Effect of calculus bovis cultured in vitro on quality of life and immune function of patients with non-small cell lung cancer undergoing chemotherapy

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Abstract: Randomly dividing 160 cases into two groups, the research group was given conventional chemotherapy while the other was exposed to in vitro cultured calculus bovis, in order to evaluate the impact of this on the quality of life and immune function of those with non-small cell lung cancer undergoing chemotherapy. The clinical efficacy, quality of life scale (QLQ-C30, QLQ-LCL3) scores and immune indexes (CD4+, CD8+, CD4+/CD8+) were evaluated after two chemotherapy cycles. The comparison of clinical efficacy between the two groups yielded significant results (P >0.05). After treatment, physical, emotional, and fatigue scores in the comparison group increased significantly (P <0.05); shortness of breath in the research group decreased (P <0.05); loss of appetite in the comparison group rose (P<0.05); and total health in the research group increased significantly (P<0.05). ③ The research group's CD4+, CD4+/CD8+ levels after treatment were greater than those in the comparison group, and CD8+ was lower (P <0.05). In vitro cultivation of cattle can enhance the clinical efficacy, quality of life, and immune function of those suffering from non-small cell lung cancer.

1. Trial review & treatment

1.1. Case Review

From March 2018 to November 2020, a total of 160 patients diagnosed with non-small cell lung cancer received chemotherapy treatment and were hospitalized at our facility. There cases were eliminated from the research group due to their incapacity to endure the side effects of chemotherapy, while two more patients withdrew because of financial issues. Additionally, two participants in the comparison group also left the trial due to their inability to tolerate the chemotherapy's side effects. In the end, 153 complete cases were collected, including 75 in the research group, 78 cases in the comparison group. Within the research group, there are 45 males and 30 females, ranging from 32~75 years old, average age of them was 57.64±9.33 year. Within this group, there are 55 instances of adenocarcinomas, 19 instances of squamous cell carcinomas, 1 instance of large cell carcinoma, 8 instances of stage IIIA cases, 22 instances of stage IIIB cases, and 45 instances of stage IV cases. The comparison group consisted of 42 males and 36 females (aged between 28 and 72 with an average age of 55.70±12.23 years) with 52 cases of adenocarcinomas, 26 cases of squamous cell carcinomas, 10 cases of stage IIIA, 24 cases of stage IIIB, and 44 cases of stage IV. No distinction in the pathological type, gender, age and TNM stage between the two patient groups was observed(P>0.05), with their statistics being comparable.

1.2. Case Selection

1.2.1. Western medicine diagnostic standards

The criteria for recognizing non-small cell lung cancer, as set out in the National Comprehensive Cancer Network's (NCCN) pertinent recommendations, are the basis of TNM-based lung cancer staging, which is guided by the 8th edition of the Union International Against Cancer's (UICC) lung cancer staging[1,2].In 2014, the "Guidelines for TCM Diagnosis and Treatment of Malignant Tumors (Lung Cancer Part)" [3] was used to create diagnostic standards for Traditional Chinese Medicine (TCM) syndrome differentiation of heat-toxin stasis, phlegm-dampness stasis, and heat-toxin obstruction of the lungs.

1.2.2. Inclusion criteria:

① Patients with non-small cell lung cancer at stages III and IV, confirmed by histopathology or cytology, and receiving concurrent chemotherapy;

② Those who satisfy the TCM syndrome differentiation criteria of heat-toxic stasis, phlegm-dampness stasis, and heat-toxic lung obstruction;

③ Aged 18 to 80 years old;

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④ The expected survival time for an ECOG score of less than two points is more than three months.
⑤ Voluntarily accept drug treatment;
⑥ All enrolled patients signed informed consent.

1.2.3. Exclusion criteria:

① Those with heart, liver, kidney, and other vital organ dysfunction;
② Those who cannot follow the treatment course;
③ Those who cannot cooperate with follow-up visits.

1.2.4. Elimination and dropout criteria:

① Those suffering from cardiac, liver, kidney, and other vital organ dysfunction;
② Those without any trial records;
③ Those who experience serious adverse occurrences, complications, or extraordinary physical alterations during the trial and are not fit to continue to partake in the trial are not suitable;
④ Early withdrawal from the trial or a lack of follow-up may be attributed to other causes.

1.3. Treatment

The comparison group was routinely given platinum-containing two-drug chemotherapy. Paclitaxel (produced by Yangzijiang Pharmaceutical Group Co., Ltd., approval number: H20058719)175 mg/m2, intravenous infusion,+ cisplatin on day 1(Shandong Phoenix Pharmaceutical Co., Ltd.The total dose, with an approval number of H20056422, is 75 mg/m2 and is administered through an intravenous infusion, with days 1-3, 21 days as a single cycle, and 2 cycles of chemotherapy.

In addition to the above treatments, the research group also took 0.15g of in vitro cultured bezoar orally, 2 times/d starting from the day of chemotherapy for 2 cycles.

1.4. Observation indicators and efficacy evaluation standards

The standards of solid tumor efficacy evaluation, referred to as efficacy evaluation, are outlined in [4].The efficacy of chemotherapy is divided into three categories when comparing CT examination results of patients before and after 2 cycles: Complete Response (CR): All target lesions vanish; Partial Response (PR): Target lesions are decreased by at least 30% compared to the baseline total diameter; Disease Progress (PD): The total diameter of the target lesion is increased by 20% or more than the minimum total diameter in the study, including the baseline total diameter.Should the minimum value in the study be the case, the total diameter must be augmented by more than 5mm or when one or more new lesions are identified; stable disease (SD): the lesions shrink, yet do not meet the criteria for PR. or compared with the minimum total diameter after treatment, the lesions increase but do not meet the criteria for PD.The effective rate is equal to the sum of CR cases + PR cases multiplied by the total number of cases, which is 100%.

The quality of life of the patients was evaluated through the EORTC's QLQ-C30 and QLQ-LC13 scales, both before and after the treatment.Within the QLQ-C30 core module, there are a total of 30 components, encompassing two functional domains (physical and emotional) that are particularly relevant to lung cancer.In addition, 3 symptom types (fatigue, pain, nausea and vomiting) are included, with 1 section dedicated to overall health and quality of life; additionally, 6 individual elements (breathlessness, sleep disturbances, loss of appetite, constipation, diarrhea and financial strain) are present. Supplementary to this core module is the QLQ-LC13, which specifically addresses symptoms related to lung cancer and side effects resulting from treatment.The scale is filled in by the patients themselves and is divided into four levels:"none" is scored as 0 points,"a little" is scored as 1 point,"somewhat" is scored as 2 points, and "very much" is scored as 3 points.The scale of quality of life varies from 1 to 7 points, with higher numbers indicating improved performance. As show in figure 1.

EORTC QLQ-C30 (version 3) Quality of Life Questionnaire

We would like to gather some information about you and your health condition. Please answer all the following questions independently and circle the answer that best fits you. There are no "right" or "wrong" answers. The information you provide will be kept strictly confidential.

Please fill in your: Name: _____Date of birth (year, month, day):_____Today's date (year, month, day):_____

In the past week:	None	A little bit	Quite a bit	Very much
1. When doing strenuous activities, such as lifting heavy shopping bags or suitcases, do you feel difficulty?	1	2	3	4
2. When walking long distances, do you feel difficulty?	1	2	3	4
3. When walking short distances outdoors, do you feel difficulty?	1	2	3	4
4. During the day, do you need to stay in bed or sit in a chair?	1	2	3	4
5. Do you need help from others with eating, dressing, washing, or using the toilet?	1	2	3	4
6. Has your work or daily activities been limited by physical ability?	1	2	3	4
7. Have your hobbies and leisure activities been limited by physical ability?	1	2	3	4
8. Have you felt short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Have you needed to rest?	1	2	3	4
11. Have you had poor sleep?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lost your appetite?	1	2	3	4
14. Have you felt nauseous or vomited?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you had constipation?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Have you felt tired?	1	2	3	4
19. Does pain interfere with your daily activities?	1	2	3	4
20. Do you have difficulty concentrating on things, such as reading a newspaper or watching TV?	1	2	3	4
21. Do you feel nervous?	1	2	3	4
22. Have you felt worried?	1	2	3	4
23. Do you feel irritable?	1	2	3	4
24. Have you felt depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or treatment affected your family life?	1	2	3	4
27. Has your physical condition or treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or treatment caused you financial difficulties?	1	2	3	4
For the following questions, numbers 1-7 represent a scale from "very poor" to "excellent"				
29. How would you rate your overall health in the past week?				
1 2 3 4 5 6 7				
30. How would you rate your overall quality of life in the past week?				
1 2 3 4 5 6 7				
EORTC QLQ-LC13 Quality of Life Questionnaire				
31. Have you been coughing frequently?	1	2	3	4
32. Have you been coughing up blood (blood in sputum)?	1	2	3	4
33. Do you feel short of breath at rest?	1	2	3	4
34. Do you feel short of breath while walking?	1	2	3	4
35. Do you feel short of breath while climbing stairs?	1	2	3	4
36. Have you had oral or tongue pain?	1	2	3	4
37. Have you had difficulty swallowing?	1	2	3	4
38. Have you had numbness/tingling in hands or feet?	1	2	3	4
39. Have you experienced hair loss?	1	2	3	4
40. Have you had chest pain?	1	2	3	4
41. Have you had arm or shoulder pain?	1	2	3	4
42. Have you had pain in other parts of your body?If yes, please specify the location!	1	2	3	4
43. Have you taken pain medication?	1	2	3	4
If used, was the pain relief significant?	1	2	3	4

Figure 1. QLQ-C30 and QLQ-LC13 scales table.

In the context of immunology, the terms CD4+, CD8+, and the CD4+/CD8+ ratio are pivotal indicators used to assess the status of an individual's immune system.T helper cells, otherwise known as CD4+ cells, are a critical part of the immune system. By differentiating into Th1, Th2, and Th17 subsets, they are able to activate and control immune responses, thus playing a role in both cellular and humoral immunity. CD8+cells, also referred to as cytotoxic T lymphocytes (CTLs), are responsible for

the direct elimination of cells infected with viruses or transformed into cancerous cells. They are crucial in controlling viral infections and preventing the progression of malignancies. CD4+/CD8+ Ratio represents the proportion of CD4+ T cells to CD8+ T cells. Under normal conditions, the CD4+/CD8+ ratio typically ranges from 1.5 to 2. Deviations from this range, either an increase or decrease, may suggest an underlying issue with the immune system.A decrease in CD4+ T cell count in those with HIV/AIDS can cause a decrease in the CD4+/CD8+ ratio, for example.

In the morning, 2 ml of fasting cubital venous blood from patients was taken before and after the immune index treatment, and changes in immune function indices CD4+, CD8+, and CD4+/CD8+ were observed.

1.5. Statistical Method

Using IBM SPSS Statistics 26 software, data analysis was conducted. Measurement data was expressed as mean ± standard deviation x±s, with independent samples t test or Mann-Whitney U test employed. Counting data was expressed through chi-square test or Fisher's exact probability method. A P<0.05 indicates that the difference is statistically significant.

2. Result

Table 1 revealed that, despite the research group's overall effective rate being slightly higher than that of the comparison group, the difference was not statistically significant (P>0.05).

Table 1. Comparative examples of clinical efficacy between two groups (%)

Group	CR	PR	SD	PD	Total Efficiency
Research Group(n=75)	0(0.0%)	19(25.33%)	36(48.00%)	20(26.67%)	55 (73.33%)
Comparison Group(n=78)	0(0.00%)	20(25.64%)	34(43.58%)	24(30.76%)	54 (69.23%)

2.1. QLQ-C30 scale scores

The comparison group's physical function, emotional function, and fatigue scores were markedly higher than those of the research group after treatment, a difference that was statistically significant (P<0.05). Additionally, the research group's shortness of breath symptom score was significantly lower than that of the comparison group, a difference that was also statistically significant (P<0.05).The comparison group's appetite loss score was significantly greater than that of the research group, a difference that was statistically significant (P<0.05). Furthermore, the total health status score of the research group was higher than that of the comparison group, and the difference was also statistically significant, as demonstrated in Tables 2 and 3.

Table 2. Comparison of QLQ-C30 scale (function and symptom scale) rating scales

Group	Time	Physical Function	Emotional Function	Fatigue	Pain	nausea
Research Group (n=75)	Before	7.1±1.2	5.5±1.6	3.1±1.2	2.1±1.3	3.4±2.0
	After	6.3±1.3*	5.9±1.5*	3.9±1.6*	3.3±1.5	4.1±1.7
Comparison Group （n=78)	Before	6.8±1.1	5.8±1.6	3.3±1.1	2.3±1.4	3.6±1.5
	After	10.5±2.1	9.1±2.3	6.5±2.2	3.1±1.6	4.5±1.8

Note: compared to comparison group after treatment, *P<0.05.

Table 3. Comparison of changes in QLQ-C30 scale (single measurement items, total health status) scores

Group	time	Shortness of breath	Insomnia	Low appetite	Constipation	Diarrhea	Economic difficulties	Total Health Condition
R	B	3.1±1.2	2.5±1.1	3.2±1.3	2.2±1.3	0.8±0.3	1.4±1.0	5.4±1.5
75	A	1.3±0.8	3.0±1.2	3.9±1.6	3.0±1.1	0.7±0.2	1.8±0.7	4.8±1.1
C	B	3.8±1.4	2.8±1.6	3.4±1.1	2.3±1.5	1±0.3	1.6±0.5	5.0±1.2
78	A	3.0±1.1	3.1±2.3	5.5±2.2	2.7±1.2	0.9±0.2	1.5±0.6	3.4±0.9

Note: compared to comparison group after treatment, *P<0.05.
R stands for Research Group; C stands for Comparison Group;
B stands for before treatment; A stands for after treatment;

2.2. Changes in QLQ-LC13 scale scores

Table 4 reveals a significant difference between the research group's cough and chest pain scores before and after treatment, with the former decreasing (P<0.05) and the latter increasing (P<0.05).

Table 4. Comparisons of changes in QLQ-LC13 scale scores

G	t	Cough	Hemoptysis	Hoarse voice	Alopecia	Chest Pain	Peripheral Neuropathy
R	B	3.2±0.2	1.2±0.3	0.6±0.1	0.0±0.0	1.3±0.4	0.0±0.0
75	A	1.3±0.3#	1.0±0.5	0.7±0.1	2.8±1.2#	0.5±0.2#	2.1±1.1#
C	B	3.5±1.1	1.3±0.6	0.5±0.2	0.0±0.0	1.2±0.4	0.0±0.0
78	A	2.9±0.9*	1.1±0.3	0.6±0.2	3.0±1.3#	1.3±0.6*	2.5±1.3#

Note: A comparison between the group before and after the treatment revealed a significance level of P<0.05, while the comparison group's significance level was also lower, with a p-value of p<0.05, indicating a n-value of 78.

2.3. A contrast of the immune system's performance between the two groups

No significant disparity in immune function indicators was observed between the two groups prior to treatment (P>0.05); however, post-treatment, the research group's CD4+ and CD4+/CD8+ levels were higher than the comparison group's, and the CD8+ levels were lower, and this difference was statistically significant (P<0.05), as Table 5 demonstrates.

Table 5. Comparison of immune function (%, $\bar{x}\pm s$)

Group	CD4+		CD8+		CD4+/CD8+	
	Before	After	Before	After	Before	After
Research Group (n=75)	34.20±7.763	41.07±11.03	25.56±7.24	20.13±9.4	1.55±0.71	2.58±1.87
Comparison Group(n=78)	33.84±7.28	35.23±10.03*	24.32±8.35	23.50±7.06*	1.54±0.61	1.64±0.82*

Note: In contrast to the comparison group, post-treatment, a significance level of P<0.05 was observed.

3. Discussion

The respiratory system's lung cancer, a malignant tumor with extreme morbidity and mortality [5], necessitates comprehensive treatment for intermediate and advanced tumors in order to control tumor development, prolong survival, and enhance quality of life [6].A meta-analysis and a multitude of randomized controlled studies demonstrate that chemotherapy is more efficacious than symptomatic and supportive treatment in enhancing the quality of life and overall survival of those with locally advanced non-small cell lung cancer [7]. However, chemotherapy has serious toxic and side effects, which can reduce the patient's physical condition and gradually increase disease symptoms, making the patient's immune function low, quality of life reduced, and unwilling to accept aggressive chemotherapy regimens again.The combination of paclitaxel and cisplatin, employed in this study, is a chemotherapy technique that hinders tumor formation by hindering and obstructing the proliferation and replication of cancer cells. However, certain adverse reactions also occurred, and the immune function was also suppressed, which affected the overall efficacy.Consequently, the key to successful treatment is to enhance the patient's immune system and enhance their quality of life. Combining traditional Chinese medicine with chemotherapy can reduce toxicity and enhance efficacy, thereby improving the patient's outlook and quality of life.

Based on its symptoms, traditional Chinese medicine classifies lung cancer into the categories of "cough" and "lung accumulation".The origin of lung cancer is invariably due to a lack of Benxu and Biaoshi. The lack of Benxu is caused by an absence of Qi and Yin, as well as the lungs, spleen and kidneys, with Benxu being the root cause. The lack of Biaoshi is mainly seen in Qi stagnation, blood stagnation, phlegm coagulation, cancer toxins, and Biaoshi is essential for the commencement of the illness.Common among them are syndromes of heat-toxic stasis, phlegm-dampness stasis, and heat-toxic lung obstruction. Clinical and experimental studies have demonstrated that traditional Chinese medicine for detoxifying and clearing heat can either directly or indirectly combat cancer and suppress it by eliminating the buildup of cancer-causing toxins in the body. It can also improve the body's immunity, promote macrophage function, and help control the development of cancer [8].

The 2015 edition of the "Pharmacopoeia of the People's Republic of China" reveals that bezoar has a range of benefits, such as heat-clearing, phlegm-removal, detoxification, analgesic, and more. Modern pharmacology research shows that bezoar has antipyretic, analgesic, anti-inflammatory, immunity-improving, anti-tumor and other activities [9]. In vitro cultured bezoars are cultivated by using fresh bile of bovine cattle as mother liquor, adding deoxycholic acid, cholic acid, complex bilirubin calcium, etc.[10], and the efficacy is equivalent to that of natural bezoars [11]. Some domestic clinical studies have confirmed that culturing bezoars in vitro can improve the quality of life of cancer patients, and has certain effects on digestive tract tumors, liver cancer, head and neck malignant tumors, etc., especially on hepatobiliary toxic heat, phlegm and blood stasis-type tumors [12-13]. For the quality of life of lung cancer, QLQ_C30 and QLQ_LC13 are commonly used to comprehensively evaluate the quality of life [14].The quality of life of those suffering from non-small cell lung cancer undergoing chemotherapy was evaluated through the utilization of the QLQ-C30 and QLQ-LC13 scales, which are commonly employed to provide a comprehensive evaluation [15-16].The synergistic effect of in vitro cultured bezoar combined with chemotherapy on non-small cell lung cancer patients was demonstrated by the results, yet no statistically significant difference between the clinical symptoms of the two groups was found. Nevertheless, physical, emotional, and overall quality of life were all significantly improved. Additionally, tumor-related symptoms such as fatigue, shortness of breath, cough, chest pain, and anorexia were also improved.

Relevant studies have confirmed that improving immunity can control distant metastasis and thereby reduce mortality [17-18].The body's perception of exogenous evil ("Waixie" in TCM terms) has a certain inhibitory effect on T cell activity, which is mainly demonstrated by a decrease in CD4+ T cells and a rise in CD8+ T cells. Among them, CD8+ are cytotoxic T cells that exert cytotoxicity in the immune system.CD4+ is a

helper T cell, capable of stimulating antibody secretion, B cell synthesis, and controlling immune defense reactions, yet it can also cause damage and have adverse regulatory effects. The results of this study showed that after treatment, CD4+ and CD4+/CD8+ in the research group were higher than those in the comparison group, while CD8+ was lower than that in the comparison group. It shows that culturing bezoar in vitro can improve the immune function of patients.

To conclude, the clinical efficacy of chemotherapy for non-small cell lung cancer patients in vitro culture of cattle can be improved to a certain degree, leading to improved quality of life and a heightened immune system, which has a clinical application. Unfortunately, the limited sample size and lack of long-term efficacy in this study make the results of this study still inadequate and necessitate further investigation.

4. Conclusion

The QLQ-C30 and QLQ-LC13 quality of life scales were employed in this study to assess the quality of life of those suffering from non-small cell lung cancer undergoing chemotherapy. Results indicated that in vitro cultured bezoar combined with chemotherapy had a synergistic effect on the patients with non-small cell lung cancer, yet there was no statistically significant distinction between the clinical symptoms of the two groups.Significant impacts on physical, emotional, and overall quality of life can be seen; moreover, it can ameliorate tumor-related symptoms such as fatigue, shortness of breath, coughing, chest pain, and anorexia.

After treatment, CD4+ and CD4+/CD8+ in the research group were higher than those in the comparison group, while CD8+ was lower than that in the comparison group. It shows that culturing bezoar in vitro can improve the immune function of patients.

To conclude, in vitro cattle culture has been found to have a positive effect on the clinical efficacy of those with non-small cell lung cancer undergoing chemotherapy, as well as improving their quality of life and enhancing immune function - all of which are clinical benefits. Therefore, when treating patients with NSCLC, it may be advantageous to consider combining other therapeutic approaches, particularly chemotherapy.Contemplation of administering a minuscule amount of Calculus bovis in vitro cultured may be beneficial in reducing chemotherapy side effects, augmenting immune system, and enhancing therapeutic results for patients.

Despite the limited sample size and lack of long-term efficacy, the findings of this study still have many deficiencies and necessitate further examination. Subsequent research will involve conducting additional clinical trials to verify the long-term efficacy, safety, and optimal dosage of in vitro cultured Calculus bovis in humans. The investigation will also explore potential drug interactions of in vitro cultured Calculus bovis to prevent adverse reactions or to enhance therapeutic effects. Furthermore, the research will delve into whether in vitro cultured Calculus bovis possesses potential therapeutic benefits for other diseases.

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