Kampo medicine originated in ancient China and developed uniquely in Japan. More than 70% of Japanese physicians use Kampo medicine in daily practice. As for cancer treatment, Kampo medicine is widely used by surgeons and oncologists. It is used in the regular practice for the treatment of cancer and cancer-related symptoms from the early stage to the terminal care. This paper describes Kampo treatment for cancer, making references to publications in clinical and basic research.

Introduction

Kampo medicine originated in ancient China and developed uniquely in Japan. It has been both taught to, and used by, conventional Western physicians for the last 30 years.

Currently, more than 70% of Japanese physicians (including nearly 100% of Japanese obstetrics and gynaecology (Ob/Gyn) doctors) use Kampo medicine in daily practice including the university hospital, together with high-tech medical treatments like organ transplantation or robotic surgery. Kampo medicine is considered a government-regulated prescription drug and currently 148 formulas are listed on the Japanese national insurance program.

As for cancer treatment, Kampo medicine is widely used by surgeons and oncologists. It is widely used in the regular practice for the treatment of cancer and cancer-related symptoms from the early stage to the terminal care. Because Kampo medicine has been totally integrated into Western medicine in Japan, motivation to promote clinical trials is lacking. On the contrary, basic research concerning cancer treatment have piled over the last 30 years by the physicians and pharmaceutical researchers. Prevention of recurrence or metastasis of cancer cells have been well studied in basic research, however there is little data in the clinical study because it takes time to accomplish.

In this review article, Kampo treatment for cancer will be described based on the clinical and basic research articles.

Prevention of Cancer

Chemoprevention is one of the topics in cancer treatment since it has been reported that non-steroidal anti-inflammatory drugs (NSAIDs) reduce the prevalence of colon cancer.

Shosaikoto (小柴胡湯) for the prevention of the hepatocellular carcinoma

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levels of AST and ALT, it has been widely used for the treatment of chronic hepatitis. Because chronic hepatitis is very common in Japan as well as other Asian countries and no established treatment is available, Shosaikoto is widely used for the purpose of liver protection. Oka et al. reported on a five-year follow-up study of liver cirrhosis patients. The subjects were 260 patients and randomly divided into two groups, one treated with Shosaikoto and the other without. Onset of the hepatocellular carcinoma and survival rate were evaluated. The results revealed that the onset of hepatocellular carcinoma decreased and longevity improved in the group with Shosaikoto especially in the group of liver cirrhosis by non-B viruses. In the US, the effectiveness of Shosaikoto, Hochuekkito and Ninjinyoueito as well as glycirrhizine are listed as the effective treatment for the chronic hepatitis.

Shoseiryuto (小青竜湯) for the prevention of lung cancer

In the basic research, there are several reports. One is the Shoseiryuto (小青竜湯) for the prevention of lung cancer. Lung cancer was induced in the mouse model by 4-nitroquinolone-N-oxide (4NQO) s.c. followed by the glycerol intake. This treatment induced the lung tumor in 93.3% of mice without Shoseiryuto, and 33.3% with Shoseiryuto. This data showed the reduction of the onset of lung cancer with Shoseiryuto.

Shosaikoto (小柴胡湯) for the prevention of melanoma

Another study was done by Kato et al. He established a RET-transgenic mouse line (304/B6) in which stepwise development of a skin melanocytic benign tumor and malignant melanoma can be observed. In this mouse model, he demonstrated that the herbal medicine Shosaikoto has anti-tumor and anti-metastatic effects on malignant melanoma through regulation of protein expression levels of matrix metalloproteinase (MMP) and its inhibitor. This study was followed by additional evidence showing that Ret protein expression levels of tumors in Shosaikoto-treated mice were higher than those of tumors in untreated mice at benign, malignant, and terminal stages of the tumors. The reduced Ret expression at the terminal stage was partially restored. From this experiment, it was concluded that the anti-tumor effect of Shosaikoto involves the promoted preparation of Ret protein as a tumor transplantation antigen, which probably overcomes its potentially increased oncogenic activity.

Treatment with Surgical Operation

Daikenchuto (大建中湯) for the prevention of post-surgical ileus

Daikenchuto has been shown to be effective in preventing the post-surgical ileus and widely used to prevent ileus after abdominal surgeries in the field of not only gastrointestinal but also gynecology. Daikenchuto also prevents post-surgical intestinal adhesion by gastroprokinetic and anti-inflammatory effects. Motilin, Kampo medicine is considered a government-regulated prescription drug and currently 148 formulas are listed on the Japanese national insurance program.

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Steam manipulation is observed in converting the Gingerol to Shogaol in the ginger and this Shogaol is important in secreting CGRP leading to the increase of blood flow of the gut as a result.

Prolonged paralytic ileus occurring in the hepatectomized patients may induce hyper-ammonemia. **Daikenchuto** is used to suppress the elevation of serum ammonia in hepatectomized patients. Presumably, **Daikenchuto** stimulates the peristalsis and does not allow the growth of the intestinal bacteria producing ammonia. Imazu *et al.* showed this hypothesis with a different Kampo formula, **Juzentaihoto**. He showed that the change of the intestinal flora is the main resource of the serum ammonia elevation and this is suppressed by **Juzentaihoto**, because with **Juzentaihoto**, the change of the intestinal flora was suppressed.

**Treatment with Chemotherapy**

There are many reports that Kampo treatment reduces the side-effects of chemotherapy. **Juzentaihoto** alleviates the side-effect of UFT (Uracil-Tegafur, anti-cancer drug). Six months follow-up study of gastric cancer patients with UFT after curative operation revealed that suppressor T cell function was lower and cytotoxic/killer cell function higher in the group with **Juzentaihoto**. This study also showed that subjective and objective adverse symptoms caused by UFT were less with **Juzentaihoto**.

**Saireito** (柴芩湯) alleviates the side-effects of CDDP

Another study examined 26 cases of lung cancer, which was divided into 2 groups, one with **Saireito** (n = 10) and the other without (n = 16). Nephrotoxicity with cis-diamminedichloroplatinum (CDDP) was evaluated. Serum levels of BUN increased in the group without **Saireito**, while serum BUN levels were not elevated in the group with **Saireito**. Also, creatinin clearance became lower and N-acetyl-D-glucosaminidase increased, while those markers stayed as normal in the group with **Saireito**. This study showed that **Saireito** is effective in alleviating the nephrotoxicity of CDDP.

**Juzentaihoto** (十全大補湯)

alleviates the side-effects of CDDP

Sugiyama *et al.* screened 11 Kampo formulae to evaluate the protection of nephrotoxicity induced by CDDP. Among the 11 Kampo formulae, nine formulae showed significant reduction of nephrotoxicity. Although Flosemide also reduced the nephrotoxicity, it also diminished the effectiveness of CDDP. Among nine Kampo formulae that reduced the nephrotoxicity, **Juzentaihoto** was the most effective. **Juzentaihoto** also protected the liver and suppressed the liver injury. Among the herbs in **Juzentaihoto**, *Angelicae radix* showed the most effectiveness in liver and kidney.

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Among the herbs in Juzentaihoto, Angelicae radix showed the most effectiveness in liver and kidney protection. Sodium malate in Angelicae radix was responsible for protecting the liver and kidney functions. The mechanism of action of sodium malate was that this compound binds to CDDP and forms the diammino-platinum(II) malate, which has a similar chemical structure to the CDDP-derived chemical, Carboplatin (CBDCA). This CBDCA is used clinically and it has less toxicity against the kidney, however, the effect is weaker. Also, this sodium malate did not increase bone toxicity; Juzentaihoto protected the bone marrow and blood cell count was not decreased with Juzentaihoto. Hangeshashinto (半夏瀉心湯) alleviates the side-effects of CPT-11

Another good example that showed the reduction of the side-effects of chemotherapy is Hangeshashinto. Irinotecan hydrochloride (CPT-11), a semi-synthetic derivative of camptotecin, is an anti-cancer drug which inhibits nucleic acid synthesis by topoisomerase I inhibition. CPT-11 possesses a wide anti-tumor spectrum and is widely used for the treatment of lung cancer, colon cancer and malignant lymphoma. Diarrhea is the main side-effect that occurs in the early stage and causes the discontinuation of the drug administration. Hangeshashinto is used to stop the irinotecan-induced diarrhea. Mori et al. reported the result of RCT of Hangeshashinto and CPT-11. Of the 41 patients with advanced lung cancer, 18 took Hangeshashinto and 23 did not. Among 41 patients, 39 experienced diarrhea. Although there were no differences of diarrhea frequency and duration, severe diarrhea (grades 3 and 4) was reduced in the group with Hangeshashinto (one among 18 patients) as compared to the group without Hangeshashinto (nine among 23 patients). This study showed that Hangeshashinto is recommended for use with CPT-11. The mechanism of action is also well studied. CPT-11 is changed to 7-ethyl-10 hydroxy-camptotecin (SN-38) in the liver and SN-38 undergoes glucronate conjugation changing into inactive SN-38 glucronide. Later, it is excreted into the bile, and is then deconjugated by β-glucronidase, which was contained in the intestinal bacteria to become SN-38 again. This SN-38 induces delayed diarrhea. Hangeshashinto contains baicalin, which serves as another resource of β-glucronidase. This competitive action of baicalin against SN-38 glucuronide inhibited the formation of active form of SN-38 without glucronide. As a result, the delayed diarrhea caused by deconjugated SN-38 was alleviated by Hangeshashinto.

Treatment with Irradiation

There is a report that the irradiation with Kampo improved the survival rate in the progressive uterus cervical cancer. Treatment was the combination of low dose in situ irradiation and external irradiation. Kampo formulae were Juzentaihoto (十全大補湯), Ninjinyoueito (人参養榮湯) and Hochuekkito (補中益氣湯). Irradiation only survival rate is higher in the group treated with Kampo formulae. Five- and ten-year survival rates were 65.6% and 49.1% in the irradiation only group (total number was 119; stage IIb, 64 cases and stage IIIb, 55 cases). On the other hand, these were 75.6% and 65.9% in the irradiation with Kampo group (total number was 82; stage IIb, 43 cases and stage IIIb, 39 cases). This study showed that the combination of Kampo formula and irradiation improved the survival rate of progressive uterus cancer patients.

Juzentaihoto for the hematopoiesis after irradiation

Effects of Juzentaihoto on the recovery of hematopoietic systems from radiation injury are analyzed. Colony-forming unit-spleen (CFU-S) are hematopoietic colonies formed in the spleen of recipient mice that have been lethally irradiated and injected with donor bone marrow cells. Day-14 CFU-S represents primitive hematopoietic stem cells (HSCs) and day-9 CFU-S represents more mature HSCs. The mice injected with Juzentaihoto-treated bone marrow cells showed better general condition, heavier spleens with larger and more numerous colonies than the control mice on day 14. On the other hand, there was no difference in the number of CFU-S between Juzentaihoto-treated and control groups on day 9. Since the day-14 CFU-S assay is thought to reflect the most primitive progenitor cells in the hematopoietic system, these results

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strongly suggested that Juzentaihoto acts on stem cells in the G0 phase to manifest recovery-enhancing effects from radiation injury. After this study, the same group fractionated Juzentaihoto to obtain oleic acid and found that linolenic acid in Juzentaihoto was the responsible compound.

**Prevention of Recurrence and/or Metastasis**

This is one of the very interesting points with Kampo treatment. There are a lot of basic research studies and several clinical studies currently ongoing. The mechanism is also being studied.

**Juzentaihoto for the prevention of colon cancer metastasis**

Oral administration of Juzentaihoto before tumor inoculation resulted in the dose-dependent inhibition of liver metastasis of colon 26-L5 carcinoma cells and significant enhancement of survival rate compared to the untreated control. This effect was lost when macrophages and T-cells were eliminated. These data support the fact that immunological function plays a central role in the mechanism of Juzentaihoto.

**Palliative Care**

Kampo medicine is also used in palliative care. Ninjinto (人参湯), Shikunshito (煎君湯), Rikkunshito (六君子湯) and Bukuryoshigyakuto (茯苓四逆湯) were often used to improve patients’ appetite and help them recover from the cachexia.

**Daikenchuto for the constipation by morphine**

Morphine is the most effective anti-nociceptive agent and is used to manage pain experienced by terminal cancer patients. However, it induces severe constipation, causing an obvious reduction in quality of life. Daikenchuto is evaluated in the mouse model and has been shown to improve the gastrointestinal movement. The mechanism is assumed to enhance the contraction of longitudinal muscle and relax the tonic contraction of circular muscle. This mechanism explains the mechanism of action of Daikenchuto for the constipation induced by morphine.

**Conclusion**

I introduced a part of the evidences of Kampo medicine for the treatment of cancer. As a matter of fact, Kampo medicine is broadly used for the treatment of cancer from the early stage to the end of life care. Juzentaihoto and Hochuekkito are the most commonly used; Juzentaihoto is investigated to a greater extent than Hochuekkito. However, we need to further investigate the indications and mechanism of action and clarify the usefulness of Kampo treatment for cancer.

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**Biography**

Kenji Watanabe, MD, PhD, FACP

**PRESENT ACADEMIC RANK AND POSITION**

Current Position Title:
2001–present  Associate Professor
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**EDUCATION**

Degrees:
1984  MD, Keio University School of Medicine, Tokyo, Japan
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Residency:
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Postdoctoral Training:
1991–1993  Department of Genetics, Stanford University, California, USA
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**BOARD CERTIFICATION**

1987  Japanese Board of Internal Medicine
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2003  Fellow of American College of Physician

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