INPLASY PROTOCOL

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Conflicts of interest:
None.

The effects of PD-1 and PD-L1 expression on the prognosis of lymphoma: A protocol for systematic review and meta-analysis

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Review question / Objective: **The purpose of this systematic review and meta-analysis is to study the expression of immune checkpoints PD-1/PD-L1 in lymphoma, and whether it affects the survival of patients with lymphoma and other prognostic indicators.**
Condition being studied: **Malignant lymphomas are immune cell tumors that originate in lymph nodes or extranodal lymphoid tissues and organs. Its mortality rate ranks 7th among all malignant tumors in developed countries and 9th in developing countries, and its morbidity ranks first among all malignant hematological diseases.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 December 2020 and was last updated on 23 December 2020 (registration number INPLASY2020120115).

INTRODUCTION

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rate ranks 7th among all malignant tumors in developed countries and 9th in developing countries, and its morbidity ranks first among all malignant hematological diseases.

METHODS

Search strategy: According to the Eligibility criteria, we will search the literature database by combining both Medical Subject Heading (MeSH) and free-text terms which contain various synonyms. Author information, date restrictions, country/region, publication status or publication year will be not restricted.

Participant or population: Patients with lymphoma were diagnosed by pathology or histology. Randomized lymphoma patients, the expression of PD-1/PD-L1 has been detected at least once before or after treatment, and the treatment methods including chemotherapy, radiotherapy, surgery, immunotherapy, etc.

Intervention: Patients which positively express PD-1/PD-L1 will be considered as intervention group.Using standard chemotherapy, radiotherapy, surgery, targeted therapy and other protocols for lymphoma, studies that detect the expression of PD-1/PD-L1 at least once will be included. Studies that do not detect the expression of PD-1/PD-L1 will be excluded.

Comparator: Patients with negative/low expression of PD-1/PD-L1 were considered as control group.

Study designs to be included: All related and published RCTs will be included, for example, earlier I/II, Phase III trials, as well as retrospective and prospective observational studies, such as case-control studies, cross-sectional studies or cohort studies. Only consider English studies and published as full-text articles.

Eligibility criteria: The results of different treatment methods for lymphoma were analyzed, including chemotherapy, radiotherapy, surgery, immunotherapy and other therapies. These studies must be conducted on the basis of PD-1/PD-L1 detection. In addition, this research will contain some clinical trials. All related and published RCTs will be included, for example, earlier I/II, Phase III trials, as well as retrospective and prospective observational studies, such as case-control studies, cross-sectional studies or cohort studies. But it will exclude reviews, case reports, meta-analysis, and studies with insufficient research results. The studies must reported PD-1/PD-L1 survival-related data. Only consider English studies and published as full-text articles.

Information sources: A comprehensive search was conducted on PubMed, Embase, ClinicalTrials.gov database and Cochrane library using a completed search strategy. The Newcastle-Ottawa Scale (NOS) or the Cochrane Collaboration's tool for assessing risk of bias will be used to access the methodological quality of included studies, and GRADE will be used to assess the evidence quality of outcomes. All analyses were performed by Stata 15.0.

Main outcome(s): (1) The expression rate of PD-1/PD-L1 will be detected; (2) Overall response rate (ORR) and disease control rate which contain complete response and partial response will be all evaluated using the Recist criteria; (3) Randomization to death from any reason;(4) Disease-free survival (DFS) which refers to time from the date of random assignment to the date of relapse or death.

Additional outcome(s): (1) Karnofsky score, Quality of Life (QOL) scale score, improvement of symptoms; (2)Immunological related indicators: the percentage of CD3 +, CD4 +, CD8 + and NK cells, the ratio of CD4 + / CD8 + cells, and the level of serum cytokines (such as IL-2, IL-4, IFN-γ and TNF- α); (3) Treatment-related adverse reactions: the severity of treatment-related toxic reactions range from 0 to IV according to the recommendations of the World Health Organization.

Quality assessment / Risk of bias analysis: We will use Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to access the level of evidence for each result. The quality of all evidence will be evaluated at 4 levels which include "high", "moderate", "low" and "very low". Two reviewers will separately evaluate the quality of the RCTs included, they will use the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions Review Manual: The generation of random sequences, the concealment of allocation, the blinding of participants and personnel, the blinding of result assessment, incomplete data of result, selective reporting and other biases. The quality of evidence will be judged into "low risk", "high risk" or "unclear risk". Assessing non-RCT risks will use effective nursing practices and organizational guidelines. Any differences will be resolved through discussions with the third researcher.

Strategy of data synthesis: We will evaluate the results of the literature search by using a 3-steps process. At first, two independent researchers will conduct an evaluation to determine preliminary trials by screening titles and abstracts, and deleting records that do not meet the criteria. We will then download and carefully read the full text of the remaining studies to ensure they meet the final inclusion criteria. We will use Endnote X8 software to manage literature and search records. If there is a disagreement, the third investigator will resolve it through discussion with the two reviewers. The studies excluded and the reasons for exclusion will be clarified. According to the Cochrane System Intervention Review Manual, two reviewers will extract data independently. We will extract the following data from documents that meet the criteria: (1) Research characteristics and methods: research country/region, name of first author, publication year, data collection time and follow-up time, randomization method. (2) Participant features: sample size, age, sex ratio, stage of the lymphoma (according to the AJCC TNM classification for OC), tumor size, et al. (3) Interventions: the expression rate of PD-1/PD-L1. (4) Outcomes: overall remission rate, disease control rate, overall survival rate, disease-free survival rate, quality of life, immune indicators such as the percentage of CD3+, CD4+, CD8+ and NK cells, the ratio of CD4+ / CD8+ cells, and level of serum cytokines including IFN-γ and TNF-α, IL-2, IL-4, as well as adverse reactions.

Subgroup analysis: Subgroup analysis will be used to analyze clinical heterogeneity such as the age, sex ratio, tumor staging of lymphoma, region, therapeutic regimens and courses. If there is no obvious clinical and methodological heterogeneity, random effect model will be used to conduct and analyze the statistical heterogeneity. For studies with high clinical heterogeneity, we will only perform descriptive analysis instead of meta-analysis.

Sensibility analysis: If necessary, a sensitivity analysis will also be carried out, the purpose of which is to eliminate the influence of trials that may have a high risk of bias on the reliability and robustness of the assessment results. The results of the sensitivity analysis will be reported in the summary table.

Language: English, Chinese-Simplified.

Country(ies) involved: China.

Keywords: lymphoma, PD-1/PD-L1, prognosis, systematic review, study protocol.

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