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Advances in the Study of Adverse Reactions to Immune Checkpoint Inhibitors in Chinese and Western Medicine

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Abstract: Lung cancer is currently the second most prevalent malignancy worldwide. The approval and clinical application of immune checkpoint inhibitors (ICIs) have led to a number of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) with varying degrees of disease Lung cancer has entered the era of immunotherapy with different degrees of benefit in progressionfree survival (PFS) and overall survival (OS). However, with the widespread clinical application of ICIS, several aspects of immune-related adverse events (irAEs) have emerged, posing a problem for the clinical application and exploration of ICIs. The use of Chinese medicine can significantly reduce the incidence of irAEs as well as alleviate the symptoms of adverse reactions, and also has a significant role in improving the quality of patient survival and prolonging patient survival.

Lung cancer is one of the common malignant tumors that threaten human life, with high incidence and mortality. Lung cancer is mainly classified into NSCLC and SCLC according to histopathological characteristics. Non-small cell lung cancer accounts for approximately more than 85% of lung cancers, with a predicted 5-year survival of 16%[1]. In 2020, there will be approximately 2.2 million new lung cancer cases and 1.8 million deaths worldwide, accounting for 11.4% and 18.0% of cancer incidence and deaths, respectively. For the treatment of advanced NSCLC, there are approximately three categories: i. When the driver mutation is negative, i) programmed death-ligand 1 (PD-L1) expression ≥ 50%, Pembrolizumab monotherapy is recommended at the first level; ii) 1% ≤ PD-L1 ≤ 49%, Pembrolizumab is recommended at the first level for squamous carcinoma (Pembrolizumab) monotherapy, non-squamous cancer level I recommends Pembrolizumab monotherapy or Pembrolizumab combined with platinum plus pemetrexed; ③ PD-L1 <1% or unknown, non-squamous cancer level I recommends Pembrolizumab combined with platinum + pemetrexed, squamous cancer level II recommends Pembrolizumab combined with platinum + paclitaxel; II. EGFR mutation-positive advanced NSCLC, Osimertinib is preferentially recommended in first-line treatment; iii. without the above indications, chemotherapy or local radiotherapy can be chosen. Currently, there are two types of ICIs approved for marketing in China, one is programmed cell death protein 1 (PD-1) antibodies such as Pembrolizumab, Sintilimab, Nivolumab, Carrelizumab, and Terelizumab, and

Tririplizumab; and PD-L1 antibodies such as Durvalumab and Atezolizumab. Studies have shown that PD-1 and PD-L1 can suppress T cells and allow tumor cells to escape host immunity[2]. ICIS can block the PD-1 pathway and greatly enhance anti-tumor immunity. With the widespread use of ICIs in clinical practice, more and more irAEs affect patients' confidence in receiving treatment leading to refusal of treatment and even threatening patients' lives. Because the special mechanism of ICIs is different from targeted drugs and traditional chemotherapy drugs, there are many types of irAEs in the clinic. Such as skin (rash, vitiligo), gastrointestinal (diarrhea, abdominal pain, colitis), endocrine system (abnormal thyroid function), and lung (immune-related pneumonia)[3]. Most irAEs require long-term glucocorticoid therapy, but this is known to bring about many adverse effects, such as Cushing's syndrome, triggering or exacerbating infections, and osteoporosis. Moreover, a few severe irAEs can lead directly to permanent discontinuation of treatment. Therefore it is particularly important to treat irAEs brought about by immunotherapy. Traditional Chinese medicine has the effect of reducing toxic side effects and anti-tumor in the treatment of combined ICIs, and at the same time, traditional Chinese medicine has little side effects of its own, which can make the process of immunotherapy smoother for patients and play a role in improving their quality of life and prolonging their survival.

1. Mechanism of Occurrence

The mechanisms of immune checkpoint adverse reactions are still in the exploration stage and inconclusive. It is generally believed to be related to immune tolerance imbalance, and there are four recognized mechanisms: (1) ICIs bind to immune checkpoint-related molecules other than lymphocytes and induce complement activation, and for six autopsies of unfortunate deaths treated with ICIs, all had varying degrees of CD4+ T-cell infiltration[4]; (2) cross-reactivity between tumor cell-related antigens and non-target tissues, one manifesting as different tissues with the same antigen recognized by T-cell receptors, and the other manifesting as different antigens with homology. (ii) cross-reactivity between tumor cell-associated antigens and non-target tissues, one manifested by the recognition of the same antigen by T-cell receptors between different tissues, and the other by the homology of different antigens, with a large number of amplified T cells present in tumor and myocardial tissues in a study of myocarditis treated with ICIs. (iii) Autoantibody production, ICIs have a regulatory effect not only on T-cell immune responses, but also on humoral immunity. In experimental animal models regarding PD-1 mice, antibody formation to anti-troponin I was detected in PD-1 knockout mice with myocarditis, whereas clinical reports did not detect IgG autoantibodies[5]. ④ Increased pro-inflammatory cytokines, several studies have reported that the development of irAEs is closely associated with the release of large amounts of cellular inflammatory factors. Interleukin 17 (IL-17) was significantly elevated compared to other levels in a study of patients with immunogastrointestinal toxicity[6], and elevated levels of many inflammation-related markers have been reported frequently in cases treated with ICIs. The variability in both the type of organs involved and the degree of injury associated with irAEs suggests the possibility of other mechanisms of adverse reactions, and more in-depth studies of the mechanisms of their occurrence are needed.

The book "Suwen the Theory of Life and Energy" says: "If yin and yang are secret, the spirit is cured; if yin and yang are separated from the decision, the essence is extinguished". According to traditional medicine, the occurrence of various diseases is related to the disruption of the dynamic balance between yin and yang, which is manifested by the bias in the power of evil The immune system is a powerful and powerful force in Chinese medicine[7]. According to Guo Jing, immunity is related to the five organs of Chinese medicine: liver, heart, spleen, lung, and kidney, especially the kidney, lung, and spleen are most closely related to immunity[8]. ICIs inhibit the immune

escape of cancer cells and enhance the immune response of T cells, but also disrupt the body's autoimmune balance, causing the imbalance of yin and yang in the body, which is manifested by the dysfunction of the lung, spleen, and kidney. According to Chinese medicine, "kidney is the essence of the innate nature" and "kidney collects essence", the innate essence comes from parents and constitutes the original material of human embryo, which is the initial source of human immunity; spleen is the essence of the innate nature, the source of biochemical energy and blood, after birth, human life activities depend on the acquired spleen and stomach The spleen is the main organ of transportation, which transports water and grain essence, nourishes kidney essence, maintains the balance of qi and blood, and constantly provides energy for immunity; the lung is the main organ of qi, which regulates the movement of qi in the whole body and maintains the balance of qi, blood and fluid in the human body, including guard qi, zong qi and ying qi, which plays the role of defense against external evil, regulates fluid metabolism, and maintains the balance of yin and yang in the human body. When the balance between internal organs is broken, the lungs, spleen and kidneys become dysfunctional, which leads to a number of symptoms, such as lung deficiency, no source of Qi and blood biochemistry, the latter cannot nourish the innate, lung deficiency cannot restrain the liver, which leads to liver vigor, liver fire rebellion, qi disorder, resulting in liver depression, at the same time, tumor patients have more stasis and toxicity, which easily depletes yin and fluids, resulting in a series of complex symptoms over time.

2. irAEs Types

2.1 Adverse Skin Reaction

In general, the appearance of skin-associated irAEs is the earliest in a series of irAEs, appearing approximately 2-3 weeks after drug administration. They manifest as maculopapular rash, pruritus, dry skin, erythema, and vitiligo[9]. In Western medicine, grade 1 dermatitis does not require specific treatment and can continue to receive immunotherapy. Grade 2 dermatitis requires topical glucocorticoid cream treatment with oral anti-itch medication and optional cortisol steroids. Grade 3-4 skin adverse reactions require skin biopsy for definitive pathologic diagnosis, suspension of ICIs in grade 3, and oral corticosteroids. Grade 4 dermatitis requires permanent discontinuation of ICIs should be permanently discontinued and intravenous glucocorticoids should be administered. After the dermatitis returns to grade 1 or less, the hormones are tapered for a minimum of 4 weeks. [10]

According to the theory of traditional Chinese medicine, skin-related irAEs belong to the category of "drug rash poison" according to their symptoms, also called drug dermatitis, which is believed to occur due to the patient's congenital deficiency and internal invasion of evil toxins, coupled with repeated exposure to drug toxins and the weakness of the internal organs of advanced cancer patients, resulting in the entry of drugs into the body, leading to dampness, wind, heat and other evil spirits. In addition, the drugs enter the body and cause dampness, wind, heat and toxicity, and the toxicity goes out to the skin, resulting in a drug rash. The study of immune-related skin toxicity in Chinese medicine is rare in the domestic literature, and there are very few reports on it. In clinical practice, most of the evidence is based on the symptoms of the skin combined with the patient's constitution, as well as the tongue and pulse. In clinical practice, it is usually classified into blood deficiency, blood heat, wind-heat and yin deficiency according to the symptoms of the skin and the patient's constitution. Most of them are treated with Chinese herbal medicine and oral medication to dispel wind and invigorate blood. The drugs include Scutellariae Sinensis, Radix sophorae flavescentis, Radix Angelicae Sinensis,, etc.

2.2 Immune-Associated Pneumonia

If a patient develops a cough, dyspnea, suffocation, or an increase in the underlying symptoms during treatment with ICIs The possibility of immune-associated pneumonia should be highly suspected if the patient develops cough, dyspnea, suffocation, or worsening of the underlying symptoms during treatment with ICIs. The most common imaging findings are unilateral or bilateral The most common imaging findings are unilateral or bilateral ground-glass, solid, fibrous streaks, lobular septal thickening, distended branching, nodules, and reticular opacities[11]. Laboratory tests often show elevated white blood cells and neutrophils, and elevated C-reactive protein and sedimentation, but other serologic findings are often unremarkable. Because the clinical manifestations, signs, and ancillary tests of ICIs pneumonia are often nonspecific, they need to be differentiated from pulmonary infections, tumor progression, and other diseases causing pulmonary dyspnea and pulmonary infiltrative shadowing, requiring a clear diagnosis by pathology, which in most patients with ICIs pneumonia is reported as lymphocytic infiltration, granulomatous inflammation, mechanized pneumonia, and diffuse alveolar damage[12].Immune-associated pneumonia is classified into four grades according to clinical symptoms and lung CT inflammation. Grade 1: no respiratory symptoms, limited to unilateral lung or involving <25% of the lung parenchyma, lung CT and pulmonary ventilation should be reviewed in 3-4 weeks. Level 2: mild respiratory symptoms, limited to one lung or involving 25% to 50% of the lung parenchyma, suspension of ICIs until ≤ G1, methylprednisolone 1 to 2 mg/kg/d IV for 3 to 4 days, if symptoms improve, gradually reduce 5 to 10 mg/week for 4 to 6 weeks, if no improvement, refer to level 3 treatment. Level 3: limited general activity, with symptoms such as dyspnea, requiring hospitalization for symptomatic management, involving >50% of the lung parenchyma; level 4. For patients with grade 3 to 4, ICIs should be permanently discontinued, and in case of co-infection, empirical antibiotic treatment can be given, while consultation with respiratory and infection departments is requested. Methylprednisolone 2-4mg/kg/d should be administered intravenously for 4-6 weeks, and if there is no improvement after 2 days, immunosuppression can be considered.

Traditional medicine mostly attributes the symptoms to "cough" and "asthma", and believes that immune checkpoint inhibitors cause imbalance of yin and yang in the body, and the lung qi is not properly declared and lowered, resulting in cough. The key to the pathogenesis is medicine (poison), phlegm, stasis, and deficiency, and the main aspect is the deficiency of the positive and the standard. The treatment firstly identifies the deficiency and the real, and the deficiency should be based on the method of benefiting qi and nourishing yin, while the real should be based on the method of promoting the lung and dispersing evil to stop the cough. Commonly used drugs include Astragalus, Pinellia ternata, Codonopsis pilosula, pericarpium citri reticulatae, etc..

2.3 Immune-Mediated Hepatitis

Immune-mediated hepatitis is often associated with clinical symptoms such as jaundice, emesis, and liver discomfort. The delayed side effects have been reported to last from 1 to several years after drug administration and should be taken into account during follow-up[13]. Therefore, liver function should be monitored before and after clinical use. Therefore, liver function should be monitored before and after drug administration, and once liver function increases compared with the pre-drug level, it should be evaluated promptly and blood biochemistry, hepatitis B and C antibodies, and other antibodies should be improved as soon as possible. If the level of liver function increases compared with that before medication, it should be evaluated promptly, and blood biochemistry, antibodies against viral hepatitis B and C, and liver imaging should be improved as soon as possible. If necessary, liver biopsy and other tests should be performed [14]. The gold standard for the diagnosis of immune-mediated hepatitis is histopathological examination

of the liver, which shows edema in the confluent area, lymphocytic infiltration within and outside the hepatic sinusoids or around the bile duct opening [15]. For the management of immune-mediated hepatitis toxicity, usually grade 1 requires no discontinuation and weekly monitoring of liver function; grade 2 requires temporary discontinuation, 0.5 to 1 mg/Kg of prednisone orally, with slow reduction if liver function improves and a total course of four weeks, with prednisone reduced to 10 mg/day and hepatotoxicity ≤ grade 1, with the option of resuming treatment with ICIs; grade 3 to 4 suggests permanent discontinuation of treatment with ICIs and intravenous Methylprednisone 1-2mg/Kg, after the hepatotoxicity is reduced to grade 2, the treatment can be changed to equivalent oral prednisone and slowly reduced to a total course of four weeks, if the liver function does not improve after three days, consider adding mescaline (500-1000mg, 2 times/day), and infliximab is not recommended.

Immune-mediated hepatitis is mostly classified as "dysmenorrhea", "diarrhea" and "jaundice" in Chinese internal medicine, and the disease is mostly located in the liver and spleen, and related to the stomach, gallbladder and kidney. It is believed that the disease is mostly caused by deficiency of positive energy, internal invasion of drugs and toxins, loss of drainage of the liver, blockage of the qi mechanism, loss of transportation and transformation of the spleen, and accumulation of dampness and heat. The general principle of the treatment is based on the outline of deficiency and actuality, and the principle of supporting the righteous and eliminating the evil. The commonly used drugs are bupleurum root, Scutellaria baicalensis, Stringy Stonecrop, roasted Rhizoma Atractylodis Macrocephalae,etc.

2.4 Immune-related myocarditis

Immune-related myocarditis is characterized by chest tightness, dyspnea, pulmonary edema and palpitations. The diagnosis can be made based on cardiac biomarkers and imaging examinations, which show elevation of creatine kinase, troponin, and brain natriuretic peptide. In clinical practice, the diagnosis can be made based on cardiac biomarkers and imaging tests, including elevation of creatine kinase, troponin, and brain natriuretic peptide[16]. Grade 1 often shows mild transient reactions, no need to interrupt treatment and intervention; Grade 2 requires treatment or interruption of infusion, symptomatic management, and active management of underlying diseases (heart failure, atrial fibrillation, etc.) by the cardiology department and active control of heart disease; Grade 3 often shows delayed onset, or recurrence of symptoms after initial treatment, or failure to resolve symptoms after treatment. If necessary, the cardiology department should be consulted and the ICIs should be permanently stopped, and methylprednisone shock should be given at 1g/day for 3-5 days until the baseline cardiac function is restored, and the dosage should be gradually reduced within 4-6 weeks. If hormonal therapy does not improve within 24 hours, consider adding ATG or infliximab.

The symptoms of immune myocarditis are mostly classified as "chest paralysis" and "palpitations" in Chinese medicine, and the disease is located in the heart and is closely related to the liver, spleen, lung and kidney. The deficiency is mainly due to deficiency of heart blood, spleen deficiency, yin deficiency and heart yang deficiency, while the actual symptoms are mainly due to water-drinking, stagnation and phlegm-fire, and the principle of tonic deficiency and diarrhea is the principle of deficiency.

2.5 Gastrointestinal Adverse Reactions

Gastrointestinal irAEs are commonly associated with diarrhea and colitis and are characterized by abdominal pain, diarrhea, nausea and vomiting, blood in the stool, and peritoneal irritation, and in some patients, fever. If diarrhea occurs while the patient is receiving immunotherapy, the

possibility of diarrhea, colitis or infectious colitis caused by irAEs should be considered, with the exception of radiation enteritis, infectious diarrhea, etc., to improve the inflammatory indexes and fecal intestinal pathogens detection, combined with the actual clinical situation, whether to perform enteroscopy and pathological biopsy, enteroscopy mostly see mucosal erosion, ulceration with the formation of bleeding and erythema[17], pathology is mostly manifested as Grade 1 patients are usually asymptomatic, with the number of stools ≤4 times/day, and can continue ICIs treatment, with oral rehydration and antidiarrheal symptomatic treatment if necessary. Grade 2 patients may have abdominal pain, mucus or blood in the stool, with the number of stools 4-6 times/day, suspend ICIs treatment, and start hormone therapy without waiting for the results of colonoscopy. Prednisone 1mg/Kg.d, if there is no improvement or aggravation in 48-72h hormone therapy, increase the dose to 2mg/Kg.d and consider adding infliximab; if patients develop grade 3-4 diarrhea or colitis, grade 3 patients with severe abdominal pain and peritoneal irritation with stool frequency ≥7 times/day need to suspend ICIs; grade 4 patients usually have life-threatening symptoms and should permanently stop ICIs Patients in grade 4 usually have life-threatening symptoms and should be permanently discontinued from ICIs; complete abdominopelvic CT, colonoscopy and biopsy without waiting for the results of colonoscopy, and treat with methylprednisolone 2 mg/(kg-d), and add infliximab if there is no improvement or worsening with 48 h of hormone therapy.

Gastrointestinal irAEs are classified as "diarrhea", "abdominal pain", "intestinal wind" and "dirty poison" according to their clinical symptoms. "The basic pathogenesis is "heat and toxicity, dampness, blood stasis, and deficiency", which is a combination of deficiency and deficiency. The basic pathogenesis is "heat, dampness and turbidity, blood stasis and deficiency". In the literature, there are very few studies on the TCM patterns of irAEs-related gastrointestinal tracts. Based on the clinical manifestations and complications of the patients, combined with the tongue and pulse, the classification is often divided into cold and dampness, dampness and heat, dietary stagnation, liver depression and spleen deficiency, spleen and stomach weakness, spleen and stomach dampness and heat, and spleen and kidney yang deficiency.

3. Conclusion

In the course of malignancy treatment, patients treated with ICIs have a lower risk of discontinuing treatment for sensory neurotoxicity, hematologic toxicity, gastrointestinal and other adverse effects compared to patients treated with conventional radiotherapy, and most irAEs are reversible. Clinicians are required to manage patients in a way that allows them to benefit from the treatment of ICIs by seeing the smallest and most important, carefully screening for early recognition, timely diagnosis and treatment, and reducing the degree of damage caused by irAEs. Because of the many types of injuries and insidious symptoms, it is more difficult for clinicians to identify them. Currently, Western medicine has limited means to manage the toxicity of irAEs, choosing to suspend the treatment of ICIs or hormonal symptomatic treatment, while glucocorticoids have a suppressive effect on the efficacy of ICIs[18], Chinese medicine, as a treasure of traditional culture, has a dual effect on immune function, in a dynamic balance between immune enhancement and immune suppression, and it is believed that as the clinical research of Chinese medicine combined with immune checkpoint inhibitor therapy continues to improve, more patients will benefit from the treatment of ICIs. Clinical research continues to deepen and more scholars are involved, it will bring greater benefits to patients with advanced cancer.

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