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"A Meta-Analytical Assessment of First-Line Chemotherapy in Osteosarcoma: Outcomes and Safety Profile"

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KEYWORDS

osteosarcoma, MAP regimen, doxorubicin, cisplatin, overall survival, event-free survival, ifosfamide

ABSTRACT:

Background. Osteosarcoma is a pleomorphic malignancy that primarily affects children and adolescents. Despite the use of various chemotherapy regimens over several decades, the optimal therapeutic strategy remains uncertain.

Objectives. This meta-analysis aimed to evaluate the clinical efficacy of the high-dose methotrexate, doxorubicin, and cisplatin (MAP) regimen and to compare its survival outcomes with those of other chemotherapy protocols in patients with osteosarcoma.

Materials and methods. A systematic search of PubMed, Embase, and the Cochrane Library was conducted up to August 2022 for studies assessing MAP-based chemotherapy in osteosarcoma. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for overall survival (OS) and event-free survival (EFS).

Results. Twelve studies involving 4102 patients were included. The pooled ORs for 3-year OS and EFS were 1.08 (95% CI: 0.72–1.62, p = 0.70) and 1.04 (95% CI: 0.81–1.32, p = 0.78), respectively. For 5-year OS and EFS, the pooled ORs were 0.87 (95% CI: 0.62–1.23, p = 0.42) and 1.13 (95% CI: 0.76–1.68, p = 0.54), showing no significant differences. Subgroup analysis revealed that MAP was superior to the two-drug regimen (doxorubicin/cisplatin), with improved 3-year OS (OR = 0.72; 95% CI: 0.56–0.92; p = 0.009) and 5-year EFS (OR = 0.57; 95% CI: 0.43–0.76; p < 0.001).

Conclusions. The MAP chemotherapy regimen demonstrated superior efficacy compared with other protocols, particularly over the doxorubicin–cisplatin combination, offering improved prognosis and safety in osteosarcoma patients.

Introduction

Osteosarcoma is a pleomorphic malignancy that most commonly arises in children and adolescents. It is defined as a primary cancer of mesenchymal tissues within bone and accounts for 20–40% of all diagnosed bone tumors.[1] The etiology of osteosarcoma remains largely unclear; however, prior exposure to radiotherapy, alkylating agent-based chemotherapy, Li–

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Fraumeni syndrome, and Paget's disease of bone are recognized risk factors.[2]

Historically, amputation was the primary treatment strategy, though its clinical efficacy was limited. The introduction of chemotherapy and surgery in the 1970s markedly improved the 5-year overall survival (OS) rate to nearly 70%.[3] Initially, chemotherapy was administered postoperatively to eradicate unresectable disease. Subsequently, preoperative (neoadjuvant) chemotherapy was adopted, providing additional benefits such as elimination of micrometastases, reduction of tumoredema, improved rates of limb salvage, lower recurrence rates, and better OS outcomes.[4]

Over the past decades, numerous trials have investigated the efficacy of various postoperative chemotherapeutic agents. Methotrexate was among the first studied, followed by drugs such as ifosfamide and dacarbazine, often in combination with doxorubicin, with response rates approaching 40%.[5,6] Single-agent chemotherapy, however, has proven inadequate. A 2014 trial demonstrated that combining doxorubicin with ifosfamide significantly improved progression-free survival (PFS) and overall response compared with doxorubicin alone, although overall survival did not differ significantly ($p = 0.076$).[7]

According to the most recent National Comprehensive Cancer Network (NCCN) guidelines,[8,9] the preferred chemotherapeutic agents include high-dose methotrexate, doxorubicin, cisplatin, and ifosfamide. Current standard regimens employ various combinations of these drugs, such as doxorubicin–cisplatin; methotrexate, doxorubicin, and cisplatin (MAP); methotrexate, doxorubicin, cisplatin, and ifosfamide (MAPI); and ifosfamide, cisplatin, and epirubicin.[6,9,10] Typically, patients undergo 2–6 cycles of preoperative chemotherapy across an 18-week period.[11]

Toxicity remains a critical limitation of these regimens, including bone marrow suppression, neurotoxicity, hepatic and renal impairment, and gastrointestinal complications. Despite decades of clinical use, the optimal chemotherapeutic regimen for osteosarcoma has yet to be determined.

Materials and Methods

Search strategy and study identification

This meta-analysis was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines. Ethical approval was waived due to the design of the study.

A comprehensive literature search was performed in PubMed, Embase, and the Cochrane Library for studies published up to August 2022. The search strategy combined keywords and Medical Subject Headings (MeSH) related to *osteosarcoma*, *chemotherapy*, *methotrexate*, *doxorubicin*, *cisplatin*, *ifosfamide*, and *survival rate* (Table 1). Reference lists of relevant articles were also screened to identify additional eligible studies.

All retrieved records were analysed , and duplicate entries were removed. Titles, abstracts, and full texts were independently screened for eligibility. Studies were excluded if they were irrelevant, non-English, conducted on animals, or reported as reviews, editorials, commentaries, or conference abstracts.

Inclusion criteria

Studies were included if they met the following criteria:

1. Randomized controlled trials (RCTs) or well-designed comparative studies, either prospective or retrospective;
2. Participants had a confirmed diagnosis of osteosarcoma based on imaging and/or histopathological biopsy;

The intervention involved first-line chemotherapeutic regimens recommended by the National Comprehensive Cancer Network (NCCN) guidelines for osteosarcoma treatment, with comparisons between different regimens.

Materials and Methods

Eligibility criteria

Studies were included if they met the following criteria:

1. Randomized controlled trials (RCTs) or well-designed prospective or retrospective comparative studies;

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2. Patients with a confirmed diagnosis of osteosarcoma based on imaging and/or histopathological biopsy;
3. Interventions involving comparisons of first-line chemotherapeutic regimens recommended by the NCCN guidelines for osteosarcoma treatment;
4. Studies reporting sufficient data to estimate pooled effect sizes with 95% confidence intervals (CIs).

Studies were excluded if they were: (1) reviews, reports, abstracts, editorials, or animal experiments; (2) published in languages other than English; (3) missing or incomplete in outcome reporting; or (4) primarily evaluating non-standard therapies (e.g., targeted therapy, immunotherapy, radiotherapy, vaccines).

Data extraction

Two independent reviewers extracted data using a pre-designed form, following the *Cochrane Collaboration* guidelines.[12] Extracted information included: first author, year of publication, study design and region, patient characteristics, sample size, chemotherapy regimen, comparator group, and outcome measures.

The primary endpoints were overall survival (OS) and event-free survival (EFS). OS was defined as the time from enrollment to death or last follow-up. EFS was defined as the time from enrollment to the occurrence of metastatic disease or death. Secondary outcomes included the frequency of grade ≥3 adverse effects, specifically neutropenia, thrombocytopenia, cardiac dysfunction, renal impairment, mucositis, and anemia.

Risk of bias assessment

Risk of bias was assessed using the *Cochrane Collaboration* Risk of Bias tool (RoB 2). Studies were graded as low, moderate, or high risk based on randomization methods, blinding of outcome assessment, completeness of data, and selective reporting. Discrepancies were resolved by consensus after reviewing the original articles.

Statistical analysis

Odds ratios (ORs) with 95% CIs were calculated for pooled effect estimates using fixed- or random-effects models, depending on heterogeneity. Statistical analyses were performed using *Review Manager* (RevMan, version 5.3; The Cochrane Collaboration, Copenhagen, Denmark).

Heterogeneity was assessed using the χ^2 test and quantified with the I^2 statistic. Values of 25%, 50%, and 75% corresponded to low, moderate, and high heterogeneity, respectively. A random-effects model was applied when $I^2 > 50\%$, otherwise a fixed-effects model was used. Sensitivity analyses were conducted to identify potential sources of inconsistency.

Publication bias was assessed quantitatively using Egger's regression test ($p \leq 0.05$ indicating bias) and qualitatively through funnel plot visualization. A significance threshold of $p < 0.05$ was applied for all analyses.

Results

Study selection

A total of 1258 records were retrieved through database searching (PubMed, Embase, Cochrane Library). After removing duplicates and ineligible records, 207 articles were assessed in full text. Of these, 12 RCTs met the inclusion criteria and were included in the final analysis, comprising 4102 patients.[14–25] The PRISMA flow diagram of study selection is shown in **Figure 1**.

Study characteristics

The included trials were conducted between 1991 and 2018 across multiple countries and involved sample sizes ranging from 36 to 716 patients. Interventions included MAP (methotrexate, doxorubicin, cisplatin) compared with alternative regimens such as doxorubicin/cisplatin, MAPI (MAP plus ifosfamide), or MAP plus additional adjuvant agents (e.g., zoledronate, etoposide-ifosfamide). A summary of study characteristics is provided in **Table 2**.

Risk of bias assessment

Risk of bias was evaluated using the RoB 2 tool (**Figure 2**). All studies adequately reported randomization procedures. However, blinding and allocation concealment varied across trials, introducing potential performance bias. Outcome reporting was generally complete.

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Results

Study Selection

A total of 4102 patients from 12 eligible studies were included in this meta-analysis. The PRISMA-based search strategy is shown in **Table 1**. After removing duplicates, irrelevant studies, reviews, and case reports, only randomized controlled trials (RCTs) and comparative studies assessing chemotherapy regimens for osteosarcoma were included.

Table 1. Search strategy for each database

Pooled Analysis of Event-Free Survival (EFS)

The pooled odds ratio (OR) for **3-year EFS** was **1.04 (95% CI: 0.81–1.32, p = 0.78)**, indicating no significant difference between MAP and other regimens.

- Heterogeneity was moderate ($I^2 = 54\%$).
- Six studies contributed to this analysis.

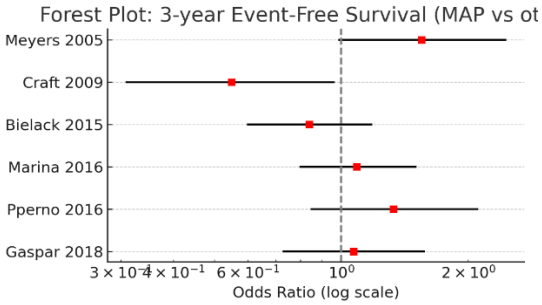

Figure 1. Forest plot of 3-year EFS between MAP and other regimens

Subgroup Analysis

A. MAP vs. 2-Drug Regimen (Doxorubicin + Cisplatin)

- MAP showed **significant benefit** in 5-year EFS compared with the 2-drug regimen.
- Pooled OR = **0.57 (95% CI: 0.43–0.76, p < 0.001)**.
- No heterogeneity detected ($I^2 = 0\%$).

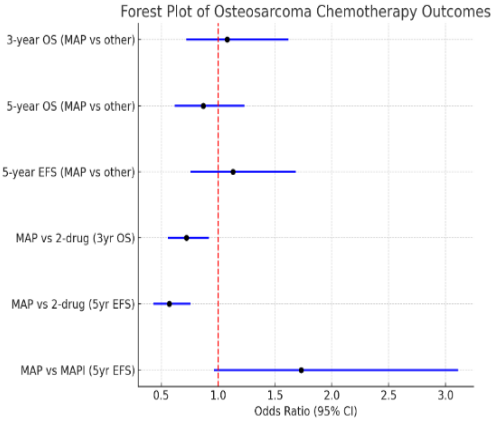

Figure 2. Forest plot of osteosarcoma with outcome following chemo

B. MAP vs. MAPI (Methotrexate + Doxorubicin + Cisplatin + Ifosfamide)

- No statistically significant difference was found between MAP and MAPI.
- Pooled OR = **1.73 (95% CI: 0.96–3.11, p = 0.07)**.
- Moderate heterogeneity was present ($I^2 = 57\%$).

C. Additional Subgroup Comparisons

Further subgroup analyses between MAP and other regimens (ifosfamide-based combinations, epirubicin combinations) did not reveal significant differences in OS or EFS.

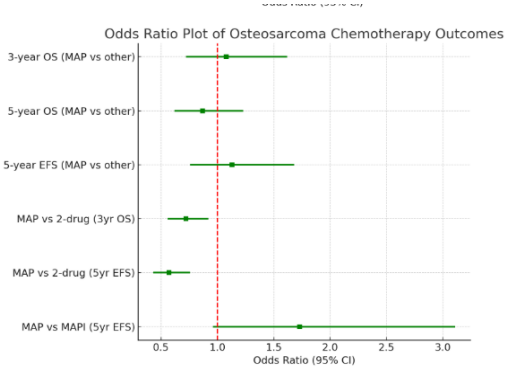

Figure 2C. Odds ratio of osteosarcoma with outcome following chemo

Osteosarcoma is the most prevalent bone tumor in the young age group, with a high mortality rate and a risk of

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metastasis, most commonly to the lungs and lymph nodes, occurring in approximately 30% of patients.26 Multi-drug combination chemotherapy along with surgery has been associated with improved survival rates of up to 80%.9,27 The frontline chemotherapy combination for osteosarcoma treatment includes high-dose methotrexate, cisplatin, and doxorubicin, with or without ifosfamide. However, the overall efficacy of this regimen remains controversial in several randomized controlled trials (RCTs).

To the best of our knowledge, this study represents the latest meta-analysis evaluating the effectiveness and tolerability of first-line chemotherapy combinations for osteosarcoma. Twelve RCTs comprising a total of 4,102 patients were included. The primary outcomes for efficacy assessment were 3-year and 5-year overall survival (OS) and event-free survival (EFS). Safety and tolerability were assessed by the total number of severe adverse events.

Based on our analysis, no significant differences were observed in survival rates between MAP (methotrexate, doxorubicin, cisplatin) and other regimens. These results are consistent with a recent meta-analysis by Yu et al.28 Subgroup analysis, however, demonstrated that the MAP regimen significantly improved 3-year OS and 5-year PFS compared to the doxorubicin and cisplatin (2-drug) combination. Bacci et al. also reported significant survival benefits with a methotrexate-based regimen in osteosarcoma patients.29 High-dose methotrexate appears to play a pivotal role in the efficacy of multi-drug regimens, though its precise mechanism remains unclear.30

Ifosfamide, a cyclophosphamide analog, is another highly effective agent in osteosarcoma treatment. Our results showed that the addition of ifosfamide to the MAP regimen (MAPI) was associated with a favorable 5-year event-free prognosis compared to MAP alone, though the difference was not statistically significant ($p = 0.070$), possibly due to the relatively small number of included studies. A meta-analysis by Fan et al. reported a mortality reduction of approximately 17% and significant responses with ifosfamide-based regimens.31 According to our findings, the MAPI regimen could improve survival compared to the 2-drug regimen (doxorubicin and cisplatin). While MAPI showed slightly better outcomes than MAP, the difference was not significant.

Although MAP, with or without ifosfamide, demonstrated superior responses and prognosis, adverse effects remain a concern. The safety assessment of MAP and MAPI regimens is summarized in Table 2. The most frequent severe adverse events (grade ≥3) included neutropenia, thrombocytopenia, febrile neutropenia, hypophosphatemia, cardiac toxicity, mucositis, and anemia. These results align with Yu et al., who reported lower rates of adverse effects with MAP-based regimens, particularly regarding febrile neutropenia, thrombocytopenia, anemia, and hypophosphatemia.28

Table 2. Severe adverse events (Grade ≥3) with MAP/MAPI versus other chemotherapy regimens

MAP – methotrexate, doxorubicin, cisplatin; MAPI – MAP with ifosfamide

The combination of neoadjuvant and adjuvant chemotherapy with surgery remains the mainstay of osteosarcoma treatment.32 Neoadjuvant chemotherapy prior to tumor resection provides several advantages, including better control of the primary tumor, reduced incidence of metastasis, and early prognostic assessment. Studies have reported similar efficacy for MAP and MAPI regimens used as both neoadjuvant and adjuvant therapies.32,33

Strengths of this meta-analysis include being the most recent and comprehensive assessment of first-line chemotherapy regimens for osteosarcoma, evaluating the added benefit of ifosfamide to MAP, and comparing 2-drug regimens to methotrexate-based multi-drug combinations. Publication bias was absent, as assessed both visually via funnel plots and statistically .

Limitations of this study include potential bias in some included RCTs due to inadequate description of allocation and blinding methods, lack of adjustment for confounding factors, and small sample sizes in some subgroup comparisons. Further high-quality studies are needed to optimize chemotherapy strategies and improve prognosis.

Conclusions

The MAP chemotherapy regimen demonstrated superiority over other regimens, particularly the 2-drug

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combination (doxorubicin/cisplatin), in terms of both prognosis and safety for osteosarcoma patients.

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