

Traditional Chinese Medicine - Old Formulas Offer New Hope to Treat Advanced Gastric Cancer

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1. Abstract

Gastric Cancer (GC) is one of the most common malignancies worldwide. The incidence of GC is particularly high in most countries in East Asia, including China, where a large proportion of GC cases are diagnosed with late-stage or Advanced Gastric Cancer (AGC). Among the possibilities in treating AGC, chemotherapy has been demonstrated to have high efficacy. However, serious side effects or toxicities occur in patients who receive chemotherapy. In recent years, it has been increasingly recognized that patients with AGC can benefit from Traditional Chinese Medicines (TCMs). In fact, TCMs have emerged in clinical studies in the treatment of GC. To date, the review on this specific topic has been limited. In the present review, the investigators synthesized the existing studies of TCMs, either alone or in combination with chemotherapy for GC, with focus on AGC. Clinical studies have shown that TCMs exert a synergistic effect on chemotherapy, leading to the enhancement of efficacy and reduction in toxicities. Previous studies in cell cultures and animal models have also investigated the potential mechanisms underlying the therapeutic effects of TCMs. Hence, these new findings on TCMs, as the old formula, may offer new hope to treat patients with AGC.

2. Introduction

Gastric Cancer (GC) is among the most common malignancies, and

ranks as the third cause of cancer-related death, globally. The incidence of GC is particularly high in East Asian countries, such as Japan, Korea and China. It has been noted that newly diagnosed GC cases have increasing [1].

The present treatments for GC include surgery, chemoradiotherapy and palliative care, in which surgery combined with chemotherapy is preferred for the treatment of GC. Notably, in approximately 50% of GC patients with atypical early symptoms, the cancer has already progressed to middle- and late-stage cancer, or Advanced Gastric Cancer (AGC) at the time of diagnosis [2]. This is the main reason why the 5-year survival rate after surgery is considerably low, with the effective rate of chemotherapy only ranging within 40%-50% [3]. Some non-surgical therapies, including chemotherapy, radiotherapy, targeted therapy and immunotherapy, have become available for GC patients. However, due to the numerous serious side effects caused by these non-surgical treatments, many patients are unwilling or refuse to accept such treatments [4]. In addition, when GC progresses to late-stage or advanced cancer, in which metastases have already occurred, patients experience severe weight loss, gradually appear skinny, and eventually develop cachexia, which is a clinical condition with extreme weight loss, emaciation, anorexia, fatigue, metabolic disorders, lipolysis, muscle wasting and hypoproteinemia [5]. More than 50% of patients with malignant tumors develop advanced ca-

cachexia [6], and AGC-associated cachexia would severely reduce the physical performance, sensitivity and tolerance to chemoradiotherapy, leading to the susceptibility of patients to infection and other adverse reactions. This has also led to difficulty in treatment, reduced life quality, and shortened survival of patients.

Traditional Chinese Medicines (TCMs) have long been used to treat various diseases, including GC, in China, in accordance with one of the most important classics of Chinese medicine named, ‘Yellow Emperor’s Classic of Internal Medicine’. At present, TCMs have been widely used by clinicians to treat GC in China. Recently, extensive studies have shown that TCMs combined with chemotherapy significantly reduce the risk of developing adverse reactions to chemotherapy, promote immune function, and improve the quality of life of cancer patients [7, 8]. Some TCMs have been shown to exert a synergistic effect on chemotherapy, leading to both the prolongation of patient survival, and the reduction of tumor recurrence and metastasis [9, 10]. Many studies in cell cultures and experimental animals have also shown that TCMs directly inhibit tumor cell growth and proliferation, and directly or indirectly mediate the autophagy and apoptosis [11, 12, 13]. These findings gained in basic research support the use of TCM formulations from the ancient wisdom of Chinese clinicians in the treatment of GC patients, especially for patients diagnosed with late-stage GC or AGC.

In the present review, the investigators synthesized the studies of some TCM formulations, either alone or in combination with chemotherapy for GC, with focus on AGC.

3. Traditional Chinese Medicines for Gastric Cancer

In accordance with the principles of TCMs in the treatment of diseases, GC falls in the categories of ‘fu liang’, ‘ji ju’, ‘ye ge’, and ‘wei fan’ [14]. GC was first recorded in ancient Chinese medicine in the text of an ancient book, the ‘Synopsis of the Golden Chamber’: ‘wei fan’ refers to ‘Anorexia, obstruction of the chest and throat’, ‘Evening vomiting of food eaten in the morning, and morning vomiting of food eaten in the evening, combined with dyspepsia, is referred to as fan wei’ [15]. In centuries of clinical practice with TCMs, Chinese clinicians and practitioners have gained rich experience in the diagnosis and treatment of GC with TCMs, such as Yi Zong Bi Du·Ji Ju, stating that ‘A tumor that accumulates lacks healthy qi, and the evil qi is occupied’ [16]. He proposed that GC was mainly caused by the deficiency that lays the foundation for modern Chinese medicine in the treatment of GC.

In TCM, it has been considered that GC is caused by internal and external factors. The internal factors mainly include spleen and stomach weakness, phlegm-dampness endogenesis, liver qi stagnation, qi obstruction, and weakness of blood circulation, which cause qi stagnation, phlegm coagulation and blood stasis. The external factors consist of unregulated diet, penchants for spicy foods, tobacco and alcohol, emotional imbalance, and suffering from external evil. Hence, GC arises as a result of the accumulation of these internal

and external factors [17]. At the early stages of the disease, the patient would have an intemperate diet, with liver qi discomfort, and liver and stomach disharmony. If the qi and blood deficiency persists for a long period of time, patients with intermediate and advanced GC would begin to become weak [18]. Hence, the continuous use of anticancer drugs can further make these patients weaker, and become skinny and dysfunctional, eventually leading to death. However, the inappropriate use of tonifying TCM can aggravate the symptoms of anorexia, abdominal distension, hiccups, etc. Therefore, the treatment should be flexible, based on the condition of each patient, in order to reinforce the healthy qi and eliminate the evil qi, according to the growth and decline of the healthy qi and evil qi, respectively [19].

At present, the syndrome differentiation of TCM aims to divide patients into different types, mainly on the basis of the two diagnostic methods. One method is based on the ‘Guidelines for traditional Chinese medicine Diagnosis and Treatment of Malignant Tumors’, which can be classified, as follows: liver and stomach disharmony, cold deficiency of the spleen and stomach, intermingled phlegm and blood stasis, stomach heat injury yin, and qi and blood deficiency [20]. The other method is based on combining the syndrome differentiation of AGC by various clinicians, which can be classified into six common syndrome types: liver and stomach disharmony, cold deficiency of the spleen and stomach, phlegm-toxin-stasis, phlegm-dampness coagulation, qi and blood deficiency, and gastric heat injury Yin [21].

Clinical studies have been performed on the basis of the principle of combining syndrome differentiation with disease differentiation, and the theory of spleen and stomach homology, using the method of heat-clearing and detoxification [22], strengthening the healthy-qi and eliminating the evil-qi [23], promoting blood circulation and removing blood stasis [24], and dispelling dampness and resolving phlegm [25], as well as regulating the spleen and stomach to treat AGC [26]. TCMs have the following unique beneficial effects in the treatment of GC: enhancing effectiveness and alleviating chemotherapy-induced adverse effects or toxicities [27], tonifying the deficiency, and improving the survival of patients with AGC [28].

4. Efficacy and Safety of Traditional Chinese Medicines for Gastric Cancer

TCMs alone or in combination with chemotherapy on the whole body and functional recovery have achieved good clinical efficacy in various malignant tumors, including GC, in China [29]. In order to assess the efficacy and safety of TCMs for GC, a literature research and review of publications during the period that spanned from January 2017 to January 2021 was performed in the following databases: PubMed, Wanfang Data, Web of Science, Chinese Science and Technology Journals (CQVIP), China Academic Journals (CNKI), and Chinese Biomedical Literature database. The keywords used for the literature search were, as follows: “Transitional Chinese

medicine OR Chinese herb OR Chinese medicine” and “gastric cancer OR stomach cancer”. The quantitative 5-point Jadad scale was used to evaluate the quality of the included trials, and clinical trials with a jadad scale of 2 or greater were considered. As a result, a total of 433 articles were obtained from these databases. After excluding 143 duplications, 201 articles that were irrelevant to chemotherapy

or TCM, 51 non-randomized controlled trial articles, and 13 articles with unspecified intervention measures and research objects, a total of 25 studies were identified and further reviewed [30-54]. The major findings of these studies are summarized in Table 1. Notably, all 25 studies were conducted in China, including 20 oral and five injectable TCMs.

Table 1: Summary of the included studies on traditional Chinese medicines for gastric cancer

References	Sample size (T/C n)	Study arm	Drug delivery routes	Jadad scale
Jie Shao et al. ^[30]	64(32/32)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Oral	3
Wanzhen Chen et al. ^[31]	68(34/34)	(DTX+DDP+TCM) vs. (DTX+DDP)	Oral	5
Weina Qian et al. ^[32]	92(46/46)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Oral	3
Jing Wang et al. ^[33]	42(21/21)	(Chemotherapy plus TCM) vs. (Chemotherapy)	Oral	3
Jianfeng Quan et al. ^[34]	60(30/30)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Oral	2
Tong Yu et al. ^[35]	40(20/20)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Oral	2
Chaoyan Li et al. ^[36]	205(87/118)	(Ox+5-Fu or xeloda or S-1 plus TCM) vs. (Ox+5-Fu or xeloda or S-1)	Oral	2
Qi Ma et al. ^[37]	80(40/40)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Oral	2
Juan Wu et al. ^[38]	90(51/39)	(Chemotherapy plus TCM) vs. (Chemotherapy)	Oral	2
Na An et al. ^[39]	180(90/90)	(Ox+ xeloda plus TCM) vs. (Ox+ xeloda)	Oral	3
Yang Li et al. ^[40]	80(40/40)	(Ox+S-1 plus TCM) vs. (Ox+S-1)	Oral	3
Qiong Lu et al. ^[41]	64(32/32)	(Ox+ xeloda plus TCM) vs. (Ox+ xeloda)	Oral	4
Yaouxuan Li et al. ^[42]	60(30/30)	(Ox+S-1 plus TCM) vs. (Ox+S-1)	Oral	2
Ling Qin et al. ^[43]	50(25/25)	(Ox+ xeloda plus TCM) vs. (Ox+ xeloda)	Oral	3
Xiangyin Li et al. ^[44]	120(60/60)	(EPI+5-Fu+DDP plus TCM) vs. (EPI+5-Fu+DDP)	Oral	3
Lei Zhou et al. ^[45]	80(40/40)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Oral	4
Yong Yang et al. ^[46]	80(40/40)	(Ox+ xeloda plus TCM) vs. (Ox+ xeloda)	Oral	3
Baoxinsi Li et al. ^[47]	90(45/45)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Injection	3
Dandan Wang et al. ^[48]	100(50/50)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Oral	4
Rui Wang et al. ^[49]	78(39/39)	(Ox+S-1 plus TCM) vs. (Ox+S-1)	Injection	4
Qingqing Lv et al. ^[50]	64(32/32)	(Ox+S-1 plus TCM) vs. (Ox+S-1)	Injection	2
Lijuan Zhao et al. ^[51]	68(34/34)	(EPI+Ox+xeloda plus TCM) vs. (EPI+Ox+xeloda)	Injection	4
Pei Hu et al. ^[52]	88(44/44)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Injection	3
Ruilin Li et al. ^[53]	60(30/30)	(Ox+CF+5-Fu plus TCM) vs. (Ox+CF+5-Fu)	Oral	5
Xiaoting Pan et al. ^[54]	210(140/70)		Oral	5

Oral route of administration of TCMs: The main principle of TCM treatment for a disease is to modulate the Qi and blood, and balance the Yin and Yang. In the Qi-Blood theory, the purpose of the treatment is to ‘relieve the Qi and blood, and let it become smooth and peaceful’. The Yin and Yang theory originated from Taoism, in which the Yin and Yang should stay in balance, because an imbalance may increase the risk of developing diseases. It has been noted that GC patients treated with chemotherapy are susceptible to various degrees of systemic symptoms, liver and kidney toxicities, and gastrointestinal symptoms. Since cancer can weaken the immune system, patients with cancer generally have a weak immune function, and even have intolerance to chemotherapy. Furthermore, some TCMs, as supporting treatments, have been shown to improve the therapeutic effect, and reduce chemotherapy-induced side effects or toxicities. A number of studies have investigated TCM in combination with chemotherapy in the treatment of GC, and reported the significant clinical effects and safety, including the effective promotion of immune function and physical status, and the improvement in living quality [30, 31, 46, 48]. In clinical studies, it has been shown that TCM combined with chemotherapy for AGC has a good regulatory effect on the levels of serum tumor markers, and improves the prognosis of GC [30, 43, 44, 48, 53, 54]. Qian et al., reported that TCMs can also inhibit tumor neovascularization [32]. Wu et al., reported that the Jian pi Yang

wei fang can reverse the chemotherapy-related changes of intestinal bacteria in patients with GC, thereby leading to the improvement in the quality of life of patients [38]. In recent years, studies have also confirmed that TCMs, such as dang shen, bai zhu, hang qi and yi yi ren, can not only improve the immune function of patients, but also diminish the chemoradiotherapy-induced suppression on tissue and organ function [33-35, 53, 54]. An in vitro study with cell cultures have shown that these prescriptions can affect the apoptosis and cell cycle of GC cell line MGC803 cells. Furthermore, it has been confirmed that the compound exerts a significant inhibitory effect on the proliferation of GC cells, mainly by promoting the apoptosis of GC cells, and blocking the cell division cycle in the G2-M phase [55]. In recent years, a large number of studies on TCM monomers and their active ingredients have been conducted, and it was found that these can inhibit the proliferation of GC cells, promote apoptosis, reverse the immune escape, increase the sensitivity to chemotherapy, and reverse the multiple drug resistance. For instance, the Elemene injection (the extract of TCM Zedoary) [56], Kanglaite injection (the extract of TCM Semen Coicis) [57], and Xiaoaiping injection (the extract of TCM Marsdenia tenacissima) [58].

In recent years, some researchers have assessed the efficacy and safety of TCMs combined with chemotherapy in the treatment of AGC, and these TCMs included the ya dan zi injection [59], ai di

injection [60], shen qi fu zheng [61] and kang ai injection [62]. The resulting data suggested that the combination of the injection with chemotherapy regimens can significantly enhance the effectiveness of chemotherapy in patients with GC, improve the quality of life of patients, and reduce the risk of abnormally low white blood cell counts, gastrointestinal reactions and liver damage.

The external administration of TCMs include applicator therapy, acupuncture, auricular acupressure, etc. This route of administration of TCMs has a number of advantages, which include simple operation, fewer adverse events, and significant curative effects. The Sheng Xue Fang acupoint application combined with chemotherapy for spleen and kidney deficiency in AGC patients has achieved significant clinical efficacy and high safety [63]. The Zu san li acupoint injection with the huang qi injection adjuvant chemotherapy regimen has been shown to alleviate the side effects or toxicities caused by chemotherapy, modulate the inflammatory response, improve the index situation, enhance the compliance to chemotherapy, and improve the prognosis of patients with AGC [63].

The advantages of TCMs in treating malignant tumors are to strengthen the healthy qi and eliminate the evil qi, improve symptoms, and enhance immunity. The chemotherapy in Western medicine eliminates the primary and metastatic tumor. These two organically combine and synergize. Furthermore, these can alleviate or even avoid the toxic side effects of Western medicine, and improve the efficacy. Many studies have shown that chemotherapy combined with TCMs has greater efficacy, but with fewer toxicities, when compared to chemotherapy alone, for GC [65].

5. Conclusion

TCM, as an important component of individualized comprehensive treatments, have long been used to treat GC in China, and have increasingly received attention, globally. In particular, TCMs have exhibited beneficial effects in prolonging survival time, improving quality of life, and attenuating chemotherapy-associated adverse events in patients with GC [49-63]. This may bring a fundamental change to the concept of cancer treatment. For patients with advanced cancer, the strategy of management has also been adjusted, that is, based on prolonging survival, more attention should be given in improving the quality of life.

During chemotherapy, TCMs can not only enhance the therapeutic effect of chemotherapy in patients with AGC, but also alleviate the side effects or toxicities caused by the chemotherapy. The unique benefits of TCMs can improve the quality of life of patients. First, it takes advantage of the characteristics of syndrome differentiation and the treatment of TCM, and combines the patient's physique to prescribe syndromes to reduce complications. Second, from the perspective of the overall concept, it improves the quality of life of patients, reduces the risk of GC recurrence, and reflects the characteristics of treating the disease.

However, it was also realized that TCMs have a number of limitations

in the treatment of GC. For instance, there are still deficiencies in the clinical application of TCM in preventing and treating chemotherapy complications, and improving the quality of life of patients. Most of the selected formulations of TCMs have been adjusted based on medical prescriptions, but the effectiveness and adverse side effects have not been well-studied. Therefore, large-scale, long-term and controlled prospective clinical studies are needed in the future. In addition, the active compound in the formulation of TCMs and its action mode remains largely unknown. Future basic studies with cell cultures and experimental animals, human studies with a large sample size, and further assessments on the efficacy and safety of TCMs in combination with chemotherapy are necessary [66].

In summary, the present review highlights the findings for TCM in the treatment of GC. TCMs exert a synergistic effect on chemotherapy, leading to enhancements in efficacy and the reduction of toxicities. Therefore, patients with GC at the late stage or AGC may benefit from TCMs, and the old formula may offer new hope in treating patients with GC at the late stage.

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