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Development and Validation of a New Evaluation Index for Oxaliplatin-Induced Cold Hypersensitivity Symptoms

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ABSTRACT

Purpose: *Peripheral neuropathy (PN) is a dose limiting factor and reduces the quality of life. However, many studies have not provided a distinction between cold hypersensitivity symptoms (CHS) and chronic neuropathy. We developed a new evaluation index for CHS and examined its efficacy.*

Method: *The subjects were patients who received mFOLFOX6 therapy ± molecular target drug for colorectal cancer. The new evaluation index (Cold-Hypersensitivity Symptom-specific Evaluation Scale; C-HSES) was quantified based on living activities such as the presence or absence of symptoms and avoiding refrigeration, with the hand and mouth as target sites (total 24 points). We compared C-HSES with existing neuropathy evaluation indices (CTCAE JCOGver.4.02, Patient Neuropathy Questionnaire (PNQ), the Quick Disability of the Arm, Shoulder, and Hand (Quick DASH), and Numeric Rating Scale (NRS) for each chemotherapy cycle.*

Results: *Twenty-three patients were evaluated. The CHS showed deterioration over time on C-HSES ($p < 0.001$, ANOVA). C-HSES showed a significant correlation with NRS ($p < 0.001$, spearman). The C-HSES cutoff value indicating Grade ≥2 CTCAE was 12 points. It was able to detect Grade ≥2 CTCAE and Grade ≥D PNQ equivalent symptoms earlier than the existing indices*

(median duration of cold sensation was 9 vs. 22 courses, p < 0.046 vs. CTCAE Grade ≥2. 50% median cooling sensation period was 9 courses vs. not reached, p <0.001 vs. PNQ grade D).

Discussion: *Existing indicators did not distinguish CHS from chronic PN, causing patients to experience distress. In effect, we may have underestimated the CHS-induced impairment of life. It was suggested that the C-HSES that we created could detect CHS (acute PN) peculiar to oxaliplatin, and thus can accurately apprehend the patient's distress. Thus, it was considered that the timing of drug withdrawal and dose reduction by PN could be optimized.*

Conclusion: *C-HSES is expected to be a tool that can detect CHS earlier for treatment than the existing evaluation indices and can be used as a tool for assessing patients' distress and disability.*

Keywords: Neuropathy, Hypersensitivity, Chemotherapy, Colorectal cancer, Diabetes, Parkinson's disease.

INTRODUCTION

Peripheral neuropathy (PN) is an unsolved and potentially life-compromising problem for most patients receiving chemotherapy. PN is long lasting, makes daily life inconvenient, and reduces the quality of life [1]. It is a problematic side effect of taxane and platinum anticancer drugs. Therefore, reduction of its dose was prescribed at Grade ≥2 PN for chemotherapy-related clinical trials inducing PN [2,3]. Reduction or discontinuation of PN-inducing drugs based on appropriate evaluation and early detection is an important component of the management of chemotherapy. It is classified as acute or chronic. Oxaliplatin (L-OHP) is a key drug in colorectal cancer. L-OHP-induced PN is a critical toxic effect that limits the dosage of L-OHP. Acute PN is specific to L-OHP and occurs in many patients within hours after administration [4]; it is characterized by CHS, throat discomfort, and dysesthesia of the peripheral regions including the hand, foot, and perioral regions, affecting the patients' daily living activities. In addition, continued exposure to L-OHP also induces chronic PN in approximately 70% of the patients, causing temperature insensitive paresthesia, hypoesthesia and dysesthesias of the hands and feet [5]. Currently, the typical evaluation indicators of PN include Common Terminology Criteria for Adverse Events (CTCAE), Patient Neuropathy Questionnaire (PNQ), and Disability of the arm shoulder and hand (DASH). CTCAE is an evaluation method used by medical staff and is widely used in clinical practice. Health care workers tend to underestimate when comparing their assessments with patient subjective assessments, resulting in disagreements [6]. Therefore, CTCAE has recently adopted the concept of subjective patient-reported outcome [7].

PNQ is an evaluation method that can evaluate the subjective symptoms of a patient in terms of both sensory and motility and apprehend the specific obstacles to the daily activities [6]. DASH is an evaluation method that includes inconvenience and pain in the daily activities of the upper limbs [8]. However, many studies have not provided a distinction between CHS (acute PN) and chronic PN [9]. Existing evaluation indicators may not accurately apprehend the symptoms of CHS. In order to properly evaluate PN, it is essential to establish appropriate evaluation indicators. In this study, a new evaluation index (C-HSES) for CHS was created in patients treated with mFOLFOX6 therapy ± molecular target drug, and its validity was verified.

MATERIALS AND METHODS

Study subjects

Subjects were patients who received mFOLFOX6 therapy ± molecular target drug at the International University of Health and Welfare Hospital. Patients received mFOLFOX6 therapy ± molecular target drug once every 2 weeks (L-OHP 85 mg/m^2, LV 200 mg/m^2, bolus 5-FU 400 mg/m^2, continuous 5-FU infusion at 2400 mg/m^2 ± Bevacizumab 5 mg/kg or Panitumumab 6 mg/kg or Cetuximab 500 mg/m^2). Patients were recruited between August 2018 and August 2019 according to the following inclusion criteria: planned administration of oxaliplatin for a cumulative dose of at least 500 mg/m^2) and Eastern Cooperative Oncology Group Performance Status ≤ 2. The exclusion criteria were as follows: peripheral sensory/motor neuropathy (CTCAE grade ≥ 2), patients who were receiving drugs that induce PN other than L-OHP, patients who could not properly judge the degree of PN (such as patients with dementia).

Evaluation methods

The study evaluated PN at baseline and on day 1 immediately before each chemotherapy cycle. PN was evaluated by the Cold-Hypersensitivity symptom-specific evaluation scale (C-HSES), CTCAE, PNQ, Quick DASH, and the Numeric Rating Scale (NRS).

Cold-Hypersensitivity symptom-specific evaluation scale (C-HSES): We developed a new evaluation index for L-OHP-specific cold sensitivity symptoms. (Figures 1A and 1B) C-HSES is patient-subjective and can easily apprehend the degree and duration of cold sensitivity symptoms. C-HSES targets the hands and oral cavity. The question items are roughly divided into two for each target area. The first question aimed to understand when the patient felt numbness during one cycle in three temperature categories, that is, frozen, cold, and normal temperature. The second question aimed to determine which of the three temperatures prevented touching or swallowing. The data obtained from the questions was quantified by the presence or absence of CHS and daily living activities such as avoiding refrigeration (Table 1). For example, if the patient takes gloves from the refrigerator at 8 days after chemotherapy, it will be 9 points. Moreover, even tap water can cause numbness, so if the patient always used warm water it was considered as 24 points.

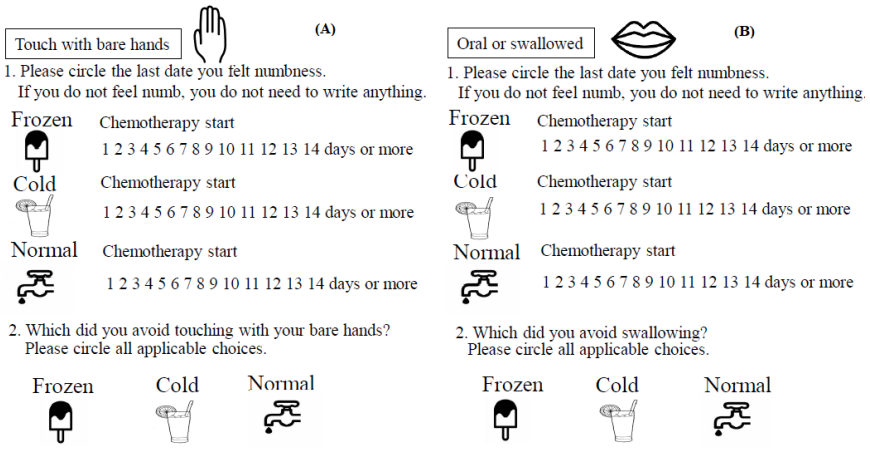

Figure 1: (A) The new evaluation index (Cold-Hypersensitivity Symptom-specific Evaluation Scale; C-HSES) hand version; **(B)** The new evaluation index (Cold-Hypersensitivity Symptom-specific Evaluation Scale; C-HSES) Oral version.

Table 1: This is a numerical representation of C-HSES. Scores were categorized by the duration of time CHS occurred and avoided to prevent symptoms. Having a symptom at room temperature is more severe and therefore has a higher score. The maximum value for both C-HSES is 24 points.

Variables	CHS	Avoided	7 days or more	14 days or more
Frozen	1	1	1	1
Cold	2	2	2	2
Normal	3	3	3	3
				Total 24 Points

Common Terminology Criteria for Adverse Events (CTCAE JCOG ver.4.02): The severity of PN was evaluated by a medical staff using peripheral sensory neuropathy / peripheral motor neuropathy (CTCAE JCOG ver.4.02). The severity grades are as follows; Peripheral sensory neuropathy Grade 0, No symptoms; Grade 1, Asymptomatic /loss of deep tendon reflexes or paresthesia; Grade 2, Moderate symptoms or limiting instrumental Activities of daily living (ADL); Grade 3, Severe symptoms or limiting self-care ADL; Grade 4, Life-threatening consequences or urgent intervention indicated. Peripheral motor neuropathy Grade 0, No symptoms; Grade 1, Asymptomatic/clinical or diagnostic observations only/intervention not indicated; Grade 2, Moderate symptoms or limiting instrumental ADL; Grade 3, Severe symptoms or limiting self-care ADL or assistive device indicated; Grade 4, Life-threatening consequences or urgent intervention indicated.

Patient Neuropathy Questionnaire (PNQ): The severity of PN was assessed using peripheral sensory neuropathy/peripheral motor neuropathy (PNQ) by the patient. The severity grades are as follows: Peripheral sensory neuropathy Grade A; I have no numbness, pain, or tingling in my hands or feet, Grade B; I have mild tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living, Grade C; I have moderate tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living, Grade D; I have moderate to severe tingling, pain or numbness in my hands or feet. This interferes with my activities of daily living, Grade E; I have severe tingling, pain or numbness in my hands or feet. It completely prevents me from doing most activities. Peripheral motor neuropathy Grade A; I have no weakness in my arms or legs, Grade B; I have mild weakness in my arms or legs. This does not interfere with my activities, Grade C; I have moderate weakness in my arms or legs. This does not interfere with my activities of daily living, Grade D; have moderate to severe weakness in my arms or legs. This interferes with my activities of daily living, Grade E; I have severe in my arms or legs. It completely prevents me from doing most activities.

Quick Disability of the Arm Shoulder and Hand (DASH): The severity of PN was assessed by the patient in the Quick DASH. Quick DASH evaluates upper limb disorders. The dysfunction section has 11 items, with 5 grades from 1-5. The items are as follows: 1. Open a tight or new jar, 2. Do heavy household chores (e.g. wash the walls, wash the floors), 3. Carry a shopping bag or briefcase, 4. Wash your back, 5. Use a knife to cut food, 6. Recreational activities which you exert some force or impact through your arm, shoulder or hand, 7. During the past week, to what extent has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbors or groups? 8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?, 9. Arm, shoulder or hand pain, 10. Tingling (pins and needles sensation) in your arm, shoulder or hand, 11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? The grades are as follows: No difficulty, mild difficulty, moderate difficulty, severe difficulty, unable.

Numerical Rating Scale (NRS): The NRS divides the pain into 11 stages from 0 to 10, with 0 being no pain at all, and 10 being the worst possible pain, the pain score is asked. This time, we evaluated not the pain but the inconvenience on daily life. It was

expressed as how inconvenient it was to be unable to perform the activities that were possible until then due to the expression of CHS.

For example

- I could not touch cold objects.
- I avoid touching a cold object and wait until it reaches room temperature.
- I needed something like gloves in order to touch cold things

To assess the extent of inconvenience to the patient, inconvenience on daily life was divided into 11 stages from 0 to 10, with 0 being no inconvenience, and 10 being the worst possible inconvenience.

Statistical Analysis

Cronbach's alpha was used for the internal consistency (reliability) of C-HSES. A one-way analysis of variance was used for Dunnett's test for the transition of cold-sensitivity symptoms in C-HSES and each evaluation. The correlation between C-HSES and each evaluation was plotted on a scatter plot and analyzed by Spearman's rank correlation coefficient. The receiver operating characteristic (ROC) curve of each evaluation with CTCAE grade ≥2 was drawn, and the cut-off value of C-HSES and each evaluation was obtained. The Kaplan-Meier curve was used to estimate the cycle period until the occurrence of PN, and the log-rank test was used for analysis. Statistical analyses were performed using Excel® Statistics software version 3.00 (Social Information Service, Tokyo, Japan).

Ethical approval

This study was conducted in accordance with the "Ethical Guidelines for Medical Research on Humans", with the approval from the Ethics Committee of the International University of Health and Welfare Hospital (13-B-311). All patients provided written informed consent.

RESULTS

Patient background

Between July 2017 and January 2020, 25 patients received mFOLFOX6 therapy ± molecular target drug. Among these patients, two patients with refusal to participate and poor follow-up due to hospital transfer were excluded. Patient characteristics are shown in Table 2. The mean age of the patients was 67 (range 44-85) years. Of the 23 patients retained, 16 were male and 7 were female. The cancer types in patients were 14 with colon cancer and 9 with rectal cancer. Adjuvant chemotherapy was administered in 7 patients while advanced cancer chemotherapy was administered in 16 patients. Some patients had other diseases that could cause PN, such as diabetes and Parkinson's disease. As a baseline, we confirmed that there was no development of PN due to these diseases before the onset of the study.

Table 2: Patient characteristics (n=23)

Characteristics (min-max)	n	%
Mean age (years)	67 (44-85)	
Gender		

Male	16	69.6
Female	7	30.4
Mean body surface area (mg/m^2)	1.48 (1.05-1.98)	
Clinical stage		
II	5	21.7
IIIa	2	8.7
IIIb	1	4.3
IIIc	3	13.1
IV	12	52.2
Cancer		
Colon	14	60.9
Rectal	9	39.1
Treatment		
Adjuvant	7	30.4
Advanced	16	69.6
Underlying chronic diseases		
None	19	82.6
Diabetes mellitus	3	13.1
Parkinson's disease	1	4.3
Treatment line		
First line	22	95.7
Other line	1	4.3
Chemotherapy		
mFOLFOX6	11	47.9
mFOLFOX6+Bevacizumab	10	43.5
mFOLFOX6+Cetuximab	1	4.3
mFOLFOX6+Panitumumab	1	4.3
Worker	13	56.5
Partner	15	65.2
AST (IU/L)	23 (14-83)	
ALT (IU/L)	27 (7-93)	
Scr (mg/dl)	0.70 (0.38-1.4)	

Internal integrity

Table 3 shows the results of Cronbach's alpha. For each item, Cronbach's alpha was 0.8 or more. The total number of C-HSES items was 0.92.

Table 3: Cronbach's alpha for all C-HSES items.

Items	Cronbach's alpha
Symptoms of touching frozen objects	0.92
Frozen numb period	0.9
Symptoms of touching cold objects	0.91

Cold numb period	0.89
Symptoms of touching normal temperature	0.9
normal temperature numb period	0.92
Avoided touching frozen objects	0.92
Avoided touching cold objects	0.91
Avoided touching normal temperature	0.9
All items	0.92

CHS transition in each course

The CHS of L-OHP showed deterioration with time in most of the evaluation indexes (Figure 2). PNQ (sensory and motor) showed a significant deterioration over time (p = 0.01, ANOVA). CTCAE (sensory and motor) showed a significant deterioration over time (p = 0.001, p = 0.024 ANOVA). C-HSES (hand and oral) showed a significant deterioration over time (p < 0.001, p = ANOVA). Inconvenience NRS showed a significant deterioration over time (p < 0.001, p = ANOVA). Quick DASH showed no deterioration over time.

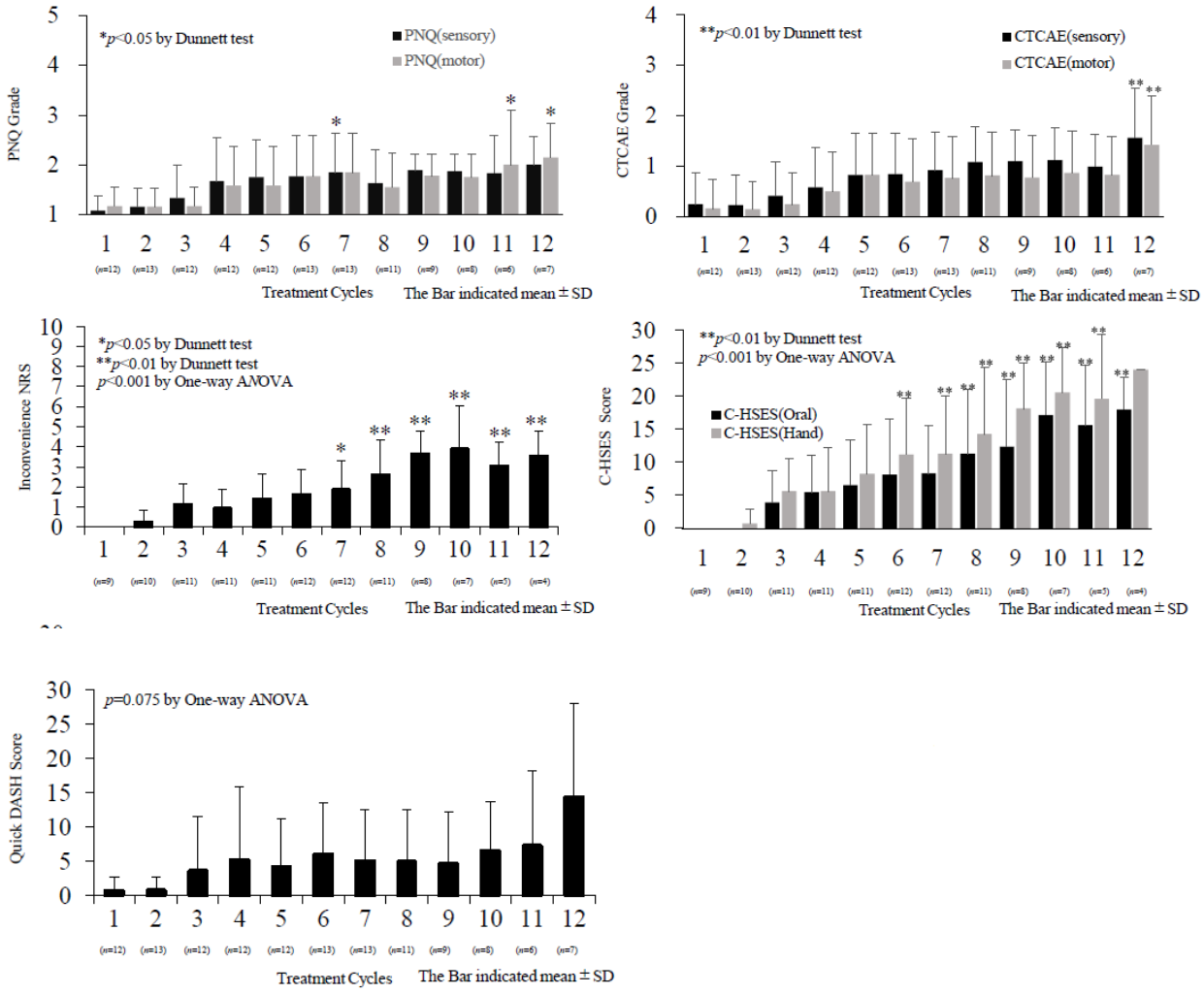

Figure 2: Transition of each evaluation index in treatment cycle.

Relationship between each evaluation index and inconvenience NRS

Figure 3 shows the relationship between each evaluation index and inconvenience NRS. The coefficient of determination of both C-HSES (hand) and C-HSES (oral) showed high values compared with other evaluation indexes (Table 4).

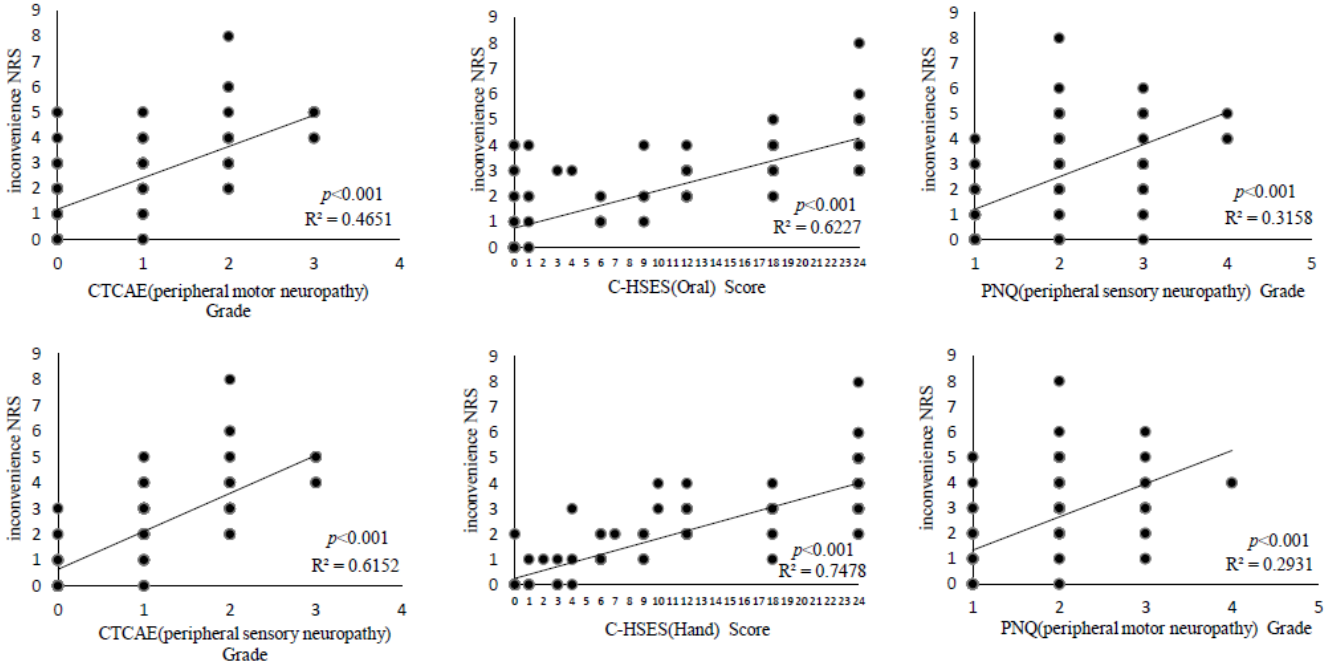

Figure 3: Correlation between each evaluation index and inconvenience NRS.

Table 4: Correlation between each evaluation index and inconvenience NRS.

Evaluation index	Coefficient of Determination
PNQ (peripheral motor neuropathy)	0.2931
PNQ (peripheral sensory neuropathy)	0.3158
CTCAE (peripheral motor neuropathy)	0.4651
CTCAE (peripheral sensory neuropathy)	0.6152
C-HSES (Oral)	0.6227
C-HSES (Hands)	0.7478

Receiver operating characteristic curve (ROC curve) of each evaluation index with CTCAE (sensory) Grade ≥2.

ROC curves of each evaluation index with CTCAE (sensory) Grade ≥2 are shown in Figure 4 and Table 5. CTCAE (sensory) Grade ≥2, PNQ (sensory and motor) grade was B. CTCAE (sensory) Grade ≥2, Quick DASH score was 6.8. CTCAE (sensory) Grade ≥2, C-HSES score was 12 points. CTCAE (sensory) Grade ≥2, Inconvenience NRS was 3.

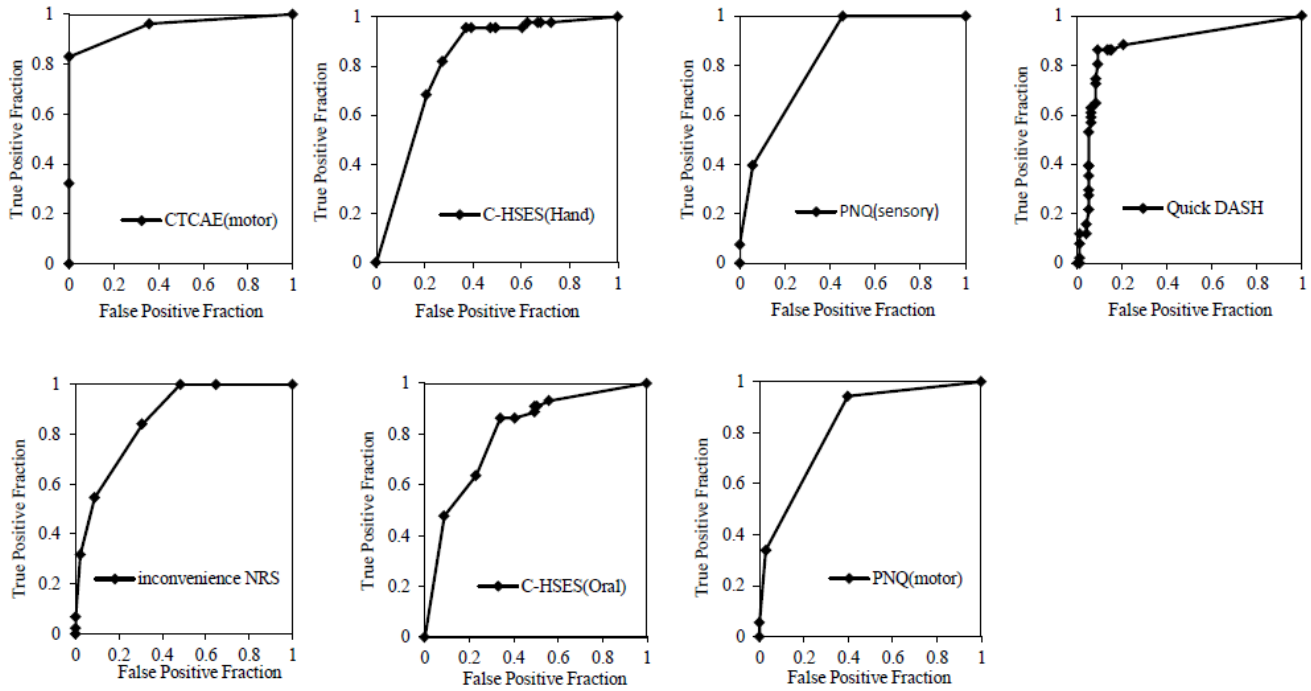

Figure 4: ROC curves of each evaluation index

Table 5: AUC (Area under Curve) of each evaluation index of CTCAE (sensory) Grade ≧ 2

Evaluation index	AUC	Cut-off value	FPF	TPF	P value
Inconvenience NRS	0.8634	3	0.31	0.84	P < 0.001
C-HSES (Oral)	0.8019	12	0.34	0.86	P < 0.001
C-HSES (Hand)	0.8181	12	0.37	0.95	P < 0.001
Quick DASH	0.8785	6.8	0.09	0.86	P < 0.001
PNQ (sensory)	0.8353	B	0.46	1	P < 0.001
PNQ (motor)	0.8273	B	0.4	0.94	P < 0.001

Evaluation index sensitivity

When C-HSES score was 12 points, CHS onset period of Grade ≥2CTCAE and Grade ≥D PNQ was compared (Figure 5). C-HSES could detect Grade ≥2 CTCAE and Grade ≥D PNQ equivalent symptoms earlier than these indicators (50% median duration of cold sensation 9 *vs.* 22 courses, $p < 0.046$ *vs.* CTCAE Grade ≥ 2, 50% Median cold sensation period 9 courses *vs.* not reached, $p < 0.001$ *vs.* PNQ grade D).

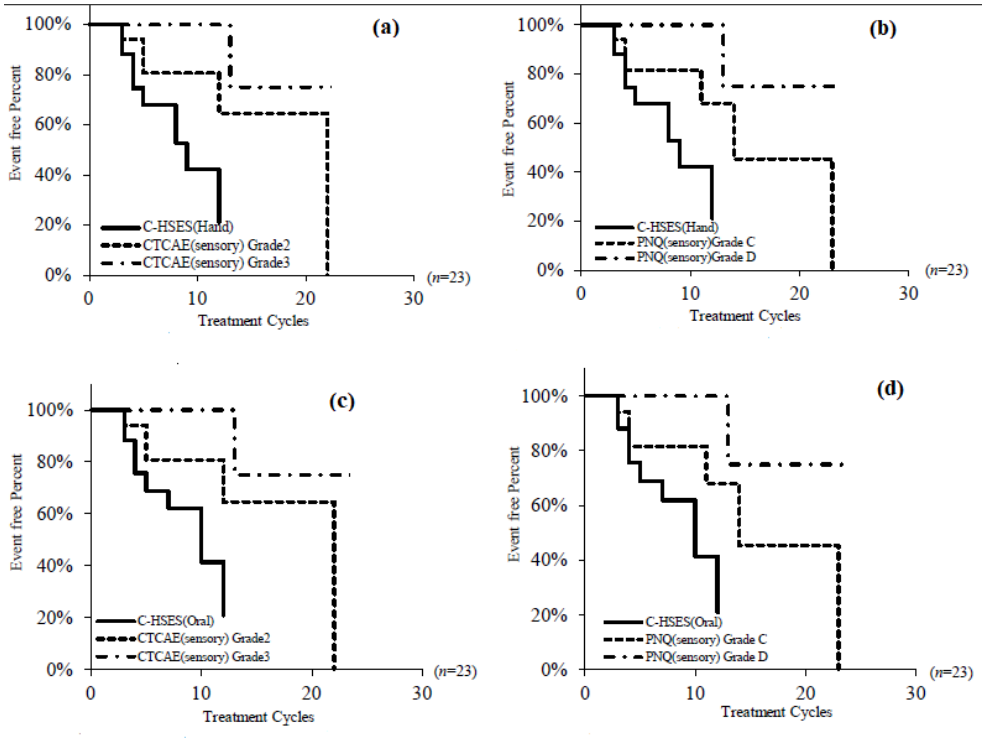

Figure 5: (a). Kaplan-Meier Curves of the time to CIPN incident by C-HSES (Hand) Score ≧12 *vs.* CTCAE (sensory) grade 2 *vs.* CTCAE (sensory) grade 3; **(b).** C-HSES (Hand) Score ≧12 *vs.* PNQ (sensory) grade C *vs.* PNQ (sensory) grade D; **(c)**. C-HSES (Oral) Score ≧12 *vs.* CTCAE (sensory) grade 2 *vs.* CTCAE (sensory) grade 3; **(d).** C-HSES (Oral) Score ≧12 *vs.* PNQ (sensory) grade C *vs.* PNQ (sensory) grade D.

DISCUSSION

In this study, a new evaluation index for CHS of L-OHP was created and verified. From the result of Cronbach's α, it was confirmed that C-HSES is an index with high internal consistency and high reliability. Although there are various evaluation indicators for PN, there is no evaluation indicator that captures the characteristics of PN in each anticancer drug [10-12]. Therefore, it is necessary to have an evaluation index that can appropriately evaluate the important side effects unique to each anticancer drug. The conventional evaluation indicators did not target avoidance.

For example, in a phase II study of a preventive drug for oxaliplatin-induced PN, CHS in the placebo group was worsened in up to 1-3 courses, but improved from 4-5 courses [13]. It is speculated that this is because patients avoided CHS and masked CHS expression. Therefore, acute PN (CHS) may not be accurately assessed despite its potential expression. The difference between our invented C-HSES and the conventional evaluation index is that C-HSES can appreciate whether patients with CHS avoid cold objects. C-HSES can accurately capture CHS with a small number of patient-subjective questions. Generally, acute PN in L-OHP can be prevented by avoiding refrigeration and symptoms are considered mild [14]. However, it became clear from the results of the change of CHS in each course that it deteriorated over time. In the change of CHS on the 12th course in C-HSES (Hand), all cases scored the highest value of 24 points (Figure 2). This proves that PN (CHS) has a long-term symptom and no symptom recovery throughout one course. CHS may have been judged to be transient, as it has not been evaluated in the past to evade avoiding cold foods. It was suggested that Quick DASH is an index for evaluating upper limb

function and may not fit the PN characteristics of L-OHP. In addition, it became clear that there is a correlation between the relationship between each evaluation index and the inconvenience NRS. Therefore, the behavior restriction that refrigeration is avoided in daily life is likely to be inconvenient for patients. There are also reports that the onset of acute PN (CHS) is involved in the onset and severity of chronic PN [15-18]. Therefore, it is important to accurately recognize acute PN (CHS). Furthermore, existing assessment indicators may not adequately assess L-OHP PN as they do not distinguish between CHS and chronic PN. In other words, we may not have been able to accurately assess CHS. In this study, it was suggested that the C-HSES we developed can accurately apprehend CHS (acute PN) peculiar to L-OHP. From this, it was considered that the timing of drug withdrawal and dose reduction by PN could be optimized.

Limitations of the study

This study had some limitations. The number of study participants was small and it was limited to a single center. In the future, it is necessary to prove that this method can be applied to multicenter and cancer patients worldwide other than Japan. Also, this survey was a subjective evaluation only. In the future, it will be necessary to perform both objective and subjective evaluations and improve the accuracy based on two evaluation approaches. Furthermore, study participants may have varied with those who participated in the study from the initial chemotherapy or those who participated in the study during the course of chemotherapy, which may have caused bias.

CONCLUSION

C-HSES is expected to be a tool that can detect cold hypersensitivity symptoms earlier in treatment than the existing evaluation indicators, and can easily evaluate patient distress and disability. In other words, by optimizing the timing of drug withdrawal and dose reduction due to PN, there is a possibility that the severity of PN can be prevented. In the future, we would like to investigate how C-HSES correlates with the objective index, and to investigate its applicability in a larger sample size.

REFERENCES

[1]. Deirdre, R.P., Rui, Q., Drew K., et al. Clinical course of oxaliplatin-induced neuropathy: Results From the Randomized Phase III Trial N08CB (Alliance). J Clin Oncol, 2015. 33:3416-3422.

[2]. André, T., Boni, C., Navarro, M., et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol, 2009.27:3109-3116.

[3]. Katsumata, N., Yasuda, M., Takahashi, F., et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: A phase 3, open-label, randomised controlled trial. Lancet, 2009.374:1331-1338.

[4]. Wilson, R.H., Lehky, T., Rebecca, R.T., et al. Acute oxaliplatin-induced peripheral nerve hyperexcitability. J Clin Oncol, 2002.20:1767-1774.

[5]. Grothey, A., Deschler, B., Kroening, H., et al. Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo)*vs.* weekly high-dose 24h 5-FU infusion/FA+oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). Proc Am Soc Clin Oncol, 2002. 21:129a.

[6]. Shimozuma, K., Ohashi, Y., Takeuchi, A., et al. Feasibility and validity of the Patient Neurotoxicity Questionnaire during taxane chemotherapy in a phase III randomized trial in patients with breast cancer: N-SAS BC 02. Supportive care in cancer, 2009.17 (12):1483-1491.

[7]. Tan, A.C., McCrary, J.M., Park, S.B., et al. Chemotherapy-induced peripheral neuropathy-patient-reported outcomes compared with NCI-CTCAE grade. Support Care Cancer, 2019.10:1-7.

[8]. Christina, G., Isam, A., Charlotte, E., The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: Longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskeletal Disorders, 2003.4:11.

[9]. Jeremy, N.P., Gavin, M., Factors associated with the development and severity of oxaliplatin-induced peripheral neuropathy: A systematic review. Asia Pac J Clin Oncol, 2017.13:345-355.

[10]. Haryani, H., Fetzer, S.J., Wu, C.L., et al. Chemotherapy-induced peripheral neuropathy assessment tools: A systematic review. Oncol Nurs Forum, 2017.44:111-123.

[11]. Curcio, K.R., Instruments for assessing chemotherapy-induced peripheral neuropathy: A review of the literature. Clin J Oncol Nurs, 2016.20:144-151.

[12]. Richardson, P.G., Sonneveld, P., Schuster, M.W., et al. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phaseIII APEX trial in relapsed multiple myeloma: Impact of a dose modification guideline. Br J Haematol, 2009.144:895-903.

[13]. Bengt, G., Nebojsa, M., Per, P., et al. Persistent prevention of oxaliplatin-induced peripheral neuropathy using calmangafodipir (PledOx ®): A Placebo-Controlled Randomised Phase II Study (PLIANT). Acta Oncol, 2018.57:393-402.

[14]. Andreas, A .A., Panagiotis, P., Gregoris, I., et al. A review on oxaliplatin-induced peripheral nerve damage. Cancer Treat Rev, 2008. 34:368-377.

[15]. Beijers, A.J., Mols, F., Vreugdenhil, G., A systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration. Support Care Cancer, 2014. 22:1999-2007.

[16]. Vincenzi, B., Frezza, A.M., Schiavon, G., et al. Identification of clinical predictive factors of oxaliplatin-induced chronic peripheral neuropathy in colorectal cancer patients treated with adjuvant Folfox IV. Support Care Cancer, 2013.21:1313-1319.

[17]. Argyriou, A.A., Cavaletti, G., Briani, C., et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. Cancer, 2013.119:438-444.

[18]. Attal, N., Bouhassira, D., Gautron, M., et al. Thermal hyperalgesia as a marker of oxaliplatin neurotoxicity: A prospective quantified sensory assessment study. Pain, 2009.144:245-252.