

INPLASY PROTOCOL

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None.

The relative risk of immune-related colitis with immune checkpoint inhibitors among various therapeutic patterns: a systematic review and meta-analysis

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Review question / Objective: What are the differences in immune-related colitis with immune checkpoint inhibitors among various therapeutic patterns?

Condition being studied: Immune checkpoint inhibitors (ICIs) have radically changed the treatment modalities for a wide range of tumor types. Colitis is a life-threatening and common immune-related adverse event in patients receiving ICIs. Due to the incidence and severity of immune-related colitis, an improved understanding of the risk of and mechanisms underlying this adverse event is desperately needed in clinical oncology.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 May 2020 and was last updated on 17 May 2020 (registration number INPLASY202050072).

INTRODUCTION

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understanding of the risk of and mechanisms underlying this adverse event is desperately needed in clinical oncology.

METHODS

Search strategy: We searched for articles in PubMed, EMBASE, and Cochrane Library from their inception date to January 2020. The following keywords were used: “ n e o p l a s m ” , “ m a l i g n a n t neoplasm”, “carcinoma”, “nivolumab”, “ pembrolizumab”, “cemiplimab”, “pidilizumab”, “cetrelimab”, “camrelizumab”, “toripalimab”, “sintilimab”, “tislelizumab”, “durvalumab”, “atezolizumab”, “avelumab” , “ b i n t r a f u s p alfa”, “envafolimab”, “ipilimumab”, “randomized controlled trial.” Finally, references to the studies included in the final selection were also checked. There is no language limitation in the literature search.

Participant or population: Inclusion criteria: patients who were treated with ICIs in phase II or III randomized clinical trials (RCTs) of the solid malignant tumor.

Intervention: The immune checkpoint inhibitors are the main interventions, including anti-PD-1 inhibitors (nivolumab, pembrolizumab, cemiplimab, pidilizumab, cetrelimab, camrelizumab, toripalimab, sintilimab, tislelizumab), anti-PD-L1 inhibitors (durvalumab, atezolizumab, avelumab, bintrafusp alfa, envafolimab), anti-CTLA-4 inhibitors (ipilimumab, tremelimumab). ICIs could be applied as monotherapy or in combination with other drugs.

Comparator: The comparators mainly comprise placebo, chemotherapy, targeted therapy, and immunotherapy. The combination of ICIs or vaccine should be excluded.

Study designs to be included: Only phase II or III randomized controlled trials were included.

Eligibility criteria: (1) phase II or III randomized clinical trials (RCTs) of the solid malignant tumor; (2) providing the number of all-grade (grade 1-5) colitis and high-grade (grade 3-5) colitis events in each arm respectively; (3) with ICIs administered as monotherapy or in combination with other traditional cancer treatment in the experimental arm.

Information sources: We searched for articles in PubMed, EMBASE, and Cochrane Library from their inception date to January 2020. We also expanded our search by reviewing abstracts and presentations from major conferences, including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) meeting, in order to make sure that all eligible articles could be screened. Finally, references to the studies included in the final selection were also checked.

Main outcome(s): The relative risk of all-grade colitis developed from ICIs among varied treatment regimens.

Additional outcome(s): The relative risk of all-grade colitis developed from ICIs among varied treatment regimens.

Data management: The following records were collected from the eligible studies: the name of first author, publication year, phase of RCT, type of cancer, line of therapy, treatment regimen of study arm, number of safety analysis patients, number and classification of colitis events (all-grade and high-grade) in each arm. Two investigators extracted data from the articles independently, and controversies were resolved via discussion or determined by the third reviewer.

Quality assessment / Risk of bias analysis: The evaluation of study quality was carried out by the “Risk of bias” tool in Review Manager (RevMan 5.3; The Cochrane Collaboration, Oxford, United Kingdom). Two investigators evaluated the risk of bias independently. All discrepancies were settled by consulting the third reviewer.

Strategy of data synthesis: Relative risks (RRs) and 95% confidence intervals (CIs) were applied to evaluate the risk of colitis in patients, with $RR > 1.0$ indicating a higher risk of colitis in the experimental arm. RRs of different treatment regimens and 95% CIs were used to calculate the relative risk ratio (RRR) with 95% CIs between diverse treatment regimens. Statistical analysis and forest plots were performed using Review Manager (RevMan 5.3; The Cochrane Collaboration, Oxford, United Kingdom), while Begg's and Egger's tests for detecting publication bias and sensitivity analysis were performed using Stata version 16.0 (Stata Corp, College Station, TX).

Subgroup analysis: Subgroup analyses were conducted to explore whether PD-1 inhibitor or PD-L1 inhibitor impacted RR of colitis.

Sensitivity analysis: Sensibility analysis was utilized to examine whether the results could have been influenced by a single study by removing one study at a time. We use STATA 16 software to conduct it.

Language: English.

Country(ies) involved: China.

Keywords: Meta-analysis; Immune-related colitis; Immune checkpoint inhibitors; PD-1 inhibitor; PD-L1 inhibitor.

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