

# Therapeutic observation of grain-sized moxibustion for chemotherapy-induced myelosuppression for non-small cell lung cancer

## 麦粒灸对非小细胞肺癌化疗后骨髓抑制的疗效观察

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### Abstract

**Objective:** To observe the clinical efficacy of grain-sized moxibustion in treating chemotherapy-induced myelosuppression for non-small cell lung cancer (NSCLC) and its effect on quality of life (QOL).

**Methods:** Eighty NSCLC patients admitted to the Inpatient Department of Zhejiang Cancer Hospital between September 2016 and March 2018 were recruited and divided into an observation group and a control group by random number method, with 40 cases in each group. The two groups both received chemotherapy with paclitaxel plus cisplatin (TP regimen). The control group received oral administration of leucogen tablets starting from the first day of chemotherapy, 20 mg each time, three times a day, for consecutive 14 d; the observation group was additionally given grain-sized moxibustion, once a day, five days per week at a two-day interval, until the fourteenth day. The myelosuppression severity was observed and compared between the two groups prior to chemotherapy, at the 3rd, 7th and 14th days of chemotherapy; the QOL in the two groups was evaluated before chemotherapy, at the 14th and 21st days of chemotherapy.

**Results:** Regarding myelosuppression, the peripheral blood indicators increased significantly at the 3rd day of chemotherapy in both groups ( $P < 0.05$  or  $P < 0.01$ ); at the 7th and 14th days of chemotherapy, the peripheral blood indicators presented a decreasing tendency in the two groups, but the level in the observation group was still significantly higher than that before chemotherapy ( $P < 0.01$ ); at the 3rd, 7th and 14th days of chemotherapy, the peripheral blood indicators in the observation group were higher than those in the control group ( $P < 0.05$  or  $P < 0.01$ ); the occurrence rate of myelosuppression in the observation group was significantly lower than that in the control group ( $P < 0.01$ ). The QOL score in the observation group was markedly higher than that in the control group at the 14th and 21st days of chemotherapy (both  $P < 0.05$ ).

**Conclusion:** Grain-sized moxibustion can effectively improve myelosuppression after chemotherapy for NSCLC, reducing its occurrence and enhancing the patient's QOL.

**Keywords:** Acupuncture-moxibustion Therapy; Moxibustion Therapy; Moxibustion with Grain-sized Moxa Cone; Lung Neoplasms; Chemoradiotherapy; Drug-related Side Effects and Adverse Reaction; Myelosuppression; Quality of Life

**【摘要】目的:** 观察麦粒灸治疗非小细胞肺癌(NSCLC)化疗后骨髓抑制的临床疗效及对生活质量的影响。**方法:** 选取2016年9月至2018年3月浙江省肿瘤医院住院部收治的NSCLC患者80例,采用随机数字表法分为观察组和对照组,每组各40例。两组患者均采用紫杉醇与顺铂(或卡铂)联合化疗方案(TP方案);对照组在化疗开始第1天口服利可君片,每次20 mg,每日3次,连续14 d;观察组在口服利可君片基础上施麦粒灸,每日1次,每周治疗5 d,停2 d,直至第14天。分别于化疗前、化疗第3天、化疗第7天及化疗第14天比较两组患者骨髓抑制情况;分别于化疗前、化疗第14天、化疗第21天评估两组患者的生活质量。**结果:** 在骨髓抑制方面,化疗第3天时两组外周血象均较化疗前明显提高( $P < 0.05$ 或 $P < 0.01$ );而化疗第7天及化疗第14天时两组外周血象均呈现下降趋势,但观察组仍高于化疗前( $P < 0.01$ );化疗第3天、化疗第7天及化疗第14天时,观察组外周血象均高于同期对照组( $P < 0.05$ 或 $P < 0.01$ );观察组骨髓抑制分级发生率明显低于对照组( $P < 0.01$ )。在生活质量评分方面,化疗第14天及化疗第21天时观察组的生活质量评分均明显高于同期对照组,且差异具有统计学意义(均 $P < 0.05$ )。**结论:** 麦粒灸可以有效改善非小细胞肺癌化疗后的骨髓抑制情况,减少骨髓抑制发生率,同时可以明显提高化疗后患者的生活质量。

**【关键词】** 针灸疗法;灸法;麦粒灸疗法;肺肿瘤;放化疗;药物相关的副作用和不良反应;骨髓抑制;生活质量

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Primary lung cancer is one of the most common types of cancer in China, greatly endangering people's health. The 2017 report by China National Cancer Center showed that lung cancer remained the first place in the cancer list among males in urban areas<sup>[1]</sup>. Clinically, lung cancer is categorized into small cell lung cancer and non-small cell lung cancer (NSCLC), while the latter accounts for about 80%. Eighty percent of the patients diagnosed with NSCLC are often in middle-advanced stage. Having lost the chance to receive surgery, they can only choose chemoradiotherapy as the major treatment.

Myelosuppression is one significant adverse effect of chemotherapy, referring to decreased activation of hemocyte precursors in bone marrow. It may have severe effect on chemotherapy progress. The worse the myelosuppression, the higher the cost for chemotherapy<sup>[2]</sup>. Numerous studies have proven the effect of acupuncture-moxibustion on myelosuppression state amongst cancer patients after chemotherapy<sup>[3-7]</sup>. Zhao XX, *et al*<sup>[8]</sup> performed an experimental study and found that acupuncture-moxibustion increased white blood cell (WBC) count, which might be related to promoting the release of bone marrow cells to peripheral blood, extending the life span of WBCs, increasing the activation of serum colony-stimulating factor, boosting the proliferation of hematopoietic stem/progenitor cells and reducing the damage brought by chemotherapeutic drugs to these cells. We enrolled 80 NSCLC patients hospitalized in Zhejiang Cancer Hospital between September 2016 and March 2018, and used grain-sized moxibustion to treat chemotherapy-induced myelosuppression. The report is given as follows.

## 1 Clinical Materials

### 1.1 Diagnostic criteria

Referring to the diagnostic criteria of tumor in *Handbook of Clinical Oncology*<sup>[9]</sup>, diagnosed with NSCLC by pathological and/or cytological tests, or by imaging tests in combination with specific tumor markers.

### 1.2 Inclusion criteria

Conforming to the diagnostic criteria; aged 18-70 years old; life expectancy >3 months; clear consciousness, stable vital signs, Karnofsky (KPS)  $\geq 60$ ;

no intelligent or mental disorder, with normal language expression ability, able to give a fair evaluation towards his own condition and cooperate with the staff to complete the required tests; with full knowledge about the study process and informed consent signed.

### 1.3 Exclusion criteria

Mental disorder or severe cognitive impairment; coupled with hypersplenism, connective tissue disorders, hypoadrenocorticism, or hyperthyroidism which may lead to leucopenia; severe heart, lung, liver or kidney disorders, primary hematological disease, or hematopoietic dysfunction; skin lesions around the to-be-treated acupoint areas or sensory neuropathy, decreased or loss of the sensation to warmth; concurrently participating in other clinical trials that may influence the result evaluation of this study.

### 1.4 Rejection criteria

The subject voluntarily quit; when there occurred serious adverse events; when there occurred serious complications or significant deterioration; the patient could no longer follow the clinical observation; poor compliance, unable to cooperate with the staff.

### 1.5 Statistical methods

The SPSS version 19.0 statistic software was used for data processing. The enumeration data were dealt with rank sum test. The measurement data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ), with between-group comparisons analyzed by independent sample *t*-test and intra-group comparisons analyzed by paired *t*-test.  $P < 0.05$  was taken to indicate statistical significance.

### 1.6 General data

Eighty NSCLC patients hospitalized in Zhejiang Cancer Hospital were enrolled between September 2016 and March 2018. The SPSS version 19.0 was used to randomize numbers 1-80 into two groups at 1:1 and the numbered cards were then hidden in envelopes and concealed accordingly. The 80 patients were randomly divided into an observation group and a control group based on the allocated number, with 40 cases in each group. The two groups had no cases dropped out or rejected during the study. There were no significant differences in gender, age, height, weight and life expectancy between the two groups (all  $P > 0.05$ ), indicating the comparability (Table 1).

**Table 1. Comparison of the general data**

Group	<i>n</i>	Gender (case)		Average height ( $\bar{x} \pm s$ , cm)	Average weight ( $\bar{x} \pm s$ , kg)	Life expectancy ( $\bar{x} \pm s$ , month)
		Male	Female			
Observation	40	21	19	162.6 $\pm$ 7.69	55.44 $\pm$ 7.65	6.00 $\pm$ 1.89
Control	40	22	18	163.6 $\pm$ 7.81	57.21 $\pm$ 8.80	6.20 $\pm$ 1.92

## 2 Treatment Methods

Paclitaxel plus cisplatin (TP regimen) was adopted in both groups for chemotherapy which lasted for 21 d.

If severe myelosuppression occurred following chemotherapy (for instance, significant decrease in WBCs or blood platelets), recombinant human granulocyte colony-stimulating factor (rhG-CSF) or recombinant human interleukin-11 (rhIL-11) could be offered as symptomatic treatment.

### 2.1 Control group

From chemotherapy day 1, patients in the control group were given leucogen tablets for oral administration, 2 pills (20 mg) each time, 3 times a day, for consecutive 14 d.

### 2.2 Observation group

From chemotherapy day 1, patients in the observation group were given leucogen tablets for oral administration following the same dose as that in the control group. In addition, grain-sized moxibustion was offered.

Acupoints: Dazhui (GV 14), bilateral Zusanli (ST 36), Pishu (BL 20), Geshu (BL 17) and Shenshu (BL 23).

Method: The patient took a comfortable position. Moxa wool was well kneaded and made into grain-sized moxa cones. The moxa cones were placed at the above acupoints and ignited by incense, 9 cones for each acupoint. The moxa cone should be replaced immediately with tweezers when the patient felt burning pain. The treatment was performed once a day, 5 d each week following a 2-day interval, until chemotherapy day 14.

## 3 Observation of Therapeutic Efficacy

### 3.1 Observation items

3.1.1 Peripheral blood indicators and the grading and occurrence of myelosuppression

Before chemotherapy, and at chemotherapy day 3, day 7 and day 14, blood routine was tested. Peripheral blood was drawn at empty stomach in the morning. WBC count, granulocyte count and blood platelet count were observed. The grading and occurrence of myelosuppression were calculated at chemotherapy day 14.

The grading of myelosuppression referred to the grading standard of toxic and side effects of anti-cancer drugs issued by the World Health Organization (WHO).

Grade 0: WBC count  $\geq 4.0 \times 10^9/L$ ; granulocyte count  $\geq 2.0 \times 10^9/L$ ; blood platelet count  $\geq 100 \times 10^9/L$ .

Grade I: WBC count  $\geq 3.0 \times 10^9/L$ , but  $< 4.0 \times 10^9/L$ ; granulocyte count  $\geq 1.5 \times 10^9/L$  but  $< 2.0 \times 10^9/L$ ; blood platelet count  $\geq 75 \times 10^9/L$ , but  $< 100 \times 10^9/L$ .

Grade II: WBC count  $\geq 2.0 \times 10^9/L$ , but  $< 3.0 \times 10^9/L$ ; granulocyte count  $\geq 1.0 \times 10^9/L$ , but  $< 1.5 \times 10^9/L$ ; blood platelet count  $\geq 50 \times 10^9/L$ , but  $< 75 \times 10^9/L$ .

Grade III: WBC count  $\geq 1.0 \times 10^9/L$ , but  $< 2.0 \times 10^9/L$ ; granulocyte count  $\geq 0.5 \times 10^9/L$ , but  $< 1.0 \times 10^9/L$ ; blood platelet count  $\geq 25 \times 10^9/L$ , but  $< 50 \times 10^9/L$ .

Grade IV: WBC count  $< 1.0 \times 10^9/L$ ; granulocyte count  $< 0.5 \times 10^9/L$ ; blood platelet count  $< 25 \times 10^9/L$ .

### 3.1.2 Quality of life (QOL)

Before chemotherapy, and at chemotherapy day 14 and 21, Karnofsky (KPS) was used to estimate the QOL of the two groups. KPS is a scale established by Eastern Cooperative Oncology Group (ECOG) for scoring patient's physical capacity from the perspectives of movement ability, disease condition and self-care ability. The full score is 100 points, with 10 points as one level. The higher the score, the better the health status, the more tolerant to side effects brought by treatment and more possible to complete the treatment. Vice versa, the lower the score, the worse the health status. A score lower than 60 points usually means that many potential anti-cancer therapies would be impossible to implement.

100 points: Normal, no symptoms or signs.

90 points: Able to carry on normal activity, but with minor symptoms and signs.

80 points: Normal activity but with effort, with some symptoms and signs.

70 points: Cares for self, but unable to carry on normal activity or to do active work.

60 points: Able to care for most of his personal needs but requires occasional assistance.

50 points: Requires considerable assistance.

40 points: Disabled and requires special care and assistance.

30 points: Severely disabled.

20 points: Very sick and hospital admission necessary along with active supportive treatment.

10 points: Moribund, fatal process progressing rapidly.

0 point: Dead.

### 3.2 Treatment results

#### 3.2.1 Comparison of peripheral blood indicators

Before chemotherapy, there were no significant differences in WBC, granulocyte and blood platelet counts between the two groups (all  $P > 0.05$ ). At chemotherapy day 3, the WBC, granulocyte and blood platelet counts all increased significantly in both groups ( $P < 0.05$  or  $P < 0.01$ ); at chemotherapy day 7, the WBC count presented an increasing tendency and the granulocyte and blood platelet counts showed a decreasing tendency compared with the baseline data in the control group, while these changes were all statistically insignificant (all  $P > 0.05$ ); the WBC and granulocyte counts were significantly higher than the baseline in the observation group ( $P < 0.05$  or  $P < 0.01$ ), and the decrease in blood platelet count was statistically insignificant ( $P > 0.05$ ). At chemotherapy day 14, the three indicators all decreased significantly

compared with the baseline in the control group ( $P<0.05$  or  $P<0.01$ ); in the observation group, only the blood platelet count dropped significantly compared with the baseline ( $P<0.05$ ), while the WBC and granulocyte counts were still higher than the baseline, though the differences were statistically insignificant (both  $P>0.05$ ). At chemotherapy day 3, the three indicators in the observation group were all higher than those in the control group, but significant difference was only found in the granulocyte count ( $P<0.05$ ); at chemotherapy day 7, the three indicators in the observation group were all higher than those in the control group, while significant difference was found in the WBC and granulocyte counts (both  $P<0.05$ ). At chemotherapy day 14, the three indicators in the observation group were all significantly higher than those in the control group ( $P<0.05$  or  $P<0.01$ ), (Table 2).

3.2.2 Comparison of myelosuppression grading and occurrence

The occurrence of myelosuppression was calculated

based on each grade, i.e., grades 0, I, II, III and IV. In the control group, the occurrence rate was 25.0%, 50.0%, 12.5%, 7.5% and 5.0%, respectively, versus 50.0%, 37.5%, 10.0%, 2.5% and 0% in the observation group, and the between-group differences were statistically significant ( $P=0.016$ ), (Table 3).

3.2.3 Comparison of the QOL

The QOL was estimated by KPS before chemotherapy, and at chemotherapy days 14 and 21, respectively. The between-group difference in QOL was statistically insignificant before chemotherapy ( $P>0.05$ ). At chemotherapy days 14 and 21, KPS score declined in both groups compared with the baseline, but the difference was found significant only at chemotherapy day 14 in the control group ( $P<0.05$ ). The between-group comparison at chemotherapy days 14 and 21 showed that KPS score in the observation group was significantly higher than that in the control group (both  $P<0.05$ ), (Table 4).

**Table 2. Comparison of the peripheral blood indicators ( $\bar{x} \pm s, \times 10^9/L$ )**

Group	n	Indicator	Pre-chemotherapy	Chemotherapy day 3	Chemotherapy day 7	Chemotherapy day 14
Observation	40	WBC count	4.51±0.45	7.06±0.86 <sup>1)</sup>	6.63±1.98 <sup>1)3)</sup>	5.45±1.56 <sup>4)</sup>
		Granulocyte count	2.67±0.34	3.91±0.54 <sup>1)3)</sup>	3.65±1.18 <sup>2)3)</sup>	2.94±0.95 <sup>4)</sup>
		Blood platelet count	184.90±66.45	213.10±54.52 <sup>1)</sup>	179.90±60.63	140.60±36.73 <sup>2)3)</sup>
Control	40	WBC count	4.87±0.62	6.40±0.56 <sup>1)</sup>	4.91±1.27	3.77±0.95 <sup>1)</sup>
		Granulocyte count	2.88±0.20	3.44±0.28 <sup>1)</sup>	2.50±0.80	1.68±0.59 <sup>1)</sup>
		Blood platelet count	161.80±60.09	192.80±45.44 <sup>2)</sup>	159.90±43.75	110.30±20.57 <sup>2)</sup>

Note: Intra-group comparison, 1)  $P<0.01$ , 2)  $P<0.05$ ; compared with the control group, 3)  $P<0.05$ , 4)  $P<0.01$

**Table 3. Comparison of the myelosuppression grading after chemotherapy (case)**

Group	n	Grade 0	Grade I	Grade II	Grade III	Grade IV
Observation	40	20	15	4	1	0
Control	40	10	20	5	3	2
Z-value				-2.420		
P-value				0.016		

**Table 4. Comparison of KPS score ( $\bar{x} \pm s, \text{point}$ )**

Group	n	Pre-chemotherapy	Chemotherapy day 14	Chemotherapy day 21
Observation	40	81.00±7.39	77.00±9.49 <sup>2)</sup>	80.00±0.00 <sup>2)</sup>
Control	40	79.00±5.68	66.00±8.53 <sup>1)</sup>	75.00±1.67

Note: Intra-group comparison, 1)  $P<0.05$ ; compared with the control group, 2)  $P<0.05$

4 Discussion

Primary lung cancer remains one of the most common malignant tumors today. The 2015 report by China National Cancer Center<sup>[10]</sup> showed that 1.302 million people developed lung cancer and the prevalence rate was 1/100 000 in China during

2006-2011, including 846 000 male and 456 000 female patients, which gave it the second place in males and the fourth in females on the list of malignant tumors. About 80% of lung cancer is NSCLC, and most of the NSCLC patients are already in the middle-advanced stage when diagnosed. Lung cancer in this stage, is inoperable, and patients mostly have to rely on

chemotherapy. However, most of the chemotherapy drugs may inhibit the proliferation of hematopoietic stem cells, resulting in the decreased number of blood cells released to peripheral blood system. This is the major cause of myelosuppression in chemotherapy, which may significantly hinder the chemotherapy.

Relevant studies have suggested the aging of hematopoietic stem cells mainly involves p53-p211 (Cipl/Wafl) and p16 (Ink4g)-Rp pathways<sup>[11-12]</sup>. The inhibition of the two pathways will halt the cells in G1 or G2 phase and hamper their self-renewal ability, subsequently leading to cell aging. Granulocytes suffer the most serious influence produced by chemotherapy, mainly manifested by the decrease of WBCs in peripheral blood<sup>[13]</sup>.

In traditional Chinese medicine (TCM), myelosuppression can be categorized into consumptive diseases, blood syndrome, or fever due to internal injuries. Liu QY, *et al*<sup>[14]</sup> summarized the experience of Professor He Ruo-ping in treating chemotherapy-induced myelosuppression based on three perspectives: Deficiency of healthy qi with retained pathogenic qi; the deficiency of Zang-fu organs, especially the spleen and kidney; intermingled toxins, deficiency and stasis. Yang S, *et al*<sup>[15]</sup> believe that chemotherapy drugs harm both the congenital foundation and the acquired constitution by destroying bones and consuming essence, and damaging the spleen and stomach, cutting the source of blood and qi. Some doctors<sup>[16]</sup> hold that cancer patients usually bear a poor constitution in the first place, and the toxic chemotherapy drugs can easily invade Zang-fu organs and cause damages, especially the spleen and kidney. Therefore, the pathogenesis of consumptive diseases can be summarized as deficiency of healthy qi along with retained pathogenic factors.

So far, the effect of acupuncture-moxibustion on myelosuppression has been proved by many studies. Liu SH, *et al*<sup>[17]</sup> pointed out that remarkable results had been obtained in molecular biology study on the mechanism of acupuncture-moxibustion for chemotherapy-induced myelosuppression. They managed to summarize and analyze the mechanism studies based on the effects of acupuncture-moxibustion on Notch signaling pathway, repair of DNA, cytokines and cell cycle of bone marrow. There are multiple acupuncture-moxibustion methods for myelosuppression after chemotherapy, including acupuncture, warm needling, moxibustion, acupoint application, and acupoint injection, etc. Meanwhile, acupuncture-moxibustion has showed many advantages, such as a low cost, significant efficacy, convenient, and environment-friendly. Therefore, it is worth promoting in clinic.

The *Ling Shu · Guan Neng* (the 73rd Chapter of *Spiritual Pivot*) states that 'moxibustion can be used where acupuncture cannot reach...moxibustion works for deficiency of yin and yang...insufficient meridian qi and collateral stagnation can both be treated with moxibustion'. It is indicated that compared with acupuncture, moxibustion is more recommended to treat the deficiency of yin and yang, deficient meridian qi and collateral stagnation. Hence, we used grain-sized moxibustion to achieve more significant efficacy without producing blisters or leaving scars on the skin and it could be better accepted by the patients especially those who were afraid of needles. Multiple studies<sup>[5,18-22]</sup> have discovered the effect of Zusanli (ST 36) and Dazhui (GV 14) in boosting blood production, up-regulating the WBC count and regulating immune system. By relating TCM theories to modern research, we selected Zusanli (ST 36) and Pishu (BL 20) to invigorate the spleen yang and tonify qi in the middle Jiao; Dazhui (GV 14) was used to modulate the meridian qi in the six yang meridians, warming and tonifying yang qi generally; Geshu (BL 17) was to regulate qi flow and sooth the chest, activate blood circulation and unblock vessels; Shenshu (BL 23) was used to warm and consolidate the kidney yang and the foundation.

In this study, the peripheral blood indicators were found to present an increasing tendency since the third day of chemotherapy in the two groups, but then start to turn down at day 7 and day 14. The WBC, granulocyte and blood platelet counts in the observation group were always higher than those in the control group at the same time points, especially the WBC and granulocyte counts. Meanwhile, the occurrence rate of myelosuppression was significantly lower in the observation group than in the control group. The results suggested that grain-sized moxibustion can produce remarkable efficacy in improving chemotherapy-induced myelosuppression. Besides, the KPS score in the observation group was higher than that in the control group despite a decrease in both groups, indicating that grain-sized moxibustion can help maintain the QOL while improving the myelosuppression.

In summary, the current study has proved the effect of grain-sized moxibustion in improving chemotherapy-induced myelosuppression in NSCLC. Its merits range from significant improvement of WBC and granulocyte counts to the maintenance of QOL, allowing patients to get through chemotherapy in a relatively comfortable way. It somehow can also improve the compliance and tolerance. Grain-sized moxibustion is convenient, cost-effective, environment-friendly, side-effects free and effective, and thus worthy of further application.

**Conflict of Interest**

The authors declared that there was no potential conflict of interest in this article.

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**Statement of Informed Consent**

Informed consent was obtained from all individual participants.

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