Research Paper

Efficacy of Camrelizumab with Raltitrexed in the Therapy of Advanced Gastric Cancer on Postoperative Recurrence and Metastasis

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To authenticate the clinical outcome of camrelizumab united with raltitrexed in the therapy of advanced gastric cancer and postoperative recurrent and metastatic gastric cancer. From January 2018 to March 2021, the clinical data of 80 sufferers with advanced gastric cancer and postoperative recurrent and metastatic gastric cancer treated in our hospital were estimated retrospectively. According to the different therapy methods, the sufferers were separated into two subgroups. 42 sufferers in the survey subgroup were treated with camrelizumab monoclonal antibody plus raltitrexed plus routine chemotherapy, and 38 sufferers in the control subgroup were treated with raltitrexed plus routine chemotherapy for 3 consecutive cycles. The short-term efficacy, serum tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9), adverse reactions and survival were compared among the two subgroups. The objective response rate and disease control rate in the survey subgroup were 54.76 % and 80.95 % respectively, which were notablely boosted than those in the control subgroup (31.58 % and 57.89 %). After therapy, the concentrations of serum carcinoembryonic antigen and carbohydrate antigen 19-9 in the survey subgroup were notablely lessened than those in the control subgroup. There were no IV grade serious adverse reactions and fewer III grade adverse reactions among the two subgroups. There was no notable divergence in the incidence of common adverse reactions such as nausea and vomiting, liver and kidney function damage, myelosuppression, skin rash, anemia and reactive cutaneous capillary endothelial proliferation among the two subgroups. The median progression-free survival in the survey subgroup and the control subgroup was 9.31 mo and 6.57 mo respectively, and the divergence was statistically notable. Camrelizumab united with raltitrexed can improve the short-term and long-term efficacy of advanced gastric cancer and postoperative recurrent and metastatic gastric cancer with high safety and no increase of drug side outcomes.

Key words: Advanced gastric cancer, mortality, gastric cancer, camrelizumab, raltitrexed, tumor markers, chemotherapy

According to the epidemiological survey[1,2], the incidence of gastric cancer ranks 5th in the world, and the mortality rate ranks 4th in the world. Its morbidity and mortality rank 2nd in malignant tumors in China, which seriously threatens people's lives and health. Early gastric cancer can be cured by surgery, but most of the sufferers with gastric cancer in our country have entered the middle and advanced stage at the time of diagnosis and cannot undergo radical operation[3]. The median survival time of metastatic gastric cancer is <1 y, but targeted drugs can be used to improve survival and reduce toxicity[4]. There is no definite and effective therapy for advanced gastric cancer or postoperative recurrent and metastatic gastric cancer, mainly chemotherapy[5]. Although chemotherapy drugs used in the treatment of unrespectable advanced or metastatic gastric cancer patients will lead to adverse reactions of physical function, patients with poor tolerance and poor prognosis, but chemotherapy remains a major obstacle that reduces efficacy[6,7].

Raltitrexed, a specific Thymidylate Synthase

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(TS) inhibitor, can inhibit Deoxyribonucleic Acid (DNA) synthesis and promote tumor cell apoptosis by inhibiting TS. It has been approved for advanced colorectal cancer[8]. Related clinical trials found that raltitrexed also has a certain therapeutic outcome on advanced gastric cancer[9], and the side outcomes can be tolerated. Advanced gastric cancer and postoperative recurrent and metastatic gastric cancer have always been the focus of clinical attention. However, treatment-related mortality is high in metastatic colorectal cancer patients taking raltitrexed, which restricts the use of raltitrexed[10]. A study found that the combination of cisplatin and raltitrexed improved the prognosis of patients with mesothelioma without affecting the quality of life[11]. In addition, both S1 and 5-Fluorouracil (5-FU) were used in combination with raltitrexed, thus improving the therapeutic effect of raltitrexed[12,13]. Therefore, it is particularly important to explore a new combination of raltitrexed therapy in the treatment of advanced gastric cancer.

In recent years, Immune Checkpoint Inhibitors (ICIs) have been favored. Camrelizumab, a Programmed Death receptor 1 (PD-1) inhibitor developed by China, was approved to market on May 29th, 2019. The main indications are recurrent or refractory Hodgkin's lymphoma, esophageal cancer, lung cancer and liver cancer[14]. Clinical trials found that camrelizumab corroborated good anti-tumor outcome on a variety of solid malignant tumors[15]. Camrelizumab combined with trastuzumab has been reported to be beneficial and well tolerated in Human Epidermal Growth Factor Receptor 2 (HER2) positive patients with advanced gastric cancer[16]. In addition, camrelizumab combined with abraxane+carboplatin has been found to be an effective method for the treatment of advanced gastric cancer and can improve the survival rate of patients[17]. However, the effect of camrelizumab united with raltitrexed in the therapy of advanced gastric cancer and postoperative recurrent and metastatic gastric cancer is unknown. At present, camrelizumab is rarely utilized in advanced gastric cancer and postoperative recurrent and metastatic gastric cancer. Based on this, this report explored the efficacy of camrelizumab united with raltitrexed in the therapy of advanced gastric cancer and postoperative recurrent and metastatic gastric cancer, in order to provide ideas and references for clinical optimization of therapy.

MATERIALS AND METHODS

General information:

From January 2018 to March 2021, the clinical data of sufferers with advanced gastric cancer and postoperative recurrent and metastatic gastric cancer treated in our hospital were estimated retrospectively.

Inclusion criteria: 18 y-70 y old; diagnosed as advanced gastric cancer or postoperative recurrent and metastatic gastric cancer by gastroscopy or pathological examination; at least one detectable lesion with an estimated survival time of >3 mo; Karnofsky (KPS) ≥70; took camrelizumab united with raltitrexed and routine chemotherapy or raltitrexed and routine chemotherapy and the clinical data were complete[18].

Exclusion criteria: Sufferers merged with other malignant tumors; sufferers with abnormal function of heart, liver and kidney; sufferers who were treated with other regimens midway and pregnant or lactating female sufferers. Finally, 80 sufferers were included and divided into two subgroups according to different therapy schemes. 42 sufferers in the survey subgroup were treated with camrelizumab monoclonal antibody plus raltitrexed plus routine chemotherapy, and 38 sufferers in the control subgroup were treated with raltitrexed plus routine chemotherapy for 3 consecutive cycles. In the survey subgroup, there were 25 males and 17 females, 20 instances of advanced gastric cancer, 22 instances of recurrent and metastatic gastric cancer after operation, the age was 35 y to 68 y old, mean (54.81±12.34) y, and the pathological type was adenocarcinoma (n=37) and other 5 instances. In the control subgroup, there were 22 males and 16 females, 17 sufferers with advanced gastric cancer, 21 sufferers with recurrent and metastatic gastric cancer after operation, the age was 38 y-67 y old, mean (53.52±13.80) y, and the pathological type was adenocarcinoma (32 instances) and other 6 instances. There was no notable divergence in the general data among the two subgroups ($p>0.05$)[19].

Therapy methods:

The control subgroup was treated with raltitrexed plus routine chemotherapy (platinum+fluorouracil). The dose of raltitrexed was 3 mg/m^2, which was infused intravenously on the day of chemotherapy. In the survey subgroup, on the basis of the control

subgroup, united with camrelizumab monoclonal antibody, the dose was 200 mg, intravenous drip on the day of chemotherapy. Both subgroups took 3 w courses for 3 consecutive courses of therapy.

During the therapy, symptomatic therapies were given, such as anti-allergy, anti-vomiting, protection of gastric mucosa, liver protection and maintenance of water and electrolyte balance.

After each course of therapy, blood routine examination and Computed Tomography (CT) examination were performed to record the occurrence of adverse reactions. After the therapy, the sufferers were followed up by telephone once a month until March 2022.

Observation indicators:

Short-term efficacy: Referred to the evaluation criteria of Response Evaluation Criteria in Solid Tumors (RECIST)[20] to evaluate the short-term efficacy of the two subgroups, Complete Remission (CR) means tumor lesions disappeared and no new lesions were found; Partial Remission (PR) means the maximum diameter of tumor was reduced by >30 %; Disease Stabilization (SD) means the maximum diameter of the tumor shrank by <30 % or increased by <20 % and Disease Progression (PD) means the maximum diameter of the tumor increased by >20 % or new lesions were found. Objective Response Rate (ORR)=(CR+PR) number of instances/total number of instances×100 %

Disease Control Rate (DCR)=(CR+PR+SD)/total number of instances×100 %

Concentration of serum tumor markers: Fasting venous blood 5 ml was collected before therapy and within 1 w after therapy, the supernatant was collected after centrifugation. The expression of Carcinoembryonic Antigen (CEA) and Carbohydrate Antigen 19-9 (CA19-9) in serum was detected by Chemiluminescence immunoassay.

Adverse reactions: The intensity of adverse reactions (I-IV) of the two subgroups was evaluated according to the classification and evaluation standard of common toxic and side outcomes of anticancer drugs (National Cancer Institute Common Toxicity Criteria (NCICTC) 3.0) formulated by World Health Organization (WHO) [21]. The common adverse reactions included nausea and vomiting, liver and kidney function damage, bone marrow suppression, rash, anemia, Reactive Cutaneous Capillary Endothelial Proliferation (RCCEP), etc.

Long term efficacy: Estimated the follow-up data of the two subgroups within 1 y after the end of therapy, counted the survival of the sufferers, and estimated the median Progression Free Survival (PFS) (the time from the start of therapy to the time when the illness progresses or dies) by drawing the survival curve.

Data statistics:

Statistical Package for the Social Sciences (SPSS) 22.0 software was utilized to analyze the data. The measurement data conformed to the normal distribution and had uniform variance, which was expressed by ($\bar{x}\pm s$) and tested by independent sample t-value; the counting data were expressed by n (%) and tested by Chi-square (χ^2)/Fisher exact probability method; Kaplan Meier method was utilized to plot the survival curve, and log-rank test was performed. With $p<0.05$ as the statistical significance was shown in fig. 1.

RESULTS AND DISCUSSION

The ORR and DCR of the survey subgroup were 54.76 % and 80.95 % respectively, which were notably boosted than those of the control subgroup (31.58 % and 57.89 %, $p<0.05$). As corroborated in Table 1 and fig. 2.

Before therapy, there was no notable divergence in the concentrations of serum CEA and CA19-9 among the two subgroups ($p>0.05$), but after therapy, the concentrations of serum CEA and CA19-9 in the two subgroups were notably lessened than those before therapy ($p<0.05$), and the concentrations in the survey subgroup were notably lessened than those in the control subgroup ($p<0.05$). As corroborated in Table 2 and fig. 3.

There was no serious adverse reaction of grade IV among the two subgroups, and there was no notable divergence in the incidence of nausea and vomiting, liver and kidney function damage, myelosuppression, rash, anemia and RCCEP among the two subgroups. As corroborated in Table 3 and, fig. 4 and fig. 5.

The median PFS of the survey subgroup was 9.31 mo (95 % CI 8.797~9.827), and that of the control subgroup was 6.57 mo (95 % CI 5.873~7.264). The median PFS of the survey subgroup was notably longer than that of the control subgroup, and the

divergence was statistically notable (χ^2=20631, p<0.001). As corroborated in fig. 6.

With the development of medical science and technology, and the change of diet life structure, malignant tumor has become a common clinical illness, and tens of millions of people are plagued by malignant tumor every year. According to the report[22], the incidence of gastric cancer in China is the highest in the world, and the 5 y survival rate is only 27.4 %. Although the mortality rate has declined in recent years, it is becoming younger, and the situation is not optimistic. The reason why gastric cancer has become a difficult problem in clinical diagnosis and therapy is that some sufferers are already in the late stage, and they are easy to relapse and metastasis after operation, so they cannot be cured by operation. At the same time, the outcome of systemic chemotherapy is limited. At present, there is no standardized therapy plan in the world. The Chinese society of Clinical Oncology (CSCO) guidelines for the diagnosis and therapy of primary gastric cancer proposed that the first-line therapy scheme should be determined according to the expression of HER2 in sufferers with advanced gastric cancer[23]. Trastuzumab+cisplatin+fluorouracil should be utilized for HER2 positive sufferers, and cisplatin+fluorouracil should be utilized for HER2 negative sufferers; paclitaxel+ramucirumab is recommended as the second-line therapy scheme; the third line of therapy is apatinib and pembrolizumab. In conclusion, the clinical therapy of advanced gastric cancer and postoperative recurrent and metastatic gastric cancer still needs to be breakthrough.

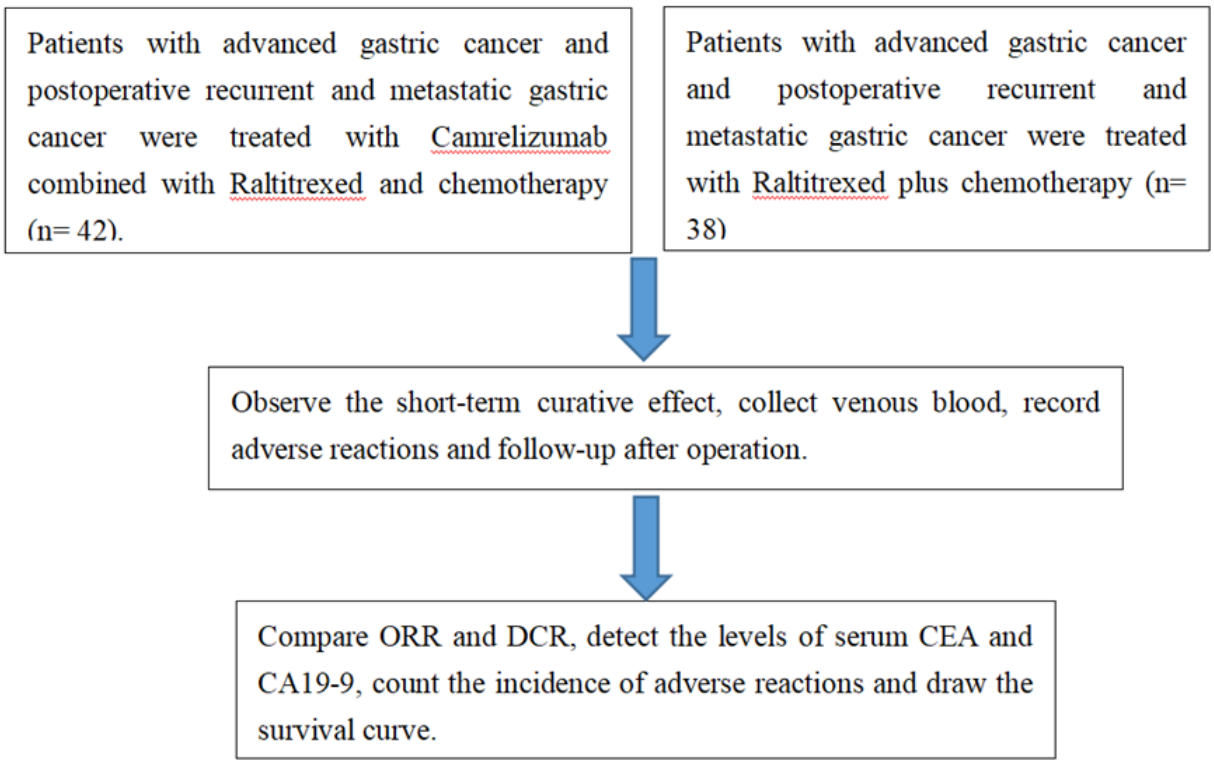

Fig. 1: Schematic representation of research design

TABLE 1: DIVERGENCE OF SHORT-TERM EFFICACY AMONG THE TWO SUBGROUPS n (%)

Group	n	CR	PR	SD	PD	ORR	DCR
Survey	42	3 (7.14)	20 (47.62)	11 (26.19)	8 (19.05)	23 (54.76)	34 (80.95)
Control	38	0 (0.00)	12 (31.58)	10 (26.32)	16 (42.11)	12 (31.58)	22 (57.89)
χ^2						4.357	5.051
p						0.037	0.025

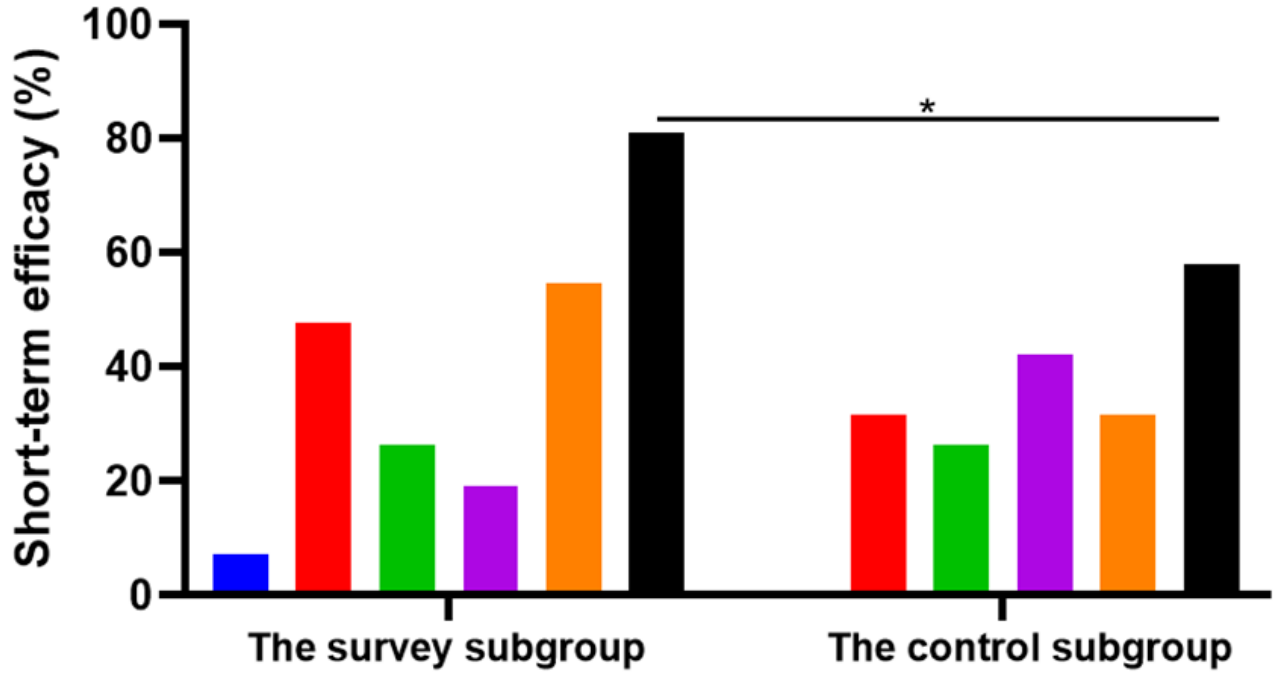

Fig. 2: Short-term efficacy among the two subgroups
Note: *p<0.05, ( ): CR; ( ): PD; ( ): ORR; ( ): PR; ( ): SD and ( ): DCR

TABLE 2: DIVERGENCE OF SERUM CEA AND CA19-9 CONCENTRATIONS AMONG THE TWO SUBGROUPS (x̄±s, mg/l)

Group	n	CEA		CA19-9	
		Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
Survey	42	67.85±9.54	21.27±4.81[a]	436.50±52.13	180.34±22.01[a]
Control	38	67.46±10.33	30.38±5.25[a]	440.62±54.00	245.62±28.05[a]
t		0.176	8.1	0.347	11.636
p		0.861	<0.001	0.73	<0.001

Note: [a]p<0.05, contrasted to the same subgroup before therapy

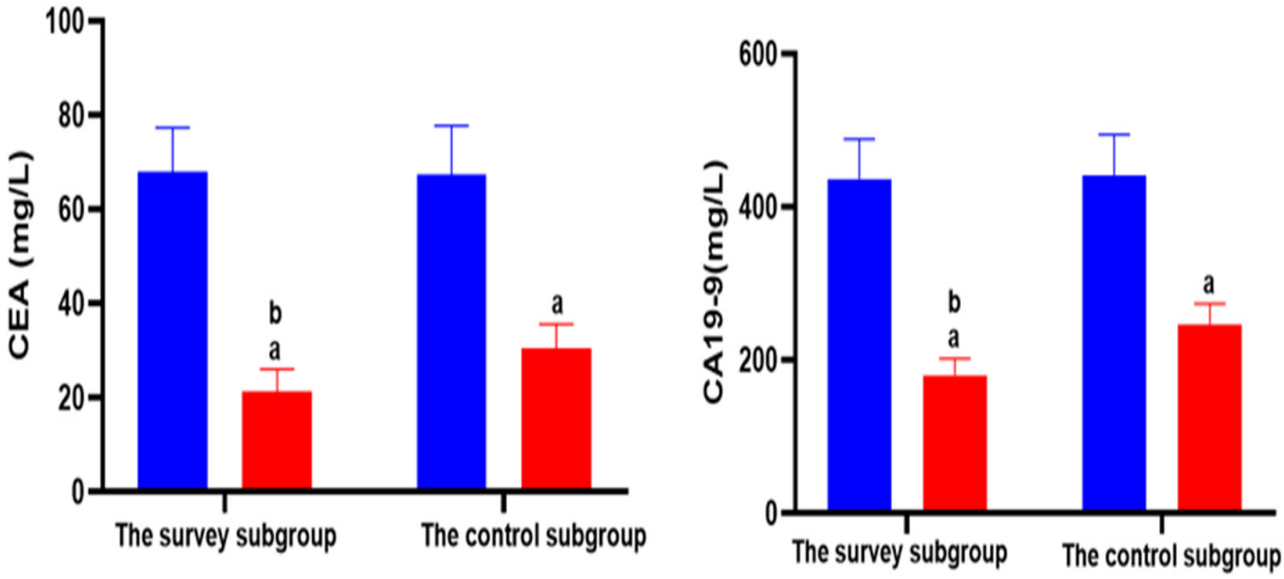

Fig. 3: Serum CEA and CA19-9 concentrations
Note: Compared with the same group before therapy, [a]p<0.05 and compared with the control subgroup after therapy, [b]p<0.05, ( ): Pre-therapy and ( ): Post-therapy

TABLE 3: DIVERGENCE OF ADVERSE REACTIONS AMONG THE TWO SUBGROUPS n (%)

Adverse reaction	Survey subgroup (n=42)				Control subgroup (n=38)					
	Stage I	Stage II	Stage III	Total incidence rate	Stage I	Stage II	Stage III	Total incidence rate	χ^2	p
Nausea and vomiting	9 (21.43)	4 (9.52)	2 (4.76)	15 (35.71)	7 (18.46)	5 (13.16)	1 (2.63)	13 (34.21)	0.02	0.888
Damage of liver and kidney function	7 (16.67)	5 (11.90)	0 (0.00)	12 (28.57)	5 (13.16)	3 (7.89)	1 (2.63)	9 (23.68)	0.246	0.62
Myelosuppression	6 (14.29)	7 (16.67)	3 (7.14)	16 (38.10)	8 (21.05)	4 (10.53)	2 (5.26)	14 (36.84)	0.013	0.908
Rash	3 (7.14)	2 (4.76)	0 (0.00)	5 (11.90)	1 (2.63)	2 (5.26)	0 (0.00)	3 (7.89)	-	0.715
Anemia	3 (7.14)	1 (2.38)	0 (0.00)	4 (9.52)	6 (15.79)	1 (2.63)	1 (2.63)	8 (21.05)	2.08	0.419
RCCEP	5 (11.90)	3 (7.14)	1 (2.38)	9 (21.43)	5 (13.16)	0 (0.00)	1 (2.63)	6 (15.79)	0.416	0.519

Note: (-): Fisher exact probability method

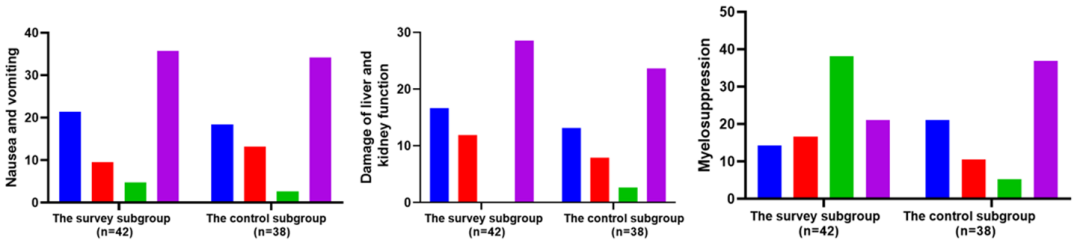

Fig. 4: Nausea and vomiting, damage of liver and kidney function and myelosuppression in two subgroups
Note: ( ): Stage 1; ( ): Stage 2; ( ): Stage 3 and ( ): Total incidence rate

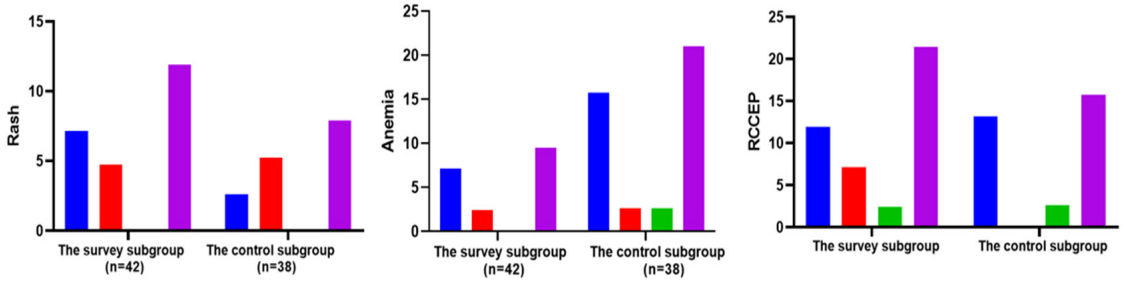

Fig. 5: Rash, anemia and RCCEP in two subgroups
Note: ( ): Stage 1; ( ): Stage 2; ( ): Stage 3 and ( ): Total incidence rate

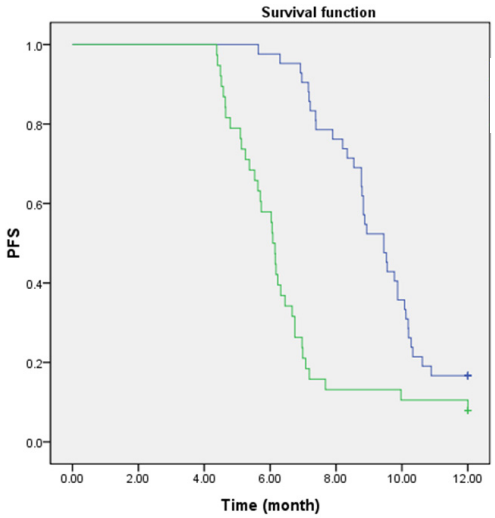

Fig. 6: Divergence of survival curves of two subgroups of PFS
Note: ( ): The survey subgroup; ( ): The control subgroup; ( ): The survey subgroup-deleted and ( ): The control subgroup-deleted

On the basis of conventional chemotherapy regimen, this report compared the efficacy of camrelizumab combined with raltitrexed and raltitrexed alone in the therapy of advanced gastric cancer and postoperative recurrent and metastatic gastric cancer, the results corroborated that the ORR and DCR of the survey subgroup were 54.76 % and 80.95 %, which were boosted than those of the control subgroup (31.58 % and 57.89 %), indicating that camrelizumab monoclonal antibody united with raltitrexed could improve the short-term outcome of advanced gastric cancer. Wang *et al.*[24] also found that after the observation group was treated with irinotecan on the basis of chemotherapy in the control group, the short-term effect of the observation group was better than that of the control group. Systemic chemotherapy is the main therapy for advanced gastric cancer, but conventional chemotherapy program with platinum+fluorouracil is not effective and the curative outcome is limited[25]. With the emergence of new anti-tumor drugs, chemotherapy combined regimens have improved and advanced the therapy of advanced gastric cancer. As an anti-tumor drug officially approved to be marketed in China in 2010, raltitrexed was initially utilized to treat sufferers with advanced colorectal cancer who were intolerant to 5-FU/calcium folinate, and then it was also utilized in esophageal cancer, advanced gastric cancer, malignant pleural mesothelioma and other solid tumors. It has been proven that it can improve the short-term efficacy of sufferers[26]. After entering the cells, raltitrexed is metabolized into polyglutamic acid under the action of folylpolyglutamate synthase, which inhibits DNA synthesis of tumor cells by inhibiting thymus synthetize, thus promoting cell death and playing an anti-tumor role. At the same time, the drug does not need activation, has a long half-life and is well tolerated[27]. A report has corroborated that contrasted to 5-FU+oxaliplatin, raltitrexed+oxaliplatin has more advantages in the therapy of advanced gastric cancer[28], with higher ORR (47.6 % *vs.* 31.8 %), longer PFS (7.8 mo *vs.* 6.6 mo) and tolerable side outcomes. Camrelizumab is a PD-1 inhibitor independently developed in China. It can target and bind PD-1 molecules, block the binding of PD-1 with its ligands PD-L1 and PD-L2, thereby relieving the immunosuppression mediated by this signaling pathway, activating T lymphocytes, and continuously exerting anti-tumor outcomes[29]. The anti-tumor mechanism of camrelizumab is different from that of raltitrexed. The combination of camrelizumab and raltitrexed has synergistic outcome, stronger anti-tumor outcome and better curative outcome. Recent related report also pointed out that PD-1 inhibitor united with apatinib and chemotherapy had better efficacy in the therapy of HER2 negative advanced gastric cancer, and the DCR increased from 44.4 % to 75.7 %[30]. In this report, the serum concentrations of CEA and CA19-9 in the survey subgroup were notably lessened than those in the control subgroup after therapy, which also shows that the combination of camrelizumab and raltitrexed can improve the short-term efficacy of advanced gastric cancer, and postoperative recurrent and metastatic gastric cancer.

Adverse reactions are the main factors affecting the anti-tumor outcome of drugs, a report on the safety of clinical application of camrelizumab pointed out that the main adverse reactions of camrelizumab were immune related adverse events[31], which could involve the skin, lung, liver and endocrine system, most of which were mild to moderate, and few were severe adverse reactions. The results of this report corroborated that there were no grade IV adverse reactions in the two subgroups, and there was no statistical divergence in the incidence of nausea and vomiting, liver and kidney function damage, myelosuppression, rash, anemia, RCCEP and other common adverse reactions, indicating that camrelizumab is safe and effective in the therapy of advanced gastric cancer, and postoperative recurrent and metastatic gastric cancer, and the sufferers have good tolerance. Some studies believe that camrelizumab will increase the risk of grade III or higher REECP[32-34], which may be caused by the imbalance among angiogenesis enhancers and inhibitors, resulting in capillary endothelial proliferation, but it is notably improved after symptomatic therapy, which also shows that camrelizumab is safe and feasible for the therapy of advanced gastric cancer. This report also estimated that the median PFS of the survey subgroup was longer than that of the control subgroup (9.31 mo *vs.* 6.57 mo), indicating that camrelizumab united with raltitrexed can benefit the survival of sufferers with advanced gastric cancer and postoperative recurrent and metastatic gastric cancer. The recent ATTRACTION-3 clinical trial corroborated that the PD-1 inhibitor

nivolumab united with chemotherapy can prolong the PFS of sufferers with HER2 negative advanced gastric cancer (10.45 mo *vs.* 8.34 mo), which is similar to the results of this report[35].

To conclude, camrelizumab united with raltitrexed can control the illness progression of sufferers with advanced gastric cancer and postoperative recurrent and metastatic gastric cancer, prolong PFS, and tolerate toxic and side outcomes. At the same time, there are some limitations in this report, such as the small number of included instances and the short follow-up time. The results need to be further verified by large sample size and multi center studies.

Author contributions:

Chao Liu was major contributors in writing the manuscript. Tianping Chen and Mingkui Liu collected the patient data, did literature searches, and revised the manuscript. All authors read and approved the final manuscript. And Chao Liu and Tianping Chen have contributed equally to this work and share first authorship.

Conflict of interests:

The authors declared no conflict of interests.

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