Investigational New Drugs (2020) 38:485–492
https://doi.org/10.1007/s10637-019-00836-x

PHASE II STUDIES

Prospective, randomized, cross-over pilot study of the effects of Rikkunshito, a Japanese traditional herbal medicine, on anorexia and plasma-acylated ghrelin levels in lung cancer patients undergoing cisplatin-based chemotherapy

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Received: 5 March 2019 / Accepted: 9 July 2019 / Published online: 19 August 2019

Summary

Purpose Anorexia induced by cytotoxic chemotherapy on delayed phase is a highly frequent adverse event. We aimed to determine the effects of rikkunshito (RKT) on chemotherapy-induced anorexia (CIA) in patients with lung cancer. *Methods* This prospective, randomized, cross-over pilot trial included 40 lung cancer patients scheduled to undergo cisplatin-based chemotherapy and randomized to either a group given RKT 7.5 g/day for 14 days (Group A, $N = 20$) or not (Group B, $N = 20$), then the treatments were switched. All patients received dexamethasone, palonosetron hydrochloride and aprepitant regardless of group assignment. Rescue drugs were allowed as required. The primary and key secondary endpoints were changes in caloric intake and in plasma acylated ghrelin (AG) levels, respectively. Average daily caloric intake during days 3 to 5 was compared with that on day 1 of each course. *Results* The primary and key secondary endpoints were analyzed in 31 patients (per protocol population) completing the study. Reduction rate of caloric intake was lower in RKT, than in control courses (18% vs. 25%, $P = 0.025$). Plasma AG levels significantly declined between days 1 and 3 in RKT (12.3 vs. 7.5 fmol/mL, $P < 0.001$) and control (10.8 vs. 8.6 fmol/mL, $P < 0.001$) courses. However, those obviously increased to 8.5 fmol/mL ($P = 0.025$) by day 5 in RKT course but not in control course (7.7 fmol/mL, $P = 0.28$). *Conclusions* Rikkunshito could mitigate CIA and ameliorate plasma AG levels during the delayed phase of CDDP-based chemotherapy in lung cancer patients. Clinical trial registration numbers: UMIN000010748.

Keywords Antiemetic · Cytotoxicity · Malignancy · Kampo · Cisplatin · Appetite stimulation

Abbreviations

CDDP	Cis-dichloro-diamine-platinum
CI	Cranial irradiation
CIA	Chemotherapy-induced anorexia
CINV	Chemotherapy-induced nausea and vomiting
FLIE	Functional Living Index-Emesis
HEC	Highly emetogenic chemotherapy
HT_3	Hydroxytryptamine$_3$
NK-1	Neurokinin-1
QOL	Quality of life
RKT	Rikkunshito

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Introduction

Highly emetogenic cis-dichloro-diamine-platinum (Cisplatin; CDDP) is a key chemotherapeutic drug with formidable antineoplastic effects on lung cancer. However, chemotherapy-induced nausea and vomiting (CINV) are major adverse effects of CDDP that can severely impair the quality of life (QOL) of patients. Combining a 5-hydroxytryptamine$_3$

(HT_3) receptor antagonist with corticosteroid could significantly improve CINV because various types of receptors in the supraspinal central nervous system are related to CINV [1]. In addition, a novel antiemetic neurokinin-1 (NK-1) receptor antagonist has achieved excellent control of CINV [2]. Therefore, antiemetic guideline recommends a prophylactic combination of these three agents that target multiple molecular pathways of emesis during the administration of highly emetogenic chemotherapy (HEC); these include a 5-HT_3 receptor antagonist, dexamethasone and a NK-1 receptor antagonist [3]. Recently, a new oral fixed-combination antiemetic drug was developed which is called NEPA comprising netupitant (300 mg), a highly selective NK-1 receptor antagonist, and palonosetron (0.50 mg), a pharmacologically and clinically distinct 5-HT_3 receptor antagonist**.** NEPA targets dual antiemetic pathways and improves delayed nausea [4] in patients receiving cisplatin-based HEC [5].

Most patients receiving HEC experience appetite loss, even though the antiemetic combination therapy has clearly decreased the incidence of CINV [6, 7]. Chemotherapy-induced anorexia (CIA), even in the absence of CINV, remains an important problem to be solved from the perspectives of maintaining adequate patient nutrition and completing chemotherapy courses. This adverse effect must be overcome, however, few drugs that specifically target CIA are not yet available [6, 8].

Rikkunshito (RKT) is a Japanese traditional herbal medicine that is widely applied to treat upper gastrointestinal symptoms. The ability of RKT to potentiating the orexigenic action of the appetite-stimulating hormone, ghrelin, has recently received focus [9], and several studies have clarified the mechanisms of appetite improvement through ghrelin signaling [10–14]. Additionally, RKT suppresses cisplatin-induced anorexia via 5-HT_2 receptor antagonism in rats [10] and in humans [15].

We hypothesized that adding RKT to the standard antiemetic therapy might affect appetite loss and reduced food intake, through upregulating plasma acylated ghrelin (AG) levels in patients with lung cancer undergoing HEC. We estimated objectively food intake and plasma AG levels and evaluated the effects on daily activities by CINV using a patient-subjective scale.

Materials and methods

Study design

This prospective, randomized, cross-over pilot trial was assembled according to the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. The study protocol and informed consent form were approved by the Ethics Committee of Hiroshima University (Rin 389).

Enrollment began in July 2013. The last patient completed the study in March 2016. The patients were randomly assigned after registration to either group A ($N = 20$) or group B ($N = 20$). Patients in group A received RKT 7.5 g/day (TJ-43; Tsumura & Co., Tokyo, Japan) for a 14-day treatment period (days 1–14), and those in group B did not receive RKT (Fig. 1). This period was followed by a washout of 1–2 weeks. After the washout, treatments were switched. The study treatment consisted of RKT 2.5 g, administerd orally, in the fasting state, three times daily, before each meal for 14 consecutive days.

Written informed consent was obtained from all participating patients. This study was registered in the University Hospital Medical Information Network (Registration number, UMIN000010748).

Patients

Forty patients who had histologically confirmed diagnosis of lung cancer and were scheduled to receive at least two courses of chemotherapy with CDDP were recruited at two departments of Hiroshima University hospital. The inclusion criteria were as follows: Eastern Cooperative Oncology Group performance status 0 or 1; age between 20 and 80 years; life expectancy ≥3 months at screening; adequate major organ and adequate hepatic function defined as aspartate amino transferase and alanine amino transferase concentrations ≤100 IU/L, total bilirubin ≤1.5 mg/dL, adequate renal function defined as creatinine ≤1.5 mg/dL, absolute neutrophils >1500/mm^3, platelets >100,000/mm^3 and hemoglobin >9.0 g/dL within 21 days before recruitment. Patients with known brain metastases or diabetes were included. All regimens and cycles of ongoing chemotherapy were allowed.

Exclusion criteria comprised a history of gastric surgery, administered with other types of Japanese traditional herbal medicines within 2 weeks before recruitment, scheduled to undergo radiotherapy, oral intake inability, simultaneous multiple organ cancers, allergy to RKT or considered ineligible by an investigator. Women who were pregnant, breastfeeding, or of childbearing potential were not enrolled. Patients were

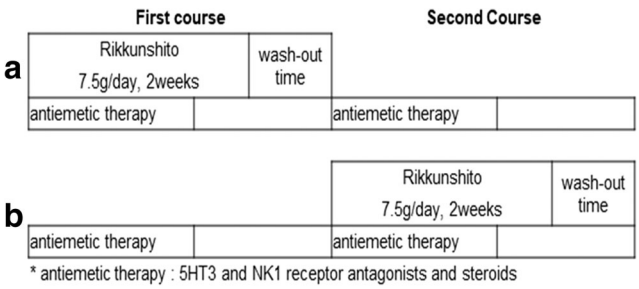

Fig. 1 Study protocol. Patients in groups **a** and **b** administered with rikkunshito on days 1–14 of first and second courses of CDDP-based chemotherapy

randomly assigned (1:1) to group A or B by a centrally managed, computed-generated randomization algorithm. No identical placebo drug was provided.

Procedures

All patients received dexamethasone, palonosetron hydrochloride ($5HT_3$ receptor antagonist) and aprepitant (NK-1 receptor antagonist) without olanzapine regardless of group assignment. Dexamethasone (8.25 mg) was administered intravenously on day 1, followed by 3.3 mg intravenously on days 2 and 3, and 4 mg orally on days 4 and 5. Palonosetron (0.75 mg) was administered intravenously on day 1. Aprepitant (125 mg) was administered orally on day 1, followed by 80 mg orally on days 2 and 3. Any rescue drugs were allowed as required.

Endpoint

The primary endpoint was the changes in daily caloric intake. The key secondary endpoint was the changes in acylated ghrelin levels. The other secondary endpoints were Functional Living Index-Emesis (FLIE) scores to determine the effects of RKT on patients' daily activities, the incidence of vomiting, adverse events, and clinically significant changes in laboratory values.

Efficacy assessments

To precisely measure daily caloric intake including snacks between meals, all patients recorded their total food intake from days 1 through 5 (0–120 h). Nurses checked their intake records and a nutritionist estimated daily dietary intake as calories. Average daily caloric intake during days 3 to 5 (delayed phase) was compared with that on day 1 (early phase) defined as a baseline and reduction rate (%) was calculated in RKT and control courses, respectively.

Blood samples collected before breakfast on days 1, 3 and 5 were immediately mixed in chilled tubes containing disodium ethylenediamine tetra-acetic acid (EDTA) and aprotinin, then promptly separated by centrifugation (3,000 rpm at 4 °C) for plasma sampling. The supernatants were acidified with 10% volume of 1 mol/L hydrochloric acid and stored at −50 °C. Ghrelin levels were determined using Active Ghrelin or Desacyl Ghrelin Enzyme - Linked Immunoassay Kits (LSI Medience Corporation, Tokyo, Japan).

The effect of CINV on daily activities following chemotherapy was measured by the Japanese version of the FLIE questionnare, a validated patient self-assessment tool. The FLIE comprises nine items in each of two domains, nausea and vomiting. Patients marked responses to each of 18 items with a vertical line on a 100-mm visual analogue scale, with anchors being none and a great deal, and completed the FLIE questionnaires between days 1 through 6. Scores range from 18 to 126, with a higher score indicating a more negative effect on daily activities. A total score under 36 represents no effect of CINV. The questionnaires completed on day 2 were reflected the acute effect of CINV on daily life activities during the first 24 h (day 1) following chemotherapies. Those completed between days 4 through 6 were also reflected the delayed effect of CINV on daily life activities during days 3–5 (3-day assessment).

Statistical analyses

The primary aim of the present study was to demonstrate the efficacy of RKT on CIA based on the reduction rate of daily caloric intake during the delayed phase. The primary efficacy analysis comparing between RKT and control courses in each patient who completed the present study, was carried out using a Wilcoxon signed rank test. RKT was to be declared superior if the two-sided P – values was ≤ 0.05 and in favor of RKT. The sample size was estimated to be 40 patients (20 per group). Because there were no experience and previous reports performing the examination with our study design, based on our historical data, a sample size of 16 assessable patients per group was needed to ensure 90% power to detect the 20% difference of the reduction rate of daily caloric intake, using the significance level $(\alpha) = 5\%$ and the detected level $(1 - \beta) = 80\%$. This number was increased to 20 per group to ensure an adequate number of assessable patients.

Changes in plasma AG levels were also compared using the Wilcoxon signed rank test (days 1 vs. 3 and 3 vs. 5) for each course to determine key secondary outcomes. Fisher's Exact Test and Wilcoxon signed rank test were used to compare the proportion of no impact on daily life and scores assessed for the FLIE nausea-specific domain between RKT and control courses on early phase (day 1) and delayed phase (days 3–5). The full analysis set population was defined as all the patients who were randomized and received protocol-required HEC and study treatment. The safety analysis population consisted of all the patients who received the RKT.

Demographics and baseline characteristics are summarized using descriptive statistics. Data are presented as numbers (N) or ratios (%) unless otherwise stated. Continuous variables were compared using Mann-Whitney U test and FLIE scores using paired T-test. Frequencies were compared using Fisher's Exact test for categorical variables when appropriate. All statistical tests were two-sided; P values of <0.05 were taken to represent statistically significant differences unless otherwise specified. All data were statistically analyzed using EZR (Kanda Y, Saitama Medical Centre, Jichi Medical University, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0).

Results

Forty eligible patients were randomly assigned to group A or B. One patient in group A became acutely allergic to the chemotherapy drugs on day 1 of the former course and dropped out of the study. Therefore, data from 39 patients (median age, 67 years; male, $N = 35$; female, $N = 4$) were analyzed. Eight patients (groups A and B: $N = 4$ each) received only one course of chemotherapy (Table 1, Fig. 2). The primary endpoint was analyzed in 31 patients (per protocol population) who completed the study. The key secondary endpoint was also analyzed in the same 31 patients. Due to adverse chemotherapy-induced hemotoxicity, doses had to be reduced in one patient on a CDDP/gemcitabine regimen and two on a CDDP/TS-1 regimen during the latter course. Safety was analyzed in 35 patients who received RKT (group A, $N = 19$; group B, $N = 16$).

Table 1 shows the baseline characteristics and all regimens administered to the patients. The major histological type was adenocarcinoma (54%), followed by small cell carcinoma (18%). Most patients had advanced cancer, but others with preoperative, postoperative or recurrent status were also included. Eight of the 39 patients had brain metastasis. Among four patients diagnosed before the present study period, one and three had received cranial irradiation (CI), and γ-knife surgery, respectively. One patient had received CI before enrollment in the present study and another had undergone surgery followed by CI among the remaining four patients with brain metastasis concurrently diagnosed at the enrollment. Concomitant complicating conditions comprised hypertension ($N = 15$), diabetes

Table 1 Characteristics of the patients and chemotherapeutic regimens

Variables	All ($n = 39$)	Group A ($n = 19$)	Group B ($n = 20$)	*P*
Gender				0.34
Male	35 (90%)	16 (84%)	19 (95%)	
Female	4 (10%)	3 (16%)	1 (5%)	
Median age (y),	67 (34–78)	69 (59–78)	67 (34–78)	0.56
Performance status				0.45
0	30 (76%)	16 (78%)	14 (70%)	
1	9 (24%)	3 (22%)	6 (30%)	
Body mass index	23 (16–28)	23 (19–28)	22(16–25)	0.18
Tobacco use				0.34
Never	2 (5%)	0 (0%)	2 (10%)	
Previously	29(74%)	13 (68%)	16 (80%)	
Currently	8(21%)	6 (32%)	2 (10%)	
Histology				0.74
Adenocarcinoma	21 (54%)	12 (63%)	9 (45%)	
Squamous cell carcinoma	5 (13%)	1 (5%)	4 (20%)	
Small cell carcinoma	7 (18%)	3 (16%)	4 (20%)	
Large cell neuroendocrine carcinoma	2 (5%)	1 (5%)	1 (5%)	
Other	4 (10%)	2 (11%)	2 (10%)	
Chemotherapy				0.45
Induction	9 (23%)	5 (26%)	4 (20%)	
Adjuvant	9 (23%)	3 (16%)	6 (30%)	
Recurrent cancer	3 (8%)	1 (5%)	2 (10%)	
Advanced cancer	18 (46%)	10 (53%)	8 (40%)	
Chemotherapeutic regimens (Cisplatin plus)		Reasons for non-compliance		
Pemetrexed/bevacizumab	13 (33%)	A, Prognosis; B, Renal insufficiency		
Irinotecan	4 (11%)	A, Liver insufficiency		
Etoposide	5 (13%)	B, Febrile neutropenia		
Pemetrexed	7 (18%)	A and B, Renal insufficiency		
		A, Gastric ulcer bleeding		
Gemcitabine	1 (2%)			
Vinorelbine	3 (8%)	B, Renal insufficiency		
TS-1	6 (15%)			

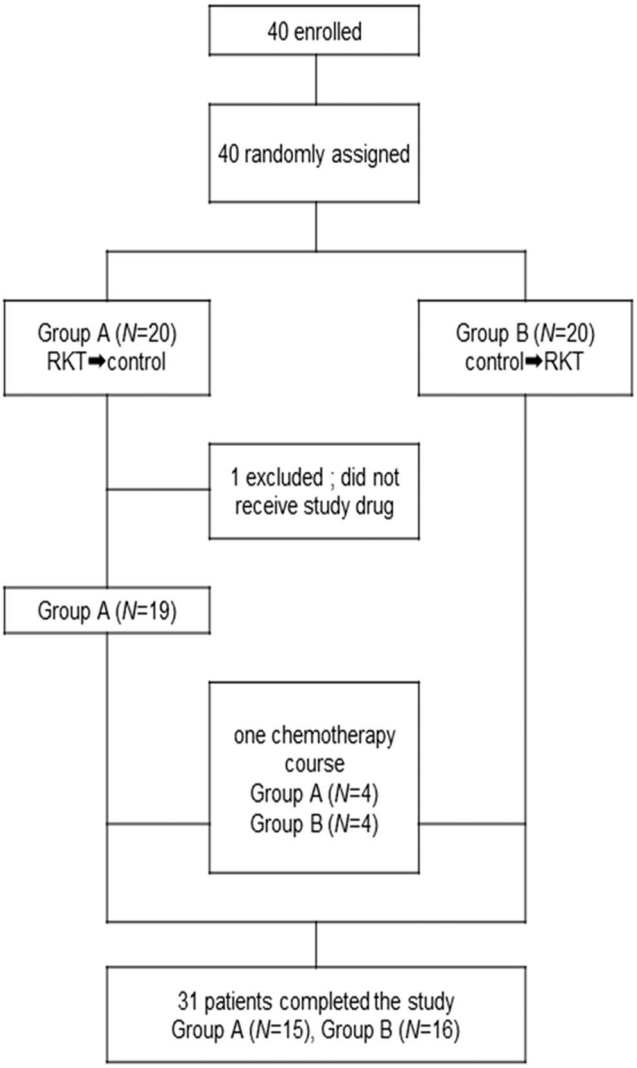

Fig. 2 Flow diagram of patients throughout the study

mellitus ($N = 8$), hyperlipidemia ($N = 6$), cerebral infarction ($N = 4$), atrial fibrillation ($N = 4$), myocardial infarction ($N = 2$) and angina pectoris ($N = 2$). Baseline characteristics did not significantly differ between groups A and B.

Median dietary intake on day 1 vs. days 3–5 (delayed phase) was 1,553 vs. 1,233 kcal ($P < 0.001$; Fig. 3a) in RKT course and 1,692 and 1,191 kcal ($P < 0.001$; Fig. 3b) in control course. The reduction rate of daily caloric intake was significantly lower in the RKT, than in the control course (18% vs. 25%; $P = 0.025$; Fig. 3c). Plasma AG levels in the 31 patients completing the study obviously declined between days 1–3 in both RKT (12.3 vs. 7.5 fmol/mL, $P < 0.001$) and control (10.8 vs. 8.6 fmol/mL, $P < 0.001$) courses. However, plasma AG levels significantly increased by day 5 in the RKT (8.5 fmol/mL, $P = 0.025$), but not in the control (7.7 fmol/mL, $P = 0.28$) course (Fig. 3d, e).

Analysis using the FLIE questionnaire was performed on 30 patients because one patient's FLIE diary could not be received. The rates of patients affected by CINV were not significantly different between RKT and control courses in both early and delayed phase (early phase: RKT, 10% vs. control, 13%, $P = 1$; delayed phase: RKT, 30% vs. control, 33%, $P = 1$) (Fig. 4a, b). In the comparison of FLIE scores, there tended to be different between the courses in the delayed phase (RKT: 10.7 (9–20.1), control: 11.8 (9.5–26.3), $P = 0.074$) (Table 2). The goal of no vomiting in the entire study period was achieved in 96% of the 31 patients. No adverse events and clinically significant changes in laboratory values were associated with RKT.

Discussion

The present study included patients with preoperative, postoperative, recurrent and advanced status. Patients with recurrent or advanced cancer had already received various therapeutic regimens. Our prospective, randomized, cross-over pilot study demonstrated that regardless of background, the oral administration of RKT in addition to the standard antiemetic combination therapy of corticosteroid, NK-1 receptor antagonist, and 5-HT_3 receptor antagonist could mitigate reduced caloric intake and ameliorate plasma AG levels during the delayed phase of CDDP-based chemotherapy.

Rikkunshito is a Japanese traditional herbal medicine (Kampo) that is extracted with hot water from a mixture of eightcrude [9]. Matsumura et al. showed that RKT significantly increases plasma AG levels in healthy human volunteers and healthy mice and upregulates ghrelin mRNA expression in the mouse stomach [16]. Ghrelin, a 28-amino acid peptide discovered in 1999 by Kojima et al. [17] is an endogenous ligand of the growth hormone secretagogue receptor. Furthermore, ghrelin is structurally similar to motilin [6] and it is an appetite stimulatory signal from the stomach that triggers a positive energy balance through a central mechanism involving hypothalamic neuropeptides [12]. The brain-gut axis is influenced by various factors, but ghrelin plays a major role in linking the enteric and central nervous systems [18].

The mechanism underlying CIA has been elucidated. Therapies based on CDDP induce appetite loss through excessive serotonin (5-HT) relapse onto 5-HT receptors in tissues [7]. Especially, the activation of 5-HT_{2b} and 5-HT_{2c} receptors plays an important role [19] because it results in reduced gastric and hypothalamic secretion of the appetite-stimulating hormone, ghrelin [6]. Some studies have shown that RKT induces endogenous ghrelin secretion via its component flavonoids including heptamethoxyflavone, hesperidin and isoliquiritigenin, which antagonize 5-HT_{2b} and 5-HT_{2c} receptors [7, 20]. Furthermore, another component of RKT, 10-gingerol, has inhibitory activity against ghrelin deacylating enzymes [21, 22]. Therefore, it was important to measure plasma AG levels simultaneously with caloric intake.

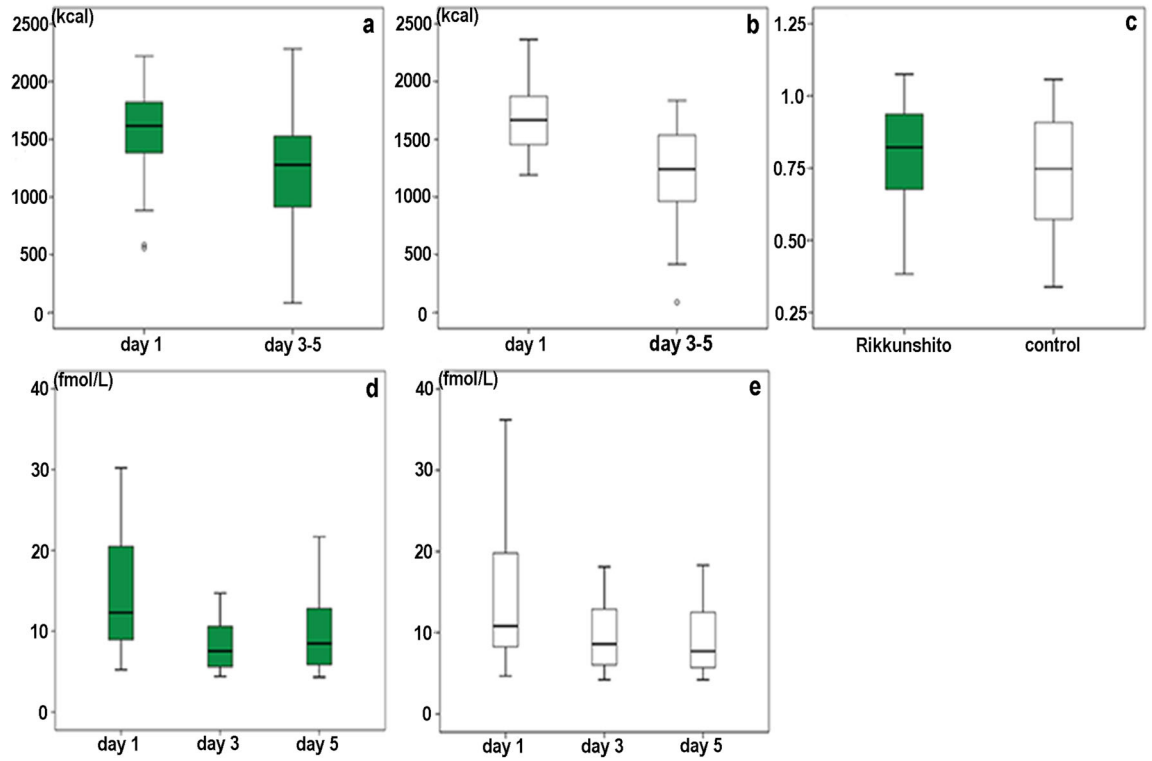

Fig. 3 Caloric intake and plasma acylated ghrelin levels. Median intake on day 1 vs. days 3–5 (delayed phase) of (**a**) RKT (1,553 vs. 1,233 kcal,) and (**b**) control (1,692 vs. 1,191 kcal) courses ($P < 0.001$ for both) in 31 patients who completed the study. Rate of decreased caloric intake (**c**) is significantly higher in control, than in rikkunshito course (25% vs. 18%, $P = 0.025$). Significant decline in plasma acylated ghrelin levels between days 1 and 3 in (**d**) Rikkunshito and (**e**) control courses (12.3 vs. 7.5 fmol/mL, and 10.8 vs. 8.6 fmol/mL, respectively, $P < 0.001$ for both). Plasma acylated ghrelin values increased by day 5 in rikkunshito, but not in control course (8.5 fmol/mL, $P = 0.025$ and 7.7 fmol/mL, $P = 0.28$, respectively)

To assess delayed-onset CIA, we analyzed the reduction rate of daily caloric intake in 31 patients who completed this study. Furthermore, in order to investigate the relationship with dietary intake, plasma AG levels were measured on days 1, 3 and 5. In both RKT and control courses, AG levels from day 1 to 3 significantly decreased and dietary intake during the delayed phase was significantly reduced. Notably, AG levels significantly increased from day 3 to 5 in the RKT, but not in the control course. The reduction rate of daily caloric intake in the RKT course was significantly lower than that in the control course. These findings could suggest that RKT mitigates the decrease in caloric intake due to improved AG levels during the delayed phase of CDDP-based chemotherapy regimens**.** To the best of our knowledge, there was no previous study that the effects of RKT on daily caloric intake and plasma AG values have been simultaneously evaluated in lung cancer patients undergoing only HEC. Improvement of plasma AG levels during the delayed phase could be responsible for the beneficial effect of RKT on CDDP-induced anorexia.

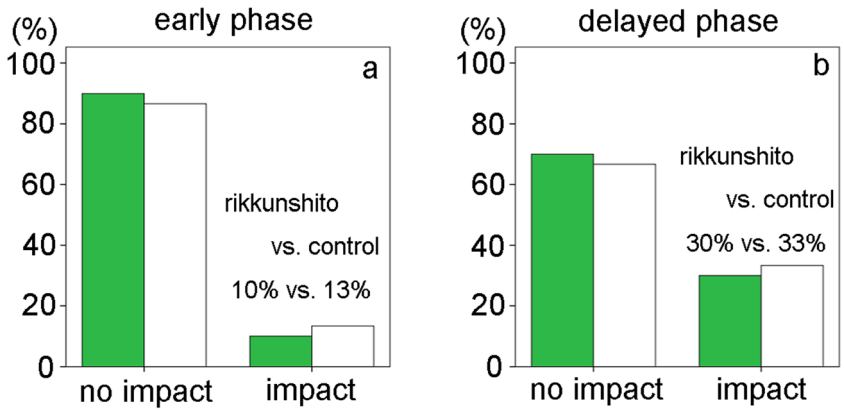

Fig. 4 Functional Living Index-Emesis. The rates of patients affected by CINV were not significantly different between RKT and control courses in both early (**a**) and delayed phase (**b**) (early phase: RKT, 10% vs. control, 13%, $P = 1$; delayed phase: RKT, 30% vs. control, 33%, $P = 1$)

Table 2 Functional Living Index-Emesis scores

	Rikkunshito	Control	*P*
Early phase*	9 (9–9)	9 (9–15.5)	0.15
Delayed phase*	10.7 (9–20.1)	11.8 (9.5–26.3)	0.074

*Median (interquartile range)

The FLIE score is a subjective evaluation of patients' nausea, appetite, and emotional function. Most patients indicated that CINV did not affect their daily activities on early phase in both RKT and control courses. The rates of patients who had no impact on daily life by CINV were not also significantly different between the courses on delayed phase, although, in the comparison of FLIE scores, there tended to be different between RKT and control courses on the delayed phase. Symptoms of patients affected by CINV could not be clinically alleviated by adding RKT to standard antiemetic therapy.

Patients with advanced cancer frequently experience anorexia and cachexia, which are associated with reduced food intake, altered body composition, decreased functionality and a worse QOL [23]. Plasma AG levels are higher in cachectic, than in non-cachectic patients [24]. Rikkunshito not only activates ghrelin secretion but also enhances ghrelin signaling via enhanced binding between AG and growth hormone stimulating receptor 1a [25]. The RKT component, atractylodin, has an allosteric effect on ghrelin receptors. Anamorelin, an orally active, high-affinity, selective ghrelin-receptor agonist, significantly increases lean body mass, but not handgrip and strength in patients with inoperable stage III or IV non-small-cell lung cancer and cachexia [26]. Therefore, RKT and anamorelin might offer treatment options for patients with cancer-induced anorexia and cachexia, which might otherwise reduce tolerance of, or responsiveness to therapy and result in decreased survival [27, 28].

Limitations

There are some limitations to the present study. First, caloric intake on day 1 in each course was taken as the baseline for comparing average daily caloric intake during days 3 to 5. We recognize that baseline caloric intake should be estimated more carefully because it largely affects the reduction rate of oral intake. Many studies reported that most patients receiving HEC achieved good control in the acute phase with standard antiemetics combination therapy [3–5]. All patients in this study received CDDP after lunch on day 1 regardless of regimens. Therefore, we considered that the effects of CDDP on appetite were relatively small on day 1 and thus the definition is valid. Second, this study included patients with a history of receiving chemotherapy multiple times. It is well known that the existence of a history of chemotherapy affects the incidence of CINV. Patient's anxiety from previous experience is a risk factor for the future development of CINV. An evaluation between treatments in patients who receive HEC for the first time should be planned in future studies. Third, RKT comprises many components of which the active ingredients and their pharmacological functions are gradually being elucidated. Thus, additional mechanistic evaluations are needed to conclusively determine the effects of RKT. Fourth, identical placebo drug was not used. Fifth, we selected a cross-over design for the present study due to the relatively small sample size. The present findings require confirmation in a large-scale, prospective, double-blind, placebo-controlled randomized trial.

Conclusions

Considering the results of daily caloric intake and acylated ghrelin values, the addition of RKT mitigated reduced caloric intake and ameliorated plasma AG levels during the delayed phase of CDDP-based chemotherapy. Maintaining dietary intake is of importance during chemotherapy with respect to keep physical and psychological status in good condition. Therefore, RKT could be an optimal drug for use in patients undergoing HEC without severe adverse events.

Acknowledgements We are grateful to Takeshi Mimura, Hideaki Hanaki, Keizo Misumi, Norifumi Tsubokawa and Daisuke Ueda (Department of Surgical Oncology) for the important contribution of data analyses, to Kanako Amano and Hisako Oka (Department of Nutrition Management) for the data collection of daily caloric intake, and to Hiroshi Sakurashita (Department of Pharmaceutical Services) for the confirmation of proper drug administration.

Compliance with ethical standards

Conflict of interest We have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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