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INPLASY

Efficacy of immune checkpoint inhibitors combined with tyrosine kinase inhibitors in advanced or metastatic colorectal cancer patients with metastatic microsatellite stable (MSS) or mismatch repair profcient (pMMR) : a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 September 2023 and was last updated on 06 September 2023.

INTRODUCTION

Review question / Objective The purpose of this systematic review and Meta-analysis is to analyze the relevant studies of ICIS combined with tyrosinase inhibitors in the treatment of advanced or metastatic CRC patients with MSS/ pMMR, to evaluate its efficacy and safety, and to provide a reference for the treatment of advanced or metastatic CRC patients with MSS/ pMMR.

Condition being studied Colorectal cancer (CRC) is the third most prevalent cancer and the second leading cause of death in the world. More than 800 000 people die from CRC every year worldwide, and its incidence and mortality are still increasing. Early colorectal cancer can be treated with radical surgery and adjuvant chemotherapy, and the prognosis is good. However, due to the lack of obvious symptoms in the early stage of CRC, most patients have advanced CRC or metastatic CRC at the time of diagnosis, and their prognosis is poor, with a low 5-year overall survival rate (5-8%). Chemotherapy is still the standard treatment for metastatic colorectal cancer, but it has the disadvantages of obvious systemic adverse reactions, low selectivity and tumor site drug concentration. Immunotherapy has shown promising outcomes in treating various malignant tumors in recent years. Studies have shown that immune checkpoint inhibitors (ICIs) show promising efficacy in patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) mCRC. However, MSI - H/dMMR tumor accounted for all mCRC 2-4% of cases. Most patients with colorectal cancer have microsatellite stable (MSS) or mismatch repair-good (pMMR) status and benefit little from ICIs . Clinical studies have shown that anti-angiogenic drugs combined

with immune checkpoint blocking can significantly improve the effectiveness of malignant tumor treatment , and in addition to their anti-angiogenic effects, they can also inhibit the expression of immunosuppressive molecules, thereby restoring the immunosuppressive tumor microenvironment. Therefore, ICI combined with tyrosinase inhibitors with anti-angiogenesis effect may overcome the resistance of MSS or pMMR mCRC to immunotherapy.

METHODS

Participant or population Patients with advanced or metastatic pMMR/MSS colorectal cancer.

Intervention Immune checkpoint inhibitor + tyrosine kinase inhibitors.

Comparator Before study in the same patient.

Study designs to be included Case-control studies, or cohort studies.

Eligibility criteria A population (P), intervention (I), comparator (C), outcome (O), and study design (S) (PICOS) framework was used to describe the eligibility of studies. Specifically, the criteria below were included:- Population (P): patients with advanced or metastatic pMMR/MSS colorectal cancer;- Intervention (I): immune checkpoint inhibitor + tyrosine kinase inhibitors;- Comparison (C): before study in the same patient- Outcomes (O): objective response rates (ORR) , disease control rates (DCR) and adverse reaction rate;- Study design (S): case-control studies, or cohort studies.

Information sources The PubMed, Embase, Cochrane, Web of Knowledge, and ClinicalTrials.gov databases were searched from inception to July 28, 2023. Articles in all languages were searched.

Main outcome(s) Objective response rates (ORR) , disease control rates (DCR) and adverse reaction rate.

Quality assessment / Risk of bias analysis The literature screening was conducted by two researchers (JL and QLX) independently, through reading the subject, selecting the standard subject, and subsequently reading the abstract and the full text. The Newcastle-Ottawa scale (NOS) was used for quality assessment of case-control and cohort studies; this includes eight items divided into three areas, namely, population selection, comparability, and exposure or outcome evaluation, using a scale of 0-9 points with scores above 5 rated as high quality .The risk of publication bias was assessed using funnel plots, with the asymmetry of the plot indicating potential bias; asymmetry was analyzed by Egger's and Begg's tests. Intercept significances were assessed using t-tests ($P < 0.05$).

Strategy of data synthesis The objective response rate(ORR), disease control rate(DCR), adverse reaction rate and Grade≥3 adverse reaction rate with their 95% confdence intervals (CIs) were evaluated for the studies included in the meta-analysis. Inter-study heterogeneity was evaluated using the I2 statistic and Cochran's Q test, with cut-off values of 25%, 50%, and 75% considered as low, moderate, and high, respectively[20]. Sensitivity analysis was performed in relation to the assessed effect sizes and heterogeneity of the studies. The risk of publication bias was assessed using funnel plots, with the asymmetry of the plot indicating potential bias; asymmetry was analyzed by Egger's and Begg's tests. Intercept significances were assessed using t-tests ($P < 0.05$).

Subgroup analysis Not applicable.

Sensitivity analysis Sensitivity analysis was performed in relation to the assessed effect sizes and heterogeneity of the studies.

Country(ies) involved China.

Keywords immune checkpoint inhibitor, tyrosine kinase inhibitors, colorectal cancer, microsatellite stable, mismatch repair profcient, meta-analysis.

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