REVIEW

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Evaluating the Outcome and Patient Safety of Methotrexate, Doxorubicin, and Cisplatin Regimen for Chemotherapy in Osteosarcoma: A Meta-Analysis

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Abstract

Background: Several studies of multi-drug regimens for osteosarcoma have shown different efficacies and are still controversial. Meanwhile, chemotherapy options have remained largely unchanged over a couple of decades. This study is designed to ascertain the outcome and safety of Methotrexate, Doxorubicin, and Cisplatin regimen for chemotherapy in osteosarcoma patients through the utilization of meta-analysis. **Methods:** We interrogated trials that compared the MAP regimen with other regimens as chemotherapy for osteosarcoma from several databases encompassing PubMed, Science Direct, and grey literature (Google Scholar) until December 2022. The analyzed outcomes including Event-Free Survival (EFS), Overall Survival (OS), Tumor Necrosis (TN) rate, and Adverse Event (AE) were then analyzed using RevMan 5.4 software in fixed or random effect models. **Results:** Our meta-analysis comprised 8 prospective articles that evaluated a cumulative number of 2920 OS patients. The analysis results indicated no meaningful difference in 5-year EFS (OR=0.99, 95% CI=0.77–1.27, [P = 0.91]) and neoadjuvant chemotherapy response (TN) (OR=0.76, 95% CI=0.49-1.17, [P = 0.22]) between the MAP and control groups. Furthermore, 5-year OS analysis revealed a significant association in the control group (OR=0.82, 95% CI=0.68-0.99, [P = 0.04]). However, the control group was associated with statistically meaningful AE compared to the MAP group, particularly in thrombocytopenia (OR=0.46, 95% CI=0.23-0.90, [P = 0.02]) and fever (OR=0.34, 95% CI=0.26-0.46, [P < 0.00001]). **Conclusion:** The present meta-analysis showed that the MAP regimen remains preferable in treating osteosarcoma patients despite no significant outcome compared to the other regimens considering the less frequent AE in the MAP regimen.

Keywords: Chemotherapy- event-free survival- MAP- meta-analysis- osteosarcoma- overall survival

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Introduction

Osteosarcoma or Osteogenic Sarcoma is the most prevalent neoplasm originating in the bones, primarily impacting the pediatric and adolescent population. While it represents the most frequent form of bone malignancy, it remains classified as a rare disease with an annual occurrence of 2-4 individuals per million [1,2]. Chemotherapy was implemented as a therapeutic approach for osteosarcoma during the early 1970s. At first, osteosarcoma displayed resistance towards chemotherapy; however, subsequent findings on the effectiveness of adriamycin and high-dose methotrexate agents brought favorable outcomes among osteosarcoma patients [3–5]. Subsequently, additional therapeutic agents such as cisplatin, ifosfamide, and cyclophosphamide have demonstrated efficacy in the eradication or induction of regression in neoplastic growths [3]. Combination therapies utilizing these agents have markedly enhanced the overall survival rate of individuals afflicted with osteosarcoma [4]. Nevertheless, in spite of these advancements, there has been a lack of progress in the general prognosis for patients diagnosed with osteosarcoma over the last four decades [5].

Methotrexate, doxorubicin, cisplatin, ifosfamide, gemcitabine, decitabine, etoposide, and vincristine are the most frequent agents to be used as the treatment for osteosarcoma [6,7]. The Indonesian Committee of Cancer (KPKN) has adopted the National Comprehensive Cancer Network (NCCN) guidelines to approve methotrexate, doxorubicin, cisplatin, and ifosfamide as the first-line treatment of choice for osteosarcoma [8,9]. These multiple drugs have been extensively employed in numerous studies utilizing two or more combinations such as doxorubicin + cisplatin (AP), doxorubicin + cisplatin + ifosfamide (API), methotrexate + doxorubicin + cisplatin (MAP), or methotrexate + doxorubicin + cisplatin + ifosfamide (MAPI) [10]. The 5-year survival rate of

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osteosarcoma has risen to a range of 70-80% from the implementation of these drug combinations in addition to surgical approaches. Consequently, the single-treatment approach in osteosarcoma is now deemed insufficient [11,12]. However, it is difficult to decide which is superior amidst these combinations while multiple studies revealed different efficacy outcomes. Additionally, multi-drug chemotherapy toxicity could affect the patients quality of life [13]. Hereby, we carried out a meta-analysis approach to assess the efficacy and safety of a specific combination of MAP regimen compared to other regimens as chemotherapy protocols for the treatment of osteosarcoma.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 was used as a guideline when compiling this meta-analysis. These guidelines were followed to guarantee the appropriate reporting about a randomized controlled trials (RCT) meta-analysis [14]. This study has been registered in the PROSPERO database (CRD42023482205).

Database searching

We ran an electronic database search using Google Chrome as the search engine software to distinguish all previously published RCT studies that investigated the use of multi-drug chemotherapy for osteosarcoma. Several databases such as PubMed, Science Direct, and grey literature (Google Scholar) were explored. The search strategy used several keywords, for PubMed we used ((“osteosarcoma”[MeSH Terms] OR “osteosarcoma*”[Title/Abstract] OR “osteosarcoma tumor*”[Title/Abstract] OR “osteogenic sarcoma*”[Title/Abstract]) AND (“loattrfree full text”[Filter] AND “loattrfull text”[Filter]) AND ((“neoadjuvant therapy”[MeSH Terms] OR “chemotherapy, adjuvant”[MeSH Terms] OR “methotrexate”[Title/Abstract] OR “adriamycin”[Title/Abstract] OR “doxorubicin”[Title/Abstract] OR “cisplatin”[Title/Abstract]) AND (“loattrfree full text”[Filter] AND “loattrfull text”[Filter]))) AND ((ffrft[Filter]) AND (fft[Filter])), while the keywords used for Science Direct was osteosarcoma AND adjuvant chemotherapy, and the keywords used for Google Scholar was Osteosarcoma or Osteogenic Sarcoma or Osteosarcoma Tumor and Adjuvant Chemotherapy or Neoadjuvant Chemotherapy or Methotrexate or Adriamycin or Doxorubicin or Cisplatin. The literature search was started in September 2023 and was limited to articles published up to December 2022. A manual search from other literature was also performed to obtain potential studies that were cited in other meta-analyses.

Inclusion criteria

All studies that were included must adhere to the subsequent criteria: (1) Randomized controlled trials article, (2) All patients were histologically diagnosed with osteosarcoma, and (3) The use of MAP regimen as one of the interventions.

Exclusion criteria

The criteria for exclusion were as follows: (1) Studies that overlapped with others or were reported by the same authors, (2) Incomplete data regarding treatments and outcomes, (3) Studies involving animals, (4) Studies that reported in a language other than English, and (5) Studies that classified as letters, case reports, case-control studies, editorials, or reviews.

Study selection

Two researchers (MDI and RHR) conducted the database search autonomously and obtained the articles that corresponded to our specified search terms. In the event of any discrepancies, they were resolved through discussion and reaching a consensus with all the authors involved (MDI, IGEW, and RHR). The final determination was solely derived from the concurrence of all the authors.

Data extraction

The name of the first author, the year of publication, the country of the studied population, the study design employed, the number of patients allocated to each group, the nomenclature of chemotherapy protocol, the name of specific drugs and their dosages, as well as the clinical outcomes were extracted from each article into a structured form. The primary outcome under analysis pertains to event-free survival (EFS), while the secondary outcomes encompass overall survival (OS), the tumor necrosis rate (TN), and the occurrence of severe adverse events (AEs). EFS was operationally confined to the period from patient randomization to the initial manifestation of radiographic or clinical progression, or demise. In a similar vein, OS was operationally confined to the period from patient randomization to death. Lastly, TN was operationally confined to the histopathological findings subsequent to neoadjuvant chemotherapy. A tumor necrosis rate of more than 90% is considered a good response, while a necrosis rate of less than 90% is considered a poor response based on the HUVOS score [15] while the severity of AEs were defined as WHO grade > 3 severity [16].

Quality assessment

The quality assessment of the included RCTs will be conducted by two reviewers (MDI and RHR) using the Cochrane risk-of-bias tool for randomized trials (RoB 2), which comprises seven criteria. These criteria encompass selection bias, performance bias, detection bias, attrition bias, reporting bias, and other forms of bias [17].

Data analysis

The analysis was performed utilizing Review Manager 5.4 software (The Cochrane Collaboration, UK). For the outcomes, odds ratios (ORs) of logarithmic alteration with 95% confidence intervals (CIs) were computed to assess the magnitudes of the impacts. We additionally employed either fixed or random effect model presumptions following the heterogeneity of the data. Heterogeneity below 50% will be adjusted with a fixed random effect model, otherwise, it will be adjusted to a random effect model. Inverted funnel plots were executed to identify any presence of publication bias.

Results

Study selection

The PRISMA flow diagram (Figure 1) revealed a total of 3991 studies that were initially acquired through the process of electronic and grey literature database searching. Amidst them, 311 were excluded as duplicated studies. After screening the titles and abstracts we excluded 3630 irrelevant studies, leaving 50 potential full-text articles to be assessed. Eventually, as many as 8 articles were included after excluding 6 non-RCT studies, 16 studies without MAP intervention, 13 phase II trial studies, 6 incomplete outcome data studies, and 1 study without intervention as the comparator. These 8 studies recruited 2920 osteosarcoma patients consisting of 1440 patients in the MAP group and 1484 patients in the control group (Table 1).

Event-Free Survival

Eight studies reported 5-year EFS from 2924 patients. These studies randomized 1440 patients into the MAP regimen and 1484 patients to other regimens [18-25]. The 5-year EFS rate was 56.11% (808/1440) in the MAP regimen group versus 55.45% (823/1484) in the other group. Despite the higher rate of 5-year EFS in MAP, there was no notable difference in 5-year EFS between the group receiving MAP regimen and the other group (OR=0.99, 95% CI: 0.77-1.27, [P = 0.91]) as illustrated in Figure 2. The fixed random effect model was deployed because the heterogeneity among these studies was considerably high (I^2: 59%; P = 0.02).

Overall Survival

The 5-year overall survival (OS) was reported in six studies comprised of 2119 patients [18,19,21,22,23,25]. A total of 1051 patients were randomized to receive the MAP regimen and 1068 patients received the other regimens. The 5-year OS rate was reported to be 65% (687/1051) in the MAP regimen versus 69% (741/1068) in the other group. In addition to the higher rates of OS in the other group, the analysis result also revealed a statistically significant association (OR=0.82, 95% CI: 0.68-0.99, [P = 0.04]) as illustrated in Figure 3. The fixed random effect model was utilized because of the low heterogeneity among these studies (I^2: 18%; P = 0.30).

Tumor Necrosis Rate

The histological response of neoadjuvant chemotherapy was determined from the tumor necrosis rate (TN) and classified as good (>90%) and poor (<90%) response according to the HUVOS score. TN rate was reported in four studies that collected 1115 histopathological samples after introducing MAP in 530 patients and other regimens in 585 patients as neoadjuvant chemotherapy [18-20,24]. The MAP regimen reported 45.47% of good response after being introduced as a neoadjuvant treatment. Meanwhile, the other group reported 53.16% of good response after being introduced as a neoadjuvant treatment. Despite a better response rate in the other group, the analysis result revealed no statistical difference in tumor necrosis rate between MAP regimen and other regimens as neoadjuvant chemotherapy (OR=0.76, 95% CI: 0.49-1.17, [P = 0.22]) (Figure 4). The random effect model was deployed due to the high heterogeneity among these studies (I^2: 59%; P = 0.06).

Toxicity

Six kinds of chemotherapy toxicities were collected for analyses, ranging from hematological aspects such as leukopenia, thrombocytopenia, and anemia (Figure 5, 6, 7), hepatological aspects such as increased SGOT/SGPT/ hypophosphatemia, hyperbilirubinemia (Figure 8), renal problems which manifested as disturbance of creatinine clearance (Figure 9), cardiac problem (Figure 10), infection (Figure 11), and fever (Figure 12) as the adverse events. Leukopenia became the most frequent toxicity, the incidence rate from both groups were 86.1% (899/1044), followed by the incidence rate of thrombocytopenia by 71.5% (753/1052), and the incidence of fever by 57.2% (508/887). However, compared to the other regimens, MAP demonstrated a lower incidence rate of toxicities,

Table 1. A Total Number of 2920 Osteosarcoma Patients were Recruited in 8 Studies, Consisting of 1440 Patients in the MAP Group and 1484 Patients in the Control Group

Author	Year	Region	Protocol	Regimen	Sample		Outcome
					MAP	Control	
Bramwell et al [18]	1992	Europe	EOI	MAP vs AP	99	99	EFS, OS, TN, AE
Ferrari et al [19]	2012	Italy/Europe	ISG/OS-1	MAP vs MAPI	123	123	EFS, OS, TN, AE
Meyers et al [20]	2005	USA	INT-0133	MAP vs MAPI	292	292	EFS, TN
Bielack et al [21]	2015	17 countries	EURAMOS-1	MAP vs MAPF	359	357	EFS, OS
Marina et al [22]	2016	17 countries	EURAMOS-1	MAP vs MAPIE	310	308	EFS, OS, AE
Senerchia et al [23]	2016	Brazil Argentina Uruguay	N/A	MAP vs MAPMC	157	139	EFS, OS
Bacci et al [24]	2001	Italy/Europe	IOR/OS-3 IOR/OS-5	MAP vs MAPI	79	142	EFS, OS, TN
Chou et al [25]	2009	USA	INT-0133	MAP vs MAPI+MT	21	24	EFS, OS, AE

MAP, methotrexate + adriamycin/doxorubicin + cisplatin; I, ifosfamide; E, etoposide; F, interferon; MC, metronomic chemotherapy; MT, Muramyl Tripeptide; EFS, event-free survival; OS, overall survival; AE, adverse event.

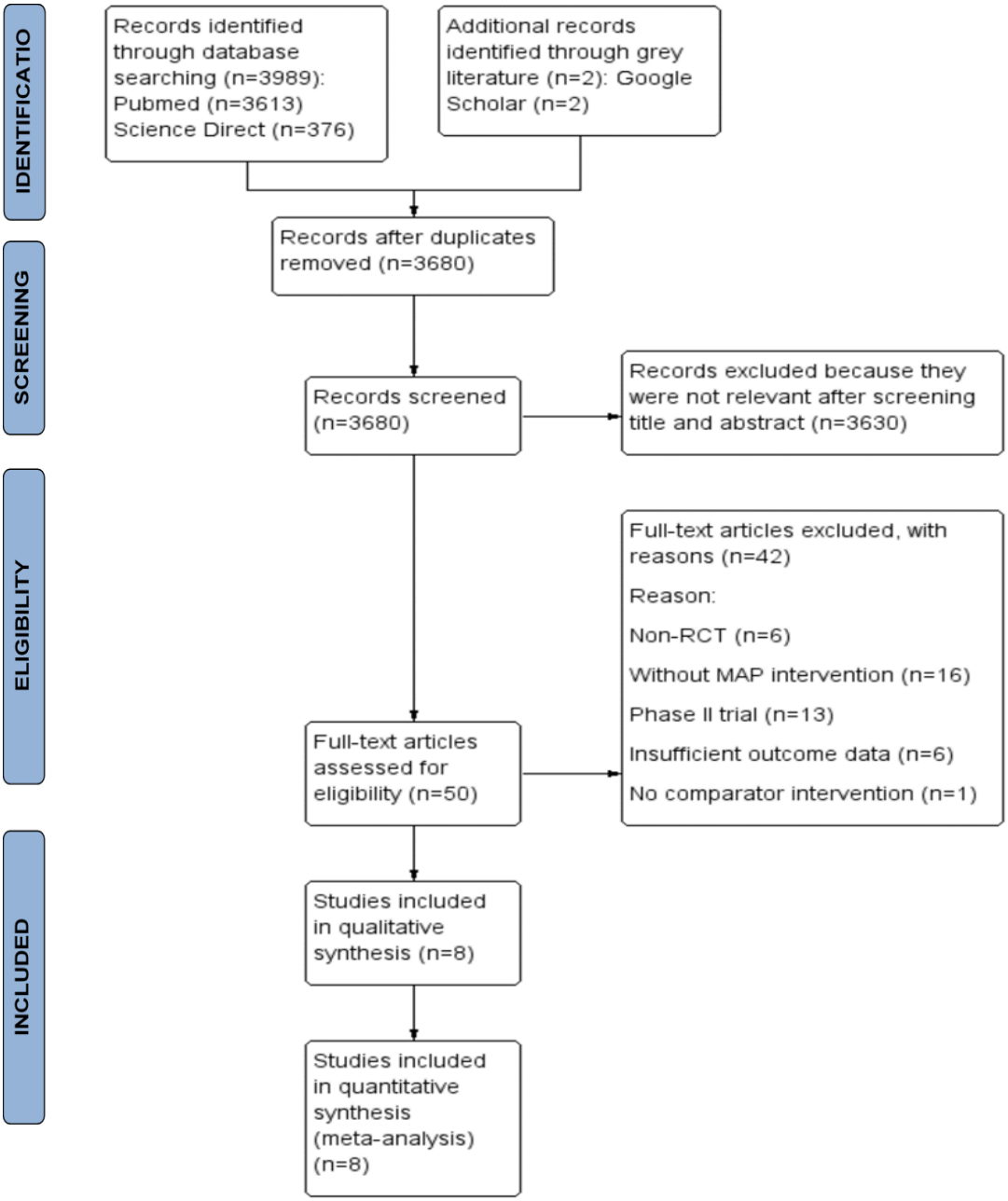

Figure 1. The PRISMA Flow Diagram of the Study Selection Process Included 8 Potential Articles.

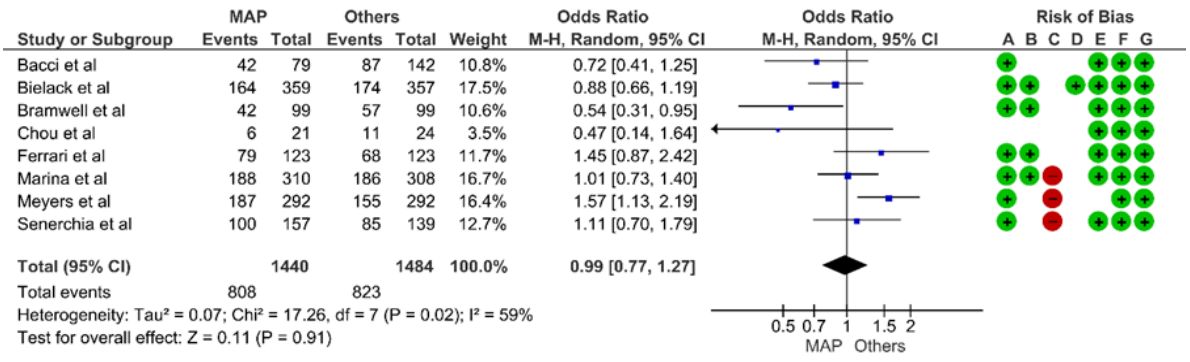

Figure 2. Forest plot (RE) of 5-year EFS between MAP and Other Regimens as Chemotherapy Strategies. EFS = event-free survival, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other= MAP + ifosfamide or etoposide or other adjuvant drugs, RE = random effect, OR = odds ratio.

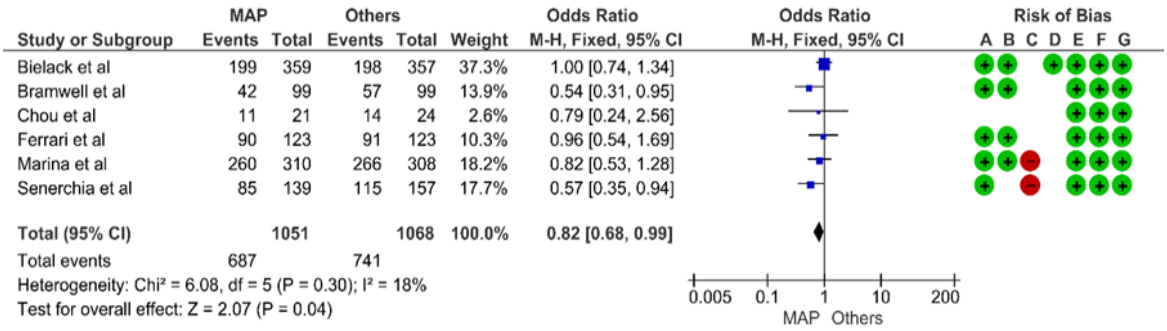

Figure 3. Forest Plot (FE) of 5-year OS between MAP and Other Regimens as Chemotherapy Strategies. OS = overall survival, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

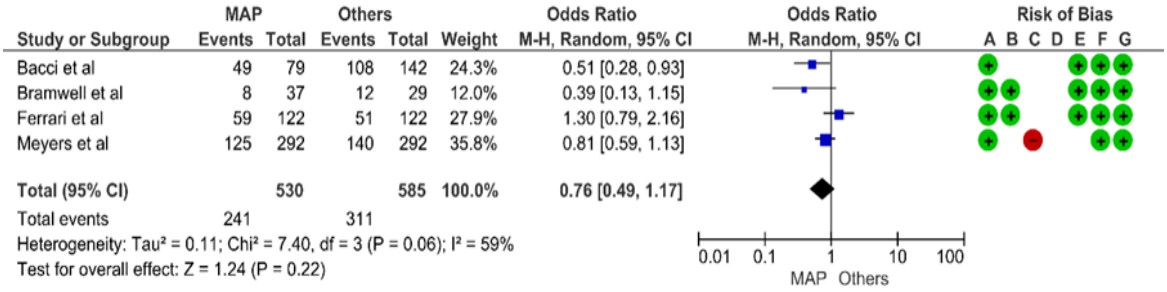

Figure 4. Forest Plot (RE) of TN Rate between MAP and Other Regimens as Neoadjuvant Chemotherapy. TN = tumor necrosis rate, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

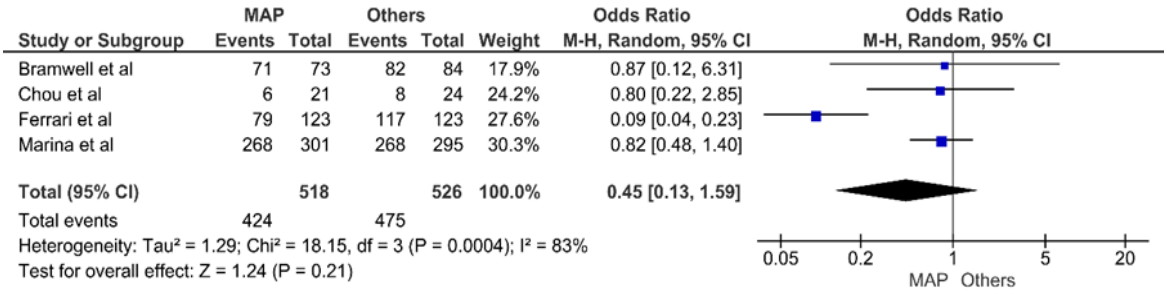

Figure 5. Forest Plot (RE) of AE Leukopenia between MAP and Other Regimens as Neoadjuvant Chemotherapy. AE = adverse event, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

particularly statistically significant in thrombocytopenia (OR=0.46, 95% CI:0.23-0.90, [P = 0.02]) and fever (OR=0.34, 95% CI:0.26-0.46, [P < 0.00001]) (Figure 6, 12).

Discussion

Osteosarcoma is a neoplastic condition originating from the bones and primarily impacting pediatric and

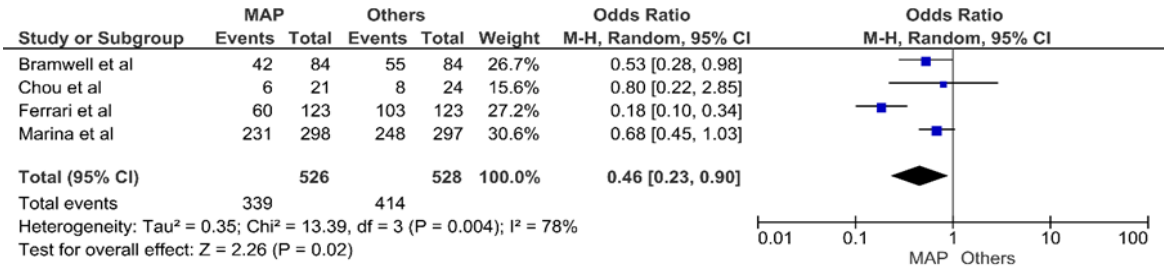

Figure 6. Forest Plot (RE) of AE Thrombocytopenia between MAP and Other Regimens as Neoadjuvant Chemotherapy. AE = adverse event, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

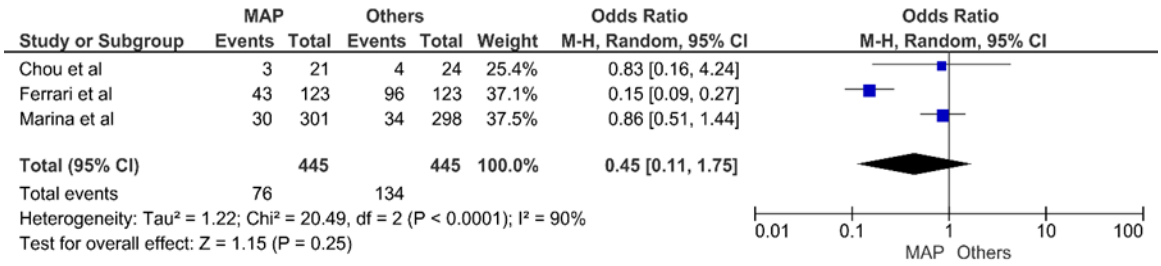

Figure 7. Forest Plot (RE) of AE Anemia between MAP and Other Regimens as Neoadjuvant Chemotherapy. AE = adverse event, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

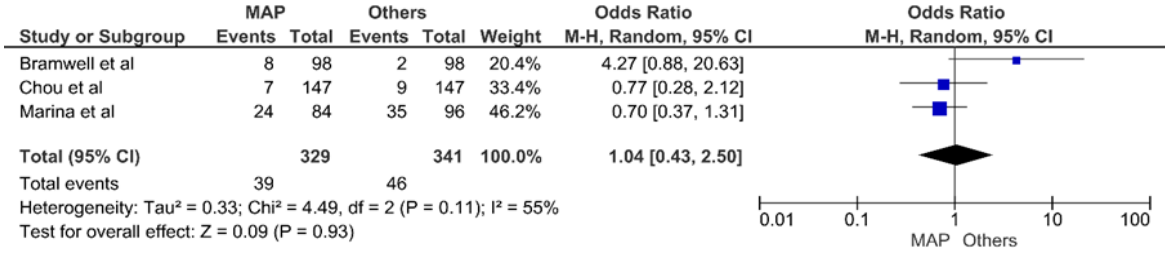

Figure 8. Forest Plot (RE) of Hepatic AE (increased SGOT/SGPT, hypophosphatemia, hyperbilirubinemia) between MAP and other regimens as neoadjuvant chemotherapy. AE = adverse event, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

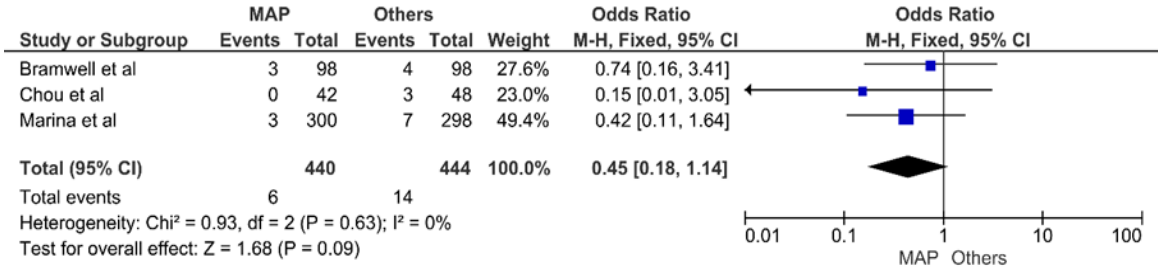

Figure 9. Forest Plot (RE) of Renal AE (creatinine clearance) between MAP and other regimens as neoadjuvant chemotherapy. AE = adverse event, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

adolescent populations. The advancements in surgical and systemic interventions, including neoadjuvant and adjuvant chemotherapy have culminated in remarkable enhancements in disease-free recurrence and overall survival rates [26]. However, the effectiveness of the therapy has reached a point of stagnation since the 1980s, and has exhibited incongruous outcomes in numerous randomized controlled experiments [1]. Chemotherapy combination such as MAP was mainly used for osteosarcoma patients, while MAP in addition to other drugs was used for patients with metastatic disease [18-20]. However, several randomized controlled trials reported different conclusions and remain controversial [18-25]. Therefore, we performed this meta-analysis

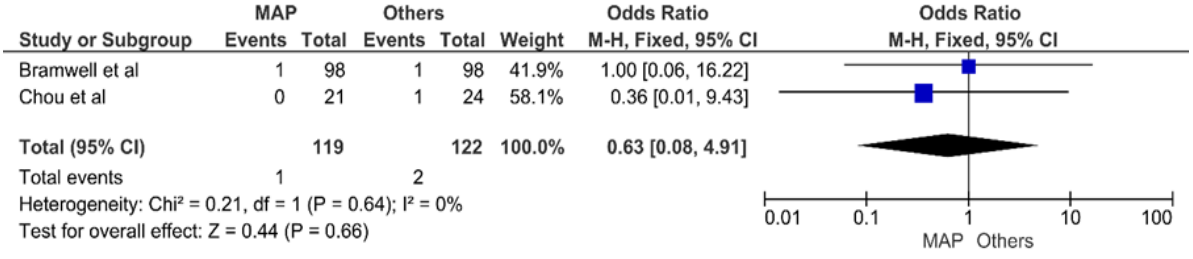

Figure 10. Forest Plot (RE) of Cardiac AE between MAP and Other Regimens as Neoadjuvant Chemotherapy. AE = adverse event, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

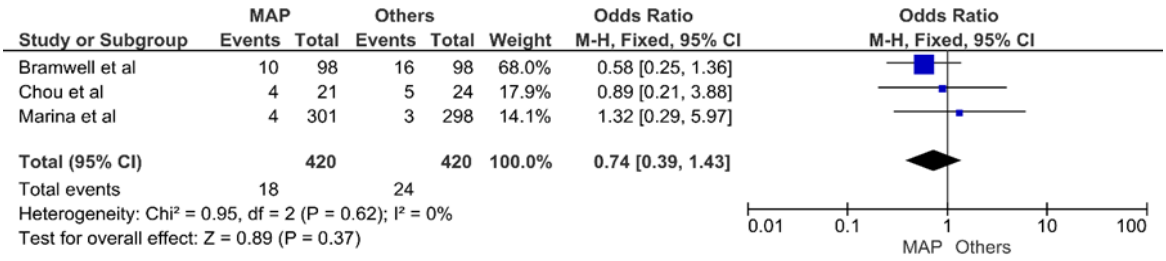

Figure 11. Forest Plot (RE) of AE Infection between MAP and Other Regimens as Neoadjuvant Chemotherapy. AE = adverse event, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

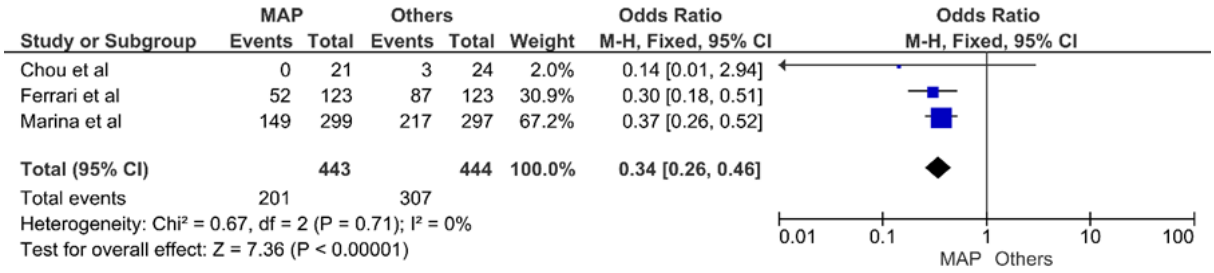

Figure 12. Forest Plot (RE) of AE Fever between MAP and Other Regimens as Neoadjuvant Chemotherapy. AE = adverse event, MAP = methotrexate + adriamycin/doxorubicin + cisplatin, Other = MAP + ifosfamide or etoposide or other adjuvant drugs, FE = fixed effect, OR = odds ratio.

to verify whether MAP combination significantly differs in efficacy and safety as a treatment strategy for osteosarcoma patients.

Our meta-analysis revealed no meaningful statistical discrepancy of 5-year EFS amidst osteosarcoma patients that received MAP regimen compared to other regimen (Figure 2). However, the 5-year OS observed in our meta-analysis showed a significant association in osteosarcoma patients who received other regimen group compared to MAP regimen (Figure 3). Additionally, our meta-analysis also revealed no statistical difference but a less frequent number of good response results (TN>90%) in osteosarcoma patients who received MAP regimen as neoadjuvant chemotherapy compared to other regimen (Figure 4). Kendall's T test for EFS (0.327) and OS (0.067) indicated no publication bias, while TN subgroup (0.000) displayed a publication bias.

Event-free survival rates amidst osteosarcoma patients are between 55 and 75%, which has not improved significantly over the last decade [27]. The survival rates change depending upon factors, for example, the phase of the illness, the age of the patient, and the histopathological reaction to chemotherapy. Our meta-analysis results are similar to several previous meta-analyses that compared MAP with another regimen as chemotherapy strategies for treatment in osteosarcoma patients. Yu et al reported no statistical significant difference in 3 and 5-year EFS and OS amidst osteosarcoma patients who received MAP compared to MAP+ regimen [28]. A network analysis by Zhang et al also reported no significant difference in EFS between osteosarcoma patients who received MAP regimen compared to MAPI. However, they also reported that MAPI was ranked first in OS and EFS compared to other regimens [29]. To our knowledge, the rate of tumor necrosis holds a significant role in evaluating the response of neoadjuvant chemotherapy as a meaningful prognostic factor in patients with osteosarcoma [15]. Patients with >90% tumor necrosis were classified as good responders, whereas patients with <90% were defined as poor responders. Neoadjuvant chemotherapy includes the addition of chemotherapy before resection, and they have advantages such as reducing the chance of surgical tumor invasion, eliminating the micrometastasis and avoiding metastasis caused by delayed surgery or low-resistance, evaluate the effect of chemotherapy and guide comprehensive treatment after surgery, as well as provide an early prognosis for the patients [30].

Despite the efficacy results aforementioned above, our study demonstrated that MAP regimen exhibited less frequent incidences of chemotherapy toxicities compared to the other regimens of chemotherapy, particularly a significant reduced association in thrombocytopenia and fever (Figure 6 and 12). Chemotherapy-induced unfavorable occurrences can exert a noteworthy influence on the quality of life of individuals afflicted with osteosarcoma. Negative occurrences such as nausea and vomiting, hepatotoxicity, anemia, neutropenia, and thrombocytopenia were discovered to be widespread in pediatric osteosarcoma patients enduring chemotherapy [13]. Factors linked with chemotherapy-induced liver toxicity comprised of increased chemotherapy quantities, elevated plasma methotrexate levels, and a more gradual pre-hydration velocity [31]. The quality of life of patients undergoing treatment for osteosarcoma was assessed in a prospective international study, which found that the disease itself and the treatment applied to the patients may negatively impact the patients quality of life [5]. Another study evaluated the quality of life of individuals

with cancer undergoing chemotherapy was reported symptoms such as nausea, vomiting, reduction in appetite, fatigue, constipation, and diarrhea might influence the patients quality of life [32]. It is crucial to comprehend the ramifications of chemotherapy-induced unfavorable occurrences on the quality of life of individuals afflicted with osteosarcoma to formulate suitable measures and enhance their comprehensive welfare [4,33].

In conclusion, considering the outcome and safety of chemotherapy strategies, our meta-analysis study demonstrated that the multi-drug combination of MAP remains a suitable option as a chemotherapy regimen. A more detailed comparison between each combination of multi-drug chemotherapy is needed to confirm which regimen is superior to another.

Author Contribution Statement

I Gede Eka Wiratnaya: Conceptualization, supervision, reviewing; Mohamad Dimas Ismail: Data curation, methodology, software, writing – original draft preparation, reviewing; Risang Haryo Raditya: Visualization, writing, reviewing, and editing.

Acknowledgements

Ethical Declaration

This research did not involve human subjects, therefore ethical clearance is not required.

Data Availability

The datasets created and analyzed in this study are available in public databases.

Study Registration

This meta-analysis has been registered in the PROSPERO database (CRD42023482205)

Conflict of Interest

The authors declare that they have no potential conflict of interest.

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