INPLASY PROTOCOL

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None declared.

Comprehensive curative effect of targeting PD-1 or traditional single-agent chemotherapy in second-line therapy for terminal or metastatic esophageal cancer：A systematic review and meta-analysis

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Review question / Objective: **P: advanced or metastatic esophageal cancer I: PD-1 inhibitors C: single-agent chemotherapy O：OS, PFS, ORR, DCR S: RCT.**
Condition being studied: **ESCC patients' prognosis is poor, with a 5-year overall survival rate of less than 15%. Chemotherapy is often the conventional second-line therapy for terminal or metastatic EC. Fluorouracil combined with platinum is the preferred therapy for locally terminal or metastatic EC. If the first-line treatment is not effective, the second-line therapy is usually monotherapy. Commonly used second-line drugs are paclitaxel, docetaxel, and irinotecan. However, these drugs cause leukopenia, neutropenia, and neurotoxicity. Therefore, there is an urgent need to find second-line chemotherapy drugs that can improve the prognosis of terminal or metastatic EC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 July 2022 and was last updated on 05 July 2022 (registration number INPLASY202270019).

INTRODUCTION

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METHODS

Participant or population: Patients who use PD-1 inhibitors or traditional single-agent chemotherapy as second-line monotherapy drugs for esophageal cancer.

Intervention: PD-1 inhibitors.

Comparator: traditional single-agent chemotherapy.

Study designs to be included: All RCTs of esophageal cancer under treatment with PD-1 inhibitors and conventional second-line chemotherapeutics between January 2015 and April 2022 were collected.

Eligibility criteria: Qualified literature will be included in this study according to the following criteria: (1) RCTs of locally terminal or metastatic EC that becomes more severe after first-line therapy; (2) The PD-1 inhibitor treatment group used a single PD-1 inhibitor for chemotherapy, and the chemotherapy group used conventional EC second-line chemotherapy drugs; (3) Trials must include at least three of the following primary outcomes: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and treatment-related adverse events (TRAEs). Reviews, repeated studies, case reports, non-RCTs, animal studies, irrelevant studies and literature for which no valid data could be obtained were excluded.

Information sources: A comprehensive search of published literature was conducted on PubMed, Web of Science, Embase and Cochrane Library databases. In addition, conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched.

Main outcome(s): In comparison with conventional single-agent chemotherapy, PD-1 inhibitors greatly improved patients' OS (HR = 0.77, 95% CI 0.70-0.85, P < 0.001), but PFS (HR = 0.93, 95% CI 0.77-1.12, P = 0.431) and DCR (RR = 0.93, 95% CI 0.71-1.22, P = 0.609) were not greatly improved. In addition, PD-1 inhibitors improved ORR (RR = 1.83, 95% CI 1.16-2.89, P = 0.009).

Quality assessment / Risk of bias analysis: The quality assessment of all included studies was relatively low risk.

Strategy of data synthesis: All data were statistically analyzed by Stata 12.0 and Review Manager 5.3. All OS and PFS use HRs and 95% confidence intervals (CI) as the effect size of statistical indicators. For other variables, such as ORR, DCR, TRAEs, RRs and 95% CIs were used. Heterogeneity assessment of these studies was the Cochran's Q test or Higgins I2 statistic. If P < 0.1 or I2 > 50%, it was taken for high heterogeneity among the studies, and the analysis would use random-effects model; otherwise, the fixed-effects model would be used. When there was heterogeneity between studies, subgroup analyses were performed to look for sources of heterogeneity. When P < 0.05, the difference was considered statistically significant. After excluding each study one by one, the combined effect size was re-estimated and compared with the results of the meta-analysis before the exclusion, and then the impact of the study on the combined effect size and the robustness of the meta-analysis results were discussed. Finally, publication bias was detected by Egger's and Begger's test. If P > 0.05, it was considered that publication bias did not exist; otherwise, there was publication bias.

Subgroup analysis: To better investigate which factors affected OS, we combined data from the two treatment regimens and performed a subgroup analysis of 9 factors

that might affect OS, including age, gender, region, smoking history, PD-L1 expression, ECOG PS, organ metastasis and lymph node metastasis.

Sensitivity analysis: **The combined results of OS, PFS, ORR and DCR are stable, indicating that the results of this study are stable and credible.**

Country(ies) involved: **China.**

Keywords: **chemotherapy, clinical cancer research, digestive cancer, meta-analysis.**

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