

## Preliminary Results of Combination Therapy with Chinese Herbs and Vinorelbine in Elderly Advanced Non-Small Cell Lung Cancer\*

Wanyin Wu \*\*, Xiaoshu Chai, Gaoyang Li, Haibo Zhang,  
Shunqing Long, Xiaoguang Xue, Hong Deng, Weisheng Liu

**Abstract: Objective** To observe the efficacy and toxicity of combination therapy with Xiaoji decoction (XJY), Huachansu (HCS) and Vinorelbine (NVB) in elderly patients with advanced non-small cell lung cancer (NSCLC). **Methods** 29 elderly patients with B/ NSCLC were treated with XJY 30ml/m<sup>2</sup>, p.o., twice a day for 21 days; HCS 20ml/m<sup>2</sup>, i.v., once a day for 10 days; and NVB 30ml/m<sup>2</sup>, i.v., on day1 and day8. The drugs were repeated every 21 days until 6 cycles, tumor progression, unacceptable toxicity or withdrawal of consent. **Results** 29 enrolled patients received median 3.2 cycles of therapy. The overall response rate and stabilization rate of tumors were 13.8% and 89.7%, respectively. The median survival time (MST) was 7.0 months and time-to-progression (TTP) was 5.0 months. The one year overall survival rate was 27.6%. Major toxicities include leucocytopenia, anemia and fatigue. **Conclusion** This combination regimen showed preliminary therapeutic efficacy and mild toxicity in elderly patients with advanced NSCLC and suitable for further clinical trial.

**Key words:** Chinese herbs; Vinorelbine; non-small cell lung cancer

### INTRODUCTION

Non-small lung cancer (NSCLC) comprises about 75%-80% of all lung cancers, and most of them present with advanced disease when they are diagnosed. Among the patients with advanced disease (stage B/ ), about 1/3 of them are older than 70 years, and most of the other patients are older than 60 years. Owing to the low tolerance to the renal toxicity and bone marrow suppression of the standard platinum analog based combination chemotherapy regimen, it has important significance to explore new therapeutic regimen with low toxicity and more efficacy on elderly patients with advanced NSCLC. Based on the results of our previous experimental studies <sup>[1]</sup>, we conducted the following preliminary clinical trial on the elderly patients with advanced NSCLC by the combination of Xiaoji decoction, Huachansu and Vinorelbine to observe the efficacy and toxicity of the combination regimen.

### PATIENTS AND METHODS

#### 1. Patients

From January 2002 to January 2004, 29 patients aged 60 ~ 80 years with B/ NSCLC were enrolled this clinical trial. All patients received the therapy in hospitalization. All patients signed the informed consent forms.

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\*\* Corresponding to Wanyin Wu (1964-), male, MD & PhD, professor and director of Department of Cancer, Guangdong Provincial Hospital of Traditional Chinese Medicine; Main research field: treatment of advanced lung cancer and liver cancer with combination of Chinese medicine and Western medicine; Address: Department of Cancer, Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, Postcode: 510370.

The patients' main clinical characteristics are showed in Table 1.

## **2. Eligibility criteria**

Patients who had received prior chemotherapy were ineligible for the study. The criteria for eligibility included confirmed disease pathologically and staged in B/ ; measurable tumors; an age of from 61 to 80; performance status (PS) of 0-2; adequate bone marrow, liver, kidney, heart and lung function. All patients gave informed consent. Patients with uncontrolled brain metastases or other active cancers were ineligible, either with active mental obstacle or active tuberculosis and others severe infective diseases.

## **3. Methods**

All the patients received the reference treatment: Vinorelbine was administered on days 1 and 8, at a dose of 30 mg/m<sup>2</sup>; Xiaoji-decoction was taken orally on days 1 to 21, at a dose of 60 ml/m<sup>2</sup>; and Huachansu was given on days 1 to 10 at a dose of 30 mg/m<sup>2</sup>. The regimen was repeated every 21 days for 4 cycles continuously.

## **4. Efficacy and toxicity**

The change of tumor size, 1-year survival rate, median survival time, median time to progression, ECOG PS scores and toxicity of the combination therapy were evaluated.

## **5. Statistical analysis**

Survival from the date of enrollment to dead or the end of follow-up was recorded. The primary analysis specified by one-way ANOVA for qualitative data, Kpplan-Meier and Log Rank test for survival of the SAS software.

# **RESULTS**

## **1. Characteristic of patients**

A total of 36 patients with B/ NSCLC and performance status of 0-2 were enrolled between January 2002 and January 2004. Of the 36 patients who were enrolled, 7 (19.4 percent) were subsequently found to be ineligible, which consisted of one patient with uncontrolled press of spinal cord, and 6 patients with the treatment time less than 1 year. The characteristics of 29 eligible patients were described as table 1. Enrolled patients received median 3.2 cycles of therapy. Until follow-up end, 23 of them were dead, the other six patients are in following up (the following statistic survival time is before March 2005).

## **2. Evaluation of efficacy**

The overall response rate for the 29 eligible patients was 13.8%, and stabilization rate was 89.7% (Table 2). The median survival was 7.0 months among the patients and the time-to progression (TTP) was 5.0 months. The survival rate at one year was 27.6% (Table 3).

## **3. Comparison of survival time between younger than 70 years and older than 70 years**

The median survival of both groups whose age < 70 years or = 70 years was 10.0 months and 6.0 months, respectively. Two groups' TTP were 7.0 months and 4.0 months, and the survival rate at one year was 35.7% and 20.0%, respectively (Table 4). There were no significant differences in the response rate or survival between the both different-age groups.

## **4. Comparison of survival time between male and female patients**

The median survival of male and female patients was 6.0 months and 10.0 months, respectively. The TTP of male and female was 4.0 months and 8.0 months, and the survival rate at one year was 21.1% and 40.0%, respectively (Table 5). There were no significant differences in the response rate or survival between the both

different-age groups.

#### **5. Comparison of survival time between PS0~1 and PS2**

The median survival of PS=0~1 and PS=2 patients was 13.0 months and 6.0 months, respectively. Two groups' TTP were 10.0 months and 4.0 months, and the survival rate at one year was 60.0% and 20.8%, respectively (Table 6). There were no significant differences in the response rate or survival between the both different-age groups.

#### **6. Comparison of survival time among patients with different pathology types**

The median survival of adenocarcinoma group and squamous cell carcinoma group was 7.0 months and 8.0 months, respectively. Two groups' TTP were 6.0 months and 5.0 months, and the survival rate at one year was 33.3% and 18.2%, respectively (Table 7). There were no significant differences in the response rate or survival between the both different-age groups.

#### **7. The quality of life**

According to the changes of PS (Table 8), the performance status of 6 patients were improved after treatment, 20 cases were stabilized, 3 cases were decreased, and the symptoms of 26 patients were alleviated (Table 9), synchronously, whose scores of life of quality was increased.

#### **8. The toxicity**

Assessed by WHO "The standards of effect and acute or toxicity during the treatment of carcinoma", Table 10 shows the main toxicity of the combination therapy was myelosuppression, 4 patients (13.8%) with leucocytopenia (grade 1, 1 patient; grade 2, 2 patients; grade4, 1 patients, 3.4%), 1 patients with grade 4 anemia, and 2 patients with grade 3 fatigue. There were no distinct gastrointestinal symptoms such as vomiting and diarrhea, loss of hair, and the severe dysfunction of the heart, liver and kidney. No patient was dead due to treatment.

## **DISCUSSION**

Lung cancer has become the leading cause of cancer-related mortality worldwide. Lung cancer is expected to kill more than 163,000 Americans this year. The late stage at diagnosis in many patients, and the high rate of relapse for those initially diagnosed in earlier stages, contributes to its lethality. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 80% of cases. Chemotherapy is generally indicated for patients with advanced NSCLC because the results of many large, randomized phase III clinical trials have established that modern chemotherapies offer superior survival and symptom palliation than best supportive care. Specifically, platinum-based chemotherapy has been the worldwide standard. However, as about 2/3 of patients with NSCLC are older than 60 years and these elderly population has low tolerance to the renal toxicity and bone marrow suppression of the standard platinum analog based chemotherapy, it is very meaningful to investigate non-platinum regimen with low toxicity and higher efficacy on elderly patients with advanced NSCLC.

Vinorelbine (NVB), a new generation has been proved to be very effective in treating elderly patients with advanced NSCLC. Some of the published phase clinical trial results indicated, it could prolong the median survival time (28wk vs 21wk), increase the one-year survival rate (32% vs 14%) and the quality of life (QOL)<sup>[2]</sup>. In addition, it manifested low toxicity and the better tolerance in elderly patients, thus this single-drug has been regarded as the more suitable chemotherapy treatment in the elderly patients with advanced or inoperable NSCLC.

But the effect of single NVB dose not yet reach the upper line of the median survival time (8-12 months) of the other platinum-based combination chemotherapy with new drugs in younger patients. So in this study, we assume to achieve more effectiveness and lower toxicity, increase the control of the local measurable or evaluable tumors, median survival time (MST) and quality of life (QOL) by the way of using single chemotherapy with NVB plus the Chinese anti-tumor drug tumor-reducing soup.

Lung cancer is belong to the diseases of “fei-ji”、“xi-ji”、“xi-pen”、“fei-yong” in the ancient Chinese medical literatures. Summarizing the different theories, the etiology and pathogenesis are mainly caused by “deficiency” (deficiency of qi and yin), “toxins”, “sputum”, “blood stasis”. Among these pathological factors, the combination of deficiency and excess can be the most often in advanced lung cancer. The deficiency mainly is related to *qi* deficiency and deficiencies of *qi* and *yin* and its excess includes phlegm accumulation, blood stasis, retention of toxins, *qi* stagnation. It always combines with *qi* deficiency of kidney in the elderly patients with NSCLC. So, therapeutic principle in TCM for this disease is nourishing deficiency (lung, spleen, and kidney), detoxication, removing phlegm and promoting blood circulation to resolve stasis.

Professor Liu Weisheng, a famous Chinese medical doctor in Guangdong province, summarized his clinical experience of diagnosis and treatment of lung cancer and invented the *Xiaoji decoction(XJY)* with the function of replenishing lung and kidney, detoxification and removing blood stasis, expectorating phlegm and dissolving the mass, which gained the favorable clinical efficacy in clinic. Preliminary clinical experiment indicated that XJY could improve the symptoms of media-term or advanced lung cancer, increase the ability of cellular immune function, prevent the progress and metastasis, improve quality of life, and prolong the survival time. Some clinical trial results showed it has synergistic effect with chemical drug on lung cancer<sup>[3,4]</sup>.

HCS (“extract of Chinese-toad”) is a preparation of the skin of toad which has been used as an anti-tumor Chinese medicine for many years and has the function of expelling the toxicity of cancer, removing blood stasis, alleviating pain, softening and resolving of hard masses. The studies in *vivo* or in *vitro* proved the HCS has the functions of killing several kinds of tumor cells, anti-tumor effect, leukopoiesis, and increasing the immunity. Some literatures have reported it has synergistic therapeutic efficacy with chemical drugs in treating cancers<sup>[5]</sup>. Wu *et al* reported they treated the advanced lung cancer with HCS (extract of Chinese-toad) plus chemotherapy<sup>[6]</sup>. The combination therapy could increase efficacy slightly and improve patients’ QOL significantly compared with chemotherapy alone.

On basis of cell proliferating cycles theory, Vinorelbine (NVB) belongs to cellular phase-specific drug, and its main effective phase is at G2/M. The recent experimental research indicated, XJY could decrease the expression of cellular cclinD1 of Lewis lung carcinoma in mice, influence the regulating point of G1/S cell cycle, arrest cancer cells at the phase of G0/G1 and inhibiting cells enter into phase S to copy DNA<sup>[4]</sup>. HCS is also a phase-specific drug which is mainly effective at phase S<sup>[7]</sup>. In animal experiment, we have combined three drugs to treat lung cancer carried by mice and the results showed these drugs have synergistic anti-cancer efficacy.

On basis of our experimental results<sup>[1]</sup>, in present clinical trial, we combined three drugs to treat 29 elderly patients with advanced NSCLC. The effectiveness and toxicity of this regimen and its effect on patients’ QOL were observed. The preliminary results indicated, comparing with single drug NVB, this combination regimen has similar efficacy on change of tumor volume, somewhat higher in tumor stability. This regimen obtained similar Medial survival time (MST) and one year survival rate, but the time-to-progression is longer. As to survival time, there are not significant difference between two age groups, different PS, sex and pathological types. With mild toxicity and higher overall quality-of-life this combination regimen is well to be tolerated by elderly patients. This

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clinical trial result proved this regimen could be used as a choice for the advanced NSCLC in elderly patients.

**REFERENCES**

1. Wu WY, Chai XS, Liu WS. Effect of HCS combining with Vinorelbine on cell cycle of Lewis lung cancer carried by mice. *China Oncology*. 2004, 14(4): 363-365.
2. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small-cell lung cancer. *Oncologist*. 2001, 6(S): 4-7.
3. Liu YL, Liu WS, Xu K, et al. Inhibition of Xiaoji Decoction combining with chemotherapy on metastasis and relapse in lung cancer patients post radical resection. *New Journal of Traditional Chinese Medicine*. 2004, 36(11): 26-28.
4. Lu JR, Liu YL. Experimental research on Xiaoji Decoction effecting on the cell cycles of Lewis lung cancer in mice. *Research on Chinese Medicine*. 2001, 17(3): 38-39.
5. Cui YA, Zuo XD, Qin SK, et al. Clinical trial of Huachansu Injection for anti-cancer efficacy. *Jiangsu Journal of Clinical Medicine*. 2002, 6(5): 505 - 508.
6. Wu WY, Chen CY, Zhang HB, et al. Huachansu Injection in treating 48 patients with stage II non-small cell lung cancer SCLC. *Chinese Journal of Current Practical Medicine*. 2004, 3(3): 38 - 40.
7. Zuo XD, Cui YA, Qin SK, et al. Effect of Huachansu Injection on cancer cellular cycle and expression of bcl-2 protein. *Modern Integrated Journal of Chinese Medicine and Western Medicine*. 2003, 12(6): 567-568.

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**Table 1 The main clinical characteristics in 29 patients with B/ NSCLC**

Characteristics	n	Percentage (%)
<b>Sex</b>		
Male	19	65.5
Female	10	34.5
<b>Age (years)</b>		
61 ~ 69	14	48.3
≥70	15	51.7
<b>ECOG PS</b>		
0 ~ 1	5	17.2
2	24	82.8
<b>Pathology</b>		
adenocarcinoma	18	62.1
squamous cell carcinoma	11	37.9
<b>Clinical stage</b>		
B	4	13.8
	25	86.2
<b>Symptoms</b>		
Fatigue	15	51.7
Cough	19	65.5
Phlegm	16	55.2
Dyspnea	5	17.2
Pain	17	58.6
Distress of chest	2	6.9
Anorexia	18	62.1
Constipation	5	17.2
Insomnia	16	55.2
<b>Complications</b>		
SVCS	1	3.4
Obstructive pneumonia	4	13.8
Atelectasis	6	20.7
Hydrothorax	5	17.2
Hydropericardium	2	6.9

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<b>Metastasis</b>		
Lymph nodes in mediastinum	9	31.0
Lung	10	34.5
Bone	7	24.1
Liver	3	10.2
Brain	4	13.8
Adrenal gland	1	3.4

**Table 2 Evaluation of the changes of the volume of tumor after treatment**

Evaluative standards	numbers	Percent %
<b>The changes of focus</b>		
CR	0	0
PR	4	13.8
NC	22	75.9
PD	3	10.3
<b>Objective effective rate</b>		13.8
<b>stabilization of focus</b>		89.7

**Table 3 Evaluation of survival time after treatment**

Evaluative standards	Time (months )	Percent %
<b>Survival time</b>		
MST	7.0	
TTP	5.0	
<b>One year survival rate</b>		27.6

**Table 4 The influence of age factor on the survival time**

Age	N	MST(months)	TTP (Month)	One year survival rate%
<70years	14	10.0	7.0	35.7 (5/14)
>=70years	15	6.0	4.0	20.0 (3/15)

Note: comparison of two groups  $p>0.05$ .

**Table 5 The influence of sex factor on survival time of patients with B/ NSCLC**

Sex	n	MST (Month)	TTT (Month)	One year survival rate%
Male	19	6.0	4.0	21.1 (4/19)
Female	10	10.0	8.0	40.0 (4/10)

Note: comparison of two groups  $p>0.05$ .

**Table 6 The influence of PS on survival time of patients with B/ NSCLC**

PS	n	MST (months)	TTP (months)	One year survival rate%
0 ~ 1	5	13.0	10.0	60.0 (3/5)
2	24	6.0	4.0	20.8 (5/24)

Note: comparison of two groups  $p>0.05$

**Table 7 The influence of different pathology types on survival time of patients with B/ NSCLC**

Pathology	n	MST (months)	TTP (months)	One year survival rate%
adenocarcinoma	18	7.0	6.0	33.3 (6/18)
Squamous cell carcinoma	11	8.0	5.0	18.2 (2/11)

Note: comparison of two groups  $p>0.05$

**Table 8 The evaluation of PS of 29 patients with B/ NSCLC after the treatment**

Different group	number	PS		
		Increase	Stabilization	Decrease
Treatment group	29	6	20	3