

Research Progress of Traditional Chinese Medicine External Therapy in Cancer-Related Fatigue

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Abstract: *Cancer-Related Fatigue (CRF) is a common accompanying symptom in patients with malignant tumors. It has a high incidence and long duration, seriously affecting patients' quality of life and treatment compliance. At present, the pathogenesis of CRF has not been fully clarified in Western medicine, and treatment methods are mostly symptomatic support, with limited efficacy and certain side effects. Traditional Chinese Medicine (TCM) external therapy has gained increasing research attention in the application of CRF in recent years due to its advantages of simple operation, safety, non-invasiveness, and minimal toxic and side effects. Its efficacy and safety have been verified by a large number of clinical practices. This paper systematically summarizes the current research status of CRF in both Western and Traditional Chinese Medicine, explores the clinical treatment and application effects of TCM external therapy, so as to provide reference for the clinical treatment of CRF.*

Keywords: Cancer-Related Fatigue, Traditional Chinese Medicine External Therapy, Consumptive Disease.

1. Introduction

As one of the most prevalent symptoms in tumor patients, Cancer-Related Fatigue (CRF) occurs in 60%–90% of cases, far exceeding symptoms such as pain, nausea and vomiting, and may persist for months or even years after treatment completion [1]. Distinct from simple physical exhaustion, CRF refers to a persistent severe fatigue induced by tumors or anti-tumor treatments that cannot be relieved by rest, often accompanied by inattention, low mood, muscle soreness and other manifestations. It seriously disrupts patients' daily activities, social functioning and mental health [2]. In TCM theory, CRF falls under the category of "consumptive disease". Rooted in TCM's holistic concept and treatment based on syndrome differentiation, TCM external therapies regulate visceral functions and dredge meridians, collaterals, qi and blood to strengthen vital qi and eliminate pathogenic factors for fatigue relief. Therefore, clinical practice should promote the application of TCM external therapies to exert the unique advantages of TCM and generate clinical value.

2. Definition and Diagnostic Criteria of CRF

2.1 Definition

Per the guidelines issued by the National Comprehensive Cancer Network (NCCN), cancer-related fatigue is defined as persistent subjective physical, emotional and/or cognitive exhaustion associated with cancer or anti-cancer therapies, which is disproportionate to recent physical activity and severely interferes with normal daily life [3-4]. Unlike ordinary fatigue, CRF is more severe and enduring, impairing patients' quality of life, daily function and treatment tolerance. As a tumor comorbidity, it runs through the entire progression and treatment course of malignant tumors.

2.2 Diagnostic Criteria

Currently, CRF diagnosis mainly relies on patients' subjective descriptions and standardized scale assessments, lacking

unified objective diagnostic indicators. Widely adopted diagnostic criteria include: (1) NCCN CRF diagnostic criteria: Patients report fatigue lasting ≥ 2 weeks that interferes with daily activities, after excluding other fatigue-inducing diseases such as anemia, infection and hypothyroidism [4]; (2) International Classification of Diseases, 10th Revision (ICD-10) criteria: Fatigue persists for ≥ 1 month, accompanied by at least one of the following symptoms: impaired concentration, memory decline, depression, myalgia and sleep disturbance, with symptoms correlated to tumors or anti-tumor treatments [5]. Common clinical assessment tools include the Brief Fatigue Inventory (BFI), Cancer Fatigue Scale (CFS), Piper Fatigue Scale (PFS), etc. These scales evaluate fatigue severity, its impacts on daily life and temporal variation patterns from multiple dimensions [6,7]. CRF may emerge at any stage of anti-tumor treatment. Clinicians shall select appropriate assessment tools according to research purposes and patient characteristics, and regular monitoring of fatigue changes is recommended.

3. Pathogenesis of CRF

CRF is affected by multiple demographic, medical, psychosocial, behavioral and biological factors; tumor progression, anti-tumor therapies and patients' physical conditions all contribute to its onset [8]. Its pathophysiological mechanism is complicated, involving interactions across multiple systems and factors. Previous studies have proposed and investigated various biological mechanisms underlying CRF [9,10], including cytokine imbalance, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, abnormal regulation of serotonin (5-HT) neurotransmitters, and alterations in adenosine triphosphate (ATP) metabolism and muscle metabolism.

4. Western Medical Treatments for CRF

Current clinical interventions are dominated by Western symptomatic therapies, divided into pharmacotherapy and non-pharmacotherapy.

4.1 Pharmacotherapy

Medications include hematopoietic growth factors, psychostimulants, antidepressants and corticosteroids. Erythropoietin, a hematopoietic growth factor, is applied to anemic patients receiving chemotherapy, alleviating fatigue secondary to chemotherapy-induced anemia [11]. Methylphenidate, a psychostimulant, has proven effective for CRF relief in cancer patients, while progestogens and paroxetine show no such efficacy [11]. Corticosteroids can be considered for end-stage patients; a trial targeting advanced cancer patients with moderate to severe CRF confirmed that dexamethasone significantly alleviated fatigue and improved quality of life [12].

4.2 Non-pharmacotherapy

Interventions include health education, physical exercise (brisk walking, Tai Chi and other moderate activities), psychological interventions (cognitive behavioral therapy, mindfulness-based stress reduction), nutritional support (supplementation of protein, vitamins and trace elements), sleep interventions (optimizing sleeping environment, regular work-rest schedules), etc [13].

Western medicine can mitigate CRF to a certain extent yet with limited overall efficacy and obvious drawbacks. For instance, central stimulants such as methylphenidate may trigger insomnia and anxiety, and only work for 30%–40% of patients [14]. Non-pharmacological interventions like exercise therapy and cognitive behavioral therapy are restricted by patients' physical status and poor compliance, hindering their widespread promotion. Hence, exploring safe and effective interventions has become a research priority for CRF.

5. TCM Etiology and Pathogenesis of CRF

In TCM, CRF is categorized into “consumptive disease” and “depression syndrome”. Treatise on the Origins and Manifestations of Diseases · Manifestations of Consumptive Diseases records: “Consumptive diseases encompass five strains, six exhaustions and seven injuries”. The term “consumptive disease” was first mentioned in Zhang Zhongjing's Synopsis of Prescriptions of the Golden Chamber · Pulse Manifestations, Symptoms and Treatments of Blood Impediment and Consumptive Diseases, with typical manifestations including “wasting and inability to walk”, “abdominal urgency and various deficiencies in consumptive disease”, “restlessness and insomnia in consumptive disease”, and “severe emaciation from five strains and extreme consumptive damage”. Its core etiology and pathogenesis lie in deficient vital qi and visceral dysfunction, resulting in insufficient qi and blood, yin-yang imbalance, often complicated by stagnation of phlegm, dampness, blood stasis and toxic pathogens, presenting a root deficiency with excess branch manifestations. Tumors act as “toxic pathogens” that continuously consume human qi and blood. Although surgeries, chemotherapy and radiotherapy combat tumors, they damage vital qi, leading to visceral impairment and deficiency of qi, blood, yin and yang [15]. TCM holds that CRF mainly involves the spleen, kidney and liver, closely associated with qi-blood and yin-yang imbalance. The core

therapeutic principles are consolidating vital origin, replenishing qi and nourishing blood, invigorating the spleen and tonifying the kidney, as well as dredging meridians and collaterals. Many contemporary physicians have put forward unique insights based on clinical experience: National TCM Master Liu Shangyi [16] and Professor Wang Ping [17] prioritize tonifying deficiency and consolidating qi; Professors Feng Zhengquan [18] and Zhang Zhenyong [19] emphasize soothing and nourishing the liver; Hu Zengjin et al. [20] and Zhan Pingping et al. [21] advocate warming and tonifying the spleen and kidney; Professor Tan Xinhua [22] interprets CRF pathogenesis from the perspective of “sinking of grand qi”.

6. TCM Therapies for CRF

Classified as consumptive disease in TCM, CRF is effectively treated by oral TCM decoctions, a core internal TCM therapy for advanced cancer patients with CRF. Treatments are formulated based on four diagnostic examinations and syndrome differentiation, with tonification and vital qi reinforcement as fundamental therapeutic principles to relieve fatigue by supporting healthy qi. Clinically, classical formulas (Shenling Baizhu Powder, Sijunzi Decoction, Bazhen Decoction, Guipi Decoction, etc.) [23], empirical formulas, proprietary Chinese medicines and injections (Shenfu Injection, Shenmai Injection, Kang'ai Injection, Compound Kushen Injection, etc.) are widely applied with favorable curative effects. Multiple active TCM ingredients (astragalus polysaccharide [24], resveratrol [25]) have demonstrated potential for CRF improvement and are gradually validated in clinical trials. TCM external therapies feature convenient operation and low medical costs, showing broader application prospects in CRF management.

7. Application of TCM External Therapies in CRF

TCM external therapies stimulate acupoints or skin/mucous membranes on the body surface to regulate visceral functions and dredge meridians, collaterals, qi and blood for disease treatment. With advantages of simple operation, non-invasive safety, minimal toxic side effects and high patient compliance, they are suitable for CRF patients. Major external therapies applied for CRF include acupuncture, moxibustion, acupoint application and auricular point therapy, whose clinical applications and efficacies are elaborated below.

7.1 Acupuncture

The NCCN guidelines recommend acupuncture for CRF patients receiving anti-tumor treatments [26]. TCM theory states that acupuncture dredges meridians, replenishes qi and blood, invigorates the spleen and tonifies the kidney to alleviate qi-blood stagnation and vital qi deficiency in CRF patients. Modern medical research has clarified the scientific mechanisms of acupuncture for CRF: for example, acupuncture inhibits the expression of factors related to the leptin/AMPK signaling pathway to mitigate mitochondrial dysfunction, thereby effectively improving post-chemotherapy fatigue and immune function in patients [27]; based on the gut microbiota-brain-gut axis, acupuncture modulates gut microbiota and suppresses activation of

inflammatory cytokines to regulate corticosterone (CORT) and adrenocorticotrophic hormone (ACTH) levels on the HPA axis and relieve CRF [28].

Acupuncture treatment for CRF combines syndrome-differentiated acupoint selection with local acupoint selection. Chen Liwei et al. [29] sorted and analyzed acupoints for CRF acupuncture, finding that Conception Vessel, Stomach Meridian of Foot-Yangming and Spleen Meridian of Foot-Taiyin acupoints are most frequently selected to harmonize qi and blood, balance yin and yang, and regulate the spleen, liver and kidney. Zusanli (ST36), Sanyinjiao (SP6), Qihai (CV6) and Guanyuan (CV4) are the four most commonly used acupoints. A meta-analysis incorporating 10 randomized controlled trials involving 1,327 patients revealed that acupuncture significantly ameliorates CRF, with superior efficacy in breast cancer patients and those undergoing anti-tumor therapies [30]. In addition, triple energizer acupuncture, fatigue triple needles and intradermal needles all achieve remarkable effects in mitigating CRF [31-33].

7.2 Moxibustion

Moxibustion stimulates body surface acupoints to warm and unblock meridians, harmonize qi and blood, strengthen vital qi and eliminate pathogenic factors. TCM holds that thermal stimulation from moxibustion warms yang to dispel cold, invigorates the spleen to replenish qi and tonifies the kidney to consolidate primordial qi, improving vital qi and blood deficiency in CRF patients. Modern studies indicate that the potential mechanisms of moxibustion for fatigue relief involve inflammatory factor regulation, HPA axis modulation and enhanced antioxidant activity [34]. It regulates immune function, reduces levels of inflammatory factors (TNF- α , IL-6, etc.), and elevates peripheral blood CD4⁺ and CD8⁺T cell counts and leukocyte levels to alleviate CRF [35].

Common moxibustion modalities for CRF include mild moxibustion, ginger-separated moxibustion and monkshood cake-separated moxibustion. Acupoints are mainly selected from Conception Vessel, Stomach Meridian of Foot-Yangming, Governor Vessel and Bladder Meridian of Foot-Taiyang, such as Zusanli, Guanyuan, Shenque (CV8) and Zhongwan (CV12) [36]. Clinical studies confirm moxibustion markedly relieves CRF symptoms. Thunder-fire moxibustion significantly alleviates fatigue in qi-deficient patients with non-small cell lung cancer [37]; infrared laser moxibustion, an innovative technique solving incomplete combustion and excessive smoke of traditional moxibustion, exerts favorable effects on fatigue relief and sleep quality improvement in CRF research [38]; Governor Vessel moxibustion integrates meridian, acupoint, medicinal and thermal therapy effects to warm meridians, unblock collaterals and regulate visceral functions for CRF treatment [39].

7.3 Acupoint Application

Guided by TCM meridian theory, acupoint application combines targeted herbal medication with syndrome-differentiated acupoint selection. Herbal plasters are applied to acupoints, exerting therapeutic effects via transdermal drug absorption and acupoint stimulation to ameliorate vital qi

deficiency and qi-blood stagnation in CRF patients. Modern medicine demonstrates that acupoint application improves CRF patients' quality of life and immune function [40], and significantly modulates levels of cytokines (IL-6, TNF- α , IL-1, IFN- γ , etc.) and neuroendocrine hormones [41].

TCM acupoint application for CRF focuses on reinforcing vital qi and eliminating pathogenic factors. Meta-analyses of acupoint selection show that acupoints from Conception Vessel, Governor Vessel, Stomach Meridian of Foot-Yangming and Spleen Meridian of Foot-Taiyin are preferred. In clinical trials, Yin Danqin et al. [42] applied spleen-tonifying and qi-replenishing ointment on Shenque, bilateral Tianshu (ST25), Guanyuan, Zhongwan and Qihai, observing significant improvements in post-chemotherapy deficiency constipation and CRF with high safety. Luan Yanfen et al. [43] applied soothing, depression-relieving and tranquilizing herbal plaster on Qimen (LR14), Taichong (LR3), Neiguan (PC6), Sanyinjiao and Yongquan (KI1) for breast cancer patients with liver qi stagnation, markedly alleviating liver qi stagnation symptoms, sleep disorders and fatigue. Apart from monotherapy, acupoint application combined with oral decoctions, acupuncture, auricular point pressing, Baduanjin, five-element music therapy and other interventions yields synergistic efficacy for CRF management.

7.4 Auricular Point Therapy

Spiritual Pivot · Inquiry on the Mouth states: "The ear is the convergence site of all meridians". The ear gathers all body meridians, and auricular acupoints are closely correlated with visceral organs and meridians. Stimulating specific auricular acupoints dredges meridians, regulates visceral functions and relieves fatigue. Auricular acupoints commonly used for CRF include Liver, Spleen, Shenmen, Subcortex and Sympathetic [44].

In clinical practice, Zhang Yan et al. [45] applied Vaccaria seed or magnetic bead auricular point pressing targeting lung, liver and spleen acupoints, reducing fatigue and anxiety and improving sleep quality in lung cancer patients receiving chemotherapy. Wang Zhiman et al. [46] pressed Shenmen, Sympathetic and Subcortex auricular acupoints, significantly mitigating CRF and elevating quality of life in breast cancer patients after postoperative chemotherapy.

7.5 Other External Therapies

Beyond the above mainstream modalities, tuina, herbal foot bath and acupoint catgut embedding are also applied for CRF treatment. Meridian-circulating tuina performed during Si Shi (the period when Spleen Meridian qi flourishes) remarkably relieves post-chemotherapy fatigue in lung cancer patients with qi-yin deficiency [47]. Qi-replenishing herbal foot bath combines thermal stimulation and transdermal herbal penetration to regulate visceral functions, effectively alleviating post-chemotherapy fatigue and sleep disturbance [48]. Catgut embedding at bilateral Zusanli, Guanyuan and Qihai delivers persistent benign "acupuncture stimulation", significantly improving consumptive disease symptoms and quality of life in patients [49].

8. Summary

As the most common concomitant symptom of tumor patients, CRF runs through the entire tumor progression and treatment process, severely impairing patients' quality of life and therapeutic efficacy. Current Western medical interventions have limited efficacy and obvious limitations. Rooted in TCM's holistic concept and syndrome differentiation, TCM external therapies feature low cost, convenient operation, minimal toxic side effects and high patient compliance. Through acupuncture, moxibustion, acupoint application, auricular point therapy and other modalities, they regulate visceral functions, dredge meridians and collaterals, strengthen vital qi and eliminate pathogenic factors, demonstrating prominent advantages in alleviating CRF symptoms, improving quality of life and enhancing immune function. Nevertheless, TCM interventions for CRF remain in the preliminary stage, with uneven quality of clinical research, insufficient standardization, and lack of large-scale, multi-center and interdisciplinary clinical trials and experimental data. Future research shall conduct in-depth exploration on the mechanisms of TCM external therapies for CRF intervention to provide scientific evidence for standardized CRF treatment. Meanwhile, operational specifications and quality control systems for TCM external therapies should be formulated to guarantee clinical safety and efficacy, and fully exploit the unique strengths of Traditional Chinese Medicine.

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