Effects of Yiqi Yangyin Prescription combined with radiotherapy on the tumor load and anti-tumor immune response of patients with advanced lung cancer

Zhi-An Qiao

Department of Radiotherapy, Xingtai People’s Hospital in Hebei Province, Xingtai, Hebei Province, 054031, China

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ABSTRACT

Objective: To investigate the effects of Yiqi Yangyin Prescription combined with radiotherapy on the tumor load and anti-tumor immune response of patients with advanced lung cancer.

Methods: A total of 78 patients with advanced non-small cell lung cancer who were diagnosed and treated in our hospital between August 2015 and January 2017 were reviewed and then divided into the routine group (n=41) who received chemoradiotherapy alone and the Yiqi Yangyin Prescription group (n=37) who received chemoradiotherapy combined with Yiqi Yangyin Prescription therapy. The differences in serum levels of tumor markers, Th1/Th2 cytokines and Th17/Treg cytokines were compared between the two groups before and after treatment.

Results: After treatment, serum tumor markers CA15-3, Cyfra21-1, HSP90 and CEA levels of Yiqi Yangyin Prescription group were lower than those of routine group; serum Th1 cytokines IFN-\(\gamma\) and IL-2 levels were higher than those of routine group while Th2 cytokines IL-4 and IL-5 levels were lower than those of routine group; serum Th17 cytokines IL-17 and IL-23 as well as Treg cytokines IL-10 and TGF-\(\beta\) levels were lower than those of routine group.

Conclusion: Routine chemoradiotherapy combined with Yiqi Yangyin Prescription therapy can effectively reduce the tumor load and optimize the anti-tumor immune function in patients with advanced non-small cell lung cancer.

1. Introduction

Non-small cell lung cancer is the most common type of lung cancer in clinic, patients are without any clinical symptoms in early stage and miss the best time for early diagnosis, and the disease has progressed to advanced stage when there is significant cough and hemoptysis\[1,2\]. Patients with advanced non-small cell lung cancer can not undergo surgery to remove the mass, so conservative treatment is the most effective way to prolong the survival time. Both radiotherapy and chemotherapy are the most common therapies for patients with advanced cancer, and have been proven in different studies to be able to significantly reduce the malignancy of cancer cells and delay the progress of the disease\[3,4\]. But studies have also shown that the chemoradiotherapy alone cannot fully kill the cancer cells, some patients still have early relapse after treatment, and other auxiliary therapies are needed at this time to expand the overall curative effect and optimize the patients’ outcomes. Traditional Chinese medicine has a long history of treating advanced cancer. In view of the limitations of western medicine treatment of patients with advanced cancer, many scholars recommend the combination of traditional Chinese medicine prescription to treat cancer\[5\]. Yiqi Yangyin Prescription is made from adenophora elata, Radix Ophiopogonis, Schisandra chinensis, safflower, radix isatidis and other Chinese medicines, and has the effects such as nourishing yin to lessen fire and benefiting qi for activating blood circulation. In this study, Yiqi Yangyin Prescription was used as an adjuvant therapy and added in the overall treatment of patients with advanced non-small cell lung cancer, and the effects of combined Chinese and western medicine treatment on the patients’ condition were discussed.

2. Information and methods

2.1 Inclusion and exclusion criteria

The inclusion criteria were as follows: pathologically diagnosed with advanced non-small cell lung; diagnosed for the first time, without unsystematic treatment outside the hospital; the patients themselves or family members should sign the informed consent form.
The exclusion criteria were as follows: combined with allergy to medicines in Yiqi Yangyin Prescription; with dyscrasia and could not tolerate chemoradiotherapy; combined with chronic obstructive pulmonary disease, severe asthma and other basic pulmonary diseases; with history of lung surgery; combined with systemic infectious diseases; more than 80 years old.

2.2 Case information

78 patients with advanced non-small cell lung cancer who were diagnosed and treated in our hospital between August 2015 and January 2017 were enrolled in the study, the therapies they underwent were reviewed and used to divide all patients into the routine group (n=41) who received chemoradiotherapy alone and the Yiqi Yangyn Prescription group (n=37) who received chemoradiotherapy combined with Yiqi Yangyn Prescription therapy. There were 22 males and 19 females in the routine group, and they were 37-69 years old; there were 19 males and 18 females in the Yiqi Yangin Prescription group, and they were 35-71 years old. The distribution of the above basic data was comparable between the two groups and the research plan was approved by the hospital ethics committee.

2.3 Therapy

Routine group received routine chemoradiotherapy, which was as follows: TP chemotherapy (paclitaxel 150 mg/m², by intravenous drip, on d1; cisplatin 80 mg/m², by intravenous drip, on d1), followed by three-dimensional intensity-modulated radiation therapy.

Yiqi Yangyn Prescription group received routine chemoradiotherapy combined with adjuvant Yiqi Yangyn Prescription therapy, specifically as follows: 30 g each of astragalus and radix glehniae, 20 g each of dangshen and lily, 15 g each of Rhizoma Atractylodis Macrocephalae, Radix Ophiopogonis, Poria cocos and iphigenia indica, 12 g of fritillaria and 10 g each of yam, Chinese-date and Maca pereira, 20 g each of dangshen and lily, 15 g each of Rhizoma Atractylodis Macrocephalae, Radix Ophiopogonis, Poria cocos and iphigenia indica, 12 g of fritillaria and 10 g each of yam, Chinese-date and radix polygonati officinalis were added in 500 mL of water and decocted to 300 mL, which was taken 30 min after meals, 1 dose per day. 21 d of treatment was as one course and four courses were done.

2.4 Observation indexes

2.4.1 Tumor load

Before and after treatment, fasting cubital venous blood samples were extracted from two groups of patients, put into the sterile EP tubes anti-coagulated by sodium citrate and centrifuged to separate the supernatant. Enzyme-linked immunosorbent assay was used to detect the serum contents of non-small cell lung cancer-related tumor markers, including carbohydrate antigen 15-3 (CA153), cytokeratin 19 fragment (Cyfra21-1), heat shock protein 90 (HSP90) and carcinoembryonic antigen (CEA).

2.4.2 Antitumor immune response indexes

The cubital venous blood samples were obtained from the two groups of patients at the same point in time. RIA method was used to detect the contents of Th1/Th2 cytokines interferon-γ (IFN-γ), interleukin-2 (IL-2), interleukin-4 (IL-4) and interleukin-5 (IL-5) as well as Th17/Treg cytokines interleukin-17 (IL-17), interleukin-23 (IL-23), interleukin-10 (IL-10) and transforming growth factor-β (TGF-β).

2.5 Statistical processing

The data in the study, including non-small cell lung cancer-related tumor markers, Th1/Th2 cytokines and Th17/Treg cytokines all belonged to measurement data and input in SPSS 26.0 to calculate the P value. Statistic $P<0.05$ was the standard of statistical significance between groups.

3. Results

3.1 Non–small cell lung cancer–related tumor markers

Comparison of serum non-small cell lung cancer-related tumor markers CA15-3, Cyfra21-1, HSP90 and CEA levels between two groups of patients at different points in time was as follows: before

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time points</th>
<th>CA15-3</th>
<th>Cyfra21-1</th>
<th>HSP90</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine group</td>
<td>Before treatment</td>
<td>26.48±3.19</td>
<td>180.27±11.53</td>
<td>71.26±8.53</td>
<td>51.84±6.29</td>
</tr>
<tr>
<td>Yiqi Yangyn Prescription group</td>
<td>Before treatment</td>
<td>26.36±3.42</td>
<td>181.04±20.96</td>
<td>71.19±8.46</td>
<td>51.59±5.73</td>
</tr>
</tbody>
</table>

Table 1.

Comparison of serum non-small cell lung cancer-related tumor marker levels (ng/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time points</th>
<th>IFN-γ</th>
<th>IL-2</th>
<th>IL-4</th>
<th>IL-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine group</td>
<td>Before treatment</td>
<td>2.18±0.24</td>
<td>1.98±0.23</td>
<td>4.57±0.59</td>
<td>10.27±1.63</td>
</tr>
<tr>
<td>Yiqi Yangyn Prescription group</td>
<td>Before treatment</td>
<td>2.15±0.25</td>
<td>1.97±0.21</td>
<td>4.56±0.52</td>
<td>10.24±1.78</td>
</tr>
</tbody>
</table>

Table 2.

Comparison of serum Th1/Th2 cytokine levels (pg/mL).

Compared with same group before treatment, $P<0.05$; The comparison of the two groups after treatment, $P<0.05$. 

Compared with same group before treatment, $P<0.05$; The comparison of the two groups after treatment, $P<0.05$.
Chinese medicine categories such as systemic treatment, and the drugs with other mechanisms of action may further inhibit the activity of cancer cells. Yiqi Yangyin Prescription contains Radix Adenophorae, astragalus, radix ophiopogonis, yam, lily, Chinese-date, radix polygonati officinalis and many other kinds of Chinese patent drugs. Radix Adenophorae benefits lung and engenders liquid, astragalus and yam invigorate spleen and supplement qi, radix ophiopogonis clears lung and nourishes Yin, lily and radix polygonati officinalis nourish yin and engender liquid, Chinese-date invigorates spleen-stomach and replenishes qi, and these medicines work together to replenish qi and nourish Yin as well as engender liquid and quench thirst[8,9]. In this study, based on the conventional radiotherapy and chemotherapy, the prescription was added in the overall treatment of patients with advanced non-small cell lung cancer, and the effect of combined Chinese and Western medicine treatment on such patients was explored to provide practical experience for the subsequent establishment of clinical treatment strategy for similar patients.

Tumor markers are the reliable indexes to measure the malignant tumor load, it has been discovered that the levels of a wide variety of tumor-related markers abnormally rise in colorectal cancer, cervical cancer and other malignant tumors, and their levels are closely related to tumor malignancy. The positive rate of CA15-3 is about 54% in the patients with lung cancer, its combined detection with other tumor markers is more meaningful to the diagnosis of lung cancer, the CA15-3 within the cancer cells is largely released into the blood in the case of tumor metastasis or recurrence, and its serum content increases[10,11]. Cyfra21-1 is the main marker for clinical diagnosis of lung cancer, its specificity for diagnosis of lung cancer is as high as 89%, and the sensitivity and specificity are higher for the diagnosis of squamous cell lung carcinoma[12]. HSP90α is a new tumor marker and it has been discovered that its expression significantly increases in multiple myeloma and malignant melanoma cells. At present, foreign studies have found that the positive rate of HSP90α in patients with early lung cancer is higher than that of other tumor markers, and it can be used as a good indicator for early screening of lung cancer[13,14]. CEA is a broad-spectrum tumor marker, which has low sensitivity to non-cell lung cancer detection, but can be combined with other tumor markers to increase the accuracy of disease judgment[15]. In this study, the differences in serum levels of above non-small cell lung cancer-associated tumor markers were compared between the two groups of patients, and the results showed that compared with those of routine group, the serum levels of above tumor markers of Yiqi Yangyin Prescription group were lower after treatment, indicating that the cytokines secreted by Th1/Th2 cells are involved in regulating the immune response of non-small cell lung cancer and affect the pathologic process of the disease. Th1 cells mainly mediate cellular immunity, and the cytokines secreted by them can effectively optimize the patients’ overall state.

**Table 3. Comparison of serum Th17/Treg cytokine levels (pg/mL).**

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time points</th>
<th>IL-17</th>
<th>IL-23</th>
<th>IL-10</th>
<th>TGF-β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine group</td>
<td>41</td>
<td>Before</td>
<td>36.28±4.19</td>
<td>28.71±3.42</td>
<td>5.73±0.59</td>
<td>10.91±1.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>20.17±2.84</td>
<td>19.63±2.47</td>
<td>4.12±0.46</td>
<td>7.26±0.85</td>
</tr>
<tr>
<td>Yiqi Yangyin Prescription</td>
<td>37</td>
<td>Before</td>
<td>36.19±4.25</td>
<td>28.59±3.57</td>
<td>5.69±0.58</td>
<td>10.87±1.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>11.64±1.85*</td>
<td>11.29±1.64*</td>
<td>2.77±0.32*</td>
<td>4.15±0.47*</td>
</tr>
</tbody>
</table>

Compared with same group before treatment, \(P<0.05\); The comparison of the two groups after treatment, \(P<0.05\).

3.2 Th1/Th2 cytokines

Comparison of serum Th1/Th2 cytokine levels between two groups of patients at different points in time as was follows: before treatment, serum IFN-γ, IL-2, IL-4 and IL-5 levels were not significantly different between the two groups of patients \((P>0.05)\). After treatment, serum Th1 cytokines IFN-γ and IL-2 levels of both groups were higher than those before treatment while Th2 cytokines IL-4 and IL-5 levels were lower than those before treatment; serum Th1 cytokines IFN-γ and IL-2 levels of Yiqi Yangyin Prescription group were higher than those of routine group \((P<0.05)\), shown in Table 2.

3.3 Th17/Treg cytokines

Comparison of serum Th17/Treg cytokine levels between two groups of patients at different points in time as was follows: before treatment, serum IL-17, IL-23, IL-10 and TGF-β levels were not significantly different between the two groups of patients \((P>0.05)\). After treatment, serum IL-17, IL-23, IL-10 and TGF-β levels of both groups were lower than those before treatment; serum IL-17, IL-23, IL-10 and TGF-β levels of Yiqi Yangyin Prescription group were lower than those of routine group \((P<0.05)\), shown in Table 3.

4. Discussion

Chemoradiotherapy is the main method to treat advanced non-small cell lung cancer. However, some patients are still in progress after systemic treatment, and the drugs with other mechanisms of action are needed to expand the therapeutic effect. Lung cancer belongs to Chinese medicine categories such as “lung obstruction” and “lung accumulation”, it is caused by loss of vital qi, pathogenic toxin stasis in lung, loss of pulmonary diffuse and clearing, intermingled phlegm and blood stasis with the passing of time and the accumulation to nucleate, etc., and treatment determination based on syndrome differentiation is needed to improve the patient’s overall state[6,7]. Western medicine chemoradiotherapy easily consumes the patient’s vital qi and leads to qi and blood deficiency, and the Chinese patent drugs that tonify qi and yin are needed to strengthen the vital qi and further inhibit the activity of cancer cells. Yiqi Yangyin Prescription group were lower after treatment, indicating that routine chemoradiotherapy combined with adjuvant Yiqi Yangyin Prescription therapy can more effectively reduce the tumor load and optimize the patients’ overall state.

Immune disorder is one of the common pathological features of many malignancies. Modern immunology has shown that the cytokines secreted by Th1/Th2 cells are involved in regulating the immune response of non-small cell lung cancer and affect the pathologic process of the disease. Th1 cells mainly mediate cellular immunity, and the cytokines secreted by them can effectively

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*[Zhi-An Qiao et al./ Journal of Hainan Medical University 2018; 24(1): 81–84]*
inhibit the proliferation of tumor cells. However, Th2 cells mainly mediate humoral immunity, and the cytokines secreted by them are opposite to Th1 cytokines and could promote the proliferation of tumor cells[16,17]. The functions of above two kinds of cells are in equilibrium under physiological state, but after the tumor occurs, the body's immune function is abnormal, which is specifically shown as the relative hypofunction of Th1 cells and the relative hyperfunction of Th2 cells. To measure the functional status of these two types of cells can indirectly reflect the severity of malignancy and the efficacy of clinical treatment[18]. IFN-γ and IL-2 are secreted by Th1 cells, IL-4 and IL-5 are secreted by Th2 cells, the differences in serum levels of above cytokines were compared between the two groups of patients in this study, and the results showed that compared with those of routine group, serum Th1 cytokine levels of Yiqi Yangyin Prescription group were higher while Th2 cytokine levels were lower after treatment, indicating that adjunct Yiqi Yangyin Prescription therapy can more effectively regulate the cellular immune balance and inhibit tumor cell proliferation.

Naive T cells can also secrete the Th17 cells that mediate inflammatory response and the Treg cells that mediate immune tolerance. Th17 cells mainly secrete IL-17, IL-23 and other pro-inflammatory factors, and their massive secretion can promote the malignant progression of tumor cells[19]. Treg cells mainly secrete IL-10 and TGF-β, they can physiologically maintain the homeostasis, but their expression levels continue to increase with tumor progression, which further leads to the immune tolerance of tumor cells and suppress the immune function to the tumor[20]. In this study, the differences in above cytokine levels were compared between the two groups of patients, and the results showed that compared with those of routine group, serum Th1 cytokine levels of Yiqi Yangyin Prescription group were lower and Treg cytokine levels were also lower after treatment, indicating that combined traditional Chinese and western medicine therapy can effectively adjust the Th17/Treg immune balance, inhibit the immune tolerance of tumor and enhance the killing effect of the body's own immune function on tumor cells.

Routine chemoradiotherapy combined with adjuvant Yiqi Yangyin Prescription therapy can more effectively reduce the tumor load and regulate the anti-tumor immune response as well as stabilize the illness and optimize the treatment outcome in patients with advanced non-small cell lung cancer, it is a rather ideal combined traditional Chinese and western medicine therapy, and it is worthy of popularization and application in clinical practice in the future.

References


