

## Editorial



# Traditional herbal medicine, Rikkunshito, for chemotherapy-induced nausea and vomiting

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### Conflict of Interest

No potential conflict of interest relevant to this  
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► See the article “Additive effect of rikkunshito, an herbal medicine, on chemotherapy-induced nausea, vomiting, and anorexia in uterine cervical or corpus cancer patients treated with cisplatin and paclitaxel: results of a randomized phase II study (JORTC KMP-02)” in volume 28, e44.

Chemotherapy-induced nausea and vomiting (CINV) is a common treatment-related adverse effect which is detrimental to the quality of life of cancer patients. It could even lead to dose reductions or discontinuations of chemotherapy. There has been a randomized trial involving breast cancer patients, that showed that the incidence of chemotherapy—induced emesis was almost as high as 80% when no effective antiemetic agents were prescribed [1]. Since then, the development of new antiemetics has changed the situation. An observational study reported that incidences of acute nausea and vomiting decreased to 35% and 13% respectively, among patients who received highly and moderately emetogenic chemotherapy [2]. As a result, the quality of life of cancer patients has improved, and better control of CINV has led to less dose reductions and discontinuations of chemotherapy.

CINV is classified into acute and delayed types, depending on the timing it occurs [3,4]. Acute types occur within the first 24 hours after chemotherapy, and delayed types occur after that.

Advances in the past 3 decades have helped disclose some of the mechanisms of CINV. Several neurotransmitters, including dopamine, serotonin, and substance P, have been identified as important mediators of CINV [5]. Accumulated knowledge suggests that the emetic response to chemotherapy can occur through a peripheral and a central pathway [6]. The peripheral pathway, which is activated within 24 hours after chemotherapy, is associated with acute CINV. Anticancer agents induce enterochromaffin cells in the gut to release serotonin, which activates the 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor in vagal afferents that then proceed to stimulate the vomiting center in the brainstem. Meanwhile, the central pathway is primarily located in the brain. In this case, substance P is a principal neurotransmitter which activates neurokinin-1 (NK<sub>1</sub>) receptors in the central nervous system. This pathway is mainly activated after the first 24 hours of finishing chemotherapy and is often involved in the delayed CINV, although it could also induce acute CINV at times. These revelations have led to the development of drugs such as dopamine, 5-HT<sub>3</sub>, and NK<sub>1</sub> receptor antagonists.

Several agents such as cisplatin, carboplatin, cyclophosphamide, and doxorubicin can induce both acute and delayed CINV [7]. A 4-level classification of the emetogenic potential of anticancer drugs has been established. This is based on the percentage of patients with

acute emesis caused by single agents in the absence of antiemetic drugs, from level 1 (minimal); less than 10%, to level 4 (high); more than 90% of patients with emesis [8].

The guidelines for antiemetic therapy have been developed in various cancer societies. The common principles are that prophylaxis should be the primary goal, and that it should be applied to patients who have a 10% or higher risk of CINV. All guidelines recommend the use of 5-HT<sub>3</sub> and NK<sub>1</sub> receptor antagonists as well as corticosteroids for patients undergoing treatment with highly emetogenic anticancer drugs [9,10]. The administration of 5-HT<sub>3</sub> receptor antagonists typically reduces or prevents emesis in 50% of patients. This percentage increases in combination with dexamethasone, and it increases further, when an NK<sub>1</sub>-receptor antagonist is added [11]. However, these effects of the antiemetic combinations are still insufficient, since the ultimate goal is to prevent CINV all together. In addition, food intake decreases to 25% of baseline, by a week after the administration of cisplatin-containing chemotherapy [12].

Japan's traditional herbal medicine, called Kampo, was originally imported from China 1,500 years ago, and has since developed independently [13]. Kampo medicines have been integrated into the National Healthcare System and are currently prescribed by more than 80% of medical doctors in Japan [14]. In recent years, the pharmacological mechanisms of several Kampo medicines have been investigated using animal models. Clinical trials have also been conducted to assess the effects.

One of the Kampo medicines that is known to have an antiemetic effect is Rikkunshito. Rikkunshito is composed of 8 herbal medicines and is widely used to treat various gastrointestinal disorders in Japan [15]. Through animal experiments, it has been demonstrated that Rikkunshito antagonizes the 5-HT<sub>3</sub> receptor [16]. Furthermore, it also antagonizes 5-hydroxytryptamine receptor 2B (5-HT<sub>2B</sub>) and 5-hydroxytryptamine receptor 2C (5-HT<sub>2C</sub>) receptors, preventing the cisplatin-induced decrease in ghrelin levels, which results in the recovery of food intake [17]. Since Rikkunshito is not composed of a single substance, as with other Kampo medicines, it is difficult to determine the active component responsible for the beneficial effect and reveal the underlying mechanism of it. Pharmacological studies are under way to pursue this [18]. The effect of Rikkunshito for CINV has only been investigated in 2 prospective studies with small sample sizes [19,20], so far. In this issue, Ohnishi et al. [21] reported the result of randomized multi-institutional studies, which revealed the additive effect of Rikkunshito to prevent CINV induced by cisplatin and paclitaxel in uterine cervical or corpus cancer patients. I have to say that the sample size was rather small and the study was not conducted in a blind manner. Although it is difficult to set appropriate and subjective endpoints in Kampo medicine, placebo-controlled, double-blind, randomized clinical trials similar to those of Western medicine might provide clearer evidence.

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