ORIGINAL ARTICLE

Effects of Combined Chinese Drugs and Chemotherapy in Treating Advanced Non-small Cell Lung Cancer*

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ABSTRACT **Objective:** To evaluate the efficacy and side effects of combined Chinese drugs and chemotherapy in treating advanced non-small cell lung cancer (NSCLC). **Methods:** Sixty-three patients with stage ⅢB and Ⅳ NSCLC hospitalized from October 2001 to October 2008 were enrolled and assigned to two groups using a randomizing digital table, with 33 patients in the treatment group and 30 in the control group. They were all treated with the Navelbine and Cisplatin (NP) chemotherapy, but to the treatment group the Chinese drugs Shengmai Injection (生脉注射液) by intravenous dripping and Gujin Granule (固金颗粒冲剂) by oral intake were given additionally. The main observation indexes were response rate (RR), median survival time, 1-year survival rate and median time to progression (TTP); secondary observation indexes were side effects and cycles of chemotherapy. **Results:** Altogether, 61 patients (33 from the treatment group and 28 from the control group) completed the observation and were assessable. RR was 48.5% (16/33) in the treatment group and 32.2% (9/28) in the control group, and the median survival time were 13 months and 9 months, respectively; the difference between the two groups was significant (P=0.0373 and P=0.014 respectively). However, the differences between groups were insignificant in terms of 1-year survival rate [51.5% (17/33) *vs* 46.4% (13/28), P=0.4042], median TTP (5.95 months *vs* 4.64 months, P=0.3242), grade Ⅲ or Ⅳ bone marrow inhibition occurrence rate [33.3% (11/33) *vs* 39.3% (11/28), P=0.3500], and mean cycles of chemotherapy applied (2.94±0.94 cycles *vs* 2.75±0.75 cycles, P=0.4100). **Conclusion:** Combined Chinese drugs and chemotherapy can enhance the short-term therapeutic efficacy in the treatment of NSCLC and prolong patients' median survival time, but show no evident impact on TTP.

KEY WORDS Chinese medicine, Navelbine and Cisplatin chemotherapy, advanced non-small cell lung cancer, randomized controlled

Lung cancer is one of the commonly encountered tumors that seriously threaten human health[1]. The clinical efficacy of chemotherapy on advanced non-small cell lung cancer (NSCLC) remains limited in spite of the improved effects of some new anticarcinogens (Gemcitabine, Vinorelbine and Taxol), and the third generation chemotherapy program constituted by platinum. However, patients' overall survival time has not been prolonged significantly[2].

Rich experiences have been accumulated in Chinese medicine and drugs in the treatment of lung cancer in clinical practice, and they are characterized by low response rates but high stability, and could prolong patients' survival time to some degree. In order to enhance the efficacy in treating NSCLC and prolong patients' survival time, a randomized controlled clinical trial in the treatment of NSCLC patients was conducted by the authors from October 2001 to October 2008 using integrative Chinese and Western medicine. The results are reported as follows.

METHODS

General Materials

The 63 NSCLC patients, with an age range from 20 to 75 years old, were all in-patients hospitalized at the authors' department for initial treatment or re-treatment. Their diagnoses were confirmed by pathologic and/or cytologic examination, and were classified as stage ⅢB/Ⅳ (using the Standards of the International Union Against Cancer)[3]; and in the Chinese medicine syndrome, they belonged to the qi-yin deficiency[4]. Their physical condition was scored on a scale of 0-2 (by ECOG), with measurable lesions

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and without any main organ dysfunction. Their routine analysis of blood, liver and kidney functions were normal, and their estimated survival time was over 6 months. The patients took part in the trial voluntarily, signed written inform consents with good compliance, and could be followed-up periodically. Excluded were patients undergoing other anti-tumor therapies, with uncontrolled central nerval metastatic lesion or important organic dysfunction, or with such severe diseases as dyshematopoiesis, as well as women who were pregnant or in the lactation stage, or with a history of unmanageable psychiatric disease.

Grouping

With the randomized controlled open design adopted, the 63 patients enrolled in the study were assigned to two groups, the treatment group and the control group, at a ratio of 1:1 using a randomizing digital table issued to professional staff according to statistical demand. The two groups were balanced in terms of sex, age, ECOG score, pathological type, clinical stage, and the history of treatment (P>0.05), and the details are listed in Table 1.

Table 1. General Materials of Subjects in the Two Groups

Item	Treatment (33 cases)	Control (30 cases)
Sex (Case, Male/Female)	18/15	15/15
Age [Yr., Mean (range)]	64.6 (36-80)	58.4 (29-75)
ECOG Score [Case (%)]		
0 score	9 (27.3)	8 (26.7)
1 score	18 (54.5)	16 (53.3)
2 scores	6 (18.2)	6 (20.0)
Pathological type [Case (%)]		
Squamous cell carcinoma	14 (42.4)	10 (33.3)
Adencarcinoma	17 (51.5)	15 (50.0)
Alveolar cell carcinoma	2 (6.1)	5 (16.7)
Stage [Case (%)]		
ⅢB	15 (45.5)	14 (46.7)
Ⅳ	18 (54.5)	16 (53.3)
History of treatment [Case (%)]		
Initial treatment	28 (84.8)	24 (80.0)
Re-treatment	5 (15.2)	6 (20.0)

Treatment

Chemotherapy using the Navelbine and Cisplatin (NP) rigimen was applied to all patients, that is, Navelbine (NVB) 25 mg/m^2 added into 100 mL normal saline for intravenous dripping in 30 min on the 1st and 8th day; and Cisplatin 75-80mg/m^2 added into 500 mL normal saline for intravenous dripping in 2 h for 1-3 days, with simultaneous hydration and diuresis, and 21 days constituting one cycle.

Unlike the control group which only received the NP chemotherapy, the treatment group received an additional drip of Shengmai Injection (生脉注射液) 100 mL into 500 mL normal saline once a day from the 1st day to the 14th day in the chemotherapy cycle and oral intake of Gujin Granule (固金颗粒冲剂) 10 g, three times a day for at least 6 months continuously for a year.

Shengmai Injection is a Chinese preparation consisting of red ginseng, lilyturf root and magnolia vine fruit, manufactured by Ya'an Sanjiu Pharmaceutical Co., Ltd., China, batch No. Z51021882; Gujin Granule is a Chinese herbal remedy in water soluble granular form mainly consisting of milkvetch root, asiabell root, mulberry bark, lilyturf root, balloonflower root, magnolia vine fruit and licorice root, made finely by Jiangyin Tianjiang Pharmaceutical Co., Ltd., China, based on a concerted recipe for supplementing qi, nourishing yin, and ventilating Fei (肺) to strengthen the organism. The test drugs were chosen for their convenience of use, unified source and reliable quality control.

Items and Methods of Observation

The therapeutic effect of the treatment on an individual patient was estimated after patients received at least two cycles of chemotherapy, and the efficacy evaluation was carried out four weeks after the treatment ended. Imaging specialists who did not participate in the study analyzed the imaging results.

The response rate (RR), 1-year survival rate, median survival time, and median time to progression (TTP) in the two groups were compared. RR was calculated by (case of complete remission+ case of partial response)/total case × 100%, 1-year survival rate was the percentage of patients who were alive 1 year after treatment in the group. Survival time was counted from the beginning of treatment to death or to the time of the last follow-up; TTP was the period from the time after the disease was treated until the time when the disease started to progress.

Occurrence of toxicity was estimated referring to related criteria from the WHO[5], and the cycles of chemotherapy applied were recorded.

Follow-up studies were carried out at least once every 3 months, and the content of the follow-up included examinations of their physical condition, routine analysis of blood, blood biochemistry, and tumor lesion associated imaging examination.

Efficacy Evaluation Criteria

Efficacy evaluation depended on the Standard of Response Evaluation Criteria in Solid Tumors (RECIST)[6], i.e., complete remission (CR): the disappearance of all target lesions and all non-target lesions and normalization of tumor marker level; partial response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; static disease (SD): neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits; progressive disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.

Statistical Analysis

All data were handled using SPSS 13.0 software by professionals. $P<0.05$ was regarded as having statistical significance. Kaplan-Meier was adopted for survival analysis and Log-rank testing was used for median survival time and median TTP analysis. Comparisons of RR, 1-year survival rate and occurrence of toxicity between two groups were analyzed by χ^2 test, and comparison of cycles of chemotherapy applied between groups was analyzed by *t*-test.

RESULTS

General Condition

Follow-up studies were carried out until December 30th, 2008. Two patients in the control group who dropped out of this study received only one cycle of chemotherapy and were not assessable for efficacy in the follow-up, and so the outcomes from 61 patients were entered in the analysis.

Comparison of Therapeutic Efficacy

No case reached the criterion of CR in either group. RR in the treatment group was higher than that in the control group, and the difference between them was statistical significant (P=0.0373, Table 2).

Table 2. Comparison of Therapeutic Efficacy [Case (%)]

Group	Case	CR	PR	SD	PD	RR
Treatment	33	0	16 (48.5)	12 (36.4)	5 (15.1)	48.5%
Control	28	0	9 (32.2)	10 (35.6)	9 (32.2)	32.2%*

Note: *P<0.05, compared with the treatment group

Comparisons of Median Survival Time and 1-year Survival Rate

The median survival time was 13 months in the treatment group and 9 months in the control group, showing a significant difference between them (P=0.014), however, the 1-year survival rate between the two groups was insignificantly different [51.5%, (17/33) *vs* 46.4% (13/28), P=0.4042, Table 3].

Comparison of Median TTP

As compared with the control group, the median TTP in the treatment group was somewhat higher but showed no statistical significance (P=0.4142, Table 3).

Table 3. Comparison of Median Survival Time, 1-year Survival Rate and Median TTP

Group	Case	Median survival time (Month)	1-year survival rate (%)	Median TTP (Month)
Treatment	33	13*	51.5	5.95
Control	28	9	46.4	4.64

Note: *P<0.05, compared with the control group

Comparison of Hematological Toxicity

The occurrence rate of grade Ⅲ/Ⅳ hematological toxicity in the treatment group was 33.3% (11/33) and that in the control group was 39.3% (11/28), but a comparison between them showed an insignificant difference (P=0.3100, Table 4). No other severe adverse reaction was found in the patients.

Comparison of Cycles of Chemotherapy Applied

The 61 patients entering assessment received 174 cycles of chemotherapy in total, with 97 in the treatment group and 77 in the control group; at 2-4 cycles for each patient, the mean number of cycles applied to the treatment group was 2.94 ± 0.94 cycles

Table 4. Comparison of Hematological Toxicity (Case)

Group	Case	Grade of hematological toxicity				
		0	Ⅰ	Ⅱ	Ⅲ	Ⅳ
Treatment	33	4	5	13	9	2
Control	28	3	4	10	7	4

and to the control group 2.75±0.75 cycles, and so the comparison between the two groups showed that the difference was insignificant (*P*=0.4100).

DISCUSSION

Lung cancer ranks first among malignant tumors in the cities of China, and its morbidity has been rising gradually in recent years[3]. Though the efficacy of the third generation anticarcinogens combined with platinum agents has been elevated in the treatment of NSCLC and has benefited patients' survival, it seems that it has reached its platform effect and can hardly be improved further. Thus, it is expected that the combined application of Chinese drugs and chemotherapy could enhance the efficacy and mutually help each other's effect.

Chinese medicine holds that lung cancer is a disease of deficiency in origin and excess in superficiality, that is, deficiency of the whole body and local excesses. The authors considered that the qi-yin deficiency is the basic pathological change of the asthenia side of the illness, and many clinical studies have illustrated that the qi-yin deficiency type is the dominant Chinese medicine syndrome pattern in all lung cancer patients. For example, Shen, et al[7] reported that 91.9% of advanced lung cancer patients belonged to this pattern, and the qi-yin deficiency was seen all throughout the whole course of the disease.

On the basis of the above-mentioned considerations, the Chinese drugs Shengmai Injection and Gujin Granule were selected in combination with chemotherapy for the treatment of NSCLC by the authors. The action of Shengmai Injection is supplementing qi and nourishing yin to restore pulse and relieve collapse. In the ingredients of the Gujin Granule, milkvetch root and asiabell root are used as the monarch drugs for supplementing qi and reinforcing deficiency; used in cooperation were lilyturf root, magnolia vine fruit and balloonflower root to nourish yin, moisten Shen (肾), ventilate Fei, depress the reversed Fei-qi, alleviate cough and calm dyspnea. Working together, the drugs could have the functions of supplementing qi, nourishing yin, ventilating Fei and removing toxic substances. The combined application of the two remedies could enhance their therapeutic effects in coordination to achieve favorable efficacy.

The NP regiment is the standard first-line chemotherapy for advanced NSCLC recommended worldwide. According to the report of Chevalier, et al[8],the RR of NP regimen on NSCLC is 30%, and the median survival time is 40 weeks. The authors' previous study showed that the RR was 33.3%, the median survival time was 8.3 months and the median remission time was 3.3 months[9]. The results of this study showed that in the control group treated only by NP chemotherapy, the RR was 32.2%, the median survival time 9 months, and the median TTP 4.64 months, which are similar to the data previously obtained. Meanwhile, in the treatment group, which was treated with combined Chinese drugs and chemotherapy, RR was 48.5% and the median survival time was13 months, which are apparently superior to the figures of the control group, illustrating that the combined therapy is capable of raising RR in the treatment of NSCLC and prolonging the survival time of patients.

There are also some analogous clinical studies conducted by other scholars in China. For example, Liu, et al[10] treated advanced NSCLC patients by a combined use of the Yiqi Yangyin recipe (益气养阴方, for supplementing qi and nourishing yin) and chemotherapy, resulting in a controlling rate (CR+PR+SD) of 89.47%, higher than in Chinese drug treatment (72.22%) alone or by chemotherapy alone (77.78%). Adopting the similar combined therapy, Cao, et al[11] accessed a median survival time of 10.5 months and 7 months in the treatment group and the control group respectively, and the difference between them was statistically significant (*P*<0.05). The relative results obtained in this study were basically in accord with the outcome in the above-cited reports.

Results from this trial showed that the 1-year survival rate and median TTP in the treatment group were 51.5% and 5.95 months, respectively, and in the control group 46.4% and 4.64 months, respectively, with no significant differences seen between the two groups. The relative results of the two groups were similar to those reported by Wu, et al[12] at 52.7% and

5 months, respectively. In the aspect of alleviating chemotherapy induced bone marrow inhibition and increasing the cycles of chemotherapy applied, the outcome in the two groups was not different statistically, though the treatment group proved to be somewhat superior. These results are identical to those reported by Lin[13], and this is possibly due to the insufficient size of the sample.

Pharmacological studies have shown that the mechanism of action on supplementing qi and nourishing yin therapy in treating lung cancer might be related to the improvement of the immune function of the organism. Shu, et al[14] proved via an animal experiment that Xinjia Shashen Maidong Decoction (新加沙参麦冬汤) could increase the thymus/spleen index, nature killer cell activity, lymphocyte transformation rate, etc., and reduce tumor weight and spontaneous metastasis in mice bearing Lewis lung cancer. The actions were realized not by killing the tumor directly, but through enhancing the immune function of the organism, particularly cellular immunity. At the same time, the decoction also showed an effect in prolonging the survival time of tumor bearing mice.

This study showed that Chinese drugs have definite superiority in enhancing short-term efficacy of chemotherapy for the treatment of NSCLC and in prolonging patients' survival time. The advantages and peculiarity of integrative medical therapy can be further confirmed by consistent results from studies conducted in other units[15]. The sample size should be expanded in future researches to raise the reliability of the results.

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