

Research Progress on Traditional Chinese Medicine in the Treatment of Anti-tumor Drug-Related Rash

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Abstract: *Anti-tumor drug-related rash is a specific cutaneous toxic reaction, known in Traditional Chinese Medicine (TCM) as "drug rash" or "drug toxin". Modern medicine primarily employs glucocorticoids, antihistamines, antibiotics, and steroids for treatment, yet the efficacy is suboptimal and accompanied by adverse reactions; a highly effective solution remains elusive. TCM demonstrates significant therapeutic effects in treating this condition, effectively improving patients' quality of life and prolonging survival. Therefore, this article will summarize the etiology and pathogenesis, syndrome differentiation, and TCM treatment, aiming to provide new insights for the management of anti-tumor drug-related rash.*

Keywords: Tumor, Drug-related rash, Traditional Chinese Medicine treatment, Review.

1. Introduction

With the rapid development of targeted drugs and immunotherapeutic agents, an increasing number of anti-tumor drugs are widely used in clinical practice, achieving remarkable efficacy but also causing various adverse reactions, such as cutaneous toxicities, gastrointestinal reactions, and liver/kidney function impairment. Among these, chemotherapy, targeted therapy, and immunotherapy cause rash in 18%-72%, 75%-90%, and $\geq 30\%$ of patients, respectively [1-3]. These primarily include chemotherapeutic drugs like antimetabolites, topoisomerase inhibitors, cytarabine, anti-microtubule agents, alkylating agents, etc. [4]; targeted drugs such as epidermal growth factor receptor inhibitors, anaplastic lymphoma kinase inhibitors, multi-target kinase inhibitors, etc. [5]; and immune drugs including programmed death receptor-1, programmed death ligand-1 inhibitors, cytotoxic T-lymphocyte-associated antigen-4 inhibitors, etc. [6]. Rash mostly appears 2-4 weeks after treatment initiation [5], primarily manifesting as acneiform rash, erythematous papules, measles-like rash, lichenoid rash, etc., often accompanied by itching, pain, and dry skin. These symptoms reduce patients' quality of life and, in severe cases, lead to dose reduction or even treatment interruption, impacting the efficacy of anti-tumor therapy, making it a significant concern during anti-tumor treatment.

Currently, the pathogenesis of anti-tumor drug-related rash is not fully understood. Western medicine suggests it may be related to inflammatory cytokines; patients with rash have slightly higher immune activity than normal, promoting inflammatory reactions and subsequent rash occurrence, which may worsen with prolonged medication [7]. Western medical treatment has certain limitations, unable to fully intervene in the pathogenesis of this rash, resulting in suboptimal therapeutic outcomes. TCM shows significant efficacy in treating anti-tumor drug-related rash, effectively improving patient symptoms and quality of life. This article reviews the etiology, pathogenesis, syndrome differentiation, and TCM treatment of anti-tumor drug-related rash to provide ideas for its management.

2. Etiology and Pathogenesis

In Western medicine, anti-tumor drug-related rash is termed "drug-induced dermatitis," while in TCM, it falls under the categories of "Zhong Yao Du" (Herbal Toxin) or "Yao Du Zhen" (Drug Toxin Rash). Cancer patients often have inherent deficiency of healthy Qi (Zheng Qi), compounded by anti-tumor treatments further damaging Qi, Blood, Yin, and Yang, leading to dysfunction of the Zang-fu organs. The Lung governs the skin and body hair; Lung Qi deficiency leads to weakness of the defensive (Wei) Qi, making the body susceptible to pathogenic invasion. Drug toxins are often fiery-heat toxins; internal stagnation over time damages the Spleen and Stomach. Spleen deficiency results in impaired transportation and transformation, leading to internal accumulation of damp-turbidity. The Kidney is the foundation of the congenital constitution, storing true Yin and true Yang. Cancer is a chronic consumptive disease, which over time inevitably damages the Spleen and Kidney, consuming Qi and injuring Yin [8]. Patients with anti-tumor drug-related rash have deficient healthy Qi and are attacked by drug toxins. Intense fire-toxin internally combines with wind, dampness, and heat, lodging in the skin and interstices. When healthy Qi cannot overcome the pathogen, rash erupts. Modern TCM practitioners generally agree that its core pathogenesis is a deficiency-excess complex, with deficiency of healthy Qi as the root and invasion of drug toxin as the excess manifestation.

2.1 Deficiency of Healthy Qi, Insufficiency of Lung, Spleen, and Kidney

"The Miraculous Pivot • Five Pathogens" states: "When the pathogen is in the Lung, it causes pain in the skin." "Treatise on the Origins and Manifestations of Various Diseases • Sores on the Head, Face, and Body" records: "The Lung governs Qi and manifests in the skin and body hair; the Spleen governs the muscles. Qi deficiency leads to opening of the skin and interstices, being invaded by wind-damp; internal heat leads to warming of the Spleen Qi, and warm Spleen Qi generates heat in the muscles. The combination of dampness and heat results in sores on the head, face, and body." This indicates that the disease location of rash is the Lung, related to the

Spleen and Stomach [9]. The Lung governs the skin and body hair and controls opening and closing. When external pathogens invade, the Lung-Defensive system is the first affected. Impaired diffusion and descent of Lung Qi cause pathogens to stagnate in the skin, leading to rash. Professor JIANG Yilan [10] advocates treating rash from the perspective of the Lung, believing that Lung Qi deficiency allows drug toxins to invade the body, causing rash. However, the Spleen is the mother of the Lung, and the Kidney is the child of the Lung; "fortifying the earth (Spleen) to generate metal (Lung)" and "metal and water (Kidney) mutually engender" can supplement Lung Qi and nourish Lung Yin. HUA Baojin [11] believes the disease location of rash is the Lung, but if prolonged and unhealed, it can damage all five Zang organs. FENG Zhengquan [12] holds that rash onset is mostly related to the Spleen, Kidney, and Liver, emphasizing particularly on strengthening the Spleen, tonifying the Kidney, boosting Qi, and nourishing Yin.

2.2 Invasion of Drug Toxin, Damp-Heat and Fire-Toxin Accumulating in the Skin

"Treatise on the Origins and Manifestations of Various Diseases" states: "Any drug said to be toxic or highly toxic can cause disorder and harm to humans, even killing." This clearly points out that the inherent toxicity of drugs can disrupt human physiological functions. Anti-tumor drugs are regarded as "drug toxin" or "fire toxin" pathogens. This drug toxin invades the body, combining with internal dampness and internal heat, forming "damp-heat fire toxin." LIN Fei [13], summarizing Professor PIAO Bingkui's clinical experience, proposed that internal factors include Zang-fu dysfunction, damp-heat accumulation, and constitutional intolerance, while external factors include drug toxin invasion. The interaction of internal and external factors leads to rash. WANG Hongyan [14] observed that anti-tumor drug-related rash is similar to acne. Ancient physicians believed that the occurrence of rash is mostly closely related to the three pathogens wind, dampness, and heat. Combined with patients' constitutional insufficiency, internal invasion of pathogens leads to wind, dampness, and heat pathogens penetrating the interstices and causing disease.

3. Syndrome Differentiation

Regarding TCM syndrome differentiation for anti-tumor drug-related rash, various physicians, based on their clinical experience, have unique insights and have established distinctive treatment methods, all with good therapeutic effects. Through summary and induction, this article will discuss Wind-Heat Invading the Lung syndrome, Damp-Heat Toxin Accumulation syndrome, Blood Deficiency with Wind-Dryness syndrome, etc.

3.1 Wind-Heat Invading the Lung Syndrome

ZHANG Xinyue et al. [15] observed that the clinical symptoms of patients with anti-tumor drug-related rash change with the duration of medication. In the early stage of the disease, it is primarily characterized by light red papules, with slight itching and tenderness, mostly seen on the upper body, differentiated as Wind-Heat syndrome. Patients taking anti-tumor drugs is equivalent to experiencing Wind-Heat

pathogens. The disease location is in the Lung channel, specifically Lung Channel Wind-Heat. DONG Huijing et al. [16] believe the disease location of rash is the Lung, manifesting in the skin and body hair. The early stage is primarily Wind-Heat, accompanied by dampness. Treatment should focus on dispersing wind and clearing heat, assisted by drying dampness. The initial stage belongs to the phase of resisting the pathogen; thus, expelling the pathogen should take precedence, with mild supplementation. Zhiyang Pingfu Formula can be selected. ZENG Yonglei [17] clinically treats based on both deficiency and excess aspects. If the rash is mainly on the head, face, and anterior chest, mostly confined to the upper body, it belongs to the Wind-Heat type rash. Main manifestations include red rash, itching, red tongue, floating and rapid pulse, possibly accompanied by related exterior symptoms like aversion to cold and fever, headache, nasal congestion, cough, etc. Treatment often uses methods to dispel wind, relieve itching, clear heat, and cool blood. HUA Jinbao [18] believes that clinical treatment of anti-tumor drug-related rash should be staged according to the severity of the rash. The early stage mostly belongs to Wind-Heat syndrome, treated by dispelling wind and detoxifying, using modified Xiaofeng San (Wind-Dispersing Powder).

3.2 Damp-Heat Toxin Accumulation Syndrome

Professor JIANG Yilan et al. [19] advocate treating anti-tumor drug-related rash from the "Lung" perspective, believing it is related to Wind-Heat, Damp-Heat, and Fire-Toxin pathogens. The rash is red, with both maculopapular eruptions, blisters, pustules, or even erosion, exudation, and epidermal peeling. Accompanied by burning heat, irritability, dry mouth, etc., differentiated as Damp-Heat Accumulating in the Skin syndrome. The method is to clear heat and eliminate dampness, potentially adding Xia Ku Cao (Prunella Vulgaris), Yi Yi Ren (Coix Seed), Ku Shen (Sophora Flavescens), Bai Xian Pi (Dictamnus Dasycarpus), etc. YANG Tiandi et al. [20] believe that patients initially developing rash from anti-tumor drugs are mostly physically robust, with acute onset rash, mostly excess syndromes. Manifestations include bright red skin all over the body in patches or dense millet-like papules, burning, itching, and pain in the rash area, raised above the skin, with clear borders, varying sizes, severe itching, accompanied by body fever, dry mouth and thirst, constipation, yellow urine, red tongue with yellow coating, rapid pulse, etc. This mostly belongs to Heat-Toxin Accumulation syndrome. Treatment should clear heat, resolve toxin, and cool blood, using modified Qingying Tang (Ying Level Clearing Decoction).

3.3 Blood Deficiency with Wind-Dryness Syndrome

CUI Huijuan [21] believes that dry skin often appears after the rash, in the late stage of the disease. Blood deficiency fails to moisten the skin and muscles. "Treat wind by first treating blood; when blood moves, wind disappears spontaneously." The basic principle is to nourish Yin, nourish blood, and moisten dryness. The formula selected is Zizao Yangrong Tang (Dryness-Moistening and Nourishing Decoction). GUO Peng [22] found that the severity of the disease is related to the pathogenic factors. In the late stage of the disease, Blood Deficiency syndrome appears, often manifested as generalized skin redness, dryness, desquamation, itching, like

chaff or husks, subtle itching worse at night, accompanied by thirst with desire to drink, dry stool, scanty dark urine. Crimson tongue with little coating, even fissured, thready and rapid pulse. In the late stage of the disease, the tongue and pulse are particularly crucial. A red tongue with little coating is often seen as a sign that Yin fluid is already damaged and healthy Qi is difficult to restore.

4. TCM Treatment

4.1 Internal Treatment

WANG Ting [23] used Xiaofeng San (Wind-Dispersing Powder) (Jing Jie (Schizonepeta) 15g, Fang Feng (Saposhnikovia) 10g, Chao Niu Bang Zi (Stir-fried Arctium Lappa) 15g, Chan Tui (Cicada Moults) 10g, Fu Chao Cang Zhu (Stir-fried Atractylodes) 10g, Ku Shen (Sophora Flavescens) 15g, Xiao Tong Cao (Ricepaper Plant Pith) 10g, Shi Gao (Gypsum) 20g, Zhi Mu (Anemarrhena) 15g, Di Huang (Rehmannia) 15g, Dang Gui (Angelica) 15g, Huo Ma Ren (Hemp Seed) 30g, Gan Cao (Licorice) 5g) to treat the Wind-Heat pattern of this disease, using hydrocortisone as the control group. Results showed that the total effective rate of the TCM group was significantly better than the control group. The TCM group had greater advantages in improving clinical symptoms and enhancing patients' quality of life, with no significant adverse reactions. HU Lingjing [24] used Jiedu Xiaoban Tang (Toxin-Resolving and Macule-Dispersing Decoction) (Shui Niu Jiao (Water Buffalo Horn) 15g, Mu Dan Pi (Moutan Bark) 15g, Chi Shao (Red Peony) 15g, Sheng Di Huang (Raw Rehmannia) 15g, Zao Jiao (Gleditsia Sinensis) 15g, Shi Gao (Gypsum) 15g, Zhi Mu (Anemarrhena) 15g, Bai Mao Gen (Imperata Rhizome) 30g, Dang Gui (Angelica) 10g, Chao Mai Ya (Stir-fried Barley Sprout) 30g, Di Fu Zi (Kochia Scoparia) 15g, Bai Xian Pi (Dictamnus Dasycarpus) 15g, Jing Jie (Schizonepeta) 10g, Qian Li Guang (Senecio Scandens) 30g, Jiu Huang Qin (Wine-fried Scutellaria) 15g, Gan Cao (Licorice) 6g) to treat the pattern of Internal Accumulation of Heat-Toxin and Burning in both Qi and Blood levels. Clinical experience summary found that this formula significantly alleviated patient rash. ZHANG Feng [25] used Jiawei Yangyin Tang (Modified Yin-Nourishing Decoction) (Bei Sha Shen (Glehnia) 12g, Jin Yin Hua (Lonicera), Pu Gong Ying (Dandelion), Sheng Di Huang (Raw Rehmannia), Ban Zhi Lian (Scutellaria Barbata), Fu Ling (Poria), Chao Mai Ya (Stir-fried Barley Sprout) each 15g, Mai Dong (Ophiopogon) 10g, Bai Hua She She Cao (Hedyotis) 30g, Da Zao (Jujube) 10g, Ku Shen (Sophora Flavescens), Zhi Gan Cao (Prepared Licorice) each 6g) to treat the Yin Deficiency with Internal Heat pattern of this disease. The study found that Jiawei Yangyin Tang had significant overall efficacy. Compared with the control group, it shortened the time to first disappearance of rash and alleviated the condition. MENG Sinian [26] used Yinhuang Heji (Lonicera and Scutellaria Mixture) (Jin Yin Hua (Lonicera) 12g, Lian Qiao (Forsythia) 12g, Zhu Ye (Phyllostachys) 10g, Jing Jie (Schizonepeta) 15g, Niu Bang Zi (Arctium Lappa) 12g, Bo He (Mint) 15g, Dan Dou Chi (Fermented Soybean) 8g, Jie Geng (Platycodon) 12g, Lu Gen (Phragmites Rhizome) 10g, Shui Niu Jiao (Water Buffalo Horn) 15g, Sheng Di (Raw Rehmannia) 30g, Chi Shao (Red Peony) 15g, Dan Pi (Moutan) 10g, Bai Xian Pi (Dictamnus Dasycarpus) 15g, Zi Cao (Lithospermum) 8g, She Chuang Zi (Cnidium) 15g, Gan Cao (Licorice) 6g) to treat

the Blood Deficiency with Wind-Dryness pattern of this disease. Results showed that Yinhuang Heji had a good therapeutic effect. Compared with the control group, it significantly reduced inflammatory cytokine levels and had good safety.

4.2 External Treatment

LIU Weidong [27] used Qingre Runzao Gao (Heat-Clearing and Dryness-Moistening Ointment) to treat targeted drug-related rash. The control group was treated with external application of Compound Flumetasone Ointment. Results showed that the total effective rate and quality of life score (KPS) in the observation group were higher than the control group. External application of Qingre Runzao Gao had definite efficacy and significantly improved patients' quality of life. LI Yang et al. [28] used a self-formulated Chinese herbal external wash formula to treat this disease. The control group was given Calamine Lotion. Results showed that the effective rate for patients with grade 1 rash was higher than for those with grade 2 or grade 3 rash. The milder the rash grade, the better the treatment effect. LIU Qing [29] used Jingfang Jiedu Fang (Schizonepeta-Saposhnikovia Toxin-Resolving Formula) for external washing combined with routine care to treat erlotinib-related rash. The study found that the effective rate in the TCM group was higher than the control group, and it could reduce the severity of the rash and improve itching symptoms.

4.3 Comprehensive Treatment

GAO Yajun [30] used the Chinese herbal formula Zhiyang Fang (Itch-Relieving Formula) for both internal administration and external washing to treat rash caused by targeted drugs. The control group received conventional treatment. The study found that the improvement in rash grading in the observation group was significantly better than the control group. TCM syndrome scores, NRS scores, DLQI scores, IL-6 levels, and hs-CRP levels were all significantly reduced. The internal and external use of Zhiyang Fang was significantly effective, inhibiting inflammatory reactions and promoting skin lesion repair. MA Xiaoli et al. [31] used Qingzao Jiufei Tang (Dryness-Clearing and Lung-Rescuing Decoction) combined with Yinqiao Sanhuang Gao (Lonicera-Forsythia Three-Yellow Ointment) to treat lung adenocarcinoma targeted drug-related rash, using Hydrocortisone Butyrate Cream as the control. Results showed that the treatment group was superior to the control group in terms of TNF- α , sICAM-1, IL-1 β , M-CSF, CXCL10, NF- κ B, TSLP, CYFRA21-1, CK19-2G2, TGF- α , rash area, itching score, and rash grade. Stratum corneum hydration and sebum content were higher than the control group. This medication can inhibit body inflammation, improve epidermal growth factor receptor signal transduction, enhance skin barrier function, improve rash grading, and increase clinical efficacy. ZHAO Fangmin et al. [32], based on data mining to explore the medication rules of TCM for this disease, found that heat-clearing drugs were the most widely used, followed by deficiency-tonifying drugs and blood-activating stasis-resolving drugs. The high-frequency drug was Huang Qi (Astragalus), followed by Bai Hua She She Cao (Hedyotis), Yi Yi Ren (Coix Seed), Xuan Shen (Scrophularia), and Jin Yin Hua (Lonicera).

5. Summary and Outlook

TCM considers the pathogenesis of anti-tumor drug-related rash as mostly a deficiency-excess complex. Innate deficiency of healthy Qi, combined with invasion of drug toxin, leads to dysfunction of the Zang-fu organs. The Lung is the canopy; external pathogens invading first affect the Lung. Its core disease location involves the Spleen, and prolonged course damages the Kidney. The occurrence of anti-tumor drug-related rash is closely related to the Lung, Spleen, and Kidney. Treatments often employ methods such as dispersing wind and clearing heat, supplementing Lung Qi, clearing heat and draining dampness, strengthening the Spleen and tonifying the Kidney, nourishing Yin and blood, etc., reflecting the idea of combining supporting the healthy (Fuzheng) and dispelling the pathogenic (Quxie). Treatment methods often use external therapies to reach the affected area directly, accelerating symptom relief with no significant toxic side effects; internal administration of Chinese herbs applies treatment based on syndrome differentiation via the holistic concept, balancing the body's Qi, Blood, Yin, and Yang. Used alone or in combination, both have good clinical efficacy and are worthy of clinical application and promotion.

The pathogenesis of anti-tumor drug-related rash is complex, making conventional symptomatic treatment difficult to achieve good results. Current Western medical treatment primarily relies on glucocorticoids, antihistamines, antibiotics, and steroids, with certain adverse reactions and limitations associated with long-term use [33]. Many studies [34-36] have shown that the efficacy of TCM or integrated Chinese-Western medicine in treating this disease is superior to Western symptomatic treatment groups, improving patient quality of life, alleviating clinical symptoms, and achieving the therapeutic effect of reducing toxicity and enhancing efficacy. The reason may be related to the multi-component, multi-target characteristics of Chinese herbal formulas, which can intervene in the pathogenesis of anti-tumor drug-related rash through multiple pathways. Related research [37, 38] indicates that Ma Chi Xian (Portulaca) and Ku Shen (Sophora Flavescens) can inhibit inflammatory factors, regulate immunity, and improve skin barrier function. Zi Cao (Lithospermum) preparations have anti-inflammatory, skin barrier repair, and regulation of cell proliferation and apoptosis effects [39].

Through multi-pathway, multi-target integrated regulation, TCM has definite efficacy in preventing and treating anti-tumor drug-related rash, effectively relieving symptoms, improving patient quality of life, and allowing anti-tumor treatment to proceed smoothly. However, TCM components are complex. Future research still needs to further explore its mechanism of occurrence, further clarify the action targets and pathways of Chinese herbal formulas, gradually establish unified syndrome differentiation standards, promote the standardization of clinical diagnosis and treatment, and bring benefits to patients.

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