

A Pilot Prospective Randomized Trial with Cancer Fatigue Scale and Juzentaihoto for Cancer-related Fatigue during Cisplatin-based Chemotherapy for Advanced Urothelial Carcinoma

Takahisa DOMEN*, Tomonori MINAGAWA, Hiroaki HARA
Ataru SUZUKI, Teruyuki OGAWA and Osamu ISHIZUKA

Department of Urology, Shinshu University School of Medicine

Objectives: Chemotherapy with gemcitabine and cisplatin (GC) is a standard treatment for advanced urothelial carcinoma. However, cancer-related fatigue (CRF) is frequently observed in patients receiving GC-chemotherapy. This study employed the Cancer Fatigue Scale (CFS) as a novel method to monitor CRF during GC-chemotherapy for the therapeutic effects of Juzentaihoto (JTT), a traditional Japanese (Kampo) medicine.

Methods: In this prospective single-center randomized study, 25 patients with advanced urothelial carcinoma were randomly divided into the JTT group and the control group prior to GC-chemotherapy. The 15-item CFS questionnaire was used to monitor CRF by providing a total score based on physical, affective, and cognitive subscores. CFS results were monitored daily during GC-chemotherapy for 2 weeks. Physical findings and appetite were evaluated as secondary outcomes, and adverse drug reactions were recorded.

Results: Ultimately, 10 patients in the JTT group and 12 patients in the control group were analyzed. Notable peaks in CFS total score and subscores were observed on days 6 and 10 after chemotherapy induction. Total CFS score and the affective CFS subscore were significantly decreased in the JTT group at multiple time points. Patients receiving JTT also showed significant suppression of appetite loss in the second half of the study. No adverse drug effects were noted for JTT.

Conclusions: The CFS could monitor the status of CRF during GC-chemotherapy and might be a useful method for CRF assessment. JTT may be a safe therapeutic option for CRF management in patients undergoing treatment for advanced urothelial carcinoma. *Shinshu Med J 70 : 275–284, 2022*

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Key words: Juzentaihoto, mitigates, cancer-related fatigue

I Introduction

The gold standard for the treatment of patients with advanced urothelial carcinoma (UC) is systemic cisplatin-based chemotherapy. A recent regimen for advanced UC is combination chemotherapy of gemcitabine and cisplatin (GC)⁽¹⁾⁽²⁾. Although GC-chemotherapy is highly effective against UC, it often induces general fatigue as an adverse event⁽³⁾. In-

deed, approximately 70 % of patients who receive anticancer drugs report a sense of fatigue associated with their treatment⁽⁴⁾⁻⁽⁶⁾. The general fatigue related to anticancer drugs, the cancer itself, and other surrounding factors can be considered together as cancer-related fatigue (CRF)⁽⁷⁾. To date, however, the status of CRF induced by cisplatin-based chemotherapy remains uncertain due to the difficulty in precisely evaluating it. A UC management strategy for chemotherapy-induced CRF that includes both treatment and monitoring is needed as well.

The Cancer Fatigue Scale (CFS) was developed by Okuyama et al. as a scale to assess CRF⁽⁸⁾. Its internal

* Corresponding author : Takahisa Domen
Department of Urology, Shinshu University School of
Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : sakutics@hotmail.com

Table 1 Regimen of gemcitabine-cisplatin chemotherapy

Drug	Day	1	2	3	4	8	15
Gemcitabine 1000 mg/m ²		○				○	○
Cisplatin 70 mg/m ²			○				
Dexamethasone 3.3 mg		○				○	○
6.6 mg				○	○		
9.9 mg			○				
Fosaprepitant meglumine 150 mg			○				
Palonosetron hydrochloride 0.75 mg			○				

consistency was found to be $\alpha = 0.79-0.89$. It is also considered to be simple and easy to complete and applicable to patients currently experiencing fatigue. The validity and reliability of the scale has been tested in Germany, Taiwan and Iran⁹⁾⁻¹¹⁾.

Juzentaihoto (JTT), a traditional Japanese (Kampo) medicine, is prescribed for patients with deficiency syndrome, suffering from anemia, fatigue, and anorexia¹²⁾. JTT also has been known to have anticancer effects, and in a previous study provided evidence on that JTT may be useful for patients with cancer associated anorexia¹³⁾.

We evaluated the ability of CFS to monitor CRF in advanced UC patients and assessed the CRF-attenuating effects of JTT during GC-chemotherapy.

II Methods

A Patients

Eligible patients with histologically confirmed advanced UC (stage III or IV) of the urinary bladder or upper urinary tract were enrolled in this single-center study. All patients had previously been surgically treated for or had undergone biopsy of their primary lesion, with clinical staging performed using enhanced computed tomography based on the clinical guidelines for bladder and upper urinary tract cancer¹⁴⁾¹⁵⁾. Exclusion criteria included non-consent, administration of other types of traditional Japanese herbal medicines within 2 weeks before recruitment, inability of oral drug intake, and allergy to traditional Japanese herbal medicines.

B Study Design

This study was conducted as a prospective ran-

Table 2 Constituents of Juzentaihoto

Constituent medical herb	Percentage
Astragalus root	10.5
Cinnamon bark	10.5
Rehmannia root	10.5
Peony root	10.5
Cnidium rhizome	10.5
Atractylodes lancea rhizome	10.5
Japanese angelica root	10.5
Ginseng	10.5
Poria sclerotium	10.5
Glycyrrhiza	5.5

domized trial to assess the usefulness of the CFS to monitor CRF induced by GC-chemotherapy and evaluate the ability of JTT to attenuate CRF. The protocol of this trial was approved by the Ethics Committee of Shinshu University. Written informed consent was obtained from all participants. Enrollment began in January 2015, with the last patient completing the study in February 2017. Eligible patients were randomized at a 1:1 ratio into the JTT group and the control group using the Alliance Clinical Research Supporting System, a web-based randomizing service.

C Drugs

The GC-chemotherapy regimen consisted of 1000 mg/m² gemcitabine on days 1, 8, and 15 and 70 mg/m² cisplatin on day 2. The details of the regimen are described in **Table 1**. All patients were hospitalized for at least 14 days of chemotherapy administration.¹⁾ JTT is a dry powder extracted from 10 kinds of herbs. The constituents of JTT are listed in **Table 2**. Patients in the JTT group received JTT at 7.5 g/day

Table 3 The Cancer Fatigue Scale (translated from Japanese)

This questionnaire will ask you about any sense of fatigue you may be experiencing. For each question, please circle only one number you think most aptly describes your current state. Try to answer on the basis of your initial feeling, without thinking too deeply about each question.

Right now,	No	Slightly	Somewhat	Considerably	Very much
1. Do you become tired easily?	1	2	3	4	5
2. Do you have the urge to lie down?	1	2	3	4	5
3. Do you feel exhausted?	1	2	3	4	5
4. Do you feel you have become careless?	1	2	3	4	5
5. Do you feel energetic?	1	2	3	4	5
6. Does your body feel heavy and tired?	1	2	3	4	5
7. Do you feel that you more often make errors while speaking?	1	2	3	4	5
8. Do you feel interest in things?	1	2	3	4	5
9. Do you feel fed-up?	1	2	3	4	5
10. Do you feel you have become forgetful?	1	2	3	4	5
11. Can you concentrate on certain things?	1	2	3	4	5
12. Do you feel reluctant?	1	2	3	4	5
13. Do you feel that your thinking has become slower?	1	2	3	4	5
14. Can you motivate yourself to do things?	1	2	3	4	5
15. Do you feel such fatigue that you don't know what to do with yourself?	1	2	3	4	5

Calculation Method

Add the item scores together for every factor.

Factor 1 = (items 1 + 2 + 3 + 6 + 9 + 12 + 15) - 7	points	(Physical subscale)
Factor 2 = 20 - (items 5 + 8 + 11 + 14)	points	(Affective subscale)
Factor 3 = (items 4 + 7 + 10 + 13) - 4	points	(Cognitive subscale)

Add the factor scores together. points (Total scale score)

N.B. The subtractions in calculations adjust for a score of 0 as a state of no fatigue.

during the 14 days of GC-chemotherapy, The control group did not receive JTT or any placebo. JTT was administered orally 3 times daily before each meal for 14 consecutive days from the beginning of GC-chemotherapy.

D Protocol

The primary outcome was CRF status in patients overall and in those with and without JTT administration as assessed by the CFS. The CFS consists of 15 questions based on 3 subscores : physical, affective, and cognitive. Total CFS was calculated as the sum

of the 3 CFS subscores. We monitored CFS and CFS subscores from the baseline at day 0 (i.e., the day prior to GC-chemotherapy) to day 14. Details of the CFS and its calculation method are shown in **Table 3⁸⁾**. The entire study was done with the subjects under hospitalization.

Secondary outcomes consisted of physical patient findings, including systolic blood pressure, pulse rate, and appetite (food intake) on days 0, 6, 10, and 14. The amount of food intake was objectively evaluated by medical staff (nurses and assistance nurses)

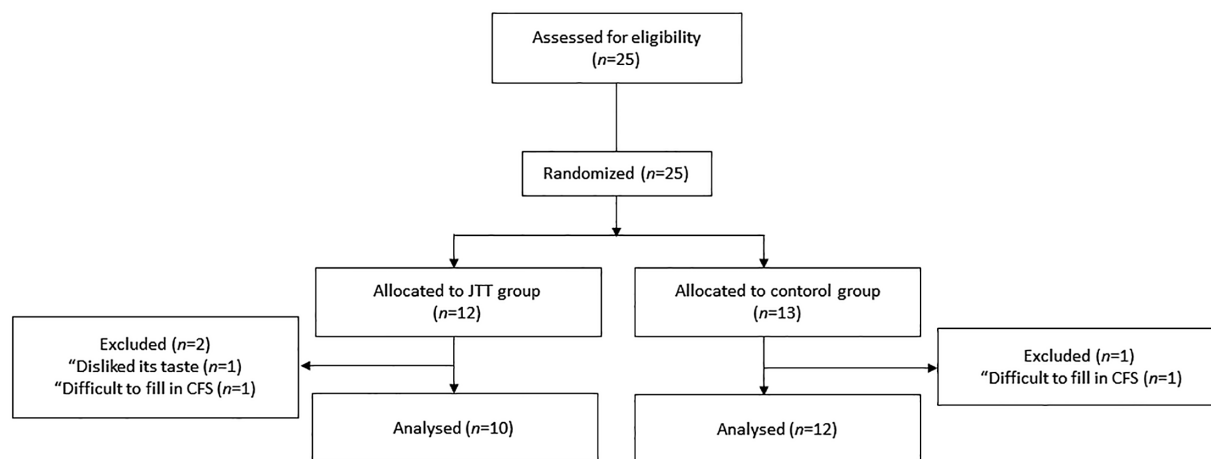


Fig. 1 Participant flow diagram. Enrolled patients were randomly assigned to the JTT group or the control group. JTT, Juzentaihoto; CFS, Cancer Fatigue Scale.

at every meal on day 0 and at 6, 10, and 14 days after the induction of GC-chemotherapy, with 100 % defined as full intake of the total amount of served meals for the day. The occurrence and severity of adverse drug reactions to JTT administration were also recorded throughout the treatment period. Blood examinations were performed on days 0, 7 and 14.

E Statistical analysis

The baseline for all measurements was set as the day prior to starting GC-chemotherapy (day 0). One-way repeated measures ANOVA was used to evaluate the change from baseline in all participants and employed to assess differences between the groups. All analyses were performed using the Excel Statistical Program File ystat2006.xls (Igakutosho Shuppan, Tokyo, Japan). A p -value of < 0.05 was considered statistically significant.

III Results

A Patients

Twenty-five eligible patients were randomly assigned to the JTT group ($n = 12$) or the control group ($n = 13$). In the JTT group, 1 patient refused to continue taking the drug due to its taste. One patient in each group withdrew from the study because of difficulty completing the CFS. Ultimately, the data of 22 patients (10 in the JTT group and 12 in the control group) were analyzed as depicted in **Fig. 1**. The primary and secondary endpoints were analyzed in the 22 patients who completed the study. Safety was

analyzed in the 10 patients who received JTT. The baseline characteristics of the enrolled patients are presented in **Table 4**. There were no remarkable differences in clinical variables between the groups. The major primary cancer was bladder (68 %), followed next by ureter (23 %) and renal pelvis (9 %). Eighteen patients (82 %) had distant metastasis.

B Primary outcome

The CRF status of all participants during GC-chemotherapy is shown in **Fig. 2**. Total CFS score was significantly increased over baseline from day 2 to day 14. CFS peaks were observed on days 6 and 10, both of which exhibited significant differences over day 0 ($p < 0.01$ and $p = 0.01$, respectively) (**Fig. 2A**). The first peak on day 6 was 5 days after the first gemcitabine administration and 4 days after cisplatin administration. The second peak on day 10 was 2 days after the second gemcitabine administration. Similar tendencies were witnessed in the CFS subscores (**Fig. 2B-D**), especially the physical CFS subscore, which appeared to be the primary contributor to the total CFS score. The physical CFS subscore was significantly increased over baseline at all time points. The affective CFS subscore was significantly higher on days 6 and 10 only. The cognitive CFS subscore was significantly increased on days 4, 6, 7, 8, 10, and 12 of GC-chemotherapy.

Comparisons of CFS results between the JTT group and the control group are displayed in **Fig. 3**. Total CFS on days 1, 2, 3, 10, 11, 13, and 14 was sig-

Table 4 Characteristics of enrolled patients

	Total (n = 22)	JTT group (n = 10)	Control group (n = 12)	p
Age, years	71.6(63-83)	71.6(64-78)	71.7(63-83)	0.33
Sex				
Male	11	5	6	0.51
Female	11	5	6	
Body mass index, kg/m ²	22.6(19.8-27.7)	22.9(20.1-27.7)	22.4(19.8-26.6)	0.17
Performance status				
0	13	7	6	0.18
1	9	3	6	
Primary cancer				
Bladder	15	5	10	0.11
Renal pelvis	2	1	1	
Ureter	5	4	1	
Clinical stage				
III	4	3	1	0.12
IV	18	7	11	
Surgery for primary site				
Yes	10	5	5	0.35
No	12	5	7	
Antidepressive/antianxiety agent				
Yes	1	0	1	0.16
No	21	10	11	

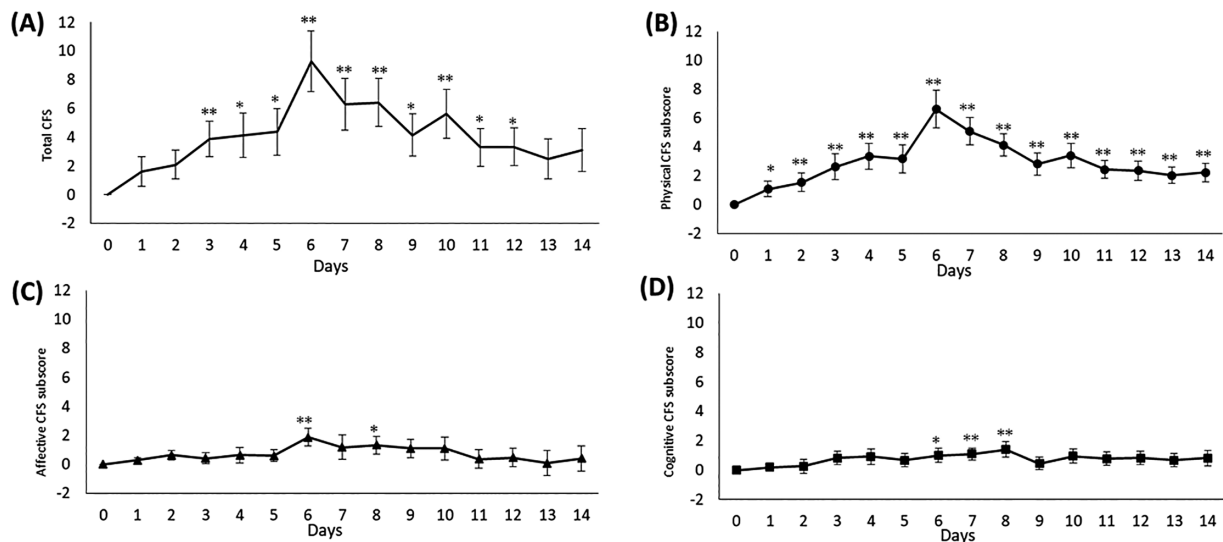


Fig. 2 Course of CFS during GC-chemotherapy for the overall cohort. Changes in total CFS score (A), physical CFS subscore (B), affective CFS subscore (C), and cognitive CFS subscore (D) are shown. Statistical differences between CFS scores and baseline were determined using one-way repeated measures ANOVA. * : p<0.05, ** : p<0.01. CFS, Cancer Fatigue Scale.

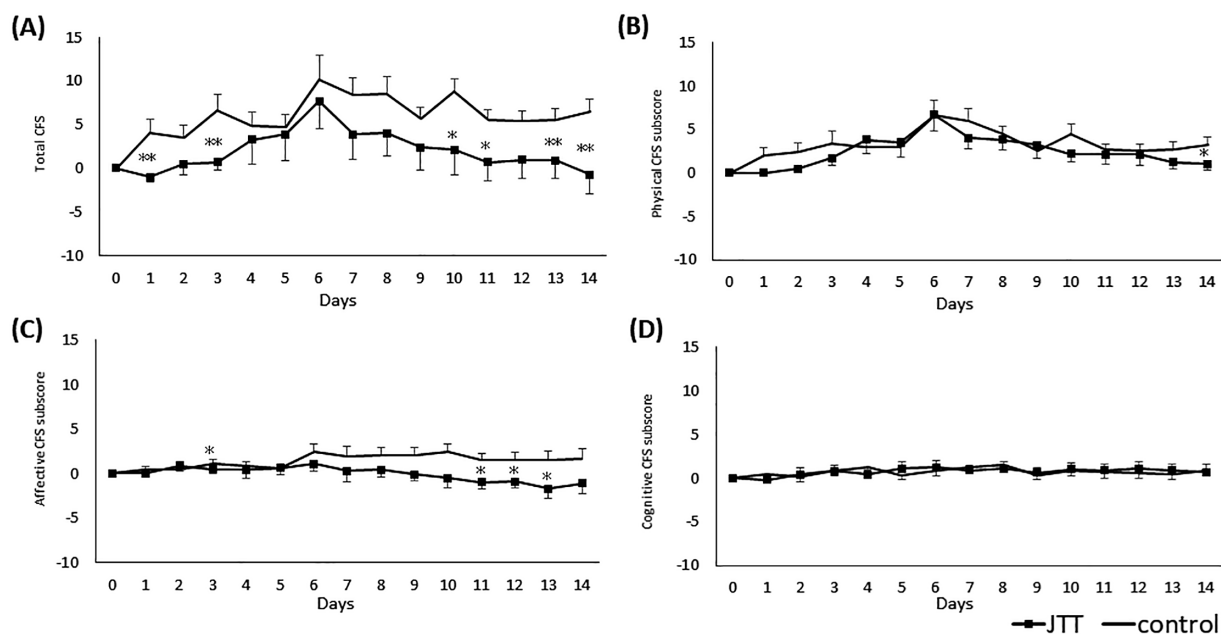


Fig. 3 Comparisons of the JTT group and the control group for changes in total CFS score (A), physical CFS subscore (B), affective CFS subscore (C), and cognitive CFS subscore (D). Total CFS and affective CFS subscore are significantly lower in the JTT group than in the control group on day 10. Statistical differences between the groups were determined using one-way repeated measures ANOVA. *: $p < 0.05$, **: $p < 0.01$. CFS, Cancer Fatigue Scale; JTT, Juzentaihoto.

nificantly attenuated in the JTT group as compared with the control group (**Fig. 3A**). No remarkable differences were detected between the groups for the physical or cognitive CFS subscores, although the affective CFS subscore was significantly attenuated in the JTT group from day 9 to day 13 (**Fig. 3B-D**).

C Secondary outcomes

There were no remarkable differences for systolic blood pressure or pulse rate throughout GC-chemotherapy in patients overall (**Fig. 4A, B**). In contrast, appetite was significantly decreased on days 6, 10, and 14 (**Fig. 4C**). In group comparisons, appetite loss on days 6, 10, and 14 was significantly attenuated in the JTT group ($p = 0.017, 0.011, \text{ and } 0.016$, respectively). No significant differences were noted for systolic blood pressure or pulse rate (**Fig. 4D-F**). Compared with the control group, no serious adverse events or laboratory data differences were detected in the JTT group apart from the common side effects of GC-chemotherapy, such as bone marrow suppression.

IV Discussion

This investigation is the first to demonstrate the effects of JTT in attenuating CRF as monitored by the CFS during GC-chemotherapy for advanced UC. Based on CFS findings, JTT appeared to mitigate overall CRF and affective stress and could attenuate a loss in appetite without any serious adverse drug reactions. The combination of the CFS and JTT may represent a novel management strategy for cancer-related fatigue.

CRF is one of the most frequent symptoms in patients with malignant tumors, with reported rates of 78–96 %⁷⁾¹⁶⁾¹⁷⁾. CRF is defined as a distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning¹⁸⁾. The disorder was found to adversely influence daily life in over half of malignant cancer patients¹⁸⁾. Therefore, CRF associated with malignant tumors is a serious clinical problem worldwide.

Passik et al. reported that cancer patients often fail

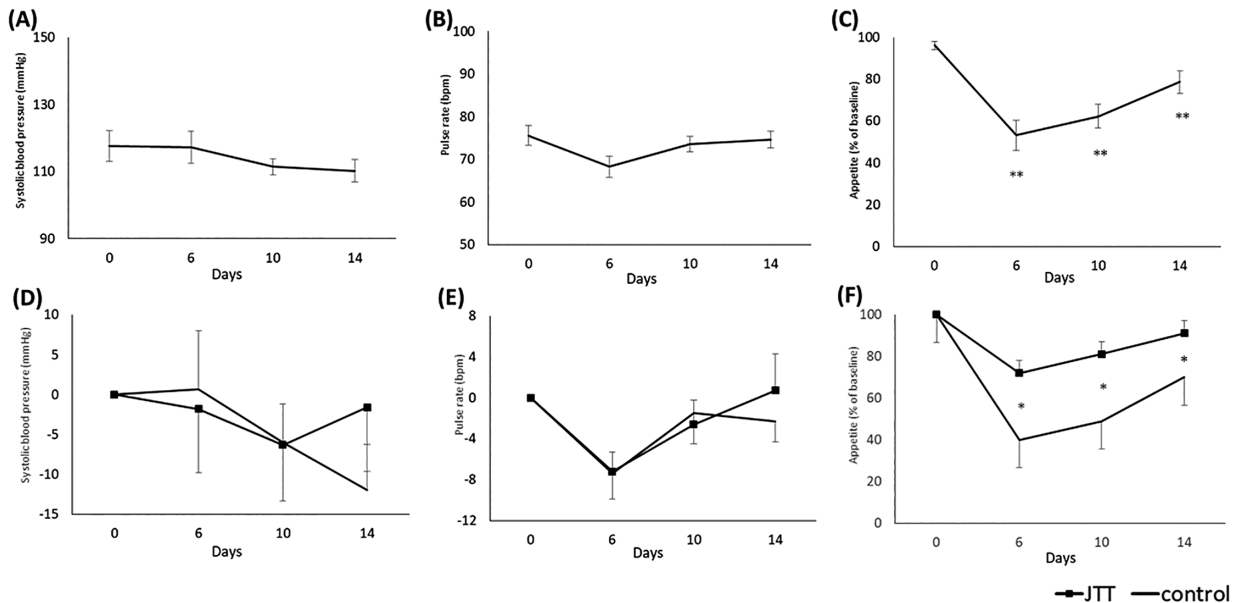


Fig. 4 Course of physical findings during GC-chemotherapy for the overall cohort. Changes in systolic blood pressure (A), pulse rate (B), and appetite (C) are shown. Statistical differences between physical findings and baseline were determined using paired *t*-tests. Comparisons of the JTT group and the control group for changes from baseline in systolic blood pressure (D), pulse rate (E), and changes in appetite (F). Appetite is significantly better maintained by JTT. Statistical differences between the groups were determined using one-way repeated measures ANOVA. * : $p < 0.05$, ** : $p < 0.01$. JTT, Juzentaihoto.

to communicate with their oncologists about fatigue¹⁹. Although the most common evaluation method for CRF among malignant tumor patients is the Common Terminology Criteria for Adverse Events, the test is objectively evaluated by clinicians²⁰. Therefore, the Common Terminology Criteria for Adverse Events loses effectiveness without close communication between the clinician and patient and may become inadequate to establish clinical evidence on CRF. In the current-day situation with no established biomarkers for CRF, general fatigue can only be evaluated using questionnaires, such as the Brief Fatigue Inventory and the Edmonton Evaluation System^{21/22}. However, problems remain regarding pathogenesis, objective parameters, and the evaluation of quantitative and qualitative aspects.

Developed by Japanese researchers, the CFS is the only self-administered questionnaire to evaluate CRF on a multidimensional fatigue scale of three dimensions: physical, affective, and cognitive⁸. Therefore, the CFS is a simple method to obtain both quantitative and qualitative assessments of CRF, which may provide useful information to establish treatments for

CRF. We previously reported on the usefulness of the CFS to monitor CRF during enzalutamide administration in patients with castration-resistant prostate cancer²³. Similarly, the CFS was able to monitor CRF status during GC-chemotherapy in this trial.

GC-chemotherapy is a standard treatment option for advanced UC. CRF is one of the most common side effects of chemotherapy; it not only impairs quality of life, but also diminishes physical activity, limits treatment, and increases morbidity³. However, the characteristics of CRF induced by GC-chemotherapy have not been defined. In this preliminary study investigating the usefulness of the CFS to monitor CRF during GC-chemotherapy, the CFS could track the changes in CRF throughout treatment. Physical fatigue appeared to be a predominant factor in the total CFS score. Indeed, the total CFS peaks were synchronized with those of the physical CFS subscore on days 6 and 10. This finding indicated that treatment of physical condition and reduction of physical stress could be especially beneficial for managing CRF during GC-chemotherapy.

Definitive evidence on effective treatment strate-

gies for CRF is lacking. Kampo medicine, also known as traditional Japanese herbal medicine, has been developed to treat various conditions and has gained a unique status in Japan²⁴⁾²⁵⁾. The treatment concepts of Kampo medicine are very different from those of modern medicine. Almost 150 Kampo formulations have been approved as prescription drugs by the Ministry of Health, Labor and Welfare of Japan and are used clinically for the treatment of a wide variety of diseases. Some Kampo medications can be used for general fatigue, including aging problems and frailty. Clinically, JTT is indicated for the relief of declined constitution during disease recovery, general fatigue, malaise, anorexia, perspiration during sleep, cold limbs, and anemia. JTT has also shown effectiveness in treating various symptoms and restoring strength in elderly people and has proven suitable for long-term administration²⁶⁾. Regarding the mechanism of JTT function, animal studies showed that the drug increased hematopoietic effects in mice²⁷⁾. JTT could improve immunological protection, including cancer immunity, by increasing hematopoietic function²⁸⁾⁻³⁰⁾. Koyohara et al. also reported that JTT decreased the toxicity (mortality and renal toxicity) of cisplatin in mice³¹⁾. Furthermore, several clinical reports have described an effect of JTT on hematopoiesis and anemia recovery³²⁾⁻³⁴⁾, and the agent has been used as an adjunctive therapy for advanced breast cancer patients³⁵⁾. The above results led us to examine the suitability of JTT to manage CRF in GC-chemotherapy in the present study.

We observed that JTT could attenuate total CFS score during the treatment period, especially for the affective CFS subscore, as well as a loss of appetite. Thus, JTT may primarily attenuate mental duress during chemotherapy under hospitalization in patients with UC. Appetite may also be better maintained throughout the treatment period, particularly in the latter half. JTT can be a supportive drug candidate to help manage patients under chemotherapy by promoting a favorable mental and physical state without serious adverse events. It was noteworthy that we observed no significant physical or cognitive CFS subscore alterations in spite of the statistical improvement in total CFS score. A larger cohort may reveal further differences in these subscores.

This study had several limitations that must be considered when interpreting the results. First, the patients in the control group did not receive a placebo, and the trial was conducted as open label. Therefore, a placebo effect cannot be ruled out. Second, the number of enrolled patients was insufficient to determine the exact effect of JTT. Previous investigations using the CFS are also few in number, and this is the first trial to employ the CFS for GC-chemotherapy. In this sense, the study can be regarded as exploratory and pilot research to investigate the applicability of the CFS and JTT. However, as we witnessed a usefulness of the CFS and a therapeutic effect of JTT, this trial might be acceptable as the first step to demonstrate the clinical merit of JTT. A randomized, double-blind, placebo-controlled study containing a large number of patients with advanced UC is required to verify the present findings. Third, no obvious mucositis, diarrhea, and taste abnormalities were observed in the patients. However, these were not actively searched for. So it is possible that the patients had such latent symptoms, which may have influenced the loss of appetite. Fourth, the observation period may not have been sufficient to monitor CRF completely with regard to GC-chemotherapy. Although the changes in the CFS persisted until the end of the observation period, CFS scores should ideally be evaluated for longer durations. Although these limitations limit the interpretation of the study results, the present study is meaningful in that such pilot study results are necessary to conduct large-scale, rigorous study. Once the above limitations are resolved, the CFS and the effect of JTT on CRF in UC patients during GC-chemotherapy could be demonstrated in future trials.

In conclusion, the present pilot study showed the CFS appeared useful for monitoring CRF during GC-chemotherapy for severe UC and JTT could be a therapeutic option for attenuating CRF symptoms. The combination of the CFS and JTT could potentially serve as a novel strategy for managing CRF during GC-chemotherapy for UC patients.

V Conflict of Interests

None.

References

- 1) von der Maase H, Hansen SW, Roberts JT, et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 18: 3068-3077, 2000
- 2) von der Maase H, Sengelov L, Roberts JT, et al: Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 23: 4602-4608, 2005
- 3) Lop A, Manfredi A, Bonura S: Fatigue in cancer patients receiving chemotherapy: an analysis of published studies. *Ann Oncol* 15: 712-720, 2004
- 4) Sandler A, Nemunaitis J, Denham C, et al: Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 18: 122-130, 2000
- 5) Campos M, Hassan B, Riechelmann R, et al: Cancer-related fatigue: a practical review. *Ann Oncol* 22: 1273-1279, 2011
- 6) Morrow G, Shelke A, Roscoe J, et al: Management of cancer-related fatigue. *Cancer Invest* 23: 229-239, 2005
- 7) Berger A, Mooney K, Alvarez-Perez A: National Comprehensive Cancer Network. Cancer-related fatigue, version 2. 2015. *J Natl Compr Canc Netw* 13: 1012-1039, 2015
- 8) Okuyama T, Akechi T, Kugaya A, et al: Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. *J Pain Symptom Manage* 19: 5-14, 2000
- 9) Kröz M, Zerm R, Reif M, et al: Validation of the German version of the cancer fatigue scale (CFS-D). *Eur J Cancer Care* 17: 33-41, 2008
- 10) Montazeri A, Haghghat S, Ebrahimi M: The cancer fatigue scale (CFS): translation and validation study of the Iranian version. *Qual Life Res* 14: 2132, 2005
- 11) Shun SC, Beck S, Pett M, et al: Psychometric testing of three Chinese fatigue instruments in Taiwan. *J Pain Symptom Manage* 32: 155-167, 2006
- 12) Ministry of health. Labour and Welfare of Japan. The Japanese pharmacopoeia, 18th Edition. 2021 (Japanese).
- 13) Cheon C, Yoo J, Yoo S, et al: Efficacy and safety of sipjeondaebo-tang for anorexia in patients with cancer: a pilot, randomized, double-blind, placebo-controlled trial. *Evid Based Complement Alternat Med* 8780325, 2017
- 14) The Japanese Urological Association. Clinical guidelines for bladder cancer 2015. Igakutosho-shuppan, Tokyo, 2015 (Japanese)
- 15) The Japanese Urological Association. Clinical guidelines for renal pelvic and ureteral cancer 2014. Medical-review, Tokyo, 2014 (Japanese)
- 16) Portenoy R, Itri L: Cancer-related fatigue: guidelines for evaluation and management. *Oncologist* 4: 1-10, 1999
- 17) Berger A, Abernethy A, Atkinson A: NCCN Clinical Practice Guidelines Cancer-related fatigue. *J Natl Compr Canc Netw* 8: 904-931, 2010
- 18) Stone P, Richardson A, Ream E, et al: Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Cancer Fatigue Forum. Ann Oncol* 11: 971-975, 2000
- 19) Passik SD, Kirsh KL, Donaghy K, et al: Fatigue Coalition. Patient-related barriers to fatigue communication: initial validation of the fatigue management barriers questionnaire. *J Pain Symptom Manage* 24: 481-493, 2002
- 20) Trotti A, Colevas A, Setser A, et al: Patient-reported outcomes and the evolution of adverse event reporting in oncology. *J Clin Oncol* 25: 5121-5127, 2007
- 21) Mendoza TR, Wang XS, Cleeland CS, et al: The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. *Cancer* 85: 1186-1196, 1999
- 22) Hui D, Shamieh O, Paiva C: Minimal clinically important differences in the Edmonton Symptom Assessment Scale in

- cancer patients : a prospective, multicenter study. *Cancer* 121 : 3027-3035, 2015
- 23) Minagawa T, Domen T, Suzuki T, et al : Effectiveness of Hochuekkito (Japanese herbal medicine) for general fatigue after introduction of enzalutamide in three cases of castration-resistant prostate cancer. *Nihon Hinyokika Gakkai Zasshi* 110 : 86-91, 2019 [Article in Japanese]
 - 24) Motoo Y, Seki T, Tsutani K : Traditional Japanese medicine, Kampo : its history and current status. *Chin J Integr* 17 : 85-87, 2011
 - 25) Fuyuno I : Japan : Will the sun set on Kampo ? *Nature* 480 : 7378, 2011
 - 26) Terasawa K : *Kampo Japanese-Oriental Medicine Insights from Clinical Cases*. K.K. Standard McIntyre, Tokyo Japan, 1993
 - 27) Hong T, Matsumoto T, Kiyohara H, et al : Enhanced production of hematopoietic growth factors through T cell activation in Peyer's patches by oral administration of Kampo (Japanese herbal) medicine, "Juzen-Taiho-To". *Phytomedicine* 5 : 353-360, 1998
 - 28) Abe S, Tansho S, Ishibashi H, et al : Protective effect of oral administration of a traditional medicine, Juzen-Taiho-To, and its components on lethal candida albicans infection in immunosuppressed mice. *Immunopharmacol Immunotoxicol* 20 : 421-431, 1998
 - 29) Kiyohara H, Matsumoto T, Takemoto N, et al : Effect of oral administration of a pectic polysaccharide fraction from a Kampo (Japanese herbal) medicine "Juzen-Taiho-To" on antibody response of mice. *Planta Med* 61 : 429-434, 1995
 - 30) Ohnishi Y, Fujii H, Hayakawa Y, et al : Oral administration of a Kampo (Japanese herbal) medicine Juzen-taiho-to inhibits liver metastasis of colon 26-L5 carcinoma cells. *Jpn J Cancer Res* 89 : 206-213, 1998
 - 31) Kiyohara H, Matsumoto T, Komatsu Y, et al : Protective effect of oral administration of a Pectic Polysaccharide fraction from a Kampo (Japanese herbal) medicine "Juzen-Taiho-To" on adverse effects of cis-diaminedichloroplatinum. *Planta Med* 61 : 531-534, 1995
 - 32) Kishida Y, Nishii T, Inoue T, et al : Juzentaihoto (TJ-48), a traditional Japanese herbal medicine, influences hemoglobin recovery during preoperative autologous blood donation and after hip surgery. *Int J Clini Pharmacol Ther* 47 : 716-721, 2009
 - 33) Nakamoto H, Mimura T, Honda N : Orally administrated Juzen-taiho-to/TJ-48 ameliorates erythropoietin (rHuEPO) resistant anemia in patients on hemodialysis. *Hemodial Int* 12 : 9-14, 2008
 - 34) Sho Y, Fujisaki K, Sakashita H, et al : Orally administered Kampo medicine, Juzen-taiho-to, ameliorates anemia during interferon plus ribavirin therapy in patients with chronic hepatitis C. *J Gastroenterol* 39 : 1202-1204, 2004
 - 35) Adachi I : Supporting therapy with Shi Quan Da Bu Tang in advanced breast cancer patients. *Biomedical Research* 11 : 25-31, 1990

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