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Traditional Chinese Medicine for Treatment of Hepatocellular Carcinoma: The Road Towards Internationalization

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Abstract: Liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Despite the remarkable progress in the management of HCC over the last several decades, the long-term outcome of these patients is still dismal. Traditional Chinese medicine (TCM) could exert beneficial effects on patients with HCC in combination with modern medical methods. Although there is growing body of evidence in clinical practice in China, the internationalization of TCM remains a great challenge. In this review, we summarized the current evidence on herbs' therapeutic effects on HCC and illustrated the road towards TCM internationalization based on the example of YIV-906 (PHY906), which originated from ancient formulas.

Keywords: Traditional Chinese Medicine; Hepatocellular carcinoma (HCC); TCM internationalization; YIV-906; Huang Qin Tang.

1. Introduction

Liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related deaths worldwide [1]. Hepatocellular carcinoma (HCC) accounts for 80% of all liver cancer cases. Almost 50% of all diagnosed cases and HCC-related deaths occurred in China, which can be attributed to the relatively high prevalence of viral hepatitis, the most common risk factor for HCC, as well as other risk factors, such as environmental toxins, alcohol, and hepatotoxic drugs [2]. There has been remarkable progress in the management of HCC over the last several decades, including liver transplantation, surgical resection, radiofrequency or microwave ablation, transarterial chemoembolization (TACE), targeted therapy, and other systemic therapy. However, the long-term outcome of patients with HCC is still dismal [3].

Traditional Chinese medicine (TCM) has been used in China for more than 2,000 years in the treatment of a wide range of medical conditions, including HCC. Traditionally, TCM practice relies on the physician's experience and the understanding of the disease's pathogenesis in individual patients with HCC. Compound decoctions are the most commonly used treatment in TCM and are modified based on the different stages of the diseases or the specific condition of the patients. Therefore, there is a lack of uniform standards for the use of herbal medicines. In the recent years, based on the study of ancient documents and the accumulating experience, many Chinese patent medicines have been introduced for the treatment of HCC, including injections and orally administered medicines. In addition, multiple clinical trials have demonstrated that TCM, in combination with modern medical methods, exerts beneficial effects on patients with HCC, such as hepatoprotection, alleviating symptoms, reducing the recurrence and metastasis rates after surgery, and attenuating the adverse reactions of routine treatment [4].

With the rise of globalization, TCM embraces a new opportunity towards internationalization, which would also benefit patients with HCC worldwide. However, the greatest challenge TCM systems face is gaining widespread trust and acceptance in the modern world. Clinical efficacy, safety, and the consistency of quality of TCM are the three key points for traditional medicines to obtain approval and respect [5].

In this review, we first summarized the current evidence on herbs' therapeutic effects on HCC and the safety in clinical practice. Next, we analyzed the example of YIV-906 (PHY906), which originated from ancient formulas, to illustrate the road towards TCM internationalization.

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2. Evidence for the efficacy and safety of TCM on HCC

In TCM theory, the basic causes of HCC are Yu (stasis), Du (toxicity), and Xu (deficiency), which lead to different Zheng (symptoms) in the patients during the different stages of the disease. Presently, there is no well-recognized TCM classification or diagnostic criteria for HCC. However, the treatment strategies could be aimed to remove the causes, including Huo-Xue-Hua-Yu (removing blood stasis), Jian-Pi-Li-Qi (regulating the flow of Qi and strengthening the spleen), or Qing-Re-Jie-Du (clearing heat and detoxifying) [6]. Generations of TCM practitioners have accumulated rich experience for treating HCC and many effective formulas have been proven to prevent HCC progression and occurrence [7]. Nonetheless, there is still an enormous gap to meet the increasing demand for effective TCM treatment for HCC. With this background, anticancer Chinese patent medicines and TCM injections have been developed and widely used in clinical practice.

These medicines are based on empirical formulas after long-term use in patients with HCC and are prepared using modern pharmaceutical technology. Compared to decoctions, the most commonly used therapeutics in TCM clinical practice, patent medicines have the following advantages: the quality is controllable, the ingredients are relatively clear, and the use is patient- and doctor-friendly. Most importantly, with the advancement of technology, randomized controlled clinical trials are more easily designed and conducted, enabling the study of the efficacy and safety of TCM in patients with HCC, which would produce high-level evidences.

In 2018, a clinical practice guideline for the treatment of primary liver cancer with integrative traditional Chinese and Western medicine was published in the Journal of Integrative Medicine based on a review of the current evidences and following the method used in the development of international guidelines [8]. In this guideline, the panel of experts focused on seven clinical questions and provided seven corresponding recommendations on TCM treatment for liver cancer. The medicines mainly included the antitumor TCM injection, orally administered Chinese patent medicines, and topical medicines. All recommendations are evidence-based with detailed data from the corresponding clinical trials.

The questions addressed the TCM treatment for different disease stages, from patients with early-stage disease undergoing surgery to those with middle- and advanced-stage disease undergoing intervention operations or supportive treatment. The first question was whether TCM treatment can reduce the recurrence after surgery in patients with early-stage HCC. A randomized clinical trial and an observational study showed that patients who received oral TCM medicines and injections after surgery had lower 1-, 2-, and 3-year recurrence rates than those who underwent hepatic artery perfusion of pirarubicin, mitomycin, and lipiodol [9, 10]. Therefore, the guideline recommended that a combination of oral administration of traditional Chinese herbal medicines and intravenous drip of an antitumor injection with Chinese herbs is beneficial in reducing the risk of postoperative recurrence. In patients with middle- and advanced-stage HCC undergoing TACE, TCM injections, such as cinobufacini, Aidi, Xiaoaiping, or Kanglaite injection, improved the treatment efficacy and reduced thegravity of adverse reactions caused by TACE [11]. In addition, in combination with some chemotherapy drugs, cinobufacini and arsenic trioxide injections reduced the adverse reactions caused by the latter and improved the patients' quality of life compared with chemotherapy drugs alone. In patients with middle- and advanced-stage HCC who are unable to undergo surgery or TACE, general symptomatic and supportive treatment with antitumor Chinese medicine injections may improve the quality of life. Cinobufacini, Aidi, arsenic trioxide, Xiaoaiping, and cantharides are the most commonly used TCM injections.

There are evidences that oral administration of antitumor Chinese patent medicines, such as Huaier granules, Cidan capsules, and Jinlong capsules, improves the quality of life, increases the survival rate, and reduces the incidence of adverse reactions. However, most are low-level evidences. The first available high-level evidence emerged in 2018, based on a multicenter, randomized, controlled, phase IV trial conducted for evaluating the benefit of Huaier granules on HCC recurrence after curative resection [12]. A total of 1044 patients from 39 centers were randomized in 2:1 ratio to receive either Huaier or no further treatment (controls) for a maximum of 96 weeks. The primary endpoint was the recurrence-free survival (RFS). The mean RFS in the Huaier (n=686) and control (n=316) groups was 75.5 weeks and 68.5 weeks, respectively (hazard ratio 0.67; 95% confidence interval 0.550.81). Thus, the results of this study demonstrated a significant prolongation

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of the RFS in the Huaier group and provided strong evidence on the effectiveness of Huaier granules as an adjuvant therapy for HCC after curative liver resection.

In summary, TCM has been proven to be beneficial to patients with HCC. However, the current evidences have been obtained only from domestic medical centers. Hence, further efforts are required for TCM to be accepted on the world mainstream market, such as getting approval of Food and Drug Administration (FDA) of the United States. According to the rules of FDA, new drugs must be proven safe and effective to FDA's satisfaction before companies can market them in interstate commerce. Manufacturers must also prove they are able to make the drug product according to federal quality standards. So clinical efficacy, and safety, quality consistency are the three key aspects reviewed by the FDA for approval of a new drug. At present, none of TCM has gotten the FDA approval yet. Fortunately, some TCM medicines are promising towards the international markets. An antient compound Huang Qin Tang is now on its way to phase II clinical trial. Although still on the way, its development exactly followed the rules of FDA and could be a good example for most of the TCM medicines.

3. An example of TCM internationalization: YIV-906 (PHY906)

3.1 From classic traditional herb formula Huang Qin Tang to antitumor agent YIV-906 (PHY906)

Approximately 20 years ago, Professor Yung-Chi Cheng and his research team at Yale University reviewed the Chinese literature in search of a Chinese herbal medicine that could prevent and/or reduce the gastrointestinal toxicities associated with irinotecan-based chemotherapy for colorectal cancer. Huang Qin Tang was identified as a classic formula that has been widely used in China and other Asian countries to treat gastrointestinal disorders, including nausea and vomiting, abdominal cramps, and diarrhea. The formula consisted of four principal herbs: *Glycyrrhiza uralensis Fisch*, *Paeonia lactiflora Pall*, *Scutellaria baicalensis Georgi*, and *Ziziphus jujuba Mill*.

In addition to its long history of use and proven efficacy, the Huang Qin Tang formula had the advantage of containing only four herbs, which would reduce the difficulty in extraction and help to easily understand its ingredients.

After selecting Huang Qin Tang to be studied, Cheng's team decided to keep the four-herb combination as a complex entity and use it to create a new modern agent that could enter the international market. Quality consistency is one of the most important aspects together with efficacy and safety reviewed by the FDA for approval of a medicine. For this ancient classic formula, the safety is guaranteed because of the long history of use in clinical practice. After ensuring the quality consistency, it could enter the phase II clinical trial, which suggested that controlling the changes of ingredients by means of best technology is the key factor for herbs modernization. In other words, quality control became the key issue for development of the medicine.

Professor Cheng and his team took the first step to control the quality of the formula by means of modern technology by following the strictest protocol to meet the requirements of the FDA of the United States. They paid attention even to the growth environment of the plants in order to ensure the consistency of the chemicals in the herbs and the absence of contaminants.

The platform for quality control termed Phytomics QC was developed later and it was a set of methodologies with chemical analysis, bioresponse analysis, and in vivo animal pharmacology to achieve quality control and batch-to-batch reproducibility in the production of YIV-906 (PHY906) [13]. It is the first novel and advanced quality control platform to ensure product quality consistency, which is expected to be applied on other herbal products as well because the lack of quality consistency has always been the bottleneck for most currently used herbs.

3.2 Clinical studies of YIV-906 (PHY906) on HCC

The clinical trial of YIV-906 (PHY906) was designed to evaluate whether YIV-906 (PHY906) could reduce the gastrointestinal toxicity of the frontline chemotherapy for colorectal cancer. The results showed that PHY906 therapy reduced the severity of diarrhea and nausea/vomiting induced by leucovorin chemotherapy by at least one grade level, and significantly reduced the incidence of grades 3 and 4 diarrhea, nausea/vomiting, and fatigue [14]. Another first-in-human phase II trial of PHY906 with capecitabine as second-line therapy in patients with advanced pancreatic cancer enrolled 25 patients. The median progression-free survival was 10.1 (range 0.454.1) weeks and the median overall survival was 21.6 (range 0.484.1) weeks. It was demonstrated that Capecitabine plus PHY906 provides a safe and feasible salvage therapy after gemcitabine failure for

advanced pancreatic cancer [15].

Based on these side-effect-relieving and antitumor effects of PHY906 on gastrointestinal cancer, the team conducted the first Phase I/II study of PHY906/capecitabine in patients with advanced HCC and the results were published in 2009, when Sorafenib was approved for targeted therapy of advanced HCC [16]. It was found that the median overall survival of patients with advanced HCC was 9.2 months and that Asian patients had a longer median overall survival (16.5 months) than that of 6.5 months with Sorafenib treatment in the Asia-Pacific region phase III randomized, double-blind, placebo-controlled trial [17].

It is well known that diarrhea is a severe side effect of Sorafenib. Therefore, the team investigated the possible effect of the combination of PHY906 and Sorafenib on HCC. They performed the preclinical examination using HepG2-bearing nude mice as a model to study the combination effect of PHY906 and Sorafenib on tumor growth. The results showed that PHY906 could: 1) enhance the antitumor activity of Sorafenib against HepG2 tumors without affecting the body weight of the animals; 2) increase the apoptosis rate in HepG2 tumors treated with Sorafenib and the expression of FasL and FasR, potentially triggering apoptosis directly via caspase-8 or indirectly via caspase-9; 3) increase both macrophage infiltration and the M1/M2 (tumor rejection) signature expression pattern in tumor cells; 4) increase autophagy associated with AMP-activated protein kinase a and ULK1 phosphorylation; and 5) increase ERK1/2 phosphorylation by inhibiting ERK1/2 phosphatase. In conclusion, PHY906 might improve the therapeutic index of Sorafenib in patients with advanced HCC.

In a pilot small-sample clinical trial in the United States, four patients with advanced HCC and resistance to Solafenib monotherapy were studied in combination with PHY 906. The combined therapy improved the curative effect and no adverse effects related to PHY906 were found. One of the patients, an Asian patient with hepatitis B-related HCC with bone metastasis and Solafenib resistance, had a survival of more than 4 years after the addition of PHY906.

Based on the above preclinical and clinical studies, a worldwide, multicenter, randomized, controlled, phase II clinical trial has been initiated for the treatment of HCC using Sorafenib with a YIV-906 adjuvant. The protocol was approved by the FDA on August 5, 2018. Centers from mainland China, Hongkong China, Taipei China, and the United States will participate in this study.

In conclusion, although TCM has been widely used in China for treating patients with HCC, there still a long way to be accepted by the world mainstream market. Some experts tried the best to follow the rules of FDA of the US for approval. Ensuring quality consistency of TCM medicines and strictly following the modern clinical trials would provide robust evidence of their efficacy and safety, which is the foundation for globalization of TCM. This review suggested a promising way for TCM towards internationalization by illustrating the development of YIV-906, which also tried to provide a platform for solving the problem of quality consistency.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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