INPLASY PROTOCOL

To cite: Zhao et al. Autologous or allogeneic hematopoietic stem cells transplantation combined with high-dose chemotherapy for refractory neuroblastoma: a systematic review and meta-analysis protocol. Inplasy protocol 2021110007. doi: 10.37766/inplasy2021.11.0007

Received: 03 November 2021

Published: 03 November 2021

Corresponding author:
Jike Liu

lchospital@163.com

Author Affiliation:
Liaocheng People's Hospital

Support: **None.**

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

Conflicts of interest:
None declared.

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

Zhao, ZS[1]; Shao, W[2]; Liu, JK[3].

Review question / Objective: **Is autologous or allogeneic HSC transplantation effective on tumor response, survival, and QoL in patients with 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 03 November 2021 and was last updated on 03 November 2021 (registration number INPLASY2021110007).

INTRODUCTION

Review question / Objective: **Is autologous or allogeneic HSC transplantation effective on tumor response, survival, and QoL in patients with refractory neuroblastoma?**

Condition being studied: **Neuroblastoma is the second most common solid malignant tumor in children, only next to central nervous system tumors. It arises from the developing sympathetic nervous system from neural crest cells, usually resulting in tumors in the adrenal glands or the sympathetic ganglia. The age-standardized annual incidence in North America is 5.5 to 11.5 cases per million people. It is the most common malignancy overall in the first year of life with a median age at diagnosis of 18 months and 90% of cases diagnosed**

by 10 years of age. Conventional treatment options for refractory neuroblastoma include surgery, radiotherapy, chemotherapy, immunotherapy, autologous stem cell transplant, or a combination of them, depending on the severity of the disease. With the improvement of therapeutic methods, although the 5-year survival rate of patients with neuroblastoma has increased from 29% to 50% over the past two decades, the long-term outcome of refractory neuroblastoma remains unsatisfactory. Some progress in the treatment of high-risk neuroblastoma is closely related to the escalation of therapeutic intensity. However, high-dose chemotherapy can also seriously damage the hematopoietic system of patients. Hematopoietic stem cell (HSC) is a kind of stem cell in bone marrow, peripheral blood or cord blood. It has the ability of self-renewal and can differentiate into a variety of blood cell precursor cells, and finally generate various blood cell components, including red blood cells, white blood cells and platelets. Healthy HSC are capable of long-term multilineage reconstitution and in situ recovery of the hematopoietic system (e.g., after massive cytotoxic injury induced by radiation or chemotherapy). In order to achieve dose escalation beyond marrow tolerance, HSC transplantation has been used for adjuvant high-dose chemotherapy against refractory neuroblastoma. Currently, a great deal of clinical trials in which neuroblastoma is being treated by high-dose chemotherapy in conjunction with HSC transplantation have been registered on ClinicalTrials.gov. Several studies have indicated that the combination of autologous or allogeneic HSC transplantation and high-dose chemotherapy not only exerts an enhanced therapeutic effect against refractory neuroblastoma, but also improve the quality of life (QoL) patients. Despite the intensive clinical studies, its clinical efficacy was still not well investigated. In this study, we are prepared to summarize the efficacy of autologous or allogeneic HSC transplantation on tumor response, survival and QoL in patients with refractory neuroblastoma through the meta-analysis, in order to provide a helpful evidence for clinicians to formulate the best treatment strategy for refractory neuroblastoma patients.

METHODS

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: Randomized controlled trials (RCTs) or prospective controlled 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. There will be no restrictions for blinding, population characteristics and duration of trials.

Eligibility criteria: 1. Types of studies. Randomized controlled trials (RCTs) or prospective controlled 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. There will be no restrictions for blinding, population characteristics and duration of trials.2. Type of participants. 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.3. Types of interventions. 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.4. Comparator. In the control group, patients with refractory neuroblastoma must be treated with high-dose chemotherapy. 5. Type of outcome measurements5.1. Primary outcomes. 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; 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; 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.5.2. Secondary outcomes. QoL obtained from the corresponding scale; Safety assessment. Monitoring of mortality, toxicity (NCI Common Criteria), acute and chronic graft versus host disease, and engraftment rate will contribute to safety assessment.Exclusion criteria. Duplicated studies, non-comparative clinical trials, papers without sufficient available data, meta-analysis, literature reviews, meeting abstracts, case reports and series, 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): 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; 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; 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.

Quality assessment / Risk of bias analysis: Two researchers 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 Organization of Care (EPOC) guidelines.Any disagreements will be resolved via discussion with a third researcher.

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.

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.

Sensitivity 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.

Country(ies) involved: China.

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

Contributions of each author:
Author 1 - ZHANGSHUAI ZHAO.
Author 2 - WEI SHAO.
Author 3 - JIKE LIU.