Trastuzumab combined chemotherapy for the treatment of HER2-positive advanced gastric cancer
A systematic review and meta-analysis of randomized controlled trial

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Abstract
Background: This systematic review and meta-analysis aimed to assess the efficacy of trastuzumab combined with chemotherapy for the treatment of HER2-positive advanced gastric cancer (HER2-PAGC).

Methods: This systematic review and meta-analysis was designed using randomized controlled trials that compared trastuzumab in combination with chemotherapy and chemotherapy alone. A comprehensive search was conducted in the following databases from their inception onwards: PubMed, EMBASE, Cochrane Library, WANGFANG, and CNKI. We also searched other literature sources to avoid missing relevant studies. Two reviewers independently performed all record selection, data collection, and methodological assessments. Any confusion was resolved by discussion or referral to a third reviewer. If there were ample data from eligible studies, we performed a fixed-effects meta-analysis. Whenever this was not possible, we conducted a narrative synthesis.

Results: Meta-analysis results showed that trastuzumab in combination with chemotherapy achieved better outcomes on response rate (trastuzumab plus CFC vs CFC: odds ratio [OR] = 1.56, 95% confidence interval [CI] [1.17–2.09], I² = 0%, P < .003; trastuzumab plus OT vs OT: OR = 2.97, 95% CI [1.74–5.09], I² = 0%, P < .001; and trastuzumab plus CC vs CC: OR = 2.62, 95% CI [1.84–3.73], I² = 0%, P < .001), and disease control rate (trastuzumab plus CFC vs CFC: OR = 1.61, 95% CI [1.17–2.21], I² = 0%, P = .004; trastuzumab plus OT vs OT: OR = 4.29, 95% CI [2.33–7.90], I² = 0%, P < .0001; and trastuzumab plus CC vs CC: OR = 2.99, 95% CI [1.99–4.48], I² = 0%, P < .0001). However, there were no significant differences in the adverse events.

Conclusions: The results of this study revealed that the efficacy of trastuzumab combined with chemotherapy was superior to that of chemotherapy alone for the treatment of HER2-PAGC. The 2 modalities showed similar safety profiles.

Abbreviations: AGC = advanced GC, CAF = cyclophosphamide+azithromycin+5-fluorouracil, CC = capecitabine+cisplatin, CFC = capecitabine or 5-fluorouracil+cisplatin, CI = confidence interval, DCF = docetaxel+cisplatin+5-fluorouracil, GC = gastric cancer, HER2 = human epidermal growth factor receptor type 2, HER2-PAGC = HER2-positive advanced gastric cancer, IC = irinotecan+cisplatin, RCT = randomized controlled trial, OF = oxaliplatin+5-fluorouracil, OL = oxaliplatin+leucovorin, OT = oxaliplatin+tegafur.

Keywords: efficacy, HER2-positive advanced gastric cancer, meta-analysis, randomized controlled trial, safety, systematic review, trastuzumab

1. Introduction

Gastric cancer (GC) is one of the most common gastrointestinal cancers and the leading cause of cancer-related deaths worldwide.1–4 More than 1 million new GC cases were reported in 2018, and approximately 780,000 GC patients died.5 Patients with GC are often diagnosed at an advanced stage, which presents challenges for management.6,7 Although surgery is recommended as a potentially curative treatment, many patients still experience regional and distant recurrence after operation.8–11 Chemotherapy is often considered the standard treatment for advanced GC (AGC).12 However, the prognosis is poor owing to the restriction of accurate targets. A previous study reported that AGC survival varies from approximately 4 to 16.6 months with chemotherapy.13–15
Trastuzumab is a monoclonal antibody utilized to manage GC.[16–18] It binds to human epidermal growth factor receptor type 2 (HER2).[19–20] It is effective against tumors that over-express HER2.[19,21] Although previous studies have reported that trastuzumab can be used specifically to treat patients with HER2-positive advanced GC (HER2-PAGC), its monotherapy efficacy remains unsatisfactory.[22–31] Fortunately, several clinical trials have investigated the efficacy and safety of trastuzumab combined with chemotherapy for the treatment of patients with HER2-PAGC with promising outcomes.\cite{32–49}

Previous similar studies investigated the efficacy of trastuzumab combined with chemotherapy in the treatment of patients with HER2-PAGC.\cite{50–52} However, the overall methodological quality of included trials in these studies was poor.\cite{50–52} In addition, there were more eligible trials published after those studies.\cite{36,38,39,43,44} This systematic review and meta-analysis summarized the evidence of latest clinical trials and updated the evidence-based medical evidence for this topic. Therefore, this study aimed to update the present evidence on the efficacy and safety of trastuzumab combined chemotherapy in the treatment of patients with HER2-PAGC.

2. Methods

2.1. Ethical statement

No ethical approval was provided for this study because the individual data were not collected. The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.

### Table 1

| Number | Search terms |
|--------|--------------|
| 1      | Gastric cancer |
| 2      | Stomach neoplasm |
| 3      | Gastric neoplasm |
| 4      | Cancer of stomach |
| 5      | Cancer, stomach |
| 6      | Cancer, gastric |
| 7      | Neoplasm, gastric |
| 8      | Human epidermal growth factor receptor 2 (HER2) |
| 9      | HER2-positive |
| 10     | Advanced |
| 11     | Or 1–11 |
| 12     | Trastuzumab |
| 13     | Herceptin |
| 14     | Monoclonal antibody |
| 15     | Trastuzumab-anns |
| 16     | Trastuzumab-dkst |
| 17     | Trastuzumab-dttb |
| 18     | Trastuzumab-pkib |
| 19     | Trastuzumab-qyy |
| 20     | Chemotherapy |
| 21     | Or 13–21 |
| 22     | Controlled trials |
| 23     | Clinical trials |
| 24     | Random |
| 25     | Randomly |
| 26     | Control |
| 27     | Allocation |
| 28     | Blind |
| 29     | Trial |
| 30     | Study |
| 31     | Or 23–31 |
| 32     | 12 AND 22 AND 32 |

2.2. Eligibility criteria

2.2.1. Inclusion criteria. This study included randomized controlled trials (RCTs) that compared the efficacy and safety of trastuzumab combined with chemotherapy with chemotherapy alone for the treatment of HER2-PAGC. For experimental intervention, any type of trastuzumab combined with chemotherapy was included. For controls, the same chemotherapy regimen as that in the intervention group was considered. We included patients with histopathologically confirmed HER2-PAGC, regardless sex, country, duration, severity, stage of HER2-PAGC, and educational background. Outcomes included efficacy (response rate, disease control rate, overall survival, progression-free survival, survival rate at month 6, 12, 18, 24, mean survival months of death) and safety (neutropenia, leukopenia, nausea and vomiting, diarrhea, liver function impairment, neurotoxicity, cardiac toxicity, rash, myelosuppression, and hand-foot syndrome).

![Figure 1. Flow diagram of study selection. RCT = randomized controlled trial.](image-url)
2.2.2 Exclusion criteria. We excluded studies of repetitive reports, animal experiments, reviews, case studies, conference abstracts, nonclinical trial, uncontrolled trial, and non-RCTs.

2.3 Data source and search strategy

We comprehensively searched PubMed, EMBASE, Cochrane Library, WANGFANG, and CNKI to check any potential studies. All electronic databases were retrieved from inception onwards. We also searched other literature, including websites of clinical trial registry, conference abstracts, and reference lists of associated reviews. The search terms included “gastric cancer”, “stomach neoplasm”, “gastric neoplasm”, “cancer of stomach”, “cancer, stomach”, “cancer, gastric”, “neoplasm, gastric”, “human epidermal growth factor receptor 2”, “HER2”, “HER2-positive”, “advanced”, “trastuzumab”, “herceptin”, “monoclonal antibody”, “trastuzumab-ans”, “trastuzumab dkst”, “trastuzumab-dttb”, “trastuzumab-pkrb”, “trastuzumab-qq”, “chemotherapy”, “controlled trials”, “clinical trials”, “random”, “randomly”, “control”, “allocation”, “placebo”, “blind”, “trial”, and “study.” The detailed search strategy for PubMed is presented in Table 1.

2.4 Study selection

All citations were managed using Endnote X8 (Clarivate Analytics) and duplicates were removed. Two reviewers independently screened the records by title and abstract, and irrelevant studies were eliminated. The full text of the remaining articles was then carefully read against all eligibility criteria. If any divergence occurred between the 2 reviewers, we invited a third experienced reviewer to resolve it through a discussion.

2.5 Data collection and management

Two reviewers independently extracted data utilizing a standardized data collection form with the following items: trial information (first author, year of publication, title, country, language, trial setting, sample size, etc); trial methods (methods of randomization, blind, allocation, concealment, etc); patient information (sex, age, type and stage of AGC, duration of AGC, onset, diagnostic criteria, inclusion and exclusion criteria, etc); intervention and control (types of interventions and controls, dosage, frequency, duration, etc); and outcomes, follow-up information, and adverse events. If any disagreement occurred between the 2 reviewers, a third experienced reviewer was consulted to settle the division.

### Table 2: General characteristics of included studies.

| Study       | Location     | Sample size (T/C) | Age (yr, T/C) | Gender (M/F) | Intervention       | Control       | Outcomes     | Follow-up (mo) |
|-------------|--------------|------------------|---------------|--------------|-------------------|---------------|--------------|----------------|
| Bang et al  | Asia, USA, Europe | 292/290         | T:59.4 ± 10.8 | C:66.3 ± 11.8 | Trastuzumab + CFC | CFC           | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 34             |
| Cao et al   | China        | 24/24            | T:56.7 ± 9.4  | C:58.5 ± 11.2 | Trastuzumab + OT  | OT            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 42             |
| Chen et al  | China        | 24/24            | T:60.4 ± 8.1  | C:58.2 ± 10.5 | Trastuzumab + OT  | OT            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 2              |
| Huang and Gao | China       | 40/40            | T:61.4 ± 5.5  | C:60.4 ± 8.1  | Trastuzumab + CFC | CFC           | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 4.2            |
| Lan et al   | China        | 39/39            | T:59.5 ± 8.2  | C:60.3 ± 8.3  | Trastuzumab + IC  | IC            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 1.5            |
| Li et al    | China        | 15/14            | T:58.5 ± 8.2  | C:58.4 ± 2.1  | Trastuzumab + OT  | OT            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 4.2            |
| Li and Shi  | China        | 100/100          | T:61.5 ± 6.3  | C:64.4 ± 6.7  | Trastuzumab + CC  | CC            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 4.2            |
| Lv et al    | China        | 38/38            | T:60.4 ± 5.5  | C:61.5 ± 6.3  | Trastuzumab + CC  | CC            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 4.2            |
| Sawaki et al| Japan        | 51/50            | T:63*         | C:60*         | Trastuzumab + OT  | OT            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 2              |
| Shen et al  | China        | 36/48            | T:58.7 ± 10.5 | C:60.0         | Trastuzumab + CFC | CFC           | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 34             |
| Song et al  | China        | 30/30            | T:63.5 ± 11.3 | C:63.5 ± 11.3 | Trastuzumab + OT  | OT            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 34             |
| Wang et al  | China        | 35/35            | T:55.5 ± 4.7  | C:55.5 ± 4.6  | Trastuzumab + OL  | OL            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 2              |
| Wu and Xie  | China        | 63/63            | T:62.2 ± 5.5  | C:61.4 ± 5.5  | Trastuzumab + CC  | CC            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 2              |
| Yang et al  | China        | 25/25            | T:56.5 ± 2.3  | C:56.5 ± 2.3  | Trastuzumab + OT  | OT            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 4.2            |
| Yang et al  | China        | 39/39            | T:63.5 ± 5.3  | C:56.4 ± 5.4  | Trastuzumab + CFC | CC            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 4.2            |
| Yu et al    | China        | 48/48            | T:58.5 ± 7.2  | C:57.5 ± 7.7  | Trastuzumab + OF  | OF            | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 24             |
| Zhu et al   | China        | 44/44            | T:59.5 ± 7.2  | C:57.5 ± 7.7  | Trastuzumab + DCF | DCF           | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 24             |
| Zhu et al   | China        | 37/35            | T:56.8 ± 4.5  | C:57.5 ± 4.5  | Trastuzumab + DCF | DCF           | ①②③④⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭  | 24             |

①Response rate; ②disease control rate; ③overall survival; ④progression-free survival; ⑤survival rate at month 6, 12, 18, 24; ⑥mean survival months of death; ⑦Neutropenia; ⑧leukopenia; ⑨nausea and vomiting; ⑩diarrhea; ⑪liver function impairment; ⑫neurotoxicity; ⑬cardiac toxicity; ⑭diabetes; ⑮myelosuppression; ⑯hand-foot syndrome.

C = control group, CAF = cyclophosphamide + doxorubicin + 5-fluorouracil, CC = capecitabine + cisplatin, CFC = capecitabine or 5-fluorouracil + cisplatin, DCF = docetaxel + cisplatin + 5-fluorouracil, F = female, IC = irinotecan + cisplatin, M = male, NR = not report, OF = oxaliplatin + 5-fluorouracil, OL = oxaliplatin + leucovorin, OT = oxaliplatin + tegafur, T = treatment group.

*Age reported as median age.
2.6. Study methodological quality assessment

Two reviewers independently appraised the methodological quality of each eligible trial using the Cochrane Risk of Bias Tool. This tool had 7 aspects, and each one was rated as “high risk of bias”, “unclear risk of bias”, or “low risk of bias”. Any differences were resolved by a third experienced reviewer through a discussion or consultation.

2.7. Statistical analysis

This study utilized the RevMan 5.4 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) for data analysis. The treatment effect of dichotomous data was calculated as the risk ratio and 95% confidence interval (CI), while that of continuous data was estimated as the MD and 95% CI. $I^2$ statistics were utilized to identify heterogeneity across eligible trials. $I^2 \leq 50\%$ indicated reasonable heterogeneity and a random-effects model was applied, whereas $I^2 > 50\%$ exerted remarkable heterogeneity and a random-effects model was used. If insufficient data were available, we performed a meta-analysis. We reported the results of a narrative and descriptive summary if insufficient data were pooled.

3. Results

3.1. Study selection

A total of 759 records were identified from electronic databases and other sources using the previously defined search criteria. After duplications were excluded, the titles and abstracts of the potential records were screened, and the remaining full-text articles were carefully read. Finally, 18 RCTs, including 1964 patients, were eligible for inclusion (Fig. 1).

3.2. General characteristics

The intervention and control arms included capecitabine or 5-fluorouracil plus cisplatin (CFC), oxaliplatin plus tegafur (OT), capecitabine plus cisplatin (CC), irinotecan and cisplatin (IC), oxaliplatin and leucovorin (OL), cyclophosphamide, azithromycin and 5-fluorouracil (CAF), oxaliplatin and 5-fluorouracil (OF), and docetaxel, cisplatin, and 5-fluorouracil (DCF) in combination with or without trastuzumab. The main characteristics of the included RCTs are summarized in Table 2.

3.3. Study quality assessment

The methodological quality of the 18 included trials was assessed using the Cochrane risk of bias tool (Fig. 2). All 18 studies reported sufficient information on random sequence generation, incomplete outcomes, selective reporting, and other bias.\[32–49\] However, only 2 studies reported details of allocation concealment and insufficient details of the binding of participants and investigators.\[32,40\] In addition, none of the 18 studies clearly reported binding to outcome assessors clearly\[32–49\] (Fig. 2).

3.4. Comparison between trastuzumab in combination with CFC and CFC

Three studies with 769 patients compared the efficacy and safety of trastuzumab in combination with CFC and CFC. Meta-analysis results showed that there were significant differences on response rate (odds ratio [OR] = 1.56, 95% confidence interval [CI] [1.17, 2.09], $I^2 = 0\%$, $P < .003$; Table 3, Fig. 3),\[32,40,41\] and disease control rate (OR = 1.61, 95% CI [1.17, 2.21], $I^2 = 0\%$, $P = .004$; Table 3, Fig. 3).\[32,40,41\] Meta-analysis results of overall survival rate showed at
6 months (OR = 1.37, 95% CI [0.98–1.92], P = .07), 12 months (OR = 1.36, 95% CI [0.99–1.87], P = .05), 18 months (OR = 1.56, 95% CI [1.04–2.32], P = .03), and 24 months (OR = 1.39, 95% CI [0.82–2.36], P = .22; Table 3, Fig. 4).

As for safety, meta-analysis results showed that no significant differences were identified on occurrence rate of adverse events: neutropenia (OR = 0.89, 95% CI [0.67–1.19], I² = 7%, P = .44; [32,40]) and leukopenia (OR = 1.91, 95% CI [0.93–3.92], I² = 0%, P = .08; [32,40,41]) nausea (OR = 1.17, 95% CI [0.85–1.61], I² = 0%, P = .35; [32,40,41]) vomiting (OR = 1.13, 95% CI [0.86–1.60], I² = 0%, P = .16; [32,40,41]) diarrhea (OR = 1.19, 95% CI [0.82–1.74], I² = 0%, P = .36; [32,40,41]) rash (OR = 1.77, 95% CI [0.62–5.06], I² = 0%, P = .28; [32,40,41]) and hand-foot syndrome (OR = 1.19, 95% CI [0.82–1.74], I² = 0%, P = .36; [32,40,41]) (Table 3, Fig. 5).

3.5. Comparison between trastuzumab in combination with OT and OT

Five studies with 235 patients compared the efficacy and safety of trastuzumab in combination with OT and OT. Meta-analysis results showed that there were significant differences in response rate (OR = 2.97, 95% CI [1.74–5.09], P < .0001; Table 4, Fig. 6) and disease control rate (OR = 4.29, 95% CI [2.33–7.90], P < .0001; Table 4, Fig. 6). However, meta-analysis results of safety showed that no significant differences were identified on nausea and vomiting (OR = 0.66, 95% CI [0.30–1.47], I² = 0%, P = .31; [32,40,41]) diarrhea (OR = 1.23, 95% CI [0.50–3.03], I² = 0%, P = .65; [32,40,41]) liver function impairment (OR = 0.91, 95% CI [0.38–2.15], I² = 0%, P = .83; [32,40,41]) neurotoxicity (OR = 0.85, 95% CI [0.44–1.63], I² = 0%, P = .62; [32,40,41]) and
cardiac toxicity (OR = 1.00, 95% CI [0.22–4.55], F = 0%, P = 1.00)[33,34] (Table 4, Fig. 7).

3.6. Comparison between trastuzumab in combination with CC and CC

Five studies with 560 patients compared the efficacy and safety of trastuzumab in combination with CC and CC. Meta-analysis results showed that there were significant differences in response rate (OR = 2.62, 95% CI [1.84–3.73], F = 0%, P < .0001, Table 5, Fig. 8).[35,38,39,44,46] and disease control rate (OR = 2.99, 95% CI [1.99–4.48], F = 0%, P < .0001; Table 5, Fig. 8).[35,38,39,44,46] However, meta-analysis results of safety showed that there were no significant differences on nausea and vomiting (OR = 1.03, 95% CI [0.64–1.67], F = 0%, P = .90),[35,38,39,44,46] liver function impairment (OR = 1.08, 95% CI [0.70–1.66], F = 0%, P = .74),[35,38,39,44,46] myelosuppression (OR = 1.08, 95% CI [0.77–1.52], F = 0%, P = .66),[35,38,39,44,46] and hand-foot syndrome (OR = 1.09, 95% CI [0.73–1.62], F = 0%, P = .69)[35,38,39,44] (Table 5, Fig. 9). One study explored the efficacy on overall survival (mean difference [MD] = 2.62, 95% CI [1.94–3.30], P < .001; Table 5), and progression-free survival (MD = 3.8, 95% CI [3.22–4.38], F = 99%, P < .001; Table 5).[36]

3.7. Comparison between trastuzumab in combination with IC and IC

One study with 78 patients compared the efficacy and safety of trastuzumab in combination with IC and IC on efficacy (response rate, disease control rate) and safety (nausea and vomiting, liver function impairment, myelosuppression, and hand-foot syndrome; Table 6).[46]

3.8. Comparison between trastuzumab in combination with OL and OL

One study with 70 patients compared the efficacy and safety of trastuzumab in combination with OL and OL on efficacy (response rate and disease control rate) and safety (leukopenia, nausea and vomiting, liver function impairment, neurotoxicity, cardiac toxicity, and rash; Table 7).[36]

3.9. Comparison between trastuzumab in combination with CAF and CAF

One study with 96 patients investigated the efficacy and safety of trastuzumab in combination with CAF and CAF on efficacy.
# Figure 5

Trastuzumab plus CFC vs CFC: occurrence rate of adverse events. CFC = capecitabine or 5-fluorouracil+cisplatin, CI = confidence interval.

| Study or Subgroup | Experimental Events | Control Events | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|----------------|-------------------------------|-------------------------------|
| **1.3.1 Neutropenia** | | | | |
| Bang 2010 | 157 | 294 | 165 | 290 | 79.1% | 0.87 [0.63, 1.19] | |
| Sawaki 2012 | 30 | 51 | 54 | 50 | 14.5% | 0.67 [0.30, 1.52] | |
| Shen 2013 | 12 | 36 | 11 | 48 | 6.4% | 1.69 [0.64, 4.42] | |
| Subtotal (95% CI) | 381 | 388 | 100.0% | 0.89 [0.67, 1.19] | |
| Total events | 199 | 210 | Heterogeneity: Chi² = 2.14, df = 2 (P = 0.34), I² = 7% | Test for overall effect: Z = 0.78 (P = 0.44) |
| **1.3.2 Leukopenia** | | | | |
| Bang 2010 | 15 | 294 | 8 | 290 | 68.3% | 1.90 [0.79, 4.45] | |
| Sawaki 2012 | 5 | 51 | 3 | 50 | 24.4% | 1.70 [0.38, 7.54] | |
| Shen 2013 | 2 | 36 | 1 | 48 | 7.2% | 2.76 [0.24, 31.74] | |
| Subtotal (95% CI) | 381 | 388 | 100.0% | 1.91 [0.93, 3.92] | |
| Total events | 22 | 12 | Heterogeneity: Chi² = 0.11, df = 2 (P = 0.95), I² = 0% | Test for overall effect: Z = 1.76 (P = 0.08) |
| **1.3.3 Nausea** | | | | |
| Bang 2010 | 197 | 294 | 184 | 290 | 87.9% | 1.17 [0.83, 1.65] | |
| Sawaki 2012 | 44 | 51 | 44 | 50 | 8.8% | 0.86 [0.27, 2.76] | |
| Shen 2013 | 4 | 36 | 3 | 48 | 3.3% | 1.89 [0.39, 9.06] | |
| Subtotal (95% CI) | 381 | 388 | 100.0% | 1.17 [0.85, 1.61] | |
| Total events | 245 | 231 | Heterogeneity: Chi² = 0.62, df = 2 (P = 0.79), I² = 0% | Test for overall effect: Z = 0.94 (P = 0.35) |
| **1.3.4 Vomiting** | | | | |
| Bang 2010 | 147 | 294 | 134 | 290 | 94.0% | 1.18 [0.84, 1.61] | |
| Sawaki 2012 | 33 | 51 | 29 | 50 | 12.4% | 1.44 [0.65, 3.21] | |
| Shen 2013 | 6 | 36 | 4 | 48 | 3.5% | 2.20 [0.57, 8.47] | |
| Subtotal (95% CI) | 381 | 388 | 100.0% | 1.24 [0.92, 1.66] | |
| Total events | 186 | 166 | Heterogeneity: Chi² = 0.97, df = 2 (P = 0.61), I² = 0% | Test for overall effect: Z = 1.41 (P = 0.16) |
| **1.3.5 Diarrhea** | | | | |
| Bang 2010 | 109 | 294 | 60 | 290 | 78.2% | 1.55 [1.09, 2.18] | |
| Sawaki 2012 | 23 | 51 | 24 | 50 | 20.5% | 0.89 [0.41, 1.95] | |
| Shen 2013 | 2 | 36 | 1 | 48 | 1.2% | 2.76 [0.24, 31.74] | |
| Subtotal (95% CI) | 381 | 388 | 100.0% | 1.43 [1.04, 1.96] | |
| Total events | 134 | 105 | Heterogeneity: Chi² = 1.99, df = 2 (P = 0.39), I² = 0% | Test for overall effect: Z = 2.21 (P = 0.03) |
| **1.3.6 Neurotoxicity** | | | | |
| Sawaki 2012 | 36 | 51 | 34 | 50 | 88.8% | 1.13 [0.49, 2.63] | |
| Shen 2013 | 0 | 36 | 1 | 48 | 11.2% | 0.43 [0.02, 10.98] | |
| Subtotal (95% CI) | 381 | 388 | 100.0% | 1.05 [0.47, 2.37] | |
| Total events | 36 | 35 | Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57), I² = 0% | Test for overall effect: Z = 0.12 (P = 0.90) |
| **1.3.7 Rash** | | | | |
| Sawaki 2012 | 10 | 51 | 5 | 50 | 76.1% | 2.29 [0.69, 6.98] | |
| Shen 2013 | 0 | 36 | 1 | 48 | 23.3% | 0.43 [0.02, 10.98] | |
| Subtotal (95% CI) | 381 | 388 | 100.0% | 1.77 [0.62, 5.06] | |
| Total events | 10 | 6 | Heterogeneity: Chi² = 0.86, df = 1 (P = 0.35), I² = 0% | Test for overall effect: Z = 1.07 (P = 0.28) |
| **1.3.8 Hand-foot syndrome** | | | | |
| Bang 2010 | 75 | 294 | 64 | 290 | 96.8% | 1.21 [0.83, 1.77] | |
| Shen 2013 | 1 | 36 | 2 | 48 | 3.4% | 0.66 [0.08, 5.74] | |
| Subtotal (95% CI) | 330 | 338 | 100.0% | 1.19 [0.92, 1.74] | |
| Total events | 76 | 68 | Heterogeneity: Chi² = 0.21, df = 1 (P = 0.63), I² = 0% | Test for overall effect: Z = 0.91 (P = 0.36) |

Test for subgroup differences: Chi² = 7.49, df = 7 (P = 0.38), I² = 6.6%
response rate and disease control rate) and safety (leukopenia, nausea and vomiting, liver function impairment, and neurotoxicity; Table 8).

3.10. Comparison between trastuzumab in combination with OF and OF

One study with 84 patients explored the efficacy and safety of trastuzumab in combination with OF and OF on efficacy (response rate and disease control rate) and safety (liver function impairment, neurotoxicity, cardiac toxicity, rash, and myelosuppression; Table 9).

3.11. Comparison between trastuzumab in combination with DCF and DCF

One study with 72 patients assessed the efficacy and safety of trastuzumab in combination with DCF and DCF on efficacy (response rate, disease control rate, overall survival rate at 6, 12, 18, and 24 months, and mean survival of death) and safety (neutropenia, neurotoxicity, cardiac toxicity, and rash; Table 10).

4. Discussion

Previous studies have explored the efficacy of trastuzumab combined with chemotherapy for the management of HER2-PAGC.

Of these 3 systematic reviews and meta-analyses, the latest one was published in 2019, and its literature search date was up to November 2017. In addition, the overall methodological quality of the included trials was very poor. In this study, we included and updated more recent clinical studies than previous systematic reviews and meta-analyses.

Additionally, the overall quality of the trials in this study was higher than that of previous studies.

This systematic review and meta-analysis included 18 RCTs with 1964 patients, and focused on investigating the efficacy of trastuzumab in combination with chemotherapy for the treatment of patients with HER2-PAGC. It summarizes the most recent evidence on eligible trials and appraises their methodological quality. Whenever available, outcome data were synthesized to provide helpful evidence-based medical evidence and bridge this gap in research in this field.

Meta-analysis results showed that trastuzumab in combination with CFC, OT, and CC achieved better outcomes in response and disease control rates than CFC, OT, and CC alone.
Figure 7. Trastuzumab plus OT vs OT: occurrence rate of adverse events. CI = confidence interval, OT = oxaliplatin+tegafur.

Table 5
Qualitative synthesis of comparison between trastuzumab plus CC and CC.

| Outcome or subgroup                      | Studies | Participants | Statistical method   | Effect estimate |
|------------------------------------------|---------|--------------|----------------------|-----------------|
| 3.1 Efficacy                             |         |              |                      |                 |
| 3.1.1 Response rate                      | 5       | 560          | Odds ratio (M-H, fixed, 95% CI) | 2.82 (1.49–4.58) |
| 3.1.2 Disease control rate               | 5       | 560          | Odds ratio (M-H, fixed, 95% CI) | 5.89 (2.78–12.52) |
| 3.2 Efficacy                             |         |              |                      |                 |
| 3.2.1 Overall survival                   | 1       | 126          | Mean difference (IV, fixed, 95% CI) | 1.1 (0.5–2.3)    |
| 3.2.2 Progression-free survival          | 1       | 126          | Mean difference (IV, fixed, 95% CI) | 1.0 (0.6–1.7)    |
| 3.3 Occurrence rate of adverse events    |         |              |                      |                 |
| 3.3.1 Nausea and vomiting                | 5       | 560          | Odds ratio (M-H, fixed, 95% CI) | 1.03 (0.64–1.67) |
| 3.3.2 Liver function impairment          | 5       | 560          | Odds ratio (M-H, fixed, 95% CI) | 1.08 (0.70–1.66) |
| 3.3.3 Myelosuppression                   | 5       | 560          | Odds ratio (M-H, fixed, 95% CI) | 1.08 (0.77–1.52) |
| 3.3.4 Hand-foot syndrome                 | 4       | 482          | Odds ratio (M-H, fixed, 95% CI) | 1.09 (0.73–1.62) |

CC = capecitabine + cisplatin, CI = confidence interval.
However, there were no significant differences in the occurrence rates of neutropenia, leukopenia, nausea and vomiting, diarrhea, liver function impairment, neurotoxicity, cardiac toxicity, rash, myelosuppression, or hand-foot syndrome. These findings indicate that trastuzumab combined with chemotherapy may have a more promising efficacy than chemotherapy alone, with a similar safety profile.

This systematic review and meta-analysis had several limitations: there was an insufficient number of eligible trials with the same combined chemotherapy; the sample size of some included studies was quite small, and their effectiveness was limited; and there was an unclear risk of bias in allocation and blinding to patients, investigators, and outcome assessors, which affected the overall quality of the included RCTs. Future studies should address these limitations.

5. Conclusion
The results of this study showed that the efficacy of trastuzumab combined with chemotherapy is superior to that of chemotherapy alone. Both modalities showed similar safety profiles.

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Table 6
Qualitative synthesis of comparison between trastuzumab plus IC and IC.

| Outcome or subgroup | Studies | Participants | Statistical method | Effect estimate |
|---------------------|---------|--------------|--------------------|-----------------|
| 4.1 Efficacy        |         |              | Odds ratio (M-H, fixed, 95% CI) |                |
| 4.1.1 Response rate | 1       | 78           | Odds ratio (M-H, fixed, 95% CI) | 2.59 (1.03–6.49) |
| 4.1.2 Disease control rate | 1 | 78 | Odds ratio (M-H, fixed, 95% CI) | 3.60 (0.89–14.51) |
| 4.2 Occurrence rate of adverse events | | | | |
| 4.2.1 Nausea and vomiting | 1 | 78 | Odds ratio (M-H, fixed, 95% CI) | 0.73 (0.15–3.50) |
| 4.2.2 Liver function impairment | 1 | 78 | Odds ratio (M-H, fixed, 95% CI) | 1.16 (0.40–3.41) |
| 4.2.3 Myelosuppression | 1 | 78 | Odds ratio (M-H, fixed, 95% CI) | 1.48 (0.54–4.06) |
| 4.2.4 Hand-foot syndrome | 1 | 78 | Odds ratio (M-H, fixed, 95% CI) | 1.18 (0.38–3.65) |

CI = confidence interval, IC = irinotecan + cisplatin.
### Table 7
Qualitative synthesis of comparison between trastuzumab plus OL and OL.

| Outcome or subgroup | Studies | Participants | Statistical method | Effect estimate |
|---------------------|---------|--------------|--------------------|-----------------|
| 5.1 Efficacy        |         |              |                    |                 |
| 5.1.1 Response rate | 1       | 70           | Odds ratio (M-H, fixed, 95% CI) | 2.00 (0.77–5.18) |
| 5.1.2 Disease control rate | 1 | 70 | Odds ratio (M-H, fixed, 95% CI) | 1.83 (0.61–5.47) |
| 5.2 Occurrence rate of adverse events | | | | |
| 5.2.1 Leukopenia    | 1       | 70           | Odds ratio (M-H, fixed, 95% CI) | 1.50 (0.43–5.28) |
| 5.2.2 Nausea and vomiting | 1 | 70 | Odds ratio (M-H, fixed, 95% CI) | 1.26 (0.49–3.22) |
| 5.2.3 Liver function impairment | 1 | 70 | Odds ratio (M-H, fixed, 95% CI) | 0.49 (0.04–5.61) |
| 5.2.4 Neurotoxicity | 1       | 70           | Odds ratio (M-H, fixed, 95% CI) | 0.52 (0.14–1.96) |
| 5.2.5 Cardiac toxicity | 1 | 70 | Odds ratio (M-H, fixed, 95% CI) | 5.67 (0.63–51.27) |
| 5.2.6 Rash          | 1       | 70           | Odds ratio (M-H, fixed, 95% CI) | 4.89 (0.96–24.97) |

CI = confidence interval, OL = oxaliplatin + leucovorin.

### Table 8
Qualitative synthesis of comparison between trastuzumab plus CAF and CAF.

| Outcome or subgroup | Studies | Participants | Statistical method | Effect estimate |
|---------------------|---------|--------------|--------------------|-----------------|
| 6.1 Efficacy        |         |              |                    |                 |
| 6.1.1 Response rate | 1       | 96           | Odds ratio (M-H, fixed, 95% CI) | 2.14 (0.95–4.83) |
| 6.1.2 Disease control rate | 1 | 96 | Odds ratio (M-H, fixed, 95% CI) | 1.84 (0.61–5.55) |
| 6.2 Occurrence rate of adverse events | | | | |
| 6.2.1 Leukopenia    | 1       | 96           | Odds ratio (M-H, fixed, 95% CI) | 1.36 (0.29–6.45) |
| 6.2.2 Nausea and vomiting | 1 | 96 | Odds ratio (M-H, fixed, 95% CI) | 0.60 (0.22–1.63) |
| 6.2.3 Liver function impairment | 1 | 96 | Odds ratio (M-H, fixed, 95% CI) | 1.28 (0.32–5.09) |
| 6.2.4 Neurotoxicity | 1       | 96           | Odds ratio (M-H, fixed, 95% CI) | 0.65 (0.22–1.88) |

CAF = cyclophosphamide + azithromycin + 5-fluorouracil, CI = confidence intervals.

### Table 9
Qualitative synthesis of comparison between trastuzumab plus OF and OF.

| Outcome or subgroup | Studies | Participants | Statistical method | Effect estimate |
|---------------------|---------|--------------|--------------------|-----------------|
| 7.1 Efficacy        |         |              |                    |                 |
| 7.1.1 Response rate | 1       | 84           | Odds ratio (M-H, fixed, 95% CI) | 2.37 (0.98–5.69) |
| 7.1.2 Mean survival months of death | 1 | 84 | Mean difference (IV, fixed, 95% CI) | 2.30 (1.04–3.56) |
| 7.2 Occurrence rate of adverse events | | | | |
| 7.2.1 Liver function impairment | 1 | 84 | Odds ratio (M-H, fixed, 95% CI) | 1.41 (0.58–3.41) |
| 7.2.2 Neurotoxicity | 1       | 84           | Odds ratio (M-H, fixed, 95% CI) | 0.78 (0.29–2.09) |
| 7.2.3 Cardiac toxicity | 1 | 84 | Odds ratio (M-H, fixed, 95% CI) | 7.38 (0.87–62.90) |
| 7.2.4 Rash          | 1       | 84           | Odds ratio (M-H, fixed, 95% CI) | 4.11 (1.06–16.02) |
| 7.2.5 Myelosuppression | 1 | 84 | Odds ratio (M-H, fixed, 95% CI) | 1.43 (0.59–3.46) |

CI = confidence interval, OF = oxaliplatin + 5-fluorouracil.

### Table 10
Qualitative synthesis of comparison between trastuzumab plus DCF and DCF.

| Outcome or subgroup | Studies | Participants | Statistical method | Effect estimate |
|---------------------|---------|--------------|--------------------|-----------------|
| 9.1 Efficacy        |         |              |                    |                 |
| 9.1.1 Response rate | 1       | 72           | Odds ratio (M-H, fixed, 95% CI) | 2.46 (0.95–6.37) |
| 9.1.2 Disease control rate | 1 | 72 | Odds ratio (M-H, fixed, 95% CI) | 2.83 (0.67–11.98) |
| 9.2 Survival rate at different follow-up visits | | | | |
| 9.2.1 6 months     | 1       | 72           | Odds ratio (M-H, fixed, 95% CI) | 3.26 (0.13–82.75) |
| 9.2.2 12 months    | 1       | 72           | Odds ratio (M-H, fixed, 95% CI) | 1.75 (0.67–4.57) |
| 9.2.3 18 months    | 1       | 72           | Odds ratio (M-H, fixed, 95% CI) | 2.64 (0.99–7.01) |
| 9.2.4 24 months    | 1       | 72           | Odds ratio (M-H, fixed, 95% CI) | 3.05 (1.06–8.74) |
| 9.3 Mean survival months of death | 1 | 72 | Mean difference (IV, fixed, 95% CI) | 2.20 (1.06–3.34) |
| 9.4 Occurrence rate of adverse events | | | | |
| 9.4.1 Neutropenia  | 1       | 72           | Odds ratio (M-H, fixed, 95% CI) | 1.42 (0.56–3.62) |
| 9.4.2 Neurotoxicity | 1       | 72           | Odds ratio (M-H, fixed, 95% CI) | 1.13 (0.34–3.76) |
| 9.4.3 Cardiac toxicity | 1 | 72 | Odds ratio (M-H, fixed, 95% CI) | 9.54 (0.49–183.98) |
| 9.4.4 Rash         | 1       | 72           | Odds ratio (M-H, fixed, 95% CI) | 1.16 (0.32–4.21) |

CI = confidence interval, DCF = docetaxel + cisplatin + 5-fluorouracil.
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