Preventive effect of Rikkunshito, a traditional Japanese medicine, on chemotherapy-induced nausea and vomiting with cisplatin: Case series

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ABSTRACT

Aim: Supportive therapies are important to treat chemotherapy-induced nausea and vomiting (CINV). Rikkunshito, a Kampo medicine, has been reported to be effective against cisplatin-induced anorexia in rats. In the present study, we evaluated the preventive effect of Rikkunshito for CINV in patients receiving high-dose cisplatin chemotherapy.

Methods: We selected patients who received chemotherapy including cisplatin (≥60 mg/m²) for gastric or esophageal cancer between April 2010 and August 2012. We identified 20 patients treated without a reduction in the dose of anticancer medications during the second course and added 7.5 g/day Rikkunshito, which was orally administered, for 7 days. All patients were treated with 5-hydroxytryptamine-3 receptor antagonist, corticosteroid, and neurokinin-1 receptor antagonist for the prevention of CINV during the first and second courses. We evaluated complete response (CR; defined as no emesis and no rescue medication) and other toxicities according to the Common Terminology Criteria for Adverse Events version 4.0.

Results: The median patient age was 63 years (range, 49–77 years). The chemotherapy regimens used were cisplatin plus 5-fluorouracil in 15 patients with esophageal cancer and cisplatin plus S-1 in five patients with gastric cancer. Rate of delayed CR was 75.0% during the first course (95% CI: 56.0–94.0%), which improved during the second course to 95.0% (95% CI: 85.4–100%, P = 0.077). There was no significant difference in other major toxicities between the first and second courses.

Conclusion: Rikkunshito has the potential to alleviate CINV in patients receiving high-dose cisplatin chemotherapy.

KEY WORDS: chemotherapy-induced nausea and vomiting, cisplatin, esophageal cancer, gastric cancer, Rikkunshito

INTRODUCTION

Platinum-based agents, such as cisplatin, are widely used in chemotherapy regimens, are key drugs for treating gastrointestinal cancers, and are used as standard therapy for treating metastatic or recurrent gastric cancer [1,2]. Cisplatin plus continuous-infusion 5-fluorouracil (5-FU) is regarded as the standard regimen for the treatment of metastatic or recurrent esophageal squamous cell carcinoma (SCC) in Japan [3,4]. Cisplatin and 5-FU are also regarded as standard chemoradiotherapy agents for treatment of locally advanced and resectable SCC [5,6].

Because side-effects, such as nausea, vomiting, and anorexia, which affect quality of life, are associated with the use of cisplatin, management of these side-effects is important in order to maintain patient tolerance to chemotherapy. It has been reported that 5-hydroxytryptamine-3 receptor antagonist (5-HT₃) has superior efficacy for preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic cisplatin-based regimens [7,8]. The addition of corticosteroid improves the anti-emetic efficacy of 5-HT₃ receptor antagonists in preventing CINV [9]. Recent studies have demonstrated that the neurokinin-1 (NK-1) receptor antagonist is also effective for preventing CINV [10–12]. Thus, the current standard therapy for CINV in high-dose cisplatin therapies includes the addition of a combination of a 5-HT₃ receptor antagonist, NK-1 receptor antagonist, and corticosteroids. CINV, however, may still occur >24 h after chemotherapy, and loss of appetite may remain problematic in many patients.

Rikkunshito (Tsumura, Tokyo, Japan), a traditional Japanese medicine consisting of eight herbal components (Table 1), is well recognized for its beneficial effects and widely used for treating upper gastrointestinal symptoms, such as decreased gastric motility after surgery and chronic idiopathic dyspepsia.

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A 3-D high-performance liquid chromatography profile of Rikkunshito is shown in Figure 1. Takeda et al. reported that Rikkunshito suppressed cisplatin-induced anorexia in rats [15]. The aim of the present study was to evaluate the preventive effects of Rikkunshito against CINV in patients receiving high-dose cisplatin therapy for gastric or esophageal cancer.

### METHODS

#### Patients

We selected patients with gastric (*n* = 63) and esophageal cancer (*n* = 88) who received high-dose cisplatin (≥60 mg/m²) regimens as first-line chemotherapy between April 2010 and August 2012. In 8 and 20 patients with gastric and esophageal cancer, respectively, we added oral Rikkunshito for 7 days to the second course treatment with cisplatin. We targeted 20 patients treated without a reduction in anticancer medication during the second course, including 5 patients with gastric cancer and 15 with esophageal cancer. The baseline patient characteristics are listed in Table 2. The median patient age was 63 years (range, 49–77 years).

#### Treatment regimen

Patients with gastric cancer received a combination therapy of oral fluoropyrimidine, S-1 (Taiho Pharmaceutical, Tokyo, Japan) plus cisplatin. S-1 was given orally twice daily after meals at a fixed dose of 80 mg/m²/day for 21 consecutive days followed by a 14 day rest period and repeated every 5 weeks.

| Components of Rikkunshito                  |
|---------------------------------------------|
| 7.5 g of Rikkunshito contains 4.0 g of a dried extract of the following mixed crude drugs |
| Atractylodes lancea rhizome (g) 4.0         |
| Ginseng (g)                                 |
| 4.0                                         |
| Pinellia tuber (g)                          |
| 4.0                                         |
| Poria sclerotium (g)                        |
| 4.0                                         |
| Jujube (g)                                  |
| 2.0                                         |
| Citrus unshiu peel (g)                      |
| 2.0                                         |
| Glycyrrhiza (g)                             |
| 1.0                                         |
| Ginger (g)                                 |
| 0.5                                         |
The S-1 dose was calculated on the basis of body surface area (BSA; BSA < 1.25 m², 80 mg; 1.25 ≤ BSA < 1.5 m², 100 mg; BSA ≥ 1.5 m², 120 mg) and 60 mg/m² of cisplatin was given i.v. on day 8. Patients with esophageal SCC received 80 mg/m² of cisplatin i.v. on day 1 and 800 mg/m² 5-FU by continuous infusion on days 1–5. Three patients received i.v. granisetron (3 mg) and 17 received i.v. palonosetron (0.75 mg) on the day when cisplatin was given. All patients received i.v. dexamethasone (12 mg) on day 1, followed by i.v. dexamethasone (8 mg) daily on days 2 and 3 when cisplatin was given. All patients received oral aprepitant (125 mg) on day 1 and oral aprepitant (80 mg) daily on days 2 and 3 when cisplatin was given. Rikkunshito (7.5 g/day) was given orally in three divided doses before or between meals for 7 days during the second course treatment with cisplatin. All patients received a 5-HT3 receptor antagonist, corticosteroid, and NK-1 receptor antagonist for the prevention of CINV during their first and second courses.

**Assessment**

We evaluated complete response (CR; defined as no emesis and no rescue medication) and defined acute CR as that occurring during the first 24 h after cisplatin treatment and delayed CR as that occurring >24 h after cisplatin treatment. Other adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0 observed during the first and second courses by viewing the medical records.

**Statistical analysis**

We compared the occurrence of adverse events during the first and second courses with the chi-squared test and Mann–Whitney U-test. All statistical analysis was done using JMP version 10 (SAS Institute, Cary, NC, USA).

**RESULTS**

During the first treatment course (without Rikkunshito), 13 patients had grade 0 nausea, 6 had grade 1, and 1 had grade 2. The severity of nausea significantly reduced during the second treatment course (with Rikkunshito); 19 patients had grade 0 and 1 had grade 1 (P = 0.039). During the first treatment course, 5 patients had grade 0 anorexia, 11 had grade 1, and 4 had grade 2, which significantly improved during the second treatment course; 12 patients had grade 0, 6 had grade 1, and 2 had grade 2 (Fig. 2). All patients experienced acute CR during the first and second courses (Fig. 3). More than 24 h after cisplatin treatment, one patient experienced grade 1 vomiting during the first and second courses. Four patients received additional anti-emetic drugs during the first course and one during the second course. Therefore, the delayed CR rate was 75.0% during the first course (95% CI: 56.0–94.0%), which improved during the second course to 95.0% (95% CI: 85.4–100%, P = 0.077, Fig. 3). Regarding other major adverse events, there was no significant difference between the first and second courses (Table 3).

**DISCUSSION**

In the present study, we investigated the prophylactic effectiveness of Rikkunshito for CINV and anorexia in patients receiving cisplatin combination chemotherapy for gastric and esophageal cancer. To investigate preventive effect of Rikkunshito on CINV with cisplatin, we selected the patients who were not given Rikkunshito during the first course of chemotherapy and were given Rikkunshito during the second course of the

**Table 2 | Patient characteristics**

| n = 20 | % |
|--------|---|
| Gender (M/F) | 15/5 | 75/25 |
| Age (years), median (range) | 63 (49–77) | — |
| ECOG PS 0/1 | 7/13 | 35/65 |
| Esophageal/gastric cancer | 15/5 | 75/25 |
| Treatment | | |
| Cisplatin + 5-FU (esophageal cancer) | 15 | 75 |
| Cisplatin + S-1 (gastric cancer) | 5 | 25 |
| Therapeutic purpose | | |
| Adjuvant treatment | 5 | 25 |
| Treatment for metastasis or relapse | 15 | 75 |
| Anti-emetics | | |
| 5-HT3 receptor antagonist | 20 | 100 |
| NK-1 receptor antagonist | 20 | 100 |
| Corticosteroid | 20 | 100 |

5-FU, 5-fluorouracil; 5-HT3, 5-hydroxytryptamine 3; ECOG PS, eastern cooperative oncology group performance status; NK-1, neurokinin-1.

![Figure 2](image-url) Proportion of patients with (a) nausea and (b) anorexia during the first and second course (n = 20). (a) Grade 1; (b) grade 2; (c) grade 0. *P < 0.05 (Mann–Whitney U-test).
chemotherapy, and we compared the toxicities of first course with those of the second course in the same patients. In addition, we excluded the patients with reduction in anticancer medication during the second course of chemotherapy to evaluate the effect of Rikkunshito more precisely.

Ohno et al. investigated the efficacy of Rikkunshito on cisplatin-induced anorexia in patients with gastric cancer receiving S-1 plus cisplatin and reported that food intake among patients with Rikkunshito supplementation was significantly greater than that among those without Rikkunshito supplementation, and the grade of anorexia in those given Rikkunshito was significantly lower than that in those who did not have Rikkunshito [16]. Furthermore, Seike et al. investigated the efficacy of Rikkunshito on CINV in patients with advanced esophageal cancer receiving chemotherapy with docetaxel and 5-FU plus cisplatin [17]. The nausea score of those on Rikkunshito supplementation was significantly lower than that in those without Rikkunshito supplementation. These results are in line with those of the present study.

Hesketh et al. reported an acute CR rate of 89.2% with a regimen of NK-1 receptor agonist, 5-HT₃ receptor agonist, and corticosteroids to prevent CINV in patients receiving highly emetogenic cisplatin-based chemotherapy [11]. This acute

![Figure 3](image)

**Figure 3**  | Proportion of patients achieving complete response (no emesis and no rescue medication) in the first and second course (n = 20).  

|                | First course | Second course | P<br>  
|----------------|--------------|---------------|------
|                | All grade    | Grade 3–4     | All grades | Grade 3–4 |       |
| Hematologic toxicity | n (%)       | n (%)         | n (%)       | n (%)       | P       |
| Leukopenia    | 7 (35)       | 0 (0)         | 8 (40)       | 1 (5)       | 0.773   |
| Neutropenia   | 7 (35)       | 0 (0)         | 6 (30)       | 1 (5)       | 1.000   |
| Anemia        | 12 (60)      | 0 (0)         | 12 (60)      | 0 (0)       | 1.000   |
| Thrombocytopenia | 6 (30)     | 0 (0)         | 7 (35)       | 0 (0)       | 1.000   |
| Non-hematologic toxicity | n (%)       | n (%)         | n (%)       | n (%)       |       |
| Allergic reaction | 0 (0)       | 0 (0)         | 0 (0)       | 0 (0)       | 1.000   |
| Alopecia      | 1 (5)        | 0 (0)         | 4 (20)       | 0 (0)       | 0.342   |
| Constipation  | 10 (50)      | 0 (0)         | 8 (40)       | 0 (0)       | 0.751   |
| Diarrhea      | 4 (20)       | 1 (5)         | 2 (10)       | 1 (5)       | 0.629   |
| Dysgeusia     | 2 (10)       | 0 (0)         | 3 (15)       | 0 (0)       | 1.000   |
| Fatigue       | 10 (50)      | 0 (0)         | 6 (30)       | 0 (0)       | 0.333   |
| Febrile neutropenia | 0 (0)       | 0 (0)         | 0 (0)       | 0 (0)       | 1.000   |
| Hand-foot syndrome | 1 (5)        | 0 (0)         | 1 (5)       | 0 (0)       | 1.000   |
| Hypokalemia   | 4 (20)       | 0 (0)         | 1 (5)       | 0 (0)       | 0.342   |
| Peripheral sensory neuropathy | 1 (5)        | 0 (0)         | 1 (5)       | 0 (0)       | 1.000   |
| Stomatitis    | 4 (20)       | 0 (0)         | 4 (20)       | 0 (0)       | 1.000   |
| Vomiting      | 1 (5)        | 0 (0)         | 1 (5)       | 0 (0)       | 1.000   |

† Mann–Whitney U-test.
CR rate was similar to the result of the first course with these three agents in the present study. During the acute phase (occurring within the first 24 h after cisplatin treatment), an apparent improvement was observed in the severity and frequency of CINV, but the delayed CR rate was 75.4% with these three agents in the Hesketh et al. study, which was similar to the delayed CR rate during the first course with these three agents in the present study. Despite the addition of these three agents to a treatment regimen, the problem of delayed-phase CINV persists. Therefore, we propose that Rikkunshito can reduce the frequency and severity of delayed-phase CINV.

The mechanism of Rikkunshito action remains to be fully elucidated. Rikkunshito has been reported to have a prokinetic action on gastric emptying [18]. Rikkunshito also reduces distal esophageal acid exposure through improved esophageal acid clearance [19]. Thus, Rikkunshito may have therapeutic potential in treatment of functional dyspepsia and gastroesophageal reflux [14]. These reports suggested that Rikkunshito has a possible beneficial effect for nausea and vomiting. In addition, it was reported that Rikkunshito suppressed cisplatin-induced decreases of plasma acylated-ghrelin and increased food intake in rats [15]. Therefore, we conducted the present study to evaluate the preventive effects of Rikkunshito against CINV in patients receiving high-dose cisplatin.

There are few reported side-effects of Rikkunshito; Glycyrrhizae radix (common name, licorice root), a component of Rikkunshito, is known to potentially induce pseudoaldosteronism [20,21]. In the present study, there were no significant differences in major adverse events between the first and second treatment courses with regard to pseudoaldosteronism. Additional adverse events associated with pseudoaldosteronism, such as hypokalemia, were not observed. Thus, the safety profile did not suggest that Rikkunshito enhanced the toxicity of chemotherapy.

In the present study, we demonstrated the effect of oral medicine, Rikkunshito, against CINV in patients with gastric and esophageal cancer. We expect that Rikkunshito can be used for CINV in patients who receive other cisplatin-based regimens such as chemotherapy for lung cancer, given that esophageal cancer patients sometimes have swallowing problems and therefore would be unable to tolerate oral medicine, whereas lung cancer patients do not usually have this problem.

The present study had some important limitations. First, it was a retrospective study that included a relatively small number of patients who received two different regimens. Second, the bias of treatment course may have affected the results. The present findings should thus be tested in future prospective clinical trials.

**Conclusion**

The traditional Japanese medicine Rikkunshito has the potential to reduce the severity of CINV in patients with esophageal and gastric cancer who receive high-dose cisplatin therapy. Further evaluation of Rikkunshito is warranted in patients receiving high-dose cisplatin chemotherapy.

**CONFLICT OF INTEREST**

No competing financial interests exist.

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