Original Article

PD-1 inhibitor combined with apatinib for advanced gastric or esophagogastric junction cancer: a retrospective study

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Background: Nivolumab and pembrolizumab were approved as immune checkpoint inhibitors for third-line treatment of advanced gastric or esophagogastric junction cancer (GC/EGJC) in 2017. However, immunotherapy monotherapy has low efficacy. Apatinib has been proven effective in advanced GC/EGJC. Numerous studies have shown that immunotherapy has a synergistic effect when combined with targeted drug therapy. Based on these facts and to assess the efficacy and safety of programmed death 1 (PD-1) inhibitor and apatinib as combination therapy in patients (pts) with unresectable locally advanced or metastatic GC/EGJC, a retrospective clinical research study was carried out.

Methods: Pts (n=24) received PD-1 inhibitor and apatinib (250 mg once daily) as second- or third-line therapy in this observational, retrospective study. The primary objectives were efficacy and safety.

Results: At data cut-off (December 31, 2019), 24 pts were enrolled. Of the 19 pts who were evaluable, the objective response rate (ORR) was 26.3% (5/19), the median progression-free survival (PFS) was 3.0 (95% CI: 1.3 to 4.7) months, and the median overall survival (OS) was not reached. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 3 (15.8%) of the 19 pts. These adverse events (AEs) included pruritus, rash, hand-foot syndrome, and increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT). No treatment-related deaths occurred.

Conclusions: Combination therapy of PD-1 inhibitor and apatinib showed encouraging clinical activity and demonstrated tolerable toxicity in pts with advanced GC/EGJC. Hence, our work provide rationale for the combination of PD-1 inhibitor and apatinib in advanced GC/EGJC.

Keywords: Programmed death 1 (PD-1); gastric cancer (GC); immune checkpoint inhibitors; immunotherapy; apatinib

Submitted Mar 04, 2020. Accepted for publication Jul 14, 2020.
doi: 10.21037/tcr-20-1333
View this article at: http://dx.doi.org/10.21037/tcr-20-1333

Introduction

Gastric or esophagogastric junction cancer (GC/EGJC) is the third leading cause of cancer-related deaths worldwide, with most of the cases diagnosed at late stages (1,2). For patients (pts) with unresectable or recurrent advanced GC/EGJC, systemic chemotherapy is the most important method used to prolong survival (3). However, research data indicate that the objective response rate (ORR) ranges from 6.8–25% and the progression-free survival (PFS) was 1.5–5.3 months in second or further lines therapy (4-6),

showing a poor prognosis. With this background, new clinical treatment approaches for advanced GC/EGJC are urgently needed, particularly in later lines. Immune checkpoint inhibitors have been shown to be effective in treating GC through blocking the interaction between programmed cell death-1 (PD-1) and its ligand (PD-L1) (7,8). Of these, nivolumab and pembrolizumab, were approved as third-line therapies for advanced GC/EGJC in 2017. However, only about 10% of advanced GC/EGJC patients benefit from monotherapy overall (9,10). Therefore, to extend the benefit to a larger population, the development of innovative strategies such as combining PD-1/PD-L1 blockade with conventional treatments is urgently needed in advanced GC/EGJC.

In recent years, studies have shown that immunotherapy has a synergistic effect when combined with molecular antiangiogenic agents (11,12). Anti-angiogenesis is a well-established tumor microenvironment (TME) targeted therapy in GC/EGJC. Combining PD-1/PD-L1 blockade with agents that can eliminate the preexisting immunosuppression of TME may overcome the primary resistance in patients with advanced GC/EGJC (13-15). Moreover, in preliminary results from an open-label clinical trial, with a combination of anti-PD-1 antibody and VEGFR1-3 inhibitor, nivolumab plus regorafenib achieved an ORR of 44% (5/9) in pts with pretreated GC (16), which provides rationale to apply immunotherapy combined with molecular antiangiogenic agents for GC/EGJC.

Apatinib, a small-molecule anti-angiogenesis targeted drug, has been approved as third-line or above therapy for pts with advanced GC/EGJC in China (17). In *in vitro* studies, apatinib and PD-1 inhibitor have shown complementary anti-tumor effects (18,19). Based on these results, we carried out a retrospective clinical research study to assess the value of clinical application of PD-1 inhibitor and apatinib as combination therapy in pts with advanced GC/EGJC. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1333).

Methods

Study population

Our study collected 24 pts with histologically confirmed, unresectable locally advanced or metastatic HER2-negative GC/EGJC treated with PD-1 inhibitor combined with apatinib in Zhejiang Cancer Hospital from May 2018 to May 2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Zhejiang Cancer Hospital (IRB-2019-155) and written informed consent was obtained from all patients. The Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 was selected. Other inclusion criteria included PD-1 inhibitor combined with apatinib for more than two cycles, and at least one target lesion that could be measured by imaging. Pts with autoimmune diseases and who had received any PD-1, PD-L1, or other drug immunotherapy were excluded. Further details are shown in *Table 1*.

Study design and assessments

Our study is a retrospective, single-center study. Pts received apatinib at doses of 250 mg in combination with PD-1 inhibitor including SHR-1210 (200 mg Q2W), nivolumab (3 mg/kg Q2W), JS001 (240 mg Q3W), or sintilimab (200 mg Q3W). Treatment was continued until disease progression, intolerable toxicity, or other reason for termination was judged by the investigator.

The efficacy and safety of PD-1 inhibitor plus apatinib in advanced GC/EGJC pts are the primary objectives to be evaluated. Tumor assessments were performed through CT or MRI after every two cycles of treatment according to the RECIST v1.1 guideline. Observed indicators included ORRs, disease control rates (DCRs), PFS, and overall survival (OS). Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (version 4.0). If any grade ≥3 AEs occurred, apatinib or PD-1 inhibitor were discontinued until the adverse reaction returned to ≤1 degree. If the adverse reactions caused by apatinib lead to treatment delays of more than 4 weeks, apatinib was discontinued.

Statistical analysis

The distributions of PFS and OS were estimated using the Kaplan-Meier (KM) method. The statistical significance of survival curves was tested with a log-rank test. All data were analyzed by SPSS 20 statistical analysis.

Results

Patient information and baseline characteristics

Twenty-four pts were enrolled to receive SHR-1210 (n=2),

Table 1 Patient information and baseline characteristics

Characteristic	No (%) (n=24)
Age, years, median [range]	60.5 [30–74]
Gender	
Male	18 (75.0)
Female	6 (25.0)
ECOG	
0	4 (16.7)
1	16 (66.6)
2	4 (16.7)
Histology subtype (Lauren classification)	
Intestinal	5 (20.8)
Diffuse	10 (41.7)
Mixed	4 (16.7)
Unknown	5 (20.8)
Number of metastatic sites	
1–2	9 (37.5)
≥3	15 (62.5)
Peritoneal metastases	
Yes	17 (70.8)
No	7 (29.2)
Liver metastases	
Yes	13 (54.2)
No	11 (45.8)
Prior therapies	
Surgery	14 (58.3)
1st line therapy	16 (66.6)
>1st line therapy	8 (33.4)
Immunotherapy drugs	
JS001	15 (62.5)
Sintilimab	6 (25.0)
Nivolumab	1 (4.2)
SHR-1210	2 (8.3)

ECOG, Eastern Cooperative Oncology Group.

nivolumab (n=1), JS001 (n=15), or sintilimab (n=6), until the data cutoff (December 31, 2019). The median age was 60.5 (range, 30–74) years and 75% (18/24) were male.

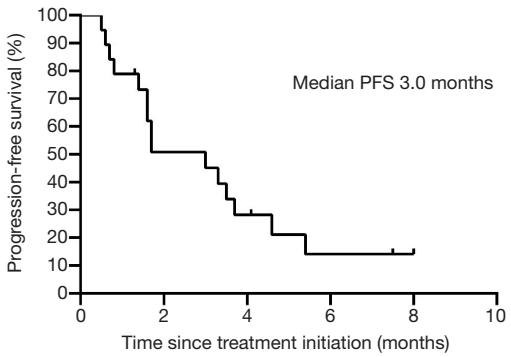

Figure 1 KM plot of PFS. KM, Kaplan-Meier; PFS, progression-free survival.

Fifteen (62.5%) pts had multiple metastatic lesions (≥3) and 58.3% (14/24) pts had undergone surgery. Of the 24 pts, 16 (66.6%) and 8 (33.4%) pts had previously received first-line treatment and more than first-line treatment, respectively. Additional details are provided in *Table 1*.

Efficacy

Of 24 pts, 19 pts were evaluable by RECIST v1.1. One patient achieved complete response (CR), four pts achieved partial response (PR), seven pts achieved stable disease (SD), and seven pts had progressive disease (PD). The ORR was 26.3% (5/19), and the DCR was 63.2% (12/19).

Median time to response was 1.7 (interquartile range, 1.6 to 2.1) months. Median duration of response was 3.0 (interquartile range, 1.8 to 3.7) months. The median PFS was 3.0 (95% CI, 1.3 to 4.7) months (*Figure 1*, *Table 2*). The median OS was not reached (*Table 2*).

Specifically to explain the efficacy and changes in tumor regression, we show the best percentage change in lesion size of the 19 pts in our study in *Figure 2A* and percentage changes over time in *Figure 2B*.

Safety

Safety analysis of this study in 19 pts is as follows. Treatment-related adverse events (TRAEs) leading to discontinuation were reported in 3 (15.8%) of the 19 pts. These included liver function damage [increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], rash and pruritus, and hand-foot syndrome. All-grade TRAEs reported in ≥5% of patients are summarized in *Table 3*. Relatively few grade 3 or 4 TRAEs occurred,

Table 2 Efficacy of PD-1 and apatinib combination treatment in pts with GC/EGJC

Evaluation	Value
RECIST v1.1 tumor evaluation	
CR	1
PR	4
SD ≥6 weeks	7
PD	7
Not evaluable	5
ORR in evaluable patients	26.30%
DCR in evaluable patients	63.20%
Median time to response	1.7 months
Duration of response	
KM median	3.0 months
PFS	
KM median	3.0 months
OS	
KM median	NR

GC, gastric cancer; EGJC, esophagogastric junction cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; NR, not reached.

but these included pruritus (5.3%), rash (5.3%), hand-foot syndrome (5.3%), and increased AST (5.3%) and ALT (5.3%). No treatment-related deaths occurred.

Discussion

In this retrospective study, the ORR following PD-1 inhibitor and apatinib combination therapy was 26.3%, and the PFS was 3.0 months. Compared with previous study results, in which that ORR ranges from 6.8–25% and the PFS was 1.5–5.3 months (4-6), a significant increase of ORR was shown. Simultaneously, DCR was observed in 63.2% (12/19) of pts in our study, with median duration of response of 3.0 (interquartile range, 1.8 to 3.7) months. Long-lasting responses existed. In a study of apatinib monotherapy for advanced GC/EGJC in third-line and above treatment, the median PFS was 2.6 months, ORR was 2.84%, and DCR was 42.05% (20). Our results show that the efficacy of PD-1 inhibitor and apatinib combination therapy turned out to be better compared to apatinib monotherapy.

Nivolumab and pembrolizumab have been approved as immune checkpoint inhibitors for third-line treatment indications for advanced GC/EGJC. But till now, the ORR of immunotherapy monotherapy is only 11–23% (21-23), which emphasizes the necessity of changing treatment options to improve efficacy. Results of this research show that PD-1 inhibitor and apatinib combination therapy improve the efficacy of treatment, mainly because first, tumor angiogenesis inhibits the extravasation of reactive T cells, which form an immunosuppressive microenvironment that leads to tumors escaping immunosurveillance. Combination therapy strengthens T-cell infiltration and activation to eliminate tumor cells (24-27). In addition, Jain *et al.* and Huang *et al.* demonstrated that anti-angiogenic therapy causes vascular normalization, mitigating hypoxia, and may allow more effective T cells to extravasate from the blood into the TME and enhance cancer immunotherapies (28,29). Moreover, anti-vascular targeted therapy apatinib may enhance anti-tumor immune responses by breaking oncogene dependence, which, in turn, causes cancer cell senescence and promotes T-cell clearance (30). Zhao and his team found that low-dose apatinib (250 mg/d) could impede the recruitment of tumor-associated macrophages, decrease TGF-β level, block tumor growth and metastasis, and eventually cause prolonged survival in mouse and *in vitro* models (31).

The safety profile of combination therapy in pts with advanced GC/EGJC was manageable. Adverse reactions are controllable. The types of adverse reactions were consistent with those known to be related to PD-1 inhibitor and apatinib (7,9,20,23). Thyroid disorders are associated with PD-1 inhibitor. All of the adverse effects we found were grades 1 and 2. This may be related to the possibility that PD-1 inhibitors may modulate the immune balance and stimulate their own immune potential (32). We found that hand-foot syndrome, proteinuria, decreased platelet count, leukopenia, and neutropenia were associated with apatinib. TRAEs leading to discontinuation were reported in three pts. These three pts had to discontinue treatment due to liver function damage (AST and ALT increases), rash and pruritus, and hand-foot syndrome. It seems that combination therapy leads to a slight increase in adverse reactions, including ALT and AST increases. No treatment-related deaths occurred. The combination therapy is safe and reliable in clinical application.

There were some limitations in our research. First,

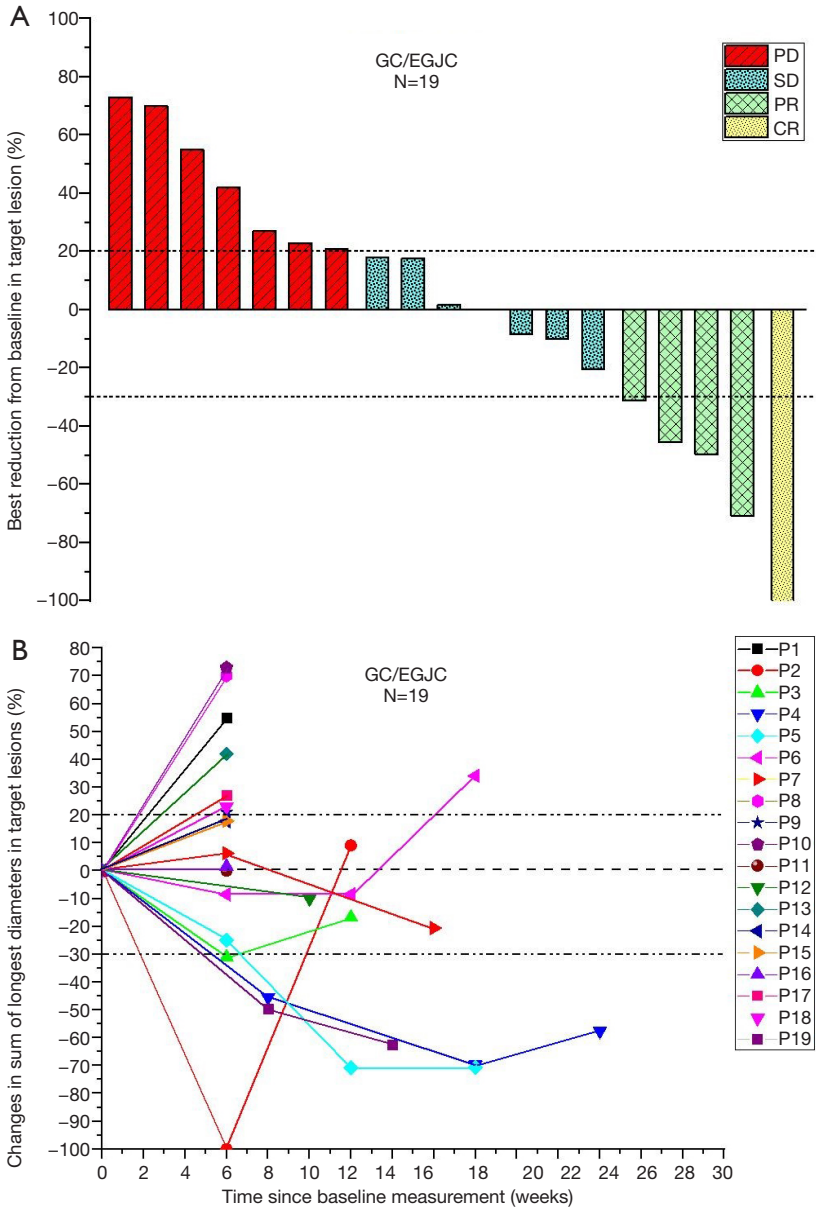

Figure 2 Best percentage change in size of target lesion and lesion diameters over time. (A) Waterfall plot of best percentage change from baseline in size of target lesion; (B) percentage change of lesion diameters over time. GC, gastric cancer; EGJC, esophagogastric junction cancer.

this report was a single-center retrospective study with insufficient sample and possibly incomplete information, resulting in recall bias. Additionally, we lacked data, including biomarkers PD-L1 and tumor mutation burden, which would have been related to the efficacy of immunological checkpoint inhibitors. We will explore this further in the future.

In conclusion, PD-1 inhibitor and apatinib combination therapy has shown encouraging clinical activity, can improve survival, and demonstrates tolerable toxicity in pts with advanced GC/EGJC as second- or third-line therapy. We expect further research, especially in the field of first-line or neoadjuvant therapy, to continue exploring the value of this combination therapy in advanced GC/ EGJC.

Table 3 Treatment-related adverse events (TRAEs)

	Total (n=19), n (%)	
	Any grade	Grade 3/4
TRAEs	3 (15.8)	3 (15.8)
Common TRAE		
Decreased appetite	5 (26.3)	0
Diarrhea	3 (15.8)	0
Nausea	3 (15.8)	0
Fatigue	6 (31.6)	0
Vomiting	4 (21.1)	0
Abdominal pain	3 (15.8)	0
Pyrexia	1 (5.3)	0
Pruritus	2 (10.5)	1 (5.3)
Rash	2 (10.5)	1 (5.3)
Hand-foot syndrome	4 (21.1)	1 (5.3)
Proteinuria	1 (5.3)	0
AST increase	7 (36.8)	1 (5.3)
Blood bilirubin increase	6 (31.6)	0
ALT increase	7 (36.8)	1 (5.3)
Hematological AE		
Platelet count decrease	5 (26.3)	0
Leukopenia decrease	4 (21.1)	0
Neutropenia decrease	4 (21.1)	0
Hemoglobin decrease	3 (15.8)	0
Additional TRAEs of special interest		
Interstitial lung disease	0	0
Colitis	0	0
Hypopituitarism	0	0
Thyroid disorder	8 (42.1)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Acknowledgments

We thank all researchers and patients for participating in this trial.

Funding: This work was supported by Zhejiang Chinese Medicine Science and Technology Program (grant number 2018ZB022).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-1333

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tcr-20-1333

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1333). 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 the Ethics Committee of Zhejiang Cancer Hospital (IRB-2019-155) and written informed consent was obtained from all patients.

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Cite this article as: Wei Q, Yuan X, Li J, Xu Q, Ying J. PD-1 inhibitor combined with apatinib for advanced gastric or esophagogastric junction cancer: a retrospective study. Transl Cancer Res 2020;9(9):5315-5322. doi: 10.21037/tcr-20-1333

