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Methotrexate, doxorubicin, and cisplatinum regimen is still the preferred option for osteosarcoma chemotherapy

A meta-analysis and clinical observation

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Abstract

Background: We designed the study to investigate whether methotrexate, doxorubicin, and cisplatinum (MAP) chemotherapy strategy was still the preferred option for the survival of osteosarcoma patients.

Method: We collected some trials of osteosarcoma to make a meta-analysis first. Then, we retrospectively collected data from 115 patients with osteosarcoma and performed further analysis to verify the impact of MAP regimen on the survival of patients.

Results: Seven studies including 3433 participants met the preliminary inclusion criteria. Meta-analysis of the 3-year disease-free survival (odds ratio [OR] = 1.06, 95% confidence interval [CI]: 0.88–1.28; $P = .52$) and overall survival (OR = 1.21, 95% CI: 0.70–2.11; $P = .54$), 5-year disease-free survival (OR = 1.07, 95% CI: 0.87–1.30; $P = .54$) and overall survival (OR = 0.86, 95% CI: 0.65–1.12; $P = .26$), and mortality rate (OR = 0.90, 95% CI: 0.70–1.17; $P = .44$), showed no statistically significant differences. The most common grade 3/4 adverse events were neutropenia (498 [85.9%] patients in MAP vs 533 [93.3%] in MAP plus ifosfamide and etoposide, or other adjuvant therapy drugs [MAP$^+$]). MAP was associated with less frequent toxicities than MAP$^+$ group with statistical significance in thrombocytopenia, febrile neutropenia, anemia, and hypophosphatemia. The same phenomenon could also be seen in the analysis of clinical data.

Conclusion: MAP regimen remains the preferred option for osteosarcoma chemotherapy.

Abbreviations: CI = confidence interval, FE = fixed effect, HR = hazard ratios, MAP = methotrexate, doxorubicin, and cisplatin, MAP$^+$ = MAP plus ifosfamide and etoposide, or other adjuvant therapy drugs, NCCN = National Comprehensive Cancer Network, OR = odds ratio, RE = random effect, RR = risk ratio.

Keywords: clinical observation, MAP, meta-analysis, osteosarcoma, survival

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1. Introduction

In recent years, many studies have shown that the development and prognosis of osteosarcoma is a pathological process involving multiple genes and factors. Although basic research on tumor markers has progressed rapidly in the field of osteosarcoma, treatment methods have changed little in clinical work.[1–5] Surgery, chemotherapy and selective radiotherapy are still the main treatments for patients with osteosarcoma.[6–12] It was reported that neoadjuvant chemotherapy including doxorubicin, methotrexate, and cisplatin with intercalated surgery is the standard of care for resectable osteosarcoma patients in those younger than 40 years.[11] The prognosis for osteosarcoma patients presenting with advanced or recurrent disease, or among those older than 40 years are generally poor. Overall prognosis has improved little for all patients with osteosarcoma, and new treatment combinations or methods are needed.[11]

As chemotherapy is the most commonly used treatment, in the field of osteosarcoma treatment, the choice of chemotherapy drugs and chemotherapy regimens or the choice of chemotherapy density are still controversial. The combination of surgical removal of the tumor and systemic multidrug chemotherapy mainly consisting of methotrexate, adriamycin, and cisplatin with or without ifosfamide is the standard strategy to treat conventional osteosarcoma.[13] Postoperative adjuvant chemotherapy definitely improves disease-free and overall survival (OS) in patients with osteosarcoma,[13] while there was no advantage in event-free survival (EFS) for patients given presurgical chemotherapy.[14] After the failure of first-line treatment, second-line chemotherapy was often given to patients with osteosarcoma who were in good condition. Gemcitabine-based combined chemotherapy predicted a good clinical application prospect as the second-line treatment for osteosarcoma patients, whether it was combined with docetaxel or sirolimus,[15,16] while dose intensification with high-dose chemotherapy did not increase the probability of survival.[17]

In other words, there were still different voices for the optimal treatment options for the treatment of osteosarcoma patients throughout the course of the disease. As more and more phase III clinical studies on chemotherapy are completed, more and more chemotherapy options are available.[18–24] So which is the best chemotherapy option for the entire course of osteosarcoma patients? In order to answer this question, we conducted a meta-analysis of the osteosarcoma chemotherapy regimen and then collected many clinical cases from 4 clinical hospitals to verify whether the meta-analysis results were consistent with the clinical observations.

2. Materials and methods

2.1. Data collection

2.1.1. Search strategy and selection criteria. We took the method called the Preferred Reporting Items for Systematic Reviews and Meta-Analyses to search materials.[25] Original articles, related to results of prospective clinical trials were verified by a Pubmed search. During the process of searching, we mainly selected English studies ranged from January 1, 2000 to August 30, 2018 (Keywords: "Osteosarcoma," "osteoma," "chemotherapy," "doxorubicin," "methotrexate," "cisplatin," "prognosis," "radiotherapy," "chemoradiotherapy," "death," "mortality"). In the process of searching data, we only focused on Phase III clinical trials. We adopted the studies just in human beings which were presented in full text, abstract, or poster form. Some ongoing clinical trials were checked from American or European clinical trial centers, while other data of interest were selected from information seeking on the internet and manual access of bibliographies. We appointed 4 staff members to take charge of confirming their eligibility, and then get agreement together.

The criteria for the selected data:

(1) available data in cases and controls provided;
(2) self-reported results and risk assessment and/or displayed data necessary for evaluating odds ratio (OR) with 95% confidence interval (CI) or other evaluable indicators such as risk ratio (RR), hazard ratios (HR), and so on;
(3) subjects were diagnosed with osteosarcoma by typical imaging changes or pathological biopsy;
(4) phase-III randomized controlled trials or comparative studies;
(5) the chemotherapy regimens involved in the clinical data in the article are in line with the chemotherapy regimen recommended by the National Comprehensive Cancer Network (NCCN) guidelines.

Exclusion criteria:

(1) studies that crossing with others or reported with data from the same authors;
(2) studies involved neonates or patients older than 65 years;
(3) serious complications not related to the purpose of the study;
(4) sarcoma but not osteosarcoma;
(5) studies with incomplete results or data;
(6) study type of letters, case reports, editorials, or reviews.

2.1.2. Data extraction and validity assessment. The extraction of the data was put into practice according to the criteria recommended by the Cochrane Collaboration.[26] Treatment groups were confirmed as patients who had received chemotherapy. We summarized necessary data of the study involving first author, year of publication, the number of patients, research design, population, chemotherapy protocol name, chemotherapy cycles, dosage and toxic side effects of chemotherapy drugs, the survival status of malignant tumor patients. If no useful data was found, we would try to get in touch with the corresponding author for more information.

2.1.3. Assessment of bias risk. We selected 4 clinicians to evaluate the extracted data separately. The quality of study was evaluated by the Newcastle–Ottawa scale as proposed by the Cochrane Collaboration.[27] We would check up HR, RR, OR, and 95% CI which were calculated with random effect (RE) or fixed effect (FE) models according to the actual situation of the data. $P \leq .05$ was considered as statistically significant.

2.1.4. Main outcome measures. The primary aims were EFS, OS, and mortality rate, while secondary outcomes were chemotherapy toxicities. Targeted toxicities included neutropenia, febrile neutropenia, fever without neutropenia, thrombocytopenia, hypophosphatemia, mucositis, cardiac dysfunction, renal dysfunction, anemia, and so on.

We designated 2 clinicians to check up dosage and toxic side effects of chemotherapy drugs, the survival status of tumor patients. Chemotherapy efficacy evaluation, according to the standard of the response evaluation criteria in solid tumors, could be diagnosed by computed tomography scan. Survival status comprised mortality rate of patients and complications affecting

the prognosis. The general condition of patients was evaluated according to the Eastern Cooperative Oncology Group score. The collection of survival time would be accurately calculated to the day. Some unclear data was gotten from the study authors. If some useful details were unavailable, the study would be deleted from the analysis. The corresponding author of the article would be responsible for disagreements and have the right to make a final decision.

2.2. Statistical analysis

All the data were collected with OR by using the Comprehensive Meta-Analysis software according to whether or not they were presented with a comparison group. The OR was considered as a much more conservative estimate and might be more likely to detect a safety signal, as the method by which an OR is calculated provided a point estimate farther from unity than that provided by a HR. A RE model was taken to check most of treatment effects which are different among all studies,[28] while a FE model was used occasionally for some analysis when the treatment effects were deemed to be the same and that differences in results were just due to random probability. Cochrane Q statistic and the I^2 statistic were used to check the heterogeneity among studies just as recommended by Higgins et al.[29] Harbord test was taken to evaluate publication bias for studies; $P \leq .05$ was considered as publication bias. We would summarize all survival information of patients including long-term follow-up data. All data consolidation and analyses were calculated by Review Manager 5.3. Statistical tests were all 2-sided.

For clinical data survival analysis, all risk evaluation processes would be easily finished with online analysis tools, SPSS 19.0 software.[30] The HR is the RR of the terms stated by 2 levels of risk groups. Survival rate was plotted using Kaplan–Meier method and analyzed by using Log-rank test method. The frequencies of categorical variables were compared using Pearson χ^2 or Fisher exact test, when appropriate. A value of $P \leq .05$ was deemed to be statistical significant.

3. Results

Among all the citations identified by our electronic and manual searches, 7 studies including 3433 participants met the inclusion criteria.[18–24] All the articles were imported into EndNote X8 and checked. The characteristics of them were listed in Table 1. All the funnel plots were provided in Supplemental Figures 1 and 2, http://links.lww.com/MD/C970.

3.1. Meta-analysis of 3-year event-free and OS rates

Five studies (n = 2891) reported methotrexate, doxorubicin, and cisplatinum (MAP) (n = 1153) versus MAP plus ifosfamide and etoposide, or other adjuvant therapy drugs (MAP^+) strategies (n = 1738) with the related data of 3 year EFS,[18,20,21,22,24] while only 3 studies of them were shown with the information of 3 year OS rates.[18,20,21] We took a RE model of meta-analysis to deal with all the data. Meta-analysis of 3-year event-free survival rate showed that there was no difference between the 2 groups (OR = 1.06, 95% CI: 0.88–1.28, $Tau^2 = 0.02$; $Chi^2 = 8.87$; df = 6 [$P = .18$]; $I^2 = 32\%$, $Z = 0.64$ [$P = .52$]; Fig. 1A).[18,20,21,22,24] Similar results could also be seen in the results of 3-year OS rates analysis (OR = 1.21, 95% CI: 0.70–2.11, $Tau^2 = 0.18$; $Chi^2 = 8.37$; df = 2 [$P = .02$]; $I^2 = 76\%$, $Z = 0.68$ [$P = .49$]; Fig. 1B).[18,20,21] We did not take the fixed model to make further analysis for the existence of heterogeneity ($I^2 = 32\%$). The funnel plots could be seen in Supplemental Figure 1A and B, http://links.lww.com/MD/C970.

3.2. Meta-analysis of 5-year event-free and OS rates

The 5-year EFS rate and OS rate were also taken into account.[19,20,22,23,24] For 4 included studies, the data of 5-year EFS rates were reported. The 5-year EFS rate was 59.9% (662/1106) in the MAP group versus 58.4% (628/1075) in the other chemotherapy group.[19,20,23,24] No difference could be found between the 2 groups (OR = 1.07, 95% CI: 0.87–1.30, $Tau^2 = 0.02$; $Chi^2 = 6.65$; df = 5 [$P = .25$]; $I^2 = 25\%$, $Z = 0.62$ [$P = .54$]; Fig. 1C).[19,20,23,24] Heterogeneity could be found ($I^2 = 25\%$), so the FE model of meta-analysis was deserted.

Three studies with 5-year OS rate data were taken to make further analysis.[19,22,23] The RE model was tried to deal with the raw data. The forest plot could be seen in Figure 1D. The overall outcome of the analysis were summarized at the bottom of it (OR = 0.86, 95% CI: 0.65–1.12, $Tau^2 = 0.00$; $Chi^2 = 0.22$; df = 2 [$P = .89$]; $I^2 = 0$, $Z = 1.12$ [$P = .26$]; Fig. 1D).[19,22,23] Harbord test statistic did not suggest obvious publication bias in funnel plots (Supplemental Fig. 1C and D, http://links.lww.com/MD/C970).

Table 1

Characteristics of all the enrolled data.

No	Study resource	Country	Name of study	Chemotherapy composition	Random controlled trial (RCT)	Phase	All patients	Patients of MAP group	Patients of 3 yr EFS	Patients of 3 yr OS	Patients of 5 yr EFS	Patients of 5 yr OS
1	Gaspar et al,[18] 2018	French	OS2006/sarcome-09	MAP vs M-EI	RCT	III	565	156	356	463	N/A	N/A
2	Senerchia et al,[19] 2017	USA	–	MAP vs MAP + MC	RCT	N/A	296	157	N/A	N/A	185	221
3	Marina et al,[20] 2016	17 countries	EURAMOS-1	MAP vs MAPIE	RCT	III	618	310	334	460	307	N/A
4	Piperno et al,[21] 2016	French	OS2006	MAP vs MAP + Zoledronate	RCT	III	315	156	191	249	N/A	N/A
5	Bielack et al,[22] 2015	17 countries	First results of EURAMOS-1	MAP vs MAP + Alfa-2b	RCT	III	716	359	542	N/A	N/A	591
6	Ferrari et al,[23] 2012	Italian	ISG/OS-1	MAP vs MAPI	RCT	N/A	246	123	N/A	N/A	147	181
7	Meyers et al,[24] 2005A	USA	–	MAP vs MAPI		N/A	677	172	471	N/A	431	N/A
	Meyers et al,[24] 2005B		–	MAP vs MAP + M	RCT							
	Meyers et al,[24] 2005B		–	MAP vs MAP-M								

AP = doxorubicin-cisplatinum, EI = etoposide-ifosfamide, M = high-dose methotrexate, MAP^+ = MAP plus ifosfamide and etoposide, or other adjuvant therapy drugs, N/A = not available, RCT = random controlled trial.

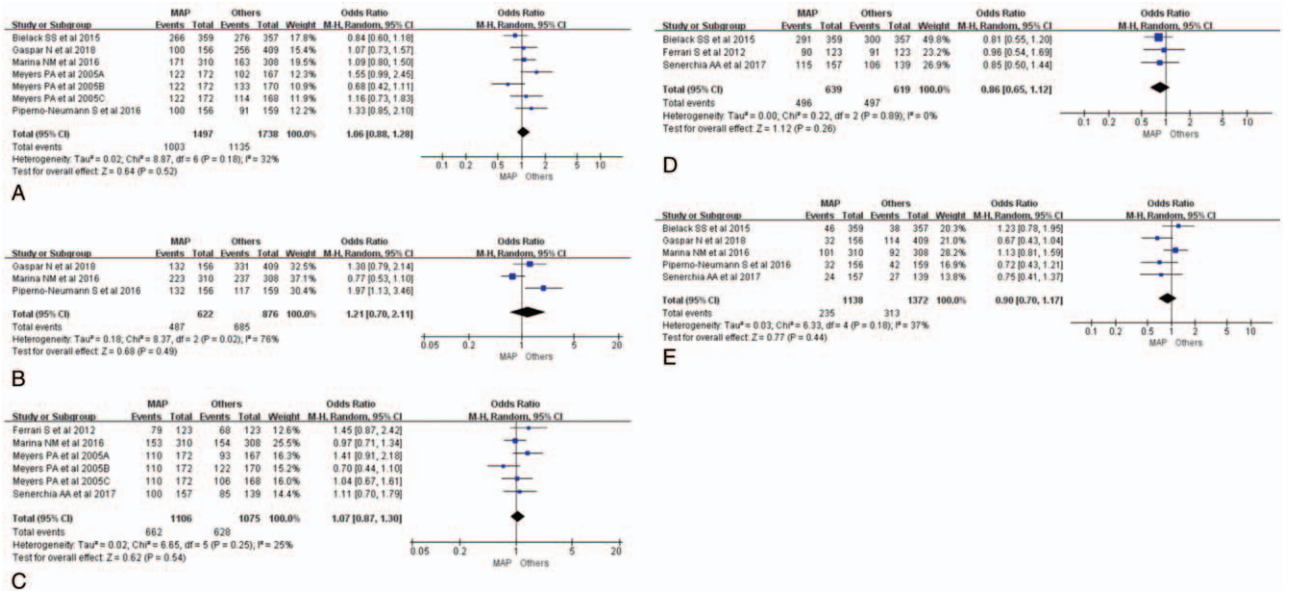

Figure 1. Meta-analysis of survival rate between MAP and other chemotherapy strategies. (A) Forest plot (RE) of 3-year EFS rates between MAP and other chemotherapy strategies. (B) Forest plot (RE) of 3-year OS rates between MAP and other chemotherapy strategies. (C) Forest plot (RE) of 5-year EFS rates between MAP and other chemotherapy strategies. (D) Forest plot (RE) of 5-year OS rates between MAP and other chemotherapy strategies. (E) Forest plot (RE) of mortality rates between MAP and other chemotherapy strategies. EFS = event-free survival, FE = fixed effect, MAP$^+$ = MAP plus ifosfamide and etoposide, or other adjuvant therapy drugs, MAP = methotrexate + doxorubicin + cisplatinum, OR = odds ratio, OS = overall survival, RE = random effect, RR = risk ratio.

3.3. Meta-analysis of mortality rates

For 5 studies, the data of mortality rate to chemotherapy was reported.[18–22] The rate of mortality was 20.7% (235/1138) in the MAP group versus 22.8% (313/1372) in other group. No statistically significant difference was also seen between the 2 chemotherapy treatments (OR = 0.90, 95% CI: 0.70–1.17, $Tau^2 = 0.03$; $Chi^2 = 6.33$; df = 4 [$P = .18$]; $I^2 = 37\%$, $Z = 0.77$ [$P = .44$]; Fig. 1E), suggesting that the MAP strategies did not decrease mortality rate of tumor to the chemotherapy which was highly correlated with longer survival.[18–22] FE model of meta-analysis is not suitable for dealing with the data of mortality rate for the existence of heterogeneity ($I^2 = 37\%$). The funnel plot was shown in Supplemental Figure 1E, http://links.lww.com/MD/C970.

3.4. Meta-analysis of toxicity incidence rates

Seven kinds of chemotherapy toxicities, including neutropenia, thrombocytopenia, febrile neutropenia, cardiac toxicity, anemia, hypophosphatemia, mucositis, infection, were collected for evaluation (Fig. 2). Compared with other combination chemotherapy regimens, MAP chemotherapy regimen showed lower incidence rates of chemotherapy toxicities, especially in thrombocytopenia, febrile neutropenia, anemia, hypophosphatemia (Fig. 2B, C, E, and F). There was obvious heterogeneity among most of enrolled studies for the differences of chemotherapy drugs in each group (Fig. 2A–G). Though Harbord test statistic did not suggest obvious publication bias in funnel plot, the heterogeneity is moderate among studies (Supplemental Fig. 2A–H, http://links.lww.com/MD/C970). So, we just took RE model of meta-analysis to deal with all the data (Fig. 2A–H).

Neutropenia was still the most common chemotherapy side effect, the incidence rates of 2 groups were 85.9% (498/580) and 93.3% (533/571).[20,21,23] The forest plot could be seen in Figure 3A, and the overall outcome of the analysis were summarized at the bottom of it (OR = 0.42, 95% CI: 0.09–1.42, $Tau^2 = 1.59$; $Chi^2 = 18.58$; df = 2 [$P < .0001$]; $I^2 = 89\%$, $Z = 1.12$ [$P = .26$]; Fig. 2A). The neutropenia difference of OR value is much more pronounced in the synchronized chemotherapy group (OR = 0.09, 95% CI: 0.04–0.23; Ferrari et al, 2012) than continuous chemotherapy (OR = 0.82, 95% CI: 0.48–1.20; Marina et al, 2016) or chemotherapy combined with other drugs (OR = 1.02, 95% CI: 0.29–3.60; Piperno et al, 2016). However, the overall outcome of analysis about neutropenia was of no statistical significance. Similar analysis results were also displayed as forest plots in Figure 2D, G, and H.[20,21,22]

Three studies related to the information of thrombocytopenia were put into practice of meta-analysis.[20,21,23] The detail of the result was shown in Figure 2B. It illustrated that there was statistical significant difference between the 2 chemotherapy treatments (OR = 0.43, 95% CI: 0.21–0.89, $Tau^2 = 0.35$; $Chi^2 = 13.35$; df = 2 [$P = .001$]; $I^2 = 85\%$, $Z = 2.27$ [$P = .02$]; Fig. 2B), suggesting that the controlled chemotherapy strategies increased thrombocytopenia incidence rate of patients which might be correlated with survival time and quality of life. Similar analysis results of statistical significance could also be seen in febrile neutropenia, anemia, and hypophosphatemia.[18,20,21,23] The forest plots could be seen in Figure 2C, E, and F, and the results of the analysis were gathered at the bottom of them.

3.5. Clinical data observation and analysis

Between April 14, 2008, and June 30, 2013, 115 patients were collected from 4 different hospitals in Shandong province of China (MAP, n = 56; MAP$^+$, n = 48; PST, n = 11). All the OS time of patients could be collected from corresponding hospital or

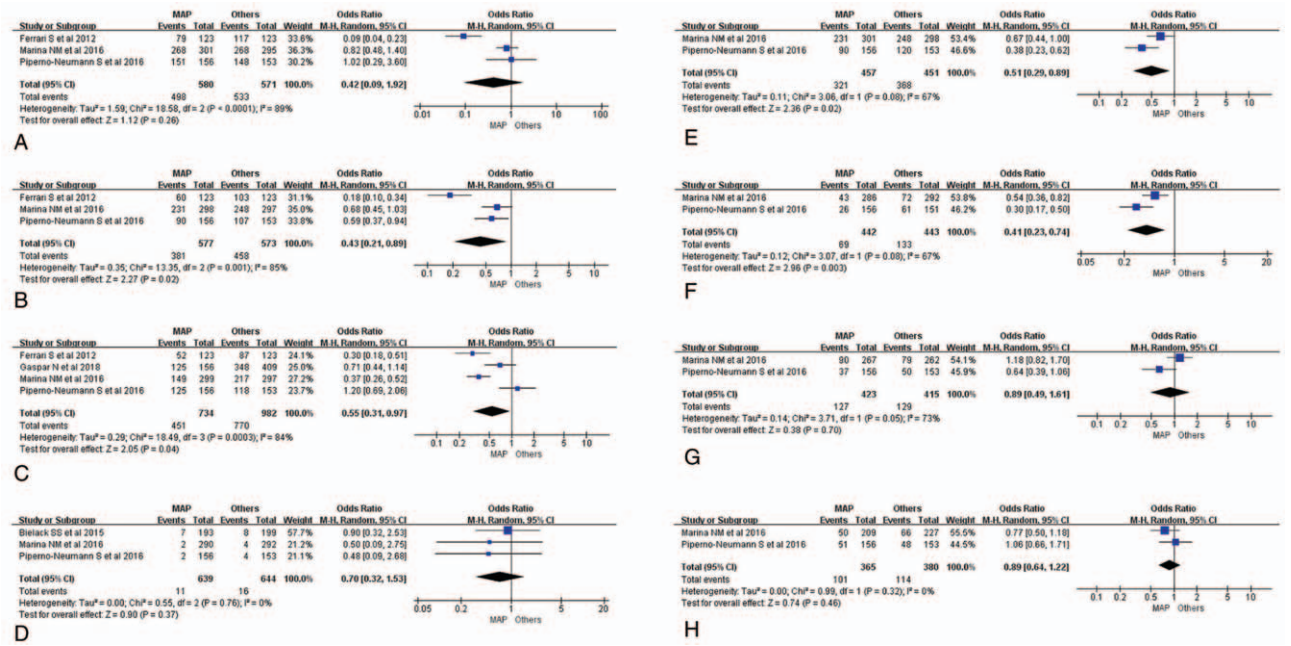

Figure 2. Meta-analysis of all kinds of toxicity rates among chemotherapy strategies. (A) Forest plot (RE) of grade 3/4 neutropenia incidence rates between MAP and other chemotherapy strategies. (B) Forest plot (RE) of grade 3/4 thrombocytopenia incidence rates between MAP and other chemotherapy strategies. (C) Forest plot (RE) of grade 3/4 febrile neutropenia incidence rates between MAP and other chemotherapy strategies. (D) Forest plot (RE) of cardiac toxicity incidence rates between MAP and other chemotherapy strategies. (E) Forest plot (RE) of grade 3/4 anemia incidence rates between MAP and other chemotherapy strategies. (F) Forest plot (RE) of grade 3/4 hypophosphatemia incidence rates between MAP and other chemotherapy strategies. (G) Forest plot (RE) of grade 3/4 mucositis incidence rates between MAP and other chemotherapy strategies. (H) Forest plot (RE) of grade 3/4 infection incidence rates between MAP and other chemotherapy strategies. EFS = event-free survival, FE = fixed effect, MAP$^+$ = MAP plus ifosfamide and etoposide, or other adjuvant therapy drugs, MAP = Methotrexate + doxorubicin + cisplatinum, OR = odds ratio, OS = overall survival, RE = random effect, RR = risk ratio.

relatives of the patient. Baseline characteristics of all enrolled patients were gathered in Table 2. Fifty-eight patients were female and 57 were male. The survival analysis of 115 patients was put into practice and the details were displayed in Figure 3A and B. Metastasis remains the most significant factor in the prognosis of patients, especially for brain metastasis (Fig. 3A). The Kaplan–Meier survival curves were obviously separated from each other, which *P* value was of statistical significance (Fig. 3A).

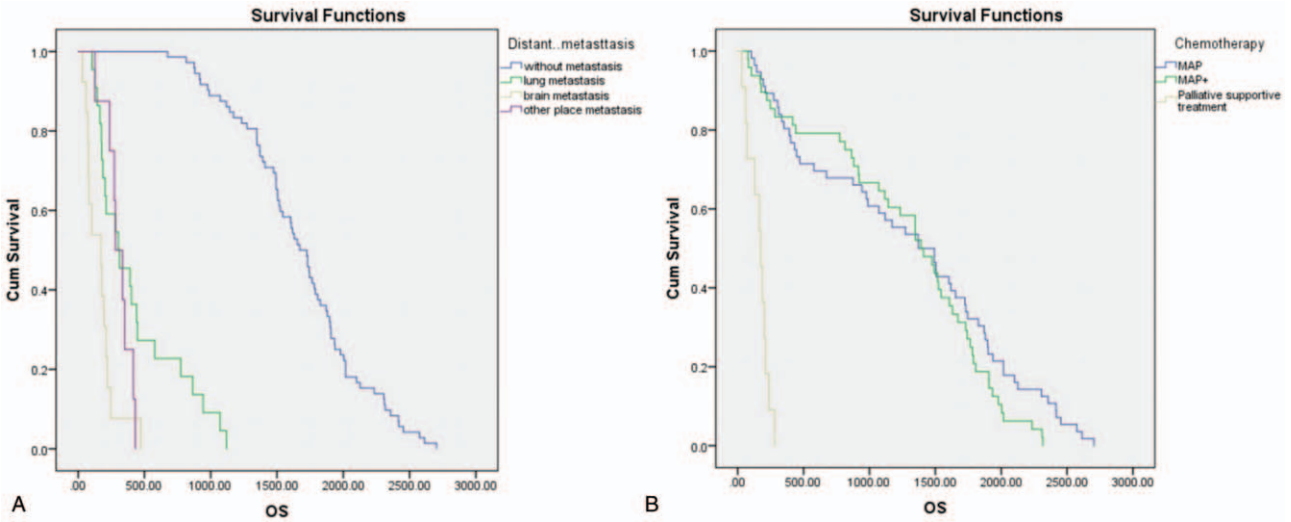

Figure 3. Kaplan–Meier curve of overall survival for 115 patients. (A) Kaplan–Meier curve of overall survival by metastases status at registration. (*P*1 = .000 [without metastasis vs lung metastasis]; *P*2 = .000 [without metastasis vs brain metastasis] *P*3 = .000 [without metastasis vs other metastasis]). (B) Kaplan–Meier curve of overall survival by treatment regimens. (PST = palliative supportive treatment; *P*1 = .151 [MAP vs MAP+]; *P*2 = .000 [MAP vs PST]; *P*3 = .000 [MAP$^+$ vs PST]). EFS = event-free survival, FE = fixed effect, MAP$^+$ = MAP plus ifosfamide and etoposide, or other adjuvant therapy drugs, MAP = methotrexate + doxorubicin + cisplatinum, OR = odds ratio, OS = overall survival, PST = palliative supportive treatment, RE = random effect, RR = risk ratio.

Table 2

Baseline characteristics of all enrolled patients.

	Overall	MAP	MAP+	Palliative supportive treatment (PST)
Sex	56	48	11	
Male	57	27	26	4
Female	58	29	22	7
Age				
≤18	95	46	42	7
>18	20	10	6	4
Site				
Femur	73	40	28	5
Tibia	34	15	15	4
Humerus	11	5	4	2
Other	2	1	1	0
Distant metastasis				
Without metastasis	72	37	35	0
Lung metastasis	22	9	7	6
Brain metastasis	13	5	5	3
Others	8	5	1	2
Histological				
Osteoblastic	67	33	34	0
No pathological information	45	20	14	11
Others	3	3	0	0

Histological classification was based on diagnostic biopsy according to the WHO 2002 classification of osteosarcoma.
MAP+ = MAP plus ifosfamide and etoposide, or other adjuvant therapy drugs, MAP = methotrexate, doxorubicin, and cisplatin.

Patients receiving chemotherapy (MAP or MAP+) had a better prognosis than patients who had just received palliative supportive treatment (Fig. 3B), while the difference between MAP and MAP+ treatment approaches, compared in pairs, was of no obvious significance ($P = .151$).

4. Discussion

As is known to all, osteosarcoma is the most common bone malignant tumour in children and adolescents and is associated with high mortality. Surgery, chemotherapy, and selective radiotherapy are still the main treatments for patients with osteosarcoma.[6–12] The 3-year EFS for high-grade osteosarcoma with multidrug chemotherapy and resection was reported to be 60% to 70%.[22,24,31,32] Chemotherapy combination, named MAP, including cisplatin, doxorubicin, and high-dose methotrexate, was mainly used for the therapy of osteosarcoma,[31,33–39] while MAP+, used for the treatment of patients with metastatic disease, seemed to improve EFS.[40–42] However, the conclusion was supported in individual clinical trials and was still controversial in many randomized controlled trials.[22,23,24,43] So, we performed this analysis and clinical observation to verify whether MAP and MAP+ have significant differences on the survival of patients.

We took the evaluation of survival time of patients with osteosarcoma as the primary evaluation index. Seven randomized trials including 3433 participants met the inclusion criteria.[18–24] The characteristics of them were listed in Table 1. As each clinical trial was collected from a different research center, the heterogeneity among the data was inevitable. So, we took a REs model to deal with the data first. The addition of mifamurtide to the MAP chemotherapy regimen for patients with localized osteosarcoma resulted in improved OS.[24] A meta-analysis of the extracted data revealed that there was no statistically significant difference in 3EFS, 3OS, 5EFS, 5OS, and mortality rates among osteosarcoma patients when MAP was compared with MAP+ regimen (Fig. 1A–E). Funnel plots were provided in Supplemental Figure 1A–E, http://links.lww.com/MD/C970. The value of I^2 in Figure 1A–D displayed the existence of heterogeneity. Though Harbords test statistic did not suggest obvious publication bias in funnel plot, the heterogeneity is moderate among studies (Supplemental Fig. 1A–D, http://links.lww.com/MD/C970). So, we just took RE model to deal with all the data (Fig. 1A–E). The FE model is not suitable for most of the data. The results of the comprehensive meta-analysis were consistent with the results obtained in each clinical trial.[18–24]

Compared with other combination chemotherapy regimens (MAP+), MAP chemotherapy regimen showed lower incidence rates of chemotherapy toxicities, especially in thrombocytopenia, febrile neutropenia, anemia, hypophosphatemia (Fig. 2B, C, E, and F) with statistical significant differences.[18–24] It meant that there was no significant difference in the prognosis survival of osteosarcoma between the MAP and MAP+ regimens, while the incidence of chemotherapy toxicities in MAP regimen was lower. The similar conclusion of OS time of patients, treated by MAP and MAP+ respectively, could be verified by the analysis of 115 patient's survival data (Fig. 3B). The data used for this meta-analysis represented a wide variety of sample sizes. It is the first time that 3-EFS, 3-OS, 5-EFS, 5-OS, mortality rates, and chemotherapy toxicities were evaluated together.

In recent years, many studies have shown that the development and prognosis of osteosarcoma is a pathological process involving multiple genes and factors. Although basic research on tumor markers has progressed rapidly in the field of osteosarcoma, treatment methods have changed little in clinical work.[1–5] Although various clinical trials for the treatment of osteosarcoma have been carried out gradually, there has been no significant improvement in the prognosis of patients with osteosarcoma.[18–24,44] The treatment of osteosarcoma seems to reach an apparent plateau. The development of strategies to better understand the pathological biology of this tumor might

aid in the identification of drug targets.[45] In view of the success of PD-1 targeted drugs in the treatment of malignant melanoma,[46–48] we also hope for the emergence of new targeted drugs for osteosarcoma treatment.

5. Conclusions

Compared with other chemotherapy combination, MAP regimen remained the preferred option for osteosarcoma chemotherapy, which was verified by clinical observation.

5.1. Ethical approval

We declared that all procedures involved in this study about human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. The ethical issues involved in the article have been filed and approved by the corresponding hospital (Ethics Committee of Qianfoshan Hospital of Shandong Province). The chemotherapy regimens involved in the clinical data in the article are in line with the chemotherapy regimen recommended by the NCCN guidelines.

Author contributions

The corresponding author (Yuan Tian) had full access to all data in the study and all authors had final responsibility for the decision to submit for publication. Dapeng Yu, Shuisheng Zhang, Deguo Xu, and Alei Feng had the full data of the paper. Dapeng Yu, Alei Feng, and Yantao Mao were responsible for the collection of clinical data. Qingshan Zhu did the literature search, data gathering, and writing of the report. Yi Zhao, Yajuan Lv, Cuiping Han, and Rujun Liu helped with study design, data collection and checked the references.

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Data curation: Dapeng Yu, Shuisheng Zhang, Alei Feng, Deguo Xu, Qingshan Zhu, Yantao Mao, Yajuan Lv, Cuiping Han, Rujun Liu.

Formal analysis: Shuisheng Zhang, Qingshan Zhu, Yantao Mao, Rujun Liu.

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