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Overview of Radiation Enteritis and Progress in Treatment of Traditional Chinese and Western Medicine

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Abstract: Radiation enteritis (RE) is one of the most severe and common complications of abdominal or pelvic tumor radiation therapy. The affected intestinal lesions are extensive, with complex pathological manifestations, severely affecting the quality of life of cancer patients after radiotherapy. However, currently there are few clinical drug treatment methods and the effects are not satisfactory, and the related basic research and new drug development are still unclear. This article reviews the relevant literature in recent years, summarizes and analyzes the pathological mechanisms, treatment strategies, and the understanding and treatment methods of radiation enteritis in Western medicine, in order to provide ideas and directions for the prevention and treatment strategies and drugs of radiation enteritis research.

1. Introduction

Radiotherapy is now one of the main methods for cancer treatment, playing an important role in the comprehensive treatment of complex abdominal and pelvic malignant tumors. It plays a vital role in improving tumor local control rate and patient quality of life [1]. In recent years, the number of patients with abdominal and pelvic malignant tumors treated with radiation therapy has increased significantly, and the incidence of radiation enteritis (RE), as a byproduct of radiation therapy for abdominal and pelvic malignant tumors, has also increased. Radiation enteritis, also known as radiation enteropathy, radiation mucositis, and pelvic radiation disease, is one of the most serious complications of intestinal tract caused by radiation therapy for abdominal and pelvic malignant tumors, which is almost unavoidable in the process of radiation therapy for abdominal and pelvic malignant tumors, because the intestine is one of the most sensitive organs in the human body, especially the small intestine. After radiotherapy, patients often experience adverse reactions such as vomiting, weight loss, loss of appetite, diarrhea, and infection, and severe damage can lead to patient death due to septic shock. Radiation enteritis is clinically divided into acute and chronic types. Acute radiation enteritis is caused by direct damage to the intestinal mucosa by radiation, leading to diarrhea, which usually resolves naturally within 2-12 weeks. Chronic radiation enteritis occurs months to years after radiation exposure, often leading to intestinal perforation, intestinal obstruction, chronic diarrhea, and malnutrition [2]. RE has attracted certain attention in clinical practice, but its pathogenesis is complex and unclear, and there is a lack of effective preventive or therapeutic drugs. The incidence of malignant tumors in Chinese mainland is increasing year by year, and the number of patients receiving radiotherapy is also increasing [3]. Radiation enteritis, as

a common complication of radiotherapy, needs more attention. Due to its atypical clinical symptoms, it is necessary to further study the pathological mechanism of radiation enteritis and more accurately differentiate it from other intestinal diseases in clinical diagnosis. At the same time, it is also possible to refer to the research results of inflammatory bowel disease with similar pathological features, and carry out in-depth research on the role of various immune cells in the course of radiation enteritis, and provide a theoretical basis for the subsequent research and development of drugs regulating immune microenvironment.

2. Mechanism of Radiation Enteritis

2.1 Effects of Radiation on Intestinal Epithelial Cells

The intestinal epithelial tissue is renewed approximately every 3-5 days, with the renewal time of intestinal stem cells being about 110 hours. Under normal conditions, the intestinal epithelium has low permeability and possesses certain secretion and absorption functions. Its dynamic balance is of great significance in maintaining the barrier function of the intestinal mucosa and electrolyte balance. Under high-energy radiation, the secretion-absorption dynamic balance of the intestinal epithelium is disrupted, permeability increases, intestinal motility accelerates, and diarrhea is more likely to occur. Studies have found that radiation decreases the secretion function of the intestinal epithelium, reduces the activity of Na-K-ATPase, and decreases water absorption by the intestines [4].

2.2 Radiation-induced Damage to Intestinal Blood Vessels

Radiation-induced vascular damage is an important cause of radiation enteritis. Evidence suggests that radiation therapy promotes endothelial cell apoptosis and swelling, increases permeability, weakens fibrinolytic enzyme activity, causes deposition of interstitial fibrosis, and leads to thrombus formation. (1) Endothelial Cells: Jerzy et al. [5] believe that radiation-induced damage to the endothelial cells of the intestinal blood vessels (capillaries) is the cause of radiation enteritis. Bradley [6] conducted another experiment to investigate the relationship between endothelial cell damage and radiation enteritis. The results showed that selective irradiation of endothelial cells did not aggravate the severity of radiation enteritis. Further research is needed to confirm the relationship between endothelial cell damage and radiation enteritis. (2) Thrombomodulin and activated protein C: Thrombomodulin is highly expressed in normal intestinal microvascular endothelial cells. After radiotherapy, intestinal microvascular injury leads to decreased thrombomodulin levels, impaired clearance of thrombin, and increased accumulation of thrombin, which exacerbates intestinal inflammation and chronic fibrosis. In surgical specimens of patients with radiation enteritis, the levels of thrombomodulin decrease more than 6 times compared to normal levels, and the degree of decrease is dose-dependent. Changes in thrombomodulin occur before the onset of radiation enteritis.

2.3 Intestinal Flora and Radiation Enteritis

Intestinal flora plays an important role in reducing the colonization of pathogenic bacteria in the gut, inhibiting the binding of pathogenic bacteria to the intestinal epithelial cells, suppressing the invasion of pathogenic bacteria, promoting the secretion of β-defensins, maintaining the normal renewal of intestinal epithelium, cultivating the intestinal immune system, and regulating development. Radiation enteritis (RE) can cause dysbiosis of the intestinal flora, which in turn affects the prognosis of RE patients and leads to various diseases including intestinal infections and

multiple organ dysfunction syndrome. It was discovered in 1900s that intestinal flora can aggravate radiation enteritis. Studies have shown that: (1) At the 50% lethal dose, germ-free (GF) mice have a higher survival rate than mice with normal flora. (2) At the lethal dose, GF mice have a longer survival time than mice with normal flora. (3) At the radiation dose that causes pathological changes in radiation enteritis, GF mice have a higher incidence than mice with normal flora. In experiments, Peter [7] found that GF mice have a stronger resistance to radiation injury. This is mainly reflected in the fact that at the same radiation dose, the mortality rate of GF mice is significantly lower than that of mice with normal flora. The mechanisms by which radiation disrupts the intestinal flora are: (1) The surface structure of intestinal epithelial cells is damaged by radiation, and indigenous bacteria such as lactobacilli, bifidobacteria, and enterococci cannot firmly attach to the intestinal epithelium. (2) The normal flora in the intestine is disrupted by radiation, inhibiting growth or even directly killing them. (3) The microvilli of RE patients are damaged, leading to a decrease in intestinal clearance ability and disruption of the flora.

2.4 Sensory Nerve with Radiation Enteritis

The severity of radiation-induced intestinal injury is determined by the interaction between enteric neurons and the immune system. Relevant experiments have shown that mice with excised enteric sensory neurons have a more severe reaction to radiation-induced enteritis. Enteric neurons release various neuropeptides, which directly or indirectly participate in neuroimmune modulation. The removal of enteric mast cells partially offsets the exacerbation of radiation-induced enteritis caused by the removal of enteric sensory neurons. Zheng[8] confirmed that mast cells can alleviate the early response of intestinal mucosa to radiation, but in the later stage, they can partially aggravate its fibrosis level through TGF.

2.5 Changes of Inflammatory Factors in Radiation Enteritis

Inflammatory factors can be divided into pro-inflammatory factors such as IL-1β, IL-6, TNF, and anti-inflammatory factors such as IL-10, IL-1ra, which antagonize and constrain each other to achieve dynamic balance. The balance between the two is disrupted under radiation. Some elevated inflammatory factors can reduce the apoptosis of intestinal stem cells after radiotherapy to a certain extent, alleviate intestinal injury, but excessive expression of inflammatory factors leads to irreversible pathological changes in the intestine, resulting in chronic fibrosis of the intestine.

3. Treatment Strategies for Radiation Enteritis

The treatment mechanism of radiation enteritis mainly focuses on radiation protection, antioxidation, and anti-inflammation.

3.1 Antioxidation

Excessive reactive oxygen species generated by radiation cause oxidative stress in the intestines, which has harmful effects on macromolecules such as DNA, lipids, and proteins inside the cells. Studies have shown that after irradiation, there is an increase in reactive oxygen species, an elevation in the level of the oxidative stress biomarker malondialdehyde, a decrease in glutathione content, and a decrease in catalase activity [9]. Reactive oxygen species can directly damage cells and tissues, as well as activate transcription factors leading to the upregulation of various pro-inflammatory cytokine genes. Therefore, antioxidation is an important approach to prevent and alleviate symptoms of radiation enteritis.

3.2 Anti-apoptosis

Toll-like receptors (TLRs) are a class of pathogen-associated molecular pattern recognition receptors that participate in controlling the stability of the intestinal environment. Several TLR members have been proven to have radioprotective effects. It has been reported that the TLR5 agonist CBLB502 effectively alleviates gastrointestinal and hematopoietic radiation damage in mice and monkeys. TLR4 has also been shown to increase the number of TLR4+ and TLR5+ macrophages in the mouse macrophage population after irradiation, and TLR4 and TLR5 agonists can improve radiation-induced macrophage recruitment, normalizing the number of TLR4+ and TLR5+ macrophages.

3.3 Anti-inflammatory

The PI3K/AKT pathway is an important regulatory factor in inflammatory responses, involved in macrophage release of cytokines. After irradiation, the expression of PI3K, AKT, and mTOR proteins in rat intestines is enhanced, radiation can activate PI3K, catalyze the translocation and phosphorylation of Akt, and then regulate the activation of mTOR through a series of signal transductions. PI3K inhibitors can reduce macrophage activation, mTOR inhibitors can exert anti-inflammatory effects by inhibiting the activation of NF-κB and T cell function. Inhibiting the PI3K/AKT/mTOR pathway can become a potential therapeutic target for radiation enteritis.

3.4 Promoting Repair

The renewal of gastrointestinal mucosal epithelial damage depends on intestinal resident stem cells, which can self-renew for a long time. Strict intestinal epithelial dynamic balance ensures that the intestine updates the epithelium every 4-5 days to maintain mucosal defense, while high-dose radiation destroys this dynamic balance, kills intestinal stem cells, and damages the repair process, leading to complete loss of mucosal barrier within 5-10 days after radiation exposure. The self-renewal, homeostasis, and repair of intestinal epithelium depend on the Wnt-β-catenin signaling pathway. The activation of the signal transfers β-catenin protein to the nucleus, initiating a series of gene expressions that support the maintenance and proliferation of intestinal stem cells. Activating β-catenin protein protects intestinal stem cells, promotes mucosal repair, and is one of the treatment mechanisms worth studying in radiation enteritis.

3.5 Regulation of Local Microecosystems

Radiation can cause significant changes in the intestinal microbiota. Studies have found that the number of aerobic bacteria in mice decreases significantly after 2 hours of radiation, and the number of Escherichia coli and Lactobacillus decreases significantly after 16 hours. The gut microbiota also undergoes similar changes after radiation in humans, and these changes are correlated with radiation-induced diarrhea. The gut microbiota can exacerbate the formation of radiation-induced intestinal damage, and studies have found that germ-free mice have stronger radiation resistance compared to normal mice. The gut microbiota can also play a protective role, such as protecting intestinal epithelial cells from radiation-induced apoptosis through AP-1 protein [10].

4. Progress of Western Medicine Treatment

4.1 Nutritional Support

Nutritional support therapy plays an important role in the treatment of radiation enteritis. Patients with radiation enteritis have impaired gastrointestinal function and their normal digestion and absorption functions are disrupted. Enteral nutrition support should consist of small, frequent meals with easily digestible liquid foods, and electrolytes should be supplemented in patients with long-term diarrhea. Enteral nutrition is in line with the physiological function of the intestine and is beneficial for the repair of damaged intestinal mucosa and epithelial cells, accelerating the normal secretion of intestinal cells, enhancing immune function, and reducing the occurrence of intestinal infections. Inflammatory markers are significantly lower in patients treated with enteral nutrition compared to those who consume food orally, and their diet recovery time is earlier than that of oral eaters. Their weight, physical strength, and mental state are also better than those who consume food orally.

4.2 Smecta Mixture Retention Enema

The main components of Simida are silicon dioxide and aluminum oxide, which combine with mucin proteins to form a mucosal barrier, reducing damage to the intestinal mucosa by harmful substances. Feng Jing et al. [11] randomly divided 65 patients who underwent radical resection of rectal cancer and received radiotherapy combined with capecitabine synchronous chemotherapy into a control group (n=31) and a Simida mixed solution (dissolved in 100ml of 0.9% sodium chloride solution with 3g of Simida, 670mg of compound glutamine granules, and 10mg of dexamethasone) enema treatment group (n=34), with a total radiation dose of 50 Gy, 2Gy/fraction, and 2 cycles of capecitabine chemotherapy. The incidence of acute radiation enteritis in the treatment group was significantly reduced at different stages, and the quality of life was also better than that of the control group.

4.3 Budenide

Budesonide (BUN) is a glucocorticoid that stabilizes endothelial cells, smooth muscle cells, and lysosomal membranes, inhibits immune reactions, and reduces the release of active mediators to exert anti-inflammatory effects. Odabasi et al. [12] used budesonide in the clinical treatment of patients with radiation enteritis. The results showed that the prophylactic use of appropriate amounts of budesonide and other glucocorticoids before radiotherapy effectively improved the clinical symptoms of radiation enteritis.

4.4 Somatostatin

Growth hormone can inhibit gastrointestinal motility, reduce the burden on the intestines, and accelerate intestinal healing. An animal experiment by Onal et al. [13] demonstrated that octreotide can effectively reduce radiation-induced intestinal injury in rats. Studies have shown that growth hormone is effective in treating radiation-induced diarrhea and has better therapeutic effects than preventive effects for radiation enteritis.

4.5 Stem Cell Transplantation

Mesenchymal stem cells (MSCs) originate from the mesoderm and are distributed in various

tissue matrices, capable of self-renewal and differentiation. Recent studies have shown that MSCs can autonomously migrate and aggregate at sites of inflammatory injury, regulate immune cells, reduce inflammation, and repair damaged tissue. Voswinkel et al. [14] believe that MSCs can promote intestinal function recovery, inhibit inflammation and fibrosis, and have potential tissue repair abilities. They applied MSC transplantation to intervene in three patients with radiation enteritis, and the results showed that after MSC application, the patients' clinical symptoms such as abdominal pain, diarrhea, and bloody stools significantly improved, and their quality of life significantly improved. MSCs have strong self-replication, multi-directional differentiation, and immune regulation functions, and can promote the repair of intestinal injury. Their application in the field of radiation enteritis may become a hot topic for future research.

4.6 Surgical Treatment

Surgical treatment is the choice when internal medicine treatment is ineffective and severe organic complications occur. Regimbeau et al. [15] followed up 109 CRE patients who underwent surgical treatment for an average of 40 months. The study showed that there were surgical deaths (5%) and surgical complications (30%), but for patients without tumor recurrence after surgery, the 1-year survival rate was 85% and the 5-year survival rate reached 69%, with an overall high survival rate. The reoperation rate for patients who underwent conservative surgery for the first time was 50%, while the reoperation rate for patients who underwent intestinal resection was 34%. The 5-year survival rate for patients in the intestinal resection group was 71%, significantly higher than the 51% for patients who chose conservative surgery. This indicates that the reoperation rate for radiation-induced intestinal damage is low, and the survival period is high, making it one of the preferred choices for patients. One study showed that 96.0% of patients with radiation enteritis complicated by acute intestinal obstruction were cured by surgical treatment. 23 patients were followed up for 6-24 months, and the long-term effective rate was 95.7%.

5. Progress of Traditional Chinese Medicine Treatment

RE belongs to the category of traditional Chinese medicine "dysentery" with symptoms such as bloody stools and diarrhea. Traditional Chinese medicine believes that radiation belongs to the evil of heat toxin. With the increase of radiation dose, the evil of heat toxin and the damp evil in the intestines entangle each other, causing stagnation in the intestines, leading to stagnation of qi and blood, disorder of conduction, abdominal pain, urgency to defecate, anal heaviness, invasion of damp heat in the intestines, burning of the yin collaterals of the intestines, resulting in bloody stools, and damp heat pressing on the intestines leading to diarrhea or mucous stools. Western medicine treatment for radiation enteritis has significant side effects and the condition is prone to recurrence. Traditional Chinese medicine has unique advantages in the treatment of intestinal inflammation, and at the same time, the promotion and application of traditional Chinese medicine prescriptions are in line with the practicality and economy of our country.

5.1 Internal Administration of Chinese Medicines

(1) Simple oral administration of Chinese medicine

Gu Feng et al. [16] compared the levels of Hb, Hct, PLT, clinical symptom scores, and KPS scores before and after 4 weeks of treatment in 38 patients with acute radiation enteritis treated with oral administration of Jianpi Qinghua Tang and levofloxacin + montmorillonite powder. The results showed that the improvement of relevant indicators in the Jianpi Qinghua Tang treatment group was better than that in the levofloxacin + montmorillonite powder treatment group, and the difference

was statistically significant. Jiang Weidong [17] used Hongyu Yin (Radix et Rhizoma Rhei, Herba Artemisiae Scopariae, Radix Astragali, Caulis Spatholobi, Radix Clematidis, Radix et Rhizoma Coptidis) for oral treatment of radiation enteritis, and the total effective rate and symptom scores before and after treatment were significantly improved, confirming the definite therapeutic effect of Hongyu Yin in the treatment of radiation enteritis. Cai Ge [18] selected 80 patients with radiation enteritis and randomly divided them into a control group and a treatment group. The control group received oral administration of levofloxacin + loratadine hydrochloride, and the treatment group received additional administration of "Changpi Tang" (Astragalus, Atractylodes macrocephala, Poria cocos, Citrus reticulata, Coix seed, Panax notoginseng, Hedyotis diffusa, and licorice). The results showed that the treatment group was superior to the control group in terms of total effective rate, improvement of clinical symptoms, and KPS score, and the difference was statistically significant.

(2) Oral Chinese medicine plus Western enema

Li Mingzhu [19] used traditional Chinese medicine for clearing heat, drying dampness, strengthening the spleen, and astringing the intestines, combined with oral administration of American cockroach powder enema to treat radiation enteritis. The control group was treated with berberine tablets, simethicone, and white-browed snake venom thrombin enema. The treatment lasted for 28 days. The results showed that the effective rate, relief of clinical symptoms, and quality of life scores in the Chinese medicine group were significantly higher than those in the control group, with statistically significant differences. Lei Miao [20] selected 60 patients with radiation enteritis, with 30 patients in the control group receiving intravenous injection of deproteinized bovine serum combined with saline, lidocaine, gentamicin, and dexamethasone enema. The treatment group of 30 patients received the same treatment plus oral administration of a formula for solidifying the intestines and stopping diarrhea. The treatment lasted for 14 days. The symptoms scores, colonoscopy pathological changes, and adverse reactions before and after treatment were compared between the two groups. The results showed that the efficacy of the Chinese medicine formula for solidifying the intestines and stopping diarrhea in the treatment of acute radiation enteritis was superior to that of traditional Western medicine preparations. Zhang Yue et al. [21] used the formula for intestinal rehabilitation combined with Western medicine enema to treat dampness-heat accumulation in the lower jiao type radiation enteritis. The serum TGF-β1 level significantly decreased ($P<0.05$), and the effective rate of symptoms and endoscopy was higher than that in the Western medicine enema group.

5.2 Chinese Medicine Enema

(1) Simple herbal enema

Fu Yang et al. [22] selected 63 patients with acute radiation enteritis, randomly divided into two groups. The treatment group used Huai Jiang Fang retained enema, and the control group used 0.9% sodium chloride solution. The treatment lasted for 30 days. The results showed that the total effective rate of the treatment group (93.9%) was higher than that of the control group (66.6%). The TCM symptom score and CRP level in the treatment group were significantly lower than before treatment. It is confirmed that Huai Jiang Fang enema has anti-inflammatory effects, can significantly reduce the CRP index of acute radiation enteritis, improve clinical symptoms, and improve quality of life. Li Zhuohong [23] randomly divided 60 patients with acute radiation enteritis into a Chinese medicine group and a control group. The Chinese medicine group was given Shao Yao Tang plus modified enema, and the control group was given Kang Fu Xin Ye + dexamethasone enema. The results showed that the total effective rate, colonoscopy effective rate, and quality of life score in the Chinese medicine group were better than those in the Western

medicine control group.

(2) Chinese medicine combined with Western medicine enema

Gai Huirong et al. [24] randomly divided 71 patients with radiation enteritis into a control group and an observation group. The control group received conventional Western medicine treatment, while the observation group received Xihuang pill combined with Kangfu Xin liquid enema on the basis of conventional treatment. The effective rate in the control group was 60%, and the effective rate in the observation group was 88.89%. Luo Juan et al. [25] classified 60 patients with radiation enteritis as spleen and stomach weakness and dampness obstruction, and randomly divided them into an experimental group and a control group. The experimental group received basic treatment plus modified Muxiang Shunqi pill enema, while the control group received basic treatment plus Simidat enema. After two treatment courses, the rectal mucosal injury, clinical efficacy, TCM symptom score, and KPS score were compared between the two groups, showing that the experimental group had better indicators than the control group.

6. Conclusion

In summary, radiation causes damage to the intestinal mucosa and leads to an inflammatory response. The treatment mechanisms for radiation enteritis mainly focus on radiation protection, antioxidant, and anti-inflammatory approaches. Both traditional Chinese medicine and Western medicine emphasize the importance of enema treatment for radiation enteritis, as it primarily affects the rectum. Traditional Chinese medicine treatment for radiation enteritis follows the principles of syndrome differentiation and treatment. Whether administered orally or through enema, the main approach is to tonify the spleen and clear heat, while also cooling the blood and promoting diuresis. This treatment method has satisfactory efficacy for both acute and chronic radiation enteritis. Radiation enteritis is a combination of deficiency and excess patterns, so it is recommended to combine oral Chinese herbal medicine with local retention enema based on syndrome differentiation. Conventional Western medicine treatment, such as medication enema and nutritional support, has limited efficacy, but it is effective in managing radiation enteritis with bleeding, obstruction, perforation, and fistula as the main manifestations. However, there is a lack of standardized specialized Chinese herbal medicine, and further research is needed to explore safe and effective formulas through large-scale multicenter trials. Clinical trials mainly focus on efficacy rates or other laboratory indicators, lacking objective indicators for intestinal mucosal pathology. Most existing studies are only preliminary clinical observations, and there is a lack of in-depth research on the mechanisms of action of traditional Chinese medicine. Therefore, future research on the prevention and treatment of radiation enteritis should combine clinical observations with discussions on the mechanisms of traditional Chinese medicine and conduct a series of studies.

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