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Prophylactic effect of rikkunshito, an herbal medicine, for chemotherapy-induced nausea in thoracic cancer patients receiving carboplatin-based chemotherapy

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Rikkunshito has been shown to improve upper gastrointestinal symptoms and anorexia. The aim of this study was to evaluate whether rikkunshito improves chemotherapy-induced nausea in thoracic cancer patients receiving carboplatin (CBDCA)-based chemotherapy. A retrospective before-and-after comparison study was conducted in patients with thoracic cancer receiving the first cycle of CBDCA-based chemotherapy. Among 61 eligible patients, 34 received standard antiemetic therapy with a combination of 5-hydroxytryptamine-3 receptor antagonist and dexamethasone from September 2012 and June 2013 (standard group), while the other 27 received the standard antiemetic therapy plus oral rikkunshito from July 2013 and December 2014 (rikkunshito group). The rates of no nausea showed no significant difference between the standard and rikkunshito group (Overall phase: 64.7 % for standard group *vs* 74.1 % for rikkunshito group, $p = 0.579$). Subgroup analysis indicated that, in female patients, the rates of no nausea in rikkunshito groups was significantly higher than in standard group (overall phase: 44.4 % *vs* 100 %, $p = 0.034$). Rikkunshito did not demonstrate an additional prophylactic effect on standard antiemetic therapy for nausea in patients with thoracic cancer receiving CBDCA-based chemotherapy, but showed a prophylactic effect of nausea in female patients.

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing adverse events in patients receiving cancer chemotherapy. CINV impairs patient quality of life and even therapeutic outcome (de Boer-Dennert et al. 1997). CINV therapy has improved in recent years, owing both to the development of the antiemetic drugs, including 5-hydroxytryptamine-3 receptor antagonists (5-HT_3RA) and neurokinin-1 receptor antagonists (NK_1RA), and to improvements in several clinical practice guidelines for antiemesis, including the Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) (Roila et al. 2016), American Society of Clinical Oncology (ASCO) (Hesketh et al. 2017), and National Comprehensive Cancer Network (NCCN) (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology 2018). Despite these improvements, the control of CINV still remains insufficient for some chemotherapy regimens.

Carboplatin (CBDCA), which is a platinum coordination complex, is used for advanced thoracic cancer, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Although CBDCA is classified as having moderate emetic risk, several recent reports have shown a moderate benefit to the addition of an NK_1RA to dexamethasone (DEX) and a 5-HT_3RA (Hesketh et al. 2016; Tanioka et al. 2013; Yahata et al. 2016; Ito et al. 2014), and triplet antiemetic therapy with dexamethasone, a 5-HT_3RA and NK_1RA was recommended for CBDCA combined chemotherapy after 2016, unlike other moderate emetic risk chemotherapies (Roila et al. 2016; Hesketh et al. 2017; National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology 2018). In their randomized Phase II study for chemotherapy-naïve patients with NSCLC, however, Ito et al. (2014) reported that although aprepitant add-on triple antiemetic therapy showed a better overall complete response rate than standard antiemetic therapy, at 80.3 % *vs* 67.2 % ($p = 0.085$), this triple antiemetic therapy did not significantly improve the frequency of nausea (46.7 % *vs* 58.3 %; $p = 0.200$). Thus, the control of nausea in patients with thoracic cancer receiving CBDCA-based chemotherapy remains insufficient, even despite the use of triplet antiemetic therapy (Ito Y et al. 2014).

Rikkunshito, an herbal medicine, is composed of 8 herbs (*Atractylodis lanceae rhizoma*, *Ginseng radix*, *Pinelliae tuber*, *Hoelen*, *Zizyphi fructus*, *Aurantii nobilis pericarpium*, *Glycyrrhizae radix,* and *Zingiberis rhizoma*) and is used for gastrointestinal disorders such as anorexia, functional dyspepsia and gastroesophageal reflux disease (Tomono et al. 2006; Arai et al. 2012; Tominaga et al. 2012). In a rat model, several indicators indicated that rikkunshito suppressed cisplatin (CDDP)-induced anorexia *via* the blockade of 5-HT_{2B} and 5-HT_{2C} receptors followed by stimulation of ghrelin release, which is an orexigenic hormone (Takeda et al. 2008; Yakabi et al. 2010; Yakabi et al. 2010). Moreover, Ohno et al. (2011) reported that rikkunshito significantly improved the grade of anorexia and dietary intake in gastric cancer patients who received a CDDP and tegafur/gimeracil/oteracil (S-1) combined regimen. These findings suggested that rikkunshito may be useful in ameliorating CINV, especially in improving nausea.

Here, we evaluated the prophylactic effect of rikkunshito for nausea in patients with thoracic cancer receiving CBDCA-based chemotherapy.

2. Investigations and results

2.1. Patient demographics

As shown in Table 1, there were no significant differences in the characteristics of the study patients, including sex, age, height,

Table 1: Patient demographics

	Standard group (N=34)	Rikkunshito group (N=27)	*p* value
Sex (male/female)	25 / 9	20 / 7	0.806 [a)]
Age (minimum-maximum), years	70.1 (59-85)	68.5 (60-77)	0.206 [b)]
Hight, cm	160.0 ± 7.8	159.7 ± 8.3	0.882 [c)]
Weight, kg	59.6 ± 10.5	56.3 ± 10.4	0.221 [c)]
Body mass index	23.1 ± 2.9	22.0 ± 3.6	0.183 [c)]
Serum creatinine, mg/dL	0.78 ± 0.20	0.70 ± 0.15	0.096 [c)]
With smoking history, n (%)	28 (82.4)	24 (88.9)	0.725 [a)]
Habitual drinker, n (%)	14 (41.2)	9 (33.3)	0.725 [a)]
Type of cancer			
Non-small cell lung cancer, n (%)			0.624 [d)]
Stage I	1 (2.9)	0	
Stage II	0	1 (3.7)	
Stage III	14 (41.2)	8 (29.6)	
Stage IV	10 (29.4)	15 (55.6)	
Small cell lung cancer, n (%)			0.735 [d)]
Limited stage	5 (14.7)	2 (7.4)	
Extensive stage	4 (11.8)	1 (3.7)	
Combination therapy with carboplatin, n (%)			0.742 [d)]
Paclitaxel	12 (35.3)	10 (37.0)	
Etoposide	9 (26.5)	3 (11.1)	
Pemetrexed	8 (23.5)	11 (40.7)	
Pemetrexed + bevacizumab	2 (5.9)	0	
Gemcitabine	2 (5.9)	2 (7.4)	
Tegafur/gimeracil/oteracil	1 (2.9)	1 (3.7)	

[a)] *chi-square test*, [b)] *Mann-Whitney U-test*, [c)] *t-test*, [d)] *mxn chi-square test.*

weight, body mass index, serum creatinine, smoking history, habitual drinking, and type of cancer, between the standard and rikkunshito groups. The most frequent combination chemotherapy with CBDCA in the standard group was paclitaxel (n = 12, 35.3 %), followed by pemetrexed±bevacizumab (n = 10, 29.4 %), etoposide (n = 9, 26.5 %), gemcitabine (n=2, 5.9 %), and S-1 (n = 1, 2.9 %), while the most frequent in the Rikkunshito group was pemetrexed (n = 11, 40.7 %), followed by paclitaxel (n = 10, 37.0 %), etoposide (n = 3, 11.1 %), gemcitabine (n = 2, 7.4 %), and S-1 (n = 1, 3.7 %).

2.2. Control of CINV

Rates of no nausea did not significantly differ in any of the three phases between the standard and rikkunshito groups, as follows: 94.1 % *vs* 96.3 % for acute phase ($p = 1.000$); 70.6 % *vs* 74.1 % for delayed phase ($p = 1.000$); 64.7 % *vs* 74.1 % for overall phase ($p = 0.579$) (Table 2). Further, rikkunshito exhibited no additional improvement on the rate of no vomiting, no rescue treatment, CR or CC in all three phases (Table 2). Moreover, dietary intake did not significantly differ between the standard and rikkunshito groups for the first 5 days after CBDCA-based chemotherapy (data not shown).

2.3. Control of CINV in patients with risk factors

We subsequently conducted a subgroup analysis in patients with CINV risk factors, including female, no drinking, no smoking and age younger than 65 years. In female patients, the rates of no nausea in the overall phase in the rikkunshito group was significantly higher than in the standard group (44.4 % *vs* 100 %, $p = 0.034$). Similarly, the rates of no nausea in delayed phase in the rikkunshito group was higher than in the standard group, albeit without statistical significance (55.6 % *vs* 100 %, $p = 0.088$), although no nausea rate in the acute phase showed no significant difference between the two groups (88.9% *vs* 100%, $p = 1.000$) (Fig.).

In contrast, in patients with other risk factors, including no drinking, no smoking and age younger than 65 years, there were no significant differences in the rate of no nausea between two groups in all three phases (Fig.).

2.4. Incidence of other adverse events

There were no significant differences in the incidence of other adverse events such as diarrhea (grade ≥ 3), constipation (grade ≥ 3), leukopenia (grade ≥ 3), anemia (grade ≥ 3) or thrombocytopenia (grade ≥ 3) between the standard and rikkunshito groups (Table 3).

3. Discussion

Control of CINV, especially nausea, in patients with thoracic cancer receiving CBDCA-based chemotherapy is often insufficient even with use of antiemetic therapy according to clinical practice guidelines (Tomono et al. 2006). In this study, we evaluated the prophylactic effect of the herbal medicine rikkunshito for nausea in patients with thoracic cancer receiving CBDCA-based chemotherapy. Overall CR rate and overall no-nausea rate in thoracic cancer patients receiving CBDCA-based chemotherapy using standard antiemetic therapy with the combination of 5-HT_3RA and DEX (standard group) were 79.4 % and 64.7 %, respectively. These findings are closely similar to those from other reports in Japanese patients with thoracic cancer receiving CBDCA-based chemotherapy (overall CR rate: 65-77 %; overall no-nausea rate: 40-60 %; Tomono et al. 2006; Kusagaya et al. 2015; Suzuki et al. 2016). Our findings showed that rikkunshito did not demon-

Table 2: Control of CINV during the acute, delayed and overall periods in patients with thoracic cancer receiving the first cycle of CBDCA-based chemotherapy

	Standard group (N=34)	Rikkunshito group (N=27)	*p* value
No nausea, n (%)			
Acute	32 (94.1)	26 (96.3)	1.000
Delayed, n (%)	24 (70.6)	20 (74.1)	1.000
Overall	22 (64.7)	20 (74.1)	0.579
No vomiting, n (%)			
Acute	33 (97.1)	27 (100)	1.000
Delayed	33 (97.1)	24 (88.9)	0.647
Overall	32 (94.1)	24 (88.9)	0.647
No rescue treatment, n (%)			
Acute	33 (97.1)	27 (100)	1.000
Delayed	27 (79.4)	23 (85.2)	0.740
Overall	27 (79.4)	23 (85.2)	0.740
Complete response, n (%)			
Acute	33 (97.1)	27 (100)	1.000
Delayed	27 (79.4)	23 (85.2)	0.740
Overall	27 (79.4)	23 (85.2)	0.740
Complete control, n (%)			
Acute	33 (97.1)	26 (96.3)	1.000
Delayed	25 (73.5)	22 (81.5)	0.669
Overall	25 (73.5)	22 (81.5)	0.669

Data were compared by *chi-square-test*.

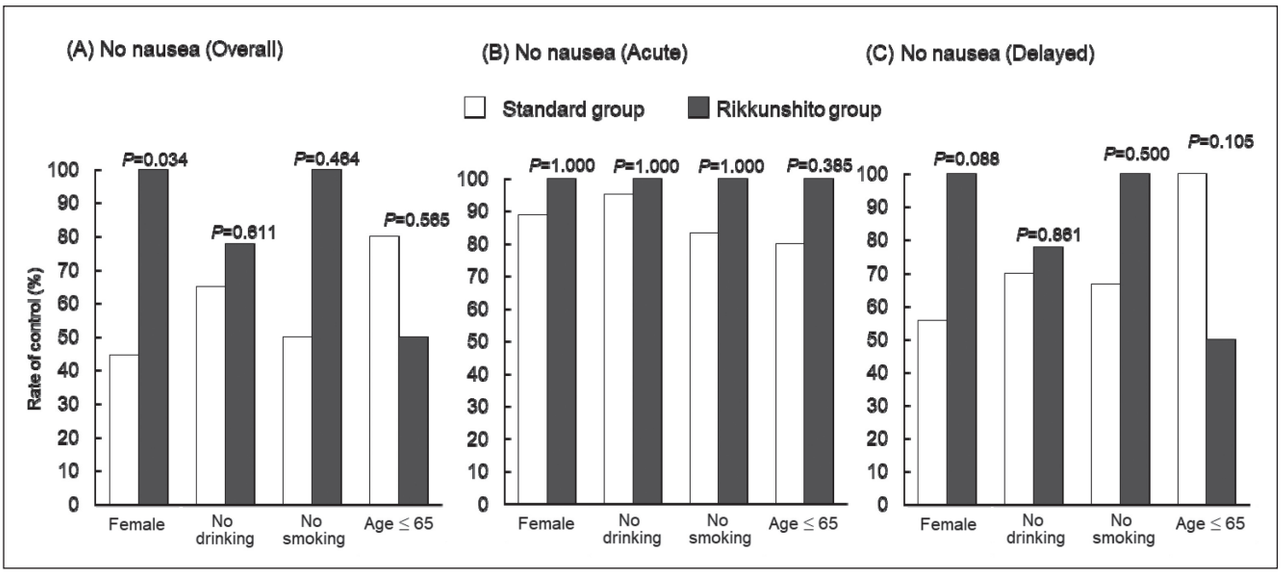

Fig.: Control of nausea during acute, delayed and overall periods in patients with antiemetic risk factors. Data were compared by *chi-square-test.*

strate an additional prophylactic effect on the standard antiemetic therapy for nausea in these patients, (overall no-nausea rate: 64.7 % for standard group *vs* 74.1 % for rikkunshito group, p = 0.579), although no severe adverse events were observed. Further, rikkunshito exhibited no additional improvement on the rate of no vomiting, no rescue treatment, CR or CC in all three phases.

The prophylactic effect of rikkunshito for CINV is controversial (Harada et al. 2018; Ohnishi et al. 2017). In their prospective randomized Phase II study in patients with lung cancer receiving CDDP- or CBDCA-based chemotherapy, Harada et al. (2018) reported that rikkunshito showed no additional benefits beyond those of standard antiemetic regimens in the prevention of CINV (overall CR rate for CDDP-based chemotherapy: 67.9 % vs 62.1 %, p = 0.65; overall no nausea rate for CDDP-based chemotherapy: 55.2 % vs 57.1 %, p = 0.88; overall CR rate for CBDCA-based chemotherapy: 83.3 % vs. 84.4 %, p = 0.59; overall no nausea rate for CBDCA-based chemotherapy: 65.6 % vs. 70.0 %, p = 0.71). In contrast, Ohnishi et al. (2017) showed in a Phase II randomized study that rikkunshito significantly improved CINV in patients with uterine cervical or corpus cancer who were to receive CDDP

Table 3: Incidence of other adverse events

	Standard group (N=34)	Rikkunshito group (N=27)	*p* value
Diarrhea (grade ≥ 3), n (%)	0 (0)	1 (3.7)	0.443
Constipation (grade ≥ 3), n (%)	8 (23.5)	3 (11.1)	0.386
Leukopenia (grade ≥ 3), n (%)	10 (29.4)	3 (11.1)	0.156
Anemia (grade ≥ 3), n (%)	1 (2.9)	0	0.907
Thrombocytopenia (grade ≥ 3), n (%)	3 (8.8)	2 (7.4)	0.787

Data were compared by *chi-square-test*.

(50 mg/m^2 day 1) and paclitaxel (135 mg/m^2 day 0) as first-line chemotherapy (overall CR rate: 84.2 % *vs* 52.9 %, $p = 0.042$). These differences in the prophylactic effect of rikkunshito for CINV might be due to differences in patient background. Several indicators demonstrated that female, younger age (cut-off value: 55-65 years), non-smoker and non-habitual alcohol intake are significant risks for the development of CINV (Sekine et al. 2013; Warr et al. 2011; Hilarius et al. 2012). The study by Harada et al. (2018) enrolled patients with lung cancer, and the rate of females was 22.8 %, whereas Ohnishi et al. (2017) studied patients with uterine cervical or corpus cancer, and all were accordingly female. We therefore conducted a subgroup analysis in patients with CINV risk factors, including female, no drinking, no smoking and age younger than 65 years. Among female patients in the standard group, the rate of overall no nausea were lower than in all patients in this group at 44.4 %. In contrast, female patients who additionally received rikkunshito to standard antiemetic therapy showed significantly improved overall no nausea rate of 100 % (44.4 % *vs* 100 %, $p = 0.034$). Rikkunshito accordingly showed a prophylactic effect against nausea in female patients who have worse control of nausea.

Details of the mechanism of the effect of rikkunshito in reducing nausea are unknown. However, in rats treated with CDDP, rikkunshito was shown to block 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors, an effect which was followed by the recovery of plasma ghrelin levels (Yakabi et al. 2010; Yakabi et al. 2010; Ohno et al. 2011). In another rat model, rikkunshito also improved a delay in gastric emptying *via* antagonism of the 5-HT$_3$ receptor pathway (Tominaga et al. 2011). Rikkunshito might therefore have improved nausea through an effect on these pathways.

Olanzapine is classified as a multi-acting receptor-targeted antipsychotic that blocks dopaminergic D$_1$, D$_2$, D$_3$ and D$_4$ receptors, serotonergic 5-TH$_{2A}$, 5-HT$_{2B}$, 5-HT$_3$ and 5-HT$_6$ receptors, histamine H$_1$ receptors, and muscarinic acetylcholine receptors M$_1$, M$_2$, M$_3$ and M$_4$ (Brafford and Glode 2014). In their phase III study comparing olanzapine with placebo in combination with DEX, aprepitant or fosaprepitant, and a 5-HT$_3$RA in patients receiving CDDP- or cyclophosphamide-doxorubicin-based regimens, Navari et al. (2016) demonstrated that the proportion of patients with no chemotherapy-induced nausea was significantly greater with olanzapine than with placebo in the first 24 hours after chemotherapy (74 % *vs* 45 %, $p = 0.002$), from 25 to 120 h after chemotherapy (42 % *vs* 25 %, $p = 0.002$), and in the overall 120-hour period (37 % *vs* 22 %, $p = 0.002$). Based on these findings, several guidelines have recommended the use of olanzapine as an optional antiemetic medication for high and moderate emetic-risk chemotherapy (Hesketh et al. 2017; National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology 2018). However, common side effects of olanzapine, including sedation and the onset of diabetes mellitus, limits this use (Allison and Casey 2011; Hale 1997; Goldstein et al. 1999; Melkersson et al. 2000). Rikkunshito may therefore represent an alternative drug in patients who cannot receive olanzapine for the above reasons.

There were several limitations to the present study. First, it was conducted under a retrospective before-and-after comparison design, and potentially relevant confounding factors might therefore have been excluded. Second, the sample size was very small and all were treated at a single institution. Finally, the study was conducted before 2016, when the standard antiemetic therapy for CBDCA based-chemotherapy did not include NK$_1$RA, which is now recommended by current clinical practice guidelines for antiemesis (Roila et al. 2016; Hesketh et al. 2017; National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology 2018). The effect of rikkunshito should therefore be evaluated in comparison with triplet antiemetic therapy with dexamethasone, a 5-HT$_3$RA and NK$_1$RA in a larger, randomized control study.

In conclusion, rikkunshito did not demonstrate an additional prophylactic effect on the standard antiemetic therapy for nausea in patients with thoracic cancer receiving CBDCA-based chemotherapy, but did appear to show a prophylactic effect in patients with worse control of nausea, such as females.

4. Experimental

4.1. Study setting and patients

We conducted a single-center, retrospective before-and-after comparison study at the 614-bed tertiary-care Gifu University Hospital. A total of 89 patients with thoracic cancer received first-cycle CBDCA-based chemotherapy between September 2012 to December 2014. Of these, 28 patients were excluded for the following reasons: taking other antiemetic drugs in addition to the standard antiemetic therapy according to JSCO clinical practice guideline 2010 (Takeuchi et al. 2016) (n=6); receipt of brain radiation therapy (n=7) or opioid analgesics (n=9) within 7 days before cancer chemotherapy; and nausea before cancer chemotherapy (n=6). Therefore, 61 patients were enrolled in the study.

Among the 61 eligible patients, 34 patients received standard antiemetic therapy with the combination of 5-HT$_3$RA and DEX in the first cycle of CBDCA-based chemotherapy from September 2012 and June 2013 (standard group). The other 27 patients received standard antiemetic therapy plus 2.5 g of oral rikkunshito three times a day on days 1–7 for prophylaxis of CINV in the first cycle of CBDCA-based chemotherapy from July 2013 and December 2014 (rikkunshito group).

4.2. Antiemetic medication

All eligible patients received CBDCA based regimen, in which CBDCA dose was area under the curve (AUC) of 5. For standard antiemetic therapy according to the JSCO clinical practice guidelines 2010 (Takeuchi et al. 2016), the combination of 5-HT$_3$RA, such as intravenous granisetron (3 mg) or oral azasetron (10 mg), and intravenous DEX (9.9 mg) was prescribed before chemotherapy for prevention of acute CINV, and oral DEX (4-8 mg/day) was administered on days 2 and 3 of chemotherapy for prophylaxis of delayed CINV. The present study was conducted before 2016, and the standard antiemetic therapy for CBDCA-based chemotherapy therefore did not included NK$_1$RA, which is recommended in the current clinical practice guidelines for antiemesis (Roila et al. 2016; Hesketh et al. 2017; National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology 2018).

Patients receiving CBDCA (AUC 5) + paclitaxel were administrated DEX (19.8 mg), ranitidine (50 mg) and diphenhydramine (50 mg) for paclitaxel hypersensitivity on day 1.

4.3. Evaluation of the control of CINV

Efficacy and safety of the antiemetic therapy were evaluated during the 5 days following administration of CBDCA in the first cycle. CINV control was evaluated as the rate of no nausea (nausea of grade < 1), no vomiting or retching, complete response (CR; no vomiting or retching and no rescue treatment) and complete control (CC; no nausea, no vomiting or retching and no rescue treatment) during the acute (within 24 h after chemotherapy), delayed (24 – 120 h), and overall (0 – 120 h) periods. Additionally, oral intake was measured from day 0 to day 5 every 24 h, using the amount of food intake on day 0 as 100 %.

All patients were provided with a checklist for daily evaluation of CINV. Using the checklist, patients kept a daily record of nausea and vomiting episodes for 5 days after chemotherapy. Physicians, pharmacists and nurses recorded the control of nausea, vomiting or retching and rescue antiemetic therapy on the electronic medical record.

4.4. Assessment of other adverse events

Adverse events included diarrhea, constipation, leukopenia, anemia and thrombocytopenia. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events (CTCAE, National Cancer Institute , MD, USA) version 4.0 (U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, 2009).

4.5. Statistical analyses

Parametric variables were statistically compared using the *t*-test, while nonparametric data were analyzed using the Mann-Whitney *U*-test, mxn chi-square test or chi-square test. *P* values of less than 0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics ver. 22 (IBM Japan Services Co., Ltd., Tokyo, Japan).

4.6. Ethics statement

This study was carried out in accordance with the guidelines for human studies outlined by the ethics committee of the Gifu University Graduate School of Medicine (Institutional Review Board Approval No. 2018-202), and notified by the Japanese government. In view of the retrospective nature of the study, the need for informed consent from subjects was not required.

Conflicts of interest: None declared.

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