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Review Article

Kampo medicines for supportive care of patients with cancer: A brief review

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ABSTRACT

Background: Kampo medicines, which are standardized traditional Japanese herbal medicines, have been tried to support patients with cancer.
Methods: Randomized controlled trials on the use of Kampo medicines for cancer supportive care and the descriptions of Kampo medicines in clinical practice guidelines were reviewed.
Results: Kampo medicines potentially ameliorate refractory symptoms in cancer patients. For example, hochuekkito, juzentaihoto, and ninjin'yoeito seem to be efficacious for fatigue/general malaise. Potential use of rikkunshito for anorexia/cancer cachexia and goshajinkigan for peripheral neuropathy is proposed from small numbers of randomized controlled trials in addition to basic research. The number of clinical practice guidelines which contain descriptions of Kampo medicines is increasing in general, but only a few in the area of cancer supportive care.
Conclusion: Kampo medicines potentially play some roles in preventing or ameliorating side effects of anticancer agents. Supportive care with Kampo medicines for patients with cancer might lead to physical, mental, and nutritional improvement.

1. Introduction

Patients with cancer often experience anorexia and general malaise. Advanced cancer causes cachexia, which is accompanied by inflammatory reactions and microcirculation disorders. Recent advances in cancer drug therapy include cytotoxic agents, molecular targeting agents, anti-angiogenic agents, and immune checkpoint inhibitors. These anti-cancer drugs have high levels of clinical evidence for both efficacy and safety. To maintain a sufficient relative dose intensity of each anti-cancer agent, supportive care is of critical importance.

Kampo is a traditional Japanese medicine derived from ancient Chinese medicine, and developed during the 16th and 19th centuries in Japan.[1] Kampo medicines can act as multitarget multicomponent therapy, thus each Kampo formula can address multiple symptoms. Evidence of the efficacy and safety of Kampo medicines for refractory symptoms in patients with cancer, such as anorexia,[2–10] fatigue,[11] and peripheral neuropathy,[12–18] has been accumulated. Adverse reactions to Kampo medicines are well documented, such as hepatic dysfunction, interstitial pneumonia, and pseudoaldosteronism,[19–22] but the incidence of these adverse reactions is extremely low. The long-term history of well-described Kampo combinations over hundreds of years, controlled quality of Kampo medicines, education of the doctors, and the small quantity of the individual herbal drug allow a safe-use of Kampo medicines alongside chemotherapy. Whilst chemotherapy interacts with DNA replication and proliferation of tumor cells, Kampo acts on the tumor microenvironment,[23] i.e. the targets of action differ. As for herb-drug interactions, basic research indicates that Kampo products would not exhibit any pharmacokinetic interactions with anticancer agents in clinical practice.[24]

In modern times, Kampo education has been propagated in all medical schools in Japan since 2001, when Kampo was incorporated into the model core curriculum of medical education.[25] Therefore, young doctors are more familiar with Kampo medicines than their solely Western-trained colleagues. This is a different from medical systems in China and Korea, where both medical systems are separate.

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Table 1
Contents of Kampo medicines in clinical practice guidelines (CPGs) for supportive care in cancer.

The name of CPG	Year	Formula	Descriptions
Guide for chemotherapy-induced peripheral neuropathy Ref. [41]	2017	goshajinkigan	Goshajinkigan is not recommended for oxaliplatin-induced peripheral neuropathy. Goshajinkigan significantly prevents taxane-induced peripheral neuropathy, compared with mecobalamin. However, evidence is lacked for any recommendation.
Guidelines for palliative care of gastrointestinal symptoms in cancer patients Ref. [42]	2017	rikkunshito	Rikkunshito improves anorexia in patients with cancer, but evidence is lacked for any recommendation.
Clinical practice guidelines for breast cancer Ref. [43]	2018	Kampo medicines in general	It is uncertain that complementary and alternative medicines including Kampo medicines are effective for hot flashes and arthralgia due to hormonal therapy
Guidelines for palliative care of genitourinary symptoms in cancer patients Ref. [44]	2016	Kampo medicines in general	Kampo medicines are effective for overactive bladder.
Guidelines for infusional therapies in terminally-ill patients with cancer ref. [45]	2013	Kampo medicines in general	Some herbal therapies including Kampo medicines are reported to improve cancer cachexia via ghrelin signals, but evidence is limited and there is no recommendation.
Guidelines for proper use of anticancer agents Ref. [46]	2005	Kampo medicines in general	There is no evidence for recommendations of complementary and alternative medicines including Kampo medicines in breast cancer treatments.

In this review, we discuss the significance of Kampo medicines as supportive measures for patients with cancer.

2. Current status of cancer medicine in Japan

Cancer is the most common disease and the most common cause of death in Japan since 1981. One in two individuals in the total population experiences cancer of some kind in life, and one-third die of cancer. Chemotherapy, especially for neoadjuvant and adjuvant treatment has to be done in close coordination with surgery. In Japan, medical oncologists and internists in gastroenterology or pulmonology have gradually become involved in drug therapy for cancer since 2004 since the Japan Society of Medical Oncology (JSMO) was established. As of April 1, 2021, there were 1,530 board-certified medical oncologists in Japan.

3. Significance of supportive care in cancer

Supportive care in cancer has been officially incorporated into treatment regimens since the Japanese Association of Supportive Care in Cancer (JASCC) was established in March 2015. Supportive care prevents or ameliorates the side effects of drug therapy and decreases complications in surgery or radiation therapy. It is now clear that supportive care should be introduced as early as possible. Various side effects of chemotherapy can be foreseen from the viewpoint of oncologists. Supportive care is of great importance to complete the standard treatment and prevent a decrease in the relative dose intensity of chemotherapeutic agents. Supportive care handles various symptoms, such as anorexia, fatigue, anxiety, and emotional distress; therefore, it requires multidisciplinary collaboration.

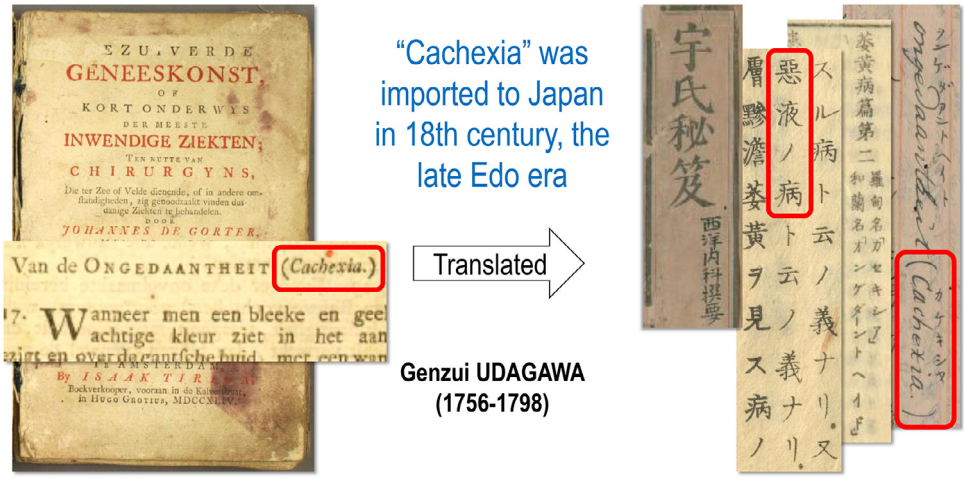
4. Significance of Kampo in cancer supportive care

The Study Group of Kampo was launched in JASCC in September 2016. Kampo can be used to treat or prevent various symptoms, such as systemic (general malaise, fatigue), gastrointestinal (GI) symptoms (anorexia, nausea, vomiting, diarrhea, constipation), peripheral neuropathy, and psychiatric symptoms. Especially, the anorexia-cachexia syndrome is a mixed pathophysiology, and could be treated with Kampo medicines.[26–30] Information of Kampo products is available in English on the website of STORK.[31] JASCC has further published clinical guidelines for various chemotherapy side-effects such as peripheral neuropathy.[32] In 2020, the Kampo Study Group of JASCC published a practical guide for the use of Kampo medicines in cancer supportive care.[33] In Japan, Kampo medical practice is well integrated into modern medicine for patients with cancer.[34,35] The International Society for Japanese Kampo Medicine (ISJKM) is its extended arm to the West.

The following prescriptions have been studied extensively for supportive care in cancer patients. As for upper GI symptoms, rikkunshito showed a significant decrease in anorexia in patients with advanced gastric cancer who received cisplatin plus S-1 therapy in a crossover randomized controlled trial (RCT).[2] Hochuekkito significantly ameliorated cancer-related fatigue.[11] Hematotoxicity, such as neutropenia, is usually treated with a granulocyte colony-stimulating factor (G-CSF). Juzentaihoto may prevent or even help in recovering from myelosuppression.[36] Anemia and thrombocytopenia are usually treated with blood transfusion. Recently, kamikihito, a Kampo medicine, was reported to accelerate the recovery of thrombocytopenia.[37] Ninjin'yoeito was effective in ameliorating ribavirin-induced anemia in an RCT, presumably owing to its stabilizing action on the red blood cell membrane.[38] It has been reported that ninjin'yoeito has multifunctional actions, especially in hematological and neurological disease status.[39]

As regards peripheral neuropathy, goshajinkigan was effective for taxane-induced peripheral neuropathy, i.e. axonopathy,[12,13] and was also effective against oxaliplatin-induced peripheral neuropathy in a phase 2 study.[14] However, goshajinkigan was not effective for oxaliplatin in a phase 3 study,[15] and meta-analyses denied its efficacy.[16,17]. Recently, ninjin'yoeito was reported to reduce the grades of chronic, accumulative peripheral neuropathy induced by oxaliplatin in an adjuvant setting in patients with colorectal cancer.[18] It is known that one of the contents: citrus unshiu pericarpium, protects demyelination by inducing differentiation of oligodendrocytes.[40]

Descriptions of Kampo medicines in clinical practice guidelines for cancer supportive care in Japan are summarized in Table 1 Ref. [41–46] However - with abundant long-term traditional evidence for standardized herbal drug combinations - large multicenter placebo-controlled trials on herbal medicines are missing and do not find financial support, hence recommendations are scarce. This phenomenon is not specific to Japan, but is reflected in other Western-medicine oncology guidelines, such as the guidelines of the German Cancer Society (DKG) as well as the Association of the Scientific Medical Societies in Germany (AWMF). The role of tra-



Simple Guideline on a Variety of Internal Disorders, Johannes de Gorter, 1744, Waseda University Library, Japan

Genzui's translation draft "Ushi Hikyu", 1793, National Diet Library, Japan

Fig. 1. Historical aspects of cachexia in Japan.

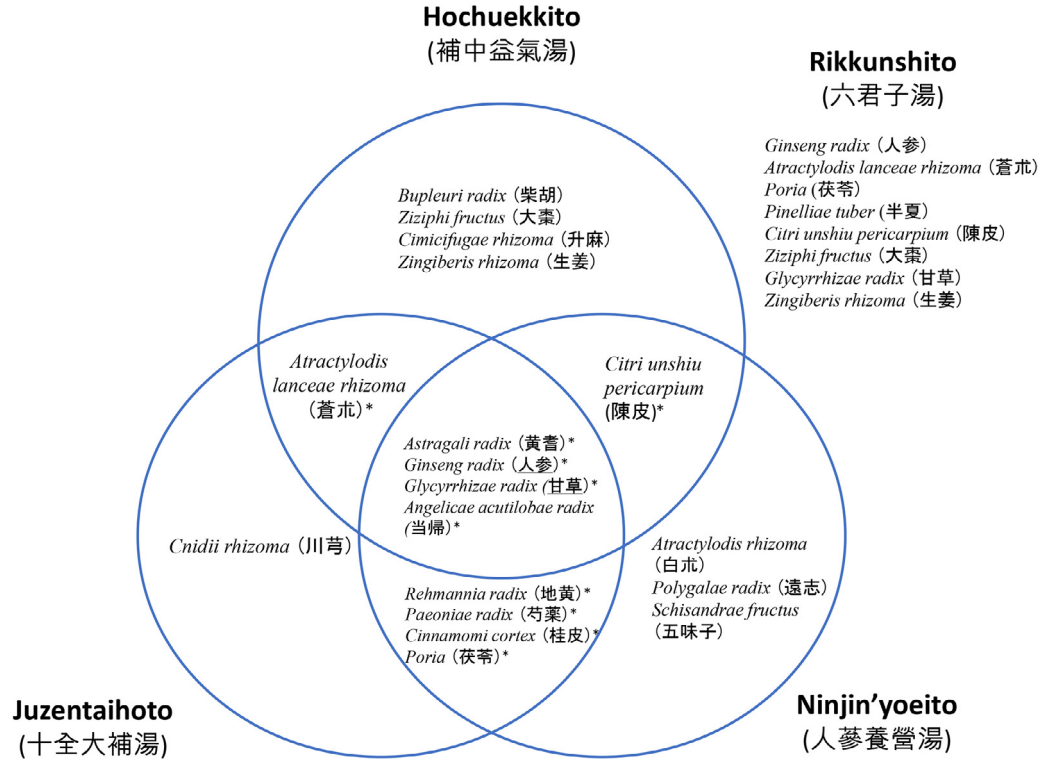


Fig. 2. The top ten herbs (with asterisks; overlapped in two or three formulae) in three major "hozai"s and the seven herbs among them contained in rikkunshito (underlined).

ditional knowledge in a modern context should however not be underestimated. And future studies will proof this point.

5. Kampo medicines for cancer cachexia

The pathogenesis of cancer cachexia includes physical inactivity, inflammation, and the cancer microenvironment.[47] Historically, UDAGAWA Genzui translated the book of Johannes de Gorter "Guideline on a variety of internal disorders"[48] into Japanese as "Ushi Hikyu" in 1793[49] (Fig. 1). It included the word "cachexia", which originates from the Greek words "kakos" (bad) and "hexis" (condition).

Cachexia is characterized by involuntary weight loss, due to appetite loss, inflammatory processes and a disequilibrium of adaptogenic redox-systems. The beginning of cachexia development is reflected in the typical triad of B-symptoms including weight loss, fatigue, night-sweat and fever which comes with deficiency symptoms. Kampo medicines have been traditionally used to enhance appetite, attenuate chronic inflammatory processes and enhance microcirculation, as well as for the treatment of a disequilibrium

Table 2
Comparative table of randomized controlled trial (RCT)s on the efficacy of Kampo medicines for chemotherapy-induced nausea & vomiting (CINV) and anorexia.

First author (reference no.)	Formula	Study design	cancer site	outcome	Number of participants: Intervention group: I; Control group: C
Ohno et al.[2]	rikkunshito	Crossover RCT (open label)	stomach	Anorexia grade was significantly improved in intervention group (1.2 vs. 2.2).	I: $n = 10$; C: $n = 10$
Oteki et al. [3]	rikkunshito	RCT (open label)	lung	Food intake in intervention group was significantly higher than control group in carboplatin-containing regimen, but not in cisplatin and non-platinum regimens.	I: $n = 74$; C: $n = 38$
Ohnishi et al. [4]	rikkunshito	RCT (open label)	uterine	The complete control rate was significantly higher in the rikkunshito group than in the control group (57.9% vs. 35.3%).	I: $n = 19$; C: $n = 17$
Harada et al.[5]	rikkunshito	RCT (open label)	lung	The complete response rates in the overall phase were similar between the control and intervention groups for the highly (67.9% vs. 62.1%) and moderately (83.3% vs. 84.4%) emetogenic chemotherapy, respectively.	I: $n = 61$; C: $n = 58$
Hamai et al.[6]	rikkunshito	Crossover RCT (open label)	esophagus	The median rate of food intake decrease between days 4 and 6 was significantly lower in the intervention than the control course (2% vs. 30%).	I: $n = 18$; C: $n = 18$
Yoshiya et al.[7]	rikkunshito	Crossover RCT (open label)	lung	Reduction rate of caloric intake was significantly lower in intervention course than in control courses (18% vs. 25%). Plasma acyl ghrelin levels significantly increased by day 5 in intervention course but not in control course.	I: $n = 20$; C: $n = 20$
Okabe et al.[9]	hochuekkito	RCT (open label)	stomach	There was no significant decrease in adverse events including anorexia between the intervention (S-1+hochuekito) and control (S-1 only) groups.	I: $n = 56$; C: $n = 57$
Cheon et al.[10]	juzentaihoto*	Double-blind RCT	various	The change in the anorexia/cachexia subscale between baseline and the end of study in the intervention group was not significantly different from that in the placebo group (−4.63 vs.−2.75).	I: $n = 16$; C: $n = 16$

* Korean formulation

within the body constitution. Kampo medicines have been utilized for disease control and supportive care for patients with refractory cancer such as pancreatic cancer.[50]

Especially "hozai," tonic formulae, have been reported to show beneficial effects on the nutritional status of patients with cancer. They include three major hozais, i.e., hochuekkito, juzentaihoto, ninjin'yoeito, and further rikkunshito (Fig. 2).

Nutritional status (anorexia) can be improved with tonic (*qi*-supplementing) formulae such as rikkunshito and hochuekkito, and frailty may be prevented with juzentaihoto and ninjin'yoeito.[51] The efficacy of Kampo medicines for chemotherapy-induced nausea and vomiting as well as anorexia are summarized in Table 2. Only RCTs are selected as high levels of evidence.

The action mechanisms have been vastly elucidated. For instance, the effect of each herb in rikkunshito has been clarified[8]: Atractylodin in *Atractylodis lanceae rhizoma* stimulates ghrelin signals, pachymic acid in *Poria*, [10]-gigerol in *Zingiberis rhizoma*, and glycycoumarin in *Glycyrrhizae radix* inhibit ghrelin deacylase. Flavonoids in *Citri unsiu pericarpium* and *Pinelliae tuber* suppress appetite-inhibiting neurons. Compounds of ginger are further mucoprotective,[52] and ginseng enhances the motility of the gastrointestinal tract through stimulation of 5-hydroxytryptophane (5HT) receptors.[53] For chemotherapy-induced anorexia, the same central and peripheral ghrelin-dependent mechanisms can be re-installed by rikkunshito[54,55] (Fig. 3). RCTs have confirmed the clinical efficacy of rikkunshito in chemotherapy-induced anorexia.[2–7]

The mechanisms of action of ninjin'yoeito in chemotherapy-induced anorexia include the activation of neuropeptide Y neurons[56] and orexin-1 receptor.[57] A clinical study is now underway to validate the efficacy of ninjin'yoeito in preventing the progression of malnutrition and cachexia in patients with advanced or recurrent colorectal cancer.[58]

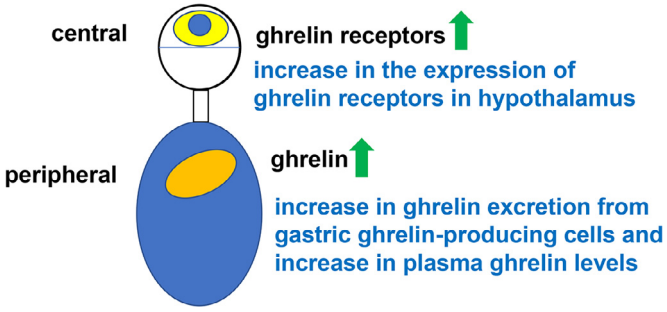


Fig. 3. Regulation of ghrelin excretion and receptor expression by rikkunshito.

The anti-inflammatory/regenerative properties of Kampo medicines[59] have also been explored in view of the anti-fibrotic, anti-oxidant and anti-apoptotic activity of saikokeishito.[60–63] Ginseng supplementation could reduce the serum levels of C-reactive protein in clinical trials.[64]

Furthermore, Ginseng oligopeptides were shown to exert radioprotective activity on the gastrointestinal tract via suppression of inflammatory cytokines and oxidative stress.[65]

When cachexia sets in, the occurrence of disability may be used to determine the survival time and quality of life. Even if no chemotherapy can be applied, various Kampo prescriptions are still possible (Fig. 4). As the nutritional status improves, patients and their family members are motivated to increase their daily ac-

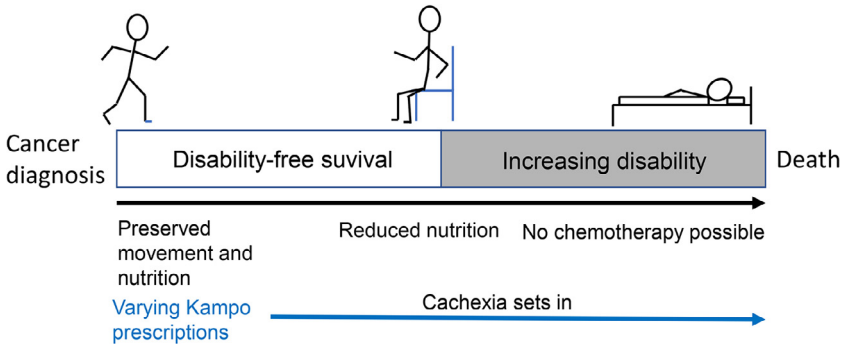


Fig. 4. What happens when cachexia sets-in?.

tivities with better concentration skills, which also prevents i.e., the danger of falling. They regain some self-confidence and mental strength, which supports not only physical functions, but also life expectancy, and thus, may restore a sense of value in life.

6. Conclusions

Kampo medicines can play an important role in maintaining or improving the nutritional status of cancer patients. Recent evidence has indicated the potential application of Kampo medicines for the prevention or amelioration of cachexia in patients with cancer.[66] The literature on action mechanisms of multicomponent, multitarget drugs such as herbal combinations has been described in cancer cachexia.[27,66] These approaches would enable patients to recover their social status and find life worth living.

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Author contributions

Writing - original draft: YM. Writing - review & editing: YM and SC. Supervision: SC.

Conflict of interest

YM received honoraria from Tsumura & Co. The authors declare that this review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. YM is an editorial board member of the journal but the editorial board membership had no bearing on the editorial process or decision.

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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