

Clinical application of traditional Chinese medicine in the treatment of neuroendocrine neoplasms

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Abstract

Neuroendocrine neoplasms (NENs) are a group of rare tumors with strong heterogeneity. Among these tumors, well-differentiated tumors can have a relatively good survival prognosis, while some tumors can have strong malignant potential and lead to increased mortality. Traditional Chinese medicine (TCM), which has a long history of thousands of years, has been widely used to treat tumors due to its unique advantages, such as economy, efficacy and few side effects. In recent years, the role of TCM in the treatment of NENs has gradually emerged. It can not only help prevent tumor recurrence and reduce the side effects of radiotherapy and chemotherapy but also relieve symptoms and improve quality of life. Various clinical studies have indicated that TCM has achieved good curative effects at different stages of treatment. We summarized the last 10 years of research progress on the clinical application of TCM in the treatment of NENs from four points of entry, aiming to provide a reference for the treatment of NENs.

KEYWORDS

clinical application, neuroendocrine neoplasms, traditional Chinese medicine, treatment

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a group of heterogeneous tumors originating from peptidergic neurons and neuroendocrine cells that can occur in multiple parts of the body such as the gastrointestinal tract, pancreas, lungs and thymus. NENs are considered rare diseases. However, with the development of relevant diagnostic techniques and improvements in people's awareness of disease, the incidence of NENs is increasing annually. According to the US Surveillance, Epidemiology, and End Results data [1], the annual incidence of NENs significantly increased to 6.98 per 100,000 in 2012. According to the degree of differentiation, NENs can be divided into well-

differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) [2]. The high heterogeneity of NENs has created great challenges for clinical diagnosis and treatment.

Like most tumors, NENs can be treated by surgery, chemotherapy, targeted therapy, interventional therapy and radiotherapy. In addition, there are relatively special treatments, such as somatostatin analogs (SSA) therapy and peptide receptor radionuclide therapy. Unfortunately, even though it seems that there are a large number of treatment options to choose from, the effect on some tumors is still not ideal and may also be accompanied by various side effects. Traditional Chinese medicine (TCM), with a history of more than

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3000 years, is a form of the wisdom of the Chinese nation's long-term medical practice. Its theoretical system of "holistic concept" and "treatment by differentiation of syndromes" further reflects the advantages of individualization and pertinence. Numerous studies have shown that TCM plays a beneficial role in the treatment of NENs and it has gradually become a potent adjuvant therapy. This article reviews the research progress related to the treatment of NENs via TCM over the past 10 years and aims to summarize the main advantages in the treatment of NENs.

TCM CLINICAL APPLICATION IN TYPE 1 GASTRIC NEUROENDOCRINE TUMORS

Type 1 gastric neuroendocrine tumors (g-NETs), which are related to autoimmune gastritis, are the most common clinical subtype of gastric neuroendocrine tumors, and some patients may have obvious gastrointestinal symptoms. Generally, the prognosis of patients with type 1 g-NETs is so good that the European Neuroendocrine Tumor Society guidelines only recommend regular follow-up after endoscopic treatment [3]. However, the recurrence of type 1 g-NETs is relatively common, and a prospective study revealed that the recurrence rate was as high as 63.6%, with a median time to recurrence of 8 months [4]. At present, clinical measures to prevent recurrence are still controversial. SSA has been used to treat type 1 g-NETs, as SSA can inhibit gastrin release and directly inhibit endocrine cell proliferation [5–7]. However, SSA cannot relieve symptoms, and in fact they may cause or aggravate gastrointestinal symptoms. Antrectomy has been suggested to suppress gastrin to prevent recurrent disease, but a few cases of recurrence even after surgery have been reported [8].

To overcome this therapeutic dilemma, many experts and scholars have explored TCM treatment for type 1 g-NETs. A prospective clinical observation [9] revealed that the recurrence rate of type 1 g-NETs treated with TCM was 37%, and the median recurrence time was 15 months. Compared with that in the literature, the recurrence rate was significantly lower. One study [10] revealed that the main TCM syndromes of type 1 g-NETs include liver stagnation and spleen deficiency, fire in the liver invading the stomach, spleen and stomach deficiency and cold, and stomach yin deficiency. The former two are the most common. Therefore, treatment should be based on soothing the liver, strengthening the spleen and harmonizing the accumulation of the stomach. Dou et al. [11] included 41 patients with type 1 g-NETs after endoscopic treatment who were treated with *Shumu Liujunzi* decoction. The recurrence rate was only 26.8%, and the median recurrence time was significantly prolonged to 19 months. Another clinical control observation [12]

suggested that the treatment of type 1 g-NETs with the herbal decoction *SMLJ01* can not only help reduce recurrence and alleviate symptoms but also prolong the time of recurrence. In addition, some scholars believe that "emotional disorders" play an important role in promoting the formation of type 1 g-NETs. Thus, TCM emotional nursing based on five-element emotional therapy significantly reduced the recurrence rate of type 1 g-NETs after endoscopic treatment and improved the quality of life of the patients [13].

TCM CLINICAL APPLICATION IN PANCREATIC NEUROENDOCRINE NEOPLASMS AFTER SURGERY

The pancreas is one of the most common primary sites of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) [14]. Pancreatic neuroendocrine neoplasms (p-NENs) include both pancreatic neuroendocrine neoplasms (p-NENs) associated with a functional syndrome (functional p-NENs) and those associated with no distinct clinical syndrome (nonfunctional p-NENs). Radical surgery is recommended as a first-line treatment for patients with early p-NENs. However, there are still some cases of recurrence and metastasis after radical surgery. It has been reported that the recurrence rate after radical resection is as high as 24.5%–36.3% [15, 16], and the prognosis of patients with recurrence is relatively poor. Nonetheless, whether patients who undergo radical resection of early well-differentiated p-NENs need adjuvant treatment is still unclear internationally [17]. Therefore, exploring the risk factors for postoperative recurrence of p-NENs and timely intervention in patients with high-risk factors may reduce recurrence and metastasis. A recent meta-analysis revealed that G2 grade, lymph node metastasis, positive resection margins, and neural and vascular invasion may be high-risk factors for postoperative recurrence [18]. However, treatments such as SSA and targeted therapies currently have no evidence to support postoperative adjuvant treatment. Therefore, it is particularly important to explore effective treatment options to prevent postoperative recurrence and prolong survival.

In recent years, TCM has also been used to prevent recurrence after radical surgery for p-NENs and has shown good efficacy. Zhang [19] studied 47 patients with postoperative p-NETs and reported that these patients were prone to spleen-qi deficiency and liver-qi stagnation after surgery. TCM treatment should be based on the principle of strengthening the spleen and nourishing qi, soothing the liver and regulating qi. The 1-, 2-, and 3-year recurrence rates of the TCM group treated with *Xiaoyao San* and *Xiangshaliujunzi* decoction were 5.9%, 25.1%, and 25.1%, respectively, which were significantly lower than those of the control group.

Wang [20] enrolled 85 patients with postoperative p-NETs for long-term follow-up and reported that the 3-year recurrence rate of the TCM group treated with the effect of soothing the liver and strengthening the spleen was only 13.1%, which was significantly lower than the 30.7% in the simple follow-up group. Yu et al. [21] retrospectively analyzed the clinical data of 181 postoperative patients with pancreatic neuroendocrine tumors and reported that the cumulative recurrence-free survival rates at 1, 2, and 3 years in patients who received the *Qizhen Yiliu* formula for 6 months or more were higher than those in the control group, and in patients with pathological grades of G1, G2, or clinical stage II, TCM treatment had a significant advantage ($P < 0.05$).

TCM CLINICAL APPLICATION IN ADVANCED GASTROENTEROPANCREATIC NEUROENDOCRINE NEOPLASMS

The treatment of advanced GEP-NENs needs to be comprehensively evaluated according to the specific conditions of the patient's primary lesions and metastases. An expert consensus [22] recommends that for advanced GEP-NENs with positive SSTRs, slow growth and $Ki67 \leq 10\%$, SSA can be used to control tumor growth, but systemic chemotherapy is not recommended. However, SSA may cause adverse gastrointestinal reactions, and their long-term use may lead to gallstones. Therefore, for patients with well-differentiated G1 or G2 grades in advanced GEP-NENs, when the tumor burden is small, treatment with TCM alone can strengthen the body and suppress the tumor to stabilize the disease; however, when the tumor burden is high, it is recommended to administer integrated treatment, such as TCM combined with SSA, TCM combined with targeted drugs, or TCM combined with interventional therapy, to achieve synergistic effects between TCM and Western medicine.

Li et al. [23] analyzed 39 patients with advanced GEP-NETs and reported that the most common TCM syndromes were stagnation of liver qi, deficiency of the spleen and heat of the stomach, qi deficiency in the spleen and stomach, and yin deficiency in the liver and kidney. TCM combined with SSA was used for treatment, and the median TTP was 22.9 months, which was significantly longer than the 13–14.3 months reported in the literature [24, 25], suggesting that TCM combined with SSA has a synergistic effect. One study [26] included 32 patients with advanced GEP-NETs who received only TCM combined with SSA, and 18 patients received TCM combined with surgery, chemotherapy, targeted therapy, or interventional therapy. The final median follow-up time was 29.0 months, and only 14 patients experienced disease

progression. The study also analyzed the prescriptions and found that the most commonly used herbs were those that nourish qi, eliminates accumulated food, regulate qi, nourish yin and blood, and resolve phlegm and dampness. Some scholars [27] have reported that SSA greatly impair the liver and kidney, so they carried out a randomized controlled clinical observation of patients taking the *Jiannaobushen* pill combined with SSA for the treatment of gastrointestinal NENs and reported that the combined treatment had better efficacy with fewer adverse effects.

CLINICAL APPLICATION OF TCM IN NEUROENDOCRINE CARCINOMAS

NECs are poorly differentiated and exhibit highly malignant biological behaviors, leading to increased mortality. Most patients with NECs are diagnosed with multiple metastases and cannot be treated by radical surgery. The CSCO guidelines [28] recommend that the most commonly used combination chemotherapy regimens for the first-line treatment of locally advanced, unresectable or metastatic NECs are EP and EC [29]. Rapidly progressing NECs are mainly treated with integrated traditional Chinese and Western medicine; that is, chemotherapy is the mainstay, and TCM treatment acts as a supplement. It has been reported [30] that TCM treatment can alleviate the adverse reactions of patients caused by chemotherapy, reduce toxicity and enhance efficacy and can improve patients' quality of life. For patients who are inoperable and intolerant to radiotherapy and chemotherapy or insensitive to radiotherapy and chemotherapy, TCM can be used for maintenance treatment to improve symptoms and enhance physical strength. Zhang et al. [31] reported that treating uterine NEC patients who refused chemotherapy with TCM combined with surgical total resection improved patient survival to a certain extent. Xu and Huang [32] reported that a patient with chemotherapy-insensitive mediastinal NEC with supraclavicular lymph node metastasis who was treated with TCM for warming yang and resolving phlegm had a good survival outcome.

CONCLUSION

Overall, research on TCM for the treatment of NENs is still relatively rare and has focused mainly on clinical observations in recent years. Large-scale prospective randomized controlled trials are necessary in the future to provide stronger supporting evidence, and the exact mechanism of action needs to be further studied. Nonetheless, the data show TCM may play a positive role in the treatment of NENs. TCM has prominent clinical effects by itself and synergistic

effects in combination with different treatments, which are based on harmonizing the liver and spleen and strengthening the body, unlike ordinary tumors that mainly attack pathogenic factors. It can not only prevent postoperative recurrence in early-study patients but also mitigate toxic side effects, improve symptoms, and prolong survival in advanced patients by synergizing with other treatments. The positive role of TCM in the treatment of NENs is becoming more obvious, and we believe that this brilliant gem of TCM will show great potential in the field of NEN treatment over time. With the development of science and technology, the mechanism of action of TCM treatment will become increasingly clear.

AUTHOR CONTRIBUTIONS

Ying-Ying Chen: Data curation; investigation; writing – original draft. **Shao-Bo Hu:** Investigation; writing – original draft. **Fei Su:** Investigation; resources. **Fu-Huan Yu:** Investigation; resources. **Ru-Ao Chen:** Investigation; resources. **Zi-Xuan Cheng:** Investigation; resources. **Huang-Ying Tan:** Methodology; writing – review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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