Original Article

Efficacy and safety of camrelizumab in combination with trastuzumab and chemotherapy as the first-line treatment for patients with HER2-positive advanced gastric cancer

Mengli Xu, Xiangrui Meng, Yao Lu, Feng Wang

Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Contributions: (I) Conception and design: M Xu; (II) Administrative support: F Wang; (III) Provision of study materials or patients: F Wang, X Meng; (IV) Collection and assembly of data: M Xu, Y Lu; (V) Data analysis and interpretation: M Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Feng Wang. Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China. Email: zzuwangfeng@zzu.edu.cn.

Background: Trastuzumab plus chemotherapy is the standard-of-care (SoC) first-line therapy for HER2-positive advanced gastric cancer. Combining PD-1 antibody with SoC first-line therapy showed encouraging results in the KEYNOTE-811 study. The retrospective study aims to evaluate the efficacy and safety of SoC *vs.* SoC plus camrelizumab (PD-1 antibody) as a first-line treatment for HER2-positive advanced gastric cancer in a real-world setting.

Methods: This study included 41 patients with HER2-positive advanced gastric cancer who received SoC or SoC plus camrelizumab from June 2017 to December 2020. The endpoints were objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Thirteen patients received SoC (SoC group) and 28 patients received SoC plus camrelizumab (camrelizumab group). As of December 2020, the median follow-up time was 10.0 months. In the camrelizumab and SoC groups, the ORRs were 75.0% and 46.2% (P=0.032), respectively. The DCR was 96.4% in the camrelizumab group and 69.2% in the SoC group (P=0.003). The median OS was 18.4 in the camrelizumab group and 13.2 months in the SoC group [hazard ratio (HR) =0.343; 95% confidence interval (CI): 0.151–0.783; P=0.008]. The median PFS was 3.78 in the camrelizumab group and 1.74 months in the SoC group (HR =0.416; 95% CI: 0.186–0.932; P=0.027). In the HER2 subgroups in the camrelizumab group, the median PFS of immunohistochemistry (IHC) 3+ *vs.* IHC 2+ fluorescence in situ hybridization (FISH) was 11.3 *vs.* 9.0 months (HR =1.684; 95% CI: 0.710–3.994; P=0.047). The incidence rates of reactive cutaneous capillary endothelial proliferation (RCCEP) (P<0.001), abnormal liver function (P=0.040), and hypothyroidism (P=0.039) between the two groups were significantly different. RCCEP and hypothyroidism were considered to be related to camrelizumab.

Conclusions: First-line treatment with camrelizumab combined with SoC showed significant clinical benefits and good tolerance compared with SoC for HER2-positive advanced gastric cancer.

Keywords: Retrospective study; HER2-positive advanced gastric cancer; camrelizumab; efficacy; safety

Submitted Dec 03, 2021. Accepted for publication Mar 04, 2022.
doi: 10.21037/jgo-21-897
View this article at: https://dx.doi.org/10.21037/jgo-21-897

Introduction

According to the GLOBOCAN 2020 database (1), the rankings of the incidence rate and mortality rate of gastric cancer worldwide were sixth and third, respectively. In China, the rankings of the incidence rate and mortality rate of gastric cancer were second and third, respectively,

and the number of deaths accounted for about 40% of the world's total. Furthermore, 80% of gastric cancer patients are diagnosed at the advanced stage in China (2), so the opportunity for surgical resection is often lost. So far, chemotherapy is still the main treatment for advanced gastric cancer (3). However, the therapeutic effect of chemotherapy is limited, and the median survival is generally no more than 1 year.

HER2-positive gastric cancer is a special type of gastric cancer. HER2 positive gastric cancer accounts for 10–22% of the total gastric cancer (4). HER2 screening data from ToGA (a phase III clinical study using standard chemotherapy combined with trastuzumab as the first-line treatment in HER2 receptor positive advanced gastric cancer) demonstrated a positive rate of 22.1% in 3,665 patients with advanced gastric cancer and gastroesophageal junction adenocarcinoma (5,6). The ToGA study (6) investigated trastuzumab, a humanized anti-HER2 monoclonal antibody used as a standard treatment for breast and metastatic gastric cancer when the cancer cells overexpress HER2, combined with chemotherapy as the standard-of-care (SoC) first-line treatment of HER2-positive advanced gastric cancer. The median overall survival (OS) of trastuzumab combined with chemotherapy was 13.8 months, and the objective response rate (ORR) was 47%. Exploratory analysis showed that the OS of trastuzumab combined with chemotherapy reached 16.0 months in patients with immunohistochemistry (IHC) 2+/fluorescence in situ hybridization (FISH) + or IHC 3+. However, the selection of anti-HER2 agents after first-line treatment progression has been inconclusive. Despite negative clinical results of lapatinib, trastuzumab emtansine, and pertuzumab, the search for the optimal treatment for HER2-positive gastric cancer is ongoing.

Preclinical studies have shown that the combination of trastuzumab and PD-1 inhibitors has synergistic activity (7). Trastuzumab up-regulates the expression of PD-L1 in gastric cancer cells by interacting with natural killer (NK) cells (8). In addition, trastuzumab up-regulates the expression of PD-L1 by stimulating the secretion of IFNγ from immune effector cells (9,10). In addition to directly up-regulating PD-L1, anti-HER2 therapy can also indirectly exert a synergistic effect with PD-1 monoclonal antibodies by affecting the tumor microenvironment. After anti-HER2 therapy, it down-regulates the release of cytokines, such as CCL2, CCL21, VEGF, and CXCL1, and improves the immunosuppressive factors of the tumor microenvironment. A previous study (11) found that HER2 can inhibit the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon gene (STING) pathway by recruiting AKT1. It is suggested that anti-HER2 therapy relieved the inhibition of the cGAS-STING pathway (12) and restored the activity of the innate immune system to a certain extent. In addition, trastuzumab can enhance the HER2-specific T cell response, promote the transport of T cells and dendritic cells, and induce peripheral memory T cell expansion, thereby combining with the anti-tumor immune effect mediated by PD-1 monoclonal antibody function (13,14).

Based on the synergistic mechanism of immunotherapy and anti-HER2 therapy, immunotherapy combined with anti-HER2 therapy is also a feasible treatment option for HER2-positive gastric cancer. At the 2020 American Society of Clinical Oncology (ASCO) meeting, the phase 2 study PANTHERA (15) showed good efficacy and survival data. The pathological complete response (pCR) was 35% immunotherapy combined with the FLOT regimen and 12% in the FLOT regimen. In addition, immunotherapy combined with the XELOX regimen achieved similar results. The results of the phase III study KEYNOTE-811, released at the 2021 ASCO meeting (4), showed that pembrolizumab combined with trastuzumab and chemotherapy improved the ORR to 74.4% compared with 51.9% for placebo plus SoC. Preliminary data from KEYNOTE-811 led to accelerated FDA approval of pembrolizumab combined with trastuzumab and chemotherapy for HER2-positive gastric cancer patients.

Based on the ATTRACTION-02 (16) and KEYNOTE-059 (17) trials, nivolumab and pembrolizumab have been included as a third-line treatment recommendation in gastric cancer guidelines. Subsequently, the results of the CheckMate 649 (18) and ATTRACTION-4 (19) trials confirmed the role of immunotherapy combined with chemotherapy in the first-line treatment of gastric cancer. In recent years, first-line exploratory studies of domestic anti-PD-1 antibodies in advanced stage patients have been published one after another. Camrelizumab, a humanized, selective IgG4-κ monoclonal antibody against PD-1, exerted antitumor activity in a wide range of tumors, shows promising antitumor activity in advanced or metastatic gastric or gastroesophageal junction (GC/GEJC) adenocarcinoma. Multiple studies of camrelizumab in gastric cancer have shown its safety and effectiveness in gastric cancer (20-22). As part of the 2019 ASCO meeting, a study was published in which camrelizumab combined with CAPOX was followed by camrelizumab combined with apatinib for the first-line treatment of HER2-negative

patients with advanced or metastatic GC/GEJC after 4 to 6 cycles, and the study was published in Clinical Cancer Research in March 2021. A total of 48 patients were enrolled in this study, with an ORR of 58.3%, a median OS of 14.9 months, and progression-free survival (PFS) of 6.8 months (20). Based on this result, a nationwide multi-center phase III clinical study was initiated in March 2019.

However, the efficacy and safety data of PD-1 antibody combined with SoC in a real-world setting is limited. Therefore, the efficacy and safety of camrelizumab combined with SoC in the first-line treatment of HER2-positive advanced gastric cancer were investigated through retrospective analysis. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-897/rc).

Methods

General information of patients

The clinical data of 41 patients with HER2-positive advanced gastric cancer who received SoC or SoC plus camrelizumab in The First Affiliated Hospital of Zhengzhou University from June 2017 to December 2020 were included in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20220008). Individual consent for this retrospective analysis was waived.

The selection criteria included patients aged 18 to 75 years with gastroscopic pathology-confirmed gastric adenocarcinoma and IHC results of HER2 (3+) or IHC (2+) and positive FISH. The HER2 staining scoring criteria referred to guidelines for HER2 detection of gastric cancer. The expected survival of eligible patients was more than 3 months. Patients had measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

The exclusion criteria included patients who previously received PD-1/PD-L1 antibody, CTLA-4 antibody, or other treatments with PD-1/PD-L1 inhibitors, or received treatment with trastuzumab or other HER2-targeted biological agents (such as pertuzumab). Patients complicated with serious or uncontrollable systemic diseases, active autoimmune diseases, medical history of congestive heart failure, myocardial infarction, brain metastases, and active peripheral nervous system metastases were also excluded.

Treatment methods

The SoC group received trastuzumab combined with chemotherapy. An intravenous loading dose of 8 mg/kg trastuzumab was administered, followed by 6 mg/kg once every 3 weeks (Q3W). A regimen consisting of S-1 plus oxaliplatin (SOX) was widely used for chemotherapy. Patients received oxaliplatin (130 mg/m^2) intravenously for 2 h on the first day. S-1 was administered orally (b.i.d.) at a dose of 40 mg [body surface area (BSA) <1.25 m^2], 50 mg (1.25 m^2 ≤ BSA <1.5 m^2), and 60 mg (BSA≥1.5 m^2) for 14 days. This treatment was repeated Q3W. In addition, other chemotherapy regimens included the FP (5-fluorouracil and cisplatin) regimen and CAPOX (capecitabine and oxaliplatin) regimen. The camrelizumab group received camrelizumab and trastuzumab combined with the above chemotherapy regimens. Patients also received camrelizumab 200 mg/time which was repeated Q3W. The dose of chemotherapy could be adjusted according to the patient's tolerance.

Efficacy evaluation

After 2–3 cycles of treatment, all patients were evaluated by enhanced computed tomography or magnetic resonance imaging. Responses were assessed using RECIST v1.1. The primary endpoint was ORR, which was defined as the proportion of patients with complete response (CR) or partial response (PR). The secondary endpoints included disease control rate (DCR), OS, and PFS. DCR was the proportion of patients with stable disease (SD), PR, or CR. OS was defined as the time from random assignment to death from any cause. PFS was defined as the time from random assignment to disease progression or death from any cause.

Statistical analysis

SPSS 22.0 software package was used for statistical analysis. The chi-square test (χ^2 test) was used to compare differences in baseline characteristics between the two groups. The Kaplan-Meier method was used to calculate the survival rate and univariate analysis of prognosis. The log-rank test was used to show significant differences. Cox's proportional hazard model was used to calculate hazard ratios (HRs). P values less than 0.05 were considered statistically significant.

Table 1 Baseline characteristics

Baseline characteristics	Camrelizumab group (n=28), n (%)	SoC group (n=13), n (%)	P value
Age, years			0.762
<60 years	17 (60.7)	9 (69.2)	
≥60 years	11 (39.3)	4 (30.8)	
Sex			0.590
Male	26 (92.9)	10 (76.9)	
Female	2 (7.1)	3 (23.1)	
ECOG PS			0.608
0	22 (78.6)	9 (69.2)	
1	4 (14.3)	2 (15.4)	
2	2 (7.1)	2 (15.4)	
Histological grade			0.893
Well differentiated	7 (25.0)	3 (23.1)	
Moderately differentiated	5 (17.9)	3 (23.1)	
Poorly differentiated	16 (57.1)	7 (53.8)	
Histological subtypes			0.837
Intestinal	16 (57.1)	8 (61.5)	
Diffuse	8 (28.6)	3 (23.1)	
Hybrid	4 (14.3)	2 (15.4)	
HER2 status			0.301
IHC (3+)	15 (53.6)	9 (69.2)	
IHC (2+) and FISH (+)	13 (46.4)	4 (30.8)	
PD-L1 (CPS scores)			0.344
≥1	17 (60.7)	4 (30.8)	
<1 & unknown	11 (39.3)	9 (69.2)	
Chemotherapy			0.344
SOX regimen	21 (75.0)	10 (76.9)	
Others	7 (25.0)	3 (23.1)	

SoC, standard-of-care; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; CPS, combined positive score; SOX, S-1 plus oxaliplatin.

Results

Baseline data

Between June 2017 to December 2020, a total of 41 patients were diagnosed with HER2-positive advanced gastric cancer at The First Affiliated Hospital of Zhengzhou University. The baseline data of the two groups were sorted and recorded, including age, sex, ECOG scores, degree of differentiation, pathological types, HER2 status (IHC 3+ or IHC 2+ FISH amplification), PD-L1 [combined positive score (CPS)], and chemotherapy regimen. The baseline characteristics are shown in *Table 1*.

Efficacy

The efficacy of the camrelizumab group and SoC group

Table 2 Comparison of efficacy between the camrelizumab group and SoC group

Efficacy	Camrelizumab group (n=28), n (%)	SoC group (n=13), n (%)	P value
CR	0	0	–
PR	21 (75.0)	6 (46.2)	–
SD	6 (21.4)	3 (23.1)	–
PD	1 (3.6)	4 (30.8)	–
ORR (%)	75.0	46.2	0.032
DCR (%)	96.4	69.2	0.003

SoC, standard-of-care; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table 3 Efficacy comparison of PD-L1 subgroups in the camrelizumab group

Efficacy	PD-L1 (CPS <1 & unknown) (n=15), n (%)	PD-L1 (CPS ≥1) (n=13), n (%)	P value
CR	0	0	–
PR	7 (46.7)	7 (53.8)	–
SD	6 (40.0)	5 (38.5)	–
PD	2 (13.3)	1 (7.7)	–
ORR (%)	46.7	53.8	0.061
DCR (%)	86.7	92.3	0.274

CPS, combined positive score; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table 4 Comparison of the efficacy of HER2 subgroups in the camrelizumab group

Efficacy	IHC (2+) and FISH (+) (n=13), n (%)	IHC (3+) (n=15), n (%)	P value
CR	0	0	–
PR	7 (53.8)	7 (46.7)	–
SD	3 (23.1)	8 (53.3)	–
PD	3 (23.1)	0	–
ORR (%)	53.8	46.7	0.827
DCR (%)	76.9	100.0	0.274

IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

are shown in *Table 2*. Among the 28 patients in the camrelizumab group, 21 (75.0%) patients reached PR, 6 (21.4%) patients reached SD, and 1 (2.6%) patient had progressive disease (PD). Of the 13 patients in the SoC group, 6 (46.2%) patients had PR, 3 (23.1%) patients had SD, and 4 (30.8%) patients had PD. Compared with the SoC group, the camrelizumab group had significantly improved ORR (75.0% *vs.* 46.2%; P=0.032) and DCR (96.4% *vs.* 69.2%; P=0.003). The efficacy of the PD-L1 subgroups in the camrelizumab group is shown in *Table 3*. There were 13 patients in the PD-L1 (CPS ≥1) group, including 7 (53.8%) patients with PR, 5 (38.5%) patients with SD, and 1 (7.7%) patient with PD. There were 15 patients in the PD-L1 (CPS <1 & unknown) group, including 7 (46.7%) patients with PR, 6 (40.0%) patients with SD, and 2 (13.3%) patients with PD. The ORR (53.8% *vs.* 46.7%; P=0.061) and DCR (92.3% *vs.* 86.7%; P=0.274) of the two groups were not significantly different. The efficacy of HER2 subgroups is shown in *Table 4*. Of the 15 patients with IHC 3+, 7 (46.7%) patients had PR and 8 (53.3%) patients had SD. Of the 13 patients with IHC 2+ FISH amplification, 0 patients had CR, 7 (53.8%) patients had PR, 3 (23.1%) patients had SD, and 3 (23.1%) patients had PD. There was no significant difference in ORR (46.7% *vs.* 53.8%; P=0.827) and DCR (100% *vs.* 76.9%; P=0.274) between the two groups.

Survival analysis

As shown in *Figure 1A*, the median follow-up time was 10.0 months. The median PFS was 10.1 months in the camrelizumab group and 6.0 months in the SoC group [HR =0.343; 95% confidence interval (CI): 0.151–0.783; P=0.008]. The median OS was 18.4 months in the camrelizumab group *vs.* 13.2 months in the SoC group (HR =0.416; 95% CI: 0.186–0.932; P=0.027). As shown in *Figure 1B*, in the PD-L1 subgroups of the camrelizumab group, the median PFS of the PD-L1 CPS <1 & unknown *vs.* PD-L1 CPS ≥1 was 11.0 *vs.* 9.8 months (HR =3.896; 95% CI: 0.772–19.656; P=0.077), while the median OS of the PD-L1 CPS <1 & unknown *vs.* PD-L1 CPS ≥1 was 17.5 *vs.* 19.7 months (HR =1.302; 95% CI: 0.411–4.123; P=0.653). As shown in *Figure 1C*, in the HER2 subgroups in the camrelizumab group, the median PFS of IHC 3+ *vs.* IHC 2+ FISH was 11.3 *vs.* 9.0 months (HR =1.684; 95% CI: 0.710–3.994; P=0.047), and the median OS was not reached (NR) *vs.* 17.2 months (HR =1.386; 95% CI: 0.604–3.184; P=0.492).

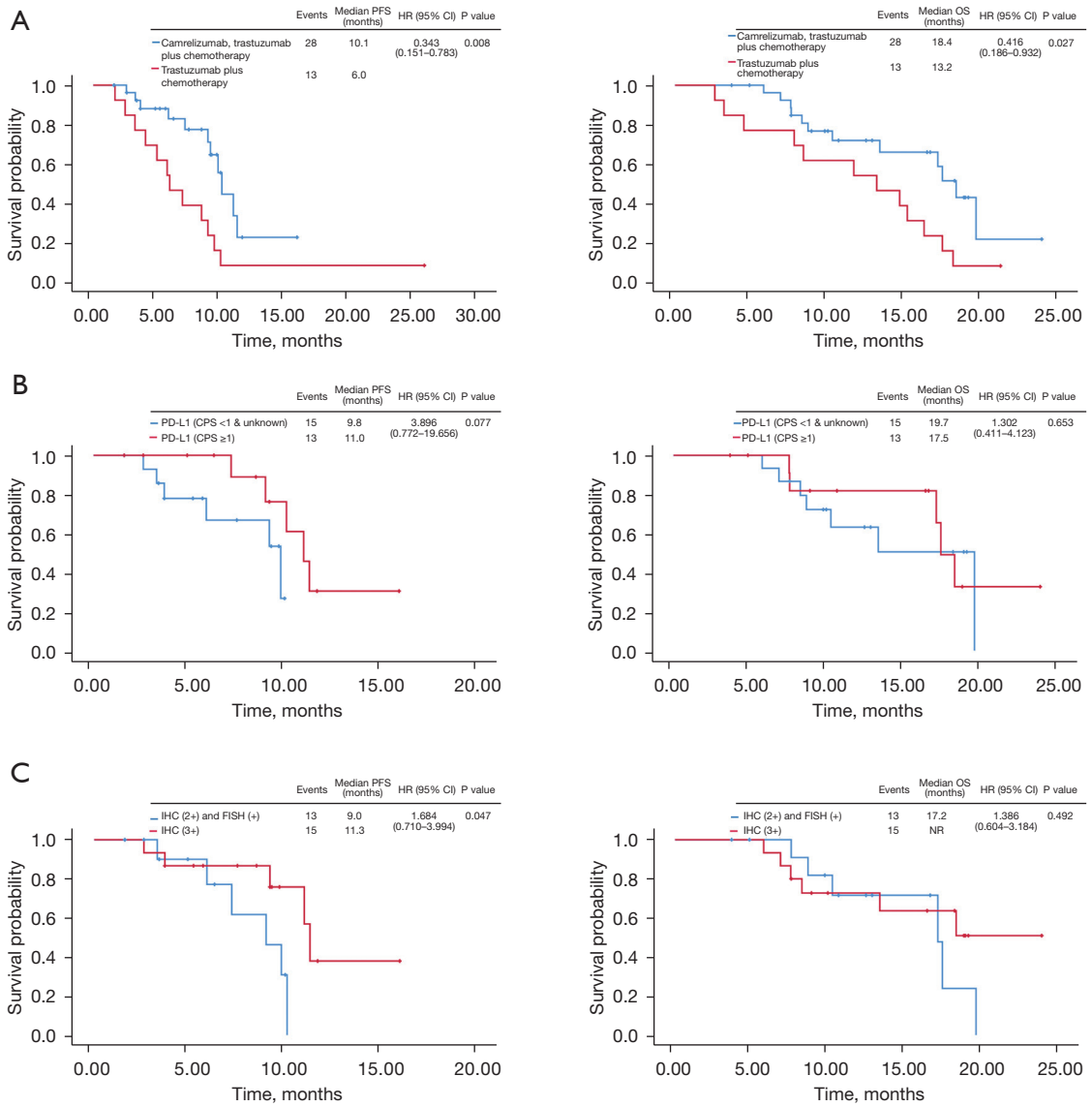

Figure 1 The result PFS and OS in different groups. (A) Comparison of PFS and OS between the camrelizumab group and SoC group. (B) Comparison of PFS and OS between PD-L1 subgroups in the camrelizumab group. (C) Comparison of PFS and OS between HER2 subgroups in the camrelizumab group. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; CPS, combined positive score; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; SoC, standard-of-care.

Adverse events (AEs)

The most common AEs with an incidence over 20% in the two groups included bone marrow suppression, neurotoxicity, nausea and vomiting, diarrhea, constipation, stomatitis, hand-foot syndrome, and rash. These were not significantly different between the two groups (P>0.05). Reactive cutaneous capillary endothelial proliferation (RCCEP) (P<0.001), abnormal liver function (P=0.040), and hypothyroidism (P=0.039) between the two groups were significantly different. RCCEP and hypothyroidism are considered to be related to camrelizumab. The most common grade 3–5 AEs between the two groups (incidence >10%) were bone marrow suppression (17.9%) and abnormal liver function (10.7%). There was no statistically significant difference in grade 3–5 AEs between the two groups (P>0.05). There was no discontinuation of treatment due to AEs, and there were no treatment-related deaths

Table 5 Comparison of AEs of any grade between the camrelizumab group and SoC group

AEs	Camrelizumab group (n=28), n (%)	SoC group (n=13), n (%)	P value
Bone marrow suppression	22 (78.6)	10 (76.9)	0.906
Neurotoxicity	11 (39.3)	5 (38.5)	0.960
Nausea and vomiting	18 (64.3)	8 (61.5)	0.865
Diarrhea	10 (35.7)	5 (38.5)	0.741
Constipation	7 (25.0)	3 (23.1)	0.946
Stomatitis	9 (32.1)	8 (61.5)	0.013
Hand-foot syndrome	6 (21.4)	3 (23.1)	0.837
RCCEP	21 (75.0)	0	<0.001
Rash	4 (14.3)	1 (7.7)	0.562
Abnormal liver function	10 (35.7)	1 (7.7)	0.040
Hypothyroidism	7 (25.0)	0	0.039

AEs, adverse events; SoC, standard-of-care; RCCEP, reactive cutaneous capillary endothelial proliferation.

Table 6 Comparison of grade 3–5 AEs between the camrelizumab group and SoC group

3–5 AEs	Camrelizumab group (n=28), n (%)	SoC group (n=13), n (%)	P value
Bone marrow suppression	5 (17.9)	2 (15.4)	0.845
Neurotoxicity	2 (7.1)	1 (7.7)	0.950
Nausea and vomiting	2 (7.1)	1 (7.7)	0.950
Stomatitis	1 (3.6)	1 (7.7)	0.569
Hand-foot syndrome	1 (3.6)	0	0.490
RCCEP	1 (3.6)	0	0.490
Rash	2 (7.1)	0	0.323
Abnormal liver function	3 (10.7)	0	0.220
Hypothyroidism	1 (3.6)	0	0.490

AEs, adverse events; SoC, standard-of-care; RCCEP, reactive cutaneous capillary endothelial proliferation.

in both groups. The comparison of AEs between the two groups is shown in *Tables 5*,*6*.

Discussion

Trastuzumab has been approved as a first-line treatment for HER2-positive metastatic gastroesophageal adenocarcinoma. After the ToGA study 10 years ago, international exploration of the second-line and above treatment of HER2-positive advanced gastric cancer has never stopped, but the road to pursuing effective treatments has been unusually challenging. The clinical research results of lapatinib, trastuzumab emtansine, and pertuzumab all failed. Continuous improvement of new pharmaceutical processes such as antibody-drug conjugates (ADC) and bispecific antibodies has brought benefits to more HER2-positive gastric cancer patients, such as RC48 (23) and DS-8201 (24). Furthermore, research on HER2-positive gastric cancer has focused on the exploration of the immune microenvironment.

In recent years, more and more evidence supports the application of immune checkpoint inhibitors in advanced gastric cancer. In March 2020, nivolumab was approved in China for advanced gastric cancer as a second-line treatment

and above, becoming the first PD-1 monoclonal antibody approved in China for gastric cancer. In terms of second-line treatment, based on the comprehensive analysis of the KEYNOTE-059 (17) (cohort 1), KEYNOTE-061 (25), and KEYNOTE-062 trials (26), the Chinese Society of Clinical Oncology (CSCO, 2021) guideline II recommends increasing the use of pembrolizumab as a single-agent treatment for patients with microsatellite instability-high (MSI-H) gastric cancer.

In terms of the first-line treatment of HER2-negative gastric cancer, both pembrolizumab/nivolumab combined with chemotherapy and pembrolizumab as a single agent have entered the 2021 CSCO guidelines. The recommendation is based on the CheckMate 649 study (18). Among the population with PD-L1 CPS ≥5, the median PFS of the nivolumab plus chemotherapy group and the chemotherapy group was 7.7 *vs.* 6.0 months. The median OS of the nivolumab plus chemotherapy group and the chemotherapy group was 14.4 *vs* 11.1 months, which significantly reduced the risk of death by 29%. In the ATTRACTION-4 study (19), the median PFS of the nivolumab + chemotherapy group and the chemotherapy group were 10.45 and 8.34 months, respectively (HR =0.68; P=0.0007), and the median OS results of the two groups were similar. In the KEYNOTE-062 study, the OS of pembrolizumab and chemotherapy for PD-L1 CPS ≥1 was not inferior to chemotherapy, and PFS and ORR had moderate benefits. Subgroup analysis showed that the risk of death in Asian populations treated with pembrolizumab was reduced by 46%.

Based on the synergistic mechanism of immunotherapy and anti-HER2 therapy, immunotherapy combined with anti-HER2 therapy is also a feasible treatment option for HER2-positive gastric cancer. The results of the PANTHERA study were announced at the ASCO annual meeting in 2020, which explored the safety and efficacy of pembrolizumab, trastuzumab, and chemotherapy in the first-line treatment of patients with HER2-positive advanced gastric cancer (4,27). The results showed that the ORR reached 76.7%, 95.3% of the lesions shrank, and the expression of PD-L1 was not correlated with tumor shrinkage. The median OS was 19.3 months (95% CI: 16.5–NA), the median PFS was 8.6 months (95% CI: 7.2–16.4), and the median DOR was 10.8 months (95% CI: 7.17–NA). On this basis, the KEYNOTE-811 trial is a multi-center, randomized, double-blind, placebo-controlled phase III clinical study enrolling HER2-positive (the center confirms IHC 3+ or IHC 2+/FISH >2.0) advanced stomach cancer patients or patients with adenocarcinoma of the junction of the esophagus. Patients were randomly assigned (1:1) and were given pembrolizumab 200 mg or placebo Q3W, combined with trastuzumab and fluorouracil + cisplatin or capecitabine + oxaliplatin. Preliminary results showed that the pembrolizumab combination treatment group had increased ORR by nearly 20%, that is, from 52% to 74%. Thus, pembrolizumab obtained US FDA approval for locally advanced unresectable or metastatic HER2-positive GC/GEJC as a first-line treatment.

In this paper, the survival and safety of camrelizumab combined with trastuzumab and chemotherapy, compared with trastuzumab combined with chemotherapy, were investigated through retrospective analysis. The results showed that the ORR (75.0% *vs.* 46.2%; P=0.032) and DCR (96.4% *vs.* 69.2%, P=0.003) were significantly increased in the camrelizumab group compared with the SoC group. The median OS in the camrelizumab group was 18.4 months compared with 13.2 months in the SoC group (HR =0.343; 95% CI: 0.151–0.783; P=0.008). The median PFS in the camrelizumab group was 10.1 months compared with 6.0 months in the SoC group (HR =0.416; 95% CI: 0.186–0.932; P=0.027), showing significantly better survival than the SoC group. The results were similar to those of a phase II study exploring the trastuzumab + pembrolizumab + capecitabine + oxaliplatin regimen presented by the Memorial Sloan-Kettering Cancer Center (MSKCC) at the European Society for Medical Oncology (ESMO) Annual Meeting [2019] (28), in which the ORR was 89%, the DCR was 100%, the median PFS was 13 months (95% CI: 8.59–NA), and the median OS was 27.17 months (95% CI: 18.85–NA) in patients with HER2-positive gastric cancer.

In an exploratory analysis of biomarkers (15), low HER2 expression was associated with shorter duration of response, but PD-L1 expression status was not a predictor of efficacy. In other words, patients benefited from camrelizumab combined with trastuzumab and chemotherapy regardless of PD-L1 expression status. In this study, the efficacy and survival of the PD-L1 and HER2 subgroups were analyzed, and the efficacy of the two groups was not significantly different. Then, we analyzed the survival of the two subgroups. In the PD-L1 subgroups, the median PFS of the PD-L1 CPS <1 & unknown *vs.* PD-L1 CPS ≥1 was 11.0 *vs.* 9.8 months (HR =3.896; 95% CI: 0.772–19.656; P=0.077), and the median OS of the PD-L1 CPS <1 & unknown *vs.* PD-L1 CPS ≥1 was 17.5 *vs.* 19.7 months (HR =1.302; 95% CI: 0.411–4.123; P=0.653). The PFS and OS were not significantly different. Survival analysis of the HER2 subgroups showed that the median PFS of IHC 3+ *vs.* IHC

2+ FISH amplification was 11.3 *vs.* 9.0 months (HR =1.684; 95% CI: 0.710–3.994; P=0.047), and the PFS between the 2 groups was significantly different. The median OS was NR *vs.* 17.2 months (HR =1.386; 95% CI: 0.604–3.184; P=0.492), and the difference was not statistically significant. In other words, although high HER2 expression did not affect OS, it significantly increased PFS (2.3 months; P<0.05), again confirming that HER2 status is an important marker for predicting trastuzumab efficacy.

In terms of adverse reactions, the most common grade 3–5 AEs in the camrelizumab group were bone marrow suppression (17.9%) and abnormal liver function (10.7%). The AEs were controllable, and there were no AEs which led to death. The incidence rates of hepatic insufficiency in the camrelizumab group was 35.7% (10/28) and in the SoC group was 7.7% (1/13), respectively, and the difference was statistically significant (P=0.040). RCCEP and hypothyroidism were not found in the SoC group. The incidence rates of RCCEP and hypothyroidism in the camrelizumab group were 75.0% (21/28) and 25.0% (7/28), respectively, with significant differences between the two groups (P<0.001 and P=0.039). Grade 3–5 AEs of the camrelizumab group was 3.6% (1/28). There were no related deaths. RCCEP and hypothyroidism were considered to be related to camrelizumab. In addition, data showed that the occurrence of RCCEP was closely related to survival benefit (29), which needs to be verified in subsequent studies.

In this study, the remission rate of the camrelizumab and trastuzumab combined with chemotherapy group was 75% (21/28), which was unprecedented in this tumor type. The median OS at 18 months was superior to the previously reported median OS at 16 months with chemotherapy plus trastuzumab (the current first-line standard), and the median PFS reached 11.3 months in the HER2 IHC 3+ group. Although treatment-related AEs were observed in all patients, the incidence of grade 3–5 toxicities related to chemotherapy and immunotherapy was similar to that of trastuzumab combined with chemotherapy and camrelizumab combined with chemotherapy. In conclusion, the results showed that it was safe to add camrelizumab on the basis of trastuzumab and chemotherapy in patients with metastatic gastric cancer and may have synergistic effects.

Currently, the overall prognosis of advanced gastric cancer is poor. Fluorouracil, platinum and Taxus are the main chemotherapeutic drugs for advanced gastric cancer. Traditional chemotherapy drugs have entered the bottleneck stage, the selection of targeted drugs and the efficacy of immunotherapy is limited, and the combination therapy will be a good choice in the face of the high heterogeneity of gastric cancer. The limitations of this study mainly include its retrospective nature, small sample size, and insufficient baseline biomarker detection and sequencing in some patients. Despite these limitations, the study observed an ORR of 75.0%, a DCR of 96.4%, a median PFS of 10.1 months, and a median OS of 18.4 months, suggesting that first-line treatment with camrelizumab and trastuzumab combined with chemotherapy for HER2-positive advanced gastric cancer has the advantage of prolonging survival. Additionally, there was no increase in chemotherapy-related AEs, and immune-related AEs were controllable.

As we all know, the tumor microenvironment of gastric cancer is complex, there are many targeted research drugs for gastric cancer. At present, only trastuzumab and antiangiogenic drug apatinib have entered clinical practice, the selection of targeted drugs is limited. On the other side, the immune checkpoint inhibitor PD-1 monoclonal antibody has made a breakthrough in advanced gastric cancer, however, the single drug effect of immunotherapy is limited. Therefore, facing the high heterogeneity of gastric cancer, combination therapy can better improve the effective rate, the survival of patients and then improve the quality of life of patients.

Acknowledgments

Funding: This work was supported by the National Natural Science Funds of China (No. 81672442), Henan Provincial Science and Technology Research Project (No. SBGJ202002080), the Leading Talent Training in Henan Province (No. YXKC2020017), and Key Scientific Research Project of Henan Universities (No. 21A320040).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-897/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-897/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-897/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20220008). Individual consent for this retrospective analysis was waived.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Yang L, Zheng R, Wang N, et al. Incidence and mortality of stomach cancer in China, 2014. Chin J Cancer Res 2018;30:291-8.
3. Harada K, Baba H, Ajani JA. Recent trend in gastric cancer treatment in the USA. J Cancer Metastasis Treat 2018;4:18.
4. Chung HC, Bang YJ, S Fuchs C, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. Future Oncol 2021;17:491-501
5. Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 2015;18:476-84.
6. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
7. Janjigian YY, Maron S, Chou JF, et al. First-line pembrolizumab (p), trastuzumab (t), capecitabine (c) and oxaliplatin (o) in her2-positive metastatic esophagogastric adenocarcinoma. Ann Oncol 2019;30:v313.
8. Yamashita K, Iwatsuki M, Yasuda-Yoshihara N, et al. Trastuzumab upregulates programmed death ligand-1 expression through interaction with NK cells in gastric cancer. Br J Cancer 2021;124:595-603.
9. Chaganty BKR, Qiu S, Gest A, et al. Trastuzumab upregulates PD-L1 as a potential mechanism of trastuzumab resistance through engagement of immune effector cells and stimulation of IFNγ secretion. Cancer Lett 2018;430:47-56.
10. Okita R, Maeda A, Shimizu K, et al. PD-L1 overexpression is partially regulated by EGFR/HER2 signaling and associated with poor prognosis in patients with non-small-cell lung cancer. Cancer Immunol Immunother 2017;66:865-76.
11. Wu S, Zhang Q, Zhang F, et al. HER2 recruits AKT1 to disrupt STING signalling and suppress antiviral defence and antitumour immunity. Nat Cell Biol 2019;21:1027-40.
12. cGAS-STING Pathway Activation in cDCs Underlies TIM3 Blockade Efficacy. Cancer Discov 2021;11:OF5.
13. Mortenson ED, Park S, Jiang Z, et al. Effective anti-neu-initiated antitumor responses require the complex role of CD4+ T cells. Clin Cancer Res 2013;19:1476-86.
14. Taylor C, Hershman D, Shah N, et al. Augmented HER-2 specific immunity during treatment with trastuzumab and chemotherapy. Clin Cancer Res 2007;13:5133-43.
15. Janjigian YY, Maron SB, Chatila WK, et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. Lancet Oncol 2020;21:821-31.
16. Chen LT, Satoh T, Ryu MH, et al. A phase 3 study of nivolumab in previously treated advanced gastric or gastroesophageal junction cancer (ATTRACTION-2): 2-year update data. Gastric Cancer 2020;23:510-9.
17. Fuchs CS, Doi T, Jang RW, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol 2018;4:e180013.
18. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.
19. Boku N, Ryu MH, Kato K, et al. Safety and efficacy

of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). Ann Oncol 2019;30:250-8.
20. Peng Z, Wei J, Wang F, et al. Camrelizumab Combined with Chemotherapy Followed by Camrelizumab plus Apatinib as First-line Therapy for Advanced Gastric or Gastroesophageal Junction Adenocarcinoma. Clin Cancer Res 2021;27:3069-78.
21. Xu J, Zhang Y, Jia R, et al. Anti-PD-1 Antibody SHR-1210 Combined with Apatinib for Advanced Hepatocellular Carcinoma, Gastric, or Esophagogastric Junction Cancer: An Open-label, Dose Escalation and Expansion Study. Clin Cancer Res 2019;25:515-23.
22. Huang J, Mo H, Zhang W, et al. Promising efficacy of SHR-1210, a novel anti-programmed cell death 1 antibody, in patients with advanced gastric and gastroesophageal junction cancer in China. Cancer 2019;125:742-9.
23. Peng Z, Liu T, Wei J, et al. A phase II study of efficacy and safety of RC48-ADC in patients with locally advanced or metastatic HER2-overexpressing gastric or gastroesophageal junction cancers. J Clin Oncol 2020;38:abstr 4560.
24. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020;382:610-21.
25. Shitara K, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 2018;392:123-33.
26. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: The KEYNOTE-062 Phase 3 Randomized Clinical Trial. JAMA Oncol 2020;6:1571-80.
27. Chao J, Fuchs CS, Shitara K, et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA Oncol 2021;7:895-902.
28. Rha SY, Lee CK, Kim HS, et al. Targeting HER2 in combination with anti-PD-1 and chemotherapy confers a significant tumor shrinkage of gastric cancer: A multi-institutional phase Ib/II trial of first-line triplet regimen (pembrolizumab, trastuzumab, chemotherapy) for HER2-positive advanced gastric cancer (AGC). J Clin Oncol 2020;38:abstr 3081.
29. Chen X, Ma L, Wang X, et al. Reactive capillary hemangiomas: a novel dermatologic toxicity following anti-PD-1 treatment with SHR-1210. Cancer Biol Med 2019;16:173-81.

(English Language Editor: C. Betlazar-Maseh)

Cite this article as: Xu M, Meng X, Lu Y, Wang F. Efficacy and safety of camrelizumab in combination with trastuzumab and chemotherapy as the first-line treatment for patients with HER2-positive advanced gastric cancer. J Gastrointest Oncol 2022;13(2):548-558. doi: 10.21037/jgo-21-897

