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Addition of Zoledronate to Chemotherapy in Patients with Osteosarcoma Treated with Limb-Sparing Surgery: A Phase III Clinical Trial

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Background: Zoledronate has anti-bone resorption activity and is reported to reduce skeletal-related events. The objective of this study was to test the hypothesis that addition of zoledronate in chemotherapy is safe and effective in osteosarcoma.


Material/Methods: A total of 798 patients, age 25 years and above, with newly diagnosed high-grade surgically salvageable malignant osteosarcoma, were included in the trial. All patients had received standard chemotherapies (n=399). In addition, in a standard chemotherapy regimen, patients enrolled in the zoledronate group also received 10 courses of 4 mg intravenous infusions of zoledronate (n=399). Limb-sparing surgery was performed by orthopedic surgeons (n=798). Clinical assessment, laboratory monitoring, overall survival, event-free survival, and treatment-emergent adverse effects were evaluated. The chi-square independence-samples test was used for statistical analysis at 95% confidence level.

Results: The histopathological response was the same for both groups ($p=0.12$). Addition of zoledronate to chemotherapy improved skeletal event-free survival ($p=0.04$) but decreased overall survival ($p=0.02$). Zoledronate induced hypocalcemia ($p<0.0001$), hypophosphatemia ($p<0.0001$), cardiotoxicity ($p<0.0001$), lung metastases ($p=0.03$), flu-like syndrome ($p<0.0001$), and ototoxicity ($p=0.02$), and elevated serum aspartate aminotransferase ($p<0.0001$) and serum alanine aminotransferase ($p<0.0001$).

Conclusions: The addition of zoledronate to standard chemotherapy in high-grade resectable osteosarcoma is detrimental and is not advised.

MeSH Keywords: **Antineoplastic Combined Chemotherapy Protocols • Disease-Free Survival • Neoplasm Metastasis • Osteosarcoma • Survival Analysis • Survival Rate**

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Background

Osteosarcoma is a malignant tumor of the bone [1]. In general practice, it is treated with chemotherapeutic agents [2]. Etoposide, doxorubicin, methotrexate, ifosfamide, and cisplatin have been found effective in various stages of osteosarcoma [1]. The overall survival after a relapse and/or with metastases in osteosarcoma is low [3]. Therefore, new osteosarcoma drugs are required to improve outcome and to decrease treatment-emergent toxic effects.

Bisphosphonates are widely used to treat tumor-induced osteolysis-related bone problems of patients [2] and also can inhibit osteoclastic bone resorption [3]. Bisphosphonates inhibit the adhesion of cells of the tumor to the bone matrix [4]. Among bisphosphonates, zoledronate or zoledronic acid (third generation bisphosphonate) is approved in adults with solid tumors [5], has the highest anti-bone resorption activity, and also shows a reduction in skeletal-related events in cancer [6]. It also was reported to have anti-tumor activity and inhibits cancer cell migration [2]. A study demonstrated that a combination of chemotherapy with zoledronic acid in a predominantly white population of osteosarcoma patients treated with surgery does not improve skeletal-related events-free survival, but increased the chances of death [3]. However, another study reported that zoledronic acid can be safely added to chemotherapy for osteosarcoma patients [7]. At the same time as the other randomized study, we performed a phase III trial on zoledronate with chemotherapy to assess its efficacy and safety in patients with osteosarcoma patients treated with limb-sparing surgery in an older Asian population.

The primary aim of this study was to test the hypothesis that addition of zoledronate to the standard chemotherapy is effective and safe in osteosarcoma patients treated with limb-sparing surgeries. The secondary endpoint of the study was to compare skeletal-related events-free survival and overall survival for zoledronate and chemotherapy combined with chemotherapy alone at the level I of evidence without conflict of interest.

Material and Methods

Drugs

Methotrexate was purchased from Medac Pharma, Inc., USA. Etoposide was purchased from Pfizer Inc., USA. Ifosfamide (Ifex®) was purchased from Bristol-Myers Squibb Co. New York, USA. Doxorubicin (Adriamycin®) was purchased from Pfizer, Inc., USA. Cisplatin (Platinol®) was purchased from Bristol-Myers Squibb Co., New York, USA. Zoledronate (Zometa®) was purchased from Beijing Novartis Pharma Co., Beijing, China. Calcium and 25-Hydroxyvitamin D tablets were purchased

from Glenmark Pharmaceuticals, India. Normal saline was purchased from Shanghai Baxter Healthcare Co., Shanghai, China.

Ethical approval and consent to participate

The study was registered with the Research registry (www.researchregistry.com), UID No. researchregistry4414 dated 1 September 2009. The protocol of the study (CMU/CL/3/09 dated 15 August 2009) was approved by the Cancer Hospital of China Medical University review board. The study adhered to the law of China, consolidated standards of reporting trials (CONSORT), and the Declaration of Helsinki (V2008). The trial was reported in line with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria [8]. All patients signed an informed consent form for interventions, pathology, surgeries, and publication(s) of the study in all formats (hard and/or electronics) including patients' personal information (image or photograph if any) irrespective of time and language.

Inclusion criteria

We enrolled patients age 25 years and above with newly diagnosed high-grade surgically salvageable malignant osteosarcoma confirmed by biopsies admitted to the Cancer Hospital of China Medical University, China and the referring hospitals from 15 September 2011 to 1 August 2013. The demographic characteristics of the enrolled patients are presented in Table 1.

Exclusion criteria

Patients age below 25 years, with abnormal renal functions (the estimated glomerular filtration rate <70 mL/min/m²), liver functions (bilirubin dosage higher than twice), and cardiac functions (ventricular ejection fraction $<50\%$) were excluded from the trial. Patients who previously received standard chemotherapies were excluded from the study. Patients with small cell osteosarcoma, maxillary osteonecrosis, osteosarcoma of the jaw, history of severe dental events, and surgically unsalvageable malignant osteosarcoma were excluded from the trial.

Experimental design

A total of 798 patients who signed an informed consent form were subjected to 1: 1 randomization. Blinding was carried out by prefilled envelopes and maintained throughout the trial by the Cancer Hospital of China Medical University, China itself. The physicians involved in the randomization were not involved in the treatment. The sample size was calculated by PASS 16.0.3, NCCS, LLC, Utah, USA. The sample size was found to be 399 for both groups. Confidence intervals for both sides was 95% ($\alpha=0.05$). A CONSORT flow diagram of the study is presented in Figure 1.

Table 1. Demographical characteristics of the patients.

Characteristics		Groups		Comparison between groups
		CL	ZA	
Numbers of patients		399	399	
Intervention		Standard chemotherapy only	Standard chemotherapy with zoledronate	p-Value
Gender	Male	230 (58)	207 (52)	0.12
	Female	169 (42)	192 (48)	
Age (years)	Maximum	59	61	0.09
	Minimum	26	26	
	Mean ±SD	31.45±5.45	32.27±7.85	
	Between 25–40 years	150 (38)	150 (38)	
Anatomical tumor site	Axial	21 (5)	18 (4)	0.74
	Limb	378 (95)	381 (96)	
Tumor size*	<10 mm	221 (55)	236 (59)	0.32
	≥10 mm	178 (45)	163 (41)	
Histological subtype osteosarcoma	Small cell	7 (2)	3 (1)	0.07
	Convectional	374 (391)	371 (92)	
	Telangiectasic	3 (1)	4 (1)	
	High-grade surface	4 (1)	3 (1)	
	Giant cell	4 (1)	8 (2)	
	well-differentiated	3 (1)	4 (1)	
	Juxtacortical	4 (1)	3 (1)	
	Pleomorphic bone	0 (0)	3 (1)	
	Fibroma-chondromyxoid	8 (2)	0 (0)	
Pathologically fracture	Yes	38 (10)	29 (7)	0.31
	No	361 (90)	370 (93)	
Staging	Localized	282 (71)	267 (67)	0.07
	Possible metastases	86 (22)	81 (20)	
	Definite metastases	31 (7)	51 (13)	
Staging according to American joint committee on cancer system for osteosarcoma [#]	I-A	85 (21)	80 (20)	0.33
	I-B	115 (29)	131 (33)	
	II-A	48 (12)	21 (5)	
	II-B	95 (24)	99 (25)	
	III	25 (6)	17 (4)	
	IV-B	11 (3)	15 (4)	

Data were represented as a number (percentage) and mean ±SD for constant and continuous data respectively. For statistical analysis, the *Chi-square* Independence test was used for constant data and the two-tailed paired test was used for continuous data. A $p < 0.01$ was considered significant. * The largest diameter. All patients were from P.R. China. # I – Low and no-metastasis; II – high and no-metastasis; III – any with pulmonary metastasis; IV – any with non-pulmonary metastasis; A – <8 cm; B – >8 cm.

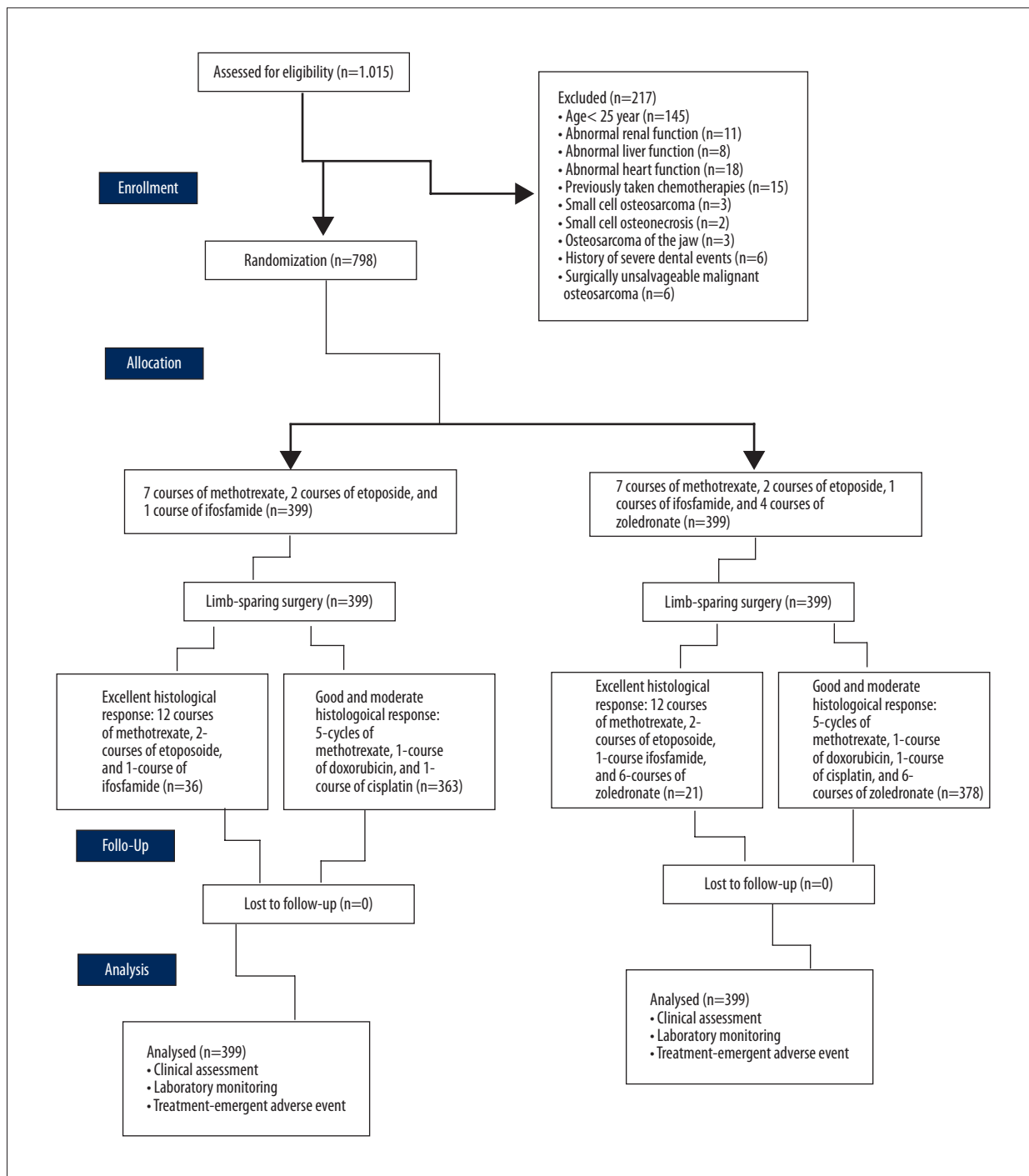


Figure 1. CONSORT flowchart of the trial. Confidence intervals for both sides was 95% ($\alpha=0.05$).

Preoperative intervention

Before surgeries, all enrolled patients received 7 courses of 12 g/m² methotrexate, 2 courses of 300 mg/m² etoposide, and 1 course of 12 g/m² ifosfamide. Two courses of the same kind had 21 days of recovery period (they were given every 3 weeks) [3]. In addition to a chemotherapy regimen, patients enrolled in the

zoledronate group (ZA group) also received 4 courses of 4 mg intravenous infusions of zoledronate/month [9].

Limb-sparing surgery

All enrolled patients were subjected to limb-sparing surgery after preoperative chemotherapies by an orthopedic surgeon

(blinded regarding randomization; minimum 3 years of experience). During surgeries, the cancerous tissue and surrounding healthy tissues were removed. Limb-sparing surgery was performed by 7 different orthopedic surgeons of the Cancer Hospital of China Medical University, China [10]. Resected bone tumors were subjected to histopathological analysis. Grade was rated as excellent (more than 90% necrosis of tumor), good (60–90% necrosis of tumor), and moderate (40–60% necrosis of tumor).

Postoperative intervention

After surgeries, patients with excellent histological response and without metastasis received 12 courses of 12 g/m² methotrexate, 2 courses of 300 mg/m² etoposide, and 1 course of 12 g/m² ifosfamide. Patients with good and moderate histological response, salvageable malignant osteosarcoma, and/or initial metastases received 5 cycles of 12 g/m² methotrexate, 1 course of 75 mg/m² doxorubicin, and 1 course of 120 mg/m² cisplatin. Two courses of the same kind had 21 days of recovery period [3]. In addition to a chemotherapy regimen, patients enrolled in the ZA group also received 6 courses of 4-mg intravenous infusions of zoledronate per month [9].

Both groups of patients received 500 mg calcium [11] with 400 IU 25-hydroxy Vitamin D/day [12] during the trial and in the follow-up period (as per requirements).

Clinical assessment

Clinical assessment was performed during chemotherapy regimens at 7 weeks and 14 weeks with X-ray and magnetic resonance imaging (MRI) for the tumor site and the chest. After completion of the regimen, a yearly X-ray assessment of the tumor site and the chest was performed. Event-free survival was considered as the time until the development of relapse or secondary tumor at the site of limb and/or lung(s) from the time of enrollment. Overall survival was considered as from the time of detection of osteosarcoma to death [3]. Only 1 radiographic center of the Cancer Hospital of China Medical University, China and its staff (blinded regarding interventions) was involved in the clinical assessments.

Laboratory monitoring

Hematological, hepatic, and renal functions were monitored. Serum calcium level and serum phosphate level were measured at 1 day and 3 days, then once a week after the first zoledronate course, and before each infusion and 2 days after infusion for the subsequent courses. Serum aspartate aminotransferase level, serum alanine aminotransferase level, serum creatinine level, and serum bilirubin level were evaluated after each cycle. Less than 6.40 mg/dL serum calcium level was considered as

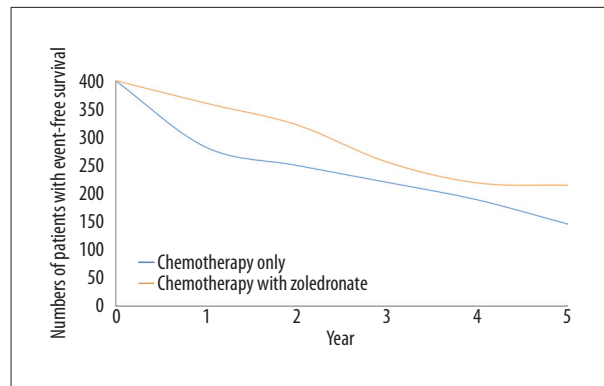


Figure 2. Event-free survival. We evaluated 399 patients in each group. The *chi-square* independent-samples test was used in statistical analysis. A $p < 0.05$ was considered significant. 0: After completion of the regimen. Event-free survival was considered as the time of enrollment to development of relapse or secondary tumor.

hypocalcemia and less than 2.50 mg/dL serum phosphate level was considered as hypophosphatemia. More than 80 unit/L and more than 100 unit/L of serum aspartate aminotransferase and serum alanine aminotransferase were considered as an elevated level. More than 1.7 mg/dL for males and more than 1.4 mg/dL for females were considered as elevated serum creatinine level, and less than 0.3 mg/dL was considered as a normal level of serum bilirubin [3]. Only 1 pathological laboratory of the Cancer Hospital of China Medical University, China and its staff (blinded regarding interventions) was involved in the laboratory monitoring.

Treatment-emergent adverse event monitoring

Adverse events were checked after each cycle. Events were considered as adverse effects according to the v3.0-Common Terminology Criteria for Adverse Events (CTCAE; v3.0) [11]. Paramedical staff (blinded regarding interventions) of the Cancer Hospital of China Medical University, China were involved in the evaluation of adverse effects. Less than 1000 absolute neutrophil count/ μ L of blood was considered as neutropenia. Less than 13 g/L of blood for males and less than 12 g/L of blood for females hemoglobin count were considered as anemia [13]. Less than 50 000 platelet count/ μ L of blood was considered as thrombocytopenia. Cardiotoxicity 5–55% was defined as reduction in left ventricular ejection fraction, signs (tachycardia and/or S3 gallop), and symptoms of heart failure [14].

Statistical analysis

InStat, GraphPad Software, IL, USA was used for statistical analysis. The *chi-square* independent-samples test [3] was used for constant data and the two-tailed paired test was used

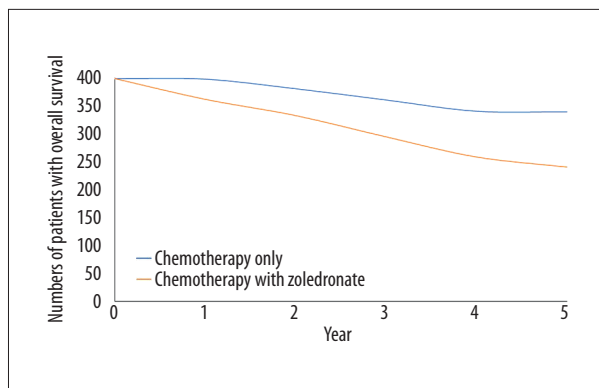


Figure 3. Overall survival of patients. We evaluated 399 patients in each group. The *chi-square* independent-samples test was used in statistical analysis. A $p < 0.05$ was considered significant. 0: After completion of the regimen. Overall survival considered from the time of detection of osteosarcoma to death.

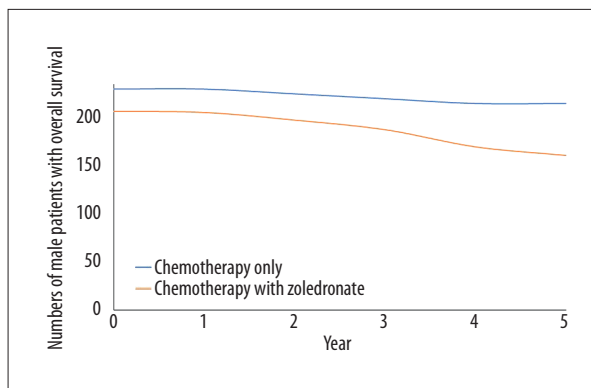


Figure 5. Overall survival of male patients. We evaluated 207 male patients for the chemotherapy with zoledronate group and 230 male patients for the chemotherapy alone group. The *chi-square* independent-samples test was used in statistical analysis. A $p < 0.05$ was considered significant. 0: After completion of the regimen. Overall survival considered from time of detection of osteosarcoma to death.

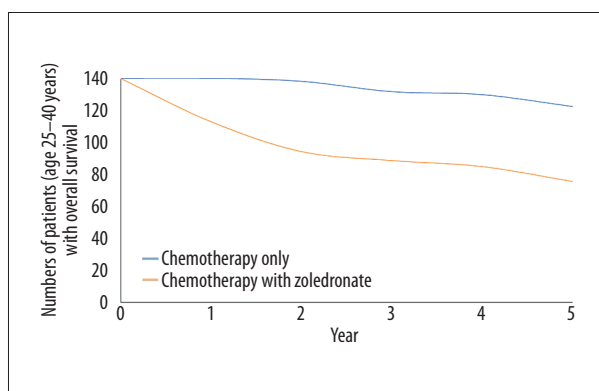


Figure 4. Overall survival of patients ages 25–40 years. We evaluated 150 patients in each group. The *chi-square* independent-samples test was used in statistical analysis. A $p < 0.05$ was considered significant. 0: After completion of the regimen. Overall survival considered from the time of detection of osteosarcoma to death.

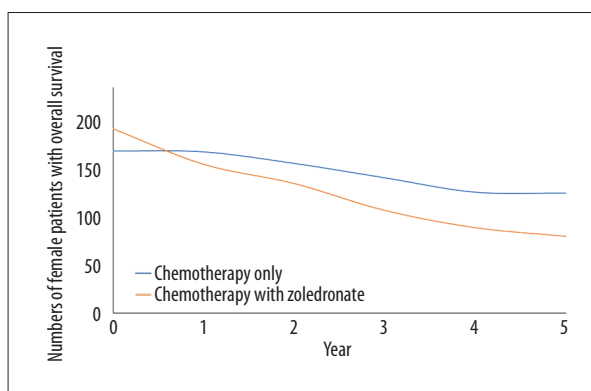


Figure 6. Overall survival of female patients. We evaluated 192 female patients for chemotherapy in the zoledronate group and 169 female patients for the chemotherapy alone group. The *chi-square* independent-samples test was used in statistical analysis. A $p < 0.05$ was considered significant. 0: After completion of the regimen. Overall survival was considered as from the time of detection of osteosarcoma to death.

for continuous data. An intention-to-treat method of analysis was used. All data were considered significant at 95% confidence level.

Results

The time required for chemotherapy before surgeries was the same between both groups ($p = 0.09$). The time taken for surgeries after preoperative chemotherapies between groups ($p = 0.08$) and the start of chemotherapy after surgeries ($p = 0.07$) were the same in both groups.

Addition of zoledronate to chemotherapy improved event-free survival ($p = 0.04$, Figure 2) but decreased overall survival

($p = 0.02$, Figure 3). There was a clear trend for worse survival even in patients age 25–40 years in the ZA group ($p = 0.06$, Figure 4). Overall survival for male patients was the same in both groups ($p = 0.74$, Figure 5) but overall survival was reduced for female patients who received zoledronate in addition to chemotherapy ($p = 0.01$, Figure 6).

Patients who received chemotherapy with zoledronate had a higher number of lung metastases than in patients receiving chemotherapy alone ($p = 0.03$). The histological response was the same for both groups ($p = 0.12$). Zoledronate was responsible for hypocalcemia, hypophosphatemia, and elevation of

Table 2. Laboratory monitoring.

Characteristics	Groups		Comparison between groups
	CL	ZA	
Numbers of patients	399		
Intervention	Standard chemotherapy only	Standard chemotherapy with zoledronate	p-Value
Hypophosphatemia	26 (7)	115 (29)*	<0.0001
Serum aspartate aminotransferase elevation	69 (17)	170 (43)*	<0.0001
Serum alanine aminotransferase elevation	125 (31)	220 (55)*	<0.0001
Creatinine elevation	138 (35)	231 (58)*	<0.0001
Bilirubin elevation	149 (37)	165 (41)	0.28
Histopathological response after completion preoperative Intervention	167 (42)	179 (45)	0.43
Excellent ¹	36 (9)	21 (5)	0.12
Good ²	254 (64)	262 (66)	
Moderate ³	109 (27)	116 (29)	
Lung metastases [#]	1 (0.25)	9 (2)*	0.03

Data were represented as number (percentage). The *Chi-square* Independence test was used in statistical analysis. A $p < 0.05$ was considered significant. < 6.40 mg/dL serum calcium level was considered as hypocalcemia and < 2.50 mg/dL serum phosphate level was considered as hypophosphatemia. More than 80 unit/L and more than 100 unit/L were considered the elevated level of serum aspartate aminotransferase and serum alanine aminotransferase. > 1.7 mg/dL for male and > 1.4 mg/dL for female were considered as elevated serum creatinine. > 0.3 mg/dL serum bilirubin was considered as the elevated level. * Significant zoledronate-emergent toxic effect. Only one pathological laboratory of the Cancer Hospital of China Medical University, China and its staff (blinded regarding interventions) was involved. # X-ray and MRI results by a radiologist(s) of the Cancer Hospital of China Medical University, China. ¹ - $> 90\%$ necrosis of tumor; ² - 60–90% necrosis of tumor; ³ - 40–60% necrosis of the tumor.

serum aspartate aminotransferase and serum alanine aminotransferase (Table 2).

Zoledronate treatment has a high probability and high impact for treatment-emergent cardiotoxicity and fracture(s) (Table 3). Zoledronate treatment increased the risk for the treatment-emergent flu-like syndrome and ototoxicity. Patients did not die of complications related to fractures. The increased number of metastases did not alter the statistics, since the worse survival was not due to osteosarcoma. Zoledronate increased rates of cardiotoxicity and neutropenia, and was associated with a very slight increase in febrile neutropenia and an increase in postoperative wound healing complications. Patients died due to cardiotoxicities, multiple organ failures, and the other problems (Table 4).

Zoledronate increased the financial burden by 1445 ± 12 ¥/for intravenous infusion.

Discussion

The addition of zoledronate to chemotherapy failed to improve the histopathological responses ($p = 0.12$). These results are in line with the available OS2006 trial [3] but failed to reach the results of the experimental study [2] and a small report [7]. In humans, osteosarcoma has aggressiveness and biological heterogeneity [15]. In consideration of results of histological response, the addition of zoledronate to chemotherapy has no additive clinical benefits over chemotherapy alone in osteosarcoma patients.

The addition of zoledronate to chemotherapy improved event-free survival ($p = 0.04$). These results of the study are in line with the OS2006 trial [3]. Zoledronate inhibits neoangiogenesis and attenuates osteosarcoma growth [2] and augmented the effect of a chemotherapy regimen [5]. The results of event-free survival suggest that the addition of zoledronate chemotherapy may improve results of osteosarcoma therapy.

Zoledronate with chemotherapy decreased overall survival ($p = 0.02$). These results of the study are in line with the available

Table 3. Treatment-emergent toxic effect.

Intervention	Groups				Comparison between groups	
	CL group		ZA group		For all grades	For severe toxicity
	399		399			
Adverse event	All grades	Severe toxicity	All grades	Severe toxicity	p-Value	p-Value
Neutropenia [#]	317 (79)	285 (71)	338 (85)	290 (73)	0.06	0.75
Anemia ^{##}	354 (89)	91 (23)	370 (93)	104 (26)	0.07	0.32
Thrombocytopenia ^{###}	265 (66)	81 (20)	271 (68)	92 (23)	0.71	0.39
Cardiotoxicity [@]	84 (21)	11 (3)	125 (31) ^{&}	46 (12) [*]	0.001	<0.0001
Fractures ^{@@}	26 (7)	3 (1)	92 (23) ^{&}	32 (8) [*]	<0.0001	<0.0001

[#] <1000 absolute neutrophil count/ μ L blood; ^{##} <13 g/L for male and <12 g/L for female hemoglobin; ^{###} <50,000 platelet count/ μ L blood. [@] 5–55% reduction in left ventricular ejection fraction, signs (tachycardia and/or S3 gallop), and symptoms of heart failure Data were represented as number (percentage). The *Chi-square* Independence test was used in statistical analysis. A $p < 0.05$ was considered significant. As per CTCAE; v3.0. Paramedical staff (blinded regarding interventions) of the Cancer Hospital of China Medical University, China was involved in the evaluation of adverse effects. ^{*} Significant zoledronate-emergent severe toxicity. [&] Significant zoledronate-emergent toxic effect (all grade). ^{@@} Most of female patients in both group and if male patient age >40 years.

Table 4. Treatment-emergent adverse event.

Adverse event	Groups		Comparison between groups
	CL group	ZA group	
	399	399	
Intervention	Standard chemotherapy only	Standard chemotherapy with zoledronate	p-Value
Weight loss	241 (60)	258 (65)	0.24
Flu-like syndrome (fever)	170 (43)	242 (61) [*]	<0.0001
Mood disturbance	30 (8)	25 (6)	0.58
Headache	27 (7)	31 (8)	0.68
Ototoxicity	124 (31)	157 (39) [*]	0.02
Skin rashes	131 (33)	141 (35)	0.51
Postoperative wound healing complications	15 (4)	25 (6)	0.14
Allergic reaction	8 (2)	13 (3)	0.38
Mucositis	171 (43)	146 (37)	0.08
Infection without neutropenia	181 (45)	191 (48)	0.52
Febrile neutropenia	355 (89)	367 (92)	0.18
Peripheral neuropathy	98 (25)	102 (26)	0.81

Data were represented as number (percentage). The *Chi-square* Independence test was used in statistical analysis. A $p < 0.05$ was considered significant. ^{*} Significant zoledronate-emergent toxic effect. As per CTCAE; v3.0. Paramedical staff (blinded regarding interventions) of the Cancer Hospital of China Medical University, China was involved in the evaluation of adverse effects.

trials [3,7], but male patients ($p=0.74$) and younger patients (25–40 years, $p=0.06$) had the same survival as that of patients receiving chemotherapy alone, with additional high event-free survival. These results of heterogeneity of age and sex were not in line with available trials [3,7]. A possible explanation for these results is that lack of statistical significance at the 5% level does not necessarily mean that zoledronate has no treatment-emergent adverse effect in young and male patients, simply that the association is unproven. Some results of the available studies are in line with the such results of the other trial, as zoledronate is more effective in younger patients than in older patients [16] and the risk of treatment is higher in Asian women and older men than in white patients [1]. However, addition of zoledronate to standard chemotherapy in patients with osteosarcoma is not recommended.

Zoledronate treatment has the risk of hypocalcemia, hypophosphatemia, fracture(s), flu-like syndrome, and ototoxicity. There were no orthopedic-related complications (except in female patients and patients age >40 years). These results of the study are in line with the available trials [3,7]. Zoledronate improves wound healing [17]. With respect to the results of a trial related to fracture and postoperative wound healing complications, there is a need to find an effective and safe alternative to zoledronate in female and older patients with osteosarcoma.

The OS2006 trial [3] and AOST06P1 study [7] have reported the same results for histological response, event-free survival, overall survival, and toxic effects, but disagree regarding sample size and evaluation methods. In the OS2006 trial enrollment was stopped prematurely [1] and enrolled white patients but included no Asian patients. Moreover, the AOST06P1 study [7] included only 24 patients, lacked a control group, and all enrolled patients were less than 40 years old at the time of enrollment.

We performed limb-sparing surgery after preoperative chemotherapies to remove the tumor. Limb-sparing surgeries and amputation surgeries have the same overall survival [18]. Amputee patients required more walking support than those who underwent limb-sparing surgery [19]. With respect to the method of surgeries performed in the trial, we were successful in improving the quality of life of patients, as well as improving with physical functioning.

We found more patients with lung metastases during 5-year follow-up for the standard chemotherapy with zoledronate group than with the chemotherapy alone group (9 vs. 1). The results of the trial were in line with the available tissue culture and cell line study [20] but not in line with the available cell line and animals study [21] and review article [6]. Zoledronate induces reduction of osteoclasts [22]. Osteoclasts inhibit the migration of osteosarcoma [20]. Therefore, there is a need for alternate chemotherapy treatment that reduces the risk of lung metastases.

There are several limitations of the study. Zoledronate also has extraskeletal effects [23]. The study did not evaluate the effects of zoledronate on the immune system and the other anti-tumor effects outside of bone. According to cell biology, zoledronate and methotrexate are antagonistic [5]. The surgeons' experience in limb-sparing surgeries improved the outcomes [18], but our study did not discuss such parameters. Secondary amputation is an important parameter for site-specific control of functional outcomes for limb-sparing surgeries of osteosarcoma [18]. In our study, orthopedic surgeons did not perform secondary amputations in any patients. Analysis of quality of life was not carried out.

Conclusions

The addition of zoledronate to chemotherapy improved event-free survival of patients with osteosarcoma. However, zoledronate induced severe adverse effects and decreased overall survival of female patients and older patients. Zoledronate also increased the risk of pulmonary metastases. Therefore, addition of zoledronate to standard chemotherapy in high-grade resectable osteosarcoma is detrimental and should not be advised.

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Conflict of interest

None.

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