the observation group were treated with HIFU and ADM. Before treatment with HIFU, X-ray, enhanced CT and bone imaging were performed to select the treatment area of the lesion. Then, focused ultrasound treatment tumor system was used to carry out HIFU under B-ultrasound monitoring and positioning system. Treatment parameters: frequency=0.8 MHz, focal length=135 mm, and treatment time=7,000 s. The therapeutic effect was evaluated 1-2 weeks after treatment.

Judgment of efficacy and adverse reactions

Efficacy classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) in accordance with RECIST criteria of World Health Organization (WHO). Overall response rate of the treatment = CR + PR/total number of cases. Disease control rate=CR+PR+SD/total number of cases. The adverse reactions to treatment were evaluated according to the criteria for toxicity evaluation of antitumor drugs, and were classified into 0-IV grades according to their severity.

Detection of related indicators

Fasting peripheral venous blood (15 mL) was collected from enrolled patients in both treatment and control groups in the morning before treatment and 1 week after treatment. The levels of serum creatinine (Cr) and alkaline phosphatase (AKP) were measured using a fully automatic biochemical analyzer. Turbidimetric inhibition immunoassay was applied to detect the content of tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2) and IL-8. Musculoskeletal Tumor Society (MSTS) 93 score and Symptom Checklist 90 (SCL-90) were used to evaluate limb function and psychological behavior of the patient.

Statistics

SPSS 19.0 software (IBM, Armonk, NY, USA) was used for data processing. All quantitative data were expressed as mean±SD. Comparison between groups was done using t-test. Chi square test was used for comparison of percent data and $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of general data before treatment between the observation and control group

No significant differences were found in age, gender, pathological type, tumor location, tumor tissue necrosis rate and surgical approach between the observation and control group ($p>0.05$; Table 1).

Comparison of short-term efficacy between the observation and control group

The overall response rate and disease control rate in the observation group were 88.9% and 94.4%, respectively, while those in control group were 66.7% and 75.0%, respectively. Both rates in the observation group were distinctly higher than those in the control group, and the differences were statistically significant ($p<0.05$; Figure 1).

Comparison of survival time between the observation and control group

There was no significant difference in the survival rate one year after treatment between the observation and control group, but the survival rates at 2 and 3 years of follow-up in the observation group were obviously higher than those in the control group (p<0.05; Table 2).

Comparison of the incidence of adverse reactions after treatment between the observation and control group

Adverse reactions including nausea, emesis, alopecia, oral and intestinal mucosal inflammation, fall of hemoglobin, increased transaminases and neutropenia were recorded and analyzed. There were no significant differences in adverse reactions between the two group (p>0.05; Table 3).

Comparisons of TNF-a, IL-2 and IL-8 between the observation and control group before and after treatment

Before treatment, serum TNF-α, IL-2 and IL-8 between the observation and control group showed no clear differences. After treatment, the levels of TNF-α, IL-2 and IL-8 in the observation group were significantly higher than those in the control group (p<0.05; Table 4).

Table 1. Comparisons of general characteristics between observation and control group

Characteristics	*Observation group (n=36)*	*Control group (n=36)*
Age (years)	29.5±5.1	28.7±3.9
Gender (male/female)	23/13	24/12
Pathologic type		
Normal	34	32
Telangiectatic	2	2
Chondroblastoma-like	1	2
Tumor location		
Upper tibia	19	18
Lower femur	6	5
Upper femur	3	2
Humerus	2	3
Upper ulna	3	2
Upper fibula	1	2
Scapula	1	3
Ilium	1	1
Tumor tissue necrosis rate (%)		
≥ 90	28	29
< 90	8	7
Surgical approach		
Limb salvage	19	20
Amputation	17	16

Comparisons of Cr, ALP and ALP between the observation and control group before and after treatment

There were no significant differences in the levels of Cr, ALP and ALP between the two groups before treatment. After treatment, the levels of Cr and ALP in both groups were increased compared with those before treatment but without significant difference. Compared with the levels before treatment, the level of ALP was significantly decreased in both groups, while the decrease in the observation group was more obvious compared to control group (p<0.05, Table 5).

Comparisons of limb function and psychological behavior between the observation and control group before and after treatment

Before treatment, MSTS 93 score and SCL-90 score in the observation and control group had no significant differences. After treatment, both the observation and control group had significantly elevated MSTS 93 score and clearly lowered SCL-90 score compared with those before treatment, and the efficacy in the observation group was better compared with the control group (p<0.05; Table 6).

Discussion

Osteosarcoma is a highly aggressive tumor derived from long bones and produces osteoid [7]. Metastasis to other sites will significantly reduce the patient survival. At present, there are many chemotherapy regimens for osteosarcoma in for-

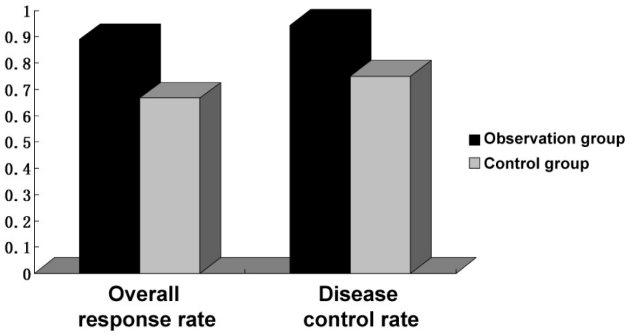

Figure 1. Comparison of short-term efficacy between observation and control group (p<0.05).

Table 2. Comparison of survival time between observation and control group

Group	*n*	*Year 1 n (%)*	*Year 2 n (%)*	*Year 3 n (%)*
Control group	36	30 (83.3)	25 (69.4)	14 (38.9)
Observation group	36	27 (75.0)	19 (52.8)	8 (22.2)
p		0.578	0.032	0.003

Table 3. Comparison of adverse reactions after treatment between observation group and control group

Adverse reactions	*Observation group (n=36) n (%)*	*Control group (n=36) n (%)*	*p*
Nausea & emesis	28 (77.8)	30 (83.3)	0.06
Alopecia	27 (75.0)	28 (77.8)	0.38
Oral and intestinal mucosal inflammation	15 (41.7)	18 (50.0)	0.29
Fall of hemoglobin	19 (52.8)	21 (58.3)	0.63
Increase of transaminases	32 (88.9)	31 (86.1)	0.5
Neutropenia	27 (75.0)	30 (83.3)	0.07

Table 4. Comparisons of TNF-α, IL-2 and IL-8 between observation group and control group

Group	*n*	*Time*	*TNF-a (U/mL)*	*IL-2 (U/mL)*	*IL-8 (U/mL)*
Observation group	36	Before treatment	45.3±7.8	60.6±7.9	57.2±8.8
		After treatment	89.8±7.2	95.1±9.4	93.8±8.5
Control group	36	Before treatment	46.3±7.0	58.3±6.9	55.9±7.0
		After treatment	62.9±8.3	73.8±7.5	71.7±6.2

Compared with that before treatment, p<0.05; compared with control group after treatment, p<0.05.

Table 5. Comparisons of Cr, ALP and ALP between observation group and control group before and after treatment

Group	*n*	*Time*	*Cr (mmol/L)*	*ALP (U/L)*	*ALP (U/L)*
Observation group	36	Before treatment	79.6±8.7	106.5±21.6	285.7±22.8
		After treatment	96.8±15.2	129.7±38.7	85.6±9.7
Control group	36	Before treatment	81.3±9.1	111.3±25.8	285.9±39.1
		After treatment	105.6±14.7	127.8±23.1	157.3±16.4

Compared with that before treatment, p<0.05.

Table 6. Comparisons of limb function and psychological behavior scores between observation group and control group before and after treatment (points)

Group	*n*	*Time*	*MSTS 93*	*SCL-90*
Observation group	36	Before treatment	9.5±7.6	7.9±2.6
		After treatment	20.5±5.8*#	2.3±0.8*#
Control group	36	Before treatment	8.9±7.1	8.1±3.2
		After treatment	13.7±4.3*	4.7±1.5*

*p<0.05 compared with that before treatment; #p<0.05 compared with the control group

eign countries. However, for individual differences, these regimens are not suitable for patients in China. There remains considerable controversy about second-line treatment(s) proposed internationally, but no unified conclusion has been reached so far. Chemotherapy is the most used and most important method for the treatment of patients with early osteosarcoma [9]. Currently, applicable first-line chemotherapy drugs are mainly cisplatin (DDP), methotrexate (MTX), ADM and ifosfamide (IFO). The application of the above-mentioned chemotherapeutics can significantly improve the response rate of osteosarcoma [10]. With the continuous improvement in clinical experience and knowledge, surgical amputation is not necessary for most patients with osteosarcoma, and tumor resection and limb reconstruction are adopted instead of amputation [11]. After local surgical resection of the tumor, there are many applicable limb reconstruction methods like implantation of prosthesis and allogeneic or autologous bone graft [12]. HIFU has substantial advantages in both focusing and positioning and achieving high temperature, focusing on tumor sites to lead to coagulation necrosis of tumor cells [13]. Osteosarcoma patients suffer of varying degrees of bone damage that makes the ultrasound feature of their damaged tissues clearly distinct from that of normal

tissue. Ultrasound is difficult to penetrate the damaged bone tissues when HIFU is therapeutically applied, so that heat is increased [14]. HIFU used in the treatment of osteosarcoma accurately locates the tumor area and causes no damage to tissues and organs surrounding the tumor [15]. Research data by Chen et al. [13] have suggested that the 5-year survival rate of patients with osteosarcoma receiving HIFU is about 50%, and that of patients at stage IIb is much higher compared to patients with stage III. The authors reported that the survival rate of osteosarcoma patients receiving ADM combined with HIFU at the first year of follow-up was similar to that of those using ADM alone, but the survival rates at the second and third year were overtly higher than those in the control group. As for adverse reactions, no obvious differences were detected in patients using ADM combined with HIFU and those receiving ADM alone.

TNF and ILs are the main cytokines that can strengthen the function of the immune system to enhance the antitumor effect [16]. This study reported that serum TNF-α, IL-2 and IL-8 levels in both the observation and control group were evidently increased after treatment compared with those before treatment, and the observation group had more obvious increases in comparison with the control group. ADM combined with HIFU adopted in the treatment of patients with osteosarcoma is capable of improving the immune function and enhancing the therapeutic effect in osteosarcoma. Furthermore, this study found that the serum level of ALP was distinctly decreased after treatment, and the application of ADM combined with HIFU in osteosarcoma increased the kill rate of tumor cells [17].

Currently, it is crucial to improve both the survival rate and quality of life of patients with osteosarcoma in clinical practice [18]. Close attention should be paid to mental health and limb function maintenance while taking survival time into account. Therefore, the judgment of overall efficacy and adverse reactions of patients with osteosarcoma includes not only the evaluation of cardiopulmonary function, but also their feelings, fear of disease and other worries [19,20]. This study revealed that both limb function and psychological behavior were affected to varying degrees before treatment, but improved clearly after treatment. Limb function and psychological behavior were not included in the analysis of adverse reactions. Osteosarcoma is no longer an incurable disease as previously described. Both survival and prognosis of such patients can be improved through new technologies such as HIFU, but above all with ever-increasing technical experience and deep knowledge of clinical and molecular disease characteristics.

Conclusions

In conclusion, the application of ADM combined with HIFU is conducive to improving efficacy on osteosarcoma, prolonging survival and improving prognosis.

Conflict of interests

The authors declare no conflict of interests.

References

1. Samimi MA, Mirkheshti N, Pazouki A. Assessing the percent of necrosis after neoadjuvant chemotherapy with 24hr infusional cisplatin/3 days Doxorubicin intermittent with Ifosfamide-Doxorubicin for osteosarcoma. Int J Hematol Oncol Stem Cell Res 2014;8:5-8.
2. Iwata S, Yonemoto T, Iizasa T, Niibe Y, Kamoda H, Ishii T. Oligo-Recurrence of Osteosarcoma Patients: Treatment Strategies for Pulmonary Metastases. Ann Surg Oncol 2015;22 (Suppl 3):S1332-8.
3. Bacci G, Picci P, Ferrari S et al. Influence of adriamycin dose in the outcome of patients with osteosarcoma treated with multidrug neoadjuvant chemotherapy: results of two sequential studies. J Chemother 1993;5:237-46.
4. Chiu TJ, Wang JW, Chen YJ, Tang Y, Huang CH. Intraarterial Cisplatin and intravenous adriamycin in nonmetastatic osteosarcoma of the extremities: a single institution experience in Taiwan. Chang Gung Med J 2009;32:72-80.
5. Meyers PA, Schwartz CL, Krailo MD et al. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival - a report from the Children's Oncology Group. J Clin Oncol 2008;26: 633-8.
6. Longhi A, Ferrari S, Bacci G, Specchia S. Long-term follow-up of patients with doxorubicin-induced cardiac toxicity after chemotherapy for osteosarcoma. Anticancer Drugs 2007;18:737-44.
7. Tsiambas E, Fotiades PP, Sioka C et al. Novel molecular and metabolic aspects in osteosarcoma. JBUON 2017;22:1595-8.
8. Hameed M, Dorfman H. Primary malignant bone tumors - recent developments. Semin Diagn Pathol 2011;28:86-101.

9. Anract P. Surgical management of primary bone cancer. Bull Acad Natl Med 2009;193:107-26.
10. Mavrogenis AF, Abati CN, Romagnoli C, Ruggieri P. Similar survival but better function for patients after limb salvage versus amputation for distal tibia osteosarcoma. Clin Orthop Relat Res 2012;470:1735-48.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006-12.
12. Kamal AF, Widyawarman H, Husodo K, Hutagalung EU, Rajabto W. Clinical outcome and survival of osteosarcoma patients in cipto mangunkusumo hospital: Limb salvage surgery versus amputation. Acta Med Indones 2016;48:175-83.
13. Chen W, Zhu H, Zhang L et al. Primary bone malignancy: effective treatment with high-intensity focused ultrasound ablation. Radiology 2010;255:967-78.
14. Wiromrat P, Jetsrisuparb A, Komvilaisak P, Sirichativapee W, Kamsa-Ard S, Wiangnon S. Incidence and survival rates among pediatric osteogenic sarcoma cases in Khon Kaen, Thailand, 1985-2010. Asian Pac J Cancer Prev 2012;13:4281-4.
15. Xu M, Xu SF, Yu XC. Clinical analysis of osteosarcoma patients treated with high-dose methotrexate-free neoadjuvant chemotherapy. Curr Oncol 2014;21:e678-e84.
16. Liu Y, Xu Y, Lin N, Jiang S, Wang Y, Ye Z. High-dose methotrexate (HD-MTX) used as an adjunct with other chemotherapeutics for the treatment of osteosarcoma. Cell Biochem Biophys 2015;71:1097-1104.
17. Tan PX, Yong BC, Wang J et al. Analysis of the efficacy and prognosis of limb-salvage surgery for osteosarcoma around the knee. Eur J Surg Oncol 2012;38:1171-7.
18. Sherman CE, O'Connor MI, Sim FH. Survival, local recurrence, and function after pelvic limb salvage at 23 to 38 years of followup. Clin Orthop Relat Res 2012;470:712-27.
19. Ferrari S, Ruggieri P, Cefalo G et al. Neoadjuvant chemotherapy with methotrexate, cisplatin, and doxorubicin with or without ifosfamide in nonmetastatic osteosarcoma of the extremity: an Italian sarcoma group trial ISG/OS-1. J Clin Oncol 2012;30:2112-8.
20. Bacci G, Longhi A, Forni C et al. Neoadjuvant chemotherapy for radioinduced osteosarcoma of the extremity: The Rizzoli experience in 20 cases. Int J Radiat Oncol Biol Phys 2007;67:505-11.