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Clinical Analysis of 15 Cases of Non-Hodgkin Lymphoma Complicated with *Pneumocystis carinii* Pneumonia Treated with R-CHOP Regimen

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Abstract: ***Objective:*** To investigate the clinical features of R-CHOP regimen in the treatment of non-Hodgkin's lymphoma with *Pneumocystis carinii* pneumonia (PCP) in order to improve the understanding of PCP and the side effects of Rituxan. ***Methods:*** A retrospective analysis of 90 patients with non-Hodgkin's lymphoma treated with R-CHOP chemotherapy in our hospital from November 2015 to November 2020, of which 15 (16.7%) patients, combined with PCP clinical data, including clinical symptoms, physical signs, chest imaging examination and treatment data were used for to analysis and summarization. ***Results:*** The clinical features of R-CHOP chemotherapy combined with PCP were fever, cough, and sputum. Some patients had fewer clinical symptoms. Common imaging manifestations were double lung membrane glass shadow, patchy shadow, and flocculent shadow. It can occur in all clinical stages, and the incidence of late stage is high, and there is no clear correlation with bone marrow suppression. Pneumocystis was found in 2 cases of sputum, and the rest of the patients were clinically diagnosed. The main therapeutic drugs are sulfamethoxazole (8/15), compound sulfamethoxazole (6/15), clindamycin (1/15, sulfa drug allergy), and adrenal cortex hormones (4/15). Fourteen cases were cured and 1 case died. ***Conclusion:*** The incidence of R-CHOP in advanced non-Hodgkin's lymphoma of PCP is high. Patients with clinical use of R-CHOP chemotherapy will encounter fever, cough, chest computed tomography (CT) film glass shadow, and diffuse patch shadow. Patients should be alert to the possibility of PCP and take sulfonamides as soon as possible for medical treatment.

Keywords: *Pneumocystis carinii*; Pneumonia; Rituxan; Sulfonamides

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1. Introduction

Pneumocystis carinii pneumonia (PCP) is an opportunistic infection that occurs mostly in people who are immunodeficient or who have been receiving immunosuppressive therapy. The R-CHOP chemotherapy regimen has become the first-line treatment standard for CD20(+) B-cell non-Hodgkin lymphoma (Non-Hodgkin's lymphoma), which can significantly improve the disease remission rate, disease progression-free survival and overall survival rate [1]. Rituximab is traded under the name Rituxan, which was approved by the U.S. Food and Drug Administration (FDA) in 1997 for the treatment of B-cell non-Hodgkin's lymphoma [2]. CD20 in B-cell type non-Hodgkin's lymphoma with a CD20 antigen expression rate of more than 95% has CD20 antigen expression [3]. Rituxan is the first monoclonal antibody approved for the treatment of cancer [4]. With the AIDS epidemic, chemotherapy, immunosuppressive agents, organ transplantation and glucocorticoids are widely used, and the incidence of PCP has been increasing significantly [5]. With the widespread use of R-CHOP in the treatment of type B non-Hodgkin's lymphoma, the number of PCP side effects following Rituxan targeted therapy has gradually increased. From

November 2015 to November 2020, a total of 15 patients with PCP used treatment that combined with R-CHOP chemotherapy in our hospital. In the present study, we summarize and analyze their clinical characteristics.

2. Subjects and method

2.1. Subjects

A total of 15 patients with PCP who were given the treatment in combination with R-CHOP chemotherapy were recruited from November 2015 to November 2020 through the computerized medical record management system. Women accounted for 60% of the 15 patients, with an average age 54±14 years old.

2.2. Diagnostic criteria

The diagnostic criteria of non-Hodgkin's lymphoma refer to the diagnosis and treatment criteria of the 6th edition of the Clinical Oncology Manual. At present, the diagnosis of PCP in China is mostly dependent on clinical diagnosis [6-7]. The diagnostic criteria of PCP are: (i) onset is insidious or subacute, characterized by dry cough, shortness of breath and aggravation after activity, fever, cyanosis, and respiratory distress in severe cases; (ii) there are few positive signs in the lungs, or a small amount of audible and scattered dry and wet rales. Signs and the severity of disease symptoms are often disproportionate; (iii) PCP typical chest computed tomography (CT) shows symmetrical ground-glass shadows and patch shadows around the hilum on both sides; (iv) standard PCP diagnosis depends on pathogenic examinations, such as sputum examination, bronchoalveolar lavage or lung biopsy, to find cysts or trophozoites of Pneumocystis.

3. Results

3.1. Study duration

From November 2015 to November 2020, a total of 90 patients treated with R-CHOP chemotherapy for non-Hodgkin's lymphoma were recruited to this study, of which 15 (16.7%) patients had PCP. Women accounted for 60% of the 15 patients, and the average age was 54±14 years.

3.2. Clinical manifestations

The clinical manifestations of the patients are as follows: fever with body temperature at 38-39.9°C (9 cases), cough (4 cases), wheezing (2 cases), expectoration (6 cases). 66.6% (10 cases) of patients had normal or thick breath sounds.

3.3. Chest imaging manifestations

The patients manifest the following imaging characteristics: double lung membrane glass shadow (7/15), diffuse patch shadow (6/15), double lung flocculent shadow (1/15), and pulmonary interstitial changes (1/15).

3.4. Types of non-Hodgkin's lymphoma

The types of non-Hodgkin's lymphoma are diffuse large B-cell lymphoma (10/15), mantle cell lymphoma (1/15), marginal zone B-cell lymphoma (1/15), follicular lymphoma (2/15), and B-cell lymphoma (1/15). Typical chest CT scan of PCP patients showed symmetrical ground glass shadows around the hilum on both sides, and it has a tendency to develop and fuse from the hilum to the peripheral lung fields. Ground glass in the lung shadow is the most characteristic imaging manifestation, which can be accompanied by varying degrees of reticular shadows or thickening of the interlobular septum. This Ang Cong "gravel road sign" can be accompanied by mediastinal lymphadenopathy, some of which may be interstitial lung air sacs, and a small amount of thoracic cavity. Uncommon signs include effusion and traction bronchiectasis [8-9].

Figure 1 shows a patient's CT before and after the treatment.

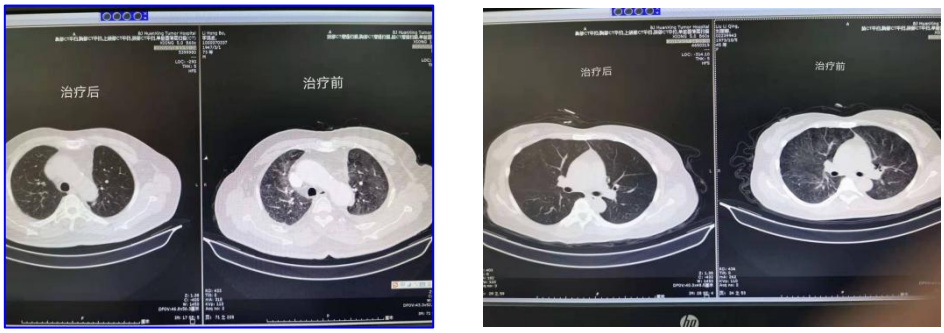

Figure 1. Patient's computed tomography (CT) before and after the treatment

3.5. Chemotherapy cycles in PCP

Cycle 1 (1/15), Cycle 2 (4/15), Cycle 3 (4/15), Cycle 4 (4/15), Cycle 5 (1/15)

3.6. Clinical staging

The patients were categorized based on stages, i.e. stage IV (8/15), stage III (1/15), stage II (5/15), and stage I (1/15).

3.7. Bone marrow suppression

The grades of bone marrow suppression in the patients are as follow: Grade IV (3/15), Grade III (4/15), Grade II (2/15), Grade I (2/15), and no bone marrow suppression (4/15).

3.8. Etiology

Pneumocystis was found in sputum (2/15). Bronchoalveolar lavage and bronchoscopy lung biopsy are very effective in the early diagnosis of PCP. The PCP detection rates of these two methods are 85%-87% and 86%-88%, respectively. The combined detection rate of the two can reach 94-100% [10].

3.9. Therapeutic drugs

The main therapeutic drugs are sulfamethoxazole (8/15), compound sulfamethoxazole (6/15), clindamycin (1/15, sulfa drug allergy), and adrenal cortex hormones (4/15).

3.10. Outcome

Fourteen study subjects were cured, but 1 case died. Among the 14 patients, 3 patients did not agree to continue using Rituxan targeted therapy to complete chemotherapy, and the other 11 patients continued to use Rituxan targeted therapy after PCP was cured, and no more targeted therapy-related PCP occurred.

4. Discussion

The destruction of the type 1 alveolar epithelial cell membrane by the trophozoites of *Pneumocystis carinii*, which causes cell necrosis and increases capillary permeability, is the pathogenic mechanism and pathological basis of PCP. The alveoli are filled with eosinophilic exudates containing trophozoites, fibrin and exfoliated epithelial cells. At the same time, type II alveolar epithelial cells proliferate and repair damaged alveolar capillary membranes. The proliferation of macrophages, plasma cells and lymphocytes in the lung interstitium leads to interstitial changes [11-12]. The PCP pathogen is *Pneumocystis carinii*. In the past, this pathogen was believed to be a protozoan, but recent studies on its ultrastructure and genetic molecular biology have supported that it is a fungus [13].The clinical manifestations of PCP are non-specific,

and can be easily missed and misdiagnosed. Most patients have fever as the first symptom, followed by dyspnea, chest tightness, shortness of breath and dry cough, etc. As the disease progresses, shortness of breath gradually worsens especially after activities, progressive dyspnea may occur, and there are few lung signs, and the disproportionate severity of symptoms is a typical clinical feature of the disease [13].

5. Conclusion

In recent years, studies have proposed a combination of rituximab and CHOP regimen (R-CHOP regimen) for the treatment of diffuse large B-cell lymphoma, and the cure rate has been significantly increased [14]. The incidence of R-CHOP in advanced non-Hodgkin's lymphoma is high. This regimen can occur in any cycle of PCP, and the incidence of stage IV patients is high. It is not significantly related to bone marrow suppression after chemotherapy. During clinical use of R-CHOP regimen, fever occurs during chemotherapy. Patients with cough, chest CT film glass shadow, and diffuse patch shadow should be alert to the possibility of PCP and be treated with sulfa drugs as soon as possible. Early diagnosis and early treatment are the keys to reducing the mortality rate and improving the prognosis of PCP patients. After the PCP is cured, the use of Rituxan targeted therapy can be continued.

Disclosure statement

The authors declare no conflict of interest.

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