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The clinical observation of verapamil in combination with interventional chemotherapy in advanced gastric cancer

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Abstract. – OBJECTIVE: We analyzed the clinical observations of target arterial infusion of verapamil combined with chemotherapy as therapy for advanced gastric cancer.

PATIENTS AND METHODS: From March 2012 to December 2015, a total of 63 patients with advanced gastric cancer were admitted to our department. The target artery in the control group was perfused with chemotherapy drugs only, and the target artery in the therapy group was injected with verapamil combined with chemotherapy drugs.

RESULTS: The therapeutic effect of the therapy group was significantly better than that of the control group in the primary foci of gastric cancer. Liver metastatic lesions: 11 patients in the control group had liver metastases and 25 patients in the therapy group had liver metastases. The effective rate (CR+PR) of the therapy group was significantly better than the control group. Clinical benefit evaluation: in the therapy group of 43 cases, 40 cases presented positive clinical benefit and 38 cases positive clinical weight in KFS scoring system; the clinical benefit of the therapy group was significantly better than control group. Survival analysis: the disease progression-free rate and survival rate of the therapy group were 12 months and 24 months, which were higher than those in the control group. The median PFS and median OS were also significantly longer than those in the control group ($p<0.01$). In the therapy group, adverse effects of chemotherapy in 43 patients were relieved in a short time.

CONCLUSIONS: Target arterial infusion of verapamil combined with chemotherapy drugs for advanced gastric cancer can significantly improve the efficacy of chemotherapy drugs and prolong the survival of patients.

Key Words
Verapamil, Chemotherapy drugs, Interventional chemotherapy, Gastric cancer.

Introduction

Gastric cancer is a prevalent human malignancy. Only less than 50% of patients with early gastric cancer are diagnosed and the majority of the patients used to be treated at a late stage[1,2]. The therapeutic effect of advanced gastric cancer is not ideal and the documented efficacy is only 5% to 40%[3]. Therefore, improving the treatment regimen for advanced gastric cancer has become an imperative task[4-6]. Since 1980s, the quality of life of advanced gastric cancer has been greatly improved due to the introduction of interventional radiology to the treatment of gastric cancer[7,8]. However, the traditional selective gastric arterial infusion (GAI) and gastric artery chemoembolization (GAE) therapy have been controversial. Given that the stomach is a cavity organ, peripheral lipiodol embolization easily induces gastric necrosis and perforation[9]. Meanwhile, the effect of intravenous chemotherapy for advanced gastric cancer is not satisfactory. It has been reported that the effective rate is only about 50%. The 12-month survival period is about 24%, and the 24-month survival period is about 12%. The reason of influencing curative effect may be less sensitive to chemotherapy of advanced gastric cancer and easy to produce drug resistance[10,11]. The

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target artery infusion of verapamil can increase the tissue drug concentration, reverse the multi-drug-resistance of malignant cells, and increase the sensitivity of tumor cells to chemotherapeutic drugs[12-14]. To further investigate the effect of verapamil via arterial infusion to improve the efficacy of chemotherapy and find a way to effectively improve the chemotherapy of advanced gastric cancer, we conducted interventional therapy with verapamil in combination with chemotherapeutic drugs via targeted arterial infusion in advanced gastric cancer. The clinical outcomes were documented and analyzed.

Patients and Methods

Patients

From March 2012 to December 2015, 63 patients with advanced gastric cancer were admitted to our department, and they or their relatives signed the informed consent. The study protocol was approved by the Hospital Ethics Committee. 63 patients were involved in the study, 43 patients in the study group and 20 patients in the control group.

Clinical Parameters

Participants in the study were patients diagnosed with the treatment of advanced gastric cancer for the first treatment and part of patients with advanced gastric cancer who were treated with intravenous chemotherapy following ineffective treatment. All patients were randomly divided into study group (n=43) and control group (n=20). All of them were diagnosed with adenocarcinoma and aged from 38 to 75 years with an average age of 62 years (52 males and 11 females). Among these patients, 27 cases of gastric cancer presented with abdominal lymph node metastasis (18 cases in study group) and 36 cases presented with liver metastasis (25 cases in study group). There was no significant difference in age, sex, and gastric cancer between the two groups (p>0.05).

Inclusion Criteria

The inclusion criteria were that patients should be 18 to 80 years old and have KPS ≥70 points, estimated survival time >3 months, and heart rate >60 beats/min. The patient was informed and voluntarily accepted the treatment with this protocol signing the informed consent. They were diagnosed with pathological cancer through surgical exploration or gastroscopy, and they had no contraindication for verapamil. The catheter can enter the malignant tumor feeding artery. The efficacy of lesions in patients can be assessed and liver metastasis in patients had maximum liver lesions ≥ 5 cm or multiple lesions (lesions ≥ 3).

Exclusion Criteria

Those patients treated by surgery. The exclusion criteria also included women in pregnancy and lactation, patients with psychiatric and mental hypoplasia, acute infection and central nervous system symptoms, and patients with allergies. Additional exclusion criteria were WBC $<4.0*10^9$ g/L, BPC $< 10.0*10^9$ g/L, Hb < 60 g/L, and patients with coagulopathy.

Exit Criteria

Those who do not strictly carry out the treatment program; those who cannot tolerate the test because of serious adverse reactions; those whose data are incomplete and those whose assessment of adverse reactions and evaluation of the curative effect could not be carried out.

Clinical Interventions

The target artery of the study group was perfused with Verapamil combined with chemotherapy drugs, while the target artery of the control group was perfused with chemotherapy drugs only. Interventional therapy was 1 time per month, each interventional therapy more than 2 times. 2 months later, the curative effect was judged. The interventional treatment used Seldinger method[15], through femoral artery puncture in the celiac artery angiography to grasp the left gastric artery or the right gastric artery blood supply, and to observe tumor blood vessels, tumor size and staining. The left lobe of the liver artery and inferior phrenic artery, gastroepiploic artery, gastroduodenal artery, which were involved in the blood supply, should be given perfusion at the same time. Patients with metastasis of liver cancer need to carry out re-selective hepatic arterial infusion of iodized oil emulsion embolization, plus 10% iodized oil 10-20 mL (iodized oil dose by lesion diameter 1 cm/ml) and rich in blood or (and) the maximum diameter of lesions ≥ 5 cm need to increase appropriate amount of gelatin sponge particles target artery embolization. At the end of treatment, angiography reviews the disappearance of tumor vessels. Next, the tube was removed to stop bleeding (according to individualized principle, the blood supply was

completely blocked as far as possible, and if restricted, the majority of blood supply was blocked to 80% as much as possible).

Chemotherapy program refer to the Chinese Society of Clinical Oncology (CSCO) 2009 Annual National Clinical Oncology Association developed guidelines for the treatment of malignant tumors, including "oxaliplatin + fluorouracil + anthracycline", "docetaxel + Platinum + anthracycline"; chemotherapy dose selection according to the patient's body surface area, KPS score, select individualized treatment.

Drug perfusion steps: 15 mg verapamil injection, 10 mg verapamil reperfusion, and chemotherapy drugs. During the process of perfusion, the catheter was washed with heparin saline intermittently 3 to 5 times. An intravenous drip of 5-10 mg tropisetron and 5-10 mg dexamethasone, respectively, were injected before and after infusion of chemotherapeutic drugs. The amount of drugs depends on the size of the tumor, the patient's general situation and heart, liver and kidney function. The postoperative routine was given to prevent vomiting, protect the stomach, rehydration therapy, and other symptomatic treatment.

Each patient was intervened 1 times a month and received a total of 2 interventions to evaluate the short-term curative effect of the patients. After 2-4 times of intervention, regular follow-up was done every 3 months. The obstruction was detected by gastroscopy and iodine water radiography. Before CT, 300-500 ml of 2% diatrizoate meglumine were taken orally; if there is a patient of subtotal gastrectomy, 100 ml of 2% diatrizoate should be taken orally. If the patient's condition is developed or recurred by evaluation, the intervention is 1-2 times and the treatment continues following the above method.

Documentation of Clinical Outcome

Blood routine, liver and kidney function, and electrocardiogram, were checked every time before the treatment and 30 days after treatment and a record was done. The gastroscopy and CT examination were performed before the treatment, 30 days after the treatment; after 60 days of treatment and adverse drug reactions, changes in symptoms and KPS score, and weight changes were recorded. After 2 times of interventional therapy, we evaluated the short-term clinical efficacy and clinical benefit of the patients, KPS scores and weight changes, and whether there were new lesions or changes in the original lesions. Before verapamil perfusion, during perfusion and 5 min after perfusion, heart rate, blood pressure changes, and cardiac function were monitored.

Evaluation of Clinical Outcome

Changes of tumor lesions

The evaluation of the lesion included primary lesion, local lymph node and metastasis[16,17]. When the tumor lesions are in the following case, the size of the tumor can be determined: 1. The primary tumor was more than 2.0 cm; 2. The lymph node was more than 1.0 cm; 3. The lymph node was more than 1.0 cm. The tumor can be evaluated in the following cases, but it cannot be accurately measured: 1. Pleural effusion 2. Ascites 3. Peritoneal lymph nodes 4. Multiple bone metastases. The size of tumor was changed by Muller standard including 4 criteria: complete response (CR), partial response (PR, reduction rate is greater than or equal to 50%), stable disease (SD, less than 50%), progressive disease (PD, increase 25% or more new lesions). Gastric wall thickness, tumor boundary clarity, and gastric serosa fat line can be investigated by gastroscopy, digestive tract angiography, and CT examination.

The metastasis of liver cancer can be identified by lipiodol deposition[18]. The clinical cure is markedly improved: the lump loss or reduction is more than 75%; the accumulation of lipiodol is uniform; the tumor vessels are completely occluded or there are only a few residual tumor vessels or tumor stains on the edge of the tumor. The clinical cure is improved: the lump was reduced by 30% to 75%; the accumulation of lipiodol is unevenly accumulated; the filling area of iodide oil was more than 1/2. The clinical cure is stable: the lump was less than 30%; the filling area of iodide oil was less than 1/2; the tumor vessels were not significantly reduced. Clinical cure was deteriorated: tumor mass increased; lipiodol was scattered in spotted deposits or there was no significant accumulation of lipiodol oil; the area of iodine oil accumulation was less than 1/3 of the tumor area; the tumor vessels increased significantly; new hepatic arterioportal fistulas or hepatic arteriovenous fistula were formed.

Evaluation of clinical benefit

An increase in KPS score greater than 10 and for 4 weeks or longer was defined as a positive clinical benefit; a decrease in KPS score was defined as negative. Any other outcome was defined

Table I. Clinical data of 63 patients with advanced gastric cancer.

Parameter	Classify	Study group (N=43)	Control group (N=20)	χ^2	*p*
Sex	Male	37	17	0.651	0.28
	Female	6	3		
Age	< 65	28	14	0.4631	0.375
	> 65	15	6		
Primary tumor diameter	≤ 4 cm	18	9	0.148	0.427
	≥ 4 cm	25	11		
The number of liver metastases		25	11	3.71	0.32
The number of abdominal lymph node metastasis		18	9	2.53	0.265

as stable. A body weight gain of 7% or more for 4 weeks or longer was defined as a positive clinical benefit; a decrease of body weight was defined as negative clinical benefit and any other outcome was defined as stable. Anyone of these parameters is positive and no negative, then the patient benefited from the treatment[19].

Survival evaluation

63 patients were followed up for 2 years of the disease progression and the last follow-up time took place on December 2017. Every 2 months during the treatment period and every 3 months after the end of treatment, thoracoabdominal CT, electronic gastroscopy, and blood tumor markers were performed. Two groups of PFS (progress-free survival) and OS (overall survival) were recorded and calculated in 12-month, 24-month progress-free survival rate, overall survival rate, respectively, to further evaluate the control and study groups.

Evaluation of toxic side effects and electrocardiogram

Toxic and adverse effects were evaluated according to the standard of NCI-CTC anticancer drug toxicity grade (0-IV)[20]. Heart functions grading were evaluated according to the New York Heart Association (NYHA) standard[18].

Statistical Analysis

Data were analyzed using GraphPad Prism 6.0 statistical software (La Jolla, CA, USA). Qualitative data were expressed as frequency and constituent ratio. The univariate analysis was performed using χ^2-test or Fisher's exact test. Kaplan-Meier method was used to analyze the survival of patients. Survival rates were compared with log-rank test. There was a significant difference ($p<0.05$).

Results

Changes of Tumor Lesions

Changes of primary tumor in gastric cancer

In the study group, 43 patients were treated with verapamil in combination with chemotherapeutic drugs for more than 2 times. 6 patients were completely relieved (CR), 31 were partially relieved (PR), and the total effective rate (CR + PR) % was 86%, among which 15 cases were in stage II radical surgical treatment. In the control group, 20 patients were treated with chemotherapeutic drugs for more than 2 times. 0 patients were completely relieved (CR), 10 were partially relieved (PR), and the total effective rate (CR + PR) % was 50% (Table I). The curative effect of the study group was significantly better than that of the control group (Table II).

Table II. Evaluation of the therapeutic effect of primary tumor lesions.

Number of cases	Clinical efficacy evaluation				Effective rate (CR+PR)/ number of cases
	CR	PR	SD	PD	
Control group (n=43)	6	31	5	1	86%
Study group (n=20)	0	10	6	4	50%

Table III. Efficacy evaluation of hepatic metastatic lesions.

Number of cases	Efficacy Evaluation of Hepatic Metastatic Lesions				Effective rate (CR+PR)/ number of cases
	CR	PR	SD	PD	
Control group (n=25)	6	15	3	1	84%
Study group (n=11)	1	5	3	2	54.5%

Change of metastatic lesions

25 cases of the 43 patients in the study group developed liver metastasis and 11 cases of the 20 patients in the control group developed liver metastasis. For liver metastases using lipiodol chemoembolization, the efficacy of lesion reduction after treatment is assessed by the degree of aggregation of iodized oil. In the study group, there were 6 cases of CR, 15 cases of PR, 3 cases of SD, and 1 case of PD, and the effective rate was 84%. In the control group, there were 1 case of CR, 5 cases of PR, 3 cases of SD, and 2 cases of PD. The curative effect of the study group was significantly better than that of the control group (Table III).

Introduction of typical clinical cases

Typical case 1: Zhang XX, male, 73 years old, gastroscopy: cancer of the gastric cardia. Abdominal CT: irregular mass of gastric wall (thickness 3.2 cm) and peritoneal multiple lymph node metastasis (cT4N2M0) in the gastric cardia and small bend side of the stomach (Figure 1A). The 3 courses of chemotherapy were given to the target arterial infusion of "oxaliplatin + epirubicin + fluorouracil + verapamil". After treatment, reexamination of the gastroscopy was carried out: the lesion was narrowed than before. CT: the irregular mass of the gastric wall in the cardia and the small side of the stomach (thickness 1.7 cm) was significantly reduced (Figure 1B). After the downgrade, the patient underwent "radical resection of the cardia cancer" and the postoperative stage was ypT4N1M0.

Typical case 2: Xu XX, male, 57 years old. Gastroscopic indication: gastric adenocarcinoma involving the cardia. Abdominal CT: a mass formed by enlargement of gastric cardia and thickening of gastric wall on small curved side of the stomach broken through the serosal to invade the adjacent omentum and mesangial. It was considered to have gastric cancer with small curvature of the stomach and retroperitoneal multiple lymph node metastasis (T4N3MX, the thickness of the stomach was 2.8 cm) (Figure 2A). After treatment, gastroscopy showed that the lesions were significantly narrowed than before. Abdominal CT: the irregular mass of gastric cardia and small bend side of the stomach (1.3 cm) were significantly reduced and the retroperitoneal lymph nodes were significantly reduced. After the downgrade, the patient underwent "radical resection of the gastric cancer" and the postoperative stage was ypT4N1M0.

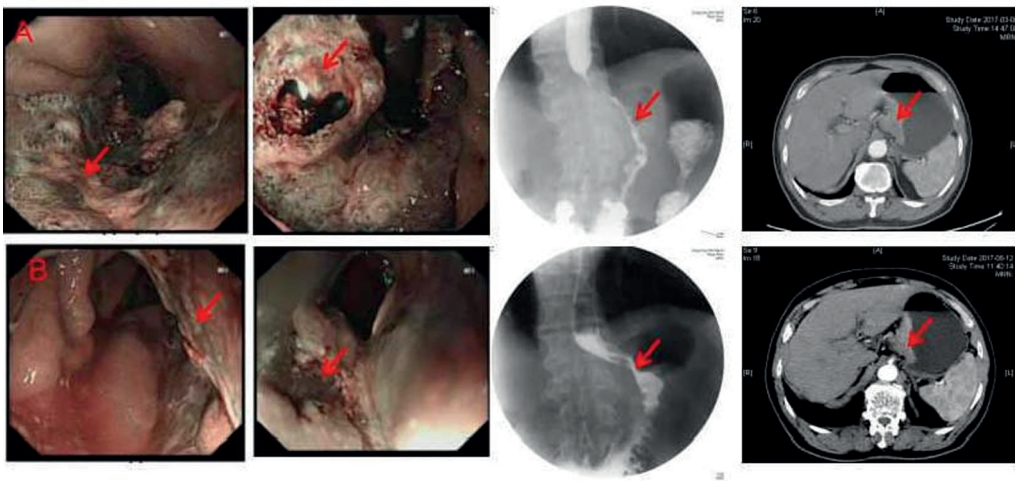

Figure 1. Typical case 1. Comparison of electron gastroscopy, CT images and radiography before (**A**) and after (**B**) intervention.

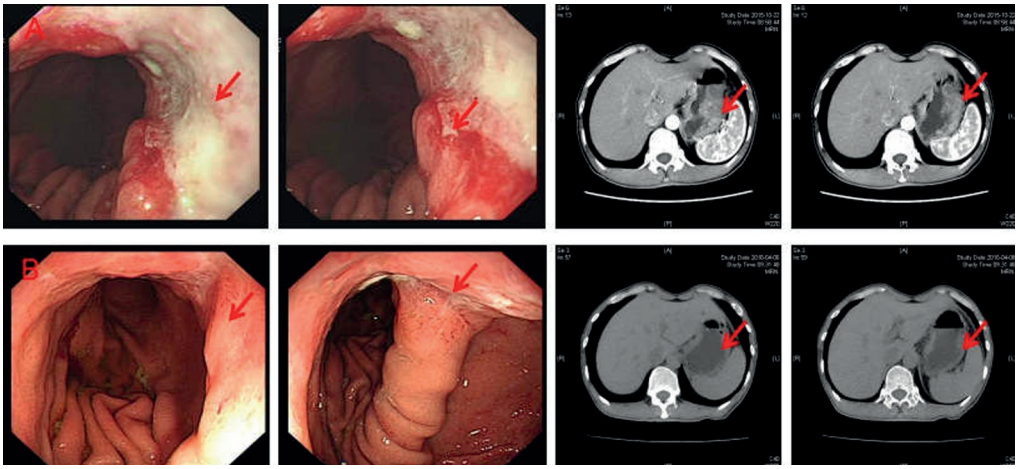

Figure 2. Typical case 2. Comparison of electron gastroscopy and CT images before (**A**) and after (**B**) intervention.

Typical case 3: Xu XX, male, 68 years old. Gastroscopy prompted gastric cardia fundic cancer. Abdominal CT: the gastric wall of gastric fundus appeared diffuse heterogeneous thickening and the patient may have infiltrative gastric cancer (*linitis plastica*) with peritoneal and retroperitoneal lymph node metastasis (Figure 3A). After treatment, gastroscopy showed that the lesions were significantly narrowed than before. Abdominal CT: the irregular mass of gastric cardia fundic was significantly narrowed and the retroperitoneal lymph nodes were narrowed (Figure 3B).

Typical case 4: Zhu XX, male, 66 years old, was diagnosed as gastric cancer with multiple liver metastases (stage IV) in March 2012 (Figure 4A) and was given arterial interventional therapy 6 times in our department. After treatment, the lesion in the stomach and liver lesions were completely relieved (cT0NOM0) (Figure 4B). The follow-up disease-free survival was 5 years to date. After treatment, gastric lesions and liver lesions were completely relieved (cT0NOM0) (Figure 4B). The follow-up disease-free survival was 5 years to date.

Evaluation of Clinical Outcome

Among 43 cases of gastric cancer in the study group, after 2 times of arterial infusion of verapamil combined with chemotherapeutic drugs, there were 40 cases of positive clinical benefit in KPS score and 38 cases of clinical benefit positive for weight. Among 20 cases of gastric cancer in the control group, after 2 times of arterial infusion of verapamil combined with chemotherapeutic drugs, there were 10 cases of positive clinical benefit in KPS score and 8 cases of clinical benefit positive for weight.

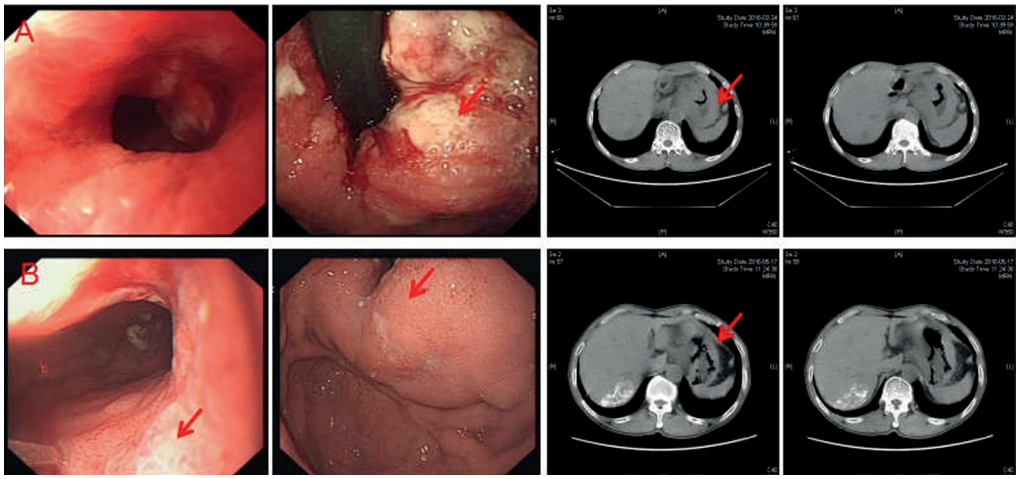

Figure 3. Typical case 3. Comparison of electron gastroscopy and CT images before (**A**) and after (**B**) intervention.

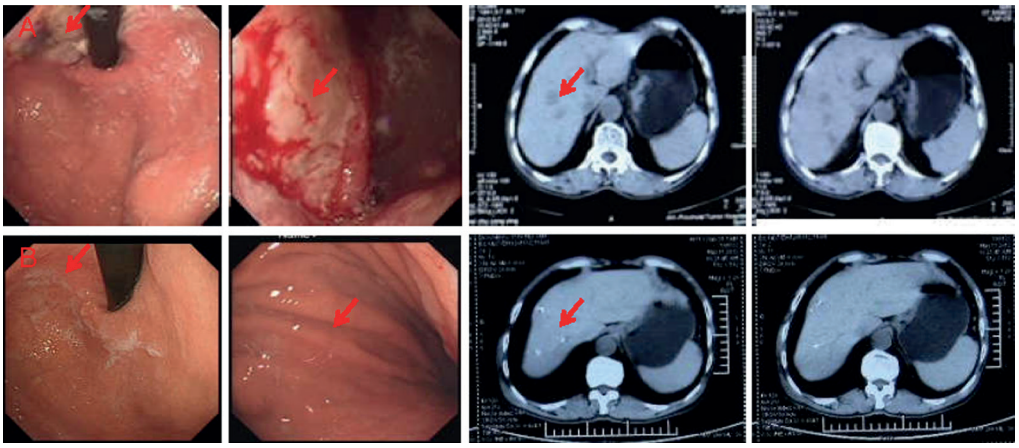

Figure 4. Typical case 4. Comparison of electron gastroscopy and CT images before (**A**) and after (**B**) intervention.

Survival Analysis

The median PFS of the study group and the control group was 20 months and 9 months, and the median OS was 13 months and 25 months (Table IV). The disease progression-free rate and survival rate of the study group in 12 months and 24 months were higher than those in the control group. The median PFS and the median OS were longer than those in the control group; the difference was statistically significant (p<0.01).

Evaluation of Toxic Effects and Cardiac Function

43 patients in the study group were treated with verapamil combined with interventional chemotherapy for more than 2 times, and the toxic effects and cardiac function were evaluated (Table V). The results showed that 15 patients (34.8%) had leukopenia, 4 patients (9.3%) had thrombocytopenia, 11 patients (25.5%) had gastrointestinal reactions, 3 patients (6.9%) had muscle joint pain, 3 patients (6.9%) had elevation of ALT/AST, and 4 patients had a fever (37.5°C-39°C) (Figure 5). No increase of BUN/Cr and anaphylaxis was found. All the above adverse reactions were relieved in a short period of time. The evaluation of cardiac function showed that there was no significant change in the cardiac function of 43 patients before and after intervention (Table VI); there was no significant difference in electrocardiogram (Table VII). This shows that the interventional therapy of verapamil combined with chemotherapy does not accompany serious side effects and abnormal cardiac function.

Table V. 43 patients were involved in the treatment of toxic and side effects.

	0	I	II	III	IV
Leukopenia	28	12	3	0	0
Hemoglobin decreased	39	4	0	0	0
Thrombocytopenia	39	3	1	0	0
Gastrointestinal reaction	32	8	3	0	0
ALT/AST rise	40	3	0	0	0
BUN/Cr rise	43	0	0	0	0
Fever	39	4	0	0	0
Muscle and joint pain	40	3	0	0	0
Allergic reaction	43	0	0	0	0

Table IV. The two groups of patients were compared with 12/24 months survival.

Group	Progression free rate (%)		PFS (month)	Survival rate (%)		OS (month)
	12 months	24 months		12 months	24 months	
Study Group (n=43)	75.6%	39.5%	20	86.5%	60.3%	25
Control Group (n=20)	30.6%	16.8%	9	65.0%	23.4%	13
χ^2			24.47			25.35
p			<0.001			<0.001

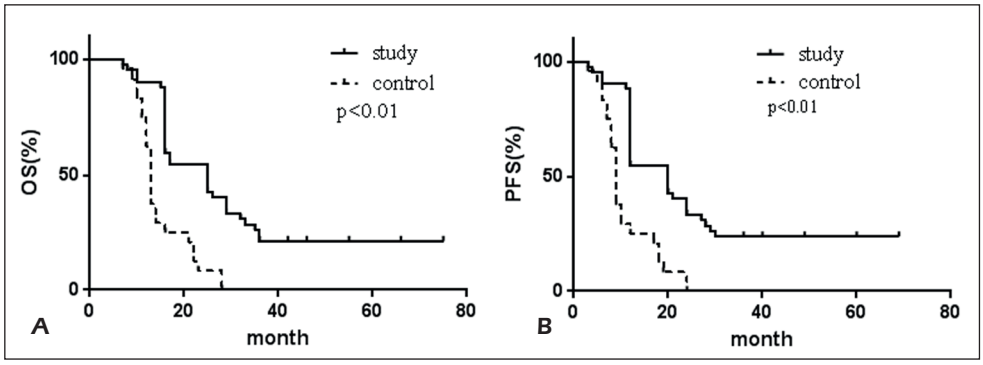

Figure 5. Survival curve of Study Group and Control Group. **A**, OS (overall survival). **B**, PFS (progress-free survival).

Table VII. Observation of electrocardiogram (n=43).

Observational index	P-R	Q-T	QRS	Heart-rate
0 minutes	0.15±0.03	0.38±0.03	0.08±0.02	76±13
5 minutes	0.15±0.02*	0.38±0.03*	0.08±0.02*	76±12*
10 minutes	0.15±0.03*	0.38±0.03*	0.08±0.02*	76±12*
20 minutes	0.15±0.03*	0.38±0.02*	0.08±0.02*	76±12*
50 minutes	0.15±0.03*	0.38±0.03*	0.08±0.02*	76±12*

Note: The time in the table is timed after infusion of verapamil. *Indicates a comparison with the 0-minute group mean (p>0.05).

Table VI. Results of cardiac function observation (n=43).

Heart function classification	Normal	I	II	III	IV
1 day before treatment	43	0	0	0	0
30 days after treatment	43	0	0	0	0
60 days after treatment	43	0	0	0	0
Muscle and joint pain	40	3	0	0	0
Allergic reaction	43	0	0	0	0

Discussion

Multidrug resistance (MDR) is one of the main reasons that restrict the clinical curative effect of cancer such as gastric cancer, and the abnormality of extracellular efflux pump is one of the mechanisms of tumor cells producing MDR[21,22]. Researches have shown that P-glycoprotein (P-gp) hydrolyzes ATP to generate ADP and releases energy. P-gp can be combined with intracellular antitumor drugs under the participation of calcium ions and pump it out of the cell, so that the intracellular concentration of drugs can be reduced and the toxic effects of drugs on tumors can be reduced, resulting in the production of MDR[23,24]. Verapamil, a calcium channel blocker, is clinically used in heart disease. However, many studies have shown that it can significantly reverse MDR (multidrug resistance) in tumor cells. It inhibits the expression of MDR-l gene and inhibits the synthesis of P-gp, thus increasing the concentration of chemotherapeutic drugs in the tumor cells, overcoming the drug resistance of the tumor cells[25]. Experimental studies have shown that 6-10 μmoL/L verapamil can completely inhibit P-gp reversal of multidrug resistance of malignant cells and can increase the sensitivity of tumor cells to chemotherapy drugs. However, adverse effects of cardiovascular system, such as decreased heart rate, may occur when verapamil is administered at a concentration of 1-2 μmol/L *in vivo*[14], which is the main reason for its wide application in clinical practice as a reversal agent of tumor resistance.

Our previous animal experiment showed that the concentration of verapamil in the local tissue reached 3-10 times that of the blood. It showed also that target artery perfusion can make verapamil in local tissue concentrations to reach 3-10 times that of the blood and verapamil formed a local concentration in the safe intravenous concentration range to reverse the drug resistance of the tumor. To achieve both reversal of tumor drug resistance and to avoid the side effects of the heart, we used a targeted arterial infusion of verapamil in combination with chemotherapeutic agents for tumor.

After targeted therapy with verapamil for patients with hepatocellular carcinoma, we found that the total effective rate of chemotherapy was increased to 71.4%, and the one-year cumulative survival rate was 81.8%; no patient had a relevant heart vascular toxicity. This shows that the arterial infusion of verapamil not only avoids the possible cardiovascular disorder, but also significantly increases the curative effect of chemotherapeutic drugs in patients with liver cancer[26].

With the increasing employment of interventional radiology in the diagnosis and treatment of gastric cancer and the improvement of interventional treatment technologies, interventional treatment is becoming the mainstream therapeutic strategy for advanced gastric cancer. The disadvantages of the traditional interventional method for gastric cancer are that terminal iodine oil embolism can easily induce gastric necrosis and perforation due to the hollow nature of the stomach. On the other hand, advanced gastric cancer has a poor sensitivity to chemotherapy and it commonly correlate with multiple-drug resistance. Target artery interventional treatment via catheter allows high concentrations of drugs to be injected directly into the lesions and to maintain a high concentration locally in tumor tissues. The distribution of drugs around the tumor and unrelated tissue and organ is low, and the systemic side effects are extremely low[27,28].

In this work, we initially performed the interventional therapy of verapamil combined with chemotherapy for advanced gastric cancer. We can analyze the efficacy of interventional therapy through the judgment of clinical treatment effect (clinical symptoms, size of cancer, etc.), evaluation of the degree of benefit (KPS evaluation and body weight), survival analysis and observation of patients' side effects (cardiotoxicity, leukocyte level, and gastrointestinal reaction). The results show that:

1. Primary gastric cancer: in the study group, 43 patients were treated with verapamil in combination with chemotherapeutic drugs for more than 2 times. 6 patients were completely relieved (CR), 31 were partially relieved (PR), and the total effective rate (CR+PR) % was 86%, among which 15 cases were in stage II radical surgical treatment. In the control group, 20 patients were treated with chemotherapeutic drugs for more than 2 times. 0 patients were completely relieved (CR), 10 were partially relieved (PR), and the total effective rate (CR+PR) % was 50%. The curative effect of the study group was significantly better than that of the control group.
2. Liver metastatic lesions: 25 cases of the 43 patients in the study group developed liver metastasis and 11 cases of the 20 patients in the control group developed liver metastasis. For liver metastases using lipiodol chemoembolization, the efficacy of lesion reduction after treatment is assessed by the degree of aggregation of iodized oil. In the study group, there were 6 cases of CR, 15 cases of PR, 3 cases of SD, and 1 case of PD, and the effective rate was 84%. In the control group, there were 1 case of CR, 5 cases of PR, 3 cases of SD, and 2 cases of PD. The curative effect of the study group was significantly better than that of the control group.
3. Clinical benefit evaluation: in the study group, 43 patients with gastric cancer were treated with verapamil combined chemotherapy after 2 courses of treatment. The KPS score was positive in 40 cases, and the weight gain was positive in 38 cases. In the control group, 20 patients with gastric cancer were treated with verapamil combined chemotherapy after 2 courses of treatment. The KPS score was positive in 10 cases, and the weight gain was positive in 8 cases.
4. Survival analysis: the median PFS of the control group and the study group was 9 months and 20 months, and the median OS was 13 months and 25 months. The disease progression-free rate and survival rate of the study group in 12 months and 24 months were higher than those in the control group. The median PFS and median OS were longer than those in the control group; the difference was statistically significant ($p<0.01$).

43 patients in the study group were treated with verapamil combined with interventional chemotherapy for more than 2 times, and the toxic effects and cardiac function were evaluated. The results showed that 15 patients (34.8%) had leukopenia, 4 patients (9.3%) had thrombocytopenia, 11 patients (25.5%) had gastrointestinal reactions, 3 patients (6.9%) had muscle joint pain, 3 patients (6.9%) had elevation of ALT/AST, and 4 patients had fever (37.5°C-39°C). No increase of BUN/Cr and anaphylaxis was found. All the above adverse reactions were relieved in a short period of time. The evaluation of cardiac function showed that there was no significant change in the cardiac function of 43 patients before and after intervention, and there was no significant difference in electrocardiogram. This shows that the interventional therapy of verapamil combined with chemotherapy does not lead to serious side effects and abnormal cardiac function.

Conclusions

Target arterial infusion of verapamil combined with chemotherapy drugs for advanced gastric cancer can significantly improve the efficacy of chemotherapy drugs as well as the clinical symptoms of patients with advanced gastric cancer, prolonging their survival rate. The incidence of serious side effects in patients is not increased and there are no serious cardiovascular adverse reactions. In the future, we will expand the sample volume of gastric cancer interventional therapy with verapamil combined with chemotherapy drugs to further observe its efficacy and follow-up survival.

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Conflict of Interests:

The authors declare that they have no conflicts of interest in the studies described.

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