Relation Between the Yin-cold or Yang-heat Syndrome Type of TCM and the EGFR Gene Status in Patients with NSCLC

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Abstract

Purpose The Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) have been used as first line treatment in advanced Non-Small Cell Lung Cancer (NSCLC) with sensitive EGFR gene mutations. In clinical practice, we found that the rate of EGFR gene mutation in patients with Yin-cold syndrome type in traditional Chinese medicine (TCM) theory was higher than those with Yang-heat type syndrome. The purpose of this study was to identify the relationship between the TCM syndrome type and the EGFR gene status as well as efficacy of EGFR-TKIs in NSCLC patients.

Methods From March 2013 to January 2014, we prospectively studied all the patients who are newly diagnosed with NSCLC without prior anticancer therapy, or those with recurrence with an interval of more than 6 months from last anticancer therapy to the recurrence. The symptoms and signs which can help for the TCM syndrome type diagnosis were recorded. The EGFR gene statuses were also tested. The Yang-heat or Yin-cold syndrome types of TCM were diagnosed respectively by 3 TCM experts of our hospital to decide the TCM syndrome type. The relationship between the EGFR gene status and the TCM syndrome type were analyzed. The patients were followed up until August 2014.

Results A total of 73 consecutive patients were enrolled in our study. 32 patients (43.84%) were with the Yin-cold syndrome type according to the TCM theory, while the other 41 patients (56.16%) were with the Yang-heat type. 17 patients (53.13%) in the Yin-cold group, while only 10 patients (24.39%) in the Yang-heat group, were with sensitive EGFR gene mutation (p=0.0120). 1 in the Yin-cold group and 1 in the Yang-heat group were with T790M at the exon 20 of EGFR gene. The EGFR genes were wild type in the other 44 patients. No significant difference was seen in PFS or OS between the TCM syndrome types for those 22 patients who took EGFR-TKIs.

Conclusion Patients with Yin-cold TCM syndrome type have more chance with sensitive EGFR gene mutation. However, no relationship was seen between the efficacy of EGFR-TKIs and TCM syndrome type.

Keywords: Yin-cold TCM syndrome type; Yang-heat TCM syndrome type; None small cell lung cancer; Epidermal growth factor receptor

I. INTRODUCTION

Lung cancer is the most common cancer worldwide, due to the first mortality with malignant tumor[1]. For the intermediate to advanced stage non small cell lung cancer (NSCLC) with sensitive epidermal growth factor receptor (EGFR) gene mutation, EGFR tyrosine kinase inhibitor (EGFR-TKI) is the preferred strategy. However, even for the exclusively EGFR-mutant advanced NSCLC patients, the median PFS was only 9-13 months for those who accepted first line EGFR-TKIs therapy[2]. Unfortunately, strategies and agents to delay the resistance to EGFR-TKIs, although widely researched, are still the blank field in NSCLC treatment.

Traditional Chinese Medicine (TCM) has been wildly used in at least 78 countries [3], especially in China. Many clinical trials have evaluated the efficacy of TCM therapies combining with EGFR-TKIs[4-9]. However, most of them focused only on one special decoction or TCM patent prescription, without universally accepted TCM syndrome type differentiate system. Besides, the TCM treatment principles in these studies were also different. In the TCM theory, doctors should first differentiate the TCM syndrome types of the patients before deciding the therapy principles and medicine. Thus, we should first find out the distribution of the TCM syndrome types for the NSCLC patients before evaluating the efficacy of TCM therapies. However, the syndrome types in the TCM theory are too complicated, including the differentiation of Yin or Yang, Cold or Hot, Interior or Exterior, Deficiency or Excess, diseases in 6 meridians and 12 zang-ju organs, and some times differentiation of diseases of qi, blood and body liquid, so that it is hard to combine the TCM with the modern evidence based medicine.
In the famous TCM book named *Huangdi Neijing*, it is suggested that we should first differentiate the Yin-cold or Yang-heat type of the diseases. Some experts also believe that the Yin-cold or Yang-heat types can guide the outline of TCM differentiation of the diseases[10]. In the ISEL trial, before the identification of EGFR gene mutation, researchers found that iressa achieved better survival in the female, non-smoker patients with adenocarcinoma[11], and the further studies confirmed that these patients have more chance with EGFR gene mutation[12-15]. In the TCM theory, female patients are more likely with Yin-cold syndrome type comparing to the male patients. Besides, cigarettes are the resource of the toxic heat, so that the non-smokers are with the Yin-cold characteristics. Thus, we believe that patients with Yin-cold syndrome type are more likely to be with sensitive EGFR gene mutation. In this study, we identified the relationship between the Yin-cold or Yang-heat TCM syndrome type and the EGFR gene status, which may be the theoretic basis for the further studies combining TCM therapies with EGFR-TKIs in NSCLC patients.

II. PATIENTS AND METHODS

A. Patients and treatments

We prospectively studied all the prior untreated patients with newly diagnosed NSCLC, or those with recurrence with an interval of more than 6 months from last anticancer therapy to the recurrence, who were admitted in Department of Oncology of Guangdong Provincial Hospital of Chinese Medicine from March 2013 to January 2014. Those with uncontrolled other malignant tumors, uncontrolled infection or tubercle bacillus (TB), underlying diseases that were severe or life threatening, or sever mental disease were excluded from this study, because of the difficulty of TCM syndrome type differentiation.

First, the Yin-cold or Yang-heat syndrome types were diagnosed by the researchers, while the symptoms and signs which can help for the TCM syndrome type diagnosis were also recorded. Then, another TCM expert differentiated the Yin-cold or Yang-heat syndrome types according to the recorded symptoms and signs, respectively. If the syndrome type diagnoses of these two experts were different, then the third TCM expert was invited to help for the decision of the diagnosis of the TCM syndrome type.

The tumor characteristics were also recorded. If the patients’ EGFR gene status had been tested in the other hospitals, we only recorded the results and methods. Otherwise, the EGFR gene mutation was detected with the amplification refractory mutation system (ARMS)[16]. The treatments were decided by the doctors and patients together, according to the NCCN guideline. Briefly, patients with sensitive EGFR gene mutation would take EGFR-TKIs as first line therapy. Those without EGFR gene mutation or refused EGFR-TKIs would accept the platinum based chemotherapy. All the patients accepted Chinese herbas or patent prescriptions as TCM therapy according to the TCM syndrome type and doctors’ decision.

All the patients have provided written informed consent for this study and EGFR gene test. This study was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine.

B. Statistical analysis

Differences in demographic and clinical characteristics between the two groups were evaluated using the t test or χ² test, with an alpha <0.05. In order to identify the relationship between the TCM syndrome type and the efficacy of EGFR-TKIs, the progression free survival (PFS) and overall survival (OS) curves of patients who accepted EGFR-TKIs in Yin-cold or Yang-heat group were calculated using Kaplan–Meier method respectively, and compared by log rank test, with an alpha<0.05. The PFS was defined as the time elapsed from the date of diagnosis of NSCLC or recurrence to either the date of progression or last follow-up information. Patients who were progression free at the end of study or lost to follow-up were censored. The OS was defined as the time elapsed from the date of diagnosis of NSCLC or recurrence to either the date of death or last follow-up information. Patients who were survival at the end of study or lost to follow-up were censored. The patients were followed up until August 2014. Data were documented using EpiData software (version 3.1, The EpiData Association, Odense, Denmark) and analyzed using Stata software (version 10.0, StataCorp LP, College Station, USA).

III. RESULTS

A. Patient characteristics

A total of 73 patients were enrolled in our study. The demographic and clinical characteristics were shown in Table I. More patients with the Yang-heat syndrome type were male (80.49% vs. 40.63%, p=0.000) and had a history of smoking (73.17% vs. 37.50%, p=0.0020). Patients in the Yang-heat group were older than those in the Yin-cold group (p=0.0347). There were no significant differences in primary location, stage or pathology between the 2 groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=73)</th>
<th>Yin-cold (n=32)</th>
<th>Yang-heat (n=41)</th>
<th>p</th>
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<tbody>
<tr>
<td>Sex(male/female)</td>
<td>46/27</td>
<td>13/19</td>
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<td>Age(year), mean ± SD</td>
<td>63.32±11.32</td>
<td>60.19±11.14</td>
<td>65.83±10.96</td>
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<td>Smoker (yes/no)</td>
<td>42/51</td>
<td>12/20</td>
<td>30/11</td>
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<td>Cancer history (newly diagnosed/recurrence)</td>
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<td>27/5</td>
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<td>Primary location (left/right lung)</td>
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<td>16/13</td>
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Pathology 0.360

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<td>3</td>
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</table>

B. Relationship between EGFR gene status and TCM syndrome type

The EGFR gene status of 2 patients was detected by direct sequencing in the other hospitals. The other 71 patients’ gene status was tested with ARMS assay. A total of 27 patients were with sensitive EGFR gene mutation. 14 patients were with exon19 deletion, 10 with exon21 mutation, including 1 with L858R mutation and 1 with L861Q. 1 patient was with both exon19 deletion and exon21 L858R mutation. 44 patients were with wild type EGFR gene. 2 other newly diagnosed patients, without any anticancer therapies, 1 in the Yin-cold group and 1 in the Yang-heat group, were with exon20 T790M. Patients with Yin-cold TCM syndrome type were more likely to be with the sensitive EGFR gene mutation than those with Yang-heat TCM syndrome type (53.13% vs. 24.39%, p=0.0120, table II).

<table>
<thead>
<tr>
<th>TCM syndrome type</th>
<th>Non-sensitive mutation(n=47)</th>
<th>Sensitive mutation(n=26)</th>
<th>( \chi^2 )</th>
<th>p</th>
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<tr>
<td>Yin-cold type</td>
<td>15(46.86%)</td>
<td>17(53.13%)</td>
<td>6.3672</td>
<td>0.0120</td>
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<tr>
<td>Yang-heat type</td>
<td>31(75.61%)</td>
<td>10(24.39%)</td>
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C. Relationship between TCM syndrome type and efficacy of EGFR-TKIs

22 patients (14 in the Yin-cold group and 8 in the Yang-heat group) with sensitive EGFR gene mutation accepted EGFR-TKIs as first line therapy. The median follow-up period of these patients was 11 months (range, 2–18 months). By the end of follow-up, 3 patients in the Yin-cold group (21.43%) and 1 in the Yang-heat group (12.5%) had died. 8 patients in the Yin-cold group (57.14%) and 3 patients in the Yang-heat group (37.5%) had progressed. 2 patients (9.10%) had withdrawn. The PFS and OS curves for the Yin-cold group and Yang-heat group patients taking EGFR-TKIs were presented in Figure 1 and Figure 2. The median PFS and OS of patients in Yin-cold group were 6 months and 13 months. The 1-year survival rates in the Yin-cold and Yang-heat groups were 78.75 ± 13.40% and 87.50 ± 11.69%, while the 1-year PFS rates in the two groups were 36.36 ± 14.50% and 36.25 ± 19.89%, respectively. No statistically significant difference was found in the PFS or OS between the two groups (p=0.2293 for PFS, p=0.3924 for OS).

Fig. 1. Kaplan–Meier estimates for PFS for patients in the two groups

Fig. 2. Kaplan–Meier estimates for OS for patients in the two groups

IV. DISCUSSION

EGFR-TKIs are the preferred strategy for the intermediate to advanced stage NSCLC with sensitive EGFR gene mutation. However, the median PFS was only 9-13 months even for the exclusively EGFR-mutant advanced NSCLC patients [2, 17-21]. TCM therapies have been widely used in cancer, including the NSCLC. Although the reported trials combining TCM with EGFR-TKIs declared that their decoctions or patent prescriptions were effective, the TCM treatment principles of these decoctions or patent prescriptions were all different. For example, the TCM treatment principle of the decoction in Xiao C’s study[7] was strengthening vital qi and clearing cancer toxicity, especially clearing heat, while the principles in Yi-tang L’s study[8] included strengthening vital qi, warming yang, nourishing yin, clearing heat, and clearing blood stasis, etc. For the TCM patent prescriptions, Huachansu Injection in Jian D’s study[5] has the effect of clearing yang-heat while Kanglaike Injection in Qing-hua S’s study[6] has the effect of warming yang. As a result, although so many studies have reported the efficacy of
TCM combining with EGFR-TKIs, we still don’t know how to choose the decoctions or patent prescriptions, because of lack of TCM treatment principles.

However, due to the complexity of TCM syndrome types, it is hard to form a widely accepted TCM syndrome type differentiation system. Since the Yin-cold or Yang-heat syndrome types can guide the outline of TCM differentiation of the diseases according to the traditional Huangdi Neijing and modern studies[10], we believe that we should first differentiate these two types of TCM syndrome to guide the TCM treatment principles for NSCLC patients in combination with EGFR-TKIs. In order to reduce the subjectivity in TCM syndrome type diagnosis and differentiation, we first recorded the TCM symptoms and signs, and then the Yin-cold or Yang-heat syndrome types were differentiated according to 3 TCM experts’ diagnosis. Besides, since the ARMS assay was more sensitive than the direct sequencing in EGFR-gene mutation detection[16], the majority of EGFR gene statuses in this study were tested with ARMS assay. As is shown in the results, we found that patients with Yin-cold TCM syndrome type were more likely to be with the sensitive EGFR gene mutation than those with Yang-heat TCM syndrome type, which is the evidence of the collection between the macroscopic TCM syndrome types and the microscopic gene status.

Because the Yin-cold or Yang-heat syndrome types can guide the outline of TCM differentiation of the diseases, our findings can guide the TCM treatment principles for NSCLC patients in combination with EGFR-TKIs. Since EGFR gene mutation patients are more likely with Yin-cold syndrome type, the EGFR-TKIs may be with the efficacy of warming yang, according to the TCM theory. Besides, the major side effect of EGFR-TKIs was red acneform rash[2, 17-21], with thirsty, red and dry tongue and yellow tongue coat, which are also the evidence for the warming yang efficacy of EGFR-TKIs in TCM theory. In order to prove this TCM efficacy of EGFR-TKIs, we need to compare the TCM syndrome types of patients before and after taking EGFR-TKIs, especially when with progression. Another question is whether the warming-yang efficacy of EGFR-TKIs is treatment effect or kind of side effect. In this study, we didn’t find statistically significant difference in the PFS or OS between the Yin-cold or Yang-heat groups, maybe because of limited samples. However, according to the PFS and OS curves in figure 1 and 2, it seems that patients with Yang-heat syndrome type achieved better prognosis. As our study and follow up going on, if we finally proved this result, then we can understand the warming-yang efficacy of EGFR-TKIs as therapeutic effect, and TCM therapies with warming yang principles may help to improve the efficacy of EGFR-TKIs, and vice versa. We can also compare the PFS and OS for those with Yin-cold or Yang-heat TCM syndrome types when with progression after taking EGFR-TKIs, so that we can find out the TCM treatment principles to delay the resistance for EGFR-TKIs. All theses researches will be meaningful in combination of TCM and EGFR-TKIs, since we have proved the relationship of Yin-cold or Yang-heat syndrome types with EGFR-gene status. In fact, all of these are part of our study which has been supported by the National Natural Science Foundation of China (NSFC).

In conclusion, we found that patients with Yin-cold TCM syndrome type have more chance with sensitive EGFR gene mutation. Although no difference was found in PFS or OS between the two groups, the relationship between the efficacy of EGFR-TKIs and TCM syndrome types is worth for further study.

Acknowledgment

This study was supported by the National Natural Science Foundation of China (81273966/H2902).

References


