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Comparative efficacy and safety of anti-HGF/MET pathway agents plus chemotherapy versus chemotherapy alone as first-line treatment in advanced gastric cancer: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Phase I/II clinical trials suggested that the hepatocyte growth factor (HGF)/mesenchymal-epithelial transition (MET) pathway-targeted agents were active in suppression of gastric cancer (GC). Randomised controlled trials (RCTs) were undertaken assessing whether the addition of anti-HGF/MET agent (rilotumumab or onartuzumab) to chemotherapy improves survival outcomes of advanced GC, but conflict conclusions were reached. Therefore, we plan to perform this systematic review and meta-analysis to synthesise evidence concerning efficacy and safety of anti-HGF/MET agents combined with chemotherapy as the first-line treatment to advanced GC.

Methods and analysis Systematic searches of the PubMed, Embase and the Cochrane Central Register of Controlled Trials will be performed with no language restriction from inception to 31 January 2022 to identify RCTs exploring the comparative efficacy and safety of anti-HGF/MET agents plus chemotherapy as first-line treatment in advanced GC. The primary outcome will be the time-to-event progression-free survival and overall survival, and the secondary outcomes will be disease control rate, overall adverse events rate and grade 3–5 adverse events rate. Statistical heterogeneity will be assessed by visual inspection of forest plots and measured using the I^2 statistics. A fixed-effect model will be used when heterogeneity is low otherwise, a random-effect model will be chosen. Publication bias will be assessed by funnel plots; subgroup analysis and sensitivity analysis will be performed in the right context. For each outcome, we will perform data synthesis using Rev Man V.5.3 software, and compile 'summary of findings' tables using GRADEpro software.

Ethics and dissemination There is no requirement for ethics approval because no individual data will be collected in this research. It is anticipated that the dissemination of results will take place at conferences and through publication in a peer-review journal, any adjustments from the protocol will be clearly documented and explained in its final report.

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Strengths and limitations

- This protocol is written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines, and we intend to conduct our study according to the PRISMA guidelines.
- Publishing this protocol ensures that we are transparent with the development process we will be using for this study, to reduce the likelihood of duplication as well as minimise the effects of bias on our study.
- Highest level of evidence for informed decision-making might be made available from this systematic review because it includes only randomised controlled trials.
- The heterogeneity of chemotherapy regimen and patient baseline characteristics may lead to the degradation of evidence quality.
- This study may also be limited by not many eligible studies and insufficient sample size.

INTRODUCTION

Gastric cancer (GC) is an important cancer worldwide and is responsible for over 1 000 000 new cases and an estimated 783 000 deaths (equating to 1 in every 12 deaths globally) in 2018, making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death.[1] Doublet or triplet chemotherapy with a platinum-fluoropyrimidine backbone remains the mainstay of treatment for fit patients with unresectable advanced GC, such as the mFOLFOX6 regimen (fluorouracil, leucovorin calcium and oxaliplatin).[2 3] Other effective therapeutics for GC in the refractory setting include taxanes, irinotecan hydrochloride and

the vascular endothelial growth factor receptor-2 inhibitor ramucirumab (in the second-line setting).[4–6] In addition, chemotherapy plus trastuzumab is standard of care for patients with human epidermal growth factor receptor (EGFR) 2 positive advanced GC.[7] Also, the addition of nivolumab to first-line chemotherapy in gastric and gastro-oesophageal junction adenocarcinoma improved survival, progression-free survival (PFS), response and findings that led to regulatory approval in some countries.[8] Despite these efforts, prognosis for unresectable advanced GC remains dismal, with reported median overall survival (OS) times inferior to 1 year.[9 10]

Other targeted therapies have been developed to counteract the deregulation of signal transduction pathways, including EGFR and hepatocyte growth factor (HGF)/mesenchymal-epithelial transition (MET) pathways.[11 12] In advanced GC, EGFR overexpression occurs in up to 50% of patients.[13] Similarly, abnormal HGF and MET upregulation occurs in GC, with MET overexpression in 18%–82% of patients.[14] The HGF receptor that activates key oncogenic pathways through RAS, PI3K and STAT3 plays an important role in tumourigenesis and is encoded by MET oncogene.[15] Signalling through the HGF/MET pathway stimulates tissue repair and regeneration in normal tissue but also can promote proliferation, survival and metastasis in tumour cells.[16] In GC, dysregulation of the MET/HGF pathway is associated with poor prognosis and more aggressive disease, with MET activation stimulating tumour invasiveness.[17 18]

Rilotumumab, a monoclonal antibody targeting HGF, was shown tolerable and active in various advanced solid tumours.[19 20] Onartuzumab is a recombinant, fully humanised, monovalent monoclonal antibody, and it prevents MET from binding with HGF and restricts cellular signalling via the MET pathway by binding with the extracellular domain of MET. Preliminary data from phase I/II studies indicated that HGF/MET-targeted agents, including rilotumumab and onartuzumab, are active in GC.[21 22] In addition, several randomised controlled trials (RCTs) have been conducted to assess whether the addition of these anti-HGF/MET agents to chemotherapy as first-line therapy for advanced GC improves efficacy outcomes when compared with chemotherapy alone, but obtained some conflict results.[9 23–25]

Therefore, we plan to perform this systematic review and meta-analysis, to first synthesise evidence concerning efficacy and safety of anti-HGF/MET pathway agents combined with chemotherapy as the first-line treatment in advanced GC. The protocol for our research is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P),[26 27] its PRISMA-P checklist file is attached (online supplemental file 1). The findings of our research will be published in a peer-reviewed journal, also in the event of insignificant results, and thereby it will be disseminated to clinicians and public available.

OBJECTIVES

The goal of this systematic review is to explore the questions as follows:

1. Whether the anti-HGF/MET agents plus chemotherapy are more effective than chemotherapy alone as first-line treatment to advanced GC.
2. And how safe is the combination regimen compared with chemotherapy alone?

METHODS AND ANALYSIS

This systematic review and meta-analysis will be conducted according to the PRISMA guidelines.[28]

Criteria for considering studies

Study characteristics

This systematic review will include only RCTs comparing the efficacy and safety of anti-HGF/MET agents plus chemotherapy versus chemotherapy alone as first-line treatment in advanced GC. Studies should have a minimum of 24-month follow-up. Duplicates and full text unavailable due to specific reasons will be excluded.

Population

Patients diagnosed as advanced GC and had not received any chemotherapy or immunotherapy previously will be included.

Intervention

The intervention will be anti-HGF/MET agent (rilotumumab or onartuzumab) plus chemotherapy.

Comparator

The comparator will be chemotherapy plus placebo or chemotherapy alone.

Outcomes

Primary outcome: time-to-event PFS and OS, or relevant data to estimate them.

Secondary outcome: disease control rate, overall adverse events rate and grade 3–5 adverse events rate, or relevant data to estimate them.

Search strategy

The search strategy will be conducted in two stages.

1. Bibliographic database searches: a systematic search of PubMed, Embase and the Cochrane Central Register of Controlled Trials will be performed with no restrictions on language from inception to 31 January 2022 to identify all relevant studies. The details of search strategy and syntax are shown in online supplemental file 2.
2. Searching for other sources: the references of relevant articles will be manually searched to further identify eligible studies, and their full texts will be retrieved.

Study selection and data extraction

Records identified according to search strategy will be exported to EndNote V.X8 software. Three reviewers (ZJ, ZC and CS) will then independently screen their titles

and abstracts. Each eligible title/abstract will require two votes. Subsequently, these reviewers will reassess the full texts of the identified studies, verifying the reasons for inclusion and exclusion.

Data extraction for included studies will be conducted by two reviewers (ZJ and QM) independently using a standardised electronic data extraction form (table 1). The following data will be extracted from all the included studies: first author, publication year, study design, study period, country(region), female rate, age (median and range), follow-up (median and range), chemotherapy regimen, anti-HGF/MET agent, sample size, Eastern Cooperative Oncology Group (ECOG) performance status, tumour site, tumour stage, histologic grade, disease control rate, overall adverse events rate and grade 3–5 adverse events rate, and survival outcomes. If multiple HRs for a survival outcome are presented in a paper, we will choose the one adjusted for the greatest number of confounders.[29] All disputes in the process of study selection and data extraction will be resolved through team negotiation.

Risk of bias assessment

Two reviewers (ZC and QM) will assess the risk of bias of included studies independently using the Cochrane Collaboration's risk of bias tool.[30] Disagreements will be resolved by discussion, where necessary, in consultation with the third reviewer (YY). Results of this meta-analyses will be interpreted in light of risk of bias assessment of the included studies.

Measurements

Time-to-event outcome will be analysed by the pooled HR, and the OR will be used to pool dichotomous outcome. Results will be presented as summary relative effect size (HR or OR) with 95% CI.

Strategy for data synthesis

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions.[31] The extracted data will be imported into Rev Man V.5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) by the first reviewer and checked by the second one. The HRs of PFS as well as OS comparing the two interventions will be pooled in the meta-analysis. As for disease control rate, overall adverse events rate, and grade 3–5 adverse events rate, we will calculate the pooled ORs. Statistical heterogeneity will be assessed by visual inspection of forest plots and measured using the I^2 statistics. I^2 <50% or ≥50% indicates low or high heterogeneity, respectively. A fixed-effect model will be used when heterogeneity is low; otherwise, a random-effect model will be chosen. When substantial heterogeneity is detected, subgroup analysis and sensitivity analysis will be performed to investigate its possible sources. If quantitative synthesis is not possible due to heterogeneity, we will perform a narrative synthesis.

Table 1 Data extraction form

Study details	
General information	
► First author	
► Year of publication	
► Region	
► Study period	
Study eligibility	
► Study design	
► Follow-up (median and range: month)	
► Population	
► Intervention	
► Comparator	
► Outcome diagnostic criteria	
► Confounding variables	
Include or exclude	Include □ Exclude □
Reason(s) for exclusion	
Characteristics of included studies	
► Sample size	Combination therapy group Chemotherapy group
► Data source	
► Age (median and range)	
► Gender (female rate)	
► Tumour size (cm)	
► Tumour site	
► Histologic grade	
► TNM stage	
► ECOG performance status	
► Chemotherapy regimen	
► Anti-HGF/MET agent	
► Subgroups	
► Key conclusion(s)	
Primary outcomes	
► HRs (comparing combination therapy and chemotherapy group) with 95% CI	
OS	
PFS	
► Relevant data to calculate HRs	
OS	
PFS	
► Other data	
Second outcomes	
► Disease control rate	Combination therapy group Chemotherapy group
► Overall adverse events rate	Combination therapy group Chemotherapy group
► Grade 3–5 adverse events rate	Combination therapy group Chemotherapy group
► Other data	Combination therapy group Chemotherapy group

.ECOG, Eastern Cooperative Oncology Group; HGF, hepatocyte growth factor; MET, mesenchymal-epithelial transition; OS, overall survival; PFS, progression-free survival; TNM, tumour, node, metastases.

Dealing with missing data

When an HR of PFS or OS and its upper or lower limit of 95% CI are provided, we can calculate its lnHR (the natural logarithm of HR) and SE, and then merge HRs. When the above data are incomplete, we will attempt to contact the authors to retrieve it. If we do not get an effective response in 2 weeks, we will try to estimate some or all of the lnHR, the logrank observed minus expected events (O–E), the logrank variance and the variance of the lnHR by indirect methods.[32] If even these indirect methods cannot be applied, we will consider to generate the necessary statistics from published Kaplan-Meier curves.[32] To pool ORs of disease control rate, overall adverse events rate, or grade 3–5 adverse events rate, we will record data on the total number of participants and the incidence of events in each arm of each study.

When a study fails to provide necessary statistics by all mentioned methods, we will contact the authors to extract details, and studies failing to provide these necessary data will be excluded from meta-analysis.

Sensitivity analysis and subgroup analyses

We will apply the leave-one-out sensitivity analysis to evaluate the robustness of the results.

Subgroup analyses are planned as follows:

1. Sex: male versus female
2. Primary tumour site: stomach versus oesophagogastric junction
3. ECOG status: 0 versus ≥1
4. Prior gastrectomy or oesophagectomy: with versus without.
5. Tumour biomarker status: MET positive versus MET negative.
6. Agent: anti-HGF agent (rilotumumab) versus anti-MET agent (onartuzumab).

Publication bias assessment

Detecting and overcoming publication bias are problematic and firm guidance is not yet offered; thus, we will use visual inspection of funnel plots to assess publication bias, with results being interpreted cautiously.[33 34]

Quality of the evidence

The overall quality of evidence for each outcome will be assessed using the five Grading of Recommendations, Assessment, Development and Evaluations approach. The direct evidence from RCTs begins at high quality, and the overall quality will be analysed on five down-grade considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) and three up-grade considerations (large magnitude of effect, dose–response relation and plausible confounders or biases), and finally rate it as high, moderate, low or very low.[35–42] We will provide all decisions to down-grade or up-grade the quality of studies with clear arguments in footnotes to aid the reader's understanding of the process.

Presentation and reporting of results

We will follow the PRISMA statement to report our findings.[28] The study selection process will be summarised by a PRISMA flow chart (online supplemental file 3). The characteristics of each enrolled study will be tabulated in detail. The forest plots generated by Rev Man V.5.3 software will be used to present the pooled estimates. For each outcome, 'summary of findings' table will be compiled by GRADEpro software (GRADEpro GDT 2015).

Patient and public involvement

Patients and the public will not be involved in the design, or conduct, or reporting, or dissemination plans of this research because it will be based on published studies without collecting raw individual data.

Ethics and dissemination

There is no ethics approval required for this systematic review due to no patient data being collected at an individual level. We will seek to present the findings at relevant conferences and publish in an influential open access journal, any deviations from the protocol will be clearly explained in its final report.

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Contributors ZJ, ZC and QM contributed equally to the research and designed the protocol and drafted the manuscript. The original idea of this research was conceived by BZ and ZJ. ZJ, ZC, ZZ, MM and XY participated in developing the eligibility criteria, search strategy, data extraction methods and data summary plan. ZJ, ZC, CC, CL and CS will search for studies and extract and analyse the data. BZ and YY will supervise this work.

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Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

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