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Research progress of integrated traditional Chinese and western medicine in the treatment of advanced gastric cancer

Ye HN *et al.* Research progress of advanced gastric cancer

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Abstract

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Gastric cancer (GC) is a malignant tumor originating from the gastric epithelium, and its incidence and mortality rates rank third among all malignant tumors worldwide. It is also one of the most common cancers in China and is treated predominantly by Western medicine in clinical practice. However, with the advancements in medical technology and informatics, the values of traditional Chinese medicine (TCM) in preventing and treating GC and improving prognosis have increasingly been recognized. According to TCM, clinical manifestations of GC can be divided into Yege (dysphagia), regurgitation, stomach pain, and Zhengxia (abdominal mass). Due to the unbalanced distribution of health care resources in China, most GC patients already have progressive or advanced-stage disease at the first diagnosis. As a result, most GC patients have poor physical function, and surgery or chemotherapy alone will aggravate the impairment to the immune function and seriously affect the quality of life. In contrast, TCM therapies have shown promising efficacy in the management of these patients. Here we review the role of the integrated TCM and Western medicine in treating advanced GC.

Key Words: Integrated traditional Chinese medicine and Western medicine; Advanced gastric cancer; Research advances

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Core Tip: The incidence and mortality rates of gastric cancer (GC) rank third among all malignant tumors worldwide. In recent years, traditional Chinese medicine (TCM) has been increasingly applied in the clinical treatment of GC. The integrated TCM and the modern medicine can, to a certain extent, improve the therapeutic effects and reduce the adverse reactions caused by the modern medication in cancer treatment.

INTRODUCTION

According to the global cancer burden data released by the International Agency for Research on Cancer, there will be 19.29 million new cancer cases and about 9.96 million deaths from cancer worldwide in 2020, including new cases (about 1.09 million) and deaths (about 770000) from gastric cancer; there will be about 4.57 million new cancer cases and 3 million deaths in China, including new cases (about 480000) and deaths (about 370000) from gastric cancer. (about 370000 cases)^[1]. Advanced gastric cancer is a common clinical malignancy of the digestive system, with up to 90% of patients already having advanced gastric cancer at the time of initial consultation, and the 5-year survival rate for patients with distant metastases is less than 10%^[2,3]. At present, Western medicine is frequently used for clinical treatment of advanced GC, in which, however, radiotherapy and/or chemotherapy are predominantly selected, and surgery is performed in selected patients, with unsatisfactory efficacy in general. As a result, more tumor patients now choose integrated traditional Chinese and Western medicine (ITCWM) for the treatment of their diseases with the wider use of traditional Chinese

medicine (TCM) in clinical practice. Here we review the role of the ITCWM in treating advanced GC.

PATHOGENESIS OF ADVANCED GC

According to the TCM principle, "Where evils converge, the qi must be deficient". Thus, the occurrence of tumors is the result of the decline of bodily functions. Phlegm-dampness, qi stagnation, blood stasis, and toxins due to spleen deficiency are the major causes of GC^[5,6]. Regarding phlegm-dampness, Wei *et al*^[7] proposed a theoretical assumption named the "Mushroom-Tumor-Phlegm microenvironment Theory", which explains the possibility of tumor recurrence after GC surgery due to the existence of a phlegm microenvironment in the remnant stomach. Cao *et al*^[8] also pointed out that the internal retention of phlegm-turbidity is the pathogenesis of GC. From the perspective of Western medicine, the occurrence and development of GC are attributed to a variety of factors, including heredity, environment, and dietary habits such as high-salt diet, *Helicobacter pylori* infection, smoking, and alcoholism^[9,10].

TCM THERAPIES

Modern medicine has developed rapidly, and most patients choose to eliminate their gastrointestinal tumors by chemotherapy, surgery, and other methods. However, the risk of recurrence and metastasis still exists due to the persistence of mutagenic (carcinogenic) factors in the body and tumor immune escape^[11]. The clinical application of TCM drugs, especially spleen-invigorating drugs, can block the effects of carcinogens on normal cells, kill cells with high metastatic potential, inhibit tumor metastasis, and thus exert a good inhibitory effect on tumors^[12]. Qiu Jiaxin, a well-known TCM oncologist in China, proposed that spleen-invigorating drug-based TCM prescriptions are superior to chemotherapy alone in the treatment of advanced GC. He found in a clinical trial that the TCM-treated group had improved immune markers (*e.g.*, E-RFC), hemoglobin level, and red blood cell count as well as decreased erythrocyte sedimentation rate and α 1-AG level; and TCM treatment enhanced the immunity and

improved the immune status^[13]. Zhao *et al*^[14] found that the spleen-invigorating Chinese herbal formula Weichangan (WCA) compound had an inhibitory effect on GC cell line SGC-7901 *in vivo*. WCA can induce apoptosis of GC cells and inhibit the proliferation of GC cells, thus suppressing the growth of SGC-7901 tumor xenografts in nude mice^[9]. In addition, Yang *et al*^[15] also conducted a research on the TCM classic formula Sijunzi Decoction, and found that this decoction could induce tumor cell apoptosis. Wang *et al*^[16] demonstrated that the TCM formula Fuzheng Kangai Granule could inhibit GC cells, especially for MKN-45 cells. Experiments have shown that the drug has a more significant effect on poorly-differentiated MKN-45 cancer cells than on well-differentiated MKN-28 cells and moderately-differentiated SGC-7901 GC cells. The drug can cause structural changes in cancer cells.

WESTERN MEDICINE THERAPIES

Chemotherapy is a commonly used clinical treatment for GC. Studies have shown that, compared with GC patients who do not receive any treatment, chemotherapy could prolong the median survival by 7-8 mo in patients treated with chemotherapy^[17]. Although patient survival is prolonged, the quality of life is decreased due to the poor immune function of the patients. In recent years, more targeted drugs (*e.g.*, apatinib and ramucirumab) have also been used in clinical practice, all of which have the VEGFR-2 inhibiting effect. Among them, apatinib is the most widely used, but with obvious adverse reactions such as fatigue, diarrhea, hypertension, and proteinuria^[18]. Surgery is also a commonly used treatment for GC. In developed countries, laparoscopic surgery is commonly used due to the high proportion of early-stage GC. In China, however, most GC cases are diagnosed too late, resulting in a high incidence of advanced GC. Therefore, laparoscopic surgery for advanced GC has become a research hotspot in China in recent years^[19,20]. During the pandemic of COVID-19, digestive endoscopy was proved to be a safe technique for the diagnosis and treatment of gastrointestinal diseases^[21]. However, the operation requires high physical performance of the patients, and most patients will suffer from spleen-stomach weakness after surgery. Therefore, it

has been proposed by Chinese authors that ITCWM can be used to treat advanced GC as it can achieve good anti-cancer effects while maintaining and improving the overall physical function^[22].

ITCWM

Some scholars emphasized two aspects in the treatment of advanced GC: (1) using Western medicine to eliminate cancer lesions; and (2) using TCM to enhance the patient's immunity^[23,24], so as to achieve the purpose of improving the quality of life. Wei *et al*^[25] developed the prescription Jinlongshe Oral Liquid and used it in combination with chemotherapy to treat GC patients; they concluded that, compared with chemotherapy alone, TCM plus chemotherapy showed more prominent efficacy in treating advanced GC. GC-related complications (*e.g.*, gastrointestinal bleeding) can also be managed by ITCWM, with a high success rate^[26]. Gastrointestinal complications such as bowel obstruction are common in patients with advanced GC. According to the TCM concept of “treatment based on syndrome differentiation”, the route of drug administration may be changed: in addition to oral administration, the drugs may be also administered by instillation through anal canal, so as to promote the intestinal mucosal absorption of the drugs and increase local drug concentration. As a result, the intestinal obstruction can be effectively relieved^[27]. The application of integrated traditional Chinese and western medicine in the treatment of advanced gastric cancer is divided into four aspects (Figure 1).

TCM-assisted surgery

While surgery is the mainstay of treatment for most GCs, most patients will suffer from spleen and stomach weakness and insufficient qi and blood after an invasive surgery. TCM therapies can strengthen the spleen and benefit qi, improve these symptoms, and reduce postoperative adverse reactions. Cai *et al* divided 59 patients into observation group and control group. The control group received only the conventional nutrition support after surgery, and the observation group received nutrition support added with

Sijunzi Decoction, which is composed of Tangshen, Atractylodes, Poria, and Licorice. It was found that the levels of T cells and immunoglobulin G (IgG) in the Sijunzi Decoction group were significantly increased on the 10th postoperative day ($P < 0.05$). Thus, Sijunzi Decoction, a TCM prescription for strengthening the spleen and nourishing qi, can correct malnutrition in GC patients after surgery and improve humoral and cellular immune functions^[28]. Previously, Yu *et al*^[29] and Peng *et al*^[30] compared the plasma total protein, albumin, and gastrointestinal function recovery among GC patients receiving different postoperative nutritional support and reached a similar conclusion that the use of a TCM prescription (Qihuang No. 1) in the early postoperative period could promote gastrointestinal motility, stimulate the recovery of digestive function, and improve the body's cellular and immune functions, thereby exerting an inhibitory effect on tumors. In 2020, Zhang *et al*^[31] used Huangqi Jianzhong Decoction in postoperative patients and compared its efficacy with that by conventional treatment in terms of gastrointestinal function recovery time, total TCM symptom score, patient albumin level, and health and economic indicators. The differences in these four indicators were all statistically significant. The Huangqi Jianzhong Decoction group recovered faster in gastrointestinal function, had a higher total TCM symptom score and a higher level of albumin on the fifth postoperative day, and it was more economical with lower hospitalization expenses^[31].

TCM-assisted chemotherapy

For modern medicine, chemotherapy is a major treatment for most cancers, especially GC. From the perspective of TCM, however, chemotherapy for cancer is a method of "fighting poison with poison", which produces major toxicities, leading to qi and blood deficiencies in spleen and stomach and even affecting liver, kidney, and bone marrow. Therefore, many researchers have tried to integrate TCM therapies with chemotherapy as TCM can invigorate the blood and qi, strengthen the spleen and stomach, and nourish the liver and kidney, thus alleviating the toxicities and side effects of chemotherapy^[32]. The selection of treatment methods for patients with advanced gastric

cancer must be based on the patient's physical condition, disease severity, and disease stage.¹⁵ The combination of traditional Chinese and Western medicine adds Chinese medicine for boosting immunity to the chemotherapy regimen, which can improve the patient's immune function, inhibit cancer cells, and enhance the anti-cancer ability, and the curative effect is more significant^[33]. Li *et al*^[34] analyzed the data of 205 patients who were treated during the period from 2001 to 2018. Compared with the control group (use of conventional chemotherapy drugs), the TCM group (adding heterophyly falsestarwort root, fried *Atractylodes*, *Poria*, and immature tangerine peel based on the drugs used in the control group) had significantly longer median survival (21.271 mo *vs* 10.849 mo, $P = 0.001$) without adverse reactions related to TCM treatment. Thus, the safety and tolerance of the TCM therapy were good. The authors concluded that spleen-strengthening TCM combined with oxaliplatin and fluorouracil could improve the long-term survival in patients with advanced GC. Pan *et al*^[35] also demonstrated that adding TCM prescriptions during chemotherapy significantly improved the overall survival and quality of life in GC patients.⁶ Li *et al*^[36] believe that the main purpose of chemotherapy for advanced gastric cancer is to relieve symptoms, but due to many adverse reactions, and traditional Chinese medicine can alleviate these negative symptoms, it is necessary to treat advanced gastric cancer with integrated traditional Chinese and Western medicine.¹⁴ In the process of treatment, the application of traditional Chinese medicine should be as early as possible, and increasing "stomach qi" is the key to anti-cancer, because traditional medicine believes that "with a share of stomach qi, there is a share of vitality". Wang *et al*^[37] treated the syndrome of qi and blood deficiency in elderly patients with advanced GC using Biejia Huajian Decoction combined with Tegafur (S-1). Compared with the control group (S-1 capsules alone), the combination group had significantly better efficacy. For patients with advanced GC, the combined therapy achieved a good short-term therapeutic effect, delayed disease progression, and improved the quality of life. In addition, it had a protective effect on leukocytes and gastrointestinal tract in patients with qi-blood deficiency caused by the advanced GC, thus reducing the treatment-related toxicities. The combinations of

surgery, chemotherapy, and TCM therapy may also be valuable. Postoperative patients have weakened disease resistance, which will be further decreased after the use of postoperative chemotherapy. The TCM therapies for supporting the vital qi and eliminating evils, when used in combination with chemotherapy, can significantly improve the body's immunity and reduce the chemotherapy-related toxicities while effectively fighting against tumors^[38].

TCM-assisted interventional therapy

Due to the scarcity of medical resources in China, most of the GC patients are diagnosed in the advanced stages, and surgery can cause severe damage to the patients. In recent years, with the advances in medical technology, interventional therapy is increasingly accepted by physicians and patients as a less invasive technique with fewer side effects^[39]. The role of TCM in interventional therapy has been explored. In 2010, Xu *et al*^[40] confirmed that, compared with interventional chemotherapy (oxaliplatin, 5-fluorouracil, and epirubicin) alone, the supplementation with Shenyi Jianzhong Decoction (which is composed of Tangshen, coix seed, Atractylodes, Zedoray rhizome, cassia twig, debark peony root, Salvia chinensia Benth, garden balsam seed, and Radix Glycyrrhizae) significantly improved the Karnofsky performance score and quality of life and relieved abdominal distension, anorexia, fatigue, stomach pain, and other symptoms ($P < 0.05$); in addition, the combination reduced toxic and side effects and prevented postoperative tumor recurrence. During the hepatic artery interventional therapy for liver metastases from GC, the combination with Sijunzi Decoction could improve immune function, promote gastrointestinal motility, reduce adverse reactions, and improve the quality of life^[41].

TCM-assisted molecularly-targeted therapies

Molecularly-targeted therapy (MTT) has developed rapidly in recent years and has become an important treatment option for many tumors. By binding to the specific targets of tumor cells, MTT drugs can control apoptosis of tumor cells^[42]. Apatinib is a

commonly used MTT drug for the treatment of GC; however, it has many adverse effects such as hypertension, proteinuria, skin damage, blood toxicity, and gastrointestinal reactions. Tiaowei Hexue Decoction could enhance the anti-tumor effect of apatinib and meanwhile alleviate the above-mentioned adverse reactions^[43], highlighting the advantage of TCM therapies in removing toxicities. In addition, apatinib can also be combined with Chaihu Guizhi Ganjiang Decoction in the treatment of advanced GC. Compared with apatinib monotherapy, the combined treatments significantly improved the clinical symptoms and reduced the incidence of adverse reactions, thus improving the physical status and quality of life of GC patients^[44]. In 2014, Wilke *et al*^[45] found that ramucirumab combined with paclitaxel prolonged survival in patients with advanced GC, providing strong evidence for the combination of TCM therapies with targeted therapy.

CONCLUSION

The past decades have witnessed major progress in the treatment of cancers using surgery, chemotherapy, radiotherapy, MTT, immunotherapy, and other methods. However, each single therapy has its limitations and is associated with many adverse reactions. In recent years, with the tremendous efforts in the popularization of TCM in China, TCM has increasingly been applied in clinical settings. The combinations of TCM therapies with the modern treatments can, to a certain extent, improve the therapeutic effects and reduce the adverse reactions caused by modern medical technology. However, there is still a lack of understanding of TCM, and the value of ITCWM in the treatment of GC needs to be further explored in large-scale clinical trials.

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