Original Article

The efficacy and safety comparison of PD-1/PD-L1 antibody, chemotherapy and supportive treatment for pretreated advanced esophagogastric cancer: a network meta-analysis

Chuan Liu[1,2#], Wancong Wang[1#], Jiahui Yang[3#], Pan Song[4], Fuhao Li[1,2], Bin Liu[1,2], Jinpeng Li[1,2], Huimei Xu[5], Yang Mi[1,2], Youcai Tang[2,6], Pengyuan Zheng[1,2]

[1]Department of Gastroenterology, The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [2]Marshall B.J. Medical Research Center of Zhengzhou University, Zhengzhou, China; [3]Department of Gastroenterology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [4]Department of Urology, West China Hospital of Sichuan University, Chengdu, China; [5]Department of Gastroenterology, The Second Affiliated Hospital of Lanzhou University, Lanzhou, China; [6]Department of Children's Rehabilitation Medicine, The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Contributions: (I) Conception and design: C Liu, W Wang, J Yang; (II) Administrative support: Y Mi, Y Tang, P Zheng; (III) Provision of study materials or patients: F Li, B Liu, J Li, H Xu; (IV) Collection and assembly of data: C Liu, W Wang, J Yang; (V) Data analysis and interpretation: C Liu, W Wang, J Yang, P Song; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this article.

Correspondence to: Prof. Pengyuan Zheng, MD, PhD. Department of Gastroenterology, The Fifth Affiliated Hospital of Zhengzhou University; Marshall B.J. Medical Research Center of Zhengzhou University, Kangfu Street No. 3, Zhengzhou, China. Email: medp7123@126.com.

Background: Immunotherapy is important for the treatment of esophagogastric cancer. The purpose of this study is to compare the efficacy and safety of PD-(L)1 antibody, chemotherapy, and supportive treatment in the management of pretreated advanced esophagogastric cancer.

Methods: The randomized controlled trials were identified by searching electronic databases including PubMed, Cochrane Library and Embase database. The network meta-analysis (NMA) was carried out using software R 3.3.2. Main outcomes including overall survival (OS), progression-free survival (PFS), all grades and serious treatment-related adverse events (TRAEs) were extracted and analyzed. The ranking results for all outcomes were performed to identify the best treatments.

Results: Seven high-quality RCTs involving 1,891 patients were taken into analysis. Compared with supportive treatment, PD-(L)1 antibody and chemotherapy both had a significantly longer OS time. Chemotherapy could obvious improve PFS than supportive treatment, but it had more all grades and serious TRAEs than PD-(L)1 antibody and supportive treatment. No significant difference was found in other comparisons. The probabilities of rank plot showed that PD-(L)1 antibody was the best in the outcome of OS. Chemotherapy ranked first in PFS and ranked last in all grades and serious TRAEs.

Conclusions: According to our results, PD-(L)1 antibody had excellent survival benefits and tolerable TRAEs for pretreated advanced esophagogastric cancer. It might be a suitable potential choice, especially for patients with high PDL1 CPS or with gastroesophageal junction cancer.

Keywords: Esophagogastric cancer (EGC); PD-(L)1 antibody; chemotherapy; network meta-analysis (NMA)

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Introduction

Esophagogastric cancer (EGC) remains an important health issue, of which gastric cancer (GC) ranks fifth most prevalent cancer globally, with an increase of around 1 million cases in 2018, and esophageal cancer (EC) is the seventh, with 0.57 million diagnoses cases in 2018 (1). Gastroesophageal junction cancer (GEJC) is a type of lethal malignancy at the junction between the esophagus and stomach. Even though EGC have improved due to the early screening and extensive local excision (2), many EGC patients still diagnosed at advanced malignancy. First-line chemotherapy comprising platinum and fluoropyrimidine (3) significantly extends overall survival (OS) by close to seven months for advanced EGC patients (4), but most patients continued to have disease progression after treatment. As for second- or third-line therapy, chemotherapy also has been widely used in the clinic for many years (5), including paclitaxel, docetaxel, irinotecan single or combined treatment (6). In addition, HER-2 antibody trastuzumab and VEGFR-2 antibody ramucirumab also applied as second or third line treatments for EGC patients (7-9).

In recent years, with the close relationship between the development of tumors and immune escape (10), the immune checkpoint pathway is critical in cancer treatment (11), such as programmed death-1 (PD-1) (12). The PD-1 receptor, expressed mainly on activated T-cells (13), is specifically bound to the PD-1 ligand1 (PD-L1) on the tumor cell to cause T-cell apoptosis and promote neoplastic growth (14,15). Therefore, PD-1 antibody (anti-PD-1) can restore antitumor immune response by blocking the PD-L1 signaling pathway (16). Moreover, overexpression of PD-L1 in GC (17) makes inhibition of PD-1 pathway a reasonable target for advanced EGC patients. It has become an effective treatment option for a variety of cancers, and anti-PD-(L)1 have demonstrated broad antitumor activity in early trials (14,18). Recent studies have also shown that anti-PD-(L)1 play an active role in the treatment of pretreated advanced EGC (19-21).

Notably, the anti-PD-(L)1, including pembrolizumab, nivolumab and avelumab, were approved in the United States and Europe for the treatment of patients who have already been treated for advanced EGC recently (22). However, it is unclear which of the anti-PD-(L)1 and chemotherapy has more benefit for the treatment of EGC. Therefore, we performed this network meta-analysis (NMA) to evaluate the difference of anti-PD-(L)1, chemotherapy and supportive treatment, and to find out the optimal choice for pretreated, advanced EGC.

Methods

Search strategy

Two independent the investigators searched online databases, such as PubMed, Embase and the Cochrane Library, from their inception to July 1, 2019. The keywords and related synonym including "advanced esophagogastric cancer", "gastric cancer", "esophageal cancer", "PD-1", "programmed death 1", "pembrolizumab", "nivolumab", "avelumab", "chemotherapy", "docetaxel", "paclitaxel", "irinotecan", "RCT", etc. were applied in the search strategy. References to related articles, such as meta-analysis, comments and other styles, was also manually searched. The qualifications of these retrieved documents were carefully checked using the EndNote software. Irrelevant studies were excluded by carefully looking at their title, abstract and even the full text.

Selection criteria

In general, the studies meeting the following criteria were considered eligible for inclusion: (I) patients were diagnosed as pretreated advanced gastric cancer or esophageal cancer; (II) interventions of the trails at least included anti-PD-(L)1 or chemotherapy; (III) randomized controlled trials.

The trials meeting the following exclusion criteria were considered ineligible: (I) Besides anti-PD-(L)1 or chemotherapy treatment, patients adopted with other therapies such as vaccine therapy and radiotherapy; (II) sufficient data of necessary information was not provided.

Data extraction and quality assessment

The extracted data were as follows: NCT number, the first author, publication year, journal, study phase, interventions of experimental and control groups, the sample size of each group and relevant clinical outcomes. The main outcomes included OS, progression-free survival (PFS), all grades treatment-related adverse events (TRAEs) and serious TRAEs. Serious TRAEs were defined as grade 3–5 TRAEs.

Two authors independently assessed the methodological qualities. For each included study, the following criteria were assessed and assigned a grade of low, medium or high risk bias: random sequence generation, allocation concealment, blinding of participants and personnel,

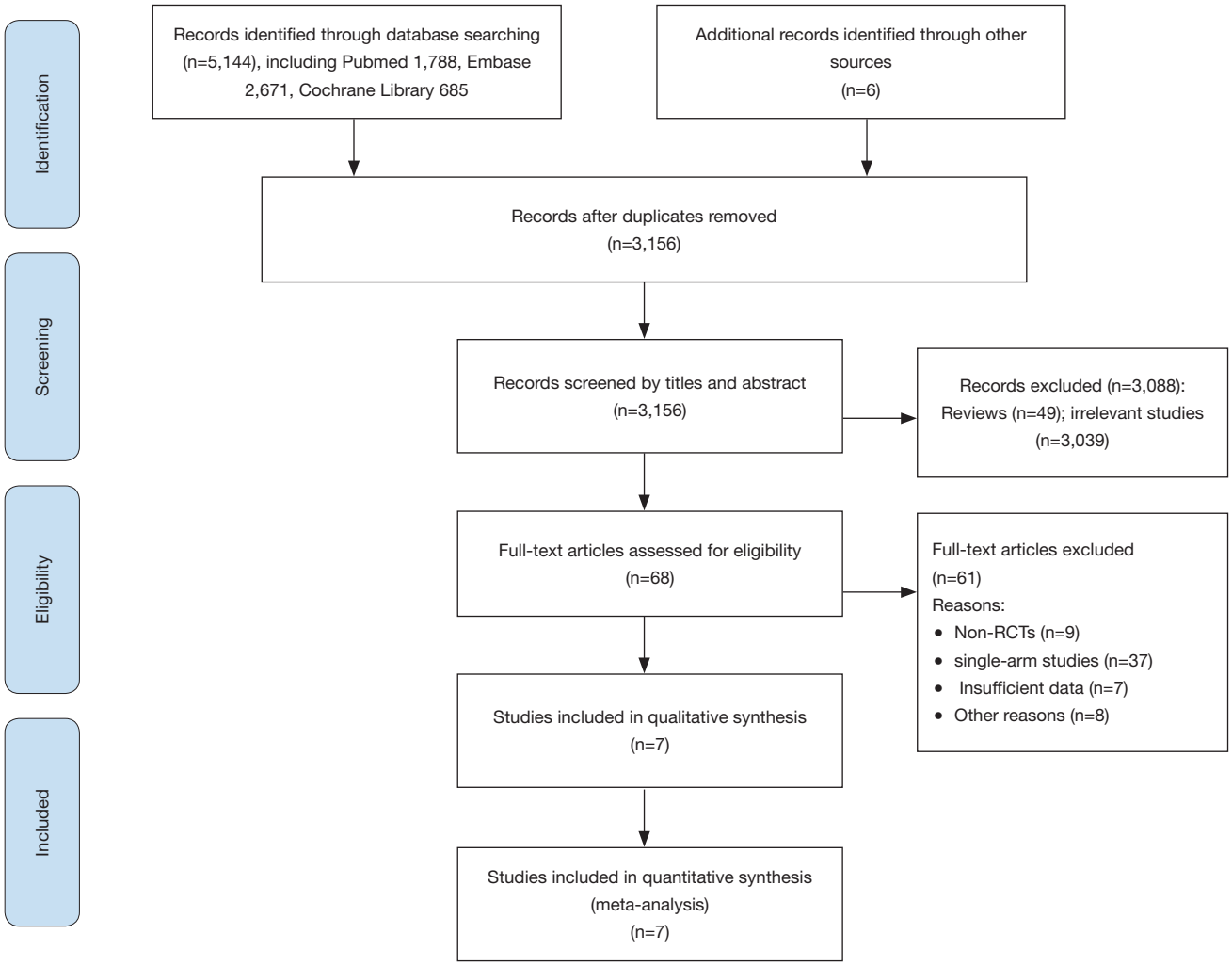

Figure 1 PRISMA flow diagram of the study selection process for network meta-analysis.

blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Any discrepancies between the two reviewers were regularly resolved by consulting with a third reviewer.

Data synthesis and analysis

Our NMA was carried out using R 3.3.2 software based on the Bayesian framework model, compared by both direct and indirect evidences. The pooled hazard ratio (HR) and 95% credible intervals (CIs) were used to estimate the two outcomes of OS and PFS. Dichotomous data, such as AEs, were calculated with odd risks (OR) and 95% CI. A random-effects model was used to calculate the evidence inconsistency. The relative ranking results of the different approaches were presented as the probabilities. Node splitting was used to evaluate consistency. Subgroup analysis was performed according to PD-L1 combined positive score (CPS) and cancer type.

Results

Baseline characteristics of the studies included

The flow diagram of the article search and screening was shown in *Figure 1*. In total, 7 (23-29) RCTs including 1,891 patients were enrolled into our analysis. Baseline characteristics of selected articles were summarized in *Table 1*. The methodological quality of all included studies was

Table 1 Main characteristics of the included studies in network meta-analysis

NCT number	Authors, year	Journal	Study phase	Study design	Experiment group	Control group	Line of therapy	Samples (E/C)	Main outcomes
NCT02267343	Kang *et al.*, 2017	*The Lancet*	III	RCT	Nivolumab 3 mg/kg Q2W	Placebo 3 mg/kg Q2W	Previously treated	330/163	OS, PFS, OR, DC, DOR, TTR, BOR, TRAEs
NCT02370498	Shitara *et al*., 2018	*The Lancet*	III	RCT	Pembrolizumab 200 mg Q3W	Paclitaxel 80 mg/m^2 on days 1, 8, and 15 of 4-week cycles	Previously treated	294/276	OS, PFS, RR, TRAEs
NCT02564263	Manish *et al*., 2019	*Journal of Clinical Oncology*	III	RCT	Pembrolizumab 200 mg Q3W	Paclitaxel 80–100 mg/m^2 on days 1, 8, and 15 of 4-week cycle, or Docetaxel 75 mg/m^2 Q3W, or Irinotecan 180 mg/m^2 Q2W	Previously treated	107/115	OS, PFS, ORR, TRAEs
NCT02625623	Bang *et al.*, 2018	*Annals of Oncology*	III	RCT	Avelumab 10 mg/kg Q2W	Paclitaxel 80 mg/m^2 on days 1, 8, and 15 or Irinotecan 150 mg/m^2 on days 1 and 15, each of a 4-week cycle	Previously treated	185/186	OS, PFS, ORR, TRAEs
ISRCTN13366390	Ford *et al.*, 2014	*The Lancet Oncology*	III	RCT	Docetaxel 75 mg/m^2 Q3W	Active symptom control	Previously treated	84/84	OS, PFS, BOR, TRAEs
NCT00144378	Thuss *et al.*, 2011	*European Journal of Cancer*	III	RCT	Irinotecan 250-350 mg/m^2 q3w	Best supportive care	Previously treated	21/19	OS
NCT00821990	Kang *et al.*, 2012	*Journal of Clinical Oncology*	III	RCT	Docetaxel 60 mg/m^2 Q3W or Irinotecan 150 mg/m^2 Q2W	Best supportive care	Previously treated	133/69	OS, TRAEs

OS, overall survival; PFS, progression-free survival; OR, objective response; DC, disease control; ORR, objective response rate; DOR, duration of response; TTR, time to response; BOR, best overall response; TRAEs, treatment-related adverse events.

estimated. All 7 trials articles were randomized. The risk-of-bias assessment of six studies were illustrated in *Figure 2*. The evidence network of three interventions were displayed in *Figure 3*.

NMA of OS

All 7 studies provided the HR value and 95% CI, recruiting of 1891 patients. The NMA results of OS were shown in *Table 2*. Compared with supportive treatment, anti-PD-(L)1 and chemotherapy had a significant longer OS time [anti-PD-(L)1: HR =0.59, 95% CI (0.42, 0.80); chemotherapy: HR =0.66, 95% CI (0.49, 0.86)]. However, no significant difference were found between anti-PD-(L)1 and chemotherapy [HR =0.89, 95% CI (0.69, 1.2)]. Besides, the ranking results showed that anti-PD-(L)1 ranked 1st (85.56%), chemotherapy ranked 2nd (85.23%) and supportive treatment ranked 3rd (99.20%). Among these interventions, ranking 1st and 3rd had the longest and the shortest OS time, respectively. The results of ranking analysis were presented in *Figure 4A* and *Table 3*. In ranking plots of *Figure 4*, the lightest gray meant the first ranking, and the black meant the third ranking.

NMA of PFS

Three articles with 1,259 patients reported the HR value and 95% CI for PFS. The NMA results of PFS were presented in *Table 2*. Chemotherapy had a significant longer PFS [HR =0.41, 95% CI (0.18, 0.94)] than supportive

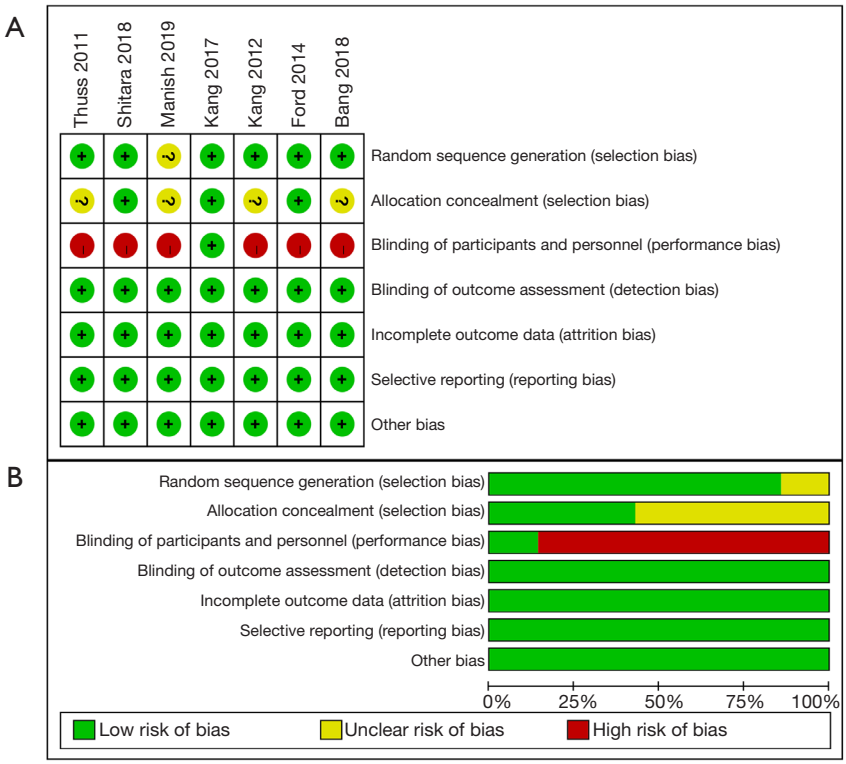

Figure 2 Risk of bias graph and summary of the included RCTs: (A) reviewers' judgements about each risk of bias item for eligible studies and (B) the judgements about each risk of bias item presented as percentages across all eligible studies.

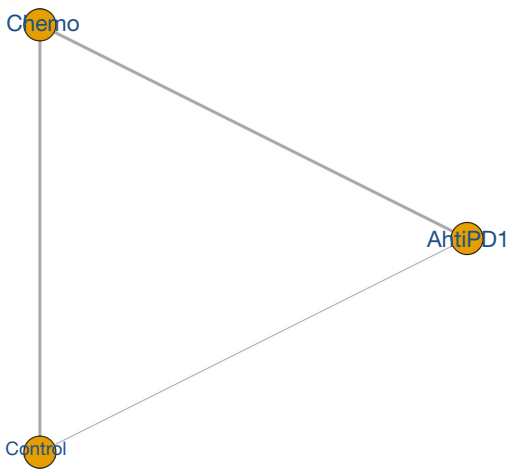

Figure 3 Network geometry of three interventions.

treatment. There were no obvious differences in the comparisons of anti-PD-(L)1 and chemotherapy. The probabilities of rank plot were as follows: chemotherapy ranked 1st (90.83%), anti-PD-1 rank 2nd (94.23%) and supportive treatment ranked 3rd (94.07%). This ranking result were illustrated in *Figure 4B* and *Table 3*.

NMA of all grades TRAEs

Three studies included with 1,422 patients described all grades TRAEs. The AE rates for anti-PD-(L)1, chemotherapy and supportive treatment were 47.77%, 80.13% and 26.70%, respectively. The NMA results showed that all grades TRAEs induced by chemotherapy were obvious higher than that of anti-PD-(L)1 and supportive treatment [anti-PD-(L)1: OR =3.79, 95% CI (2.41, 5.98); supportive treatment: OR =7.69, 95% CI (3.57, 16.67)]. And more all grades TRAEs were observed in the anti-PD-(L)1 compared to supportive treatment [OR =2.04, 95% CI (1.09, 3.85)] (*Table 2*). The results of rank plot analysis were showed in *Figure 4C* and *Table 3*, which showed that supportive treatment ranked 1st (86.79%), anti-PD-1 ranked 2nd (86.14%) and chemotherapy ranked

Table 2 Network meta-analysis results of treatment comparisons

Treatment	Anti-PD-(L)1	Chemo	Control
Overall survival, HR (95% CI)			
vs. anti-PD-(L)1	1	1.1 (0.87, 1.5)	1.7 (1.2, 2.4)
vs. chemo	0.89 (0.69, 1.2)	1	1.5 (1.2, 2.1)
vs. control	0.59 (0.42, 0.80)	0.66 (0.49, 0.86)	1
Progression-free survival, HR (95% CI)			
vs. anti-PD-(L)1	1	0.68 (0.42, 1.1)	1.7 (0.84, 3.3)
vs. chemo	1.5 (0.90, 2.4)	1	2.5 (1.1, 5.7)
vs. control	0.6 (0.31, 1.2)	0.41 (0.18, 0.94)	1
All grades TRAEs, OR (95% CI)			
vs. anti-PD-(L)1	1	3.79 (2.41, 5.98)	0.49 (0.26, 0.92)
vs. chemo	0.26 (0.17, 0.41)	1	0.13 (0.06, 0.28)
vs. control	2.04 (1.09, 3.85)	7.69 (3.57, 16.67)	1
Serious TRAEs, OR (95% CI)			
vs. anti-PD-(L)1	1	3.73 (2.41, 5.79)	0.4 (0.17, 0.93)
vs. chemo	0.27 (0.17, 0.41)	1	0.11 (0.04, 0.28)
vs. control	2.5 (1.08, 5.88)	9.09 (3.57, 25)	1

3rd (96.24%).

NMA of serious TRAEs

As for serious TRAEs, 4 articles with 1,644 patients were taken into analysis. This NMA results showed that chemotherapy had an obvious more serious adverse events than the anti-PD-(L)1 and supportive treatment [anti-PD-(L)1: OR=3.73, 95% CI (2.41, 5.79); supportive treatment: OR =9.09, 95% CI (3.57, 25)]. Anti-PD-(L)1 was associated with more serious TRAEs than supportive treatment [OR =2.5, 95% CI (1.08, 5.88)] (*Table 2*). Furthermore, probabilities of rank plots were followed as: supportive treatment ranked 1st (88.37%), anti-PD-(L)1 ranked 2nd (87.45%) and chemotherapy ranked 3rd (96.71%) (*Figure 4D* and *Table 3*).

Subgroup analysis

Subgroup analysis based on PDL1 CPS and cancer type showed that anti-PD-(L)1 could significantly extend OS than supportive treatment for patients with GEJC [HR =0.42, 95% CI (0.20, 0.90)]. No obvious differences were detected in other comparisons in terms of improving OS in *Table 4*. But it shows in the ranking result that anti-PD-(L)1 ranked 1st in OS in patients with PDL1 CPS ≥1 or with EC and GEJC (*Figure 5* and *Table 5*).

Consistency and convergence analysis

The node-splitting analysis was carried out to assess whether direct and indirect evidence in agreement. No significant inconsistency was found among the various treatments. That indicated that the consistency assumption was accepted. There was no significant publication bias among the included studies by the funnel plots. In addition, the potential scale reduction factor was limited to 1, and the research had good convergence efficiency.

Discussion

In the past decade, esophagogastric cancer was the second most common cause of cancer-related death globally, with an estimated 1.6 million newly diagnosed and 1.25 million deaths per year (30). After first-line chemotherapy, some patients still have a risk of disease progression and

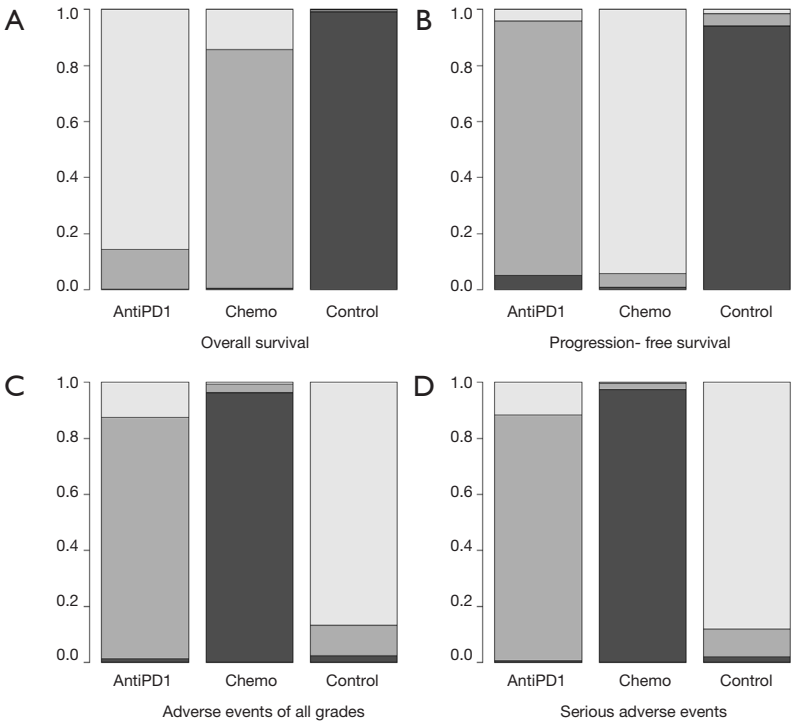

Figure 4 The relevant rank plots based on probabilities of interventions: (A) OS; (B) PFS; (C) all grades TRAEs; (D) serious TRAEs. OS, overall survival; PFS, progression-free survival; TRAEs, treatment-related adverse events.

Table 3 Rankings based on simulations

Endpoints (%)	Ranks	Anti-PD-(L)1	Chemo	Control
OS	Rank 1	85.56	14.30	0.14
	Rank 2	14.11	85.23	0.66
	Rank 3	0.33	0.47	99.20
PFS	Rank 1	4.16	94.23	1.61
	Rank 2	90.83	4.85	4.32
	Rank 3	5.01	0.92	94.07
All grades TRAEs	Rank 1	12.49	0.72	86.79
	Rank 2	86.14	3.04	10.82
	Rank 3	1.37	96.24	2.39
Serious TRAEs	Rank 1	11.23	0.40	88.37
	Rank 2	87.45	2.89	9.66
	Rank 3	1.32	96.71	1.97

Rank 1 is the best; rank 3 is the worst.

have a poor prognosis. For many years, chemotherapy, as traditional treatment, has been the most widely used for advanced EGC. Recently, immunotherapy, especially anti-PD-(L)1, have been introduced as a relatively new treatment paradigm for advanced EGC patients. The therapeutic efficacy has been examined at different phases currently. In this study, we analyzed systematically the efficacy and safety of anti-PD-(L)1 and chemotherapy in pretreated advanced EGC patients.

In our NMA, 7 high-quality RCTs recruiting 1,891 patients were included in the analysis. The efficacy was assessed by the outcomes of OS and PFS, and the safety was evaluated in the outcome of all grades and serious TRAEs. We observed that, (I) Anti-PD-(L)1 could significant extend OS than supportive treatment. Anti-PD-(L)1 ranked first in OS and second place in PFS. In safety outcomes, anti-PD-(L)1 was ranked 2nd following supportive treatment. (II) Anti-PD-(L)1 showed no significant difference with

Table 4 Network meta-analysis results of OS in subgroup analysis

Treatment	Anti-PD-(L)1	Chemo	Control
PDL1 CPS <1, HR (95% CI)			
vs. anti-PD-(L)1	1	0.83 (0.60, 1.1)	1.4 (0.84, 2.3)
vs. chemo	1.2 (0.88, 1.7)	1	1.7 (0.93, 3.1)
vs. control	0.72 (0.43, 1.2)	0.60 (0.33, 1.1)	1
PDL1 CPS ≥1, HR (95% CI)			
vs. anti-PD-(L)1	1	1.3 (0.69, 2.3)	1.9 (0.63, 6.1)
vs. chemo	0.78 (0.43, 1.4)	1	1.5 (0.43, 5.6)
vs. control	0.52 (0.16, 1.6)	0.66 (0.18, 2.3)	1
PDL1 CPS ≥10, HR (95% CI)			
vs. anti-PD-(L)1	1	1.5 (0.98,2.3)	–
vs. chemo	0.67 (0.44, 1.0)	1	–
Gastric cancer, HR (95% CI)			
vs. anti-PD-(L)1	1	0.95 (0.70, 1.3)	1.4 (0.91, 2.1)
vs. chemo	1.1 (0.77, 1.4)	1	1.5 (0.94, 2.2)
vs. control	0.72 (0.48, 1.1)	0.68 (0.44, 1.1)	1
Gastroesophageal junction cancer, HR (95% CI)			
vs. anti-PD-(L)1	1	1.4 (0.78, 2.4)	2.4 (1.1, 5.1)
vs. chemo	0.72 (0.42, 1.3)	1	1.7 (0.83, 3.6)
vs. control	0.42 (0.20, 0.90)	0.58 (0.28, 1.2)	1
Esophageal cancer, HR (95% CI)			
vs. anti-PD-(L)1	1	1.1 (0.73, 1.7)	1.5 (0.61, 3.8)
vs. chemo	0.89 (0.58, 1.4)	1	1.4 (0.61, 3.1)
vs. control	0.65 (0.26, 1.6)	0.73 (0.32, 1.6)	1

chemotherapy in OS and PFS, but anti-PD-(L)1 were associated with an obvious decrease in all grades and serious TRAEs compared with chemotherapy. According to the ranking plot results anti-PD-1 seemed to be more effective and safer than chemotherapy excepting PFS. (III) Chemotherapy could significant improve OS and PFS than supportive treatment. Nevertheless, the incidences of all grades and serious TRAEs of chemotherapy were higher than that of supportive treatment.

On the OS, some previously published reports have come to with our results to similar conclusions. Kang *et al.* (24) analyzed 493 patients, and revealed that anti-PD-1 could significant improve OS than supportive treatment for advanced GC patients, with a median OS of 5.26 months with anti-PD-1 versus a median OS of 4.14 months with control group. Ford *et al.* (27) concluded that chemotherapy had a longer OS time than supportive treatment. Similar results were seen in other studies (28,29). Shitara *et al.* (25) found that the median OS of anti-PD-(L)1 and chemotherapy were 9.1 months and 8.3 months respectively in patients with a PD-L1 CPS≥1, which showed they were not significantly different. Bang's study (23) reached similar conclusions. However, Shah *et al.* (26) reported that anti-PD-(L)1 could have a statistical improvement in median OS than that of chemotherapy in patients with CPS ≥10. This might be due to the higher PD-L1 CPS patients, the better its immunogenicity and response to anti-PD-(L)1 treatment, due to the high neoantigen burden and PD-

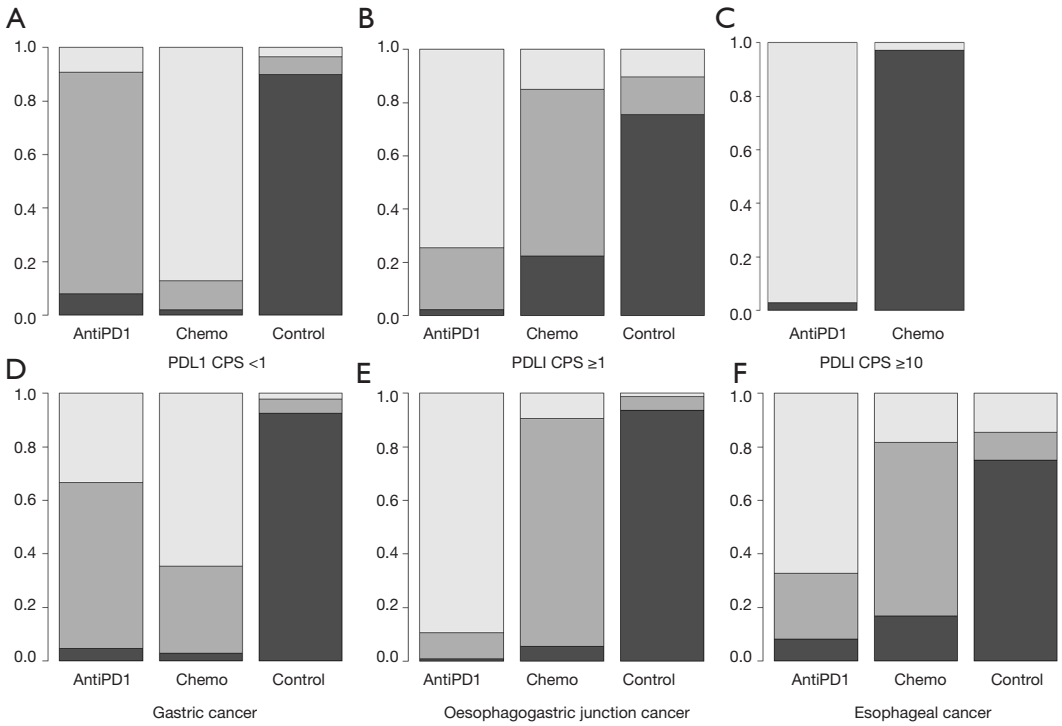

Figure 5 The relevant rank plots of subgroup analysis.

L1 expression (31,32). The relationship between higher expression of PD-L1 and better therapeutic effect for anti-PD-(L)1 was also found in the trial (20) and some studies in other tumor types (33,34). For PFS, Shitara *et al.* (25) concluded that the lack of a PFS benefit with anti-PD-1 compared with chemotherapy. Similar results were found in Shah's study (26). Even Bang *et al.* (23) found chemotherapy had longer PFS than anti-PD-L1. So in terms of increasing PFS, anti-PD-(L)1 was not as significant as chemotherapy. According to the ranking results, anti-PD-(L)1 had the longest OS and chemotherapy had the longest PFS.

As for the outcome of all grades and serious TRAEs concerned, we did find significant differences in these comparisons. Several previous trials (27,29) also proved that the TRAEs was more frequent in chemotherapy group than the supportive treatment group. Even through anti-PD-(L)1 was associated with more TRAEs than the supportive treatment, its safety in advanced EGC patients were tolerable and manageable (24), and consistent with findings in patients with other advanced solid tumors (35,36). Shitara *et al.* (25) found that anti-PD-(L)1 was less toxic (serious TRAEs, 14.2% for anti-PD-1 *vs.* 34.8% for chemotherapy) compared to chemotherapy (23,26). Compared with chemotherapy in the RCTs, anti-PD-(L)1 could significantly decrease the risk of common TRAEs, such as fatigue, anemia, asthenia, nausea, rash, pruritus, diarrhea, AST increased, neutropenia and leukopenia. This may be speculated that chemotherapy could damage epithelium-derived cells, while anti-PD-(L)1 may not. So for patients with poor basic function, in order to avoid side effects, we can properly consider the use of anti-PD-(L)1. However, anti-PD-(L)1 are associated with increased incidence of immune-related AEs, such as pneumonitis and thyroid disease, which requires clinicians to pay more attention to potential TRAEs when using anti-PD-(L)1. As for supportive treatment, there are minimal AEs, such as infusion-related reactions and fatigue, because not treated with specific drugs. In a meta-analysis (37), it was demonstrated that anti-PD-(L)1 might be more effective and safer than the chemotherapy, which is consistent with our research.

PDL1 expression is considered a good biomarker. Subgroup analysis based on PDL1 CPS and cancer types were carried out to explore which patients are more likely to benefit. Anti-PD-(L)1 could significantly extend OS than the supportive treatment for patients with GEJC.

Table 5 Rankings based on simulations of OS in subgroup analysis

Endpoints (%)	Ranks	Anti-PD-(L)1	Chemo	Control
PDL1 CPS <1	Rank 1	9.16	87.54	3.30
	Rank 2	82.83	10.38	6.79
	Rank 3	8.01	2.08	89.91
PDL1 CPS ≥1	Rank 1	74.47	14.62	10.91
	Rank 2	23.24	62.22	14.54
	Rank 3	2.29	23.16	74.55
PDL1 CPS ≥10	Rank 1	97.14	2.86	–
	Rank 2	2.86	97.14	–
Gastric cancer	Rank 1	33.27	64.58	2.15
	Rank 2	62.13	32.50	5.37
	Rank 3	4.60	2.92	92.48
Gastroesophageal junction cancer	Rank 1	89.36	9.41	1.23
	Rank 2	9.73	85.05	5.22
	Rank 3	0.91	5.54	93.55
Esophageal cancer	Rank 1	67.15	18.25	14.60
	Rank 2	24.75	64.94	10.31
	Rank 3	8.10	16.81	75.09

Rank 1 is the best; rank 3 is the worst.

But this study did not analyze the significant differences in other comparisons, which might be limited by the number of documents included. However, according to the ranked chart, anti-PD-(L)1 seemed to be more suitable for patients with high PDL1 CPS or with EC and GEJC. Patients with low PDL1 CPS or with GC, anti-PD-(L)1 did not show a clear advantage over chemotherapy. Previous studies have found that some tumor cells can escape immune recognition and destruction by expressing PDL1. Anti-PD-(L)1 can restore the tumor-suppression effect of T cells by blocking the PDL1 signaling pathway. So for immunotherapy, patients with tumors harboring PD-L1 expression exhibited higher responses than tumors without PD-L1 expression, so that they have better efficacy. As for cancer types concerned, different tissue types have different immune infiltration, so that they respond differently to immune checkpoint inhibitors, which is worthy of further discussion.

To the best our knowledge, this is the first NMA to compare anti-PD-(L)1, chemotherapy and supportive treatment for pretreated advanced EGC with direct and indirect evidences. Nevertheless, our study still has certain limitations. Firstly, availability of good data, only 7 high-quality RCTs were taken into analysis, so it might not being convincing enough to perform a comprehensive NMA. Secondly, the supportive treatment were not identical, including placebo, active symptom control or best supportive care, which might interfere with the results. Thirdly, due to the lack valid data in included RCTs, some other outcomes such as objective response (OR) and disease control (DC) were not analyzed. This might also effect our evaluation.

In conclusion, anti-PD-(L)1 and chemotherapy could significant improve OS than supportive treatment. Chemotherapy could increase PFS, but it was associated with all grades and serious TRAEs. Considering ranking results, anti-PD-(L)1 might be the optimal potential choice for pretreated advanced EGC, especially for patients with high PDL1 CPS or with GEJC. However, because of the limitations of this NMA, more high-quality researches are necessary to assess the options further.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-19-670). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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