

Effect of rikkunshi-to treatment on chemotherapy-induced appetite loss in patients with lung cancer: A prospective study

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Abstract. The aim of the present study was to investigate the effect of rikkunshi-to, a Japanese herbal medicine, on post-chemotherapeutic appetite loss. Patients with unresectable lung cancer, who were treated with carboplatin (CBDCA)-containing, cisplatin (CDDP)-containing or non-platinum chemotherapy between 2011 and 2014, were recruited for the prospective study. For each course of chemotherapy, the patients were randomized into two groups, with or without a rikkunshi-to prescription. In patients treated with CBDCA-containing chemotherapy, food intake at day 7 following the initiation of chemotherapy in the rikkunshi-to treatment group was significantly higher compared with the group not treated with rikkunshi-to ($P=0.0078$). However, a significant improvement in food intake with rikkunshi-to treatment was not observed in the CDDP-containing and non-platinum chemotherapy groups. An improved assessment of the incidence rate of chemotherapy-induced appetite loss is essential for achieving adequate control. The results of the present study indicated the possibility of the clinical application of rikkunshi-to for improving post-chemotherapeutic appetite loss.

Introduction

Rikkunshi-to, a Japanese herbal medicine, is known to have a beneficial effect on the gastric mucosa (1). By the development of novel antiemetic agents such as aprepitant, a high control rate of chemotherapy-induced nausea and vomiting was achieved. However, chemotherapy-induced appetite loss has been one of the uncontrolled adverse events and any promising drugs targeting such appetite loss have not yet been developed. Recently, attention has been focused on the appetite-stimu-

lating effects of rikkunshi-to (2), and the mechanisms through which rikkunshi-to improves appetite have been clarified in previous studies (3-7). However, to the best of our knowledge, no previous study has investigated the potential clinical role of rikkunshi-to in improving the food intake of patients with lung cancer undergoing chemotherapy treatment. Therefore, the aim of the present study was to investigate the effect of rikkunshi-to on post-chemotherapeutic appetite loss. The effects on food intake and body weight were examined in patients with lung cancer who were undergoing treatment with chemotherapy. The serum albumin levels and total protein levels were also assessed in order to evaluate the effect of rikkunshi-to on the nourishment state of the patients.

Patients and methods

Patients. This prospective observational study was conducted at the Mito Medical Center (Mito, Japan) between October 2012 and April 2014. Patients with unresectable lung cancer, who were admitted to the 2-WEST Ward of the hospital and treated with cisplatin (CDDP)-containing, carboplatin (CBDCA)-containing and non-platinum chemotherapies, were recruited for participation in the study. Written informed patient consent was obtained from the patient. During each course of chemotherapy, the patients were randomly divided into two groups. Patients received rikkunshi-to treatment for some chemotherapeutic cycles and not for others. One group received a rikkunshi-to (TJ-43; Tsumura & Co., Tokyo, Japan) prescription, which was administered at 7.5 g/day, t.i.d. (three doses at 2.5 g per day.), prior to meals for seven days, while the other group did not receive rikkunshi-to treatment. This study was approved by the Ethics Committee of the Mito Medical Center, University of Tsukuba, Mito, Japan.

Assessment of experimental parameters. Food intake was evaluated in the patients with or without a prescription of rikkunshi-to. Documentation of the total food intake for each meal was performed by the nursing staff of the 2-WEST Ward, and the percentage of food intake was subsequently calculated. An estimation of the daily dietary intake of staple food and the main dish of every three meals in hospital was recorded by nurses and was summed up to rate the dietary intake (range 0 to 100). In addition, the levels of serum albumin and total serum

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Table I. Overall characteristics of the patients included in the study.

Characteristics	Study population
Median age (range), years	67 (41-88)
Gender (male/female), n	25/23
Pathology	
Adenocarcinoma	29 patients, 81 courses
Small cell lung cancer	15 patients, 53 courses
Other	4 patients, 6 courses

protein, and the body weight of the patients, were measured prior to and at day 7 following the initiation of chemotherapy. The experimental protocols of the current study were approved by the Ethics Committee of the Mito Kyodo General Hospital, and informed consent was obtained from all patients prior to their participation in the study.

Statistical analysis. The Mann-Whitney U test was used to compare the daily food intake between the two groups of patients (with or without rikkunshi-to therapy) and the software SPSS 10.1 for Windows (SPSS, Chicago, IL, USA). In addition, a non-parametric test was used to compare the change in the levels of serum albumin and total serum protein, and the body weight of the patients. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. During the study period, 140 courses of chemotherapy in 48 patients were analyzed. All the courses were performed in an inpatient setting. The patient characteristics are shown in Tables I and II. The median age of the 48 patients was 64 years (range, 41-88 years). Of the 48 patients, 25 were male and 23 were female; 29 cases were diagnosed as lung adenocarcinoma, while 15 cases were diagnosed as small cell lung cancer. Amongst the other 4 patients, 2 cases had large cell carcinomas, 1 case had squamous cell carcinoma and 1 case had adenosquamous cell carcinoma. In total, 91 courses were CBDCA-containing chemotherapy (64 with rikkunshi-to and 27 without rikkunshi-to), 21 courses were CDDP-containing chemotherapy (10 with rikkunshi-to and 11 without rikkunshi-to) and 28 course were non-platinum chemotherapy (16 with rikkunshi-to and 12 without rikkunshi-to). In order to evaluate the effect of rikkunshi-to efficiently, patients with CBDCA-containing chemotherapy were allocated into two groups in a ratio of 2:1. In patients with CDDP-containing chemotherapy and those with non-platinum chemotherapy, patients were subdivided in a ratio of 1:1 with and without rikkunshi-to, respectively. With regard to the rikkunshi-to treatment, there were no severe complications observed ($>$ grade 2 in the Common Terminology Criteria for Adverse Events (8).

CBDCA-containing chemotherapy. No statistically significant differences were observed between the two groups of

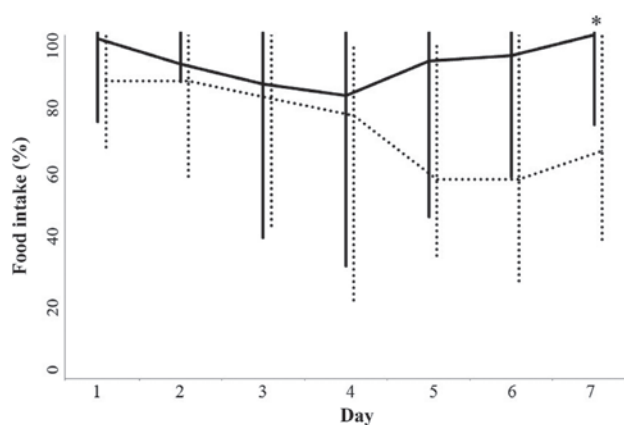


Figure 1. Food intake on days 1-7 following the initiation of carboplatin-containing chemotherapy in the two groups, with (bold line) or without (dotted line) rikkunshi-to therapy. Error bars show the 25th and 75th percentiles. * $P < 0.05$, the without rikkunshi-to group.

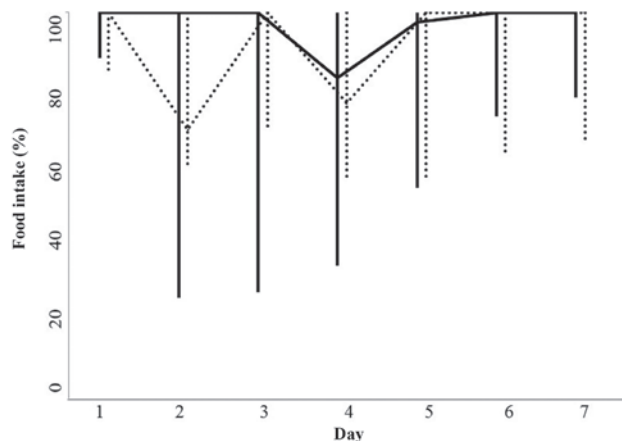


Figure 2. Food intake on days 1-7 following the initiation of cisplatin-containing chemotherapy in two groups, with (bold line) or without (dotted line) rikkunshi-to therapy. Error bars show the 25th and 75th percentiles.

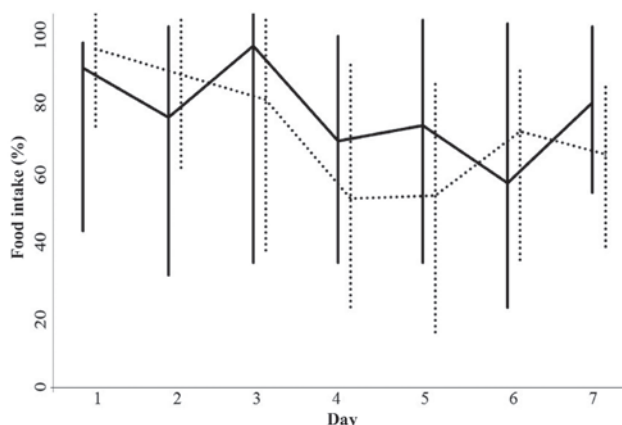


Figure 3. Food intake on days 1-7 following the initiation of non-platinum containing chemotherapy in two groups, with (bold line) or without (dotted line) rikkunshi-to therapy. Error bars show the 25th and 75th percentiles.

patients (with or without rikkunshi-to treatment) in terms of age ($P = 0.6221$), gender ($P = 0.4905$) and histology ($P = 0.3010$).

Table II. Characteristics of the patients treated with or without rikkunshi-to.

Chemotherapy treatment	With rikkunshi-to	Without rikkunshi-to	P-value
CBDCA-containing			
Median age (range), years	74 (41-82)	69 (43-82)	0.6221
Gender (male/female), n	27/37	14/13	0.4905
Pathology ratio AD:SCLC:other, n	30:29:5	13:13:1	0.3010
CDDP-containing			
Median age (range), years	51 (49-67)	51 (50-68)	0.9999
Gender (male/female), n	4/6	7/4	0.3949
Pathology ratio AD:SCLC:other, n	10:0:0	9:2:0	0.4762
Non-platinum			
Median age (range), years	79 (43-88)	67 (61-86)	0.1839
Gender (male/female), n	6/10	8/4	0.2519
Pathology ratio AD:SCLC:other, n	12:4:0	7:5:0	0.4319

CBDCA, carboplatin; AD, adenocarcinoma; SCLC, small cell lung cancer; CDDP, cisplatin.

Food intake between days 1 and 5 following the initiation of chemotherapy in the two groups was not significantly different (Fig. 1). The food intake at day 6 in the rikkunshi-to treatment group was higher compared with the untreated group; however, this difference was not statistically significant ($P=0.0626$). By contrast, the food intake on day 7 following the initiation of chemotherapy was significantly higher in the rikkunshi-to treatment group compared with the untreated group ($P=0.0078$; Fig. 1).

There was no statistically significant difference in the change of the level of serum of albumin between pretreatment and day 7 in the two groups (rikkunshi-to treatment group, median, 0 g/dl; range, -1.1-0.9 g/dl; untreated group, median, 0 g/dl; range, -0.7-0.9 g/dl; $P=0.3028$). In addition, no statistically significant differences in the total serum protein level ($P=0.2604$) and body weight ($P=0.6860$) were observed between pretreatment and day 7 in the patients with and without rikkunshi-to treatment (data not shown).

CDDP-containing chemotherapy. No statistically significant differences were observed in the patients with or without rikkunshi-to therapy with regard to age ($P=0.9999$), gender ($P=0.3949$) and histology ($P=0.4762$). Food intake between days 1 and 7 after the initiation of chemotherapy in the patients with or without rikkunshi-to therapy was not significantly different (Fig. 2). In addition, no statistically significant differences were observed in the serum albumin level ($P=0.5698$), total serum protein level ($P=0.6764$) and body weight ($P=0.7243$) between pretreatment and day 7 in the two groups (data not shown).

Non-platinum containing chemotherapy. No statistically significant differences were identified between the patients with or without rikkunshi-to therapy in terms of age ($P=0.1839$), gender ($P=0.2519$) and histology ($P=0.4319$).

Food intake between days 1 and 7 following the initiation of chemotherapy in the two groups was not significantly different (Fig. 3). Furthermore, no statistically significant differences

were observed in the serum albumin level ($P=0.5569$), total serum protein level ($P=0.9290$) and body weight ($P=0.4153$) between pretreatment and day 7 in the patients with or without rikkunshi-to treatment (data not shown).

Discussion

Despite the development of novel antiemetic agents, such as aprepitant, a considerable proportion of patients receiving chemotherapy continue to experience appetite loss and a decreased food intake (9). In a previous study, a high control rate of nausea and vomiting was achieved through aprepitant administration; however, appetite loss was one of the uncontrolled chemotherapy-induced symptoms (10), which is consistent with the results of additional studies (11,12). At present, a promising drug targeting chemotherapy-induced appetite loss has yet to be developed. However, the ability of rikkunshi-to to increase food intake has been increasingly studied (2). Therefore, the current study investigated the effect of rikkunshi-to administration on post-chemotherapeutic appetite loss.

The mechanism underlying chemotherapy-induced appetite loss has yet to be elucidated. In addition, the mechanism of action of rikkunshi-to on appetite loss following chemotherapy is unclear. However, a number of studies have investigated chemotherapy-induced appetite loss (2,13,14). Hattori *et al* demonstrated that CDDP-induced appetite loss was, similarly to the onset of nausea and vomiting, caused by large amounts of serotonin (5-HT) release, as a result of CDDP administration on 5-HT receptors in the tissue (14). Among the 5-HT receptors, the activation of 5-HT_{2b} and 5-HT_c receptors plays a major role in CDDP-induced appetite loss (14). Following activation of these two receptors, there is reduced gastric and hypothalamic secretion of the appetite-stimulating hormone, ghrelin (2). There is substantial evidence demonstrating the efficiency of exogenous ghrelin and synthetic ghrelin agonists in the clinical treatment of appetite loss (13,14). The endogenous ghrelin signal-enhancer, rikkunshi-to, is also

expected to play a significant role in preventing appetite loss and improving food intake following chemotherapy in patients with various types of cancer (3,13,14).

The present study evaluated food intake in patients undergoing three types of chemotherapeutic regimens. In the patients treated with CBDCA-containing chemotherapy, an improvement in food intake was observed at day 7, although improvements in food intake were not observed during days 1-5. In the patients who did not receive rikkunshi-to treatment, food intake decreased gradually following the initiation of chemotherapy and was lowest at days 5-6. By contrast, in the patients who were administered rikkunshi-to treatment, an improvement in food intake was observed from day 4. However, no improvement in food intake was observed in the patients treated with CDDP-containing chemotherapy. In the two groups of patients, with or without rikkunshi-to administration, food intake decreased at days 3-4, but improved on day 5. The reason why a significant difference in food intake was not observed between the two groups of patients may be associated with the younger age of the patients treated with this chemotherapy regimen compared with the other two regimens, although there were significant differences in the characteristics of patients in both groups (with or without rikkunshi-to). In all the patients undergoing non-platinum chemotherapy, food intake on day 1 was lower when compared with the patients in the other chemotherapy groups. The food intake decreased gradually until day 5 in the patients not receiving rikkunshi-to treatment. In the patients treated with rikkunshi-to, food intake improved at day 3 and 7, however, the difference between the two groups was not statistically significant. In the non-platinum chemotherapy regimen, the poorer clinical condition of the patients and that a chemotherapy line performed second or later may have influenced the poor control of food intake in both groups of patients. In all the chemotherapy regimen groups, no improvements in the levels of serum albumin and total serum protein, or patient body weight, were observed.

Although the present study demonstrated an improvement in food intake with rikkunshi-to administration at day 7 in the patients undergoing CBDCA-containing chemotherapy, whether rikkunshi-to has sufficient power to improve food intake is unable to be concluded, since the results may have been influenced by the small sample size included in the present study. Thus, the results of the current study require conformation in well-planned, larger-scale prospective studies.

Appetite loss remains a problem for patients with lung cancer undergoing chemotherapy, and the incidence rate may be underestimated by medical staff. An improved assessment of the incidence rate of chemotherapy-induced complications is essential for achieving adequate control. In conclusion, the present study indicated the possibility of using rikkunshi-to in clinical practice to improve appetite loss in patients with lung cancer undergoing chemotherapy.

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