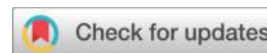




Professor Li Ping's Experience in Treating Advanced Gastric Cancer by Applying the Collateral Disease Theory with the Collateral-Dredging Method Combined with Anti-Angiogenic Drugs

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Abstract: Anti-angiogenic drugs have shown some efficacy in the clinical treatment of gastric cancer, but at present, there are fewer kinds of anti-angiogenic drugs for gastric cancer, which are only used in the treatment of advanced gastric cancer and are prone to drug resistance. Prof. Li Ping believes that there are many similarities between the theory of complex disease in Chinese medicine and the theory of angiogenesis in modern medicine. Based on this theory, Prof. Li Ping found that using Tongluo method combined with anti-angiogenic drugs to treat advanced gastric cancer can play a synergistic effect, which can effectively control the growth rate of tumors, improve the quality of life of patients and prolong the survival time of patients.

Keywords: Advanced Gastric Cancer; Collateral Disease Theory; Collateral-Dredging Method; Anti-Angiogenesis; synergy

Gastric cancer is one of the most common malignant tumors with poor prognosis, posing a serious threat to human health and life ^[1-2]. China is a count

ry with a high incidence of gastric cancer. In 2020, China accounted for more than 40% of new and fatal cases of gastric cancer in the world, and its incidence rate and mortality rate ranked fifth and fourth in the world respectively [3].

At present, the traditional treatment for gastric cancer is surgery, combined with adjuvant chemotherapy and radiotherapy [4-5]. However, most gastric cancer patients are already in advanced stages when discovered, losing the opportunity for surgical treatment. Even if some patients undergo surgery, postoperative recurrence and distant metastasis remain the main risk factors [6]. Therefore, for patients with advanced gastric cancer, choosing an appropriate treatment plan is crucial. With the development of personalized precision therapy, emerging therapies such as targeted therapy and immunotherapy have provided more treatment options for patients with advanced gastric cancer [7-9]. Among them, anti angiogenic therapy belongs to a targeted therapy. In recent years, anti angiogenesis has made certain achievements in the treatment of advanced gastric cancer, but there are still problems such as limited drug types, limited applicability to advanced gastric cancer, and susceptibility to drug resistance. As an important adjuvant therapy for gastric cancer, traditional Chinese medicine (TCM) has shown better results in improving patients' sensitivity to drugs, enhancing efficacy, and reducing drug side effects [10]. Professor Li Ping, in his clinical practice, started from the theory of complex diseases and used a combination of traditional Chinese medicine and anti angiogenic drugs to treat advanced gastric cancer, achieving significant therapeutic effects and providing new ideas for the clinical treatment of advanced gastric cancer.

I. The relevance of the theory of complex disease to the doctrine of tumor angiogenesis

1. Understanding malignant tumours from the theory of complex disease

The collaterals are components of the meridians, and the role of the collaterals is to change the flow of qi and blood in the meridians from linear perfusion to facultative diffusion, thus infiltrating and moistening the whole organism [11]. If the collateral veins are damaged, the flow of qi and blood will be af

fects, leading to the occurrence of various diseases. Diseases caused by abnormalities in the function or structure of collaterals are called collateral diseases.

Zhang Zhongjing pioneered the treatments of "pungent warmth to clear the channels" and "insect medicine to clear the channels", and used the "Cirrhospira Soup" and "Rhubarb and Turtle Pill" to treat liver attachment, deficiency, and other diseases. He also used the "Clover Flower Soup" and "Rhubarb and Pellet Bug Pill" in treating the diseases of the complexes, such as liver adhesion, deficiency labour, and drying up of blood, laying a solid theoretical foundation for the treatment of the complexes. Ye Tianshi put forward the concepts of "long-time illness into the complex" and "long-time pain into the complex" in "Clinical Guidelines for Medical Cases", stressing that "at the beginning of the gas knot in the meridian, for a long time, the blood will be injured into the complex", and developed the theory of the complex disease, thinking that most of the symptoms such as long-time illness and long-time pain are caused by the liver, and that most of the symptoms are caused by the blood. He also developed the theory of "collateral disease", thinking that most of the symptoms such as chronic disease and chronic pain are caused by blood stasis in the collaterals, and introduced the concept of "collateral disease" into the diagnosis and treatment of internal injuries and miscellaneous diseases ^[12]. Modern Professor Wu Yiling further perfected the theory of complex disease, and he advocated that complex disease is a kind of disease with the main pathological changes such as complex deficiency and lack of glory, hyperactivity of complex channels, and accumulation of complex interest ^[13]. Malignant tumour is the evidence of the basic deficiency. The collaterals are the place of infiltration and transmission of qi, blood and fluid, and various factors lead to the emptiness of collaterals, and when they are empty, all evils invade the collaterals through the meridians, the collaterals are out of harmony with qi, the blood line is not smooth, and the qi stagnation and blood stasis are transformed into cancerous venom and developed into cancer over a long period of time. The course of malignant tumour is often long, and patients with malignant tumour often have pain a

and other clinical manifestations, which is consistent with the characteristics of "prolonged illness" and "prolonged pain" of collaterals. Therefore, from the point of view of the development process of malignant tumour, it should belong to the category of *luo* disease. Professor Li Ping believes that under physiological conditions, the body's vital energy through the *San Jiao* into the twelve meridians, and then reach the five viscera and six bowels, thus promoting and regulating the physiological activities of the viscera, meridians, the body and the official orifices. After suffering from the six evils, emotional and internal injuries, or diet, water and soil inappropriateness, phlegm, stasis and blood stagnation, insect venom and stones and other disease-causing factors, it can lead to abnormal metamorphosis of the vital energy, which in turn produces a strong pathogenic nature of the material, known as the "tumour poison". Tumour poison has the characteristics of insidious onset and easy to change. In the early stage of oncotoxin formation, it is mainly manifested as consuming positive *qi*, and the oncotoxin spreads around the primary lesion through the disease channels and is difficult to be detected; in the middle and late stages, the oncotoxin spreads along the meridians through the disease channels and stays in the suitable environment to form the metastatic lesion, which is manifested as the toxic obstruction of the disease channels and the toxic birth of the channels^[14]. Based on this, Prof. Li Ping proposed that "abnormal metabolism of vital energy, internal tumour toxicity" is the fundamental cause of malignant tumour formation, "toxicity to positive decline" is the significant feature of tumour toxicity, "toxicity to illness" is the most common cause of malignant tumour formation. "These theories also coincide with the theory of complex disease, which confirms that malignant tumour belongs to the category of complex disease^[15].

2.Tumour angiogenesis in the management of gastric cancer

Dr. Folkman of Harvard University formally proposed the theory of tumor angiogenesis in 1971, stating that neovascularization is a necessary condition for tumor growth and metastasis. Tumor angiogenesis is a complex phenomenon that requires a large amount of oxygen and nutrients during the growth of tum

or cells due to their high metabolic activity and rapid proliferation. However, the vascular supply around the tumor is limited and cannot meet these needs. Therefore, tumor cells release signaling molecules that promote angiogenesis, leading to the proliferation and migration of nearby endothelial cells, ultimately forming a new vascular network to provide the nutrients and oxygen needed by tumor cells [17]. At the same time, the neovascularization structure in tumor tissue is still incomplete and easily permeable, allowing tumor cells to easily enter the bloodstream through blood vessels, leading to distant metastasis [18].

Modern gastric cancer treatment methods based on the theory of tumor angiogenesis have emerged, whose main principle is to inhibit the formation of tumor neovascularization, reduce the blood supply to tumor tissue, thereby limiting the growth and metastasis of tumor tissue, and ultimately exerting anti-tumor effects [19-21]. The anti angiogenic drugs for gastric cancer mainly include monoclonal antibodies and small molecule tyrosine kinase inhibitors [22-23], among which the representative drug for monoclonal antibodies is remdesizumab, and the representative drug for small molecule tyrosine kinase inhibitors is apatinib, which can exert its effect by specifically antagonizing VEGFR-2 [24]. In vitro studies [25] have shown that remdesizumab significantly inhibits the proliferation of gastric cancer cell lines and induces their apoptosis. A randomized three-phase study on advanced gastric cancer showed that the first-line treatment with ranibizumab extended the survival time of patients with advanced gastric cancer compared to placebo [26]. Based on the results of this study, remdesizumab was approved by the US Food and Drug Administration in 2014 for the treatment of advanced gastric cancer. Apatinib is a small molecule selective tyrosine kinase inhibitor independently developed in China, targeting the PI3K/Akt signaling pathway [27], which can effectively inhibit the proliferation of gastric cancer cells and promote their apoptosis. Multiple clinical studies [28-30] have shown that apatinib is of great significance in prolonging the median progression free survival of patients with advanced gastric cancer. In 2014, the China Food and Drug Administration approved apatinib for second-line and above treatment of advanced gastric cancer [31].

Professor Li Ping found in clinical treatment of gastric cancer that the progression-

free survival of second-line anti-angiogenic therapeutic drugs for advanced gastric cancer is still limited, drug resistance is easy to appear, and the adverse reactions of some patients are obvious. The theory of Chinese medicine and modern medicine have great similarity in the pathophysiological process, such as capillaries, which is the place where blood and fluids are exchanged, and has the function of infiltrating qi and blood and moistening the internal organs. Modern research shows that microvessels are the basic unit of material exchange and energy metabolism in human body ^[32]. And the neovascular tumour is different from normal blood vessels in morphology, structure and function, which is equivalent to the theory of disease in the complex, when the complex is damaged, stasis of blood, phlegm, dampness and toxicity and other factors, long-term stagnation in the channel, resulting in poor functioning of the complex, the evil and poisonous internal obstruction forcing the complex to be born beside the other branch of the channel, proliferation of the unchecked, hyper as a change, and the complex generation of the hyperactive, which led to the formation of the disease complex ^[33]. Based on this, Professor Li Ping proposed the use of the method of collateral circulation combined with anti-angiogenic drugs in the treatment of gastric cancer, which obtained remarkable clinical efficacy and provided a new direction for the clinical synergistic treatment of gastric cancer with Chinese and Western medicines.

II. Treatment of gastric cancer based on the theory of complex disease

Stomach cancer belongs to the categories of "regurgitation", "volvulus" and "accumulation" in Chinese medicine. Obstruction of gastric channels and lack of yang qi is the main pathogenesis of gastric cancer. Many pathogenic factors, such as feeling external evils, dietary irregularities, and emotional disorders, can lead to abnormal transport and transformation of the spleen and stomach, and the formation of pathological products such as qi stagnation, phlegm-dampness, and blood stasis, etc. When the gastric collaterals are blocked for a long time, yang qi is not reached, and the positive qi is incapable of dispelling evils, and the pathological products of qi stagnation, blood stasis and stagnation are "lodged in the past and become accumulations", thus leading to the formation of gastric cancer ^[34]. The basic pathological feature of the disease is "stagna

tion and obstruction", therefore, the treatment of the disease should focus on dredging^[35]. Gastric cancer and other malignant tumours belong to collateral disease, and the gastric organs are smooth with circulation and descending, therefore, in the diagnosis and treatment of gastric cancer in TCM, collaterals should be opened and closed as the main method of treatment, and dredging the meridians and channels of human body and inhibiting the disordered proliferation of collaterals and channels of disease should be regarded as one of the important diagnostic and therapeutic principles. Based on the above understanding of the pathogenesis of gastric cancer, Prof Li Ping pointed out that the TCM method of collateral circulation should be used as a synergistic therapy for the anti-angiogenic treatment of advanced gastric cancer, and he believed that advanced gastric cancer should be subdivided into three stages.

1. Initially moving Qi, activating blood circulation and opening up the channels.

Traditional Chinese medicine (TCM) believes that the onset of stomach cancer is related to factors such as uncontrolled diet and emotional disorders. Unhealthy dietary habits, such as long-term consumption of spicy, greasy and other stimulating foods, or consumption of unclean food, long-term overeating, may lead to stagnation of stomach qi, blood stasis and coagulation, which may damage the function of the stomach and spleen. Chinese medicine believes that the spleen and stomach are the foundation of the later life, and the spleen and stomach are not normal in their transportation, and it is difficult for the infusion of fluids to generate phlegm and dampness, which in turn obstructs the collaterals, and triggers the occurrence of gastric cancer. In addition, as liver is the main regulator of excretion, factors such as emotional disorders, depression and long-term mental stress may lead to stagnation of qi, affecting the normal operation of qi and blood in internal organs and meridians, thus inducing gastric cancer. Professor Li Ping believes that qi is the foundation of human life activities, and the smooth running of qi is closely related to human health. By regulating the operation of qi, the self-healing ability of the body can be promoted.

ted. In the treatment of stomach cancer, the main principle should be to move qi, activate blood and pass the collaterals, which can regulate the qi of the stomach, promote the metabolism of the stomach and enhance the body's ability to fight against tumours. At this stage, some Chinese medicines with pungent aroma to promote circulation can be used, such as ChuanXiong^[36], Chenpi, Xiangsui, Clove, Houpu and Cyclamen, etc. Pungent can move qi, in order to promote qi and blood circulation, regulate local microcirculation, increase the nutrient supply to tissues and metabolism and excretion, so as to inhibit the development of tumour.

2. Invigorating blood, dispelling dampness and clearing collaterals in the middle and late stages of the disease

In the middle and late stages of gastric cancer, endogenous growth caused by long-term internalisation of dampness and toxicity, uncontrolled diet and dysfunction of spleen and stomach may be further aggravated in the middle and late stages. According to Prof. Li Ping, dampness and turbidity block qi and blood, and qi and blood are not smooth, further forming the pathological state of qi stagnation and blood stasis, in which case, blood stasis accumulates in local tissues, obstructing normal qi and blood circulation, making tumour growth intensify. At this time, the focus of treatment is to activate blood circulation, dispel dampness and clear up the stasis of blood and dampness in the body, in addition to continuing to activate blood circulation, to prevent stasis of blood and dampness from stagnating and aggravating the condition. For treatment, some traditional Chinese medicines are used, such as peach kernel, angelica sinensis, danshen, wulingzhi, Houpu, Cangzhu, etc., to promote excretion of stasis blood and recovery of local microcirculation, and to alleviate compression and destruction of surrounding tissues by the tumour. In addition, for middle and late stage gastric cancer patients with qi stagnation and blood stasis blocking the collaterals, and the positive qi is not yet deficient, Prof. Li Ping also emphasised the importance of applying insect-based traditional Chinese medicines. Insect-based traditional Chinese medicine has the function of promoting qi, bre

aking blood stasis, detoxifying and dispersing knots, which is quite suitable for the core pathogenesis of gastric cancer in traditional Chinese medicine. Insect-based Chinese medicines commonly used in the treatment of mid-stage gastric cancer include centipede, scorpion, tianlong, dilong, earthworm and so on.

3. Terminal stage benefiting Qi, tonifying blood and clearing collaterals

Rapid proliferation and infiltration of cancer cells in the terminal stage of gastric cancer cause the body to consume a large amount of nutrients, thus resulting in a state of deficiency of qi and blood. Secondly, the development of gastric cancer may affect the normal function of stomach. Spleen is responsible for transporting and transforming water, grain and essence, and stomach is responsible for accepting and puttingrefying, and the dysfunction of spleen and stomach leads to the inability to fully digest and absorb food, reduces the utilisation of nutrients, and aggravates the deficiency of qi and blood. At this time, the lack of qi and blood causes the stomach to lose its glory, the local qi is more stagnant, and the blood stasis is more stagnant. At this time, the focus of treatment is to benefit the qi, tonify the blood and open the channels, and in addition to continuing to eliminate stasis, it is also necessary to replenish the body's positive qi and strengthen the body's resistance, so as to improve the therapeutic effect and quality of life. The method of replenishing qi and promoting blood circulation can adopt some Chinese medicines that replenish qi, nourish blood and promote circulation, such as *Codonopsis pilosulae*, *Poria*, *Atractylodes macrocephala*, *Angelica sinensis*, *Rhizoma Ligustici Chuanxiong*, *Radix Rehmanniae Praeparata*, *Paeonia lactiflora* and so on^[37-40], in order to promote the recovery of energy metabolism and immune function of the body, so as to increase the body's resistance to the tumour and the ability to heal itself.

4. Case examples

Hu XX, male, 73 years old, hospitalisation number: 17134933, married, address: new street of Boutasi, Shiqiao town, Jinan district, Lu'an city. Present medical history: the patient underwent radical total gastrectomy and oesophagojejunal Roux-en-Y anastomosis in the Department of Gastrointestinal Surgery of our hospital on

25.10.2018. Post-operative pathology: total stomach: infiltrating poorly differentiated adenocarcinoma of ulcerated side of cardia minor curvature, the size of the mass was 6.0cm×5.5cm×0.8cm, invading the whole layer, nerve invasion (+), cancer embolism in the chorda tympani (+). The anastomosis was sent to 2 circles and the upper and lower margins of the anastomosis were not involved in the cancer. Thirteen lymph nodes were detected in the lesser curvature, of which 7 showed cancer metastasis; 3 lymph nodes were detected in the greater curvature, none of which showed cancer metastasis. There was one lymph node in group 8, with no cancer metastasis. Postoperative staging: stage IIIB (T3N3aM0). After surgery, the patient recovered well, and was treated with 4 cycles of chemotherapy with the regimen of "paclitaxel liposome 210mg d1 + oxaliplatin 150mg d1 + tiglio 40mg bid d1-14" in the Department of Medical Oncology of the hospital from November 2018 to February 2019, and was treated with the regimen of "paclitaxel liposome 210mg d1 + oxaliplatin 150mg d1 + tiglio 40mg bid d1-14" in the Department of Medical Oncology of the hospital from 2019.3-2019.4 changed to "oxaliplatin 200mg d1+tiglio 40mg bid d1-14" regimen chemotherapy for 2 cycles. Professor Li Ping believes that the patient's surgical pathological stage is late, although the patient has undergone surgery and chemotherapy, the tumour is not easy to be removed and remains in the body, which secretly depletes the positive qi and leads to deficiency of qi and yin, and is prone to recurrence and metastasis. Therefore, the patient should be treated with tigafur+Chinese traditional medicine consolidation therapy, in order to reduce the patient's recurrence and metastasis risk, and the Chinese traditional medicine should be "Benefiting qi, nourishing yin, and removing toxins formula". Specific prescription: raw Astragalus 40g, Atractylodes macrocephala 10g, Poria 10g, Citrus aurantium dulcis 10g, Codonopsis pilosula 10g, Radix et Rhizoma Ginger 10g, Pericarpium Citri Reticulatae 10g, Salvia miltiorrhiza 10g, Ophiopogon flexuosus 10g, Scutellaria baicalensis 10g, Centipede 1, Soft-shelled turtle shell 10g, Fructus Lycopodium Chinense 20g, Radix et Rhizoma Glycyrrhizae 5g. Take with decoction of water, 1 dose daily, divided in the morning and evening.

After that, the patient was regularly rechecked, and on 2020.8.26, the patient was

rechecked and found that postoperative gastric cancer was accompanied by liver metastasis. 2020.8.27-2021.8.16, the patient was treated with "Karelizumab 200mg ivgtt q3w+Apatinib mesylate 0.25 qd+Tiglio capsule 40 mg bid d1-d14", combined with traditional Chinese medicine "Wen Yang Tongluo Detoxification Formula". "The treatment is combined with the traditional Chinese medicine "Warming Yang and Opening Collaterals and Detoxification Formula", the specific prescription: Epimedium 30g, Folium 10g, Stir-fried Atractylodis Macrocephalae 30g, Radix Codonopsis Pilosulae 20g, Stir-fried Hovenia Citri Reticulatae 20g, Folium Neijin 20g, Scutellaria Baicalensis 10g, Semenemba Japonica 10g, Glycyrrhiza Glabra 5g, boiled water to be taken, 1 dose daily, morning and evening, divided into two doses. Take 1 dose daily in the morning and 1 dose in the evening. The condition was found to be stable after several reviews, and this formula was added or subtracted according to the symptoms, and the patient was followed up until 2022.6.10.

III. Conclusion

Malignant tumour is a local manifestation of systemic disease, so is gastric cancer, treatment of gastric cancer should have a general view, adopt integrated treatment, comprehensive and three-dimensional intervention. It is unrealistic to rely on Chinese medicine or modern medicine alone to solve stomach cancer completely, so we advocate synergistic treatment of Chinese and western medicine. Therefore, we advocate synergistic treatment of Chinese and Western medicines. Synergistic treatment of Chinese and Western medicines is not a simple combination of traditional Chinese medicine and Western medicine, but the first step to be taken is to understand the strengths and weaknesses of Chinese medicine and modern medicine, and to give full play to the strengths and make up for the weaknesses. Gastric cancer is a common and highly malignant digestive tract tumour with limited effect and poor prognosis of traditional treatment. The combination of anti-angiogenic therapy with the method of circulation circulation proposed by Professor Li Ping provides a new choice for gastric cancer patients, and Professor Li Ping's treatment concept reflects the advantages of synergistic treatment of advanced gastric cancer with Chinese and Western medicines. Tongluo method is a traditional therapy in Chinese medicine, which emphasises on

regulating the meridian system of human body, promoting the smooth flow of qi and blood, and adjusting the balance of yin and yang of human body, so as to achieve the purpose of treating diseases. And anti-angiogenesis therapy is an important technique in modern medicine, which aims to inhibit tumour growth by inhibiting the formation of tumour blood vessels. By combining these two therapies and giving full play to their respective advantages, Professor Li Ping can not only effectively control the growth of the tumour, but also improve the quality of life and prolong the survival time of the patients, which provides a reliable reference for the formulation of collaborative treatment plans of Chinese and Western medicine for patients with advanced gastric cancer.

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