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Traditional Chinese Medicine Herbal Treatment May Have a Relevant Impact on the Prognosis of Patients With Stage IV Adenocarcinoma of the Lung Treated With Platinum-Based Chemotherapy or Combined Targeted Therapy and Chemotherapy

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Abstract

Background: Targeted therapy (TT), chemotherapy, and traditional Chinese medicine herbal treatment (TCM) can improve the prognosis of advanced pulmonary adenocarcinoma patients. Their independent prognostic value is unknown. **Objective:** To study whether TCM improves survival in stage IV pulmonary adenocarcinoma patients with platinum-based chemotherapy (PBT), or combined PBT and second-line TT. **Methods:** Retrospective analysis of 133 fully ambulant clinical outpatients treated with PBT alone or PBT with/without second-line TT, with/without TCM. Univariate (Kaplan–Meier) and multivariable (Cox model) survival analysis were performed, using disease-specific mortality as an endpoint. **Results:** Gender ($P = .002$), TT ($P < .0001$), and TCM ($P < .0001$) had univariate prognostic value but not age, radiotherapy, or TCM syndrome differentiation ($P > .10$). TCM herbal treatment ($P < .0001$) and TT ($P = .03$) had multivariable independent prognostic value. TCM-treated patients (n = 103, PBT+TT+TCM+ = 62; PBT+TT−TCM+ =41) had 88% 1-year overall survival rate with median survival time (MST) of 27 months, contrasting 27% 1-year overall survival and MST of 5.0 months for non-TCM-treated (n = 30) patients. Patients with chemotherapy/TT/TCM (PBT+TT+TCM+, n = 62), TCM without TT (PBT+TT−TCM+, n = 41), or chemotherapy only (PBT+TT−TCM−, n = 30), had 1-year survival rates of 94%, 78%, and 27% respectively; for these 3 groups, respectively, MST was not reached (MST of 30.9 months), 22.6, and 5.0 months ($P < .0001$). **Conclusions:** TCM herbal treatment may improve survival of stage IV pulmonary adenocarcinoma patients treated with chemotherapy without or with second-line TT. This warrants formal phase 1 and 2 trials and ultimately properly designed prospective clinical validation trials with adequate methodology developed for data collection.

Keywords

pulmonary adenocarcinoma, stage IV, TCM herbal treatment, chemotherapy, targeted therapy, prognosis

Introduction

Primary lung carcinoma is one of the most common malignant tumors in the world.[1] In 2005, the lung cancer mortality rate in China was 30.8% making it the leading cause of cancer deaths.[2] A total of 85% of all lung cancer patients are classified as non–small cell lung cancer (NSCLC).[3,4] For patients with early-stage NSCLC, surgery is the first therapeutic choice, but the majority is already at an advanced stage by the time of diagnosis[1] leaving radiotherapy, chemotherapy or targeted therapy (TT) as the only therapeutic options. The median survival time (MST) of advanced NSCLC when treated with modern systemic therapy has increased over the past decades.[5] Targeted therapy for treating adenocarcinoma

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patients is especially effective in preponderant groups such as Asian, female, and nonsmokers and especially effective in adenocarcinomas with epidermal growth factor receptor (EGFR) mutations and amplifications, nonsmokers and in women.[6-8] Unfortunately, TT is very expensive and thus unaffordable for many patients in developing countries.

In China, herbal medicine is often combined with chemotherapy in the treatment of lung cancer. Traditional Chinese medicine (TCM) herbal treatment is relatively inexpensive and has been reported to increase chemotherapy efficacy, reduce toxicity, prolong survival time, and improve the quality of life and also immune functions.[9] In one prospective randomized trial of 304 patients with stage IIIb and IV adenocarcinomas of the lung, TCM herbal treatment was more effective than using vincristine, 5-fluoro-uracil, and methotrexate chemotherapy, with 1-year survival rates of 61% versus 37% ($P < .01$), median survival times of 13.7 and 8.7 months ($P < .01$), and 5-year survival rates of 24% and 0% ($P < .01$).[10] However, target treatment was still unknown when the latter study was performed in 1995, and chemotherapy has also become more effective since then.[11,12]

We therefore investigated whether TCM herbal treatment has independent prognostic value in 133 fully ambulant patients with clinically, radiologically, and pathologically diagnosed stage IV adenocarcinoma of the lung, all treated with platinum-based (PBT) chemotherapy, with or without second-line TT. We recruited these patients from the outpatient clinics of 2 hospitals in fairly close proximity (12 miles apart) in Shanghai, China. One hospital was a TCM-Western hospital, the other a Western medicine hospital for lung diseases. Patients from the outpatient clinics of the 2 hospitals who were treated with conventional PBT were matched by age, gender, and diagnosis date. We were thus able to select 2 groups who differed only with regard to TCM treatment but were otherwise similar. We then compared the survival of these 2 groups of patients.

Materials and Methods

The study was approved by the institutional research boards of the hospitals where the patients had been treated. Regarding the size of the 2 samples, we were interested in detecting a survival difference between the chemotherapy and TCM + chemotherapy group of at least 20%. On the basis of leading articles,[1,12] and our own experience,[10] we expected the 2 death rates to be equal to 70% (ie, death rate at 1 year after chemotherapy only) and 45% (death rate after chemo + TCM treatment). For type 1 error (α-level) of .05 and type 2 error (β-level) of .10, this would require 58 patients in each group (116 in total); however, to be on the safe side, we took a slightly larger sample size of 133 patients.

Patients

In this retrospective study, the TCM-treated patients were selected from the outpatient clinics of 2 different hospitals, as follows.

First, of all new consecutive lung cancer patients treated by one of us (LJX) between January 2006 and January 2009 at the TCM outpatient clinic of the Longhua Hospital, Xuhui district, Shanghai, China (further denoted to as "hospital A"), we studied 135 patients suffering from pathologically and radiologically confirmed stage IV adenocarcinoma of the lung. We planned to study stage IV patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 (asymptomatic), 1 (symptomatic, fully ambulatory), or 2 (symptomatic, in bed <50% of the day, but ambulant and fully able to visit the outpatient clinic), with known age and follow-up and not treated with explorative surgery. Patients were excluded for the following reasons: (*a*) age unknown (n = 8), (*b*) date of first visit unknown and consequently no accurate follow-up time (n = 23), and (*c*) lost to follow-up (n = 36). This left 68 patients for further analysis who were all treated with PBT before and during TCM herbal treatment (see below). Moreover, 46 of these 68 patients also received second-line TT (for details of the chemotherapy and TT, see below).

To find an adequate group of patients treated with conventional chemotherapy, we used a database of consecutive patients with pathologically proven adenocarcinoma of the lung, diagnosed and treated at the Respiratory Hospital, Yangpu district, Shanghai, China (further denoted to as "hospital B"). From these, we selected for each hospital A outpatient clinic patient, one hospital B outpatient clinic patient, diagnosed and treated in the same month as the hospital A patients, and further matched by (*a*) stage IV; (*b*) ECOG performance status (PS) 0-2, but only PS = 2 if the patients were fully ambulant to attend the treatment; (*c*) diagnosis date; (*d*) gender; and (*e*) age.

With those criteria, 66 patients from hospital B treated with PBT, with or without second-line TT (see below for details of the chemotherapy and TT) were selected. However, while doing the analyses for the current study, an article was published showing that more than two thirds of Chinese cancer patients believed that combining integrated Chinese and Western medicine was effective and 63% of those receiving chemotherapy used Chinese medicine before/during/after Western medicine treatment. Interestingly, nearly two thirds did not tell their physicians they were using traditional Chinese medicine herbs.[13] We therefore considered that the same may also have occurred with the patients from hospital B. One of us (HG) therefore personally contacted each patient or their relatives and discovered that 35 of the 66 patients from hospital B also "secretly" used TCM herbal treatment provided by different TCM specialists (ie, had consulted TCM specialists elsewhere in Shanghai outside

the supervision of the treating Western medicine specialist). We kept these patients in the study and grouped them with the patients for hospital A for some analyses. There were no differences ($P > .10$) in the diagnosis month, age, gender, or PS of these 2 subgroups of hospital B patients with chemotherapy alone versus chemotherapy + TCM herbal treatment.

This resulted in 68 + 66 = 134 patients; 30 treated with chemotherapy alone (PBT+/TT−/TCM−), 41 with chemotherapy + TCM but no TT (PBT+/TT−/TCM+), 62 with chemotherapy, TCM, and TT (PBT+/TT+/TCM+) and 1 patient (from hospital B) with chemotherapy and TT but no TCM. As we had only one patient with PBT+TT+TCM−, this patient was left out, leaving 133 patients for analysis. Comorbidity consisted of diabetes, hypertension, and goiter, but these did not play an important role and did not significantly differ between groups ($P > .10$).

Chemotherapy, Targeted Therapy, Radiotherapy

The following PBT regimens were used as first line treatment in the 133 patients: cisplatin + gemcitabine (n = 54), cisplatin + vinorelbine (n = 38), cisplatin + paclitaxel (n = 16), cisplatin + docetaxel (n = 16), and carboplatin + paclitaxel (n = 9). The dosages were designed as described elsewhere.[12,14] The hospitals treating lung cancer adhere strictly to these guidelines as malpractice suits are increasingly popular in Shanghai. Under no circumstances were the chemotherapy dosages adapted to the additional use of the herbal therapies. In agreement with the findings of others,[12] there were no differences detectable in the survival of patients in the different chemotherapy regimen groups ($P = .16$). In case of progression during or shortly after chemotherapy, second-line treatment consisted of either mono-chemotherapy (pemetrexed, n = 19; docetaxel, n = 22) or TT.

The TTs were always used second-line to chemotherapy and consisted of gefitinib (AstraZeneca, Alderley Park, UK), erlotinib (Roche Pharma, Reinach, Switzerland), or initial gefitinib followed by erlotinib in case of gefitinib treatment failure. There was no difference between the 2 hospitals in their treatment regimes ($P = .20$). TTs are costly and gefitinib and erlotinib are given according to EGFR mutations. They were always given in trials, paid by pharmaceutical companies. Therefore, receiving TT was independent of the patients' ability to pay.

Radiotherapy was not given routinely but as indicated by the individual clinical and radiologic findings. Again, there were no differences between the hospitals ($P = .17$) in radiotherapy treatment; nor was there a correlation with age ($P = .18$), gender ($P = .37$), or different systemic therapies given ($P = .27$).

Syndrome Differentiation and Principles of TCM Herbal Treatment

In China, TCM herbs are given on the basis of the TCM syndrome differentiation as diagnosed by the TCM herbal specialist. Patients with the same disease (ie, stage IV adenocarcinoma of the lung) may have different TCM syndromes. The TCM herbs are adjusted to the individual patient's syndromes to improve the prognosis. It is not our intention to evaluate whether the patients received the correct herbal treatment but rather whether TCM treatment in general was associated with a prolonged survival time. Moreover, TCM syndrome differentiation is general knowledge and described in many textbooks. The following therefore is only a general outline of the TCM syndrome differentiation used and the herbal treatment given to the patients (see Table 1).

TCM syndrome differentiation for the TCM herbal medicine–treated patients was only known to us for the patients visiting hospital A, in which it was performed by one of us (LJX) who has many decades of experience in performing syndrome differentiation (for details of the different TCM terms such as Qi and Yin, and the TCM syndrome differentiation methods, see Zheng[15]). The syndromes can be diagnosed if any 2 of the main symptoms with any 2 of the secondary symptoms are present (see below). The herbal treatment is adapted to the syndromes.[16]

Syndrome of Deficiency of both Qi and Yin. Main symptoms are cough, little phlegm, low spirit, weakness, spontaneous sweating or night sweating, red or pink tongue, or teeth-marks at the margins of the tongue, thin tongue coating, and thready, weak pulse. Secondary symptoms are phlegm with blood, faint low voice or cough, dry mouth, and little desire to drink. The treatment principle is strengthening Qi and nourishing Yin.[15] Commonly used herbs are Radix Astragali seu Hedysari, Rhizoma Atractylodis Macrocephalae, Radix Glehniae, Radix Asparagi, Radix Ophiopogonis, and Semen Armeniacae Amarum.

Syndrome of Deficiency of Yin and Internal Heat. Main symptoms are cough, no phlegm, low fever, night sweating, red tongue, eroded fur or mirror-like tongue, and thready, rapid pulse. Secondary symptoms are phlegm with blood, chest pain, shortness of breath, dry mouth, and insomnia. The treatment principle is nourishing Yin and clearing Lung Heat. Frequently used herbs are Radix Glehniae, Radix Asparagi, Radix Ophiopogonis, Bulbus Lilii, and Semen Armeniacae Amarum.

Syndrome of Deficiency of Qi. Main symptoms are cough, phlegm, low spirit, weakness, pale and plump tongue or tongue-margin teeth-marks, white greasy fur on the tongue, and soft moderate or soft slippery pulse. Secondary symptoms are shortness of breath, pale complexion, anorexia, and loose stool. The treatment principle is strengthening Qi. Typical herbs used are Radix Pseudostellariae,

Table 1. The Most Commonly Used Herbs per Traditional Chinese Medicine Syndrome[a]

Chinese Name	Chinese Name (Pinyin)	Pharmaceutical Name	English Name	Dosage (g)
Syndrome of Deficiency of Qi and Yin				
黄芪	Huangqi	Radix Astragali seu Hedysari	Membranous milkvetch root/ Mongolian milkvetch root	30
白术	Baizhu	Rhizoma Atractylodis Macrocephalae	Largehead atractylodes rhizome	9
北沙参	Beishashen	Radix Glehniae	Coastal glehnia root	15
天门冬	Tiandong	Radix Asparagi	Cochinchinese asparagus root	15
麦冬	Maidong	Radix Ophiopogonis	Dwarf, lilyturf tuber, ophiopogon	15
杏仁	Xingren	Semen Armeniacae Amarum	Bitter apricot seed	9
Syndrome of Deficiency of Yin and Internal Heat				
北沙参	Beishashen	Radix Glehniae	Coastal glehnia root	30
天门冬	Tianmen Dong	Radix Asparagi	Cochinchinese asparagus root	15
麦冬	Maidong	Radix Ophiopogonis	Dwarf lilyturf tuber, ophiopogon	15
百合	Baihe	Bulbus Lilii	Lanceleaf lily bulb	15
杏仁	Xingren (Kuxingren)	Semen Armeniacae Amarum	Bitter apricot seed	9
Syndrome of Deficiency of Qi				
太子参	Taizishen	Radix Pseudostellariae	Heterophylly falsestarwort root	9
白术	Baizhu	Rhizoma Atractylodis Macrocephalae	Largehead atractylodes rhizome	9
茯苓	Fuling	Poria	Indian bread	15
黄芪	Huangqi	Radix Astragali seu Hedysari	Membranous milkvetch root/ Mongolian milkvetch root	30
Syndrome of Deficiency of Yin and Yang				
北沙参	Beishashen	Radix Glehniae	Coastal Glehnia Root	30
天门冬	Tianmen Dong	Radix Asparagi	Cochinchnese asparagus root	15
麦冬	Maidong	Radix Ophiopogonis	Dwarf lilyturf tuber, ophiopogon	15
仙灵脾	Xianlingpi	Herba Epimedii	Epimedium herb	15
菟丝子	Tusizi	Semen Cuscutae	Dodder seed	15

[a]The dosage is in grams of dried herbs.

Rhizoma Atractylodis Macrocephalae, Poria, Pericarpium Citri Reticulatae, and Rhizoma Pinelliae, whereas some other herbs are flexibly changed according to the symptoms.

Syndrome of Deficiency of both Yin and Yang. Main symptoms are: cough, shortness of breath, severe dyspnea after movement, frequent nocturnal urination, aversion to cold and cold limbs, pink tongue, thin tongue coating, deep and thready pulse. Secondary symptoms are severe dyspnea, soreness and weakness of waist and knees, tinnitus, low spirit, and weakness. The treatment principle is strengthening Yin and Warm Kidney. Frequently used herbs are Radix Glehniae, Radix Asparagi, Radix Ophiopogonis, Herba Epimedii (Epimedium herb), and Semen Cuscutae (dodder seed).

The TCM herbs used for the different treatments mentioned above are adapted to the TCM syndromes, which can vary over time in the same patient. Details of some of the herbs are reported in several studies.[17-26] Side effects of TCM herbs used were minimal and consisted of mild temporary abdominal distension, nausea, and diarrhea. There were no toxic or allergic effects. None of the patients stopped TCM herbal treatment because of side effects.

Statistical Analysis

We used SPSS version 16 for the statistical analyses (SPSS, Chicago, IL) and MedCalc (MedCalc Software, Mariakerke, Belgium) for power calculations and assessment of the sample size. Age and gender were compared in the clinical outpatients from the 2 hospitals, and the clinical outpatients of hospital B with and without TCM treatment alongside the PBT using Student's t test and the χ^2 test. In all analyses, $P < .05$ was used as the level of significance. To evaluate the prognostic significance of the features, univariate (Kaplan–Meier) and multivariate (Cox model) survival analysis were performed, using overall distant metastasis-related death as endpoint (apart from smoking, all other data analyzed were complete). The percentage of patients alive at 1 and 2 years, the median survival time (MST, the

time at which half of the patients were still alive), and median follow-up time were calculated. Continuous features were discretized using quartiles and receiver operating curve analysis, and then tested for their prognostic significance. When neighboring value classes of a feature divided in 4 subgroups appeared to have the same prognostic value, they were combined into one class. The threshold values for the different features with this method were often very similar to the ones obtained with receiver operating curve analysis. Comorbidity, gender, age, and all other features analyzed were evaluated as confounders, using stepwise enter, forward Wald, and forward backward methods. The models gave stable results.

Results

The median age was 58 years (range 29-82 years); 27% of the patients were younger than 50 years. There were slightly more females than men (51% vs 49%). There were no differences between the hospitals in gender or age ($P = .29$ and .84, respectively). Performance scores were assessed before the treatment was started and all patients were fully ambulant and capable of visiting the outpatient clinic without any help.

In the following, it is important to emphasize and remember that all 133 patients (including the TT and TCM patients) received PBT. With a median follow-up of 12.0 months (range 1-39 months), 47 (35%) of the entire group of 133 patients died, in contrast to 22 (73%) of the 30 patients treated with chemotherapy alone. The 68 patients from the outpatient clinic from hospital A had a better survival than the 65 from the outpatient clinic from hospital B (71% vs 59%, $P = .001$; Table 2) and median survival times also differed (26.9 vs 19.1 months). As 35 patients from hospital B were treated with herbal TCM by TCM doctors other than the TCM doctors in the Longhua Hospital, we analyzed whether the survivals were different between these 2 TCM groups (ie, from hospitals A and B). This was not the case and the TCM patients were therefore grouped together and further studied as such.

The following features were prognostic with univariate analysis (Table 2): gender ($P = .002$), hospital where the outpatient clinic patients were treated ($P = .001$), TT ($P < .0001$), TCM herbal treatment ($P < .0001$). Performance status at the time of diagnosis was not prognostic. This was not surprising as we only studied fully ambulant outpatient clinic patients. Neither were age, radiotherapy, and TCM syndrome differentiation prognostic nor was there a prognostic difference between different chemotherapy regimens given. Smoking was not prognostic, but this feature was only known in 30 patients (17 smokers, 13 nonsmokers) in this retrospective study, which was not enough to come to any conclusion. Two patients treated with chemotherapy only were alive with disease at 1 and 2 years follow-up, but died at 27 and 28 months. Such long survivals are rare events but can occur under platinum chemotherapy.

With multivariable analysis, only TCM herbal treatment ($P < .0001$; hazard ratio [HR] = 0.14, 95% confidence interval [CI] = 0.08-0.25) and TT ($P = .03$, HR = 0.41, 95% CI = 0.19-0.92) had independent prognostic value. The other features that were prognostic with univariate analysis were not significant once TCM herbal treatment and TT were included (Table 3). Patients with chemotherapy only (PTB+TT−TCM−) and chemotherapy with TT (PTB+TT+TCM+) had 1- and 2-year survival rates of 27%, 27%, 94%, and 78% ($P < .0001$; Table 4). The 3-year survival rate of PTB+TT+TCM+ patients is 52%.

When PBT+TCM+ patients were stratified by use of TT (PBT+TT−TCM+ vs PBT+TT+TCM+), a reduced risk of cancer death by adding targeted therapy to TCM was observed (overall survival rates 63% and 84%; $P = .01$; Table 2). For patients with both TCM herbal treatment and TT (PBT+TT+TCM+), the 1- and 2-year survival rates were 94% and 78% (16% absolute difference), respectively. Median survival was not reached (see also Figure 1), but to give an impression we calculated the mean survival time for this subgroup, which was 30.9 months. For patients taking TCM herbal treatment without TT (PBT+TT−TCM+), the 1- and 2-year survival rates were 78% and 42% (36% absolute difference), respectively, with a median survival time of 22.6 months. For non-TCM, non-TT, chemotherapy-only patients (PBT+TT−TCM−), the 1- and 2-year survival rates were 27% and 27% with MST of 5.0 months (Figure 1; for a summary of these data, see Table 4). The survival difference between chemotherapy plus TCM without TTT (PBT+TT−TCM+ versus chemotherapy only (PBT+TT−TCM−), was significant ($P < .0001$, HR = 0.22). Likewise, chemotherapy plus TCM plus TT (PBT+TT+TCM+) versus chemotherapy only (PBT+TT−TCM−) was also significantly different ($P < .0001$, HR = 0.09).

Discussion

In this retrospective study on stage IV adenocarcinoma of the lung, TCM herbal treatment does improve prognosis of patients, compared with those treated with chemotherapy alone. These results are in agreement with an earlier 1995 study on advanced adenocarcinomas of the lung.[10] In the present study, combined chemotherapy and TCM herbal therapy were much more effective than chemotherapy alone. However, patients with combined chemotherapy, TCM herbal treatment, and TT had an even better prognosis than chemotherapy and TCM without TT (see Figure 1). The results are in agreement with the previous study mentioned above[10] and also with the clinical experience of many TCM specialists. They are also supported by cell culture and animal experiments in which TCM herbs decrease proliferation,

Table 2. Overall Disease Specific Related Survival Results in Relation to the Clinicopathologic Features Analyzed[a]

Characteristic	Overall Survival: No. of Events/Total (% Alive)	*P* (Log Rank)	HR	HR (95% CI)
Hospital				
A	20/68 (71)			
B	27/65 (59)	.001	2.60	1.40-4.70
Gender				
Male	32/65 (51)			
Female	15/68 (78)	.002	0.40	0.22-0.74
Age (years)				
<51.1	14/39 (64)			
51.1-60.0	14/37 (62)			
60.1-67.0	12/32 (63)			
>67	7/25 (72)	.83	NS	NS
Syndrome differentiation				
Deficiency of Qi + Yin	7/27 (73)			
Deficiency of Yin + Internal Heat	4/13 (69)			
Deficiency of Qi	4/15 (73)			
Deficiency of Yin + Yang	5/13 (62)	.88	NS	NS
Chemotherapy				
Cisplatin + paclitaxel	6/16 (63)			
Cisplatin + gemcitabine	14/54 (74)			
Cisplatin + docetaxel	8/16 (50)			
Carboplatin + paclitaxel	1/9 (89)			
Cisplatin + vinorelbine	18/38 (53)	.16	NS	NS
Radiotherapy[b]				
No radiotherapy	27/75 (64)			
Radiotherapy	19/56 (66)	.20	NS	NS
Targeted therapy				
No targeted therapy	37/71 (49)			
Targeted therapy	10/62 (84)	<.0001	0.22	0.11-0.45
TCM herbal treatment				
No TCM herbal treatment	22/30 (27)			
TCM herbal treatment	25/103 (76)	<.0001	0.14	0.08-0.25
TCM, targeted therapy, and chemotherapy				
PBT+ TT− TCM−	22/30 (27)			
PBT+ TT− TCM+	15/41 (63)		0.22	0.11-0.43
PBT+ TT+ TCM+	10/62 (84)	<.0001	0.09	0.04-0.20

Abbreviations: *P*, probability of no difference; HR, hazard ratio; 95% CI, 95% confidence interval; NS, not significant; TCM, traditional Chinese medicine herbal treatment; TT, targeted therapy; PBT, platinum-based chemotherapy.

[a]The hazard ratios (HRs) were calculated using Cox regression survival analysis. With 2 groups, there is 1 HR comparing the risk of the second group versus the first group. With 3 groups, there are 2 HRs (HR1 and HR2). HR1 compares the hazard of the second versus the first group, and HR2 compares the hazard of the third group versus the first group.

[b]In 2 patients, data regarding radiotherapy were lacking.

induce apoptosis in tumor cells, and also strengthen the immune system.[27-31]

The survival of patients treated with chemotherapy plus TCM herbal treatment studied by us was better than usual in stage IV lung cancers treated with conventional chemotherapy alone.[1,9,14] It is unlikely that this is the result of bias in selection of the patient population. First, selection of patients from the outpatient clinic from hospital B was only based on diagnosis date, gender, and age matching with hospital A patients. Second, the patients with platinum-based chemotherapy only (without TT and without TCM herbal treatment) had a survival comparable with other large studies[12] (1-year survival rate of 33% vs 27% in our sample). TT as second-line treatment improves the survival

Table 3. The Independent Prognostic Value of TCM Herbal Treatment, Targeted Therapy, and Other Features

Variables in the Equation							
						95% CI	
		β	SE	*P*	HR	Lower	Upper
Step 1	TCM_or not	−10.9	0.30	<.0001	0.14	0.08	0.25
Step 2	TCM_or not	−10.5	0.34	<.0001	0.22	0.11	0.43
	Targeted therapy	−0.9	0.41	.03	0.41	0.19	0.92

Variables Not in the Equation[a,b]				
		Score	df	Significance
Step 1	Targeted therapy	5.0	1	.03
	Hospital	0.5	1	.48
	Gender	4.1	1	.04
	Age	4.8	3	.19
Step 2	Hospital	1.4	1	.23
	Gender	3.2	1	.07
	Age	4.6	3	.20

Abbreviations: TCM, traditional Chinese medicine herbal treatment; SE, standard error; HR, hazard ratio; 95% CI, 95% confidence interval; df, degrees of freedom.
[a]Residual χ^2 = 150.4 with 6 df; significance = .02.
[b]Residual χ^2 = 90.2 with 5 df; significance = .10.

Table 4. Summary of the Survival Results of the Patients by Treatment

Type of Treatment	1-Year Survival (%)	2-Year Survival (%)	Median Survival Time (Months)	Median Follow-Up Time (Months)
TCM	88	62	27.0	14.0
No TCM	27	27	5.0	4.7
Target therapy	94	78	Not reached	14.5
No target therapy	59	42	19.0	9.0
Chemotherapy, target therapy, TCM (PBT+ TT+ TCM+)	94	78	Not reached	14.5
Chemotherapy, no target therapy, TCM (PBT+ TT− TCM+)	78	42	22.6	12.0
Chemotherapy, no target therapy, no TCM (PBT+ TT− TCM−)	27	27	5.0	4.7
Overall	76	50	26.0	12.0

Abbreviations: TCM, traditional Chinese medicine herbal treatment; PBT, platinum-based chemotherapy; TT, targeted therapy.

to about 40% to 50% at 1 year.[36,37] In our patients, survival of the TT (PTB+TT+) patients (all of whom were treated additionally with TCM) at 1 and 2 years was 94% and 78%, respectively. Only at 36 months did survival drop to 52%, a figure close to the 40% to 50% 1-year survival in other studies of TT-treated patients. The major difference between these studies is that a group of patients in the present study have been treated with TCM herbal medicine. This makes it plausible that the better survival of our stage IV adenocarcinomas patients treated with chemotherapy plus herbal TCM is because of TCM herbal treatment. The resulting median survival advantage in our material of getting TCM herbal treatment compared with PBT only is approximately 30 months in patients treated with second-line TT, and 18 months in those without second-line TT (see Figure 1).

One could also ask whether the differences in treatment results could be explained by racial or socioeconomic differences between the patients from the outpatient clinics from 2 different hospitals, or those with and without TCM treatment. However, neither is the case. Both hospitals are located in Shanghai, China, which is a wealthy, modern, and very "Western" city with 22 million inhabitants. The

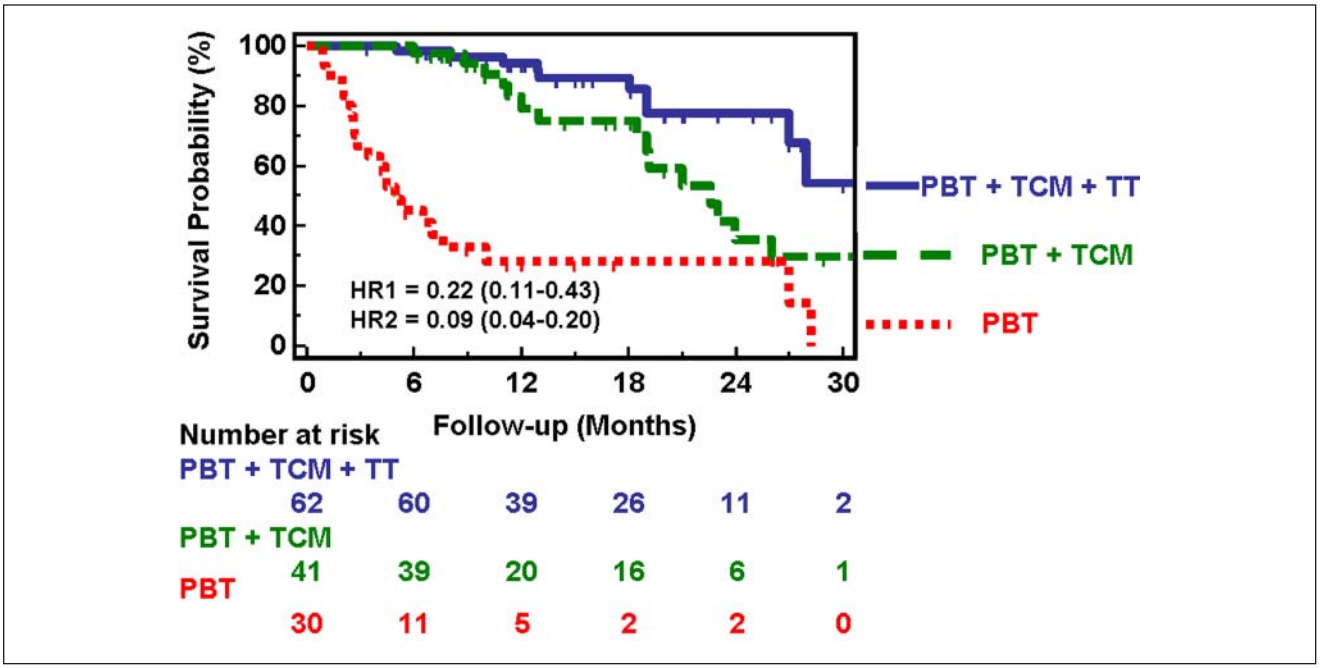

Figure 1. The prognosis of patients treated with chemotherapy, with or without TCM herbal treatment and targeted therapy
Abbreviations: TCM, traditional Chinese medicine herbal treatment; PBT, platinum-based chemotherapy; TT, targeted therapy; HR1 = hazard ratio between patients with PBT versus PBT + TCM; HR2 = hazard ratio between patients with PBT versus PBT + TT + TCM+. Values within parentheses are the 95% confidence intervals.

2 hospitals are located in middle-class suburbs, have good medical standards, and are very well organized. All patients were Chinese (excluding racial differences), and it is unlikely that there was any major difference with respect to their overall living standard. Each patient studied had received modern chemotherapy. The Shanghai government reimburses 80% of all health care costs incurred by its citizens. TCM treatment is very inexpensive (one doctors visit is equivalent to US$25 and herbs cost about US$80 per month on a monthly average income of US$450-1000) and a fraction of the costs patients have to pay for chemotherapy, so access to TCM treatment is in reality, unrestricted. Using TCM herbal treatment therefore is a matter of "believing or not believing in TCM treatment" and there is no reason to assume economic bias regarding TCM treatment access.

The issue with believing or not believing in TCM is somewhat relevant in itself because of placebo or nonspecific effects. A more mechanistic concern is whether the choice to use TCM is correlated with lifestyle variables that were not measured in this study. In the United States, vitamin users are more likely to exercise and have a better diet, which might be correlated with unmeasured lifestyle variables that could impact outcome. This is an inevitable limitation of retrospective studies.

The question of self-selection for patients to visit the TCM hospital A, or TCM specialists elsewhere thus has many possible answers. We have argued above that racial or socioeconomic differences are unlikely. The distance to the hospitals is also very unlikely factor, as public transport is cheap and very well organized in Shanghai (much better than in certain Western countries). One cannot get a final answer from the current retrospective study and a prospective randomized clinical trial is needed to answer such questions.

All patients treated with TT in this study were also treated with TCM, since the single patient treated with TT without TCM was excluded. There are several hypothetical explanations for this high frequency of combined treatments. One possibility is that patients treated with TT may be more aggressive about seeking out treatments, since they all got TCM as well and thus possibly may have a better prognosis because of psychological factors unmeasured in the study. Indeed, lower quality of life and depressed mood are associated with shorter survival among patients with metastatic NSCLC.[32-34] Moreover, patients with metastatic NSCLC with early integration of palliative care and standard oncologic care not only had improvements in quality of life and mood and less aggressive care at the end of life, but also longer survival by approximately 2 months.[35] However, it is unlikely that psychological effects are the only explanation for the prolonged survival of the TCM-treated patients in our study as the survival effect of TCM added to chemotherapy is nearly 18 months,[10] much more than the 2 months that was observed with integrated palliative care. This suggests that factors other than psychological ones play a role in the favorable prognostic effect of targeted therapy plus TCM treatment. Another hypothetical

molecular cell biologic explanation is that the EGFR mutations of the lung cancers determining TT are related to lower proliferation rates of the cancers and give these patients more time to consult a TCM specialist. Likewise, the immune system of the patients may be different. However, in this retrospective study, such explanations are purely hypothetical and prospective studies must be undertaken to get final answers.

TCM syndrome differentiation was not prognostic in our study. In view of the strong and dominant prognostic value of TCM herbal treatment, it is tempting to hypothesize that this is because of the fact that herbal treatment is very effective. As a result, the original clinically poor prognosis of patients with certain TCM syndromes but without herbal treatment could have been eliminated by the TCM herbal treatment, which was carefully adapted to the TCM syndromes. Alternatively, one could ask how reproducible TCM syndrome differentiation is. Studies in other fields of medicine have shown considerable variation between and within the same observers.[38,39] with potential prognostic and therapeutic variations,[40] and this may also apply to TCM specialists. In principle, a number of the important TCM syndrome differentiation symptoms could be standardized in formalized questionnaires. Automated signal processing of pulse diagnoses may also be useful. Tongue diagnosis could no doubt be evaluated much more objectively by digital image analysis, similar to developments in pathology. One study showed that Bayesian network is a good method to deal with the symptoms and signs for syndrome differentiation.[41] However, the high development costs combined with a possibly small future commercial market may limit the realization of such decision support systems in TCM.

Although the results regarding the TCM herbal treatment in the previous and current study on stage IV adenocarcinomas of the lung are encouraging, they must nonetheless be interpreted with care, as the number of patients is relatively small and the study is retrospective. A large prospective clinical randomized trial in newly diagnosed stage IV adenocarcinoma patients treated with chemotherapy, chemotherapy plus herbal TCM, or chemotherapy plus herbal TCM plus TT to see if survival results similar to the present study can be obtained.

It is important to consider which phase (1, 2, 3, and 4) trials should be undertaken. The present study demonstrates the survival difference in the 2 hospitals close to each other. Moreover, it also shows the survival difference in the TCM plus and TCM minus groups, and third the possible relationship with TT. On the other hand, there is a lack of effect of TCM syndrome differentiation. Although this may be because of issues with reproducibility as mentioned above, it is also possible that herbal treatment according to TCM syndrome effectively eliminates possible negative prognostic effects of particular syndromes. TCM syndromes certainly dictate the herbal combinations to be given to different patients, and trials should thus at least balance the distribution of TCM syndromes among groups, or be restricted to a single TCM syndrome to equalize the herbal treatments to be applied. Thus, an initial study should assess distribution of TCM syndromes in the potential study population and assure reproducibility of syndrome differentiation among the study physicians responsible for TCM treatment. Second, a study should assess the safety and potential for adverse herb–drug interactions of the herbal formulas to be used with conventional chemotherapy-treated patients as controls. Third, a large multicenter prospective randomized trial should be undertaken comparing standardized conventional PBT, versus PBT plus TCM herbal treatment. Fourth, a similar prospective trial also including TT should be performed. Regular control of the blood values and objective diagnosis criteria by radiologic and pathologic data is of the utmost importance. There should not be the slightest doubt about these initial inclusion criteria.

We conclude from this small retrospective study on stage IV adenocarcinomas of the lung that TCM herbal treatment may improve survival of patients treated with chemotherapy alone or combined TT and chemotherapy. This warrants formal phase 1, 2, and 3 trials and ultimately properly designed prospective clinical trials with adequate methodology developed for data collection to validate TCM herbal treatment in addition to chemotherapy or chemotherapy plus TT.

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