INPLASY PROTOCOL

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None declared.

Comparative Efficacy Assessment of Different Targeted Therapies and Combinations of Chemotherapeutic Agents for Osteosarcoma: A Bayesian Network Meta-analysis

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Review question / Objective: **Which chemotherapy regimen combination is most effective for the treatment of osteosarcoma? It is recommended to utilize neoadjuvant therapy in the treatment of osteosarcoma, according to the National Cancer Institute (NCI), and preoperative neoadjuvant therapy involves a combination of various anticancer medicines and chemotherapy as adjuvant therapy for radiation and surgery. Taking into consideration the limitations and inadequacy of traditional meta-analysis in assessing the efficacy of various drugs and agents concurrently, more data revealed that the combination therapy of ifosfamide and etoposide would considerably enhance the survival rate following surgery, intending to provide clinical practice guidelines and evidence, we used a network meta-analysis to assess and evaluate several combination chemotherapeutic treatments for osteosarcoma in randomized controlled trials (RCTs) of the most afflicted teenagers.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 September 2021 and was last updated on 09 September 2021 (registration number INPLASY202190028).

INTRODUCTION

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therapy for radiation and surgery. Taking into consideration the limitations and inadequacy of traditional meta-analysis in assessing the efficacy of various drugs and agents concurrently, more data revealed that the combination therapy of ifosfamide and etoposide would considerably enhance the survival rate following surgery, intending to provide clinical practice guidelines and evidence, we used a network meta-analysis to assess and evaluate several combination chemotherapeutic treatments for osteosarcoma in randomized controlled trials (RCTs) of the most afflicted teenagers.

Condition being studied: Osteosarcoma (OS) or osteogenic sarcoma (OGS) is a malignant bone tumor that is primarily formed from mesenchymal stem cells that can develop into bone cells and malignant bone-like tumors . The global incidence of OS is estimated to be 4 cases per million per year, with adolescents and children under the age of 20 accounting for roughly 20% of all primary bone malignancies . Furthermore, Ewing's sarcoma is the second most common cancer after osteosarcoma, accounting for around 16% of primary osteosarcoma cases . The femur contains 40% of OS, the tibia contains 20%, and the humerus contains the remaining 10%.

METHODS

Participant or population: Patients must be diagnosed with osteosarcoma.

Intervention: Chemotherapy regimen combinations include High-dose methotrexate(HDMTX), Doxorubicin(DOX), cisplatin(CP), cyclophosphamide(CY), etoposide(ETP), ifosfamide(IFO), Zoledronate(ZOL), vincristine(VCR), leucovorin(LV), Adriamycin(ADR), bleomycin(BLM), Actinomycin D(ActD), and Interferon alfa-2b(IFN-α-2b).

Comparator: The control treatment will include any types of interventions and placebo.

Study designs to be included: Only RCT (randomized controlled trials) will be included.

Eligibility criteria: If the following conditions are satisfied, the study will be accepted: I randomized controlled trials (RCTs), which include phases I, II, and III; Patients must be diagnosed with osteosarcoma, and chemotherapy in the form of surgery or radiation must be used (Iv) Original data or estimates of RR (pooled relative risks), ORs (odds ratios), WMD (weighted mean difference), MD (mean difference), SMD (standardized mean difference), or HR (hazard ratio) and corresponding 95 percent CI are required for results such as OS, EFS, the incidence of relapse events, and the number of lung-metastasis. (v) At least two different combinations of therapies are compared.The study will be deemed invalid if any of the following conditions are met: (i)experimental data is incomplete, (ii)a non-RCT experiment is conducted, (iii)Ewing's sarcoma participants are included, (Iv)other treatment methods such as vaccine therapy, immunotherapy, and receptor-targeted therapy are included, (V)a review, case-report, meta-analysis, post-hock, conference, report, animal experiment, responding, etc.

Information sources: For this network meta-analysis, we looked through four important databases: 877 papers comparing different therapies studying the effectiveness and adverse effects in osteosarcoma patients were found in Pubmed, Cochrane Central Register of Controlled Trials, International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov up to 30,7, 2021

Main outcome(s): Our primary outcomes are treatment efficacy (overall survival rate and event-free/or disease-free survival rate), and secondary outcomes, recurrence and lung metastasis as an evaluation indicator of side effects.

Quality assessment / Risk of bias analysis: The Cochrane Risk of Bias Tool will be used to assess the risk of bias in each

included study. This tool contains seven items, and each item is evaluated by categorizing it as low risk of bias, unclear risk of bias, or high risk of bias. For each included study, two independent investigators will assess the risk of bias. Any disagreements will also be resolved through discussion by a third author who has been invited.

Strategy of data synthesis: We use HR (with its 95% CrI) to perform pairwise and network meta-analysis to compare the therapeutic effects of different chemotherapy combinations on osteosarcoma at the trial level. 95% confidence interval is not including 1 or the two-tailed p-value less than 0.05 is considered to be statistically significant. We first draw the overall direct comparison network diagram. and then we use the random-effects model and the forest plot of the fixed effects model to compare direct and indirect comparisons, using the statistical package 'netmeta' in R (version 3.2.3). In the network meta-analysis, we use group-level data, consistency/ume model was built for consistent and inconsistent data, the binomial likelihood is used for the binary classification results, and the normal likelihood is used for the continuous results, In order to evaluate whether our simulation leads to the convergence of the algorithm, we need to use a tracking graph to compare each iteration, and evaluate our model by observing whether there is discontinuity between the early iterations and the later iterations. The other way is Gelman and Rubin's convergence diagnostic, as the number of iterations increases, the potential size reduction factor (PSRF) shown in the curve in the figure should gradually shrink to 1. And then the random-effects network meta-analysis model combines the results to form a continuous graph to generate the P grade score and the surface under the cumulative ranking curve (SURCA) in order to determine the ranking probability of different combinations having the best effect on the treatment effect of osteosarcoma, we used Cochran's Q test and I^2 test to detect the heterogeneity of the experiment, I^2 b 25%, Within 25-50%, N50% represents mild, moderate and severe heterogeneity, we also evaluated the consistency of inferential estimates using node-splitting from hierarchical modeling, mainly based on Makarov chain Monte Carlo simulation.

Subgroup analysis: None.

Sensitivity analysis: None.

Country(ies) involved: Japan.

Keywords: osteosarcoma; sarcoma; chemotherapy; bayesian; network meta-analysis.

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