

# Effect of Modified Tongyou Decoction Combined with Epirubicin, Cisplatin and Fluorouracil Chemotherapy for Advanced Gastric Cancer

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## Ni *et al.*: Tongyou Decoction plus Chemotherapy Regimen for Gastric Cancer

To investigate the clinical efficacy of modified Tongyou decoction combined with epirubicin, cisplatin and fluorouracil regimen on the pre-thrombotic state in patients with advanced gastric cancer. 142 patients with advanced gastric cancer were selected and were randomly divided into study group and control group, each with 71 patients. The control group was treated with epirubicin, cisplatin and fluorouracil chemotherapy for 6 w, while the study group was treated with Tongyou decoction combined with epirubicin, cisplatin and fluorouracil regimen. After treatment, the levels of serum homocysteine, D-dimer, fibrinogen, blood rheology, clinical efficacy, incidence of venous thrombosis within 1 y, 6 mo survival rate, and 1 y survival rate were statistically compared. After treatment, the serum homocysteine, D-dimer, fibrinogen, whole blood high shear viscosity, whole blood middle shear viscosity, whole blood low shear viscosity, plasma viscosity, and the incidence of venous thrombosis within 1 y of the study group were higher compared with the study group, and the statistically significant difference was  $p < 0.05$ . Red blood cell deformation index, effective rate were also high in study group. Tongyou decoction combined with epirubicin, cisplatin and fluorouracil chemotherapy can improve the pre-thrombotic state of patients with advanced gastric cancer, improve the therapeutic effect, reduce the incidence of venous thrombosis, and increase 1 y survival rate, which has guiding significance for clinical practice.

**Key words:** Gastric cancer, chemotherapy, pre-thrombotic state, Tongyou decoction, curative effect

Advanced gastric cancer refers to gastric cancer that has developed to a later stage and has often spread to other organs or lymph nodes. Symptoms of advanced gastric cancer usually include indigestion, loss of appetite, nausea and vomiting, abdominal distension and pain, weight loss, etc. The tumor itself may increase the risk of thrombosis, especially substances released by cancer cells that may promote thrombosis. Pre-thrombotic state is a pathological and physiological state which is characterized by blood hypercoagulability and increased viscosity, caused by various pathological factors and is conducive to thrombosis<sup>[1]</sup>. Hypercoagulability and fibrinolysis play an important role in the development and metastasis of tumors, which is conducive to tumor cell growth, invasion, metastasis, and easily leads to venous thrombosis or secondary bleeding in patients<sup>[2]</sup>.

For patients with advanced gastric cancer, the main goals of treatment are to relieve symptoms, prolong survival time and improve quality of life. Common treatment methods include chemotherapy, targeted therapy, radiotherapy, surgery, nutritional support, traditional Chinese medicine treatment, etc. Research has shown that chemotherapy can exacerbate the hypercoagulable state in malignant tumor patients<sup>[3,4]</sup>. Chemotherapy for patients with advanced gastric cancer has obvious side effects, drug resistance, possible suppression of immune system function, and very limited efficacy. In particular, patients with advanced gastric cancer are physically weak, and the toxic side effects of chemotherapy often have negative effects on the patient that exceed the positive effects of chemotherapy itself. The feasibility of surgical treatment for late-stage gastric cancer is also

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relatively low, because late-stage gastric cancer has often spread to other organs or lymph nodes.

Surgery is highly risky, more traumatic, more difficult, prone to postoperative dysfunction and it also has an impact on quality of life. Tongyou decoction is a traditional Chinese medicine prescription that contains *Coptis chinensis*, *Scutellaria baicalensis*, *Gardenia jasminoides*, *Bombyx mori*, *Medicago truncatula*, etc. It has certain effects on the treatment of advanced gastric cancer. It is believed to have the functions of clearing away heat and detoxifying, promoting blood circulation and removing blood stasis, reducing swelling and relieving pain. These effects are suitable for treating diseases such as digestive tract cancer. Because patients with advanced gastric cancer are prone to the risk of thrombosis, Tongyou decoction has the effect of cooling blood and removing blood stasis, which can improve blood circulation and promote thrombolysis in gastric cancer patients, thereby reducing the risk of thrombosis. In addition, patients with advanced gastric cancer often suffer from loss of appetite and malnutrition. Some ingredients in Tongyou decoction have the effect of promoting appetite. This function can help patients with advanced gastric cancer improve their appetite and increase their nutritional intake, thereby improving the body's resistance. The aim of this study is to analyze the effect of Tongyou decoction combined with Epirubicin (EPI), Cisplatin and 5-Fluorouracil (5-FU) (ECF) regimen chemotherapy on the pre-thrombotic state of advanced gastric cancer patients, in order to provide theoretical and clinical basis for traditional Chinese medicine to improve the pre-thrombotic state of malignant tumors.

## MATERIALS AND METHODS

### Clinical data:

142 patients with advanced gastric cancer who underwent chemotherapy in Tongde hospital of Zhejiang Province from January 2016 to March 2022 were collected as the study subjects for this study. They were divided into study group and a control group each of 71, using a random number table method. Among 71 patients in the study group, 37 were males and 34 were females; age range was (35-69) y old, with an average age of (57.24±7.49) y; 31 patients with stage III adenocarcinoma and 40 patients with stage IV adenocarcinoma; 65

patients with adenocarcinoma, 4 patients with mucinous adenocarcinoma, and 2 patients with signet ring cell carcinoma; Karnofsky Performance Scale (KPS) score (81.32±0.86) points. There were 8 patients having lung metastasis, 31 patients having liver metastasis, 13 patients having supraclavicular lymph node metastasis, and 19 patients having abdominal lymph node metastasis. Similarly, there were 71 patients in the control group, which included 35 males and 36 females having an age of (36-72) y, with an average age of (57.72±8.64) y; 62 patients with adenocarcinoma, 5 patients with mucinous adenocarcinoma and 4 patients with signet ring cell carcinoma; KPS score (80.42±0.97) points. There were 9 patients having lung metastasis, 27 patients of liver metastasis, 15 patients having supraclavicular lymph node metastasis, and 20 patients having abdominal lymph node metastasis. There was no statistically significant difference ( $p>0.05$ ) in general clinical data such as age distribution, gender composition, pathological type, KPS score, and site of metastasis between the two groups of patients, indicating comparability. This study was approved by the ethics committee Tongde Hospital of Zhejiang Province and the patients and their families signed informed consent forms.

### Inclusion criteria:

Patients who were diagnosed to have gastric cancer by pathological histology through fiberoptic gastroscopy biopsy; patients confirming to the syndrome differentiation criteria for gastric cancer with stasis, toxins, and internal obstruction<sup>[5]</sup>; patients who have tingling pain in the stomach, localized pain, yin deficiency, vomiting blood, bloody stools, skin nail errors, upper abdominal fullness and bloating, thirst for fluids, restlessness and heartburn, thin white or yellow tongue coating, purple or dark tongue or ecchymosis, and thin and numerous veins; patients whose age >18 y old, regardless of gender; newly diagnosed gastric cancer patients who have not undergone surgery, radiotherapy, or chemotherapy in the past; patients whose KPS score  $\geq 70$  points and estimated survival time >3 mo; patients who at least have one evaluable therapeutic lesion after imaging examination; patients who have not taken anticoagulant drugs within 3 mo and received no contraindications to chemotherapy are included in the study.

**Exclusion criteria:**

Patients whose KPS score is <70 and estimated survival time is <3 mo; those who merge with primary malignant tumors in other parts; having severe liver and kidney dysfunction; patients with severe infections, thrombocytosis, and acute or chronic leukemia; individuals who are allergic to drugs such as cisplatin and calcium folinate; patients having multiple brain metastases; individuals with mental illness or cognitive impairment and patients who did not sign the informed consent have been proposed to be excluded from this study.

**Treatment method:**

The control group received ECF chemotherapy with 60 mg/m<sup>2</sup> cisplatin (Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd., approval number: Guoyao Zhunzi H20113457, specification: 50 mg), 50 mg/m<sup>2</sup> of EPI (Hainan Sida Pharmaceutical Co., Ltd., approval number: Guoyao Zhunzi H20034162, specification: 100 mg) intravenously once every 3 w, a total of 8 times along with 200 mg/m<sup>2</sup> of 5-FU intravenous injection for a total of 24 w, for every 2 w. On the basis of the control group, the research group was treated with Tongyou Tang with modified ingredients whose composition included 15 g of raw and cooked herbs, 9 g of peach kernel, *Angelica sinensis*, safflower, and *Bupleurum chinense*, 6 g of *Cimicifuga racemosa* (black cohosh) and *Glycyrrhiza uralensis* (licorice), 20 g of *Hedyotis diffusa* (White flower snake tongue grass) and *Scutellaria barbata*. The decoction was decanted to 200 ml, 1 dose per day, and both groups were treated separately in the morning and evening, for 3 regimens.

**Observation indicators:**

The fasting venous blood of patients before and after chemotherapy was checked to detect the levels of serum Homocysteine (Hcy), D-Dimer (D-

D) and Fibrinogen (FIB), and detected the blood flow changes before and after chemotherapy.

**Efficacy evaluation:** After chemotherapy, the World Health Organization (WHO) efficacy evaluation criteria were used to evaluate the treatment effect, which was divided into Complete Remission (CR), Partial Remission (PR), Stable Disease (SD) and Progressive Disease (PD). CR and PR patients underwent further imaging examinations after 4 w for confirmation.

**Survival evaluation:** Patients were followed up for 1 y to observe the 6 mo and 1 y survival rates in two groups. The incidence of venous thrombosis was observed in the two groups of patients for 1 y. The diagnostic criteria of venous thrombosis were swelling of the tissues in the venous drainage area. Color Doppler detection found thrombosis, narrow blood flow or blood flow interruption, and the diseased veins were significantly expanded, with or without peripheral circulation.

**Statistical analysis:**

The Statistical Package for Social Sciences (SPSS) 20.0 software was used to process the research data, where  $p < 0.05$  was considered as statistically significant difference. The data was analyzed by  $\bar{x} \pm s$  and t-test and rank sum test analysis was used for ranking data.

**RESULTS AND DISCUSSION**

Serum Hcy, D-D, FIB levels between the two groups before and after chemotherapy was compared. After chemotherapy, the levels of Hcy, D-D, and FIB in the study group significantly reduced compared to before chemotherapy, while the levels of Hcy, D-D, and FIB in the control group were significantly increased compared to before chemotherapy. Compared with the control group, the levels of Hcy, D-D, and FIB in the study group were significantly reduced ( $p < 0.05$ ) (Table 1).

**TABLE 1: COMPARISON OF SERUM Hcy, D-D, FIB LEVELS BETWEEN THE TWO GROUPS BEFORE AND AFTER CHEMOTHERAPY ( $\bar{x} \pm s$ )**

Group (n=71)	Time	Hcy ( $\mu\text{mol/l}$ )	D-D (ng/ml)	FIB (g/l)
Research	Before chemotherapy	18.32 $\pm$ 3.29	1675.41 $\pm$ 437.20	5.14 $\pm$ 0.62
	After chemotherapy	11.03 $\pm$ 3.07 <sup>**</sup>	854.11 $\pm$ 187.24 <sup>**</sup>	2.98 $\pm$ 0.32 <sup>**</sup>
Control	Before chemotherapy	18.44 $\pm$ 2.78	1587.29 $\pm$ 411.58	5.27 $\pm$ 0.42
	After chemotherapy	23.82 $\pm$ 2.15 <sup>*</sup>	2146.87 $\pm$ 204.35 <sup>*</sup>	5.83 $\pm$ 0.44 <sup>*</sup>

Note: <sup>\*</sup> $p < 0.05$  and <sup>\*\*</sup> $p < 0.05$ , before and after chemotherapy when compared with the control group

Similarly hemorheological levels in patients before and after chemotherapy were compared. After chemotherapy, the whole blood high shear viscosity, whole blood medium shear viscosity, whole blood low shear viscosity, and plasma viscosity in the study group significantly decreased compared to before treatment, while the control group significantly increased comparatively before treatment. The study group showed a significant increase in red blood cell deformation index compared to before treatment, while the control group showed a significant decrease compared to before treatment. Compared with the control group, the study group showed a significant decrease in whole blood high shear viscosity, whole blood medium shear viscosity, whole blood low shear viscosity, and plasma viscosity, and a significant increase in red blood cell deformation index ( $p < 0.05$ ) as shown in Table 2.

Further, clinical efficacy between two groups of patients was also compared. The effective rate of the study group significantly increased, with a statistically significant difference ( $p < 0.05$ ) compared with the control group (Table 3).

Comparison of survival rates between the two groups of patients implied that 1 y survival rate of the study group was increased significantly with a statistically difference ( $p < 0.05$ ), compared with the control group (Table 4).

The incidence of venous thrombosis between the two groups was compared. Venous thrombosis was occurred in one patient in the study group within 1 y of follow-up, with an incidence rate of 1.41 %. There were 7 patients with venous thrombosis in the control group within 1 y whose incidence rate was 9.86 % with a significant statistical difference,  $p < 0.05$ .

**TABLE 2: COMPARISON OF HEMORHEOLOGICAL LEVELS IN PATIENTS BEFORE AND AFTER CHEMOTHERAPY ( $\bar{x} \pm s$ )**

Group (n=43)	Treatment	Whole blood viscosity			Plasma viscosity (mPas <sup>-1</sup> )	Red blood cell deformation index
		High shear viscosity (mPas <sup>-1</sup> )	Medium shear viscosity (mPas <sup>-1</sup> )	Low shear viscosity (mPas <sup>-1</sup> )		
Research	Before chemotherapy	4.74±0.36	6.02±0.43	10.99±0.81	1.68±0.24	0.77±0.18
	After chemotherapy	3.28±0.29 <sup>#</sup>	4.45±0.31 <sup>#</sup>	8.99±0.38 <sup>#</sup>	1.06±0.17 <sup>#</sup>	1.37±0.25 <sup>#</sup>
Control	Before chemotherapy	4.69±0.44	5.97±0.39	10.88±0.75	1.66±0.18	0.81±0.19
	After chemotherapy	5.31±0.35 <sup>*</sup>	6.42±0.29 <sup>*</sup>	11.87±0.46 <sup>*</sup>	1.91±0.14 <sup>*</sup>	0.61±0.18 <sup>*</sup>

Note: <sup>\*</sup> $p < 0.05$  and <sup>#</sup> $p < 0.05$ , before and after chemotherapy respectively when compared with the control group

**TABLE 3: COMPARISON OF CLINICAL EFFICACY BETWEEN TWO GROUPS OF PATIENTS (%)**

Group (n=71)	CR	PR	SD	PD	Efficacy %
Research	11 (15.49)	27 (38.03)	28 (39.44)	4 (5.63)	38 (53.52)
Control	6 (8.45)	20 (28.17)	36 (50.70)	9 (12.68)	26 (36.62) <sup>*</sup>

Note: <sup>\*</sup> $p < 0.05$ , with respect to comparison with the control group

**TABLE 4: COMPARISON OF SURVIVAL RATES BETWEEN TWO GROUPS OF PATIENTS (%)**

Group	6 mo survival rate	1 y survival rate
Research	90.14 (64)	69.01 (49) <sup>#</sup>
Control	78.87 (56)	50.70 (36)

Note: <sup>#</sup> $p < 0.05$ , with respect to comparison with the control group

Malignant tumors can lead to coagulation dysfunction, and research has shown that about 95 % of malignant tumor patients, especially those with advanced tumors, have one or more abnormal coagulation indicators, which was manifested as a pre-thrombotic state<sup>[6]</sup>. The incidence of deep vein thrombosis in patients with pre-thrombotic state is about 4 %~30 % in 6~12 mo after the diagnosis of malignant tumor, which is 4~7 times of that in patients without tumor<sup>[7]</sup>. The mechanism by which malignant tumors lead to pre-thrombotic state has not yet been fully elucidated. Clinically, it is often believed to be related to the direct induction of thrombin production by tumor cells, stimulation of host cells to induce thrombin, and activation of thrombin through normal tissue destruction, infection, necrosis, etc., which are closely related to tumor development and infiltration<sup>[8]</sup>. Pre-thrombotic state can lead to increased blood viscosity, capillary blood stasis, endothelial damage, and easy formation of cancer thrombi. Activation of the coagulation system can promote tumor cell proliferation, which is closely related to tumor progression and metastasis<sup>[9]</sup>. Tumor treatment such as chemotherapy, radiation therapy, and venous catheterization can lead to endothelial damage, exacerbating the hypercoagulable state of blood in malignant tumor patients. External studies have shown that malignant tumor patients receiving chemotherapy have a 6.5-fold increased risk of thrombosis, and adenocarcinoma is the highly incident thrombosis<sup>[10]</sup>. Domestic studies have shown that patients with malignant tumors have abnormal coagulating function, manifested as enhanced coagulation function or weakened anticoagulation function, generally termed as hypercoagulable state. Cytotoxic drugs during chemotherapy can damage vascular endothelial cells, leading to the release of procoagulant substances and exacerbating the hypercoagulable state of the blood<sup>[11]</sup>.

D-D is a specific fibrin degradation fragment, generated under the action of plasmin, and the increase of the D-D level indicates thrombosis and secondary fibrinolysis. Research on new lung cancer shows that the serum D-D dimer level is closely related to the course of disease, which is helpful to judge the prognosis and guide the adjuvant treatment of surgical patients<sup>[12]</sup>. FIB is the raw material for fibrin thrombosis, and its coagulation function is linearly correlated with

FIB concentration. Elevated FIB in the body can cause an increase in whole blood viscosity and promote thrombosis. On the other hand, elevated FIB can diffuse between extravascular tumor cells and tissues, which can protect tumor cells from being killed by chemotherapy drugs to some extent<sup>[13]</sup>. Elevated Hcy levels can damage vascular endothelial cells, activate the fibrinolytic system, and promote the formation of pre-thrombotic state in malignant tumor patients. Hcy is one of the important monitoring indicators for pre-thrombotic state<sup>[14]</sup>. The results of this study showed that after chemotherapy, Hcy, FIB, D-D, whole blood high shear viscosity, whole blood medium shear viscosity, whole blood low shear viscosity, and plasma viscosity in the control group were significantly increased comparatively before chemotherapy, and the red blood cell deformation index was significantly reduced. This suggests that there is an increase in blood hypercoagulability in advanced cancer patients after chemotherapy, which is consistent with relevant studies.

Gastric cancer belongs to the category of "choking diaphragm" in traditional Chinese medicine, which is believed to be related to diet, seven emotions, accumulated fatigue, worry, depression, anger, liver depression, qi stagnation, transverse invasion of the spleen and stomach, dredging, transportation and loss of qi, phlegm dampness, obstruction of phlegm and qi, swelling of blood stasis, corrosion of coronary collaterals and its injury, internal obstruction of blood stasis and toxins, heat dissipation over time, loss of circulation, descending of the stomach, toxin accumulation, formation of sores, depletion of gastric fluid, and damage to kidney yin. Therefore, gastric cancer patients often experience internal obstruction of blood stasis and toxin, yin deficiency, body fluid injury and should be treated with nourishing yin and blood breaking knots, promoting blood stasis. Tongyou Tang originates from Li Dongyuan's "Spleen and stomach treatise" and has been clinically proven to have good effects in treating "choking and diaphragm" caused by stasis and toxin accumulation. The formula includes nourishing yin and nourishing blood with herbs such as *Rehmanniae radix*, *Angelica sinensis*, peach kernels and its red flowers are used to remove stasis and break the knots, while *Scutellaria barbata* is used to clear heat and blood stasis. *Hedyotis diffusa* is used to promote blood circulation and

relieve pain. *Bupleurum* and *Cimicifuga* are used to reduce dredging, transportation and loss of qi. When the spleen and stomach clears yan, it raises qi causing abundant blood flow. *Glycyrrhiza uralensis* is slow and moderate, and all herbs together are used to nourish and moisten yin, thereby breaking and promoting stasis<sup>[15]</sup>. Modern pharmacological studies have shown that Tongyou Tang and its disassembled formulas can inhibit the activity of Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/AKT) signaling pathway in esophageal cancer EC9706 cells, and reduce PI3K, phosphorylated (p)-PI3K, AKT, and Nuclear Factor Kappa B (NF-κB) expression activates caspase-3 mediated cell apoptosis, inhibits EC9706 cell proliferation, and has a time and dose dependent anti-tumor effect<sup>[16]</sup>. The effective component of *Angelica sinensis*, ferulic acid, can reduce Thromboxane A2 (TXA2) activity, increase Prostaglandin I2 (PGI2) activity, increase PGI2/TXA2 ratio, inhibits platelet aggregation and adhesion, and increases red blood cell deformation index<sup>[17]</sup>. Both the ethanol and ethyl acetate extracts of peach kernel can significantly reduce platelet aggregation induced by adenosine diphosphate, and the triolein ester isolated from peach kernel has anticoagulant activity<sup>[18]</sup>. The effective component of safflower yellow pigment can inhibit calcium ion influx caused by platelet activating factor, inhibit platelet activation, and have a clear anticoagulant effect<sup>[19]</sup>.

The results of this study show that Tongyou decoction combined with ECF chemotherapy can improve the pre-thrombotic state of patients with advanced gastric cancer, improve the treatment effect, reduce the incidence of venous thrombosis, increases 1 y survival rate, improve the clinical treatment effect and prognosis. The limitation of this study is that the study has been carried out in small number of patients. Thus, the results need to be verified further by increasing the number of patients and multi-center clinical studies.

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#### Conflict of interests:

The authors declared no conflict of interests.

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