

Prevention and Treatment of Different Syndrome Types of Diarrhea Caused by Irinotecan with Traditional Chinese Medicine

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Abstract: Delayed diarrhea, as one of the most common toxic reactions of irinotecan, has different degrees of influence on the progress of treatment and quality of life of patients. This article analyzes, summarizes and summarizes the related literature on the prevention and treatment of irinotecan-induced delayed diarrhea with traditional Chinese medicine, in order to provide experience guidance for clinical treatment of different syndrome types of diarrhea.

Keywords: Irinotecan, Delayed diarrhea, Traditional Chinese medicine.

1. Introduction

Irinotecan (CPT-11), a cell cyclin-specific antitumor drug [1], belongs to hydroxycamptothecin derivatives. Its mechanism of action is mainly by inhibiting the activity of topoisomerase I, interfering with DNA replication and repair process, inducing DNA single strand breaks, and finally inducing apoptosis [2] of tumor cells. The drug has been widely used in the combination chemotherapy of colorectal cancer, lung cancer, ovarian cancer and other solid tumors [1]. However, SN-38, its active metabolite, can specifically damage intestinal epithelial cells and cause delayed diarrhea in up to 82% of patients (Rosenof study data), which seriously affects treatment compliance and clinical efficacy.

Loperamide, the first-line drug for the treatment of such diarrhea in modern medicine, alleviates the symptoms of diarrhea by inhibiting gastrointestinal peristalsis, increasing the passage time of contents and selectively inhibiting bile secretion. However, with the increase of drug dose, it will increase the possibility of paralytic ileus, and preventive administration is not possible. Octreotide acetate inhibits gastrointestinal peristalsis by reducing the secretion of digestive enzymes and gastric acid, increases the absorption of water and electrolytes, and promotes gastrointestinal repair [3]. Octreotide acetate is used for the treatment of diarrhea that is ineffective with loperamide. In addition, there are sodium bicarbonate that alkalinizes the intestine, neomycin that reduces the activity of intestinal enzymes, celecoxib that inhibits the synthesis of prostaglandins, and so on. These drugs may not be effective in the treatment of diarrhea or can not be used for a long time due to excessive side effects, so there is a certain limitation in the treatment.

Recent studies have shown that traditional Chinese medicine (TCM) shows its unique therapeutic value through multi-component and multi-target mechanism of action: holistic regulation: taking into account anti-diarrhea, anti-inflammation, mucosal repair and immune regulation function; Card type partition: according to the spleen and stomach weak, such as hot and humid embodiment of TCM syndrome characteristics choose prescriptions (such as

scattered, radix scutellariae and three atractylodes soup); Reduce the side effect: MDT can reduce loperamide dependence, improve patient quality of life. Clinical evidence shows that traditional Chinese medicine has significant advantages in reducing the incidence of delayed diarrhea by 40%-60%, shortening the course of disease and improving the intestinal barrier function, which provides new ideas for optimizing the management of chemotherapy toxicity.

2. Asthenia of Spleen and Stomach

“When the pathogenic factors gather together, the qi will be deficient”, and the weak temper is the basic pathogenesis of this disease. The weakness of the spleen and stomach, the loss of spleen movement, causes diarrhea. Therefore, the treatment of the disease should be to strengthen the spleen and benefit qi. The representative prescriptions mainly include Shenling and Baizhu powder, Invigorating spleen and invigorating qi prescription, ginseng and invigorating spleen pill, etc.

Shenlingbaizhu powder is made on the basis of Sijunzi decoction with yam, lotus seed, white lentil, Coicis seed, sand seed and platycodin. It is mainly used for spleen deficiency and dampness. Tian Yanping et al [4] conducted a randomized controlled trial. The total effective rate of the treatment group (Shenlingbaizhu powder combined with loperamide) was 95.24%, which was significantly higher than that of the control group (71.43%, $P < 0.05$). The combination of traditional Chinese medicine and western medicine can simultaneously improve the clinical symptoms such as abdominal distension and poor appetite, and reduce the risk of grade 3 diarrhea.

Ginseng Jianpi pill contains ginseng, Poria, fried Atractylodes atractylodes, yam, tangerine peel, wood incense, sand kernel, fried astragalus mongholicus, Angelica sinensis, fried sour jujube kernel, and polygala. It is derived from Jianpi pill in the Criteria for Syndrome and Treatment, and has the functions of invigorating spleen, invigorating qi, and stopping diarrhea in stomach. Cui Qingli [5] et al treated the patients with auxiliary symptomatic and supportive treatment as the control group. The incidence of diarrhea in the treatment group (ginseng

Jianpi pill combined with supportive treatment) was 27.5%, which was 52% lower than that in the control group (57.5%) ($P < 0.05$). The serum levels of IL-6, TNF- α and other inflammatory factors in the treatment group were significantly decreased ($P < 0.05$), suggesting the anti-inflammatory regulatory effect of ginseng Jianpi-pill.

The spleen-instilling and Qi-instilling formula was modified and modified with Xiangsha Liujunzi Decoction (from Ancient and Present Famous Medical Prescriptions) as the basic formula. The basic ingredients included fried Astragali radix, Codonopsis cocos, Codonopsis cocos, fried Atractylodes atractylodes rhizoma, fried licorice rhizoma, rhizoma alba, rhizoma alba, rhizoma pinelliae, fried yam, Rhizoma coptidis and Coicis seed. The combination of all kinds of herbs plays a role in invigorating the spleen, regulating qi, removing dampness and stopping diarrhea. Chen Xianru et al. [6] found that the severity of diarrhea, clinical symptom score and physical status score in the treatment group were better than those in the blank control group ($P < 0.05$). The prescription could simultaneously improve irinotecan-based chemotherapy-induced neutropenia (38% reduction), showing a multi-target protective effect.

3. Pneumoconiosis Type

Originated from the theory of “harmony of smell” in Huangdi Neijing, it emphasizes the compatibility of spicy herbs (such as Pinellia, dried ginger) and bitter herbs (such as Rhizoma coptidis and scutellaria baicalensis). By using the properties of spicy powder to raise Yang and bitter powder to reduce turbidity, it regulates the rise and fall of qi mechanism of zangfu organs and balance Yin and Yang. Zhang Zhongjing’s Shang Han Za bing Lun (Treatise on Cold pathogenic Diseases) created Sanxiexin decoction based on the syndrome differentiation of six meridians, taking the method of “opening bitter and lowering, sweet herbs and Zhongzhong” as the method. The representative prescriptions mainly include Xiexin decoction (Banxia Xiexin decoction, ginger Xiexin decoction, licorice Xiexin decoction, aconitum Xiexin decoction), Tongxiexin Yao decoction, Wumei pill, Xiaochu Chaihu decoction, etc. It created a precedent for the flexible application of the Xin-Kai-Ku-jiang-method in later generations. The disorder of spleen and stomach qi is one of the pathogenic links of delayed diarrhea. Therefore, the Xin-Kai Ku-Jiang method has unique advantages [7] in clinical application.

This decoction heart soup from the eastern han zhang zhongjing “typhoid miscellaneous disease theory” (pinellia, radix scutellariae, rhizoma coptidis, dried ginger, ginseng, jujube), has the inverse of the drop and eliminate the effect of the new fights, attending heart under under the new full, vomiting, bowel, etc. Liu Shuyu et al [8] used irinotecan chemotherapy and Banxia Xiexin decoction as an adjuvant therapy. The drug was taken 1 day before chemotherapy and continued for 15 days, and the incidence of delayed diarrhea decreased to 18.0%. Banxia Xiexin decoction in the treatment of malignant tumor patients with irinotecan chemotherapy regimen can play a certain preventive effect on delayed diarrhea, reduce the drug toxicity to blood, reduce the degree of nausea and vomiting, and has certain clinical application value. Modern pharmacological studies have proved that

Banxia Xiexin decoction has the effects of anti-gastrointestinal inflammation, two-way regulation of gastrointestinal motility, anti-oxidative stress, and can repair mucosal barrier and enhance immune function [9].

Jiang-xiexin decoction is composed of two pieces of dried ginger and four pieces of ginger in Banxia - Xiexin decoction, which can enhance the power of dispersing water and air and clearing away impurities and turbidity. The control group was given FOLFIRI chemotherapy, and [10] the observation group was treated with Jiang-Xiexin decoction. The duration of diarrhea in the observation group (FOLFIRI chemotherapy + jiang-Xiexin decoction) was 58% shorter than that in the control group (2.49 ± 1.76 days vs 5.49 ± 2.58 days, $P < 0.05$), and the incidence of grade 3 to 4 diarrhea was 40% lower than that in the control group. It can effectively prevent and treat nausea and vomiting and delayed diarrhea, significantly improve the quality of life of patients with chemotherapy, reduce the risk of treatment interruption, and improve the efficacy of chemotherapy, which has significant clinical value.

Tongxie Yaofang is a famous prescription in Danxi Xinfu, a traditional Chinese medicine classic. It is composed of Atractylodes atractylodes rhizoma, Radix paeoniae alba, Tangerine peel and Fengfeng. It has the functions of regulating liver and spleen, alleviating acute and relieving diarrhea. Niu Wei- [11] ping’s randomized controlled trial showed that the incidence of delayed diarrhea in the treatment group was 35.0%, which was significantly lower than that in the blank control group (62.5%) ($P < 0.05$).

Wumei pill was found in Zhang Zhongjing’s Shang han Za bing Lun (Treatise on Cold Pathogenic and Miscellaneous Diseases) for Jueyin syndrome, which can treat diarrhea. It belongs to the category of “diarrhea” in traditional Chinese medicine. As a traditional Chinese medicine, Wumei has the functions of collecting lung, astringent intestine, promoting body fluid and relieving ascaris lumbricis. Clinical studies have found that black plum and its preparations have obvious effects on the treatment of antibiotic-associated diarrhea, diabetic diarrhea, cold and heat complex chronic diarrhea, lapatinib and capecitabine induced diarrhea. Song Yuanyuan et al [12] demonstrated that water extract of dark plum could protect the integrity of intestinal mucosa, up-regulate the ratio of colonic CD4+/CD8+ T cells ($P < 0.05$), and inhibit the expression of TNF- α , IL-1 β and other pro-inflammatory factors. It is effective in the treatment of irinotecan-related diarrhea and antibiotic-related diarrhea, and has no dose-dependent toxicity.

4. Damp-heat Internal Excess Type

Radix scutellariae soup from treatise on febrile disease, by four herbs, radix scutellariae, peony, liquorice, big jujube, attending the “sun and shaoyang disease, since the person”, has clear heat drying dampness, mediate the effect of liver and spleen, pain, for the classic prescription for the treatment of flow field under hot and humid. By establishing an irinotecan mouse diarrhea model, Liu Pingkun [13] systematically evaluated the changes of intestinal mucosal state before and after the intervention of HQ decoction. Hq decoction promoted the regeneration of intestinal epithelial cells,

up-regulated the expression of mucin (MUC2) and tight junction proteins (ZO-1, Occludin), and repaired the intestinal mucosal mechanical barrier. It also reshaped the structure of intestinal flora (increased the abundance of Bifidobacterium by 2.1 times), formed bacterial membrane barrier, and inhibited the translocation of pathogenic bacteria. It also significantly reduced the levels of TNF- α and IL-6 in colon tissue (by 45%, $P < 0.05$) and alleviated immune damage. Furthermore, it alleviates the intestinal toxic side effects such as delayed diarrhea caused by irinotecan.

Yu Yang et al. [14] observed the efficacy of modified Huangqin decoction in the prevention of irinotecan-induced delayed diarrhea. A total of 72 patients with advanced colorectal cancer who received FOLFIRI regimen were enrolled and randomly divided into control group (34 cases) and treatment group (38 cases). The incidence of delayed diarrhea in the treatment group was reduced by 53% ($P < 0.05$). The adjustment rate of chemotherapy regimen was reduced by 40%, and the incidence of nausea and vomiting was reduced by 62%. The average KPS score was increased by 15 points ($P < 0.05$).

Wu Qiong et al. [15] randomly divided 40 mice into normal control group, diarrhea model group, and low-, medium-, and high-dose HQD groups to test the dose-dependent protective effect of HQD. Compared with the model group, the incidence of diarrhea in the medium- and high-dose HQD groups (6 g/kg, 12 g/kg) decreased by 65% and 78% ($P < 0.01$). In the high-dose group, the rate of body weight recovery was increased by 2.3 times, and the colonic pathological damage score was decreased by 70%. HQD can prevent the occurrence of CPT-11 delayed diarrhea and reduce the degree of diarrhea through multi-target cooperation: Baicalin inhibits the NF- κ B signaling pathway and reduces the release of pro-inflammatory factors; Paeoniflorin activates PI3K/Akt pathway and promotes the synthesis of tight junction proteins. Glycyrrhizic acid regulates intestinal pH and optimizes the environment for probiotic colonization.

5. Spleen and Kidney Deficiency Type

Four gods pills from the universal skill party, for the treatment of spleen and kidney Yang deficiency even diarrhea caused by classical prescription, composition of nutmeg, fructus schisandrae, malaytea scurfpea fruit, evodia rutaecarpa, embody "warm the kidney and spleen, shibuya intestinal solid take off" treatment, conjunction "tonifying spleen kidney is better than" theory; The mechanism of action: psoralen activates kidney Yang, Wuzhuyu warms the middle and dissipates cold, synergistically restores spleen and kidney Yang qi, and restores the circulation of middle jiao. Xiao-lu [16] wang to stand for such as kang of late-onset diarrhea caused by chemotherapy regimens are divided into control group and treatment group, treatment group (four gods pill combined loperamide) total effective rate was 97.67%, than the control group (loperamide) 35% increased ($P < 0.05$), the difference of two groups have statistical significance. The regimen significantly shortened the duration of diarrhea (average 4.2 days), and reduced the risk of dehydration and electrolyte disturbance.

Thrift beneficial intestinal piece from the "Chinese

pharmacopoeia", efficacy mainly spleen and kidney, double filling, severely, is s for the treatment of spleen and kidney Yang deficiency type of diarrhea, by astragalus, codonopsis, atractylodes, yam, liquorice, malaytea scurfpea fruit, gun ginger, rhizoma corydalis, radix aucklandiae, red halloysite, garden burnet, catechu. The patients in the experimental group were treated with Gubenyichang tablets on the basis of the control group. The results showed that compared with the single drug group, the incidence of grade 3-4 diarrhea in the combined group (Gubenyichang tablets + loperamide) was reduced by 48% ($P < 0.05$); [17] The average daily dosage of loperamide was reduced by 62%, and the incidence of side effects such as constipation was decreased simultaneously. The patient's quality of life score (QOL-C30) was increased by 25%, and the tolerance of chemotherapy was significantly improved. Gubenyichang tablets combined with loperamide can effectively treat irinotecan chemotherapy-related diarrhea, alleviate the symptoms of diarrhea and improve the quality of life of patients, which has high clinical application value.

The self-made Hewei - Guchang decoction is composed of scutellaria baicalensis, Astragalus membranaceus, Codonopsis radix, pomegranate peel, Schisandrae fructus, chebula fructus, dried ginger, jujube, tangerine peel, fried Atractylodes rhizoma, fried yam, Wuzhuyu, nutmeg and licorice root. In the prospective study by Yang Lei [18] et al., the incidence of late-onset diarrhea in the prevention group (oral Hewei - Guchang decoction 2 days before chemotherapy) was 19.1%, which was 46% lower than that in the control group (35.4%) ($P < 0.05$). The formula could up-regulate the expression of intestinal tight junction protein Claudin-1 (1.8-fold, $P < 0.01$) and inhibit the inflammatory response mediated by TLR4/NF- κ B pathway.

6. Other Therapies

Li Jing [19] et al were randomly divided into the treatment group. One day before the chemotherapy regimen containing CPT-11, thunderfire moxibustion was applied to Geshu (BL 23), Danshu (BL 23), Dachangshu (BL 23) and Tianshu (ST 25) 2-3cm away from the skin, 30 minutes each time, once a day for 7 days. The control group was treated with chemotherapy regimen containing CPT-11 only. The incidence of delayed diarrhea in the treatment group was 40% lower than that in the control group ($P < 0.05$). The incidence of neutropenia decreased by 35%, and the patients' performance status (ECOG score) improved significantly. The use of thunder-fire moxibustion to warm the acupoints can broaden the chest and regulate qi, regulate qi and promote blood circulation, and reduce the degree of bone marrow suppression after chemotherapy. It can also adjust the function of the gastrointestinal tract, slow down the excessive peristalsis of the large intestine, promote digestion and absorption to enhance the patient's resistance, tonic temper, and strengthen the role of the spleen as the main body and astringent; It has a good preventive effect on leukopenia, neutropenia and delayed diarrhea after irinotecan chemotherapy.

Li Xiaomei [20] et al divided the experiment into two groups. On the basis of the control group, the observation group was treated with moxibustion at 5:00 to 7:00 every day for 6 consecutive days. The total incidence of delayed diarrhea in

the observation group was 28.6%, which was 50% lower than 57.1% in the control group ($P<0.05$). The duration of grade 3-4 diarrhea was shortened by 2.1 days (3.2 ± 1.5 days in the observation group vs 5.3 ± 2.1 days in the control group, $P<0.01$). The patient's appetite score (FAACT scale) increased by 30%, and the tolerance of chemotherapy was significantly improved.

Lai Xianghong [21] used self-made moxa salt package to hot iron Shenque (CV 8) 1 day before chemotherapy, once a day, 30 minutes each time, for 5 consecutive days. The adjustment rate of chemotherapy regimen (interruption due to diarrhea) in the observation group was 45% lower than that in the control group ($P<0.05$). The Shannon index of intestinal flora was increased by 1.8 times ($P<0.01$), and the Bifidobacterium/Escherichia coli ratio was significantly improved.

In the experimental group [22], they used the method of rectal instillation of traditional Chinese medicine to instillation Gegenqinlian decoction one day before chemotherapy, once a day for 7 days. The incidence of delayed diarrhea in the prevention group was 21.4%, which was 50% lower than that in the control group (42.9%) ($\chi^2=5.934$, $P=0.015$). The total effective rate was increased by 60% (85.7% vs 57.1% in the control group, $\chi^2=4.200$, $P=0.040$). The intestinal mucosal barrier index (serum diamine oxidase) level returned to the normal range (158.3 ± 21.5 U/L vs 98.7 ± 18.6 U/L, $P<0.01$).

7. Summary

In the treatment of irinotecan-induced diarrhea, the combination of traditional Chinese medicine and western medicine shows its unique advantages. Enhanced efficacy and attenuated toxicity: traditional Chinese medicine reduces the dose dependence of western medicine and alleviates the risk of paralytic ileus; Multi - target intervention: simultaneous regulation of intestinal mucosal barrier, immune inflammation and fluid metabolism; Individualized treatment: according to the characteristics of different syndromes, precise prescription selection can improve the repeatability of therapeutic effect. Traditional Chinese medicine (TCM) provides a breakthrough solution for irinotecan-related diarrhea through its unique advantages of "holistic adjustment and treatment of both symptoms and root causes". In the future, it is necessary to deeply integrate modern science and technology to promote the collaborative treatment of traditional Chinese medicine and western medicine to become the standard of supportive care for cancer.

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