INPLASY PROTOCOL

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Corresponding author:
Hongyan Wu

lcjyyzq@163.com

Author Affiliation:
Liaocheng People's Hospital

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The authors declare that they have no competing interests.

Autologous or allogeneic hematopoietic stem cells transplantation combined with high-dose chemotherapy for refractory neuroblastoma: a systematic review and meta-analysis protocol

Zhang, GH[1]; Li, BY[2]; Wu, HY[3].

Review question / Objective: **Is autologous or allogeneic hematopoietic stem cell (HSC) transplantation effective on tumor response, survival, and quality of life (QoL) in patients with refractory neuroblastoma?**
Condition being studied: **Autologous or allogeneic hematopoietic stem cell transplantation, high-dose chemotherapy, and refractory neuroblastoma.**
Information sources: **Relevant clinical trials of autologous or allogeneic HSC transplantation for the treatment refractory neuroblastoma patients will be searched in Web of Science, Cochrane Library, PubMed, Google Scholar, Embase, Medline, China National Knowledge Infrastructure, China Scientific Journal Database, Chinese Biomedical Literature Database and Wanfang Database from their inception to December 2020. Language is limited with English and Chinese.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 December 2020 and was last updated on 18 December 2020 (registration number INPLASY2020120092).

INTRODUCTION

Review question / Objective: **Is autologous or allogeneic hematopoietic stem cell (HSC) transplantation effective on tumor response, survival, and quality of life (QoL) in patients with refractory neuroblastoma?**

Rationale: **Neuroblastoma is a common solid malignant tumor in children. Despite the development of new treatment options,**

the prognosis of high-risk neuroblastoma patients is still poor. High-dose chemotherapy and hematopoietic stem cell (HSC) transplantation might improve survival of patients with refractory neuroblastoma. In this study, we aimed to summarize the efficacy of autologous or allogeneic HSC transplantation combined with high-dose chemotherapy for patients with refractory neuroblastoma through the meta-analysis.

Condition being studied: Autologous or allogeneic hematopoietic stem cell transplantation, high-dose chemotherapy, and refractory neuroblastoma.

METHODS

Search strategy: Experienced systematic review investigators will be invited to develop a search strategy, in order to perform a comprehensive search. The search terms include "neuroblastoma" or "refractory neuroblastoma" or "high-risk neuroblastoma" and "stem cell" or "stem cell transplantation" or "hematopoietic stem cell" or "hematopoietic stem cell transplantation" or "autologous hematopoietic stem cell transplantation" or "allogeneic hematopoietic stem cell transplantation" or "HSC" et al. The preliminary retrieval strategy for PubMed is provided in Table 1, which will be adjusted in accordance with specific databases.

Participant or population: Patients with histologically proved refractory neuroblastoma [High risk according COG (Children Oncology Group) or Refractory] were included in this study. No restrictions regarding age, gender, racial, region, education and economic status. Patients with other malignancies are not included.

Intervention: In the experimental group, refractory neuroblastoma patients must be treated with autologous or allogeneic HSC transplantation in combination with high-dose chemotherapy. There will be no restrictions with respect to dosage, duration, frequency, or follow-up time of treatment.

Comparator: In the control group, patients with refractory neuroblastoma must be treated with high-dose chemotherapy.

Study designs to be included: All available comparative clinical trials that investigated the efficacy and safety of autologous or allogeneic HSC transplantation for patients diagnosed with refractory neuroblastoma will be included in this systematic review.

Eligibility criteria: This study will include randomized controlled trials (RCTs) and prospective controlled clinical trials that investigated the efficacy and safety of autologous or allogeneic HSC transplantation for patients diagnosed with refractory neuroblastoma. Duplicated studies, papers without sufficient available data, non-comparative clinical trials, case reports and series, meta-analysis, literature reviews, meeting abstracts, and other unrelated studies will be excluded from analysis.

Information sources: Relevant clinical trials of autologous or allogeneic HSC transplantation for the treatment refractory neuroblastoma patients will be searched in Web of Science, Cochrane Library, PubMed, Google Scholar, Embase, Medline, China National Knowledge Infrastructure, China Scientific Journal Database, Chinese Biomedical Literature Database and Wanfang Database from their inception to December 2020. Language is limited with English and Chinese.

Main outcome(s): The primary outcomes will include: 1. Tumor response (complete response, very good partial response, and partial response). It will be assessed on day 60 after HSC transplantation. Such evaluations will include 123I-MIBG scan, CT/MRI, and urine catecholamine measurement, et al; 2. Overall survival (OS, from 1-, 3-, and 5-year after HSC transplantation), It will be measured from the date of randomization to death from any cause; 3. Event-free survival (EFS, from 1-, 3-, and 5-year after HSC transplantation). It will be measured from start of treatment until progression, death or start of another treatment.

Additional outcome(s): Secondary outcomes will include: 1. QoL obtained from the corresponding scale; 2. Safety assessment. Monitoring of mortality, toxicity (NCI Common Criteria), acute and chronic graft versus host disease, engraftment rate will contribute to safety assessment.

Data management: After screening the text, the two investigators (Guanghui Zhang and Baoyu Li) will independently extract the information contained in the eligible literature. The extracted data are as follows: 1. Study characteristics and methodology: country of study, the first author's name, year of publication, randomization, sample size, periods of data collection, follow-up duration, outcome measures, inclusion and exclusion criteria, et al. 2. Participant characteristics: age, gender, stage of disease, diagnostic criteria, et al. 3. Interventions: therapeutic means, autologous or allogeneic HSC, Number of HSC transplants, course of treatment, and duration of treatment, et al. 4. Outcome and other data: tumor response, OS, EFS, QoL, and adverse effects, et al.

Quality assessment / Risk of bias analysis: Two researchers (Guanghui Zhang and Baoyu Li) independently performed assessment of risk of bias in the included RCTs in accordance with the Cochrane Handbook of Systematic Reviewers. The assessment tool includes the following seven items: (i) random sequence generation, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessment, (v) incomplete outcome data, (vi) selective reporting and (vii) other bias. Each item is divided into three levels: low risk, unclear and high risk. The risks of included non-RCTs will be assessed by using Effective Practice and Organisation of Care (EPOC) guidelines. Any disagreements will be resolved via discussion with a third researcher (Hongyan Wu).

Strategy of data synthesis: Stata 14.0 (Stata Corp., College Station, TX, USA) and Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) statistical software will be used to carry out the data analysis. The risk ratio (RR) was calculated for dichotomous outcomes along with the corresponding 95% confidence interval (CI). Continuous data will be presented as mean difference (MD) or standardized mean difference (SMD) with their 95% CIs. A two-tailed $P < 0.05$ was considered statistically significant. For survival outcomes, Hazard ratios (HRs) with corresponding 95% CIs will be extracted from trials or be estimated from Kaplan–Meier survival curves by established methods. $\chi 2$ statistics and the I2 statistics will be used to assess the heterogeneity of treatment effects across trials. When the P value was > 0.1, and I2 was < 50%, it suggested that there was no statistical heterogeneity and the Mantel-Haenszel fixed-effects model was used for meta-analysis. Otherwise, a random-effects mode will be used to carry out the data analysis.

Subgroup analysis: When the P value was < 0.1, and I2 was > 50%. We will explore sources of heterogeneity with respect to age, region and source of HSC by subgroup analysis and meta-regression.

Sensibility analysis: Sensitivity analysis of each parameter was carried out by one-by-one elimination method to assess the reliability and robustness of the aggregation results. A summary table will report the results of the sensitivity analyses.

Language: Language is limited with English and Chinese.

Country(ies) involved: China.

Other relevant information: 1. Publication bias. Funnel plot, Begg's and Egger regression test will be performed to analyze the existence of publication bias if 10 or more literatures are included in the meta-analysis. If publication bias existed, trim-and-fill method should be applied to adjust the pooled RR. 2. Assess the quality of evidence. The quality of the evidence will be evaluated by the Grading of

Recommendations Assessment, Development, and Evaluation (GRADE) approach, which will be classified into four levels (high quality, moderate quality, low quality, and very low quality).

Keywords: **hematopoietic stem cells; refractory neuroblastoma; meta-analysis; survival; efficacy.**

Dissemination plans: **The results of this study will be published in a peer-reviewed journal, and provide more evidence-based guidance in clinical practice.**

Contributions of each author:

Author 1 - Guanghui Zhang - Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing-original draft.

Author 2 - Baoyu Li - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.

Author 3 - Hongyan Wu - Conceptualization, Project administration, Resources, Software, Supervision, Validation, Writing-review & editing.