Integrating Kampo and Evidence-Based Medicine (4) – Type 3 Case

The Effects of Kampo Medicine against the Side Effects of Anticancer Drugs

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Introduction

In this series, I define four types of use of Kampo medicine in daily clinical practices within Japan's unified medical system, and discuss the diseases that fall under each of these types, by giving relevant case examples. In the previous issue of this journal, I introduced four episodes, and explained that they fall under the four types of use of Kampo medicine in daily clinical practices. Let me recount them below.

Type 1: Kampo treatment is better than standard modern medical treatment

Type 2: The effects of standard modern medical treatment and Kampo treatment are both strengthened when the two are used in combination

Type 3: The side effects of standard modern medical treatment can be mitigated in combination with Kampo treatment

Type 4: Circumstances prevent the application of standard modern medical treatment, but treatment is needed

In this article, we shall take a look at Type 3 cases, in which Kampo treatment is used in combination with standard modern medicine to mitigate the side effects of the latter. Representative of these are cases in which Kampo medicine is used to mitigate the side effects of anticancer drugs that are commonly used against cancer. No data exists that shows that Kampo medicine could treat cancer per se, but many studies provide proof that it has the effect of mitigating the side effects of operative treatment, anticancer drug treatment, radiation treatment, and other such treatments that are used to treat cancer.

Below, I shall discuss how Kampo medicine is used against the side effects of anticancer drugs in routine clinical practice, through examples.

1. A Certain Episode

Prof. Yoshiharu Motoo (Department of Medical Oncology, Kanazawa Medical University) provides front-line treatments to cancer patients. He is a close friend of mine who also actively engages in the study of Kampo medicine, in an effort to constantly provide the best treatment to his patients by combining the two.

Dr. Motoo has treated many cancer patients to date, and has presented many papers. I have heard many stories of his experiences, but I found the following case particularly interesting.

A man in his late fifties received surgery for transverse colon cancer in March 20XX. He was at StageⅢb. Since the five-year survival rate of StageⅢb transverse colon cancer is approximately 60.1%, his prognosis was not good. Therefore, the mFOLFOX6 regimen was decided to be administered as postoperative adjuvant chemotherapy. This mFOLFOX6 is a chemotherapy regimen that combines folinic acid (Leucovorin), 5-FU, and oxaliplatin.

The side effects of FOLFOX treatment are diverse. Effects that emerge immediately after administration of the treatment include peripheral neuropathy such as numbness and pain in the hands, feet and mouth; myelosuppression; digestive symptoms such as nausea, vomiting, and loss of appetite; diarrhea and other lower digestive tract disorders; stomatitis; and taste disorders. Several weeks later, skin and nail discoloration, hand-foot syndrome, hair loss, and other symptoms begin to appear. Frequently, these side effects require a reduction in drug dose or a suspension of drug administration.

In response to this situation, Dr. Motoo prescribed 9.0 g/day of ninjin'yoeito extract for ethical use (Tsumura & Co., Ltd., Tokyo, Japan) from the first cycle of chemotherapy, to mitigate peripheral neuropathy and hematotoxicity among the side effects. As a result, mFOLFOX6 dose did not need to be reduced to the end, and the postoperative adjuvant chemotherapy was successfully completed after administering the planned 12 cycles. The cumulative dose of oxaliplatin was 1,020 mg/m^2, but no accumulative peripheral neuropathy appeared. Only acute peripheral neuropathy was noted, but it was up to grade 1, and disappeared at an early stage. At a performance status (PS) of 0, the patient was thereafter able to complete his treatment while engaging in regular work duties.

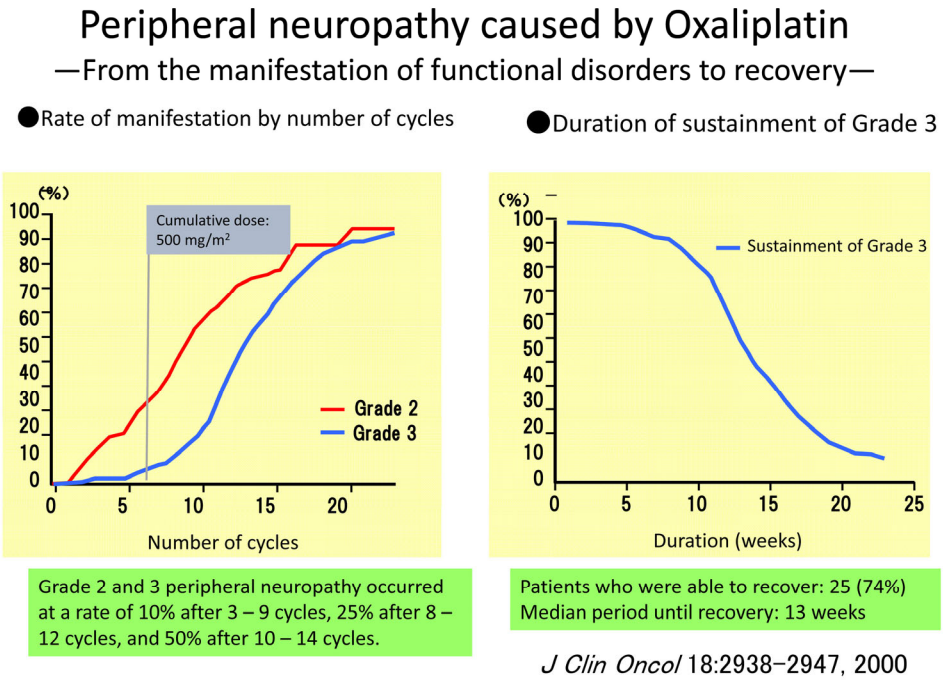
In this case, neither the physician nor the patient was optimistic of the prognosis, as the patient had Stage Ⅲb transverse colon cancer and was at high risk of recurrence. However, what was immediately necessary was to mitigate the side effects of mFOLFOX6 treatment and successfully complete the postoperative adjuvant chemotherapy to prevent recurrence.

In particular, peripheral neuropathy that occurs as a side effect of oxaliplatin was a burden for the patient, to the point that treatment is sometimes interrupted for this reason. Therefore, the fact that this particular patient's condition progressed in an extremely mild manner probably lightened his spirit. Generally, when the cumulative dose of oxaliplatin exceeds 500 mg/m^2, grade 2 peripheral neuropathy is said to occur at a rate of 30%, but this patient's dose had exceeded 1,000 mg/m^2. The administration of ninjin'yoeito helped maintain his PS at a good level and would probably lead to his good prognosis thereafter.

Dr. Motoo provides this type of treatment to many patients within his daily clinical practice. The Kampo medicine that was used here was ninjin'yoeito, chosen based on Dr. Motoo's long years of clinical experience.

Dr. Motoo has published many papers on the adjunctive use of Kampo medicine to standard cancer treatment, from which we daily benefit[1].

Reference: Peripheral neuropathy caused by Oxaliplatin (product name: L-Plat®)



De Gramont A, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18: 2938-2947, 2000

2. General Malaise, Loss of Appetite, Poor Mood, etc. during Cancer Chemotherapy

All anticancer drugs accompany side effects to some extent. It is said that hochuekkito is effective against these side effects[2) 3)], and general clinicians widely administer this prescription to patients who are undergoing chemotherapy. juzentaihoto is another prescription that is used frequently for the same purpose. Its effects against leukopenia and thrombopenia and controlling metastasis have been verified in animal experiments[4)].

In Japan, hochuekkito, juzentaihoto, and ninjin'yoeito are commonly prescribed to increase body strength and improve appetites during chemotherapy against cancer, but there are specific Kampo prescriptions for each type of symptom.

3. Utilization of Kampo Medicine to Mitigate the Side Effects of Anticancer Drugs

1) Effects of Kampo medicine against the side effects of Cisplatin and Carboplatin

In Dr. Motoo's case, ninjin'yoeito was used to mitigate the side effects of oxaliplatin. Goshajinkigan has also been reported to be effective by Shindo et al[5)].

Platinum compounds cisplatin (CDDP) and carboplatin (CBDCA) display a strong antitumor effect, but their side effects are also strong, and difficulties are often experienced in counteracting them. A number of studies regarding this are introduced below.

The first is a study of saireito against kidney damage when administering Cisplatin.

Dr. Jiro Okimoto et al. investigated renal damage after administering Cisplatin through two groups of lung cancer patients: 10 patients in the saireito group were given 9g/day of saireito extract (Tsumura Pharma, Ltd., Tokyo, Japan) for 15 days beginning on the day before administering Cisplatin, and 16 patients in the control group were not given saireito. As a result, the control group saw an increase in BUN such that average BUN was 26.5 mg/dL on the third day of Cisplatin administration and 25.4 mg/dL on the seventh day, but in the saireito group, BUN did not exceed the normal level of 20 mg/dL neither on the third nor seventh days. Furthermore, in the control group, Cisplatin administration brought about a decrease in Ccr (creatinine clearance) and an increase in NAG (N-acetyl-β-D-glucosaminidase), but such fluctuations were significantly controlled in the saireito group. From this result, Dr. Okimoto et al. suggest that saireito mitigates Cisplatin renal damage[6)].

Another study examines the effect of juzentaihoto against myelosuppression caused by the administration of Carboplatin. Dr. Jiro Okimoto et al. investigated Carbotin myelosuppression by examining 70 lung cancer patients who were not administered juzentaihoto in the first cycle but were administered 7.5 g/day of juzentaihoto extract (Tsumura Pharma, Ltd., Tokyo, Japan) for 21 days from the day before being administered Carboplatin in the second cycle. As a result, Hb decreased by 3.1 g/dL on the average when comparing the levels before and after Carboplatin administration in the first round, but decreased by only 1.4 g/dL on the average in the second round, indicating that the decrease of Hb was significantly controlled. The lowest values of leucocytes and neutrophils were 2,230/μL and 740/μL on the average, respectively, in the first round, and 2,960/μL and 1,220/μL on the average in the second round, indicating that the decrease in leucocytes and neutrophils were significantly controlled. The lowest value of platelets decreased by 5.7×10^4/μL on the average in the first round, but decreased by a mere 9.0×10^4/μL on the average in the second round, indicating that the decrease in platelets was also significantly controlled[7)].

2) Kampo medicine against the side effects of fluoropyrimidine drugs

Fluoropyrimidine drugs are antimetabolites. The most representative is Fluorouracil (5-FU), from which a number of drugs have been developed as prodrugs. Its side effects occur in the mucous

membrane of the alimentary canal and bone marrow, where cellular proliferation potential is high. As a result, digestive symptoms such as loss of appetite, general malaise, diarrhea, nausea, vomiting and stomatitis appear, in addition to myelosuppression symptoms such as leukopenia. Hair loss and hand-and-foot syndrome may also appear.

A number of clinical studies are introduced below.

Dr. Takuya Yamada conducted a randomized controlled trial (RCT) on 94 postoperative gastric cancer patients by prescribing an oral administration of 5-FU to all patients and dividing them into a group that was also given juzentaihoto in combination and a group that was not. No difference in five-year survival rate was observed among all patients and patients in Stages Ⅰ and Ⅱ, but among patients in Stages Ⅲ and Ⅳ, median survival time was 35.1 months for the combined administration group and 14.3 months for the non-combined administration group. Five-year survival rate was 25% for the combined administration group and 0% for the non-combined administration group. This showed that life expectancy was significantly extended in the combined administration group[8].

Dr. Tsuyoshi Ohara et al. conducted an RCT on a total of 178 patients who were prescribed Tegafur for gastric cancer, colorectal cancer, breast cancer, or other types of cancer, by dividing them into a hochuekkito combined administration group, a ninjin'yoeito combined administration group (as will be discussed later), and a Tegafur single administration group. As a result, significant improvements were observed in subjective symptoms, objective symptoms and general symptoms in groups administered with Kampo medicine in comparison with the control group (non-administration group). The side effects of Tegafur were observed in all groups, but they were not of a serious level in the Kampo administration group. Additionally, an improvement in appetite was observed in the hochuekkito group, and improvements in nausea, vomiting, bowel movement, motivation, fatigue and malaise were observed in the ninjin'yoeito group[9].

3) Kampo medicine against the side effects of Irinotecan

Irinotecan (CPT-11) is a semisynthetic of Camptothecin with a wide antitumor spectrum. In addition to single administration, it is frequently used in combination with other drugs, such as in FOLFIRI (Folinic acid + 5-U + Irinotecan) treatment. Its side effects include leukopenia, diarrhea, and general malaise.

Among these side effects, it has become possible to improve leukopenia by administering a human granulocyte colony-stimulating factor (G-CSF). With regard to diarrhea and general malaise, the combined use of Kampo medicine has been found to be effective to a certain extent.

Hangeshashinto is used particularly for delayed diarrhea. Dr. Kiyoshi Mori et al. performed a standard treatment against progressive non-small cell lung cancer by combining the use of Cisplatin and Irinotecan. Particularly to prevent delayed diarrhea caused by Irinotecan, he administered 7.5 g/day of hangeshashinto extract (Tsumura Pharma, Ltd., Tokyo, Japan) and evaluated its clinical efficacy through an RCT. Of the 41 patients who were able to be evaluated, there were 18 patients in the hangeshashinto administration group and 23 patients in the non-administration group. Improvements in diarrhea were evaluated from Grades 0 to 4. In the first round of treatment, a significant improvement in diarrhea grade was observed in the administration group compared to the non-administration group ($P = 0.044$), and the incidence rate of diarrhea Grade 3 and above was significantly low ($P = 0.018$)[10) 11)].

4) Kampo medicine against the side effects of taxane drugs

Paclitaxel and Docetaxel are taxane anticancer drugs. Paclitaxel was discovered from the bark of *Taxus brevifolia*, and is used singly or in combination with another anticancer drug. Among the side effects of taxane anticancer drugs, digestive symptoms such

as nausea and vomiting are rare, but leukopenia and other myelosuppression occur at a high rate, and hair loss is inevitable. With Paclitaxel, peripheral neuropathy such as numbness at the tips of hands and feet, as well as muscle pain and joint pain also appear at a high rate (35.7%).

There are a number of reports that say goshajinkigan and shakuyakukanzoto are effective in mitigating peripheral neuropathy, muscle pain and joint pain caused by Paclitaxel.

Dr. Takao Hidaka et al. examined the clinical efficacy of shakuyakukanzoto against muscle pain in 20 serous ovarian cancer patients who began receiving combination chemotherapy using Paclitaxel and Carboplatin but who displayed muscle pain of Grade 2 (degree of pain that requires several doses of analgesic) or higher even after using NSAIDs in the first round of treatment (average age: 59.8+/-7.7; 36 – 73 years of age). In the second round, the patients were given 7.5 g/day (3 times a day) of shakuyakukanzoto extract (Tsumura Pharma, Ltd., Tokyo, Japan) for 7 days from the first day in combination with NSAIDs. He then evaluated its analgesic effect using an independently developed five-stage pain evaluation system, and compared the pain scale value of each round with the index value. As a result, by using shakuyakukanzoto, the degree of the progressing muscle pain significantly decreased (P = 0.015), and its duration became significantly shorter (P< 0.01)[12].

Above, we have seen a number of cases in which Kampo medicine was able to mitigate the side effects of anticancer drugs that are used against malignant tumors. They are but a few examples. In actual clinical practice, much larger numbers of Kampo medicine are used in response to diverse situations. They shall be taken up little by little in this series.

References

1) Motoo, Yoshiharu. “Chapter Ⅲ Kampo Treatment in the Acute-care Ward and during Chronic Care: 11. Cancer Care and Kampo.” Takahiko Ono, ed. *Let’s Use Kampo Medicine*, 107-112, Kobundo, Tokyo, 2015.

2) Tai, Kiyoshi et al. “Effects of Hochuekkito in Preventing the Side Effects of Chemotherapy against Lung Cancer.” *Biotherapy* 6: 624-627, 1992.

3) Fushiki, Hiroshi et al. “Effectiveness of Hochuekkito in Mitigating the Side Effects of Anticancer Drugs.” *Recent Progress of Kampo Medicine in Obstetrics and Gynecology* 7: 72-75, 2000.

4) Saiki I：A Kampo medicine "Juzen-taiho-to"-prevention of malignant progression and metastasis of tumor cells and the mechanism of action. Bio Pharm Bull, 23：677-688, 2000

5) Shindo, Yoshiaki et al. “Study of the Effects of Goshajinkigan in Mitigating Peripheral Neuropathy Related to Oxaliplatin.” *Japanese Journal of Cancer and Chemotherapy* 35: 863-865, 2008.

6) Okimoto, Jiro et al. “Effects of Tsumura Saireito against Cisplatin (CDDP) Renal Damage.” *Diagnosis and Treatment* 79: 1497-1501, 1991.

7) Okimoto, Jiro et al. “Effects of Tsumura Juzentaihoto against Myelosuppression caused by Anticancer Drugs.” *Diagnosis and Treatment* 81: 2040-2043, 1993.

8) Yamada, Takuya. “Randomized Controlled Trial on the Combined Effects of 5-FU Oral Preparation and Juzentaihoto (TJ-48) against Stomach Cancer.” *Prog Med* 24: 2746-2747, 2004.

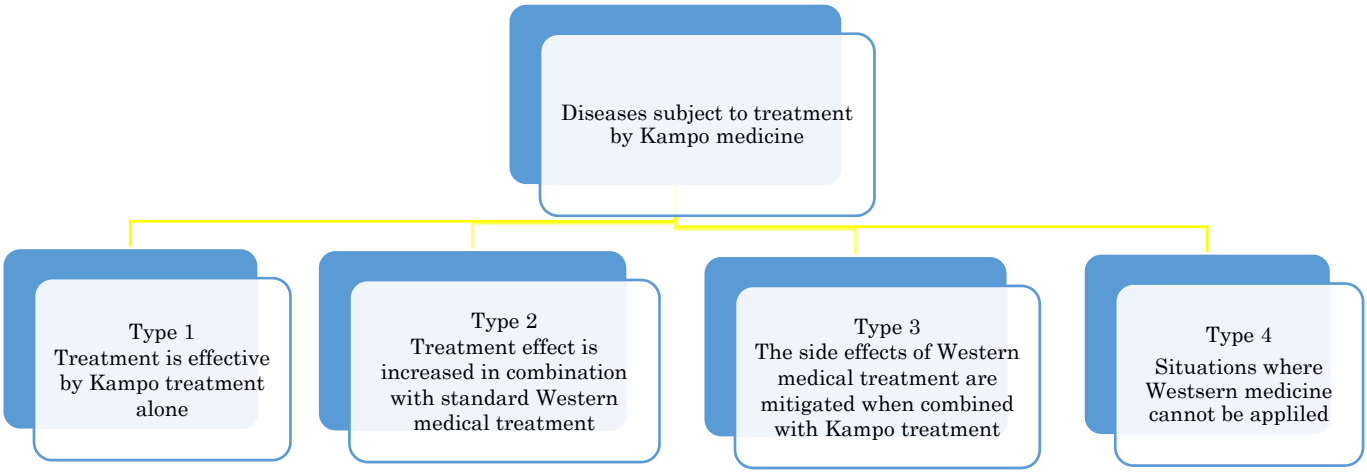
9) Ohara, Takeshi et al. “Study of the Effectiveness of Hochuekkito and Ninjinyoeito Combined with Tegafur.” *Japanese Pharmacology & Therapeutics* 21: 4423-4434, 1993.

10) Mori, Kiyoshi et al. “Study of the Effectiveness of Hangeshashinto against Diarrhea Accompanying the Use of Cisplatin and Irinotecan hydrochloride for Progressive Non-Small Cell Lung Cancer.” *Japanese Journal of Cancer and Chemotherapy* 25: 1159-1163, 1998.

11) Mori K. et al.: A phase I study of irinotecan and infusional cisplatin with recombinant human granulocyte colony-stimulating factor support in the treatment of advanced non-small cell lung cancer. Eur J Cancer 33: 503-505, 1997.

12) Hidaka, Takao, et al. “The Effects of Shakuyakukanzoto against Muscle Pain Caused by Paclitaxel Administration.” *Recent Progress of Kampo Medicine in Obstetrics and Gynecology* 17: 79-83, 2000.

The four types and their characteristics



[List of prescriptions]

ninjin'yoeito 人参養栄湯

hochuekkito 補中益気湯

juzentaihoto 十全大補湯

saireito 柴苓湯

hangeshashinto 半夏瀉心湯

goshajinkigan 牛車腎気丸

shakuyakukanzoto 芍薬甘草湯