

Effect of Shakuyakukanzoto on Chemotherapy-Induced Hiccups in Patients with Lung Cancer

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ABSTRACT

Objective: Shakuyakukanzoto, one of the traditional herbal medicines commonly used in North-East Asian countries, is known to be effective for muscle cramps. This retrospective study aimed to evaluate the effect of shakuyakukanzoto on chemotherapy-induced metoclopramide-uncontrolled hiccups.

Materials and Methods: We retrospectively investigated the medical records of all the consecutive patients with lung cancer who were prescribed with shakuyakukanzoto (Tsumura Co. Tokyo, Japan) for chemotherapy-induced hiccups in our hospital from September 2013 to November 2017. In the medical record from the initiation of shakuyakukanzoto until the start of the next chemotherapy, when there was description of "complete or partial disappearance of hiccups" after the prescription of shakuyakukanzoto, it was judged as a complete or partial response. A statement of "unchanged;" no description of improvement, or exacerbation was judged as no change.

Results: Of the 49 chemotherapy courses in 15 patients with lung cancer, 93.9% had a "partial or complete" response within a few hours after the administration of shakuyakukanzoto. The effect of shakuyakukanzoto was observed irrespective of the pathological type of lung cancer, platinum-containing or non-platinum chemotherapy, and with or without other anti-hiccup drugs. No adverse event was observed.

Conclusion: Shakuyakukanzoto may offer an effective pharmacological approach to treat chemotherapy-induced metoclopramide-uncontrolled hiccups. Well-planned prospective studies will confirm our results.

Keywords: Herbal medicine, hiccup, drug therapy, lung neoplasms

Introduction

Chemotherapy-induced hiccups are considered common and mild complications; however, they have been known to cause considerable distress in some patients [1-3]. Hiccups are a common symptom characterized by brief, abrupt involuntary sounds associated with rhythmic and spasmodic contractions of the diaphragm [4], but the exact pathophysiological significance of hiccups remains unclear. Standard therapy for hiccups associated with cancer chemotherapy has not been established. Shakuyakukanzoto, one of the traditional herbal medicines, has been prescribed in North-East Asian countries as an antispasmodic drug for the treatment of skeletal muscle cramps and intestinal cramps [5]. There has been progress in terms of the elucidation of the fundamental research results on the mechanism of the action of this drug on muscle spasms [6, 7]. However, there has been no basic research on shakuyakukanzoto as a treatment option for hiccups, which are also considered to be muscle spasms of the diaphragm. Empirically, it is expected to be effective for hiccups, but there was only 1 case report on the effect of this drug on patients with cancer who are undergoing chemotherapy [8]. In this retrospective study, we evaluated the efficacy of shakuyakukanzoto for chemotherapy-induced hiccups in patients with lung cancer.

Materials and Methods

We retrospectively investigated the medical records of all the consecutive patients with lung cancer who were prescribed shakuyakukanzoto for chemotherapy-induced hiccups in our hospital from September 2013 to November 2017. This study was approved by the ethics committee of Mito Kyodo General Hospital (No. 15-26) and written Informed Consent was obtained from

Table 1. Characteristics of patients treated with shakuyakukanzoto

Age (years), median (range)	69 (42–76)
70 years or older	33 courses
Younger than 70 years	16 courses
Sex	
Male	15 patients, 49 courses
Female	0
Clinical stage of lung cancer	
IIIB	5 patients
IV	10 patients
Histopathology of lung cancer	
Small-cell lung cancer	7 patients, 23 courses
Adenocarcinoma	8 patients, 26 courses
COPD	58 (15.4%)
Chemotherapy	
Platinum-containing	30 courses
Non-platinum	19 courses

COPD: chronic obstructive pulmonary disease

each patients. Shakuyakukanzoto (Tsumura Co. Tokyo, Japan) was orally administered once per 2.5 g, 3 times a day, or prescribed as needed.

Diagnoses of colon and lung cancer were confirmed pathologically in all patients, and the histopathological cancer types were confirmed by the World Health Organization classification. Staging was performed according to the 7th edition of the International Union for Cancer Control TNM (tumor-node-metastasis) classification of malignant tumors using chest computed tomography, brain magnetic resonance imaging, bone scan, endoscopy, and ultrasonography. In a proportion of the cases, fluorodeoxyglucose-positron emission tomography was used.

The effect of shakuyakukanzoto was evaluated. In the medical record from the initiation of shakuyakukanzoto until the start of the next chemotherapy, when there was a description of “complete disappearance of hiccups” after prescription of shakuyakukanzoto, it was judged as a complete response (CR). When there

Table 2. Patient characteristics and response to shakuyakukanzoto

	Treatment response to shakuyakukanzoto				
	CR	PR	NC	WS	p-value
Age					
≥70 years old	3	28	2	0	0.3229
<70 years old	4	11	1	0	
Pathology					
SCLC	7	15	1	0	0.0097
Adenocarcinoma	0	24	2	0	
Chemotherapy					
Platinum-containing	7	23	3	0	0.0187
Non-platinum	0	19	0	0	
Concomitant other anti-hiccup drug					
With other drugs	0	6	2	0	0.0309
Without other drugs	7	33	1	0	

CR: complete response, PR: partial response, NC: no change, WS: worsened symptom, SCLC: small cell lung cancer

was a description of “partial disappearance of hiccups” after the prescription of shakuyakukanzoto, it was judged as a partial response (PR). When there was either a statement of “unchanged” or when there was no description of improvement or exacerbation, it was judged as no change (NC). When there was description of “deterioration of hiccups,” it was judged as worsened symptom (WS).

Statistical Analysis

The statistical significance of the differences between the symptomatic and asymptomatic patient groups was determined using the Mann–Whitney and chi-squared tests. Statistical analyses were performed using the Statistical Package for the Social Sciences 10.1 for Windows (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered to indicate statistically significant differences.

Results

During the study period, 49 chemotherapy courses in 8 patients with adenocarcinoma and 7 patients with small-cell lung cancer (SCLC) were prescribed shakuyakukanzoto for chemotherapy-induced hiccups. Characteristics of the patients treated with shakuyakukanzoto are presented in Table 1. Shakuyakukanzoto was prescribed 68 times: 36 prescriptions on as-needed basis (median prescription, 5 times) and 32 prescriptions for ordinary prescription (median prescription, 5 days). As a combination with shakuyakukanzoto, metoclopramide, chlorpromazine, and baclofen were prescribed for 5 courses, 2 courses, and 1 course of chemotherapy, respectively. The study sample included all male patients, and their median age was 69 (range: 44–76) years.

A total of 46 (93.9%) of the 49 chemotherapy courses in 15 patients had CR or PR (CR: 14.3%, PR 79.6%), 3 (6.1%) had NC, and no one was evaluated as having WS.

Table 2 shows the relationship between the patient characteristics and the effect of shakuyakukanzoto. No significant difference in response was found between 16 chemotherapy courses in patients younger than 70 years and 33 chemotherapy courses in patients who were 70 years or older ($p = 0.3229$). However, with regard to the pathological type of the lung cancer, there was a statistical difference in response (CR, PR, or NC) between 23 chemotherapy courses in patients with SCLC and 26 chemotherapy courses in patients with adenocarcinoma ($p = 0.0097$); a significant difference in response was observed between 30 platinum-containing chemotherapy courses and 19 non-platinum chemotherapy courses ($p = 0.0187$). In addition, there was a statistical difference in response between 41 chemotherapy courses without other anti-hiccup drugs and 8 chemotherapy courses with other anti-hiccup drugs ($p = 0.0309$).

No side effects related to shakuyakukanzoto were noted.

Discussion

The most common chemotherapeutic agents, such as platinum, taxanes, and irinotecan, cause hiccups [1]. Dexamethasone, which is an essential agent for preventing chemotherapy-induced emesis, also causes hiccups [1, 2]. A wide variety of agents have been tried as treatments for hiccups [1, 3], but treatment with these drugs

Main Points

- As a side effect of anticancer chemotherapy, hiccups may appear, which may impair the patient's quality of life.
- Shakuyakukanzoto, an herbal medicine in North-east Asia, has been used to treat improving muscle clamps.
- Shakuyakukanzoto may offer an effective pharmacological approach to treat chemotherapy-induced metoclopramide-uncontrolled hiccups.

is largely unsatisfactory, and side effects are common [2].

Shakuyakukanzoto, which is composed of *Glycyrrhizae radix* and *Paeoniae radix*, has been traditionally used in North-East Asian countries as an antispasmodic drug for the treatment of skeletal muscle cramps and intestinal cramps [5]. This classical formula is derived from the ancient clinical text Shang Han Lun by Zhang Zhongjing, a well-known physician of traditional Chinese medicine in the third century. Although the precise mechanism is still unknown, shakuyakukanzoto may normalize the intracellular and extracellular potassium balance, while the sodium-potassium pump promotes potassium influx into the myofibers [9]. This may be a part of the mechanism for resolving muscle cramps [9].

Much clinical evidence has shown that shakuyakukanzoto has a beneficial effect on muscle cramps arising from different causes [10-13]. It is well known that the beneficial effect of shakuyakukanzoto on muscle cramps appears soon after taking this medicine [10]. There have been no reports in the English literature, however, on the use of shakuyakukanzoto to treat patients with chemotherapy-induced hiccups. In 88.5% of the chemotherapy courses in this study, chemotherapy-induced metoclopramide-uncontrolled hiccups disappeared partially or completely. Interestingly, the effect of shakuyakukanzoto on metoclopramide-uncontrolled hiccups appeared within a few hours of administration of this drug, irrespective of age, type of lung cancer, and first or later times of shakuyakukanzoto administration. This prompt effect on hiccups resembled the effect of shakuyakukanzoto on muscle cramps.

In this study, we showed that a short treatment period of shakuyakukanzoto was sufficient, spanning a few days; a long-term prescription of shakuyakukanzoto was not necessary for the control of chemotherapy-induced hiccups.

Hypokalemia is a side effect that is associated with long-term continuous use of shakuyakukanzoto. However, this side effect should not be a cause of concern given that the long-term continuous use of shakuyakukanzoto is not necessary for hiccup control the effect of shakuyakukanzoto was also low in chemotherapy courses requiring concomitant medications.

The reason why shakuyakukanzoto was more effective in chemotherapy for SCLC than for adenocarcinoma is not known and was beyond the scope of this study. In addition, there is no clarity on why it was more effective in platinum-containing chemotherapy than in non-platinum chemotherapy. We suspect that chemotherapy regimens could be involved.

This study has certain limitations. The retrospective design without a large number of patients limited the generalizability of the results. This was not a randomized controlled trial, and the indications of chemotherapy, whether shakuyakukanzoto only or shakuyakukanzoto in combination with other drugs for hiccup treatment should be used, were not provided. In addition, this study included only male patients. However, the results obtained in this study were those in unselected consecutive patients in daily clinical practice.

In conclusion, we believe that shakuyakukanzoto offers an effective pharmacological approach for treating chemotherapy-induced hiccups because of its therapeutic rationality and acceptable side effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mito Kyodo General Hospital (No. 15-26).

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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