

Role of Kampo Medicine in Modern Cancer Therapy: Towards Completion of Standard Treatment

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Kampo Medicine is a traditional Japanese medicine and is well integrated with modern medicine. Anti-cancer agents are highly developed, and evidence regarding standard treatment has accumulated. Kampo Medicine helps support patients with cancer who lack vital energy and feel cold. Cancer chemotherapy is associated with adverse reactions that are refractory to modern therapy, such as anorexia, general malaise/fatigue, and peripheral neuropathy. Recently, evidence of the effectiveness of Kampo Medicines for these symptoms has been reported in randomized controlled trials (RCTs). The Japan Society for Oriental Medicine celebrated the first 20 years of its evidence-based medicine (EBM) committee in June 2021. The activities of this committee include publication of the *Evidence Reports of Kampo Treatment*, which contains RCTs and meta-analyses, including RCTs on cancer supportive care. Evidence is accumulating for hangeshashinto for mucositis, rikkunshito for anorexia, goshajinkigan and ninjin'yoeito for peripheral neuropathy, hochuekkito for general malaise/fatigue, and shakuyakukanzoto for myalgia/arthritis. However, additional evidence and further clinical trials are needed. Supportive care with Kampo Medicine increases the likelihood of completing standard treatment for cancer. (J Nippon Med Sch 2022; 89: 139–144)

Key words: Kampo, chemotherapy, anorexia, general malaise, peripheral neuropathy

Introduction

Kampo is traditional Japanese medicine that originated from ancient Chinese medicine and developed rapidly during the period from the 16th through the 19th centuries. Since 1967, national health insurance has covered 148 Kampo products for ethical (medical) use¹. Kampo medicine can be studied after obtaining a fellowship in any medical field, and it is important to determine the indications and limitations of Kampo medicine.

Drug therapies against cancer have developed greatly and include cytotoxic agents, molecularly targeted drugs, anti-angiogenic agents, and immune checkpoint inhibitors. These drugs are effective and safe, but standard treatment (the standard of care) must be completed to the extent possible, especially against highly aggressive cancers. Tumor-bearing patients lack vital energy, feel cold, and need supportive care, including warming measures such as Kampo medicines. Therefore, we must

seek a balance between offense and defense (**Fig. 1**).

The concept of Kampo for cancer supportive care is endorsed by Japanese industry, academia, and government. Industrial support includes the establishment of *The Future Vision for Kampo Medicines 2040-Responsibility for People's Health and Healthcare* by the Japan Kampo Medicines Manufacturers Association in 2018². Academic support includes the activities of the Kampo Study Group of the Japanese Association for Supportive Care in Cancer (JASCC). A practical guide for the use of Kampo medicine for cancer supportive care was published in 2020³. Government support is shown in the description of Kampo as a supportive measure for cancer patients in the *Basic Plan to Promote Cancer Control Programs*, issued by the Ministry of Health, Labour and Welfare of Japan in 2015⁴.

Cancer chemotherapy is associated with various adverse reactions. Although nausea, vomiting, and neutro-

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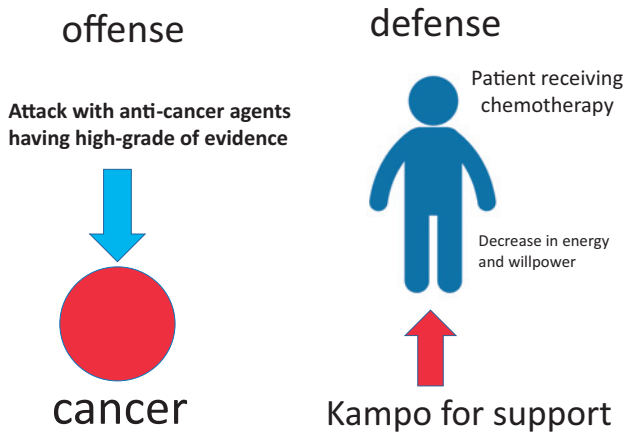


Fig. 1 Balance between offense and defense against cancer

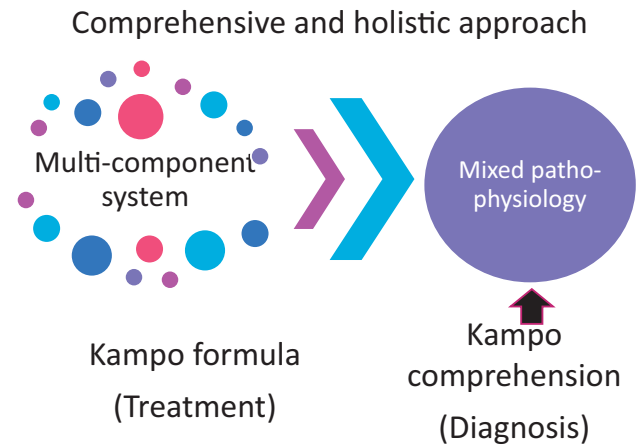


Fig. 2 Characteristics of Kampo diagnosis and treatment

penia have been largely addressed by progress in anti-emetic drugs and granulocyte colony-stimulating factors, some symptoms are refractory to modern medicine, such as anorexia, general malaise/fatigue, and peripheral neuropathy. Recently, RCTs have yielded evidence of the effectiveness of Kampo medicines against these symptoms.

The Japan Society for Oriental Medicine (JSOM) celebrated the first 20 years of the evidence-based medicine (EBM) committee in June 2021⁵. The activities of the EBM committee include publication of *Evidence Reports of Kampo Treatment (EKAT)*, which contains data from 90 RCTs and three meta-analyses on cancer supportive care⁶.

In this review, I discuss the role of Kampo Medicine in cancer supportive care and recent evidence for Kampo formulae.

Significance of Kampo in Modern Cancer Medicine

In Japan, experts in many medical fields prescribe Kampo medicines, which is important because clinicians know the natural history of each disease. Kampo medicines can be prescribed both by Kampo experts and clinicians working in Western medicine. Broad use of Kampo medicines would clarify their value and help patients and their families enjoy their benefits. The optimal selection of modern or Kampo medicines is determined after considering the disease and its stage and by understanding the value of each medicine. Therefore, I would like to propose the target “Kampo Medicine recognized and needed by modern medicine”. Kyushin Yumoto (1876-1941), a pioneer of contemporary Kampo Medicine in Japan, tried to combine Eastern and Western medicine. In his book, *Therefore, Medicine is Interesting*, Shigeaki Hinohara (1911-2017) suggests that Japanese doctors should more often prescribe Kampo Medicine when the benefits

of Western medicine are limited⁷.

Supportive care is defined by the National Cancer Institute of the United States as, “Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of supportive care is to prevent or treat as early as possible the symptoms of a disease, the side effects caused by treatment of a disease, and the psychological, social, and spiritual problems related to a disease or its treatment. It is also referred to as comfort care, palliative care, and symptom management”⁸.

A patient who develops side effects of cancer chemotherapy has a mixed pathophysiological status. There are limitations in individual care for each symptom, which leads to polypharmacy. In contrast, Kampo diagnosis is a comprehensive, holistic approach that directly suggests a proper Kampo formula (Fig. 2). Therefore, Kampo can solve the problem of polypharmacy. The problems and their Kampo solutions are summarized in Table 1.

In addition, Kampo drugs are usually recommended to be consumed “before or between meals” for three reasons. First, absorption of Kampo components might be delayed if Kampo drugs are taken after meals. Second, Kampo drugs are glycosides, which are hydrolyzed by intestinal flora. Postprandial Kampo medication would affect hydrolysis. Finally, Kampo products are approved for coverage by the national health insurance system only for administration before or between meals.

Kampo Formulae for Symptoms in Cancer Patients

1. Chemotherapy-Induced Mucositis

The health insurance system indications for hange-shashinto include oral mucositis and diarrhea.

An RCT on chemotherapy-induced diarrhea compared

Table 1 Problems in supportive care in cancer and their solutions with Kampo

Problem	Solution with Kampo
Tendency to polypharmacy	One formula for multiple symptoms
Most supportive drugs are expensive	Kampo products are cheap
Some supportive drugs have side effects	Side effects are rare for Kampo
No remedy for refractory symptoms	Kampo can ameliorate refractory symptoms
Small number of experts in supportive care	Kampo education is continuing

the efficacy and safety of hangeshashinto with a group not receiving the drug and found that the incidence of severe (grade 3 and 4) diarrhea was significantly lower in the hangeshashinto group than in the control group⁹.

A multicenter, placebo-controlled, double-blinded RCT on chemotherapy-induced oral mucositis by Matsuda et al.¹⁰ evaluated patients with grade 1 oral mucositis who were treated with hangeshashinto or placebo. Although the incidence of grade 2 or higher oral mucositis was not significantly different between the two groups, the mean duration of grade 2 oral mucositis was significantly shorter in the hangeshashinto group than in the placebo group.

Case presentation 1: A 70-year-old woman who had undergone successful surgery for pancreatic head cancer 3 years previously visited our outpatient clinic for treatment of oral mucositis, postprandial diarrhea, anorexia, and anxiety. Her physical findings were height, 162 cm; weight, 48 kg; oral cavity, reddish but not aphthous; and chest, no heart murmur. There was abdominal tenderness at the epigastrium, slightly increased intestinal peristaltic sounds, and no leg edema. Her Kampo medical findings were as follows: tongue, thick white coating; pulse, sunken; and intermediate abdominal strength, epigastric tenderness, and resistance. Hangeshashinto 7.5 g/day was prescribed. The above four symptoms resolved in 2 weeks and she was able to travel with her husband.

2-1. Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) can be roughly classified as axonopathy and neuronopathy. Taxanes such as paclitaxel and docetaxel cause axonopathy, which resolves after drug cessation or dose reduction. Platinum agents such as oxaliplatin cause neuropathy, which often becomes severe and continues for several years after therapy. Goshajinkigan has been used to treat diabetic peripheral neuropathy. RCTs have evaluated the efficacy of goshajinkigan for taxane-induced peripheral neuropathy^{11,12}. Kaku et al.¹¹ reported that goshajinkigan was effective for paclitaxel-induced peripheral grade 1 neuropathy in patients with gynecologic cancers.

The change in the incidence of abnormal current perception threshold ratio at 6 weeks of administration was significantly smaller in a goshajinkigan plus vitamin B12 group than in a vitamin B12 alone group. Abe et al.¹² reported the preventive efficacy of goshajinkigan for docetaxel-induced peripheral neuropathy in patients with breast cancer. CIPN incidence and grade were significantly lower in the goshajinkigan group than in the control group (non-administrative group).

Case presentation 2: A 50-year-old man with multiple skin tumors was diagnosed with cancer of unknown primary cause (poorly differentiated adenocarcinoma). He was treated with carboplatin and paclitaxel but reported numbness of the extremities after the second cycle of chemotherapy. The general findings were height, 168 cm; weight, 67 kg; general malaise; mild appetite decrease; and nocturnal pollakisuria. Kampo medical findings were tongue: no coating, slightly reddish; pulse: weak; abdomen: weak, with weakness of the lower abdominal region. On the basis of these findings, goshajinkigan 7.5 g/day was prescribed. CIPN did not progress after administration of goshajinkigan and remained at grade 1. The above chemotherapy regimen was administered without any decrease in dose, and six scheduled cycles were completed. The relative dose intensity was thus 100%, and treatment resulted in a complete response and diminishing of all skin tumors.

2-2. Oxaliplatin-induced peripheral neuropathy.

Retrospective¹³ and prospective single arm¹⁴, phase 2¹⁵, and phase 3¹⁶ studies, and two meta-analyses^{17,18} concluded that goshajinkigan was not effective for oxaliplatin-induced peripheral neuropathy. Recently, the efficacy of ninjin'yoeito for oxaliplatin-induced peripheral neuropathy was evaluated¹⁹ in the HOPE-2 study. The grade of oxaliplatin-induced chronic peripheral neuropathy was significantly lower in the ninjin'yoeito group than in a control group (ninjin'yoeito non-administration). In addition, the relative dose intensity of oxaliplatin was significantly greater in the ninjin'yoeito group than in the control group. Therefore, ninjin'yoeito can reduce periph-

eral neuropathy and increase the efficacy of oxaliplatin. Overall survival and recurrence-free survival were longer than in the control group, although the differences were not significant.

3. Chemotherapy-Induced Myalgia/Arthralgia

In an RCT on the efficacy and safety of shakuyakukanzoto for patients with non-small cell lung cancer²⁰, 50 patients were randomly assigned to a shakuyakukanzoto group or control group (shakuyakukanzoto non-administration). The incidence and grade of chemotherapy-induced myalgia/arthralgia were significantly lower in the shakuyakukanzoto group than in the control group.

Case presentation 3: A 60-year-old woman visited our outpatient clinic with myalgia/arthralgia after chemotherapy (carboplatin plus paclitaxel) for advanced uterine cervical cancer. She had mild renal dysfunction, and her gynecologist advised against the use of nonsteroidal anti-inflammatory drugs. Kampo diagnosis revealed that her tongue was normal, her pulse was string-like, and her abdominal muscle tension was increased. Shakuyakukanzoto 7.5 g/day was prescribed. She visited our clinic after 1 week and happily reported only mild myalgia/arthralgia after chemotherapy. She continued chemotherapy with 1-week shakuyakukanzoto administration.

4. General Malaise/Fatigue

In an RCT Jeong et al.²¹ reported that hochuekkito significantly decreased cancer-related fatigue. Although American ginseng showed significant efficacy for cancer-related fatigue in a double-blind RCT²², there has been no other RCT of the Kampo formula for this refractory symptom.

Case presentation 4: A 45-year-old woman visited our outpatient clinic for treatment of fatigue and insomnia. She had undergone surgery for breast cancer 6 months previously and received hormonal therapy with a 5-year plan. She returned to work 1 month after surgery and felt considerably more fatigue than before surgery. She slept poorly, and her fatigue gradually worsened. Physical findings were height, 150 cm; weight, 42 kg. She had mild anemia and was exhausted. She complained of general malaise, anorexia, exertional palpitations, and depression. Kampo diagnosis—tongue: covered with white fur. Pulse: small, deficient, string-like. Abdomen: weak, with mild right hypochondric discomfort. Hochuekkito 7.5 g/day was prescribed for postoperative fatigue, and sansoninto 5.0 g/day was prescribed for insomnia. Her symptoms started to improve after 2 weeks and had resolved at 1 month.

Case presentation 5: A 38-year-old woman was referred

to our outpatient clinic because of nivolumab-induced general malaise. The patient had an esophageal melanoma with liver metastases. Immune-related adverse events were excluded after biochemical tests, including thyroid function. Physical findings were height, 162 cm; weight, 38 kg; and enlarged liver palpated through the skin. Kampo diagnosis: The patient's tongue had no fur, her pulse was deficient and sunken, and her skin was markedly dry. Her abdomen was weak, and pulsation in the supra-umbilical region was brisk. Juzentaihoto 7.5 g/day was prescribed, and her general malaise was markedly better than after her previous cycle of nivolumab. She was able to continue treatment thereafter.

5. Anorexia

Basic experiments have been conducted on the efficacy of rikkunshito in treating cisplatin-induced anorexia. Rikkunshito increases excretion of ghrelin from gastric parietal cells²³ and expression of the ghrelin receptor in the hypothalamus²⁴. There is also a crossover RCT on the efficacy of rikkunshito for cisplatin-induced anorexia in patients with gastric cancer²⁵ and lung cancer²⁶.

Case presentation 6: A 63-year-old woman visited our outpatient clinic because of chemotherapy-induced anorexia. She was receiving carboplatin plus paclitaxel for recurrent ovarian cancer. She had peripheral neuropathy and general malaise, in addition to anorexia. Kampo diagnosis: She was depressed and worried about her disease. Her tongue had intermediate white fur, her pulse was deficient, and her abdomen was weak, with tenderness, resistance, and splashing sounds in the epigastric region. On the basis of these findings, rikkunshito 7.5 g/day and kososan 7.5 g/day were prescribed. Her appetite and oral intake gradually increased, and she was able to continue chemotherapy.

Case presentation 7: A 76-year-old man was referred from a urology clinic for treatment of anorexia and fatigue. He received hormonal therapy for advanced prostate cancer with multiple bone metastases. He was fragile, fatigued, and had no appetite because of taste disorders. Kampo diagnosis: His tongue had thin white fur, his pulse was floating and deficient, and his abdomen was weak, with epigastric tenderness and resistance and mild right hypochondric discomfort. Hochuekkito 7.5 g/day was prescribed, and 1 month later, he said, "That Kampo medicine was great. It made me energetic, and my appetite gradually recovered. I became able to do some farming chores." He received hormonal therapy from the urology department and Kampo treatment at our clinic.

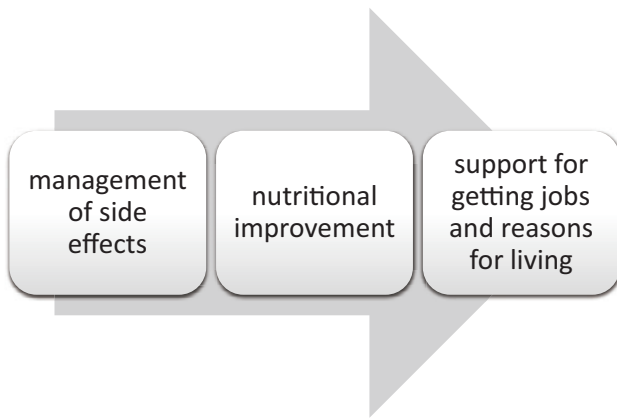


Fig. 3 Future vision of Kampo Medicine for supportive care of patients with cancer

Case presentation 8: A 70-year-old woman received carboplatin plus paclitaxel for carcinomatous peritonitis of unknown primary cancer at a cycle of 3 weeks. She experienced anorexia from day 1 to day 7 after each chemotherapy, and her performance status was 3. Kampo diagnosis: She looked exhausted. She felt coldness in her lower extremities, could not sleep well, and often awoke at night. She had anemia (hemoglobin concentration, 8.9 g/dL). Her tongue had no fur, her pulse was sunken and small, and her abdominal strength was weak with epigastric pulsation. Ninjin'yoeito 9.0 g/day was prescribed, and her appetite recovered within 3 weeks. She continued chemotherapy, which led to a complete response and disappearance of her ascites. Her chemotherapy regimen was changed to paclitaxel plus bevacizumab, and ninjin'yoeito was continued. She survived for approximately 5 years after disease onset, in good condition. She even desired to do volunteer work, which surprised her family and medical staff.

Clinical Perspectives on Selecting Kampo Formulae

We should not focus on one symptom; instead, we must observe the patient as a whole, as if we were looking at a distant mountain. It is a clinical tip to seek any subjective symptoms or objective findings other than the chief complaint by history taking and physical examination from the viewpoint of Kampo Medicine. Through these procedures, we can uncover hints regarding the proper prescription of a Kampo formula. This tip is also important for selecting the second or third choice of Kampo formula, when we do not obtain a sufficient clinical response with the first choice.

Kampo plays an important role in controlling the side effects of cancer chemotherapy. However, further contri-

butions are possible, perhaps by improving nutritional status and support for employment and reasons for living (Fig. 3).

Conclusions

Today, experts in various medical fields are able to prescribe Kampo formulae. Clinical studies, especially RCTs in English, have been published by authors from Japan. Listening to patient narratives and conducting detailed physical examinations will lead to the proper selection of Kampo formulae.

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