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Therapeutic effects and safety of apatinib mesylate on patients with gastric carcinoma peritoneal metastasis in SOX scheme

H.-F. WANG[1], H.-H. WANG[2], X.-J. YE[1], W.-J. WANG[1], L.-S. TENG[2]

[1]Department of Oncology, Beilun Branch of the First Affiliated Hospital, Zhejiang University School of Medicine, Ningbo, China
[2]Department of Surgical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Abstract. – OBJECTIVE: The aim of this study was to investigate the diagnostic values of serum tumor markers in gastric carcinoma peritoneal metastasis and the therapeutic efficacy as well as safety of apatinib mesylate combined with Geo+Oxaliplatin (SOX) scheme treatment in gastric carcinoma peritoneal metastasis.

PATIENTS AND METHODS: Sixty patients with gastric carcinoma peritoneal metastasis and 11 patients without gastric carcinoma peritoneal metastasis were selected as the research subjects. The levels of serum tumor markers [carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125, CA211, CA242, CA724, and CA19-9] and abdominal irrigating solution exosome [micro ribonucleic acid (miR)-21 and miR-320c] and the differences in their diagnostic values were compared and analyzed. The patients with gastric cancer peritoneal metastases are then divided into two groups, one for control (30 cases receiving just SOX scheme treatment) and the other for the experiment (30 cases receiving SOX scheme treatment plus apatinib mesylate). Besides, the differences in serum tumor marker level, therapeutic efficacy, overall survival (OS), complication rating, and Quality of Life Questionnaire-Core-30 (QLQ-C30) score among patients after treatment were compared.

RESULTS: Demonstrated that serum carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125, CA211, CA242, CA724, and CA19-9 levels of patients in the transfer group were remarkably enhanced compared with those of patients in the non-transfer group, and the levels of abdominal irrigating solution exosome (miR-21 and miR-320c) were reduced compared with those in non-transfer group ($p<0.05$). The area under the curve (AUC) of the diagnosis of gastric carcinoma peritoneal metastasis by each index were 0.553, 0.880, 0.832, 0.619, 0.863, 0.651, 0.918, and 0.903, respectively. Patients in the experimental group's serum levels of CEA, CA125, CA211, CA242, CA724, and CA19-9 were noticeably lower after therapy compared to those in the control group, and their median OS was also noticeably longer ($p<0.05$). After treatment, the objective remission rate (ORR) and disease control rate (DCR) of the control group and experimental group amounted to 6.7% *vs.* 30.0% and 50.0% *vs.* 86.7%, respectively. ORR and DCR of the experimental group were notably higher ($p<0.05$). Between the patients in the control group and the experimental group, there were no glaring variations in the frequency of problems (hypertension, nausea, vomiting, bone marrow suppression, hand-foot syndrome, and leucopenia) ($p>0.05$). The cognitive function, emotional function, and life health scores of patients in the experimental group were significantly higher than those in the control group ($p<0.05$), which suggested that serum tumor markers and miR-21 as well as miR-320c showed high diagnostic efficiency in gastric carcinoma peritoneal metastasis.

CONCLUSIONS: Apatinib mesylate combined with SOX scheme treatment was more effective in treating gastric carcinoma peritoneal metastasis and possessed the same safety as single SOX scheme treatment. Hence, it is worthy of clinical promotion.

Key Words:
Gastric carcinoma peritoneal metastasis, Apatinib mesylate, SOX scheme, Serum tumor markers, Overall survival.

Introduction

With the continuous improvement of treatment methods, gastric carcinoma disease is still one of the significant malignant tumors that seriously affect human health, with the 5th highest morbidity and the 4th highest mortality[1]. The incidence of gastric carcinoma in China is very high. Some statistics show that the incidence of gastric carcinoma in China ranks 2nd among all malignant tumor diseases and follows only lung cancer[2]. The

Corresponding Author: L.-S. Teng, MD; e-mail: lsteng@zju.edu.cn; tenglisong5688@163.com

incidence of stomach cancer is growing yearly in China as the population ages[3]. Relevant research[4,5] has demonstrated that *Helicobacter pylori* infection, eating habits, and inheritance are all risk factors for stomach cancer. However, there is no screening method for early gastric carcinoma at present. The early diagnostic rate is low because no evident symptom occurs at the early stage. As a result, most patients suffer from advanced gastric carcinoma when they are diagnosed[6]. Peritoneal metastasis is one of the most common metastasis patterns in patients with advanced gastric cancer. The prognosis of metastatic patients is extremely poor and median overall survival (OS) lasts for only 4 to 6 months[7]. Patients with gastric carcinoma peritoneal metastasis are prone to intestinal obstruction, large ascites, intestinal perforation, and other severe complications. Hence, the treatment is very difficult[8].

Currently, systemic chemotherapy is still recommended as the first-line standard treatment strategy for patients with gastric cancer peritoneal metastasis to improve the treatment effect and prognosis. In clinical practice, fluorouracil, platinums, taxanes, and other chemotherapeutic agents are used in combination chemotherapy regimens[9]. For gastric carcinoma peritoneal metastasis patients with excessive ascites, local control treatment such as abdominal perfusion chemotherapy can be performed according to the basic situation of patients[10,11]. Geo+Oxaliplatin (SOX) scheme is a common treatment scheme for patients with gastric carcinoma, mainly including oxaliplatin and tegafur[12]. Patients who receive oxaliplatin experience neurotoxicity and other side effects, whereas those who receive tegafur experience diarrhea, hand-foot syndrome, and other severe events[13]. As a result, the outcomes of the aforementioned therapeutic strategies are inadequate.

During cancer development, tumor cells promote the formation of more new blood vessels and provide adequate oxygen and nutrients[14]. Vascular endothelial growth factor (VEGF) is an essential factor in regulating the formation of blood vessels. Hence, antiangiogenetic is the primary clinical research direction to inhibit the growth of tumors. Apatinib mesylate is a new small molecule selective VEGF receptor 2 tyrosine kinase inhibitor[15]. Apatinib mesylate can bind VEGF in a very specific way, thereby preventing tumor blood vessel growth, altering cell permeability, promoting apoptosis, and preventing malignancy[16,17]. The China Food and Drug Administration approved the use of apatinib mesylate in 2014 for the treatment of patients with progressing metastatic gastric cancer. Some studies[18,19] confirm that the application of apatinib mesylate combined with SOX scheme patients with progressive metastatic gastric carcinoma can prolong patient OS.

The purpose of this study was to explore the efficacy and safety of apatinib mesylate combined with SOX regimen in patients with peritoneal metastasis of gastric cancer, so as to improve the early diagnosis rate. The clinical symptom remission rate, overall survival (OS), serum tumor markers, and quality of life (QoL) of patients with peritoneal metastasis of cancer after treatment were analyzed in two groups, to provide experimental data for improving the prognosis and QoL of the patients. The rest of the manuscript is organized as follows: section 2 is about material and methods and provides a detailed description of the proposed method. In section 3, the results are illustrated, and section 4 is about discussion. Finally, section 5 concludes the manuscript.

Patients and Methods

In this section, we define the research subjects, examination on serum tumor markers, real-time fluorescence quantitative polymerase chain reaction (PCR) detection, evaluation of clinical therapeutic effects, evaluation of OS, evaluation of safety, evaluation of QoL, and statistical analysis in detail.

Research Subjects

The gastric carcinoma patients admitted to Beilun Branch of the First Affiliated Hospital, Zhejiang University School of Medicine, between May 2019 and October 2021, were selected as the research subjects. According to pathological or cytological examination, all patients were divided into the peritoneal metastasis group (n=60) and the non-transfer group (n=11). The comparison and analysis of the differences in general data on the patients in the two groups revealed that the differences in gender proportion, average age, and disease course had no statistical meaning (p>0.05). After that, patients with gastric carcinoma peritoneal metastasis were selected as the research subjects to analyze the differences in the clinical therapeutic effects of different treatment methods. The inclusion and exclusion criteria of gastric carcinoma peritoneal metastasis were as follows.

Inclusion criteria:

A. Patients conforming to the diagnostic standards and diagnosed with gastric carcinoma peritoneal metastasis.
B. Patients without receiving surgery, radiotherapy, or chemotherapy before the implementation of this treatment.
C. Patients with Karnofsky function status score over 60 and expected OS longer than 3 months.
D. Patients with complete clinical pathology and follow-up data.
E. Patients aged between 18 and 75.
F. Patients and their family members who had been informed of the research procedure, volunteered to participate, and signed informed consent forms.

The exclusion criteria were as follows:

A. Patients with complicated serious cardiac, liver, and renal insufficiency.
B. Patients with other complicated malignant tumors in the last 5 years.
C. Patients with severe complicated internal medicine diseases or infectious diseases.
D. Patients allergic to apatinib and other included drugs.
E. Pregnant or breastfeeding women.
F. Patients with poor body functions, unstable vital signs, or psychological disorders and no ability to cooperate in the research.
G. Patients with massive ascites, serious intestinal obstruction, intestinal hemorrhage, or other complications.
H. Patients with incomplete clinical data or follow-up data.

Finally, a total of 60 patients with gastric carcinoma peritoneal metastasis were included as the research subjects, including 30 cases in the control group and 30 cases in the experimental group.

The implementation of this research had been approved by the Hospital Ethics Committee of Beilun Branch of the First Affiliated Hospital, Zhejiang University School of Medicine, and all patients had signed informed consent forms when they were treated.

Treatment Method for Patients with Gastric Carcinoma Peritoneal Metastasis

Single SOX scheme treatment was adopted for patients in the control group. On the 1st day of the treatment, 130 mg/m^2 oxaliplatin (JARI Pharmaceutical Co., Ltd., Tokyo, Japan, specification: 50 mg/bottle, approval number: SFDA approval number H20103049) was slowly administered intravenously. Additionally, patients were told to take tegafur capsules containing 40 mg/m^2 orally twice daily (Qilu Pharmaceutical Co., Ltd., China, specification: 20 mg/28 tablets/box, SFDA clearance number: H20100150). Medication was discontinued for 7 days after being taken continuously for 21 days. The drug was continued for four treatment regimens, each of which lasted for 28 days.

The patients in the experimental group were treated with apatinib mesylate combined with SOX scheme. On the 1st day of treatment, 130 mg/m^2 oxaliplatin was slowly administered intravenously. Besides, patients were asked to take 40 mg/m^2 tegafur capsule orally twice each day. Medication was discontinued for 7 days after being taken continuously for 21 days. Each course of treatment lasted for 28 days. 500 mg apatinib mesylate tablets needed to be taken orally 30 minutes after a meal (Jiangsu Hengrui Pharmaceuticals Co., Ltd., Suzhou, China, specification: 0.25 g/10 tablets/box, SFDA approval number: H20140103) once each day. Each treatment course lasted for 28 days, and the medication needed to last for 4 treatment courses.

Patients with effective chemotherapy underwent gastric carcinoma radical surgery and D2 lymph node dissection.

Examination of Serum Tumor Markers

Four mL of elbow vein blood was extracted from the patients in different groups in fasting state and centrifuged at 3,500 rpm and room temperature for 15 minutes. Next, the upper serum was taken for the detection of tumor markers. UniCel DxI800 automatic immune analysis system (Beckman Coulter Limited, Bria, CA, USA) was utilized to detect the levels of carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125, CA211, CA242, CA724, and CA19-9 in serum. The upper limit of concentrations of CEA, CA125, CA211, CA242, CA724, and CA19-9 in serum of normal and healthy people was 10 ng/mL, 35 U/mL, 3.3 ng/mL, 15 IU/mL, 6.9 U/mL, and 39 U/mL, respectively. The concentration exceeding the above limits indicated that the marker was positive.

Real-time Fluorescence Quantitative Polymerase Chain Reaction (PCR) Detection

Before the implementation of gastric carcinoma radical surgery, 100 mL of physiological saline was poured into a Douglas airbag. Besides, peritoneal irrigating solution was collected before the surgery. At 4°C, the irrigating solution was

centrifuged at 1,000 rpm for 15 minutes. Large cell particles and debris were removed using a 0.22 μm-thickness disposable filter. After that, the irrigating solution was placed at 4°C and centrifuged at 12,000 rpm for 1 hour. After centrifuging the exosome precipitation, phosphate buffer solution was used to rinse the exosomes, and exosomes from the peritoneal irrigating solution were recovered. Total RNA was extracted from peritoneal irrigating solution exosome in accordance with the directions provided by the miRcute micro ribonucleic acid (miRNA) extraction and separation kit (Tiangen Biotech, Beijing Co., Ltd., Beijing, China). In addition, a multi-function ultraviolet spectro-photometer (Shanghai Metash Instruments Co., Ltd., Shanghai, China) was used to evaluate the extraction of RNA concentration and purity. miRcute enhanced miRNA complementary deoxyribonucleic acid (cDNA) first strand synthesis kit (Tiangen Biotech, Beijing Co., Ltd., Beijing, China) instruction was employed for the reverse transcription of extracted RNA cDNA. Finally, miRcute enhanced miRNA fluorescent quantitative detection kit (SYBR Green) (Tiangen Biotech Co., Ltd., Beijing, China) was used to detect the relative expressions of *miR-21* and *miR-320c* and U6 was set as the internal reference gene.

Evaluation of Clinical Therapeutic Effects

According to the Response Evaluation Criteria in Solid Tumors 1.1 of the American Society of Clinical Oncology (ASCO)[20], the therapeutic effect on patients with gastric carcinoma peritoneal metastasis was evaluated. The therapeutic effect could be defined as follows:

A. Complete response (CR). All lesions disappeared, and no new lesions occurred. Besides, the tumor marker level returned to normal and lasted more than 4 weeks.
B. Partial response (PR). The maximum diameter of the target lesion was reduced by over 30% compared with the baseline level, and no new lesion appeared.
C. Stable disease (SD). The maximum diameter and reduction of the target lesion did not meet the standard of PR, and the level of increase did not meet the standard of progressive disease (PD). However, no lesion appeared.
D. Progressive disease (PD). The maximum diameter of the target lesion was increased by over 20%, or a new lesion appeared.

According to equations (1) and (2), the objective remission rate (ORR) and disease control rate (DCR) were calculated.

$$ORR=(CR+PR)/Total * 100\% \quad (1)$$

$$DCR=(CR+PR+SD)/Total * 100\% \quad (2)$$

Evaluation of OS

OS of patients with gastric carcinoma peritoneal metastasis after treatment was observed and recorded. OS refers to the period from the beginning of treatment until the death of patients or the end of follow-up.

Evaluation of Safety

According to the Common Terminology Criteria for Adverse Events 5.0[21], the adverse reactions of patients with gastric carcinoma peritoneal metastasis during treatment were observed, mainly including gastrointestinal reactions such as nausea and vomiting, leukopenia, thrombopenia, anemia, bone marrow suppression, and hypertension. According to the severity of adverse reactions, they were rated from level 0 to level 4.

A. Level 0 refers to a mild adverse reaction.
B. Level 1 represents a moderate adverse reaction.
C. Level 2 refers to a severe adverse reaction.
D. Level 3 denotes the adverse reaction posing a threat to the patient's life or causing the risk of disability.
E. Level 4 represents the adverse reaction leading to the death of patients.

Evaluation of QoL

According to Quality-of-life questionnaire score-C30 (QLQ-C30)[22] stipulated by the European Organization for Research on Treatment of Cancer, QoL of patients with gastric carcinoma peritoneal metastasis after treatment was evaluated. QLQ-C30 scale contained a total of 15 dimensions, including body, role, cognition, mood, function field including social function, fatigue, pain, symptom field including nausea as well as vomiting, life and health field, insomnia, loss of appetite, constipation, diarrhea, and shortness of breath. A higher score in the function and life health fields on QLQ-C30 scale and a lower score in the symptom field indicated a higher QoL of patients.

Statistical Analysis

Software SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used to process and analyze patient data. The Chi-square test was used for the statistical

analysis of enumeration data, which were expressed as the number of cases (%). Mean and standard deviation was used to express measurement data that followed a normal distribution. Additionally, a *t*-test using an independent sample was employed for statistical analysis. Receiver operating characteristic curve (ROC) were drawn to analyze the diagnostic efficiency of gastric carcinoma peritoneal metastasis by serum tumor marker and miRNA indexes. AUC was calculated to compare diagnostic efficiency. In addition, Kaplan-Meier was adopted to draw the survival curves of patients with gastric carcinoma peritoneal metastasis after treatment. The log-rank test procedure was used to compare differences. $p<0.05$ indicated that the differences between groups revealed statistical meaning.

Results

Comparison of Serum Tumor Marker Levels of Patients with and Without Gastric Carcinoma Peritoneal Metastasis

The differences in serum tumor marker (CEA, CA125, CA211, CA242, CA724, and CA19-9) levels between patients with and without gastric carcinoma peritoneal metastasis were compared and analyzed, as shown in Figure 1. The levels of serum CEA, CA125, CA211, CA242, CA724, and CA19-9 of patients in the non-transfer group were all remarkably lower than those in the transfer group, and the differences indicated statistical meaning ($p<0.05$).

Comparison of Levels of Peritoneal Irrigating Solution Exosome miR-21 and miR-320c Between Patients with and Without Gastric Carcinoma Peritoneal Metastasis

The differences in the expressions of miR-21 and miR-320c in peritoneal irrigating solution exosomes between patients with and without gastric carcinoma peritoneal metastasis were compared and analyzed. As illustrated in Figure 2, the expression levels of miR-21 and miR-320c in the peritoneal irrigating solution exosome of patients in the non-transfer group were notably higher than those in the transfer group, and the differences suggested statistical meaning ($p<0.05$).

Analysis of Diagnostic Values of Serum Tumor Markers, miR-21, and miR-320c in Gastric Carcinoma Peritoneal Metastasis

ROC curves were drawn to analyze the diagnostic values of serum tumor markers, miR-21 and miR-320c, in gastric carcinoma peritoneal

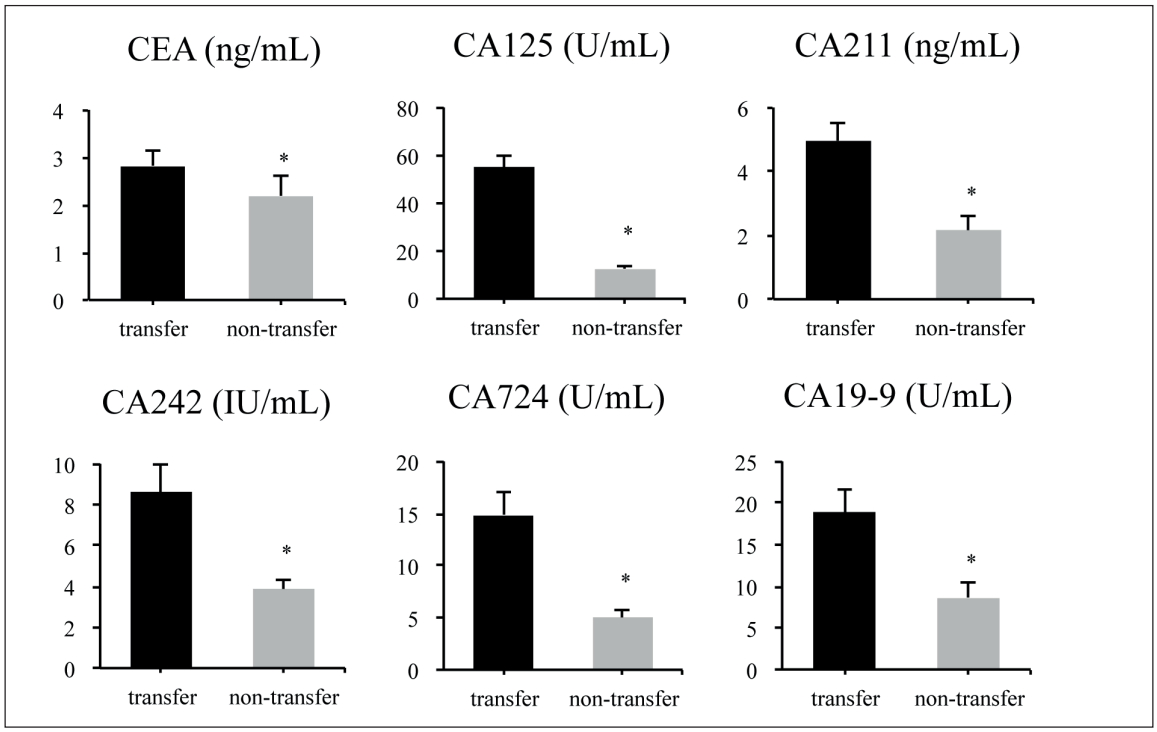

Figure 1. Comparison of levels of serum CEA, CA125, CA211, CA242, CA724, and CA19-9 between patients with and without gastric carcinoma peritoneal metastasis. *Indicated that the differences between groups demonstrated statistical meaning ($p<0.05$).

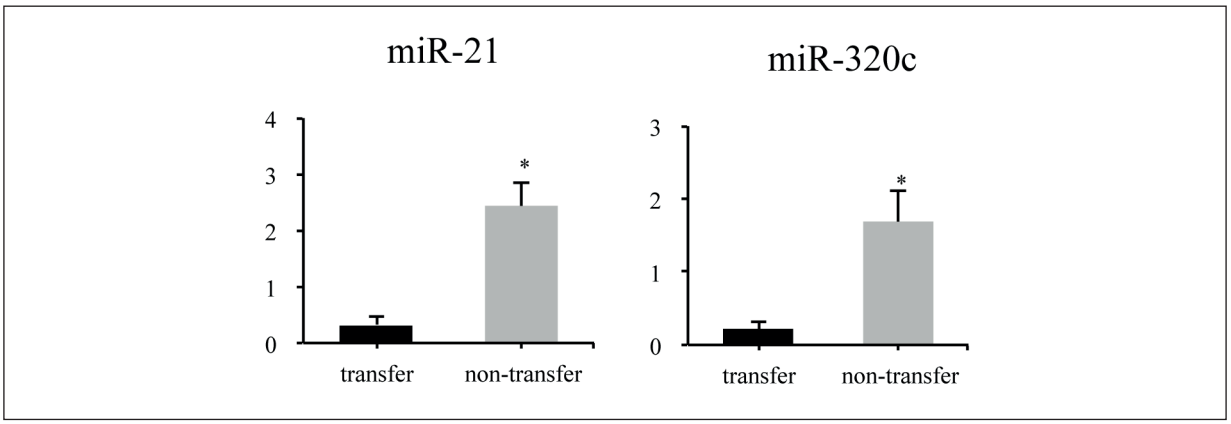

Figure 2. Comparison of levels of miR-21 and miR-320c in peritoneal irrigating solution between patients with and without gastric carcinoma peritoneal metastasis. *Indicated that the differences between groups showed statistical meaning ($p<0.05$).

metastasis. As displayed in Figure 3 and Table I, the critical values of the diagnosis of gastric carcinoma peritoneal metastasis by miR-21 and miR-320c were 1.083 and 0.671, respectively. The diagnostic sensitivity of gastric carcinoma peritoneal metastasis by CEA, CA125, CA211, CA242, CA724, CA19-9 miR-21, and miR-320c were 70.0%, 90.0%, 86.7%, 73.3%, 86.7%, 76.7%, 93.3%, and 93.3%, respectively. Besides, the specificity of gastric carcinoma peritoneal metastasis by CEA, CA125, CA211, CA242, CA724, CA19-9, miR-21, and miR-320c were 83.3%, 90.0%, 83.3%, 83.3%, 90.0%, 80.0%, 96.7%, and 90.0%, respectively.

Comparison of Clinical Data on Patients with Gastric Carcinoma Peritoneal Metastasis

The differences in the clinical data between patients with gastric carcinoma peritoneal metastasis in different treatment intervention groups were compared. As demonstrated in Table II below, the differences in age distribution, gender proportion, differentiation level, and combined metastasis to other sites between patients with gastric carcinoma peritoneal metastasis in the control group and experimental group all showed no statistical meaning ($p>0.05$).

Serum Tumor Marker Detection of Treatment of Gastric Carcinoma Peritoneal Metastasis by Apatinib Mesylate Combined with SOX Scheme

The differences in the levels of serum tumor markers (CEA, CA125, CA211, CA242, CA724, and CA19-9) of patients with gastric carcinoma peritoneal metastasis after different interventional treatments were compared. As illustrated in Figure 4, the levels of serum CEA, CA125, CA211, CA242, CA724, and CA19-9 of patients in the experimental group after treatment were all notably lower than those in the control group, and the differences had statistical meaning ($p<0.05$).

Analysis of Clinical Effects of Treatment of Gastric Carcinoma Peritoneal Metastasis by Apatinib Mesylate Combined with SOX Scheme

The differences in the clinical therapeutic effects on patients with gastric carcinoma peritoneal metastasis after interventional treatments were compared. As shown in Figure 5, the number of patients evaluated as CR, PR, SD, PD, ORR, and DCR in the control group after treatment was 0 (0.0%), 2 (6.7%), 13 (43.4%), 15 (50.0%), 2 (6.7%), and 15 (50.0%), respectively. The number of patients evaluated as CR, PR, SD, PD, ORR, and DCR in the experimental group after treatment was 0 (0.0%), 9 (30.0%), 17 (56.7%), 4 (13.3%), 9 (30.0%), and 26 (86.7%), respectively. The comparison between the two groups revealed that ORR and DCR of patients in the experimental group after treatment were both remarkably higher than those in the control group, and the differences were statistically significant ($p<0.05$).

Survival Analysis of Apatinib Mesylate Combined with SOX Regimen in the Treatment of Peritoneal Metastasis of Gastric Cancer

Within 20 months following various interventional treatments, changes in the survival rate of patients with gastric cancer peritoneal metastases were noted. As presented in Figure 6,

Table I. Comparison of diagnostic values of serum tumor markers and miRNA.

Variables	Sensitivity (%)	Specificity (%)	AUC	95% CI	*p*-value
CEA	70.0	83.3	0.553	0.388-0.705	0.023
CA125	90.0	90.0	0.880	0.770-0.914	0.001
CA211	86.7	83.3	0.832	0.738-0.927	0.004
CA242	73.3	83.3	0.619	0.521-0.763	0.012
CA724	86.7	90.0	0.863	0.733-0.916	0.001
CA19-9	76.7	80.0	0.651	0.505-0.702	0.008
miR-21	93.3	96.7	0.918	0.901-0.965	0.001
miR-320c	93.3	90.0	0.903	0.889-0.941	0.001

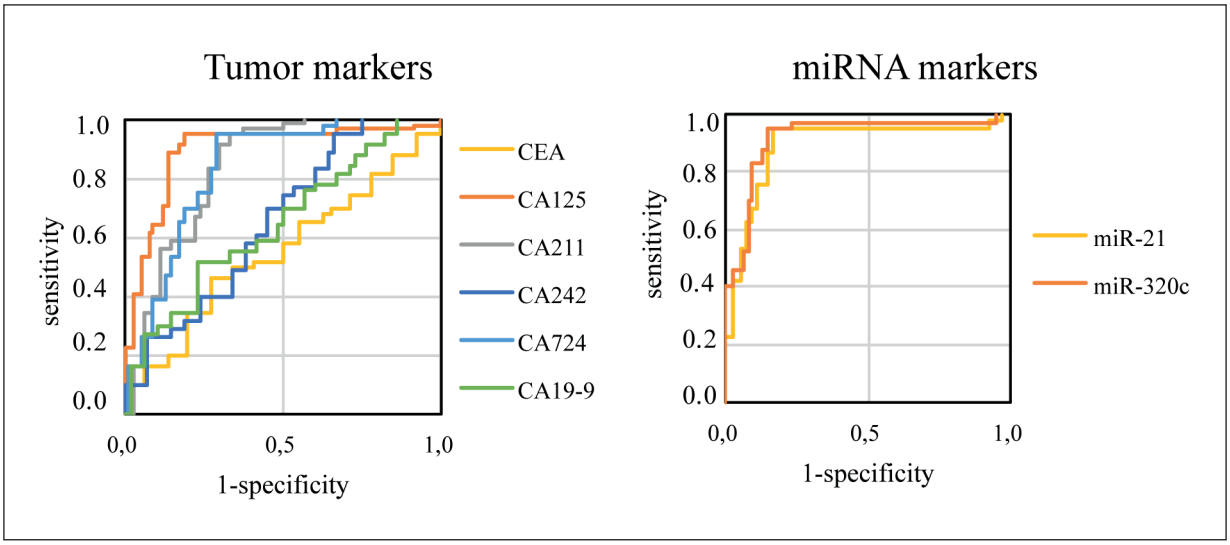

Figure 3. ROC analysis of diagnosis of gastric carcinoma peritoneal metastasis by different markers.

there were dead cases among patients in both the control group and experimental group 4.7 months after treatment. The median OS of the control group was 7.3 months (95% CI: 5.8 to 9.5 months), and the median OS of the experimental group was 9.3 months (95% CI: 7.3 to 10.2 months). The comparison showed that the difference in OS between patients in the control group and the experimental group after treatment indicated statistical meaning ($p<0.05$).

Table II. Comparison of general data on patients with gastric carcinoma peritoneal metastasis with different interventional treatments.

Data	Control group (n=30)	Experimental group (n=30)	Statistical values	*p*-value
Age			0.129	0.885
<60 years old	17 (56.7%)	18 (60.0%)		
≥60 years old	13 (43.3%)	12 (40.0%)		
Gender [n (%)]			0.207	0.843
Male	24 (80.0%)	25 (83.3%)		
Female	6 (40.0%)	5 (16.7%)		
Differentiation level			0.108	0.911
Low-level differentiation	13 (43.4%)	10 (33.3%)		
High-level differentiation	17 (56.7%)	20 (66.7%)		
Complicated metastasis to other sites			0.417	0.679
Yes	5 (16.7%)	7 (23.3%)		
No	25 (83.3%)	23 (76.7%)		

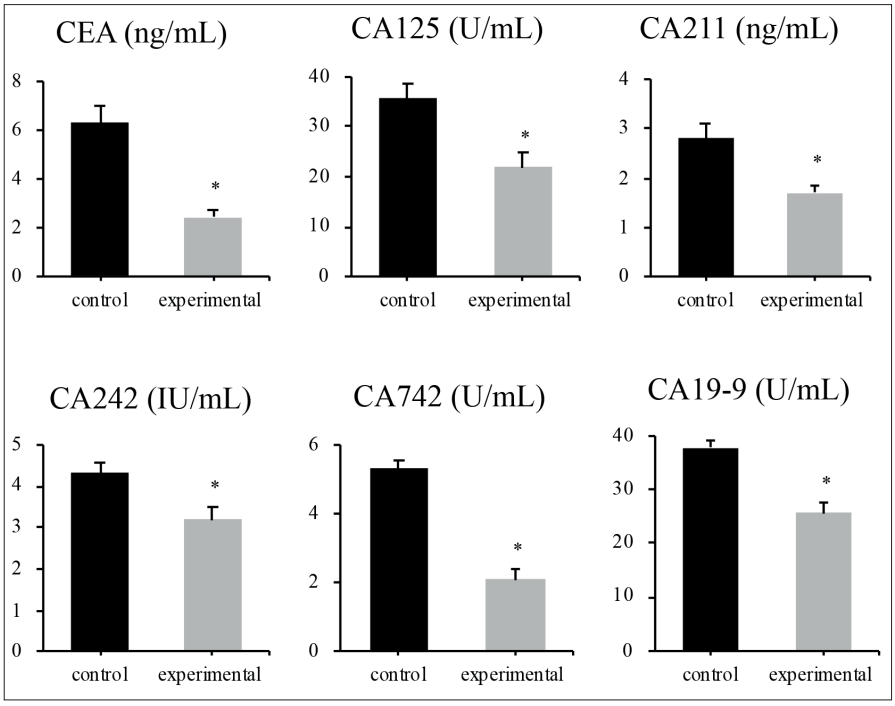

Figure 4. Influences of different interventional treatments on levels of serum CEA, CA125, CA211, CA242, CA724, and CA19-9 of patients with gastric carcinoma peritoneal metastasis. *Indicated that the differences between groups demonstrated statistical meaning ($p<0.05$).

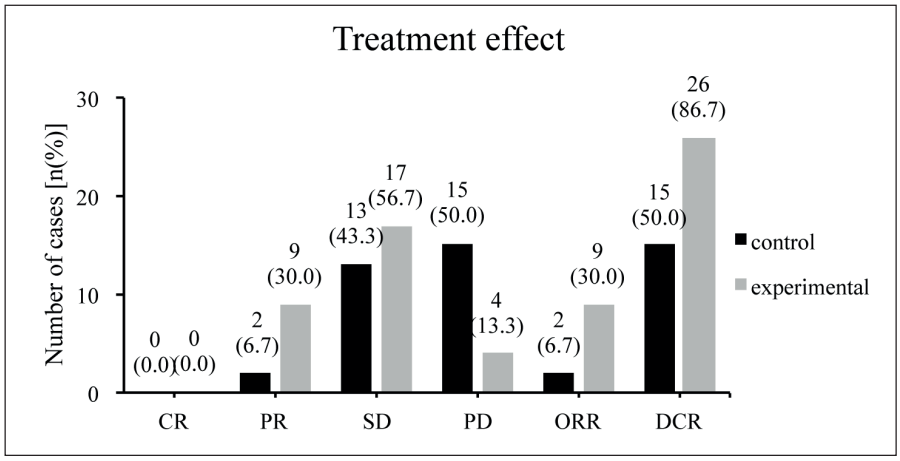

Figure 5. Evaluation of therapeutic effects on patients with gastric carcinoma peritoneal metastasis after different interventional treatments.

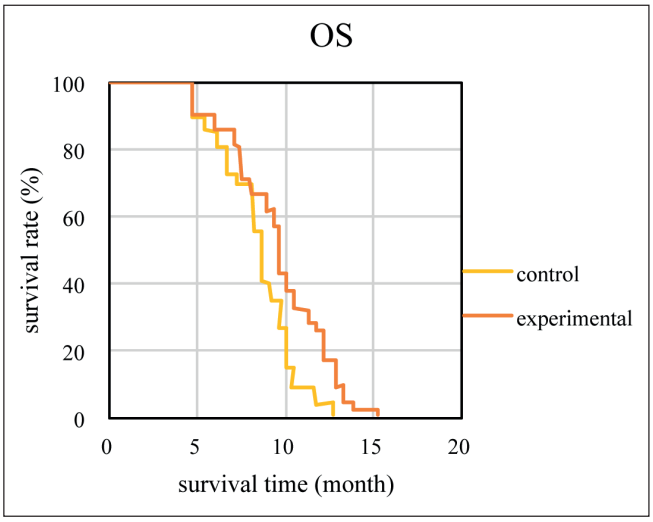

Figure 6. OS observation of patients with gastric carcinoma peritoneal metastasis after different interventional treatments.

Evaluation of Safety of Treatment of Gastric Carcinoma Peritoneal Metastasis by Apatinib Mesylate Combined with SOX Scheme

The differences in the rating and incidence of complications among patients with gastric carcinoma peritoneal metastasis after different interventional treatments were compared. As displayed in Figure 7, there were no patients with level 4 complications in the control group and experimental group. Besides, the complication of only a few patients was rated level 3, and the complication of most patients was rated level 1 and 2. Statistics showed that the number of patients with hypertension, nausea, vomiting, bone marrow suppression, hand-foot syndrome, and fatigue in the control group was 5 (16.7%), 18 (60.0%), 7 (23.3%), 14 (46.7%), 5 (16.7%), and 7 (23.3%), respectively. The number of patients with hypertension, nausea, vomiting, bone marrow suppression, hand-foot syndrome, and fatigue in the experimental group was 10 (33.3%), 16 (53.3%), 10 (33.3%), 14 (46.7%), 5 (16.7%), and 7 (23.3%), respectively. The comparison indicated that the difference in the incidence of complications among patients in the control group and experimental group demonstrated no statistical meaning (p>0.05).

Evaluation of QoL of Treatment of Gastric Carcinoma Peritoneal Metastasis by Apatinib Mesylate Combined with SOX Scheme

The differences in QoL QOQ-C30 scores of patients with gastric carcinoma peritoneal metastasis after different interventional treatments were compared. As shown in Figure 8, cognition function, mood function, life and health, diarrhea, and economic difficulties scores of patients in the experimental group after treatment were all remarkably higher than those in the control group, and the differences revealed statistical meaning (p<0.05). In contrast, the score of loss of appetite in the experimental group was notably lower than that in the control group, and the difference demonstrated statistical meaning (p<0.05).

Discussion

Gastric carcinoma is a very common digestive system malignant tumor disease in clinical practice. Because the symptoms at the early stage of gastric carcinoma are not evident, the early diagnostic rate is low[23]. Most patients have advanced gastric cancer at the time of diagnosis. Multiple metastases or locally advanced stomach cancer are present in this instance. So, the cure rate is very low. Early diagnosis of gastric cancer is very important. Imaging and endoscopy are commonly used in clinics to improve the diagnostic rate of gastric cancer. Gastric cancer metastasis involves changes in the levels of a large number of molecular markers. A tumor marker is the basis of quarantine science. Common gastric carcinoma tumor markers include CEA, CA125, CA211, CA242, CA742, and CA19-9[24]. The relationship between CEA, as well as CA and gastric carcinoma peritoneal metastasis, is analyzed. The results demonstrated that the levels of CEA, CA125, CA211, CA242, CA742,

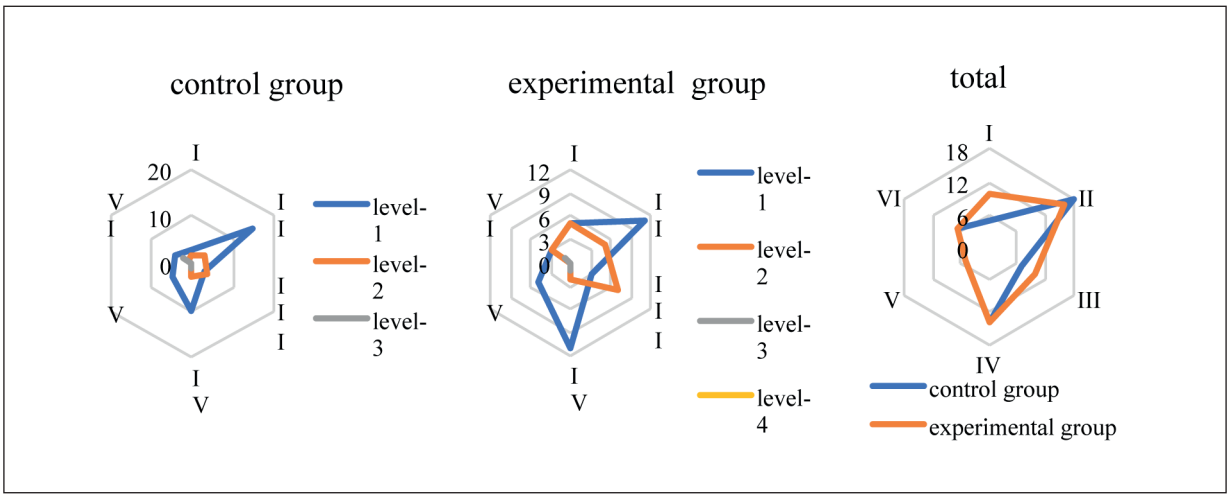

Figure 7. Evaluation of complications among patients with gastric carcinoma peritoneal metastasis after different interventional treatments. I. Hypertension. II. Nausea. III. Vomiting. IV. Bone marrow suppression. V. Hand-foot syndrome. VI. Fatigue.

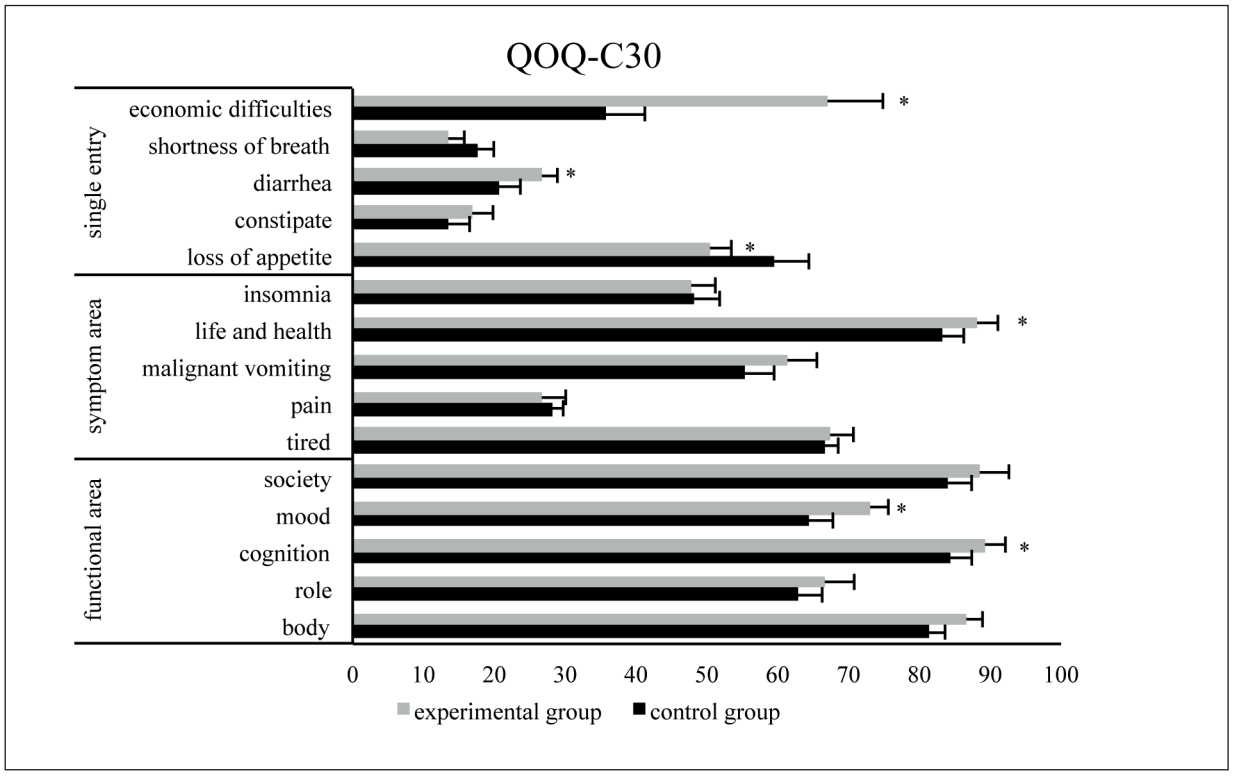

Figure 8. Comparison of QOQ-C30 scores of patients with gastric carcinoma peritoneal metastasis after different interventional treatments. *Indicated that the differences between groups showed statistical meaning ($p<0.05$).

and CA19-9 in the serum of patients with gastric carcinoma peritoneal metastasis were all remarkably up-regulated, and AUC of the diagnosis of gastric carcinoma peritoneal metastasis by CA125 was the largest. In addition to serum, peritoneal lavage fluid has gradually become the next target for the diagnosis and prediction of peritoneal metastasis of gastric cancer. Related studies[25,26] have confirmed that exosomes released by miR-21 in tumors are activated after binding to TLRs in peripheral immune cells, which promote metastatic inflammatory response and affect tumor growth and metastasis. The results showed that the levels of miR-21 and miR-320c in exosomes of peritoneal lavage fluid were significantly down-regulated in patients with peritoneal metastasis of gastric cancer, and the AUC for the diagnosis of peritoneal metastasis of gastric cancer was more than 0.9. It was revealed that CA125, miR-21, and miR-320c possessed high diagnostic effectiveness in gastric carcinoma peritoneal metastasis.

Clinically, major surgery is typically performed on stomach cancer patients to extend their lives. However, after receiving surgical treatment, roughly 40% of individuals develop peritoneal metastases. As a result, illness is made worse, and death is hastened[27]. Therefore, intraperitoneal chemotherapy or intravenous chemotherapy, such as fluorouracil, platinum, or fluorouracil combined with platinum (SOX regimen), is recommended for patients with advanced metastatic gastric cancer[28]. Although intravenous chemotherapy can inhibit the growth of tumors to some degree, it shows[29] significant toxic and side effects during treatment, which often causes poor prognosis for patients. With the progress of research, more and more specific therapeutic drugs have been developed and used to treat patients with advanced metastatic gastric cancer, such as anti-angiogenesis therapy, programmed death receptor 1 inhibitors and epidermal growth factor receptor 2 inhibitors[30]. Patients with advanced stomach cancer are treated with apatinib mesylate, which exhibits outstanding clinical results[31].

To investigate the efficacy and safety of the treatment of gastric carcinoma peritoneal metastasis with apatinib mesylate combined with SOX scheme, the differences in the therapeutic effects of single SOX scheme and apatinib mesylate combined with SOX scheme on gastric carcinoma peritoneal metastasis were compared

and analyzed. The results of the study showed a significant decrease in serum tumor marker levels after treatment with apatinib mesylate and SOX regimens. The interaction between CA125 and cells may strengthen cell adhesion and encourage the colonization of cancer cells that have exfoliated in the peritoneum or abdominal organs[32]. CA242 is a salivary acid sphingolipid antigen and shows a tendency of high expression in malignant tumors33. CA19-9 is a carbohydrate-protein antibody, and CEA is a glycoprotein, both of them can be used in the diagnosis of digestive system tumors. The research results demonstrated that ORR and DCR of patients receiving single SOX treatment were 6.7% (2 cases) and 50.0% (15 cases), respectively, and ORR and DCR of patients undergoing apatinib mesylate combined with SOX scheme treatment were 30.0% (9 cases) and 86.7% (26 cases), respectively. The research results revealed that apatinib mesylate combined with SOX scheme could play a therapeutic role in reducing serum tumor marker levels in patients with gastric carcinoma peritoneal metastasis.

The differences in OS between patients in different treatment groups were compared. Patient median OS after single SOX scheme treatment was 7.3 months (95% CI: 5.8 to 9.5 months), and patient median OS after apatinib mesylate combined with SOX scheme treatment was 9.3 months (95% CI: 7.3 to 10.2 months). The results were similar to the conclusion that the median OS of patients receiving chemotherapy was obviously higher than that of patients without undergoing chemotherapy drawn by 34) Escande et al[34]. The incidence of nausea, vomiting, bone marrow suppression and other adverse reactions was higher in patients with different treatment regimens, and there was no significant difference in the incidence of various adverse reactions among patients. Bone marrow suppression mainly includes leukopenia, anemia, neutropenia, and thrombocytopenia, suggesting[35] that apatinib mesylate combined with SOX regimen has safe and tolerable toxic side effects. After that, QOQ-C30 scale was employed to evaluate patients' QoL after different treatment plans, which revealed that patients' cognition function, mood function, life and health, and other dimensions were all improved after apatinib mesylate combined with SOX scheme treatment. Apatinib mesylate combined with SOX regimen can significantly improve the cognitive function, emotional function, and life health of patients. However, it can cause diarrhea and other symptoms. In addition, the cost of the combined drug treatment regimen is higher than that of the single SOX treatment regimen, causing a certain economic burden to the patients and their families.

Conclusions

We investigated the diagnostic utility of blood tumor markers miR-21 and miR-320c in peritoneal metastasis of gastric cancer, to observe the clinical efficacy of SOX regimen alone and combined with apatinib mesylate in the treatment of gastric cancer with peritoneal metastasis. The results showed that CA125, miR-21 and miR-320c had high diagnostic efficiency for peritoneal metastasis of gastric cancer. The efficacy of apatinib combined with SOX regimen in the treatment of gastric cancer with peritoneal metastasis is better than that of SOX regimen alone, and the median OS is prolonged. In addition, safety profiles were comparable between the two regimens. Without looking at the effect of additional apatinib mesylate treatment on longitudinal OS and patient relapse, the effect of apatinib mesylate on clinical treatment outcome was examined using the SOX regimen only. The results of this study can provide a reference for prolonging the survival time and improving the prognosis and quality of life of gastric cancer patients with peritoneal metastasis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was started prospectively after the approval of the Ethics Evaluation Committee of our faculty (188/04.06.2020).

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Informed Consent

Written informed consent was obtained from all participants.

ORCID ID

Ş.Y.: 0000-0002-7290-6798;
M.S.A.: 0000-0002-2999-2141.

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