INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None.

Effect assessment of methotrexate in combination with other chemotherapeutic agents for osteosarcoma in children: a protocol for systematic review and meta-analysis

Xiang, RM[1]; Yan, JP[2].

Review question / Objective: **Osteosarcoma is a primary form of malignant bone tumor. It is commonly prevalent among children. Treating osteosarcoma with chemotherapy has had limited clinical outcomes due to side effects and the formation of drug resistance. Presently, a mixture of doxorubicin, cisplatin, ifosfamide, epirubicin methrotrexate, and other supplementary medications are used in osteosarcoma chemotherapy. Therefore, this study aims to investigate the clinical therapeutic effects of combining methotrexate with other chemotherapeutic agents to treat osteosarcoma in children.**
Condition being studied: **Chemotherapy is a crucial therapeutic method for treating cancer. A sufficient dose of intracellular chemo-drugs should be delivered to the cancer site to kill cancer cells and treat cancers effectively. There are four main chemo-drugs, namely, high-dose methotrexate, cisplatin, doxorubicin, and ifosfamide. Existing treatment protocols primarily combine two or more of these four. In recent years, methotrexate has indicated to be the most active drug. However, at the moment, it is unknown if it is essential to improve the survival rate of children diagnosed with osteosarcoma. The present systematic review and meta-analysis are conducted to explore the clinical effects of combining methotrexate with other chemotherapeutic agents to treat children diagnosed with osteosarcoma.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 January 2021 and was last updated on 8 January 2021 (registration number INPLASY202110024).

INTRODUCTION

Review question / Objective: **Osteosarcoma is a primary form of malignant bone tumor. It is commonly prevalent among children. Treating osteosarcoma with chemotherapy has had limited clinical outcomes due to side**

effects and the formation of drug resistance. Presently, a mixture of doxorubicin, cisplatin, ifosfamide, epirubicin methrotrexate, and other supplementary medications are used in osteosarcoma chemotherapy. Therefore, this study aims to investigate the clinical therapeutic effects of combining methotrexate with other chemotherapeutic agents to treat osteosarcoma in children.

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METHODS

Search strategy: A systematic search of the electronic databases given below from their beginning to November 19, 2020 will be conducted: English databases include PubMed, EMBASE, Web of Science, and the Cochrane Library. The Chinese databases include China National Knowledge Infrastructure, WanFang, and China Biomedical Database. The language restrictions were English and Chinese. The following MESH terms and related synonyms, including osteosarcoma*, chemotherapy*, methotrexate*, "randomized controlled trial", "randomised controlled trial", randomly*, and RCT* were combined in the search strategy to search the databases mentioned above.

Participant or population: Children (aged less than 15) diagnosed with osteosarcoma who received treatment with methotrexate-based combinational chemotherapy will be enrolled.

Intervention: The treatment of methotrexate-based combinational chemotherapy was administered to the experimental group.

Comparator: The control group was treated without methotrexate-based chemotherapy.

Study designs to be included: It is intended to collect randomized controlled trials (RCTs) on methotrexate combined with other chemotherapeutic agents in children diagnosed with osteosarcoma.

Eligibility criteria: 1. Types of studies It is intended to collect randomized controlled trials (RCTs) on methotrexate combined with other chemotherapeutic agents in children diagnosed with osteosarcoma. 2. Types of participants Children (aged less than 15) diagnosed with osteosarcoma who received treatment with methotrexate-based combinational chemotherapy will be enrolled. 3. Types of interventions and comparisons The treatment of methotrexate-based combinational chemotherapy was administered to the experimental group. Meanwhile, the control group was treated without methotrexate-based chemotherapy 4. Types of outcome measures 1) Major outcomes The major outcomes are (a) overall survival rate: is the time taken to die from any cause; (b) relapse-free survival rate: is the time taken for the recurrence of osteosarcoma following surgery; (c) response rate: denotes the classical response rates. 2) Minor outcomes The minor outcomes are (a) toxicities; (b) quality of life; (c) adverse events, including gastrointestinal manifestations and hepatotoxicity.

Information sources: A systematic search of the electronic databases given below from their beginning to November 19, 2020 will be conducted: English databases

include PubMed, EMBASE, Web of Science, and the Cochrane Library.

Main outcome(s): The major outcomes are (a) overall survival rate: is the time taken to die from any cause; (b) relapse-free survival rate: is the time taken for the recurrence of osteosarcoma following surgery; (c) response rate: denotes the classical response rates.

Additional outcome(s): The minor outcomes are (a) toxicities; (b) quality of life; (c) adverse events, including gastrointestinal manifestations and hepatotoxicity.

Data management: Two authors will use EndNote X9.0 software to manage the literature. They will plan to independently extract the following information into the pre-designed Excel 2019 table: first author's name, publication date, country, study method, sample size, sex ratio, mean age, intervention and comparison measures, dosage, number of response and non-response events, duration of therapy, follow-up time, and adverse events. All disagreements will be resolved through discussion.

Quality assessment / Risk of bias analysis: Two authors will evaluate the assessment of risk of bias based on the Cochrane Risk of Bias Tool. According to these criteria (generation of random sequence, allocation concealment, blind method, incomplete data, selective reporting outcomes, and additional biases), risk of bias will be classified into three levels: "low risk", "high risk", or "unclear". All disagreements will be resolved through discussion.

Strategy of data synthesis: Relative risk (RR) with 95% confidence interval (CI) will be used to calculate the summary statistic for dichotomous variables. Meanwhile, the mean difference (MD) or standardized mean difference (SMD) with 95% CI will be utilized to calculate as the summary statistic for continuous variables.

Subgroup analysis: If possible, subgroup analysis will be performed based on the different study characteristics, age, gender, ethnicity, and dosage.

Sensibility analysis: Sensitivity analysis will be used by sequentially eliminating one study at a time to determine the stability of our findings.

Language: English.

Country(ies) involved: China.

Keywords: osteosarcoma, methotrexate, chemotherapy, protocol, meta-analysis.

Contributions of each author:
Author 1 - Rong-Mei Xiang.
Author 2 - Jun-Ping Yan.