The radiation pulmonary damage is a challenge for the radiotherapy of the lung cancer, with an incidence rate ranging from 20% to 47% (1-4). The pneumonitis and fibrosis are the main manifestations of the radiation-induced lung injuries. The acute radiation pneumonitis is more commonly seen, which severely influences the quality of life for patients and may even directly endanger the patients’ life. The radiation fibrosis that is irreversible generally develops in the area of radiation pneumonitis. The damage caused by chronic radiation pulmonary fibrosis in patients with unilateral pneumonectomy or residual pulmonary functional deficiency is a serious problem (5,6). So, it is important to find effective drugs to prevent the radiation pneumonitis.

There were some reports in China about some herbal decoctions used to prevent radiation pneumonitis; usually in the way of supplementing qi and nourishing yin, clearing heat and detoxifying (7,8). In a Wistar rat model with radiation pulmonary damage established by interval radiation with a total dose of 30 Gy, we found that the early application of Dixiong Decoction (地芎汤, a Chinese herbal decoction) could relieve a majority of the radiation damage in the rat lung (9). To further evaluate the clinical efficacy of this decoction to prevent radiation pneumonitis, we adopted a prospective randomized controlled clinical trial. Patients with non-small cell lung cancer were recruited as subjects. A common used decoction with the effects of supplementing qi and nourishing yin, clearing heat and detoxifying was used in the control group. We

**ABSTRACT**  Objective: To evaluate the efficacy of compound Dixiong Decoction (地芎汤) on early prevention of radiation pneumonitis. Methods: Forty-six patients with non-small cell lung cancer who were planning to receive radiotherapy were randomly assigned to the treatment group treated with the compound Dixiong Decoction and the control group treated with a commonly used herbal decoction which has the effects of supplementing qi and nourishing yin, clearing heat and detoxifying at the time of radiotherapy. Primary measure was the incidence of radiation pneumonitis after radiotherapy. Secondary outcomes included Watters clinical radiographic physiologic (CRP) dyspnea score, the Radiation Therapy Oncology Group (RTOG) grading score, Karnofsky Performance Status (KPS) score, and the application of corticosteroids. Results: The incidence of radiation pneumonitis in the treatment group was 10.0%, while that in the control group was 26.3% (P=0.0032). The Watters CRP dyspnea score and RTOG grading score in the treatment group were significantly lower than those in the control group (P<0.05). The KPS score in the treatment group was significantly higher than that in the control group (P<0.01). The dosage of corticosteroids was smaller with a shorter duration of therapy in the treatment group than that in the control group. Conclusion: The early application of the Chinese herbal decoction compound Dixiong Decoction can decrease the incidence of radiation pneumonitis, reduce the injury of the lung, and improve the life quality of the patients.

**KEYWORDS** radiation pneumonitis, complementary and alternative medicine, Chinese herbal medicine, clinical trial

**ORIGINAL ARTICLE**

The Study of Early Application with Dixiong Decoction (地芎汤) for Non-small Cell Lung Cancer to Decrease the Incidence and Severity of Radiation Pneumonitis: A Prospective, Randomized Clinical Trial

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observed the incidence of radiation pneumonitis, the extent of radiation pulmonary damage, and the overall patient condition.

**METHODS**

**Inclusion Criteria**

Included were patients who were clearly diagnosed with non-small cell lung cancer and made the decision to receive radiotherapy, more than 60 of Karnofsky Performance Status score (KPS score, which measures the performance status of cancer patients with respect to activities of daily living and is used to measure quality of life), and an expected survival time was more than six months.

**Exclusion Criteria**

Excluded were patients who were simultaneously receiving chemotherapy, fasting, or opposed to taking Chinese herbal medicine, and subjects participating in other clinical trials.

**General Data**

Sample size: for the sample size estimation, we assumed that the probability of type I error $\alpha = 0.05$ (one-sided test); the probability of type II error $\beta = 0.2$. According to the preliminary experiments we set the overall rate of radiation pneumonitis incidence in group 1 = 0.1 and the overall rate in group 2 = 0.4. Chinese Health Information Standardization Society (CHISS) 1.01 statistical software was used to calculate that the sample number required in each group was 23.

Randomization and blind method: CHISS1.01 statistical software was also used to draw up a random allocation sequence to randomize 46 participants. Each sequence was put into a closed envelope in which its cover was numbered. Each included patient took one envelop randomly and was sent to different groups according to the sequence.

**Study population:** forty-six patients with non-small cell lung cancer who visited our hospital were enrolled in the study and randomly and equally assigned to two groups. One patient in the treatment group was excluded from the study because she had intracranial metastasis and stopped lung radiation. There was no patient excluded from the control group. There were two cases in the treatment group lost during follow-up (one had left heart failure and pleural effusion and turned to other treatment, and the other quitted during the trial without any reason). There were four cases in the control group lost during follow-up (one died due to acute left ventricular failure, and three failed to comply with the treatment). There were 39 cases eligible for statistical analysis in total.

**Patient characteristics:** the characteristics of the 39 eligible patients are listed in Table 1. There was no statistical difference between the two groups in age, gender, actual radiation dose, clinical staging, and pathological type.

**Treatment Method**

Radiotherapy program: all patients received daily treatment of $^{60}$Co or high-energy X-rays, five days a week. The doses ranged from 50 to 78 Gy. For patients in stage T1-3 N0M0, the target region included clinical foci with no irradiation of the lymph drainage region. For patients in the stage T1-4N1-3M0, the irradiation field included the primary foci and lung hilum, the mediastinum, and affected organs if there was lymph node metastasis. When the total dose reached 40 Gy in 20 fractions during four weeks, the oblique field or multifield radiation was administered. For patients with the local late-stage or remote metastasis foci having an estimated survival time of 6-12 months, the irradiation field only included the foci which were involved in generating symptoms, and the total dose was 30 Gy in 10 fractions during two weeks or 45 Gy in 15 fractions during three weeks.

During the trial, all subjects stopped taking any other Chinese medicine. Patients who developed radiation

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>Age (Year, $\pm$ s)</th>
<th>Gender (Case)</th>
<th>Actual radiation dose (Gy)</th>
<th>Clinical stage (Case)</th>
<th>Pathological type (Case)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Treatment</td>
<td>20</td>
<td>65.2 ± 8.4</td>
<td>12</td>
<td>8</td>
<td>40-76</td>
<td>1</td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td>61.8 ± 13.5</td>
<td>12</td>
<td>7</td>
<td>40-76</td>
<td>2</td>
</tr>
<tr>
<td>P Value</td>
<td>0.3546</td>
<td>0.3234</td>
<td>0.603</td>
<td></td>
<td>&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Notes: 1 t test; 2 Fisher's exact test; 3 Group data rank sum test; 4 Wilcoxon rank sum test; 5 $\chi^2$ test

**Table 1. Clinical and Demographic Characteristics of Two Groups at Baseline**

pneumonitis during the trial were given corticosteroids. The medication of corticosteroids was recorded.

Herbal treatment: at the time of radiotherapy, Dixiong Decoction was used in the treatment group; in the control group, a decoction with the effects of supplementing qi and nourishing yin, clearing heat and detoxifying was used.

The decoction in the treatment group was composed of Radix Rehmanniae 10 g, Rhizoma Ligustici wallichii 15 g, Cortex Moutan 15 g, Semen Juglandis 12 g, Flos Carthami 10 g, Rhizoma Curcuma 10 g, Fructus Forsythiae 15 g, and Radix Astragali 15 g.

The decoction in control group was composed of Radix Codonopsis 15 g, Radix Angelicae Sinensis 15 g, Semen Armeniacae Amarum 15 g, Herba Hedysotis Diffusae 15 g, Rhizoma Atractylodis Macrocephalae 15 g, Raidix Ophiopogonis 15 g, Radix Sophorae Flavescentis 15 g, and Radix Glehniae 10 g.

All herbs were bought from the pharmacy of Chinese medicine in our hospital. They were prepared with a DHJ-D1-type drug decocting machine from Korea and were vacuum packed. Each package contained 200 mL decoction and was stored at a 4 °C refrigerator for less than seven days. The package was heated before given to the patient and taken orally twice per day. One course is four weeks, and the total period is eight weeks. The patients were followed up for six months.

**Observation Time Points and Items**

Before the treatment and in the first, second, third, and sixth months after the treatment, the patients' major symptoms, living conditions, imaging, and laboratory examinations were observed. The primary endpoint was the incidence of radiation pneumonitis. The secondary outcome was the extent of radiation damage to the lung, the physical condition, and the application of corticosteroids for radiation pneumonitis.

**Evaluation Method**

The diagnostic standard consulted for radiation pneumonitis was "Diagnosis Standard for Acute Radiation Pneumonitis" from the Ministry of Health of P.R. China (GBZ110-2002). According to this protocol, patients received a radiation dose in the lung \( \geq 8 \) Gy; usually in 1-6 months after radiation treatment, the symptoms such as cough, chest distress, chest pain, dyspneic respiration, and low fever were observed. Those with severe symptoms exhibited diminished breath sounds, dry and wet rales, and obscured shading on the lung which was meshed and with an irregular edge in the X-ray examination. Those with severe symptoms underwent a laboratory blood gas analysis, where \( \text{PO}_2 \) decreased and \( \text{PCO}_2 \) increased. A pulmonary functional examination showed that lung compliance decreased, the ventilatory capacity/ blood infusion percentage decreased, and the diffuse function decreased.

The Watters clinical radiographic physiologic (CRP) dyspnea scale was adopted to evaluate the dyspneic respiration\(^{(10)}\). The Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC)'s "The RTOG Acute Radiation Morbidity Scoring Criteria: dyspnea scale"\(^{(11)}\) was adopted for acute radiation lung damage, and physical function was evaluated according to the KPS score.

**Statistical Analysis**

Quantitative data were analyzed by the t test and the mean F test. Quantitative data with abnormal distribution such as actual radiation dose, Watters score, RTOG grading score, and KPS score were analyzed by the rank sum test. The Wilcoxon rank sum test was applied to clinical staging, and the Chi-square test was applied for comparison of radiation pneumonitis incidence.

**RESULTS**

**Comparison of Incidence of Radiation Pneumonitis**

There were two out of 20 cases in the treatment group that had radiation pneumonitis, with an incidence rate of 10.0%; five out of 19 cases in the control group had radiation pneumonitis, with an incidence rate of 26.3%. Comparing the incidence rates of radiation pneumonitis between the two groups, there was a significant difference (\( \chi^2 = 8.6721, P = 0.0032 \)).

**Comparison of the Watters Score, RTOG Grading Score, and KPS Score**

Before treatment, there was insignificant
difference in the Watters score, RTOG grading score, and KPS score between the two groups (P>0.05); after radiation, the Watters score and RTOG grading score of the control group elevated continuously, while the treatment lowered obviously, showing significant difference (P<0.05, P<0.01). This indicated that the extent of radiation lung damage and symptoms of dyspneic respiration was lower in the treatment group than that in the control group. Comparing the KPS score in the two groups, the treatment group was significantly higher than that of the control group, with an increasing trend during the observation duration, while in the control group, the score decreased significantly. This showed that the life quality in the treatment group was better than that in the control group (Table 2).

**Corticosteroid Treatment in Patients with Radiation Pneumonitis**

The patients with radiation pneumonitis in the two groups were treated with corticosteroids, and treatment was given since diagnosis. As a result, there were two patients in the treatment group that took prednisone 30 mg orally. Two weeks later, the patients recovered. While, there were five patients in the control group that need corticosteroid treatment. Most of their symptoms could be controlled by taking prednisone 40 mg orally for three weeks. Two patients had developed severe radiation pneumonitis. One of them was treated with examethasone, and the other was treated with methylprednisolone by intravenous drip for over 21 days, and then their symptoms were recurrent.

**DISCUSSION**

The results of this study showed that the incidence of radiation pneumonitis in the treatment group was significantly lower than that in the control group. The comparisons between Watters score and RTOG grading score showed that early application of this decoction could relieve the extent of radiation lung damage and improve the symptoms of dyspneic respiration for the patients that received radiotherapy. KPS score showed that this decoction could improve the physical function and life quality of the patients with radiotherapy. Corticosteroid treatment in the patients with radiation pneumonitis in these two groups showed that the dosage of corticosteroids was smaller with a shorter duration of therapy in the treatment group than that in the control group. This showed that early application of this decoction was more effective than the common used decoction in preventing and controlling the incidence of radiation pneumonitis.

The study of pathogenesis showed that radiation generates energy that caused the lung injury. Ultrastructural studies demonstrated that the changes in endothelial cells of capillary vessels, the disturbance of blood circulation, and interstitial edema were the early major pathology changes of irradiation-induced pulmonary changes\(^\text{12,13}\). According to the Chinese medicine theory, we think the pathogenesis of the radiation pneumonitis is that the heat-evil causes the Fei (肺) and blood collaterals to be damaged, makes Fei bleeding, and microcirculation disturbance. Decoction with the effects of supplementing qi and nourishing yin, heat-clearing and detoxifying can fill up a deficiency of qi and yin caused by the heat, but it is useless to the bleeding and microcirculation disturbance. So we think of a combined treatment of cooling the blood and improving microcirculation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>Time</th>
<th>Watters score</th>
<th>RTOG score</th>
<th>KPS score</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>20</td>
<td>Before treatment</td>
<td>6</td>
<td>1</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 month after treat.</td>
<td>6</td>
<td>1</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 months after treat.</td>
<td>5</td>
<td>1</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after treat.</td>
<td>4</td>
<td>1</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after treat.</td>
<td>4</td>
<td>0.5</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td>Before treatment</td>
<td>4</td>
<td>1</td>
<td>80</td>
<td>0.376</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 month after treat.</td>
<td>8</td>
<td>2</td>
<td>68</td>
<td>0.187</td>
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<tr>
<td></td>
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<td>2 months after treat.</td>
<td>8</td>
<td>1</td>
<td>82</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 months after treat.</td>
<td>6</td>
<td>1</td>
<td>84</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months after treat.</td>
<td>8</td>
<td>1</td>
<td>82</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 2. Median Comparison of Watters Score, RTOG Score, and KPS Score between the Two Groups in Different Time Points
Dixiong Decoction is prescribed according to the therapeutic principle. Most of the herbs in this decoction are of cold or pungent progent property. It is believed that the herbs of cold property as *Radix Rehmanniae* can clear away heat, cool the blood, and stop bleeding. And the herbs of pungent property as *Rhizoma Ligustici wallichii* can activate the blood and improve microcirculation. The Chinese theory is the basis of the formation of the decoction.

Radiation pneumonitis is a comprehensive reaction characterized by acute effusive pathological changes mediated by multiple cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and transforming growth factor β (TGF-β) that occur while a patient is being treated with radiation. It usually leads to radiation pulmonary fibrosis(14,15). A study of the radiosensitive status of IL-6 KO mice in the acute phase of alveolar damage after irradiation suggested an important role for IL-6 in radiation pneumonitis(16). Our animal experiment study found that in the early stage of radiation exposure, cytokines such as TNF-α, IL-6, and TGF-β were overexpressed in the rat lung tissue with the accumulation of the radiation dosage and time elongation(19). This promoted an early incidence of radiation pneumonitis and induced radiation pulmonary fibrosis in the late stage. In the treatment group of rats which received an early application of the Chinese herbal decoction Dixiong Decoction, the expression levels of the above cytokines decreased, while the duration of symptoms decreased. This may be related to Dixiong Decoction’s mechanism of action on a molecular level to adequately prevent and relieve radiation pneumonitis.

We hope to note a number of limitations that may have affected the outcomes of this study. Because there are no effect agents for the prevention and treatment of radiation lung injury, and all the allocated patients wanted to drink decoction, we adopted the decoction which is common used in control treatment. And we only included the absolute minimum sample size of patients. Some patients dropped out from the study. As a result, the sample size was a little short of enough numbers. For these reasons, the present results should be confirmed in further studies of larger samples.

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