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Original Article

Effect of *Haishengsu* as an Adjunct Therapy for Patients with Advanced Renal Cell Cancer: A Randomized and Placebo-Controlled Clinical Trial

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Abstract

Objective: The purpose of this study was to investigate the effect of *Haishengsu*, an extract from *Tegillarca L. granosa*, on the effects and side-effects of immunotherapy in patients with advanced renal cell cancer.
Methods: Fifty-five (55) patients with renal cell cancer were randomly divided into a *Haishengsu* group ($n = 27$, 2.4 mg, intravenously for 15 days) and a control group ($n = 28$). All patients were also treated with interleukin-2, interferon-α, and fluorouracil.
Results: In the *Haishengsu* group, the prevalence of gastrointestinal reactions to the immunotherapy was lower than in the control group (18.5% versus 64.3%, $p < 0.01$). In comparison with the control group, more patients from the Haishengsu group had increased food intake (74.1% versus 14.3%, $p < 0.01$), weight gain (77.8% versus 10.7%, $p < 0.01$) or an increase in Karnofsky Performance Status score (55.6% versus 17.9%, $p < 0.01$). The remission rate of cancer in the *Haishengsu* group was higher than in the control group (51.9% and 21.4%, $p < 0.01$).
Conclusions: Addition of *Haishengsu* to the conventional immunotherapy is associated with an increased remission rate in patients with advanced renal cell cancer. *Haishengsu* was also associated with a reduced rate of gastrointestinal side-effects from the immunotherapeutic agents, and an improvement in the physical functionality of the patients.

Introduction

Anorexia, gastrointestinal reaction, and progressive weight loss are common complications in patients with advanced cancer during chemotherapy, and they have a serious impact on quality of life.[1,2] Reducing the side-effects of chemotherapy and improving the quality of life is an important part of cancer care.[1,2] *Tegillarca granosa* is a Malaysian cockle that has been widely used as a Traditional Chinese Medicine in mainland China to treat cancer for more than a century. Several proteins have been purified from *T. granosa* in recent years, and their anticoagulation and anticancer actions have been assessed *in vitro* and *in vivo*.[3–5] *Haishengsu* (HSS) is a protein extract from *T. granosa,* with a molecular weight of approximately 15 KDa. HSS has a potent suppressive effect on several types of tumor cells, such as leukemia K562 cells *in vitro,* or transplanted and drug-resistant K562/ADM tumors *in vivo*.[5,6] HSS was found to inhibit the tumor cell line, blocking the cell cycle at phases G0/G1 and G2/M.[5]

HSS seems to be effective in treating patients with lung cancer. Daily intravenous administration of 2.4 mg of HSS for 4 weeks was associated with a complete or partial remission of non-small-cell lung cancer in 49% of the patients.[7] At this dose, no significant adverse effects were observed.[7] HSS also reduced the prevalence of chemotherapy-induced nausea or vomiting in patients with lung cancer, while it moderately increased the remission rate following conventional chemotherapy.[8]

The primary aim of this study was to investigate the effect of HSS as an adjunct therapy to conventional chemotherapy in patients with renal cell cancer. The effect of HSS on the remission rates, gastrointestinal side-effects, and physical functionality were assessed following standard chemotherapy for renal cell cancer.

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Patients and Methods

Patient selection

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. The selection criteria were as follows: (1) ≥18 years of age; (2) newly diagnosed renal cell cancer; and (3) no concurrent chronic illnesses such as other forms of cancer, cardiovascular or respiratory disease. Exclusion criteria were those less than 18 years old and those who were unable or unwilling to give a written consent.

Fifty-five (55) patients with newly diagnosed renal cell cancer were recruited from our hospital wards. There were 39 males and 16 females, with a median age of 54.6 years (range, 39–71 years). The TNM staging system was used to describe the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M), with stage III and IV being the more advanced stages of the cancer.[9] The TNM classification of the renal cell cancer showed TNM III in 30 and TNM IV in 25 patients, respectively (Table 1). The number of patients with TNM III cancer in the HSS and placebo group was 14 and 16, respectively ($p > 0.05$), whereas TNM IV was found in 13 and 12 patients, respectively, in the two groups (Table 1, $p > 0.05$). None of the patients had previous nephrectomy or received other therapies.

All patients underwent thorough physical examination and blood tests such as full blood cell counts, electrolytes, plasma creatinine, lipid profile, and liver function. Chest X-ray, computed tomography scans, positron emission tomography scan, and electrocardiography were also performed in these patients. Patients were also assessed for Karnofsky Performance Status (KPS) score, which is a functional status scale that is commonly used to categorize physical ability in patients with cancer.[10,11] All selected patients had a KPS score of 70 or more.

Treatment protocol

Patients were randomly divided into two groups by one of the investigators, using randomly selected numbers (1 or 2) from a container. The number allocation sequence was generated by the chief investigator, who was not involved in the assessment of the therapeutic effects of the HSS or control group. There were no restrictions in the randomization procedure.

The HSS group ($n = 27$) were treated with HSS (2.4 mg in 250 mL normal saline, intravenously (IV) over 4 hours) (Haisheng Oncology Hospital, Qingdao, China) daily for 15 days. The control group ($n = 28$) was treated only with placebo in 250 mL 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.

Patients from the HSS and control groups were also treated with a combination of interleukin-2 (IL-2), interferon-α (IFN), and fluorouracil (5-FU) between days 1 and 5 of each treatment cycle. The regimens of the three drugs were as follows: IL-2 (2 million units) IV daily; IFN 3 million units, intramuscularly, daily; and 5-FU, 750 mg IV infusion over 5 hours, daily.

The duration of each treatment cycle was 28 days. All patients completed two treatment cycles. Blood cell count and biochemistry profile were assessed weekly during the treatment.

During the trial, the HSS and the control group patients received no other antiemetic agents. No patients were prescribed a special diet or other complementary therapy known to affect the actions of HSS or the overall outcomes of the patients.

Evaluation of effects

In each group, the short-term effect of the chemotherapies was divided into complete remission, partial remission, stable, and progress, according to the World Health Organization criteria.[10]

Gastrointestinal tract reactions were evaluated on prevalence and severity of nausea and vomiting. This was measured by the patient's registration in a daily diary that was verified by healthcare professionals on the accuracy of the entry, as follows: 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 per day).[8] If gastrointestinal reactions occurred in any of the two chemotherapy cycles, it was classified as having an adverse reaction, using the most serious episodes of reactions for the classification.

Quantity of food intake before and after treatment was measured by the mean of the three meals (semisolid and solid food) on the 2 days before HSS administration and the 2 days after its administration.[8] Increase: the quantity increase was ≥50 g/meal; decrease: the quantity decrease was ≥50 g/meal; and no change: the quantity changed <50 g/meal.[8]

The weight changes were assessed before and after the completion of the second treatment cycles by the method we had previously described: Increase: increase was ≥1 kg; decrease: decrease was ≥1 kg; and no change: the change was <1 kg.[11,12]

KPS scores were obtained before and after the second cycle of chemotherapy: Improvement: KPS score increase ≥10; exacerbation: KPS score decrease ≥15; and no change: KPS score change <10.[11,12]

Table 1. Baseline Characteristics

	Haishengsu (n = 27)	*Placebo* (n = 28)	p
Age (yr)	51.3 ± 5.9	52.2 ± 5.8	0.49
Male	20	19	0.66
TNM classification			
III	14	16	0.46
IV	13	12	0.79
Body weight (kg)	62.0 ± 10.1	61.5 ± 11.4	0.54
KPS scores	72.5 ± 11.9	73.3 ± 10.0	0.68

TNM, tumor, nodes, metastasis; KPS, Karnofsky Performance Status.

Statistical analysis

SAS 8.0 software was used for data analysis. Data were expressed as means ± standard deviation. The statistical analysis of numerical data was performed using Student's t test, whereas categorical data were analyzed with x^2 test or Fisher exact probability test. $P < 0.05$ was considered statistically significant.

Results

All patients completed the treatment. In the HSS group, 1 patient had a small number of scattered red skin rashes on the back of the right hand on the first day of the second treatment cycle. The rashes, which were not accompanied by other allergic symptoms, disappeared in about a week during the continued use of HSS. No skin rashes or other side-effects were observed in other patients. There were no deaths and no episodes of febrile neutropenia. Fatigue was the most common side-effect and was recorded in almost all patients.

As shown in Table 2, intermediate to severe gastrointestinal reactions were recorded in 18.5% and 64.3%, respectively, in patients from the HSS and the control group ($p < 0.05$). In the HSS group, 74.1% of the patients had increased food intake, while in the control group, it was 14.3% ($p < 0.01$). Weight gain in the HSS and the control group was recorded in 77.8% and 10.7% ($p < 0.01$), respectively.

The complete and partial remission rate following the second cycle of chemotherapy was 51.9% and 21.4%, respectively, in the HSS and control group (Table 2, $p < 0.01$).

Before the treatment, there was no significant difference in the average KPS scores between the two groups (Table 1, $p > 0.05$). The average KPS score after treatment was 81.6 ± 10.3 and 73.0 ± 16.8, respectively, in the HSS and the control group ($p < 0.05$).

Table 2. Clinical Outcomes Following the Therapy

	Haishengsu (n = 27)	*Control* (n = 28)
Effects of chemotherapy		
Complete remission	1	0
Partial remission	13	6
Stable disease	9	17
Progression	4	5
GIT reactions		
None	14	4
Mild	8	6
Intermediate	4	11
Severe	1	7
Food intake		
Increase	20	4
No change	4	7
Decrease	3	17
Body weight		
Increase	21	3
No change	4	8
Decrease	2	17
KPS scores		
Increase	15	5
No change	7	9
Decrease	5	14

GIT, gastrointestinal tract; KPS, Karnofsky Performance Status.

The proportion of patients who had an increase in KPS score of 10 or more was 55.6% in the HSS groups, and 17.9% in the control group following the treatment (Table 2, $p < 0.01$).

Discussion

Renal cell cancer is rarely curable and advanced renal cell carcinoma is often too extensive for surgical removal. Because renal cell cancer is resistant to conventional chemotherapy, immunotherapy is often used to improve the survival of the patients. IL-2 and IFN are often used in combination as immunomodulative agents for this condition, providing a modest survival benefit and a complete remission rate of between 13% and 28%.[13,14] Triple therapies with IL-2, IFN, and 5-FU have also been reported with some success.[14] However, the triple therapies were associated with moderate to severe nausea and vomiting in almost all patients.[15]

In the present study, there was no significant difference in the TNM staging of renal cell cancer between the HSS and the control group. Triple therapy was associated with a 51.9% response rate in the HSS group, and a 21.4% response rate in the control group. Given that all other underlying conditions were similar between the two groups, it is very likely that the addition of HSS has made the difference. It is important to note that this is only a preliminary study based on a short-term follow up. It is unclear if these short-term benefits in the HSS group can be translated into long-term remission of the cancer or improved survival.

Nausea and vomiting are debilitating side-effects of chemotherapy, and are common causes of poor patient compliance to the drug therapy. In this study, addition of HSS was associated with a markedly reduced prevalence of moderate to severe gastrointestinal reactions to the triple chemotherapies. It was unclear by what mechanisms that HSS suppressed the gastrointestinal adverse effects of IL-2, IFN, or 5-FU. One thing that is certain, however, is that this beneficial effect of HSS is not limited to the triple therapies in this study, because a recent clinical trial has shown that the gastrointestinal side-effects of other cytotoxic agent, such as cisplatin and vincristine, can also be prevented by HSS.[8]

In conclusion, HSS seems to be an effective and safe adjunct therapy in patients with renal cell cancer. HSS was associated with an increased remission rate following conventional chemotherapy. It was also associated with a reduction in chemotherapy-induced gastrointestinal side-effects, an increase in food intake, and an improvement in the physical functionality of the patients. The long-term remission rate and the symptom-free survival following HSS therapy requires further investigation.

Disclosure Statement

No financial conflicts exist.

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