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Dose-intensive versus dose-control chemotherapy for high-grade osteosarcoma: a meta-analysis

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Abstract. – BACKGROUND: Tumor necrosis might be a consequence of innate sensitivity of tumor cells to changed dosage instead of the increased dosage of chemotherapeutics in the treatment of osteosarcoma patients.

AIM: To explore whether dose-intensive regimen was a better treatment method than dose-control chemotherapy for high-grade osteosarcoma patients.

MATERIALS AND METHODS: The data of the included studies was analyzed by random-effects model when there was heterogeneity, otherwise by fixed-effects method. Meta-analysis outcomes were calculated as risk ratio (RR) and 95% confidence interval (CI) for 5-year disease free survival rate, 5-year overall survival, local recurrence rate, good histological response rate and Limb salvage rate.

RESULTS: Five studies involving 1434 patients with high-grade osteosarcoma were included. All the included studies were inadequate in the information about randomization and blinding method. The meta-analysis showed that there was no significant difference between the dose-intensive group and the dose control group in 5-year disease free survival rate (RR: 1.08, 95% CI: 0.96-1.21), 5-year overall survival rate (RR: 1.07, 95% CI: 0.98-1.17), good histological response rate (RR: 1.08, 95% CI: 0.82-1.43), limb salvage rate (RR: 0.97, 95% CI: 0.93-1.02). However, the local recurrence rate (RR: 0.65, 95% CI: 0.46- 0.92) and the 5-year disease free survival rate of the good and poor histological response (RR: 1.57, 95% CI: 1.36- 1.82) were significantly different.

CONCLUSIONS: Dose-intensive regimen might not be a preferred treatment for all of the high-grade osteosarcoma patients. Although there were advantages in dose-intensive regimen, appropriate dosage of chemotherapy should be considered in clinical cases.

Key Words:
Osteosarcoma, Chemotherapy; Dose-intensive chemotherapy, Dose-control chemotherapy, Meta-analysis.

Introduction

Osteosarcoma, an aggressive malignant neoplasm arising from primitive transformed cells of mesenchymal origin, is characterized by producing osteoid fusiform stromal cells[1]. It is a most common primary malignant bone tumor only second to multiple osteosarcoma[2]. The incidence of osteosarcoma is approximately 0.3 per 100,000 and there are about 900 new cases of osteosarcoma are diagnosed in the United States every year. Moreover, a high incidence is presented in adolescents around 10 to 25 years and in elderly. As osteosarcoma is a devastating but rare disease[3], the effective therapy has become a highlighted concern all over the world. Amputation has become a routine treatment therapy targeting for osteosarcoma since the 1970s[4]. However, the prognosis and quality of life of osteosarcoma patients by amputation was still poor. The 5-year survival rate after amputation was less than 20% mainly due to lung metastases[5]. With the development of treatment techniques for osteosarcoma, adjuvant chemotherapy has greatly improved the disease-free survival rate of patients, such as the application of doxorubicin, high-dose methotrexate and cisplatin[6-8].

A number of studies have shown that dose of chemotherapy used in treatment is closely related to the outcome of patients with osteosarcoma[9-11]. Some studies suggested that patients treated by dose-intensive chemotherapy would have higher overall survival and disease-free survival rates than those by dose control regimens. While others argued that there were no sufficient evidences to display the superiority of dose-intensive regimens. In the treatment of osteosarcoma patients, tumor necrosis might be a consequence of innate sensitivity of tumor cells to changed dosage instead of the increased dosage of chemotherapeutics[12-14].

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Besides, dose-intensive chemotherapy is still poorly conducted in the clinical treatment of high-grade osteosarcoma. In this paper, we applied meta-analysis to conduct quantitative evaluation on the published clinical researches and aimed to provide certain reference for the clinical decision-making.

Materials and Methods

Literature Search

A systematic literature research was performed by retrieving from the internet retrieval systems: U.S. National Library of Medicine (PubMed), MEDLINE, EMBASE, Cochrane Controlled Clinical Trials Register (CCTR) and Google scholar. The literatures in this research were associated with clinical trials for the treatment of high-grade osteosarcoma, which were updated to June, 2012. And the language of the literatures was limited to English. The search strategies were Clinical Trial Randomized Controlled Trial, Osteosarcoma and Chemotherapy.

Literature Inclusion Criteria

All the associated articles were assessed to obtain the eligible literatures. The inclusion criteria were as followed. The studies involved in eligible literature contained randomized control trial (RCT) or clinical control trial (CCT, clearly-defined sample size, scientific data collection methods and correct data analysis method. Additionally, studies were carefully carried out or the publication time accorded to the deadline requirement; Cases surveyed were treated with adjuvant chemotherapy and clear diagnostic criteria. Results in these reports included free survival rate, overall survival rate, limb salvage rate and local recurrence rate.

Exclusion Criteria

Literatures were excluded if there were inaccessible sources of cases, non-therapeutic clinical studies or animal experiments, non-original literature, unclear number of groups, cases of unclear diagnostic criteria, studies without control group, osteosarcoma treated by other methods, unscientific methods for data collection, incorrect or unavailable data analysis method. Reviews and retrospective analysis (RA) were also excluded.

Literature Evaluation, Data Extraction and Analysis

Literature evaluation was carried out by two independent reviewers. Reviewers made evaluation on the literatures from the following aspects: (1) general information: the first author, publication year, literature source and publication date; (2) research design; (3) the number, features and treatment outcomes of the clinical cases (patients).

Statistical Analysis

Meta-analysis was performed using RevMan 5.0 software. Continuous data were normalized as standardized weighted mean difference (SMD) and 95% CI, and dichotomous data were shown as relative risk (RR) and 95% CI. The significant difference was defined as p value ≤ 0.05. Heterogeneity test of research data were conducted prior to data consolidation. The data were pooled by random-effects model which were in significant heterogeneity, otherwise by the fixed-effects model.

Results

The Characteristics of the Included Literature

After a preliminary screening on the retrieved literature, 706 potential reports were obtained, which were related to the high-grade osteosarcoma treated by chemotherapy. Through strict assessment, only 5 studies met the inclusion criteria, of which 4 studies were randomized controlled trials (RCT) and one was as a quasi-randomized control clinical trial (CCT)[12-16]. These 5 investigations included 1434 patients with the age less than 50 years. The general information for the 5 studies was shown in Table I.

The General Information and Quality Analysis of the Included Literature

Of the five studies, only one[14] made a description on the allocation concealment method. And none of them indicated that whether blind method was exploited or not. All the studies provided the baseline information of treated and control groups. Although one study[13] was the quasi-randomized controlled trials, the baselines for two sets of data were matched. It was probably because that the data in the two studies were obtained by the same team from a research institution, the same chemotherapy drug was used in the trials and only the dose of the treated group was larger than that of control group. Generally, all the results were reliable (Table II).

Table I. The general information for the included 5 studies.

Literature	Cases	Intervention measures		Outcome indexes	Follow-up time (year)
		Treated group	Control group		
Bacci G 1986[12]	106	Regimen II	Regimen I	5 year disease free survival rate; histological response rate after chemotherapy; 5 year overall survival rate; limb salvage rate	2.5-5.5
Bacci G 2003[13]	367	IOR/OS-N5	IOR/OS-N4	5 year disease free survival rate; local recurrence rate	7.5-10
Lewis IJ 2007[15]	497	Regimen DI	Regimen C	5 year disease free survival rate; 5 year overall survival rate; local recurrence rate	9-10.5
Meyers PA 1998[14]	73	Regimen II	Regimen I	5 year disease free survival rate; local recurrence rate; histological response rate after chemotherapy;	3.5-9
Souhami L 1997[16]	391	Regimen II	Regimen I	5 year disease free survival rate; histological response rate after chemotherapy; 5 year overall survival rate; limb salvage rate; local recurrence rate	5-6

Meta-Analysis of 5-Year Disease Free Survival Rate

Five studies[12-16] reported the 5-year disease free survival rates of dose-intensive regimens and dose control regimens in the treatment of high-grade osteosarcoma. A total of 1420 patients were analyzed for 5-year disease free survival rate, of which 704 cases treated by dose control regimen were classified to dose control regimen group and the remaining were defined as dose-intensive regimen group. As there was no significant heterogeneity between the two groups (p = 0.77, I^2 = 0%), the fixed-effect model analysis was conducted. Results of 5-year disease free survival rates exhibited no statistically significant difference between dose-intensive programs and dose control regimens (RR: 1.08, 95% CI: 0.96-1.21) (Figure 1). The 5-year disease free survival rate of patients did not correspondingly increase accompanied with the increase in the dose of chemotherapy drugs.

Meta-Analysis of 5-Year Overall Survival

Four studies[13-16] reported the 5-year overall survival rates of dose-intensive programs and dose control regimens in the treatment of high-grade osteosarcoma. There were a total of 1272 patients including 623 cases in dose control regimen group and 649 cases in dose-intensive program group. No heterogeneity was observed between the two groups (P = 0.56, I^2 = 0%), so the fixed-effect model analysis was conducted. Results of 5-year overall survival rates exhibited no statistically significant difference between dose-intensive and dose control regimens (RR: 1.07, 95%,CI: 0.98-1.17) (Figure 2).

Table II. Quality evaluation of included methods.

Literature	Experimental design	Random allocation	Allocation concealment	Blinded method	Baseline information
Bacci G 1986[12]	RCT	Inadequate	Undescribed	Undescribed	Comparable
Bacci G. 2003[13]	CCT	Inadequate	Undescribed	Not applicable	Comparable
Lewis IJ 2007[15]	RCT	Inadequate	Undescribed	Undescribed	Comparable
Meyers PA 1998[14]	RCT	Inadequate	Clear	Undescribed	Comparable
Souhami L 1997[16]	RCT	Inadequate	Undescribed	Undescribed	Comparable

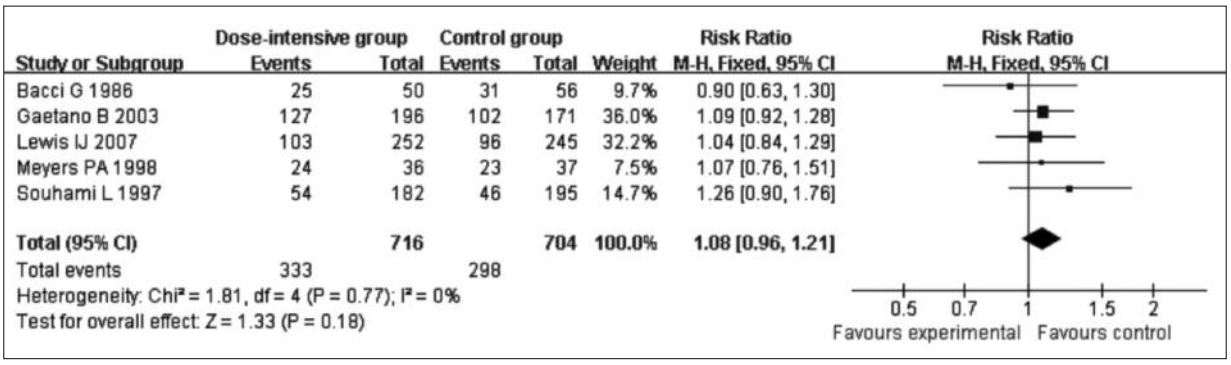

Figure 1. Meta-analysis on the 5-year disease free survival rate of patients treated with dose-intensive programs and dose control regimens.

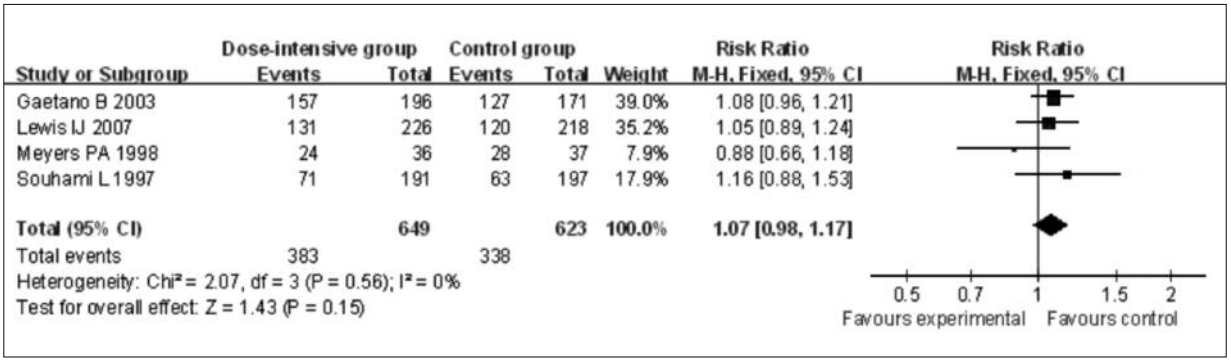

Figure 2. Meta-analysis on the 5-year overall survival rate of patients treated with dose-intensive programs and dose control regimens.

Meta-analysis of Local Recurrence Rate

Four studies[12-15] compared the local recurrence rates of dose-intensive programs with dose control regimens in the treatment of high-grade osteosarcoma. There were a total of 1043 patients, of which 509 cases were classified into the dose control regimen group and the remaining 534 cases were classified into dose-intensive program group. Because there was no heterogeneity among the studies ($p = 0.24$, $I^2 = 28\%$), the fixed-effect model analysis was conducted. Results of local recurrence rates showed statistical significance between dose-intensive programs and dose control regimens (RR: 0.65, 95% CI: 0.46-0.92) (Figure 3). Therefore, the increased cumulative doses of chemotherapy drugs could effectively reduce the local recurrence rate of patients.

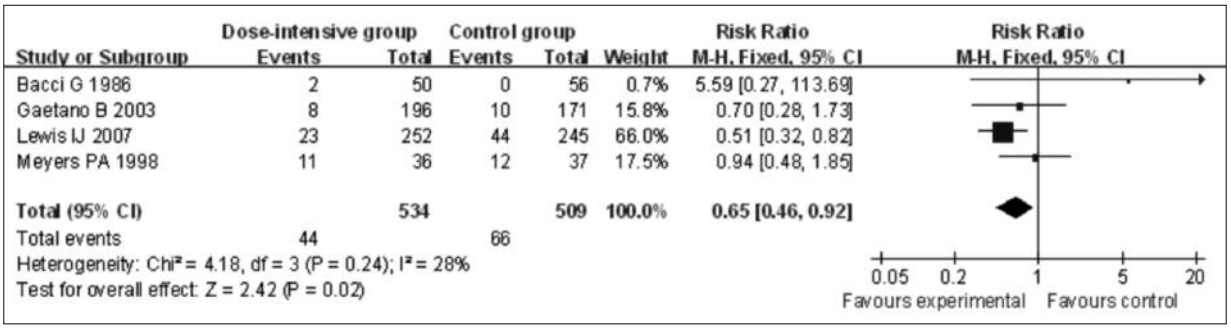

Figure 3. Meta-analysis on the local recurrence rate of patients treated with dose-intensive programs and dose control regimens.

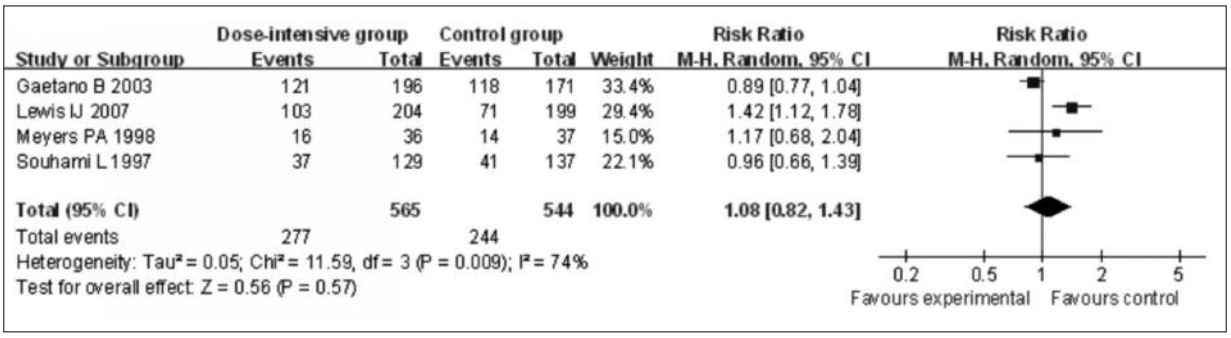

Figure 4. Meta-analysis on the good histological response rate of patients treated with dose-intensive programs and dose control regimens.

Meta-analysis of Good Histological Response Rate

Four studies[13-16] compared the differences of good histological response rates between dose-intensive programs and dose control regimens in the treatment of high-grade osteosarcoma. A total of 1109 patients were classified as dose control regimen group (544 cases) and dose-intensive program group (563 cases). Among the patients in the four studies, heterogeneity was observed ($p = 0.009$, $I^2 = 74\%$), so we applied random-effect model analysis. Results of good histological response rates exhibited no statistical significance between dose-intensive regimens and dose control regimens (RR: 1.08, 95% CI: 0.82-1.43) (Figure 4). This suggested that compared with dose control regimens, the dose-intensive regimens had similar effects on good histological response rate of patients.

The 5-Year Disease Free Survival Rate of The Good and Poor Histological Response

Three studies[14-16] reported 5-year disease free survival rates of the good and poor histological response of dose-intensive programs and dose control regimens. Total 773 patients were classified into two group: dose control regimen group (368 cases) and dose-intensive program group (365 cases). There was no heterogeneity between 2 groups ($p = 0.26$, $I^2 = 27\%$) so the fixed-effect model analysis was applied. As shown in Figure 5, the 5-year disease free survival rate of the good and poor histological response showed statistical difference between dose-intensive programs and dose control regimens (RR: 1.57, 95% CI: 1.36-1.82). This indicated that the histological responds of tumor to the preoperative chemotherapy reaction was closely related to the 5-year disease free survival rate of patients.

Meta-Analysis of Limb Salvage Rate

Three studies[13,15-16] reported the limb salvage rates of dose-intensive programs and dose control regimens in the treatment of high-grade osteosarcoma. There were total 1213 patients including 592 cases treated by the dose control regimen and 621 cases by dose-intensive regimen. As shown in Figure 6, the characteristic of the patients was similar ($P = 0.94$, $I^2 = 0\%$), so we carried out the fixed-effect model analysis. And

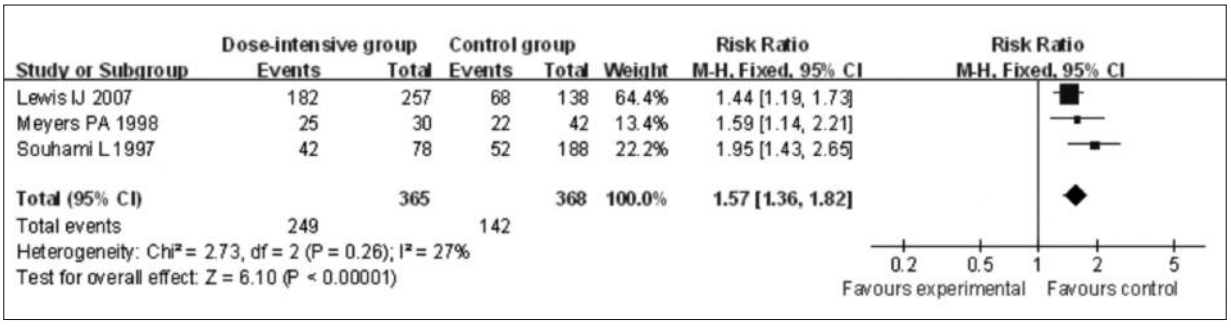

Figure 5. Meta-analysis on the 5-year disease free survival rate of the good and poor histological response of patients treated with dose-intensive programs and dose control regimens.

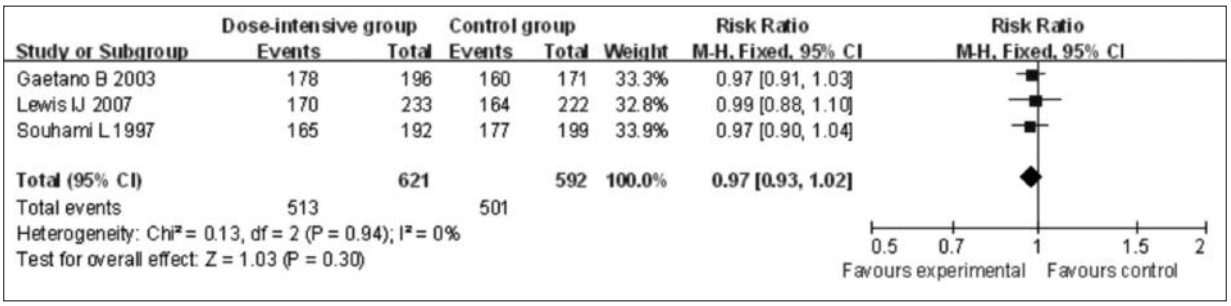

Figure 6. Meta-analysis on the limb salvage rate of patients treated with dose-intensive programs and dose control regimens.

there was no statistical significance between dose-intensive regimens and dose control regimens (RR: 0.97, 95% CI: 0.93-1.02) (Figure 6). It implied that increasing dose of chemotherapy drugs could not correspondingly improve the limb salvage rate of patients.

Discussion

Previous studies have reported that chemotherapy can improve limb salvage rate and plays a vital role in osteosarcoma treatment[17-21]. Nowadays, it is widely recognized that systemic chemotherapy can improve the prognosis and increase the survival rate of patients with osteosarcoma[22-23]. Dose-intensive and dose control chemotherapies were the common regimens for osteosarcoma currently. However, the appropriate dose of the chemotherapy drug has not yet been determined.

In this paper, we applied meta-analysis to compare therapeutic effect of the intensive and dose control chemotherapy regimens on the following efficacy indexes, including 5-year disease free survival rate, 5-year overall survival, local recurrence rate, 5-year disease free survival rate of good and poor histological response of preoperative chemotherapy and limb salvage rate. It was reported that the long-term disease-free survival rates was around 60 to 80 percent in osteosarcoma patients by dose-intensive chemotherapy regimen[18-19]. And our results showed that compared with dose control chemotherapy, dose-intensive chemotherapy regimen had no significant differences in 5-year disease free survival rate, 5-year overall survival rate, good histological response rate and limb salvage rate. It was indicated that dose-intensive and dose control chemotherapy regimen had similar therapeutic effect on osteosarcoma in survival rate, good histological response and limb salvage rate

However, there were obviously significant differences in the local recurrence rate (RR: 0.65, 95% CI: 0.46-0.92) and the 5-year disease free survival rate of good and poor histological response of preoperative chemotherapy (RR:1.57, 95% CI: 1.36-1.82) between the different dose regimens. A report suggested that the dose of chemotherapy influenced the outcome of patients with osteosarcoma[9]. The increasing dose of chemotherapy might reduce the local recurrence rate in our results. Local recurrence was found to be the indicator of poor survival for osteosarcoma patients[24]. Various prognostic factors involved in local recurrence were identified as chemotherapy response, age and surgical margins. The chemotherapy response was considered to be the most primary factor affected local recurrence rate[25]. Previous researches reported that patients with good histologic response would have higher survival rate[14,26]. Thus, tumor histologic response to preoperative chemotherapy might be an independent prognostic factor in osteosarcoma. But a previous study indicated that there was no significant difference in local recurrence between dose-intensive and dose control group (6% vs. 4%)[27]. the innate sensitivity of tumor cells to chemotherapy might result in tumor necrosis instead of the increasing dose of chemotherapy[13]. Though our study showed significant difference in 5-year disease free survival rate of good and poor histological response, the potent evidence was relatively rare, especially concerning the positive effect of dose-intensive chemotherapy on good histologic response for osteosarcoma patients. It suggests that further studies should be conducted to explore whether the intensive dose chemotherapy is associated with the reducing local recurrence rate and good histologic response.

Furthermore, there were some limitations in the meta-analysis of dose-intensive. There were only 5 literatures included, so the data collected in this work was limited. The language of the literatures was restricted in English that might result in the selective bias. In addition, there were also some methodological shortcomings for the literatures included in the meta-analysis. All the studies did not make detailed description on the random allocation method. The blinding method was hard to be carried out in the clinical trials, hence there indeed existed a certain bias in the trials for 4 RCTs. Beside, chemotherapeutics used were not unified in the five studies included in the analysis.

Conclusions

In conclusion, compared with dose control chemotherapy, dose-intensive chemotherapy might reduce the local recurrence rate in patients with osteosarcoma organizations and increase the 5-year disease free survival rate of good histological reaction under preoperative chemotherapy. But in survival rate, good histological response and limb salvage rate, dose-intensive and dose-control chemotherapy regimen showed similar effects. Considered the toxicity of dose-intensive regimen, appropriate dose chemotherapy should be applied for high-grade osteosarcoma treatment in clinical cases.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Lack W, Donigan JA, Morcuende J, Buckwalter J, El-Khoury GY. Conical utility of CT-guided biopsies in orthopaedic oncology. Iowa Orthop J 2010; 30: 76-79.
2) Chang P. Progress in the treatment of osteosarcoma. Med Clin North Am 1977; 61: 1027-1030.
3) Kansara M, Thomas DM. Molecular pathogenesis of osteosarcoma. DNA And Cell Biol 2007; 26: 1-18.
4) Dahlin DC, Coventry MB. Osteogenic sarcoma. A study of six hundred cases. J Bone Joint Surg Am 1967; 49: 101-110.
5) Enneking WF. An abbreviated history of orthopaedic oncology in North America. Clin Orthop Relat Res 2000; 374: 115-124.
6) Hudson M, Jaffe MR, Jaffe N, Ayala A, Raymond AK, Carrasco H, Wallace S, Murray J, Robertson R. Pediatric osteosarcoma: therapeutic strategies, results, and prognostic factors derived from a 10-year experience. J Clin Oncol 1990; 8: 1988-1997.
7) Meyers PA, Heller G, Healey J, Huvos A, Lane J, Marcove R, Applewhite A, Vlamis V, Rosen G. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. J Clin Oncol 1992; 10: 5-15.
8) Bacci G, Avella M, Capanna R, Boriani S, Dallari D, Galletti S, Giunti A, Madon E, Mancini A, Mercuri M. Neoadjuvant chemotherapy in the treatment of osteosarcoma of the extremities: preliminary results in 131 cases treated preoperatively with methotrexate and cisdiamminoplatinum. Ital J Orthop Traumatol 1988; 14: 23.
9) Bacci G, Picci P, Ferrari S, Casadei R, Brach Del Prever A, Tienghi A, Mancini A. 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: 237-246.
10) Bielack SS, Beron G, Winkler K. Influence of methotrexate dose intensity on outcome of patients with high grade osteogenic osteosarcoma. Cancer 1997; 80: 514-521.
11) Bacci G, Ferrari S, Picci P, Zolezzi C, Gherlinzoni F, Iantorno D, Cazzola A. Methotrexate serum concentration and histological response to multiagent primary chemotherapy for osteosarcoma of the limbs. J Chemother 1996; 8: 472-478.
12) Bacci G, Gherlinzoni F, Picci P, Van Horn JR, Jaffe N, Guerra A, Ruggieri P, Biagini R, Capanna R, Toni A, Mario M, Dante D, Mario C. Adriamycin-methotrexate high dose versus adriamycin-methotrexate moderate dose as adjuvant chemotherapy for osteosarcoma of the extremities: a randomized study. Eur J Cancer Clin Oncol 1986; 22: 1337-1345.
13) Bacci G, Forni C, Ferrari S, Longhi A, Bertoni F, Mercuri M, Donati D, Capanna R, Bernini G, Briccoli A, Setola E, Versari M. Neoadjuvant chemotherapy for osteosarcoma of the extremity: intensification of preoperative treatment does not increase the rate of good histologic response to the primary tumor or improve the final outcome. J Pediatr Hematol Oncol 2003; 25: 845-853.
14) Meyers PA, Gorlick R, Heller G, Casper E, Lane J, Huvos AG, Healey JH. Intensification of preoperative chemotherapy for osteogenic sarcoma: results of the Memorial Sloan-Kettering (T12) protocol. J Clin Oncol 1998; 16: 2452-2458.
15) Lewis IJ, Nooij MA, Whelan J, Sydes MR, Grimer R, Hogendoorn PC, Memon MA, Weeden S, Uscinska BM, van Glabbeke M, Kirkpatrick A, Hauben EI, Craft AW, Taminiau AH; MRC BO06 and EORTC 80931 collaborators; European Osteosarcoma Intergroup. Improvement in histologic response but not survival in osteosarcoma

patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. J Natl Cancer Inst 2007; 99: 112-128.

16) Souhami RL, Craft AW, Van der Eijken JW, Nooij M, Spooner D, Bramwell VH, Wierzbicki R, Malcolm AJ, Kirkpatrick A, Uscinska BM, Van Glabbeke M, Machin D. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. Lancet 1997; 350: 911-917.

17) Witting JC, Bickels J, Priebat D, Jelinek J, Kellar-Graney K, Shmookler B, Malawer MM. Osteosarcoma: a multidisciplinary approach to diagnosis and treatment. Am Fam Physician 2002; 65: 1123-1133.

18) Bacci G, Ferrari S, Mercuri M, Longhi A, Capanna R, Tienghi A, Brach del Prever A, Comandone A, Cesari M, Bernini G, Picci P. Neoadjuvant chemotherapy for extremity osteosarcoma: preliminary results of the Rizzoli's 4th study. Acta Oncol 1998; 37: 41-48.

19) Fuchs N, Bielack S, Epler D, Bieling P, Delling G, Körholz D, Graf N, Heise U, Jürgens H, Kotz R, Salzer-Kuntschik M, Weinel P, Werner M, Winkler K. Long-term results of the co-operative German-Austrian-Swiss osteosarcoma study group's protocol COSS-86 of intensive multidrug chemotherapy and surgery for osteosarcoma of the limbs. Ann Oncol 1998; 9: 893-899.

20) Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, Pritchard J, Malpas JS, Baker AR, Kirkpatrick JA. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 1986; 314: 1600-1606.

21) Eckardt J, Eilber F, Dorey F, Mirra J. The UCLA experience in limb salvage surgery for malignant tumors. Orthopedics 1985; 8: 612-621.

22) Damron TA, Pritchard DJ. Current combined treatment of high-grade osteosarcomas. Oncology-Huntington 1995; 9: 327-342.

23) Meyers PA, Gorlick R. Osteosarcoma. Pediatr Clin North Am 1997; 44: 973-989.

24) Weeden S, Grimer R, Cannon S, Taminiau A, Uscinska B. The effect of local recurrence on survival in resected osteosarcoma. Eur J Cancer 2001; 37: 39-46.

25) Picci P, Sangiorgi L, Rougraff B, Neff J, Casadei R, Campanacci M. Relationship of chemotherapy-induced necrosis and surgical margins to local recurrence in osteosarcoma. J Clin Oncol 1994; 12: 2699-2705.

26) Provisor AJ, Ettinger LJ, Nachman JB, Krailo MD, Makley JT, Yunis EJ, Huvos AG, Betcher DL, Baum ES, Kisker CT, Miser JS. Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a report from the Children's Cancer Group. J Clin Oncol 1997; 15: 76-84.