Real-world data on camrelizumab in digestive system cancers: a retrospective observational study

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Abstract

Objective: To explore the clinical efficacy and safety of camrelizumab in the treatment of digestive system malignancies in the real world.

Methods: A retrospective study was designed. A total of 34 patients with advanced gastrointestinal cancer who received camrelizumab treatment in the xx hospital from July 2019 to May 2020 were included. The follow-up endpoint was set for October 30, 2020. The primary endpoint was objective response rate (ORR) and safety. Secondary endpoint measures included progression-free survival (PFS), and overall survival (OS). Cox regression was used for the analysis of factors associated with PFS.

Results: As the best response, only 5 patients achieved a partial response and 10 patients had disease progression, with an ORR of 14.31%. Compared with gastric cancer, the ORR of esophageal cancer (3.0% vs 0.0%) (P<0.05). The PFS was 4.5 months (2-10 months). OS ranged from 4 to 11 months, and median OS has not been reached. Multivariate Cox regression analysis showed that gastric cancer (HR=1.695, 95% CI:11.216–2.435, P<0.05) was associated with still shorter PFS, and camrelizumab combined with other drugs (HR=0.512, 95% CI: 0.095–0.737, P<0.01) was associated with PFS in patients. The most common AEs were anemia (41.2%, 14/34) in all grades 1 to 2. Grade 3 AEs occurred in 3 patients (2.9%), including 1 case of immune pneumonitis, 1 case of hemangioma, and 1 case of transaminase increased. Other adverse events included diarrhea, nausea, neutropenia, thrombocytopenia, reactive cutaneous capillary proliferation (RCCEP), fatigue, and hypothyroidism, all of which did not exceed 12%.

Conclusion: Camrelizumab is effective and safe in the treatment of patients with digestive system malignancies, but the overall response rate is limited.

Keywords: Digestive System, Tumor, Camrelizumab; efficacy, Safety.

Introduction

Digestive system malignancies are a common type of malignant tumor in clinical practice [1]. In China, the incidence and mortality of malignant tumors of the digestive tract rank second, after lung cancer [2]. Such patients are basically in the middle and advanced stages at the time of diagnosis, and most patients have lost the chance of surgery. Radiotherapy and chemotherapy as the main treatment for advanced cancer have obvious double-edged sword effect. How to improve therapeutic efficacy and reduce adverse reactions remains a great challenge in clinical practice. In recent years, the continuous development and application of targeted therapeutic agents have provided more ideal and effective treatment options for patients with advanced malignancies[3,4]. Among them, programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors have been demonstrated to be effective cancer immunotherapies. Several PD-1/PD-L1 inhibitors have recently been approved by the Food and Drug Administration (FDA) and successfully used in the treatment of many types of solid tumors [5,6].

Camrelizumab, a PD-1/PD-L1 inhibitor independently developed in China, is a humanized IgG4κ anti-PD-1 monoclonal antibody obtained using recombinant technology in Chinese hamster ovary (CHO) cell line [7]. Since camrelizumab showed a good survival

benefit in a single-arm phase II clinical trial[8] of classical Hodgkin lymphoma, the drug was approved by the China Food and Drug Administration (CFDA) on May 29, 2019, for the treatment of relapsed or refractory classical Hodgkin lymphoma after at least second-line systemic chemotherapy. Camrelizumab is also being studied for the treatment of various malignancies such as lung cancer, gastric cancer, esophageal cancer, as well as liver cancer[9]. Although the current phase I and II clinical trials of camrelizumab in the treatment of gastrointestinal malignancies such as esophageal cancer and gastric cancer have preliminarily shown encouraging results [10,11], its clinical application effect in the real world is not clear.

In this study, we are designing a prospective study that included 34 patients with malignant tumors of the digestive tract including gastric, esophageal, and colorectal cancers. By analyzing the treatment response data, adverse events, and survival time of patients, to clarify the efficacy and safety of camrelizumab in the treatment of digestive tract tumors in the real world, to provide a reference for clinical practice.

Material and Methods

Patients
A total of 34 patients with metastatic digestive system cancers treated with camrelizumab admitted to our hospital between July 2019 and May 2020 were included in the study. Inclusion criteria: 1) Patients admitted to the hospital imaging examination and pathological examination confirmed the diagnosis of metastatic digestive system cancers, including gastric cancer, esophageal cancer, and colorectal cancer. 2) Expected survival>3 months. 3) Eastern Cooperative Oncology Group (ECOG) score ≤ 2; 4), all of whom received camrelizumab or combination therapy. Exclusion criteria: 1) Patients with mental illness such as cognitive dysfunction or pregnant or lactating women; 2) Patients who are intolerant to camrelizumab drugs. 3) Patients with incomplete follow-up data.

Ethical Statement
The study followed the tenets of following the Declaration of Helsinki and was approved by the Ethics Committee of our hospital for conduct. Informed consent was obtained from all patients.

Camrelizumab Treatment
All patients were treated with 200 mg camrelizumab (Jiangsu Hengrui Medicine Co., Ltd., China, strength 200 mg intravenously every 3 weeks until intolerable toxicity or disease progression occurred.

Efficacy Assessments
Best Overall Response (BOR): Patients were evaluated for a clinical response using Response Evaluation Criteria in Solid Tumors version 1.1 [12], which was classified as follows: complete response (CR): complete disappearance of tumor lesions on imaging; partial response (PR): reduction in the diameter of tumor lesions by more than 30%; stable disease (SD): tumor shrinkage, but<30%; progressive disease (PD): increase in the diameter of tumor lesions by ≥ 20%, or the appearance of new lesions. Objective response rate (ORR) was defined as the percentage of patients with CR and PR. Disease control rate (DCR) was defined as the percentage of patients with CR, PR, and SD.

Progression-free survival (PFS) is defined as the time interval from the start of treatment with camrelizumab to the occurrence of disease progression or death. Overall survival (OS) was defined as the interval from the start of treatment with camrelizumab to the occurrence of death from any cause.

Assessment of adverse events (AEs)
National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTC 4.0) was used for determination and classified into grades 1 to 5.

Observation Indicators
Primary endpoints included objective response rate (ORR) and safety. Secondary endpoint measures included factors associated with progression-free survival (PFS), overall survival (OS), and patient PFS.

Statistical Analysis
SPSS version 23.0 (SPSS, Inc., Chicago, IL, USA) software was applied for statistical analysis. Enumeration data were expressed as case (percentage) (n (%)), $\chi 2$ test or Fisher exact test was performed; patient age conformed to the normal distribution, and was expressed as mean ± standard deviation (± s). Kaplan-Meier curves for PFS in the two groups were plotted using GraphPad 7.0. Multivariate Cox regression analysis was used to evaluate the influencing factors of PFS in patients. The test level was $\alpha=0.05$, and $P<0.05$ was considered statistically significant.

Results

Baseline data of patients in the two groups
In this study, the mean age of patients was over 63 years and 70.6% of patients were male. Eight patients had an ECOG score of 2. There were 16 patients (47.1%) with gastric cancer, 8 with colorectal cancer, and 10 with esophageal cancer. Twenty-two patients (64.7%) were treated with camrelizumab in combination with other drug regimens, and a total of 22 patients (64.7%) were treated with the first-line camrelizumab. The longest metastatic sites were lymph nodes (61.7%, 21/34) and liver (44.1%, 15/34). Other clinical baseline data 1 (Table 1).

Table 1: Baseline data of patients.

Item	Number of patients (n=34)
Mean age (years, ± s)	63.3 ± 11.4
Gender, n (%)	
Male	24 (70.6)
Female	10 (29.4)
ECOG score	
0	1 (2.9)
1	25 (73.5)
2	8 (23.5)
Tumor type, n (%)	
Gastric Cancer	16 (47.1)
Colorectal Cancer	8 (23.5)
Esophageal cancer	10 (29.4)
Combination therapy drugs, n (%)	
Yes	22 (64.7)
No	12 (35.3)
First-line medication or not, n (%)	
Yes	12 (35.3)
No	22 (64.7)
Number of chemotherapy lines after recurrence, n (%)	
0	13 (38.2)
1	4 (11.8)
2	8 (23.5)
≥ 3	9 (26.5)
Number of metastatic sites, n (%)	
1	14 (41.2)
2	16 (47.1)
3	4 (11.8)
Metastatic site, n (%)	
Lung	7 (20.6)
Liver	15 (44.1)
Bone	4 (11.8)
Lymph nodes	21 (61.7)
Other	6 (17.7)
ECOG: Eastern Cooperative Oncology Group	

Efficacy

As of the follow-up by October 30, 2020, 34 patients with advanced gastrointestinal cancer were all evaluable for efficacy. Only 5 patients achieved PR, 20 patients achieved SD, and 9 patients developed PD after camrelizumab treatment. ORR was 14.3% and DCR was 71.4% (including 5 PR and 20 SD patients). A total of 24 PFS events were reported, with a PFS of 4.5 months (2-10 months) (Figure 1). Twelve patients died after camrelizumab treatment, with an OS of 4 months, and the median OS had not been reached.
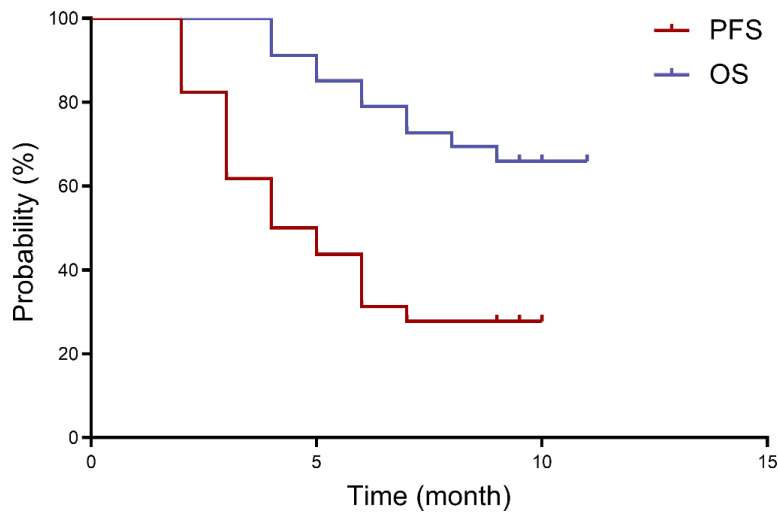
Figure 1: Kaplan-Meier curves of PFS and OS for all patients.

In camrelizumab treatment, there were no significant differences in ORR among different lines of medication, whether combined with other drugs, and different numbers of chemotherapy lines after recurrence and metastasis. Notably, the ORR of esophageal cancer (3.0% vs 0.0%) was significantly higher compared with gastric cancer (P<0.05) (Table 2).

2.3 Cox Regression Analysis of Factors Associated with PFS in Patients.

Table 2: Analysis of ORR, n (%).

Group	N	CR	PR	SD	PD	ORR (%)
Tumor type						
Gastric Cancer	16	0	0	12 (75.0)	4 (25.0)	0
Colorectal Cancer	8	0	2 (25.0)	4 (50.0)	2 (25.0)	25
Esophageal cancer	10	0	3 (30.0)	4 (40.0)	3 (30.0)	30.0*
1st line or not						
Yes	12	0	3 (25.0)	7 (58.3)	2 (16.7)	25
No	22	0	2 (9.1)	13 (59.1)	7 (31.8)	9.1
Combination						
Yes	22	0	4 (18.2)	14 (63.6)	4 (18.2)	18.2
No	12	0	1 (8.3)	6 (60.0)	5 (41.7)	8.3
Number of chemotherapy lines after recurrence and metastasis						
≤ 1	17	0	4 (23.5)	9 (52.9)	4 (23.5)	23.5
>1	17	0	1 (5.9)	10 (58.8)	5 (29.4)	5.9
*Compared with gastric cancer, P<0.05.						

The results of the univariate analysis showed that gastric cancer (HR=1.585, 95% CI: 1.136–2.692, P<0.05) was associated with shorter PFS. In contrast, first-line treatment with camrelizumab and camrelizumab in combination with other drugs were associated with PFS in patients (HR=0.805, 0.703, respectively).

By multivariate analysis, after excluding potential confounders, gastric cancer (HR=1.695, 95% CI:11.216-2.435, P<0.05) was associated with still shorter PFS, and camrelizumab combined with other drugs (HR=0.512, 95% CI: 0.095-0.737, P<0.01) was associated with PFS in patients (Table 3).

Table 3: Univariate and multivariate Cox regression analysis of progression free survival (PFS) (n=34, 24 events).

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	*HR*	95% CI	P
Age (years 60≤ vs >60 years)	0.978	0.765-1.226	0.355	-	-	-
Gender (male vs female)	1.075	0.959-1.218	0.258	-	-	-
ECOG (≤1 vs >1)	0.993	0.698-1.186	0.185	-	-	
Gastric cancer (vs other)	1.585	1.136 to 2.692	0.026	1.695	1.216-2.435	**0.015**
1st line or not	0.805	0.319-0.969	0.02	0.887	0.519-1.126	0.096
Combination use (yes vs no)	0.703	0.109-0.803	0.018	0.512	0.095-0.737	**0.006**
Number of metastatic sites (≤1 vs>1)	0.892	0.647-1.152	0.208	-	-	-
Liver metastases (yes vs no)	1.215	0.973-1.825	0.177	-	-	-
Lung metastases (yes vs no)	1.172	0.902-1.636	0.295	-	-	-
Metastases to lymph nodes (yes vs no)	1.122	0.932-1.709	0.345	-	-	
Important P values are shown in bold.						

Adverse Events

All patients were evaluated for safety. The most common AEs were anemia (41.2%, 14/34) but all were grade 1 to 2. Grade 3 AEs occurred in 3 patients (8.8%), including 1 case of immune pneumonia, 1 case of hemangioma, and 1 case of transaminase elevation, in which camrelizumab treatment was interrupted in patients with immune pneumonia and hemangioma. Other adverse events also included diarrhea (8.8%), nausea (8.8%), neutropenia (5.9%), thrombocytopenia (8.8%), RCCEP (11.8%, 4/34), fatigue (11.8%), and hypothyroidism (8.8%), all of which did not exceed 12% (Table 4). There were no deaths related to AEs. RCCEP.

Table 4: Incidence of adverse events (n (%)).

AEs	Grading		
	Grade 1-2	Grade 3-4	Total
Gastrointestinal adverse reactions			
Diarrhea	3 (8.8)	0 (0.0)	3 (8.8)
Nausea	3 (8.8)	0 (0.0)	3 (8.8)
Hematologic Adverse Reactions			
Anemia	14 (41.2)	0 (0.0)	14 (41.2)
Neutropenia	2 (5.9)	0 (0.0)	2 (5.9)
Thrombocytopenia	3 (8.8)	0 (0.0)	3 (8.8)
Other adverse reactions			
RCCEP	4 (11.8)	-	4 (11.8)
Immune pneumonitis	0 (0.0)	1 (2.9)	1 (2.9)
Hemangioma	3 (8.8)	1 (2.9)	4 (11.8)
Asthenia	4 (11.8)	0 (0.0)	4 (11.8)
Hypothyroidism	3 (8.8)	0 (0.0)	3 (8.8)
Transaminases increased	3 (8.8)	1 (2.9)	4 (11.8)
AEs: Adverse Events; RCCEP: Reactive Cutaneous Capillary Endothelial Proliferation.			

Discussion

In recent years, the signaling pathway of PD-1/PD-L1 has been widely studied in clinical practice. It has also been confirmed that it plays an important role in tumor immune escape as one of the key links of immune checkpoints in tumor immunity [13]. Newly developed camrelizumab blocks the PD-1/PD-L1 pathway by binding to PD-1, thereby activating T cells and producing sustained antitumor effects. In the current study, we evaluated the efficacy and safety of camrelizumab in the treatment of metastatic gastrointestinal malignancies in the real world. The results of the study showed that in the real world, camrelizumab has some efficacy for metastatic malignant tumors of the digestive tract, but the overall response rate is low. Only 5 of 34 patients achieved PR and 20 patients achieved SD, with an ORR of 14.3% and a DCR of 71.4%. The PFS was 4.5 months (2-10 months), the OS was 4 months, and the OS had not been reached.

In this observational study, we observed that camrelizumab in gastric cancer, no patients achieved an objective response, which was lower than that in phase Ib (20%) [11] and phase II (44%) [14] clinical studies. This may be related to the fact that the patients included in the current study were older (more than 64 years on average) and had more treatment regimens. In previous phase IB and II studies, patients were strictly screened, and the treatment regimen was sufficiently uniform. It is worth noting that the PFS of 16 patients with gastric cancer in this study (5 months vs 2.9 months) was higher than that in the phase IB clinical study, and the OS (9 months vs 11.4 months) was similar to that in the phase IB clinical study. A phase Ib trial (NCT03222440) [15] included 20 patients with newly diagnosed locally advanced esophageal squamous cell carcinoma, and the ORR of camrelizumab combined with radiotherapy was 83.3% (15 of 18). Another phase 1 dose-escalation and expansion study (NCT02742935) [10] included 30 patients who received 60, 200, and 400 mg of camrelizumab sequentially, with the first dose administered 4 weeks apart and the third dose administered 2 weeks apart; doses of 60, 200, or 400 mg were selected to continue treatment in the subsequent expansion phase. The results showed that 1 patient achieved CR and 9 patients achieved PR, with an ORR of 33.3%. In this study, 3 of 10 patients with esophageal cancer achieved PR, with an ORR of 30%, slightly lower than that in phase I clinical study. Also, 8 colorectal cancer patients were analyzed for a response to camrelizumab in this study, and 2 patients achieved PR, with an ORR of 25%. It was slightly lower than 50% of previous pembrolizumab [16], but grade 3 or higher adverse reactions were lower than pembrolizumab (0.0% vs 49.9%).

In the analysis, we found that gastric cancer had a lower ORR than the other two digestive tract tumors, especially compared with esophageal cancer (0.0% vs 30.0%, P<0.05). The results of multivariate Cox analysis also showed that gastric cancer (HR=1.695, 95% CI: 11.216–2.435, P<0.05) was associated with still shorter PFS. Therefore, the use of camrelizumab in gastric cancer warrants further assessment. In addition, camrelizumab in combination with other drugs (HR=0.512, 95% CI: 0.095–0.737, P<0.01) was associated with PFS in patients, which is consistent with previous views [17].

In the study, we observed that in metastatic digestive system cancers, camrelizumab had high safety and overall controllable toxicity. The most common AEs were anemia (41.2%, 14/34), with only 3 patients experiencing grade 3 AEs and only 2 AEs discontinuing treatment. No other adverse reactions exceeded 12%, and no patient died due to AEs. Also, many previous studies have found that RCCEP is very common after camrelizumab treatment, seems to be a unique side effect, not found in other immune checkpoint inhibitors, and the incidence of treatment is as high as 66.8% to 97.3% [10, 18,19]. However, the incidence of RCCEP in this study was low, only 11.8% (4/34). This may be related to tumor type as well as a combination with other drug therapy. A study [14] also reported that the incidence of RCCEP was only 12.1% in camrelizumab 200 mg+ apatinib for hepatocellular carcinoma, gastric, or esophagogastric junction cancer. Similar to this study.

The biggest limitation of this study is the small sample size and the fact that no comprehensive digestive system cancers were included, therefore, there may have been a selection bias. Future larger studies will allow assessment in each type of tumor.

Conclusion

The current study showed that camrelizumab treatment had some efficacy and high safety in metastatic gastrointestinal malignancies. The objective response rate we observed is lower than the data of other clinical studies. The possible reasons are: most patients in the group have undergone multi-line treatment; no PD-L1 testing is performed, and there must be some PD-L1 negative patients, etc.

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