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REVIEW ARTICLE

The efficacy and safety of targeted therapy with or without chemotherapy in advanced gastric cancer treatment: a network meta-analysis of well-designed randomized controlled trials

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Abstract

Background Advanced gastric cancer (AGC) is a severe malignant tumor associated with high mortality. Targeted therapy is an important approach for improving the therapeutic effects of AGC treatment. This study evaluates the efficacy and safety of targeted agents for AGC patients.

Methods PubMed, EmBase, and the Cochrane Library were searched for double-blind randomized controlled trials (RCTs) of AGC treatments published prior to July 2017. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and severe adverse effects (AEs) were evaluated to determine the efficacy and safety of targeted agents. A network meta-analysis with a frequentist framework was performed to assess the effects of various targeted agents for AGC treatment.

Results Our analysis included 16 articles involving 5371 patients and 11 types of agents. The network meta-analysis showed that apatinib (97.5%) was most likely to improve PFS, followed by regorafenib (86.3%) and rilotumumab (65.4%). Apatinib was similarly best for OS outcome, (95.5%) followed by rilotumumab (74.7%) and regorafenib (70%). Apatinib (89.6%) also had the best improvement on ORR, followed by rilotumumab (75.4%) and everolimus (68.4%). Bevacizumab (85.5%) was likely to get the lowest severe AEs, followed by sunitinib (63%).

Conclusions Apatinib, regorafenib, and rilotumumab improved patient PFS and OS. When combined with chemotherapy, ramucirumab and rilotumumab had high efficacy but low tolerability, and bevacizumab had moderate efficacy and tolerability for PFS. Without chemotherapy, ramucirumab and regorafenib had relatively high therapeutic efficacy tolerability for PFS.

Keywords Advanced gastric cancer · Targeted therapy · Clinical treatment · Meta-analysis

Introduction

Gastric cancer is a common malignant tumor worldwide, especially in Asia. GLOBOCAN showed gastric cancer to be the fifth most common malignant tumor, with the third highest mortality in 2012 [1]. The high mortality stems from the considerable proportion of patients already presenting late-stage tumors at diagnosis [2]. Therefore, gastric cancer treatment mainly focuses on advanced stages. Gastric cancer incidence varies by region, with high incidence in East Asia. Due to prevalent early endoscopic screenings in Japan, more patients are diagnosed in early stages, leading to better treatment outcomes [3]. Additionally, the incidence of cardiac carcinoma and gastroesophageal junction cancer (GEJC) may be related to reflux esophagitis and dysplasia in Barrett esophagus. Because of their close anatomic positions, these types of cancer are often studied together.

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The etiology of gastric cancer is still unclear, with possible factors including regional environment, diet habits, helicobacter pylori infection, and genetic factors. The main metastatic pathways of advanced gastric cancer (AGC) are local invasion, blood metastasis, lymph node metastasis, and peritoneal implantation. Because of low sensitivity, radiotherapy is not commonly used. The current top treatments for AGC are systematic chemotherapy and palliative surgery. However, the overall survival rate of AGC remains unsatisfactory, with a median survival time of 8–11 months [4].

Although the efficacy of chemotherapy has gradually increased, patient survival has not seen significant improvement. A recent chemotherapy network meta-analysis showed that 5-fluorouracil based regimens are effective in ORR and OS and that S-1 based regimens have high safety, yet the differences between the regimens were not obvious in pairwise comparisons [5]. Another network meta-analysis compared the short-term effects of chemotherapy regimens in ORR and disease control rate (DCR) results. It showed that capecitabine and S-1 based multi-drug combination chemotherapy regimens are most effective [6]. This highlights the current lack of consensus for choosing the best advanced regimen for improving OS and ORR in AGC chemotherapy.

The efficacy of targeted therapy has been confirmed in breast and colorectal cancers, but the evidence in gastric cancer is still inadequate. Gastric cancer is highly heterogeneous, with abnormal expression and dysfunction of epidermal growth factor receptors (EGFRs), vascular endothelial growth factor receptors (VEGFRs), hepatocyte growth factor receptors (HGFRs), and mammalian target of rapamycin (mTOR) pathways, providing difficult conditions for targeted therapy [7]. At present, molecularly guided targeted therapies are a promising approach for improving therapeutic effects for AGC. Targeted therapy is capable of accurately identifying and attacking aberrant proteins specifically in tumor cells while remaining safe for normal cells. However, there is still controversy regarding the optimal selection of targeted agents for clinical use.

Previous meta-analyses suggested that targeted therapy could improve ORR and PFS in AGC and GEJC patients [8]. The risk of severe AE was increased with treatment, though there was no significant increase in fatal AE [9]. Thus, targeted therapy was shown to be effective and safe for AGC. For agent selection, a recent network meta-analysis showed that ramucirumab and trastuzumab have significant advantages for improving OS and ramucirumab and endostar have significant advantages for improving PFS in AGC patients [10]. However, this study included randomized controlled trials (RCTs) which lack a blinded design so they could not eliminate psychological effects. The study also analyzed OS and PFS at different times, with overall effect never evaluated. This resulted in inconsistencies such as endostar using different rankings between 1 and 2 year PFS, which might be puzzling for clinicians in practice. Furthermore, the study combined targeted therapy with chemotherapy, which may be lead to heterogeneity among studies that could make results unreliable. In this study, network meta-analysis was used to analyze various targeted agents of advanced gastric cancer. Network meta-analysis is a more fitting analysis strategy for this study compared to traditional meta-analysis, as it can compare various targeted agents indirectly to highlight the advantages and disadvantages of each agent, providing clearer guidance for the clinical application.

Methods

Data search strategy and selection criteria

This network meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews statement for Network meta-analyses (PRISMA-NMA) (PRISMA NMA Checklist) [11].

Two authors independently searched for literature published through July 30, 2017 using the electronic databases of PubMed, EmBase, and the Cochrane Library, with the keywords, “advanced”, “late-stage”, “terminal”, “unresectable”, “metastatic”, “gastric cancer”, “gastric carcinoma”, “carcinoma of stomach”, “stomach tumor”, and “random*” without language restriction. Due to the abundant types of targeted agents, their related keywords were not used. The references of relevant systematic reviews were assessed to ensure that no relevant studies were inadvertently omitted. Publications included in the present study met the following criteria: (1) RCT with blinded design; (2) inclusion of advanced gastric cancer patients; (3) examination of two or more groups using target agents and comparison with or without combined chemotherapy; (4) inclusion of one or more of the following outcomes: PFS, OS, ORR, or severe AE. Exclusion criteria consisted of: (1) non-RCT with blinded design; (2) study not including AGC patients; (3) target agents were not used in a related controlled study; or (4) non-desired outcome study. Additionally, non-peer reviewed studies such as conference reports and dissertations were excluded due to their lack of reliability.

Data extraction and quality assessment

The following information from each eligible study was extracted independently by two authors: first author’s name, publication year, clinical register, abbreviation of research, country, sample size, age, proportion of AGC, intervention, control treatment, chemotherapy, and follow-up. In the present analysis, the primary outcome was PFS and the secondary outcomes were OS, ORR, and severe AEs. PFS and OS were defined as duration from the time of random assignment to the

time of events occurring, ORR assessed the rate of complete response plus partial response, and severe AE was defined as the grade three to five AE, per the National Cancer Institute Common Terminology Criteria for Adverse Events. The methodological quality of the included trials was assessed using the Cochrane Collaboration's tool, which assigns grades of "high risk", "unclear risk", or "low risk" of bias across seven specified domains [12].

Statistics analysis

Hazard ratios (HR) and 95% confidence intervals (CIs) results from each included study were used to evaluate the treatment effects of various targeted agents in AGC, which could reduce the heterogeneity impact cause by the different follow-up times. The HR in PFS and OS outcomes were then pooled for the meta-analysis. Odds ratios (ORs) or logarithm transformations with 95% CIs were also calculated in analyses for ORR and AE outcomes. A traditional pairwise meta-analysis was initially conducted to show the entire efficacy and safety of target agents compared to placebo. Statistical heterogeneity was assessed in each pairwise comparison using the I^2 statistic and p value. When $I^2 > 50\%$, a random-effect model was used, otherwise a fixed-effect model was used. Subgroups analyses regarding combinations with chemotherapy were also performed. A random effects network meta-analysis was used for mixed multiple treatment comparisons, which adopted a frequentist framework [13]. In the network plot, the connection of two interventions indicates a direct comparison. The nodes are weighted according to number of studies and edged according to the precision of the direct estimate for each pairwise comparison. We did not perform inconsistency analysis since targeted agents were compared to placebo in all included studies. Global and local inconsistencies were unable to be assessed because there were no closed loops in the network. Surface under the cumulative ranking (SUCRA) probabilities were used to rank the treatments for each outcome, a commonly used technique in network meta-analysis. Higher SUCRA probabilities indicate better treatment effects [14]. Comparison-adjusted funnel plots were used to determine whether small-study effects were present in the analysis [15]. All tests were two tailed, and a p value < 0.05 was considered statistically significant. Data analyses were performed using STATA software (version 13.0; Stata Corporation, College Station, TX, USA).

Results

Literature search

Our search identified 2973 articles after duplicates were removed. A total of 2922 articles were excluded after screening their titles and abstracts. Published meeting abstracts were also excluded. The full texts of the remaining 51 articles were assessed, and the following types of studies were removed: studies with an open-label RCT design ($n = 20$); duplicate publications ($n = 6$); studies not including AGC patients ($n = 4$); non-desired outcomes ($n = 2$); intergroup unbalances such as target agent versus best supportive care or surgery ($n = 2$); and dosage-related studies ($n = 1$). Ultimately, sixteen articles involving 5,371 AGC patients were included in our systematic review [16–31] (Fig. 1).

Study characteristics

The included studies were published between 2002 and 2017, with one study published in 2002 [31] and the remaining 15 published after 2010 [16–30]. Several related RCTs lacking a blinded design were published before 2010, and these were excluded. Two included studies were not registered [21, 31], and eleven studies were multicenter [16, 19, 20, 22–24, 26, 27, 29–31]. Three studies did not provide the patients' age range [25, 28, 31]. Patients with AGC, GEJC, and esophageal tumors were included in our analysis, along with treatment drugs including apatinib, bevacizumab, everolimus, lapatinib, marimastat, onartuzumab, ramucirumab, regorafenib, rilotumumab, sunitinib, and trebananib. Placebos controls were used in all studies. Ten studies used chemotherapy in combination therapies [16–19, 22–25, 29, 30]. Follow-up periods ranged from 8 months to 4 years. One study on marimastat did not report ORR outcome [29], but all primary and secondary outcomes were reported in all other studies. The general characteristics of the included studies are presented in Table 1 and Supplemental Table 1. All of the included studies used a double-blind RCT design, and the study quality was ideal and reliable. However, fourteen studies were supported by pharmaceutical companies (Supplemental Fig. 1).

Traditional meta-analysis

Traditional meta-analysis results showed that targeted agents significantly prolonged PFS in AGC patients (HR 1.50; 95% CI 1.27–1.77; $p < 0.001$), and subgroup analysis showed that the advantage of targeted agents existed whether they were combined with chemotherapy treatment (HR 1.17; 95% CI 1.02–1.33; $p = 0.026$) or not (HR 2.28; 95% CI 1.70–3.05; $p < 0.001$) (Fig. 2). For OS outcome, targeted agents were significantly better than placebo (HR 1.17; 95% CI 1.02–1.33; $p = 0.021$). The subgroup analysis showed that targeted agents were only better than placebo when not combined with chemotherapy (HR 1.42; 95% CI 1.18–1.71; $p < 0.001$); those combined with chemotherapy did not have a statistically significant effect (HR

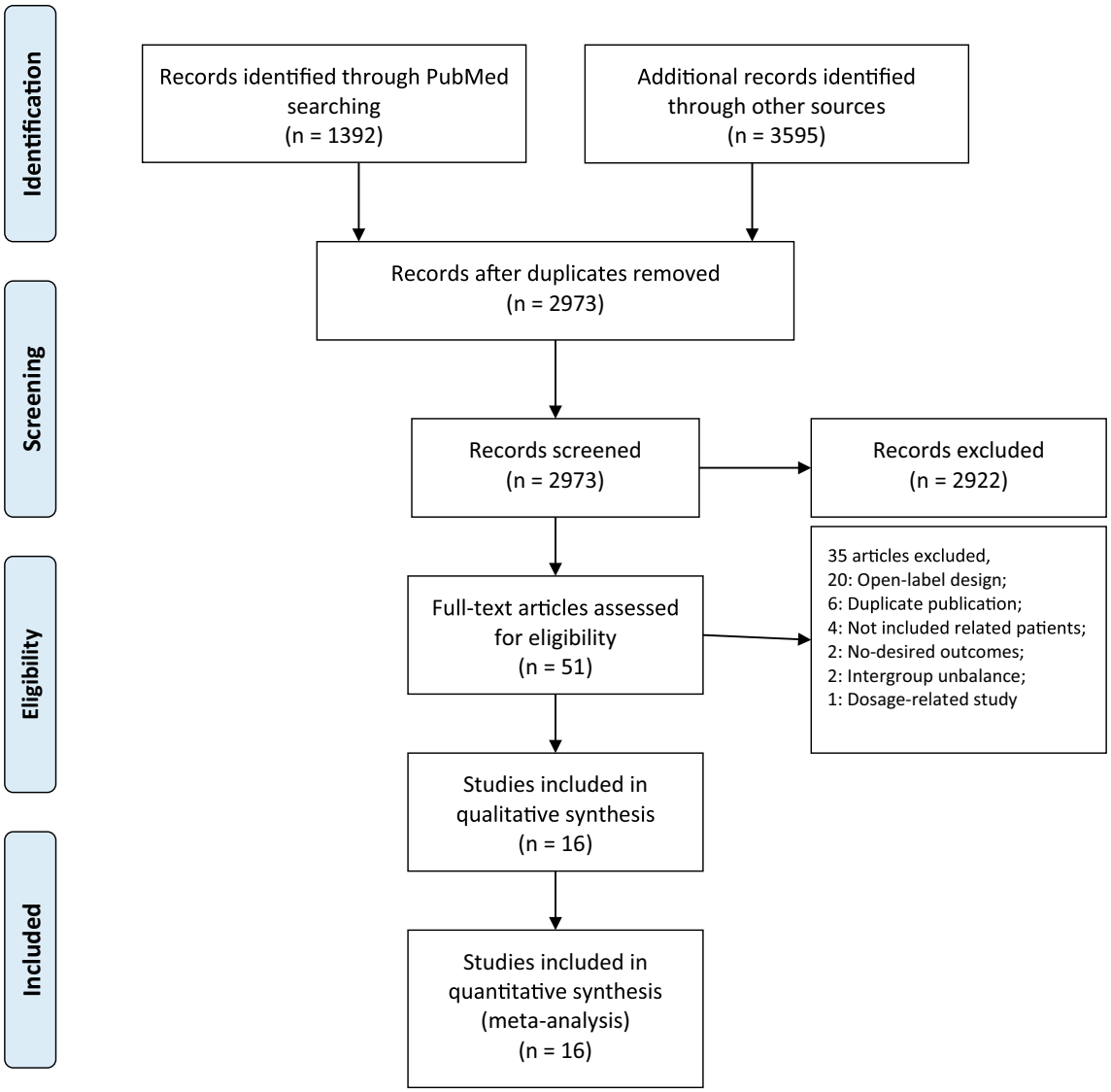

Fig. 1 Flowchart illustrating the selection of studies included in our analysis

1.02; 0.87–1.19; $p = 0.781$) (Fig. 3). For ORR outcome, the fixed effect model showed that targeted agents are better than placebo (HR 1.50; 95% CI 1.29–1.73; $p < 0.001$), and subgroup analysis showed consistent results whether the agents were combined with chemotherapy (OR 1.46; 95% CI 1.26–1.70; $p < 0.001$) or not (OR 2.36; 95% CI 1.14–4.89; $p = 0.021$) (Supplemental Fig. 2). Targeted agents had a significantly higher ratio of severe AE than placebo (OR 1.56; 95% CI 1.22–1.99; $p < 0.001$), whether combined with chemotherapy (OR 1.40; 95% CI 1.03–1.90; $p = 0.032$) or not (OR 1.88; 95% CI 1.23–2.88; $p = 0.003$) (Supplemental Fig. 3).Chemotherapy alone has high incidence of severe AE, therefore, our determination of the incidence of severe AE of targeted agents combined with chemotherapy may be an underestimation. The above results also showed substantial heterogeneity for the majority of the targeted agents.

Network meta-analysis

For the network meta-analysis of PFS, we analyzed 11 types of targeted agents, all of which were directly compared with placebo. In the network plot, nodes were weighted according to the number of studies and edges were weighted according to the precision of each comparison (Fig. 4a). Apatinib and ramucirumab were frequently investigated, and results of different trials comparing ramucirumab versus placebo were mostly precise. The results of the network meta-analyses are shown as a league table for all direct and indirect comparisons (Supplemental Tables 2–13). We ranked the comparative effects of all agents. Apatinib (97.5%) was most likely to improve PFS, followed by regorafenib (86.3%) and rilotumumab (65.4%) (Fig. 5). A comparison-adjusted funnel plot was used to assess publication bias and determine the

Table 1 Characteristics of subjects in eligible studies

Author	Year	Register	Study Abbr.	Country	Sample size	Age	Rate of AGC	Intervention	Control	Chemotherapy	Follow-up##
Shah [16]	2017	NCT01662869	YO28322	Multicenter	562	23–84	77%	Onartuzumab	Placebo	mFOLFOX6	18 M
Yoon [17]	2016	NCT01246960	NA	USA	168	27–83	23%	Ramucirumab	Placebo	mFOLFOX6	30 M
Moehler [18]	2016	NCT01020630	AIO	Germany	91	28–84	50%	Sunitinib	Placebo	Na-FOLFIRI	12 M
Shah [19]	2016	NCT01590719	YO28252	Multicenter	123	31–82	76%	Onartuzumab	Placebo	mFOLFOX6	16 M
Pavlakis [20]	2016	ANZCTR12612000239864	INTEGRATE	Multicenter	152	32-85	NA	Regorafenib	Placebo	NA	8 M
Li [21]	2016	NA	NA	China	273	23–71	42%	Apatinib	Placebo	NA	26 M
J.Randolph Hecht [22]	2015	NCT00680901	TRIO-013/ LOGiC	Multicenter	545	19-86	87%	Lapatinib	Placebo	CapeOx	45 M
Wilke [23]	2014	NCT01170663	RAINBOW	Multicenter	665	24–84	79%	Ramucirumab	Placebo	Paclitaxel	28 M
Iveson [24]	2014	NCT00719550	NA	Multicenter	121	27–79	81%	Rilotumumab	Placebo	ECX	23 M
Shen [25]	2014	NCT00887822	AVATAR	China	202	>18#	83%	Bevacizumab	Placebo	Cisplatin/capecitabine	27 M
Fuchs [26]	2014	NCT00917384	REGARD	Multicenter	355	51–71	75%	Ramucirumab	Placebo	NA	28 M
Ohtsu [27]	2013	NCT00879333	GRANITE-1	Multicenter	656	20–88	100%	Everolimus	Placebo	NA	24 M
Li [28]	2013	NCT00970138	NA	China	144	18–70#	NA	Apatinib	Placebo	NA	500D
Eatock [29]	2012	NCT00583674	NA	Multicenter	171	18–84	64%	Trebananib	Placebo	Cisplatin/capecitabine	20 M
Ohtsu [30]	2011	NCT00548548	AVAGAST	Multicenter	774	22–82	87%	Bevacizumab	Placebo	Cisplatin/capecitabine	24 M
Bramhall [31]	2002	NA	NA	Multicenter	369	> 18#	100%	Marimastat	Placebo	NA	4Y

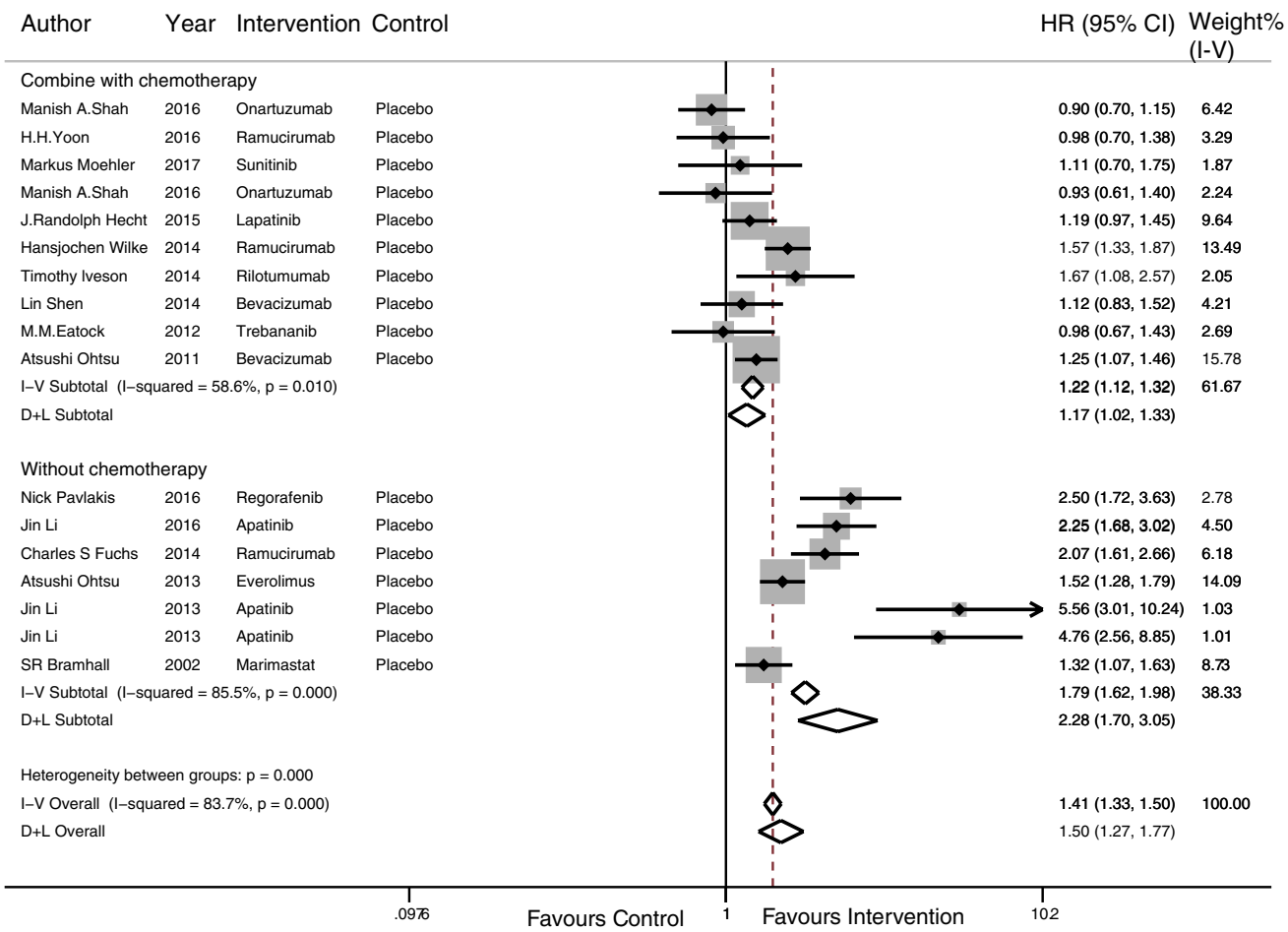

Fig. 2 Forest plot of pairwise comparisons for PFS in traditional meta-analysis

presence of small-study effects, and it did not suggest any publication bias (Fig. 6a). Targeted agents were separately analyzed alone or in combination with chemotherapy. The results for all possible comparisons are presented in the Supplemental Tables. Rilotumumab (88.6%) was found to be most likely to improve PFS with chemotherapy, and apatinib (90%) was best without chemotherapy.

For OS outcomes, all 11 targeted agents were included and the network plot analyzed similar to the PFS results (Fig. 4b). The league table is shown for each pairwise comparison (Supplemental Tables 2–13). Apatinib (95.5%) was likely best, followed by rilotumumab (74.7%) and regorafenib (70%) (Fig. 5). The comparison-adjusted funnel plot showed no potential publication bias (Fig. 6b). Subgroup analyses showed that rilotumumab (84.3%) was most likely to improve OS with chemotherapy, and apatinib (89.8%) was best without chemotherapy. For ORR outcome, ten types of targeted agents were included, not including marimastat (Fig. 4c). The league table showed that apatinib is better than sunitinib (logOR 2.35; 95% CI 0.03–4.67; $p = 0.047$). For improving ORR, apatinib (89.6%) was again best, followed by rilotumumab (75.4%) and everolimus (68.4%) (Fig. 5). No potential publication bias was seen (Fig. 6c). Similar to the PFS results, rilotumumab (87.4%) was likely best with chemotherapy, and apatinib (87.1%) was best without chemotherapy. For severe AE outcome, all 11 targeted agents were included (Fig. 4d). After pairwise comparisons, bevacizumab (85.5%) showed the lowest severe AE, followed by placebo (78.8%) and sunitinib (63%) (Fig. 5), with no evidence of potential publication bias (Fig. 6d). Bevacizumab (89.8%) had the lowest severe AE with chemotherapy, and ramucirumab (72.8%) had the lowest severe AE except placebo without chemotherapy (76.2%).

We performed a comprehensive analysis of efficacy and tolerability. The cluster ranking showed that bevacizumab had medium efficacy and high tolerability in PFS when combined with chemotherapy, and ramucirumab and regorafenib had medium efficacy and high tolerability without chemotherapy. For OS outcome, bevacizumab also had medium efficacy and high tolerability with chemotherapy, and apatinib had high efficacy and low tolerability without

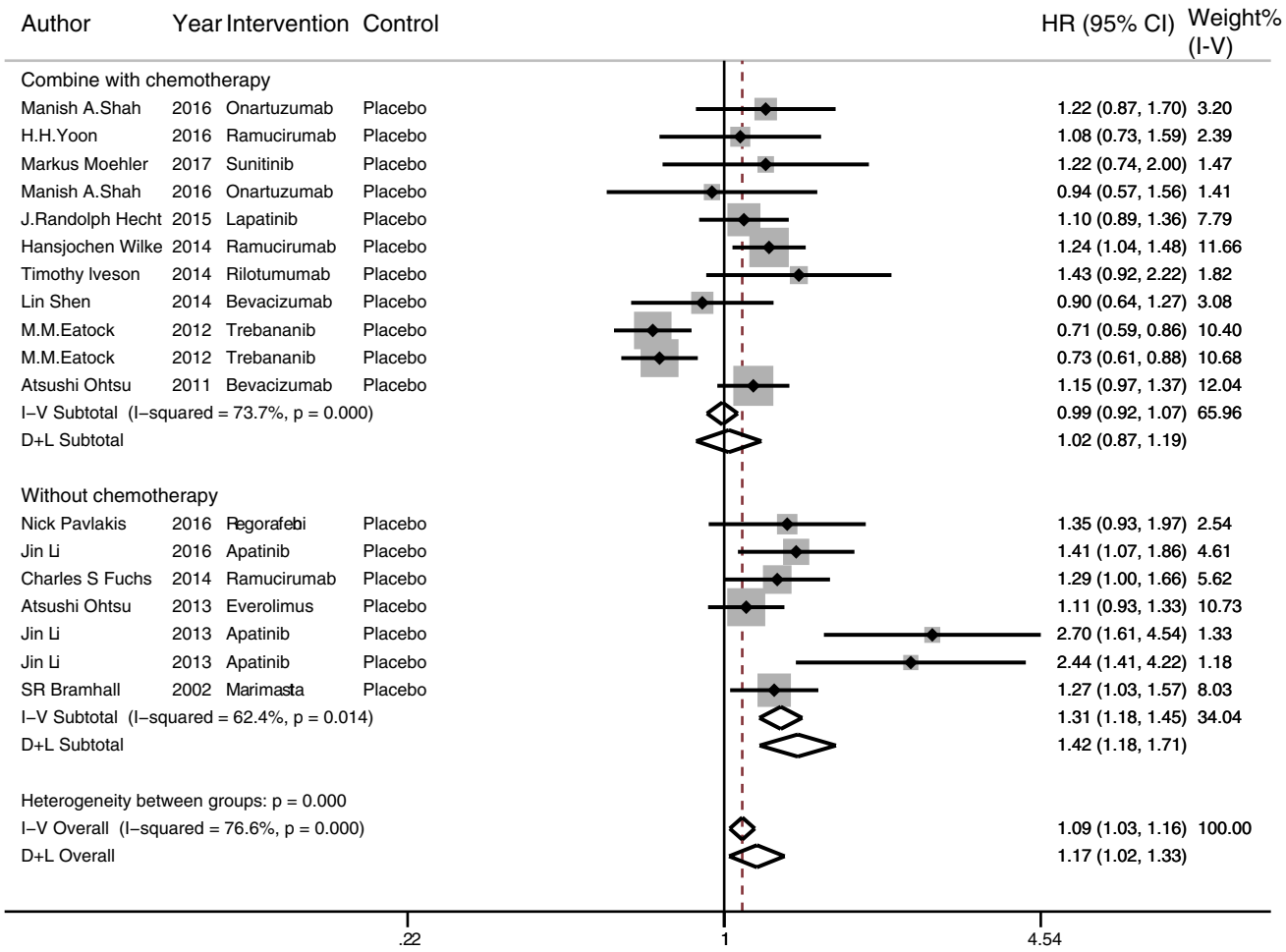

Fig. 3 Forest plot of pairwise comparisons for OS in traditional meta-analysis

chemotherapy. For ORR outcome, bevacizumab again had ideal efficacy and high tolerability, and lapatinib, ramucirumab, and rilotumumab had high efficacy and low tolerability when combined with chemotherapy (Supplemental Fig. 4).

Discussion

In this study, we performed a network meta-analysis to analyze efficacy and tolerability in AGC patients who were treated with targeted agents. We included 11 targeted agents including Apatinib, Bevacizumab, Everolimus, Lapatinib, Marimastat, Onartuzumab, Ramucirumab, Regorafenib, Rilotumumab, Sunitinib, and Trebananib. We included all relevant double-blind RCTs and comprehensively analyzed PFS and OS outcomes according to the Log-rank test results. We also performed subgroup analyses based on whether the agents were combined with chemotherapy. The findings of the traditional meta-analysis suggested that targeted therapy had significant advantages for PFS and ORR and no significant differences were seen in OS outcome between targeted therapy and placebo when combined with chemotherapy, however, the increased incidence of severe AEs with targeted therapy was also serious. In the network analysis, apatinib, regorafenib, and rilotumumab all improved patients' PFS and OS. In subgroup analyses, apatinib with no chemotherapy had the best efficacy in PFS, OS, and ORR outcomes but also had a high severe AE rate. Ramucirumab and regorafenib had relatively high therapeutic efficacy and good tolerability in PFS outcome. When combined with chemotherapy, rilotumumab and ramucirumab had high efficacy but low tolerability, and bevacizumab had moderate efficacy and good tolerability.

Angiogenesis is a common characteristic of tumors. VEGF is closely related to the prognosis for AGC patients, and high expression of VEGFR-2 also relates to AGC staging. Apatinib is a novel selective vascular endothelial growth factor receptor 2 tyrosine kinase inhibitor that has high efficacy in prolonging OS and PFS [21]. Regorafenib

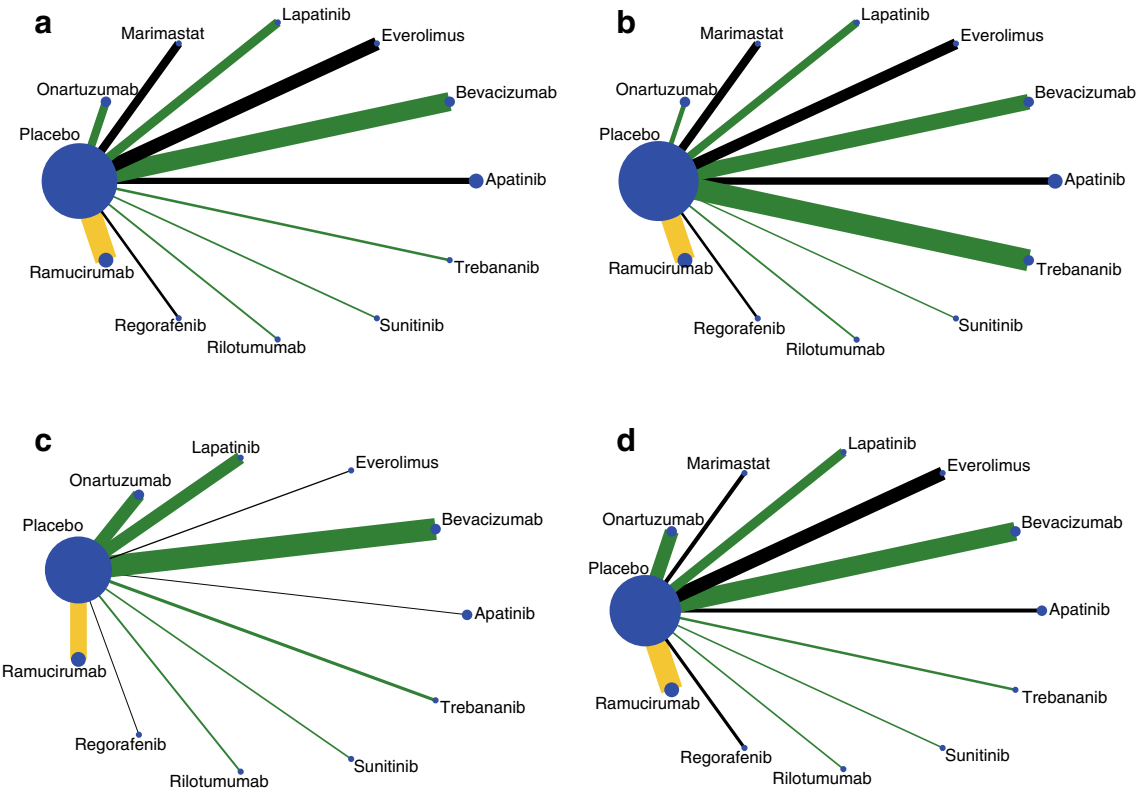

Fig. 4 Network of comparisons for all outcomes included in the analyses. **a**: PFS; **b**: OS; **c**: ORR; **d**: severe AE. The size of each circle (node) is proportional to the number of randomly assigned patients and indicates sample size. The number of studies that contributed to each direct comparison is indicated on the line between nodes

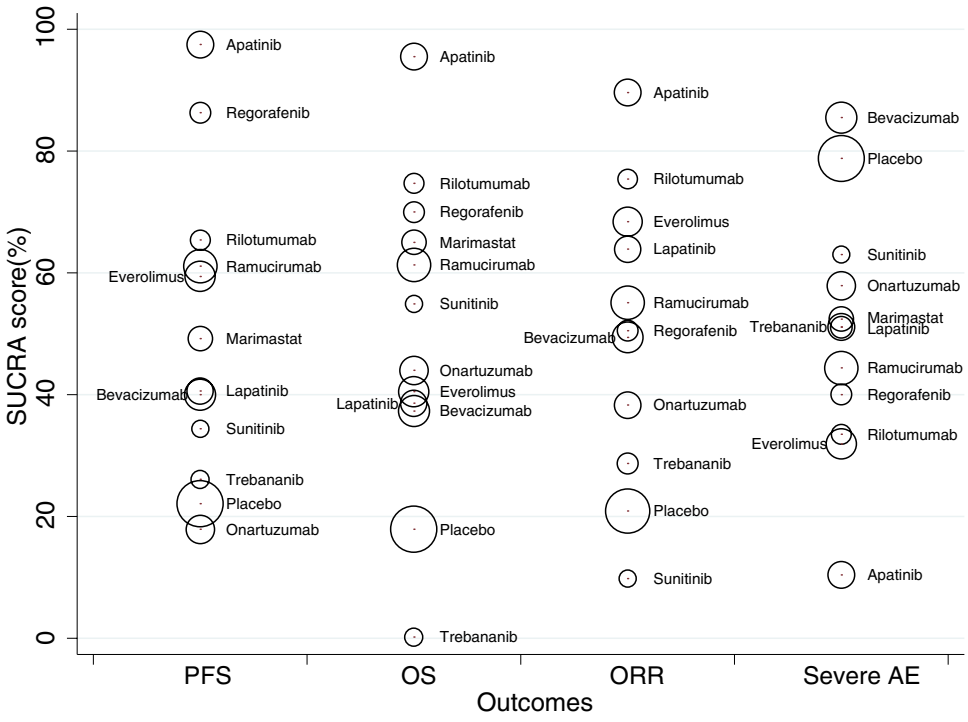

Fig. 5 SUCRA score of each targeted agent in all outcomes. The size of each circle are weighted by the square root of the patient number

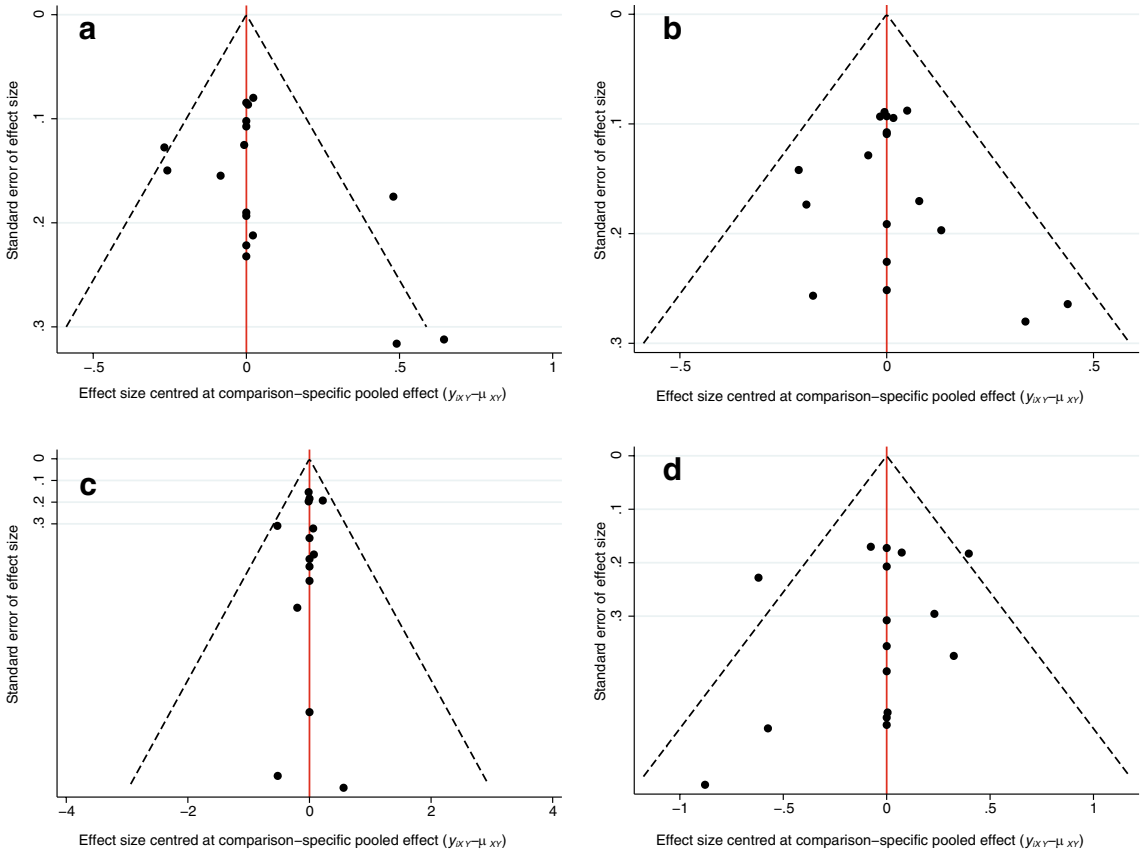

Fig. 6 Comparison-adjusted funnel plots for assessing all outcomes. **a** PFS; **b**: OS; **c**: ORR; **d**: severe AE

is a multikinase inhibitor of VEGFR1-3, c-KIT, TIE-2, PDGFR-β, FGFR-1, RET, RAF-1, BRAF and p38 MAP kinase that has been shown to inhibit cancer growth [20]. In our results, Regorafenib was found to have acceptable therapeutic effects in AGC treatment without chemotherapy. It has also been approved to treat various advanced cancers.

Rilotumumab is an IgG2 monoclonal antibody against HGF that inhibits cancer cell proliferation, metastasis, and invasion. It has therapeutic effects for patients with high MET. However, in stage III clinical trials, rilotumumab was seen to increase the mortality of AGC patients with chemotherapy, so further research was terminated [32]. Ramucirumab is an IgG1 monoclonal antibody that blocks VEGFR-2 to inhibit angiogenesis. It is currently approved for AGC and non-small cell lung cancer treatment. In this study, it was effective for AGC whether or not it was combined with chemotherapy, but the incidence of severe AE increased when it was combined with chemotherapy. Bevacizumab can inhibit the activity of VEGF and is widely used against cancers and ophthalmic diseases. Our results show that it has a low incidence of severe AE with moderate effects. Interestingly, suntinib is an oral multikinase inhibitor of VEGFRs, but the effect was unsatisfactory when compared with the other agents. Possible reasons why could be analyzed in future basic research.

A previous network meta-analysis did not include apatinib, rilotumumab, regorafenib, etc. [10]. This study showed Ramucirumab to increase PFS, and endostar had superior results in 2–3 year PFS results. Because the median survival of AGC patients was less than 1 year, the number of progression-free and surviving patients would decrease substantially over 1 year. Thus, the long-term follow-up results of this study might be inaccurate. Moreover, in endostar related studies, the small number of AGC patients could affect the accuracy of the results [33]. Trastuzumab also significantly increased OS in AGC patients. Two trials from the Trastuzumab for Gastric Cancer (ToGA) trial were included in the analysis; however, these two studies were duplicate publications and had an open-label design [34, 35]. Therefore, in an improvement over previous network meta-analyses, our study used HR to eliminate the influence of different follow-up periods. We also only included blinded RCTs with study designs that have high credibility. In addition, apatinib, rilotumumab, regorafenib were included in our study, and we find that these agents have beneficial therapeutic effects, especially apatinib.

Although targeted agents increase the incidence of severe AE, there are still few reports about fatal AE. Thus, clinicians need to make individual choices about prolonging PFS and potential AE according to each patient's condition. Additionally, gastric cancer involves multiple genes and targets, so resistance to targeted therapies can often arise through the establishment of a compensatory signaling pathway. Thus, combining chemotherapy and multi-targeted therapies is an inevitable trend. Targeted agents should be selected according to differential expression of specific proteins in AGC patients to further improve the effect of targeted therapy.

Our study has several limitations. First, the analysis was performed at the study level, resulting in lower accuracy than is possible in studies performed at the individual level. Second, the total number of studies and types of targeted agents included are small since we only analyzed high quality RCTs. Including studies with non-blinded designs would increase total numbers but reduce the reliability of our analysis. Third, we did not investigate the effects of agents according to different ethnic or protein expression profiles. Further studies could analyze the results in different ethnic groups or in patients with different protein expression profiles by subgroup analysis. Fourth, we did not analyze the different types of AE produced by the agents, so only general severe AE results were reported in our analysis. Further well-designed RCTs are still needed to supplement our results on more types of targeted agents.

In conclusion, apatinib, regorafenib, and rilotumumab all showed significant positive effects on PFS and OS, however, apatinib had a high rate of severe AE. In subgroup analyses, ramucirumab and rilotumumab had high efficacy but low tolerability, and bevacizumab had moderate efficacy for PFS and good tolerability when combined with chemotherapy. When not combined with chemotherapy, ramucirumab and regorafenib had relatively high therapeutic efficacy and good tolerability in PFS outcome.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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