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Haishengsu as an adjunct therapy to conventional chemotherapy in patients with non-small cell lung cancer: a pilot randomized and placebo-controlled clinical trial

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Abstract

Objective: To investigate the effect of Haishengsu, an extract from *Tegillarca granosa*, on non-small cell lung cancer as an adjunct to conventional chemotherapy.

Designs/settings: Randomized, double-blind, placebo-controlled trial was conducted in 83 patients. The Haishengsu (n=42, 2.4 mg Haishengsu in 250ml normal saline, iv, for 15 days) and the placebo group (n=41, 250ml normal saline, iv) were also treated with two cycles (28 days for each cycle) of conventional chemotherapy consisting mitomycin, vindesine and cisplatin.

Results: The curative effect of conventional chemotherapy was observed in 62% of Haishengsu group patients and in 39% in of the placebo group patients (*P*=0.04, RR 1.59, 95% CI: 1.01-2.49). Improvement in Karnofsky performance status scores was seen in 66.7% of Haishengsu group patients and in 17.1% of the placebo group patients (*P*<0.01, RR 3.63, 95%CI: 1.77-7.41). The ratio of patients with no or only mild gastrointestinal reaction in the Haishengsu and the placebo group was 83.3% and 39.0%, respectively (*P*<0.01, RR 2.13, 95% CI: 1.42-3.20).

Conclusions: This study suggests that Haishengsu may be an effective adjunct therapy to the conventional chemotherapy for non-small cell lung cancer. The short-term therapeutic effect of chemotherapy may be improved and the chemotherapy-induced nausea or vomiting may be reduced by concurrent Haishengsu administration.

Key words: Haishengsu; gastrointestinal reactions; non-small cell lung cancer; chemotherapy.

INTRODUCTION

Chemotherapy plays important roles in the treatment of cancer. However side effects of the chemotherapy, such as gastrointestinal tract reactions and progressive weight loss are very common. Alleviating these side effects is critical in improving patient's quality of life and compliance to chemotherapeutic agents. Tegillarca granosa (Chinese name *"xue han")* is the main type of breed aquatics seashell in China and is widely distributed and used as a traditional Chinese medicine in mainland China. It is suggested in the book of Medical Compendium (*Yi Lin Zuan Yao*) that Tegillarca granosa may help to repair injuries to the heart, dispel gore, eliminate fidget, and reduce phlegm. Purified proteins from Tegillarca granosa have several pharmacological actions such as anti-coagulation [1]. Haishengsu is an extract from Tegillarca granosa (major chemical constituents are albumen with a molecular weight ranged from 15 KDal to 23 KDal). Previous studies indicated that Haishengsu inhibit growth of tumor cells, but not of normal cells *in vitro* [2]. In normal doses it was found to have no significant adverse effects [3].

Non-small cell lung cancer is the most common form of lung cancer, accounts for about 80% of all lung cancer patients [4, 5]. Although there has been some significant improvement in the pharmacological treatment of non-small cell lung cancer, the prognosis of patients remains poor [4, 5]. In addition, chemotherapy of lung cancer is associated with a high prevalence of nausea and vomiting. The incidence varies from less than 25% with vincristine to over 90% with cisplatin [6]. Overall, approximately 60% of cancer patients receiving chemotherapy experiencing

nausea and 50% experiencing vomiting [7]. It has been estimated that failure to control side effects can lead to 25-50% of patients delaying or refusing possible life-saving therapy [8].

To the best of our knowledge, no previous studies had evaluated the effects of Haishengsu as an adjunct therapy to conventional chemotherapy in patient with non-small cell lung cancer. In this double-blind and placebo-controlled clinical trial, we hypothesized that Haishengsu may improve the anti-cancer effects of the conventional chemotherapy and reduce themotherapy-induced emesis.

MATERIALS AND METHODS

Patient selection and treatment regimens

This study was approved by the institution review board of Liaocheng People's Hospital. Written informed consent was obtained from all participant patients. Patients were given adequate advice on the freedom of seeking treatment alternatives such as withdrawal from the trial and seeking other adjunctive or anti-emetic therapies. Patients with the following conditions were selected: established diagnosis of medium to advanced non-small cell lung cancer; health grade (Karnofsky performance status, KPS) ≥50 (range, 10-100, the lower the score, the worse the survival[9]); expected life expectancy >3 months; normal cardiac, renal and liver function.

Between June 2000 and December 2005, 210 patients were assessed by the chief investigators (Li GY, Yu XM, Zhang HW) at Liaocheng People's Hospital for eligibility, and 120 met the selection criteria mentioned above. Among the eligible

patients, 37 did not give an informed consent and were excluded from this study. Eighty-three inpatients whose diagnosis of non-small cell lung cancer was confirmed by histopathology and/or affirmative cytology examination were finally recruited the chief investigators. They were randomly divided into two groups by one of the investigators (Li GY), using randomly selected numbers (group 1 or 2) from a container. The number allocation sequence was generated by Dr Li GY who was not involved in the assessment of the therapeutic effects of the study or placebo group. There were no restrictions in the randomization procedure. All other investigators who assessed the clinical outcomes of the patients were unaware of the patient's groupings.

The first group of 42 patients were treated with Haishengsu (2.4 mg in 250ml normal saline, IV over 4 hours) (Haisheng Oncology Hospital, Qingdao, China) daily for 15 days. The control group (n=41) were treated only with placebo in 250ml normal saline IV for 15 days. The active drug and the placebo were identical in color and volume. Both the patients and the assessors of the clinical outcomes of the patients were blinded to the patient groups.

The Hasishengsu treatment was commenced from day 1 of each conventional chemotherapy cycle. The conventional chemotherapy was based on Mitomycin, Vindesine and Cisplatin (MVP regimen) as follows: Mitomycin 10mg IV on day 1; Vindestine 4mg IV on days 1 and 8; Cisplatin 40mg IV on days 1, 2 and 3. Each cycle was 28 days and each patient from the two groups received two consecutive chemotherapy cycles.

Assessments

The assessment of effect of Haishengsu on gastrointestinal tract reactions was performed during the four active thermotherapy treatment days of each treatment cycle. The assessment on other objectives was performed all days during a 28-day cycle.

(1) Gastrointestinal tract reactions were evaluated on prevalence and severity of nausea and vomiting. This was measured by patient's registration in daily diary which was verified by health care professionals on the accuracy of the entry. No reaction: no nausea and no vomiting; slight reaction: some nausea during day or night but no vomiting; intermediate reaction: some nausea and vomiting (<4 times per day); and serious reaction: serious nausea and vomiting (>4 times /d).

(2) Quantity of food intake before and after treatment. This was measured by the mean of the three meals (semi-solid and solid food) on the two days before Haishengsu administration and the two days after its administration. Increase: the quantity increase was ≥50g/meal; Decrease: the quantity decrease was ≥50g/meal; and no change: the quantity changed <50mg/meal.

(3) Evaluation of weight changes before and after two cycles of chemotherapy. Increase: increase was ≥1kg; Decrease: decrease was ≥1kg; and no change: the change was <1kg.

(4) Evaluation of KPS scores before and after two cycles of chemotherapy. Improvement: KPS score increase was ≥10; Exacerbation: KPS score decrease was ≥15; and no change: KPS score change <10.

Assessment on the effect of conventional chemotherapy was based on the WHO standard on the curative effects of malignant tumor. It was defined by complete remission, partial remission, stable disease, and progression. Progressing ratio = (complete remission + partial remission)/Total*100%

Statistics Analysis

Since there were no previous studies of this nature to be used as reference, the optimal number of patients required for this study was difficult to estimate. For this pilot study we opted to recruit approximately 40 patients per group. Curative effects of chemotherapy, food intake, body weight changes and KPS scores were always assessed after the completion of the second chemotherapy cycle (Table 2). If gastrointestinal reactions occurred in any of the two themotherapy cycles, it was classified as having an adverse reaction, using the most serious episodes of reactions for the classification. Data were expressed as means ± SD. The statistical analysis of numerical data was performed using *t* test, whereas categorical data were analyzed with x^2 test or Fisher exact probability test. The relative risk (RR) and its 95% confidence internal (CI) was also calculated wherever appropriate. $P<0.05$ was considered as statistically significant.

RESULTS

Basic characteristics

The baseline clinical data of patients in the Haishengsu and the placebo group

are presented in Table 1.

Table 1. Baseline data of the Haishengsu and placebo groups.

	Haishengsu *(n=42)*	*Placebo (n=41)*	*P*
Age (yr)	59.3±5.9	59.2±5.8	0.69
Male	33	32	0.76
Histopathology			
ADCM	27	25	0.21
LPC	12	16	0.22
Other	3	0	0.98
TNM term			
III	24	18	0.52
IV	18	23	0.76
Body weight (kg)	62.7±12.1	62.5±13.6	0.36
Karnofsky grade	71.5±11.4	72.3±10.1	0.87

ADCM: Adenocarcinoma, LPC: Leprose cancer

The average age, gender ratio, type of histopathology, term of illness, body weight and KPS grade were similar between the two groups (P>0.05). None of these patients had other concurrent illnesses.

During the trial, the Haishengsu and the placebo group patients received no routine antiemetic agents during MVP chemotherapy. None of the patients were on special diet, nor had they received acupuncture, homeopathy or any other therapeutic regimens known to affect the actions of Haishengsu or the overall outcomes of the patients. All potential side effects of chemotherapeutic agents or Haishengsu, and prescribed or non-prescribed therapeutic regimens, were registered by the investigators or healthcare professionals during the trial.

All participants completed the study with no mortality at the conclusion of the trial. There was no significant change in renal (assessed by serum creatinine) and liver function (assessed by AST and ALT) in the Haishengsu and placebo groups following the trial.

Effectiveness

The therapeutic effects of the thermotherapy in the two groups are shown in Table 2. The progressing ratio was 62% in the Haishengsu group and 39% in the placebo group (χ^2=4.35, *P*=0.04, RR 1.59, 95% CI: 1.01-2.49).

The ratio of patients with no or mild gastrointestinal reaction was 83.3% in the Haishengsu group, and 39.0% in the placebo group (χ^2=17.19, *P*<0.01, RR 2.13, 95% CI: 1.42-3.20).

In the Haishengsu and the placebo group, an increase in food take was found in 71.4% and 17.1% of the patients, respectively (χ^2=24.81, *P*<0.01, RR 4.18, 95%CI 2.08-8.44). An increase in body weight was observed in 66.7% of the Haishengsu group patients, and in 14.6% of the placebo group patients **(**χ^2=23.12, *P*<0.01, RR 3.90, 95%CI: 1.92-7.92).

In the Haishengsu and the placebo group, an increase in KPS scores was found in 66.7% and 17.1% of the patients, respectively (χ^2=17.14, *P*<0.01, RR 3.63, 95%CI: 1.77-7.41).

Table 2. Clinical outcomes.

	Haishengsu *(n=42)*	*Placebo (n=41)*
Curative effects of chemotherapy		
Complete remission	1	0
Partial remission	25	16
Stable disease	12	20
Progression	4	5
GIT reaction		
None	19	6
Mild	16	10
Intermediate	4	16
Severe	3	9
Food intake		
Increase	30	7
No change	9	16
Decrease	3	18
Body weight		
Increase	28	6
No change	8	19
Decrease	6	16
KPS scores		
Increase	26	7
No change	10	18
Decrease	6	16

GIT: gastrointestinal tract

Safety

During or after the Haishengsu administration, no allergic reactions or other side effects were noticed.

DISCUSSION

Radical surgery, intensified chemotherapy and radiotheraphy have been used to treat small cell lung cancer, in the hope to prolong patient's life expectancy [4, 5]. However, these treatments may cause serious toxic and side effects, reduction in quality of life and worsening of the state of illness [10-13]. Some drugs used in chemotherapy have toxic and restraining effects on digestive system, blood system and immune system [10-13]. MVP is a popular treatment option for patients with medium or advanced non-small cell lung cancer. It was reported by Bonomi [14] and Spain [14] that MVP is effective in 20%~75% of the patients. The major side effects of MVP regimen include gastrointestinal tract reactions and bone marrow suppression [14, 15]. Given the limited life expectancy of the medium and advanced non-small cell lung cancer and significant adverse effects of many chemotherapeutic agents, treatments aiming at improving quality of life may be more preferable.

Haishengsu is an active substance extracted from seashells. It has antitumor effect *in vitro* and *vivo*. Previous studies had confirmed that Haishengsu could inhibit the growth of cultivated human tumor cells of lung cancer, breast cancer and carcinoma of stomach [2]. Subsequently we observed that Haishengsu was able to effectively countermine S180 solid tumor and liver solid tumor in mice [16]. Our results showed that the mice treated with Haishengsu lived much longer than those in the control group did [16]. In addition, the mice treated with Haishengsu lived better that those in the cyclophosphamide treated group did [17].

This study has demonstrated that that the progressing ratio was 62% in the

Haishengsu group, while 39% in the placebo group. The gastrointestinal reactions in the Haishengsu group were milder than in the placebo group. The Haishengsu group also had better KPS grade- 61.9% versus 17.1% in the placebo group. These results indicate that Haishengsu injections effectively alleviate the gastrointestinal averse reactions caused by chemotherapy, and improve patients' quality of life.

The major limitation of the present study was that the patient population was relatively small. However, four of the five major end points reached a clear cut difference between the Haishengsu and the placebo groups. There was also a 23% more improvement in the therapeutic effects (progression ratio) of the conventional chemotherapy in the Haishengsu group, but this difference was only moderate from statistical point of view. It is likely that study in a larger population may yield more convincing results. The other potential limitation is that the confounding factors, such as female sex, for Haishengsu's benefits on the chemotherapy-induced gastrointestinal reactions were not well controlled in this relatively small study. In future larger studies these confounding factors need to be adjusted.

In conclusion, Haishengsu seems to be an effective adjunct therapy in patients with non-small cell lung cancer. The addition of this agent to the conventional chemotherapeutic regimens further improves patient's the effects of the chemotherapy and reduces the chemotherapy-induced nausea or vomiting. The long-term effect of Haishengsu in patients with non-small cell lung cancer needs further investigation.

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