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Cross-Cultural Validation of the Japanese Functional Assessment of Cancer Therapy-Anemia (FACT-An)

Akinobu Yoshimura[1,2], Kunihiko Kobayashi[1,2,3], Hiyori Fumimoto[1,2], Yuki Fujiki[3], Sonya Eremenco[4] and Shoji Kudoh[1,2]

[1]East Japan Chesters Group (EJCG)
[2]Department of 4th Internal Medicine, Nippon Medical School
[3]Department of Respiratory Medicine, Saitama Medical School
[4]Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University

Abstract

Background: The Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire, which consists of a core questionnaire named the General Measure of the Functional Assessment of Cancer Therapy (FACT-G) and the Anemia additional concerns subscale, was developed in an English-speaking culture. The validation of the Japanese FACT-G was reported previously (Fumimoto et al., 2001), and, in this report, a cross-cultural validation for the subscale was performed.

Methods: The Japanese version was developed through an iterative forward-backward translation sequence used throughout the Functional Assessment of Chronic Illness Therapy (FACIT) Multilingual Translation Project. In evaluating psychometric performance, its construct validity was investigated by exploratory factor-analyses, and confirmed by Cronbach's alpha coefficient.

Results: The FACT-An was given to 180 patients with lung cancer. Using the 20 items of the Anemia subscale, a factor analysis extracted four factors of fatigue, chest condition, activities and headache. When analyzed as two extracted factors, fatigue, chest condition and headache were combined to be a major factor, although the minor factor of activities still remained. Thirteen of the 20 items construct the Fatigue additional concerns subscale. Cronbach's alpha coefficients for the Fatigue subscale (0.93) and the Anemia subscale (0.88) confirmed that, although these subscales had items that focus on different aspects of anemia or fatigue, each subscale was unidimensional. Clinical validity was indicated by moderate values of Spearman's correlation coefficients between Eastern Cooperative Oncology Group performance status rating (ECOG PSR) and the Anemia subscale (−0.50) or the Fatigue subscale (−0.48).

Conclusion: Both the Fatigue subscale and the Anemia subscale are valid in Japan, indicating that FACT-An is an instrument that is applicable across cultures and particularly with a Japanese cancer population.

(J Nippon Med Sch 2004; 71: 314–322)

Key words: anemia, quality-of-life, questionnaire, FACT-An, translation

Correspondence to Kunihiko Kobayashi MD, Ph D, Department of Respiratory Medicine, Saitama Medical School, 38 Morohongo Moroyama, Iruma-gun, Saitama 350–0495, Japan
E-mail: kobakuni@saitama-med.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Introduction

Quality of life (QOL) evaluation is considered to have an important role in clinical trials, especially in the relief of conditions such as emesis or fatigue. Technology of QOL evaluation has progressed in the past two decades, and patient-centered questionnaires assessing QOL have been developed in English-speaking cultures and other countries worldwide.

Both the Japanese language and culture are different from those of English-speaking countries. Thus, it has been questioned whether or not these tools are applicable to patients of other cultures, especially non-Western or non-European cultures. Although there is no standard method for cross-cultural validation, Hui and Triandis have postulated four conceptual dimensions of equivalence when attempting to measure a construct such as QOL internationally[1]. These dimensions are functional equivalence (adequacy of translation), scale equivalence (comparability of response scales), operational equivalence (standardization of psychometric testing procedures), and metric equivalence (transferability of scoring results from one culture to another). The four dimensions proposed by Hui et al. are considered to require three actual steps in the approach to national application of internationally available instruments[2]. The three steps involve the generation of items, the evaluation of psychometric testing, and norming. Although no gold standard for cross-cultural validation exists, the approach to procedures for the first and the second steps of equivalence, the creation of items and the evaluation of psychometric testing, are narrowing down. Many researchers consider that the translation/back-translation procedure, a review by experts whether individually or by committee comparing the source and final version, and pre-testing to check face validity are necessary steps in translation/back translation process[3,4]. Necessary psychometric tests have been studied and now tests employed in our previous reports are considered to be key analyses[5,6]. However, until recently, norming has posed a challenge[7,8].

The Functional Assessment of Cancer Therapy-General (FACT-G) scale, which is a core questionnaire to estimate general status of QOL in cancer patients, was developed and validated by Cella and colleagues in USA over the course of 10 years (1987～1997)[9]. The Japanese version of the FACT-G (version 3) was created through the standard procedures of the generation of items (translation) and psychometric testing, and it was demonstrated that detailed efforts were needed in this process[6]. We have reported on the cross-cultural validation of FACT-G, and it revealed the weak structure of Social/Family Well-Being and the conceptual difference of acceptance and coping with lung cancer in the Japanese FACT-G[6]. These findings indicated that there were cross-culturally common and culture-specific QOL items. Therefore, the FACT-G (version 4) has been created to reduce the effect of the culture-specific QOL issues in an attempt to create an instrument that is applicable across cultures[10].

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System has also developed disease/condition specific modules, for example, for breast cancer or prostate cancer, as well as symptom-specific subscales, for example, for fatigue. Specific modules aim to investigate special conditions and related QOL issues, for example, body image for breast cancer patients after mastectomy, incontinence of urine for patients with prostate cancer, or fatigue for cancer patients with anemia. These specific modules are combined with the core questionnaire, FACT-G, and named FACT-B, FACT-P, or FACT-An, respectively. In this study, we developed and examined the cross-cultural validity of the Japanese FACT-An with respect to the dimensions proposed by Hui et al.

Methods and Patients

From October 1996 through February 1998, the development and validation of the Japanese version of FACT-An scale took place in three phases. These phases were (1) item generation (translation/back-translation process), (2) pilot-testing (content

validity), and (3) estimation of reliability and validity. In the second and third phases, the procedures followed were in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Each phase will be presented in sequence.

Phase I: Item Generation (Translation)

The English FACT-An is a 47-item cancer specific questionnaire consisting of a core 27-item general questionnaire (FACT-G) plus a 20-item Anemia additional concerns subscale. Of the 20 items of the Anemia subscale, 13 items comprise the Fatigue subscale, while the remaining 7 items are considered non-Fatigue items that relate to anemia[9]. The Japanese FACT-An was developed from the English FACT-An by the FACIT Translation Project and Dr. Cella in cooperation with the Fourth Department of Internal Medicine, Nippon Medical School. The double-back translation procedure was performed as follows: Step 1) independent forward translation by two native Japanese speakers, one residing in the USA and the other in Japan; Step 2) reconciliation of the forward translations by another native Japanese speaker not involved in the forward translation process; Step 3) back-translation of the reconciled version by a native English speaker fluent in Japanese, allowing for comparison with the source document by FACIT developers; Step 4) review by 4 bilingual experts, including linguists and health professionals, who selected the most appropriate translation for each item from the reconciled or independent forward translations or provided alternative translations to improve items with inadequate pre-existing translations; and Step 5) spelling and grammatical verification of the new forward translation in preparation for pretesting with native patients in Japan[3].

Phase II: Pre-testing

To gain a measure of the instrument's comprehensibility and acceptability, i.e. for face validity, the Japanese version was pre-tested with 20 Japanese lung cancer patients at the Nippon Medical School in Tokyo. All patients were asked to complete the FACT-An by themselves and then interviewed to determine whether any questions were difficult to comprehend and/or not relevant to their QOL[3,11]. Furthermore, patients were asked to identify QOL issues not currently covered in the FACT-An. Information gathered during patient interviews was later considered in determining the final language version. Specifically, qualitative patient comments about item comprehension were recorded and compared to reviewer comments.

Phase III: Estimation of Reliability and Validity

Study sample and protocol

Subjects consisted of patients with lung cancer who were inpatients or outpatients at 8 hospitals of East Japan Chesters Group. After informed consent had been obtained to assess their QOL, the Japanese FACT-An was administered twice to each patient, at an interval of 2 weeks. After answering, each questionnaire was submitted by each patient to our QOL Center (E.P.S. Co., Ltd., Tokyo, Japan) without his/her doctor's participation. Their doctors were questioned as to the diagnosis, stage, Eastern Cooperative Oncology Group performance status rating (ECOG PSR), treatment, and degree of disclosure about the diagnosis to the patient. The latter is necessary because patients are not automatically informed of a diagnosis of cancer in Japan.

Psychometric testing

The feasibility of each item as an initial measure was calculated. Using only patients with stable PSR over 2 weeks, test-retest reliability was investigated by calculating Pearson's correlation coefficients of subscales between two measurement timepoints.

For item convergent validity, exploratory factor analyses were conducted. Promax rotation was used to extract factors. The internal consistency of each scale was estimated by Cronbach's alpha coefficient[12]. A value of 0.70 or greater was considered to indicate acceptable internal consistency[13]. For score distribution, the mean and standard deviation (SD) of the scores for the subscales were calculated according to a previously reported method[14].

To evaluate the clinical validity of the Japanese FACT-An, the relationship between the clinical

parameters of stage and ECOG PSR score and the scores of the fatigue subscale and anemia subscale were investigated by calculating Spearman's correlation coefficients.

Results

Phase I and II: Item Generation (Translation) and Pre-testing

Prior to pre-testing, reviewers modified 16 of 20 items (80%) from the reconciled version of the Japanese FACT-Anemia subscale. The Japanese language reviewers could not accept the past progressive tense in the reconciled version, opting to use the present verb tense. Most of the need to re-translate these items can be attributed to this decision.

The purpose of pre-testing was to obtain data on the acceptability, appropriateness, and comprehensibility of the Japanese FACT-An. It was expected that some further need for re-translation would become apparent. Japanese patients reported 17 significant problems with item comprehension on the FACT-G and Anemia subscales and reported 13 culturally-irrelevant items. Of these comments, only 3 items on the FACT-An were identified as difficulty to understand, and only 1 item was offensive, and in all cases only one individual complained about each item. None of the 20 items in the Anemia subscale were re-translated as a result of pre-testing because the majority of the issues were with the FACT-G items. One requirement of the re-translations based on pre-testing was altering the translations of "not at all", "a little bit", "somewhat", "quite a bit", and "very much" on the Likert scale. Japanese patients often made a mistake in choosing an answer when an item contained a negative phrase. The word "apply" was therefore added to the translation of the responses on the Likert scale as follows: "not apply at all", "apply a little bit", "apply in some degree", "apply quite a bit", and "apply very much".

Phase III: Estimation of Reliability and Validity

The demographic characteristics of the 180 patients with primary lung cancer that participated are shown in **Table 1**. There were 136 male and 44 female patients. The majority had progressive disease (stage III_B = 48 patients; stage IV = 86 patients), were inpatients (154 patients), but had good PSR (PSR 0～2, 173 patients; PS 3～4, 4 patients; data missing from 3 patients). Most of the patients were given full disclosure of their diagnosis (157 patients were informed; 23 were not informed). The feasibility of each item in Japanese at an initial measure was acceptable (rate of answering was more than 85%). For the test-retest reliability, Pearson's correlation coefficients for all the items were above 0.4, indicating sufficient reliability (**Table 2**).

Exploratory factor analyses for the Japanese version of the 20 item Anemia subscale were investigated when the number of factors extracted ranged from 2 to 5. When analyzed as four extracted factors, the item-to-factor loadings are listed in **Table 3**. Factors were considered to be named fatigue (Factor 1), chest condition (Factor 2), activities (Factor 3) and headache (Factor 4). On the other hand, when analyzed as two extracted factors (**Table 3**), the items concerned with chest condition (items B 1 and An 11) and headache (items An 9 and An 10) loaded the first factor, which was considered to be major factor in the Anemia subscale. The second factor, i.e., minor factor, by items An 5, An 7, BL 4 and An 13 was the same to Factor 3 (activities) when analyzed four extracted factors.

Cronbach's alpha coefficients for the 13-item Fatigue subscale and the 20-item Anemia subscale were 0.93 and 0.88 (**Table 4**), indicating satisfactory internal consistency within these subscales using the FACIT factor structure. Cronbach's alpha coefficient for items An 6, An 9, An 10, B 1, An 11, BL 4 and An 13, which aimed to measure other anemia-related symptoms, was 0.76. Table 4 also lists score distribution of the Fatigue subscale and the Anemia subscale.

For clinical validity, Spearman's correlation coefficients between the clinical parameters of stage or ECOG PSR score and the scores of the Fatigue subscale or Anemia subscale are listed in **Table 5**. Although correlation between stage and the score of the Fatigue subscale (−0.12) or the Anemia subscale (−0.09) was weak, moderate correlation was

Table 1 Patient Characteristics (n=180)

Variable	Category	n
Sex	Male/Female	136/44
Age	～39	3
	40～49	11
	50～59	43
	60～69	67
	70～79	49
	80～	5
ECOG PSR*1	0	51
	1	80
	2	42
	3	3
	4	1
Histology	NSCLC*2/SCLC*3	128/49
	Others	2
Stage	Ⅰ～Ⅱ	12
	ⅢA	26
	ⅢB	48
	Ⅳ	86
Truth disclosure	Cancer/Others	157/23
Patient location	Inpatient/Outpatient	154/22
Treatment	Chemo*4/Radio*5/Chemo+Radio*6	38/3/9
	Others	2
	None	68

*1 ECOG PSR: Eastern Cooperative Oncology Group performance status rating,
*2 NSCLC: non-small cell lung cancer,
*3 SCLC: small cell lung cancer,
*4 Chemo: chemotherapy,
*5 Radio: radiotherapy,
*6 Chemo + Radio: chemotherapy with concurrent radiotherapy,

observed between PSR score and the score of the Fatigue subscale (−0.48) or the Anemia subscale (−0.50).

Discussion

In determining the cross-cultural equivalence of a questionnaire, a factor analysis is useful because this can indicate that the same abstract concepts occur in each culture in the case of a cross-culturally equivalent questionnaire[6]. The results of exploratory factor analyses using 20 items of the Anemia subscale indicated that there were four factors, namely, fatigue, chest condition, activities and headache, and that, when analyzed as two extracted factors, fatigue, chest condition and headache were combined as one major factor. Although the minor factor of activities still remained, Cronbach's alpha coefficients for the Anemia subscale (0.88) confirmed that each is unidimensional. Thirteen of the 20 items construct the Fatigue additional concerns subscale, and Cronbach's alpha coefficients for the Fatigue subscale was also high (0.93). That is to say, although the Fatigue subscale or the Anemia subscale has items those focus on different aspects of fatigue or anemia, each subscale is a single construct.

Yellen SB and Cella DF et al. reported from US that Cronbach's alpha coefficients for the Fatigue subscale and the Anemia subscale were almost the same to our results (0.96 and 0.93, respectively)[15]. In their report, Cronbach's alpha coefficients of Other anemia-related symptoms (items An 6, An 9, An 10, B 1, An 11, BL 4 and An 13) were 0.59 in the first measurement and 0.70 in the second measurement, and our result was 0.76 of Cronbach's alpha[15]. These

Table 2 Results of translation/retranslation sequence and test-retest reliability for each item

Item code	Results of translation/retranslation sequence	test-retest reliability Spearman's correlation coefficient
Fatigue subscale		
HI 7	I feel fatigued 倦怠感がある.	0.51
HI 12	I feel weak all over 体全体が弱っていると感じる.	0.60
An 1	I feel listless（"washed out"） 何ごとにも関心がわかない.（疲れ切って）	0.64
An 2	I feel tired 疲れを感じる	0.62
An 3	I have trouble starting things because I am tired 疲れのせいで何事も始めるのが困難である.	0.68
An 4	I have trouble finishing things because I am tired 疲れのせいで何事も完了させるのが困難である.	0.70
An 5	I have energy 活力がある.	0.43
An 7	I am able to do my usual activities 普段していることはできる	0.55
An 8	I need sleep during the day 日中も横になって休まなければならない.	0.66
An 12	I am too tired to eat 疲れがひどく食事もできない.	0.53
An 14	I need help doing my usual activities 普段していることにも助けがいる.	0.62
An 15	I am frustrated by being too tired to do the things I want to do 疲れのため，したいことができずイライラする.	0.66
An 16	I have to limit my social activity because I am tired 疲れのため，社会的活動ができないことがある.	0.77
Other anemia-related symptoms		
An 6	I have trouble walking 歩くことが困難である.	0.79
An 9	I feel lightheaded 頭がフラフラする.（目まいがする）	0.74
An 10	I get headaches 頭痛がする.	0.49
B 1	I have been short of breath 息切れがする.	0.81
An 11	I have pain in my chest 胸の痛みを感じる.	0.71
BL 4	I am interested in sex 性行為には関心がある.	0.71
An 13	I am motivated to do my usual activities 普段していることをする意欲がある.	0.44

The responses on the Likert scale were translated as follows：not at all：全くあてはまらない，a little bit：わずかにあてはまる，in some degree：多少あてはまる，quite a bit：かなりあてはまる，and very much：非常によく当てはまる.

Spearman's correlation coefficients were more than 0.40, indicating satisfactory reliability.

values are considered borderline in terms of internal consistency. These results indicate that the Fatigue subscale and the Anemia subscales are valid, but that the items concerning other anemia-related symptoms should not be treated as an independent subscale. They also reported significantly negative relationship between PSR rating and the score of the Fatigue subscale or the Anemia subscale[15], which

Table 3 Explanatory Factor Analyses on FACT-An (n=180, Rotation Method: Promax)

Item code	Four extracted factors				Two extracted factors	
	Factor 1	Factor 2	Factor 3	Factor 4	Major factor	Minor factor
HI 7	0.93	− 0.13	− 0.01	− 0.02	0.72	0.12
HI 12	0.86	0.04	− 0.04	− 0.06	0.77	0.07
An 1	0.87	− 0.06	− 0.03	0.03	0.77	0.08
An 2	0.94	0.03	− 0.05	− 0.05	0.84	0.07
An 3	0.91	− 0.03	0.04	0.01	0.81	0.15
An 4	0.88	− 0.02	0.01	0.08	0.84	0.10
An 5	0.01	− 0.037	0.70	0.29	0.00	0.70
An 7	− 0.08	0.11	0.80	0.00	− 0.07	0.78
An 8	0.68	0.30	0.02	0.00	0.81	0.06
An 12	0.52	0.21	0.00	0.26	0.78	− 0.03
An 14	0.40	0.46	0.18	− 0.02	0.62	0.18
An 15	0.63	0.26	0.01	0.08	0.79	0.03
An 16	0.68	0.28	0.08	− 0.06	0.74	0.14
An 6	0.54	0.41	− 0.02	− 0.04	0.72	0.00
An 9	− 0.23	− 0.20	0.08	− 0.63	− 0.78	0.23
An 10	− 0.10	0.27	− 0.02	0.83	0.66	− 0.27
B 1	0.07	0.61	0.02	0.36	0.70	− 0.14
An 11	− 0.02	0.70	0.02	0.26	0.61	− 0.15
BL 4	− 0.14	0.31	0.65	− 0.26	− 0.17	0.66
An 13	0.16	0.01	0.69	− 0.04	0.06	0.73

The values of factor loading more than 0.40 are bold.

Table 4 Score distribution and Reliability analysis

	No. of items	Scores (Mean ± SD)	Cronbach's alpha
Fatigue subscale	13	67.1 ± 26.5	0.93
Other anemia-related symptoms	7	65.0 ± 18.4	0.76
Anemia subscale	20	61.9 ± 22.3	0.88

The data were from the 1st measurement. All the scores were linearly transformed to a 0 ～ 100 scale.
The values of Cronbach's alpha more than 0.70 indicate appropriate internal consistency.

Table 5 Subscale Scores by Performance Status Rating (PSR) and Clinical Staging

	PSR		Staging	
	1st	2nd measurement	1st	2nd measurement
Fatigue subscale	− 0.48	− 0.49	− 0.12	− 0.09
Other anemia-related symptoms	− 0.54	− 0.47	− 0.08	− 0.06
Anemia subscale	− 0.50	− 0.50	− 0.09	− 0.10

was reconfirmed by our study. Cella DF et al. reported in another article that mean scores of the Fatigue subscale or the Anemia subscale for patients with any malignancy were 69 and 68, respectively[16]. Comparing to **Table 4**, the former value is a little bit higher than our value (61.9). One possible explanation for these results is the difference in patient populations between the studies, as our patients were mostly inpatients, while those reported by Cella et al. were more often outpatients[16]. This indicates that norming of cross-cultural comparison was difficult in this study.

American Society of Clinical Oncology (ASCO) guidelines for using epoetin alpha for anemic patients under chemotherapy were published recently[17]. Cella et al. reported the negative impact of anemia on patients' QOL[16]. Some randomized phase III studies evaluated both blood transfusion and patients' QOL, and using epoetin alpha had an advantage in fewer blood transfusion and less fatigue[18–21]. Fatigue is only evaluated by a patient him/herself, but not by third person or any clinical data. It is considered that ASCO recognizes the importance of QOL estimation for anemic patients.

The U.S. Food and Drug Administration (FDA) welcomes the opportunity to explore with investigators the use of QOL instruments in the design of cancer clinical trials[22]. However, the success of QOL estimation in clinical trials has not reported for a long while. The reason for this has been mainly due to low compliance when QOL questionnaire have been administered to seriously ill patients[23].Despite the incomplete situation of QOL studies, FDA has continues to place importance on patients' evaluation of a therapy given because the patients' evaluation is a principle one. The FDA and European Agency for the Evaluation of Medicinal Products (EMEA) have investigated the usefulness and the limitations of QOL estimation[24,25]. Not only Japanese researchers but also the Ministry of Health, Labor, and, Welfare of Japan should recognize the usefulness and the limitations of QOL estimation.

In summary, there is still no gold standard for cross-cultural validation, but the procedures for the first step, the creation of items, are narrowing down. In this study, the Japanese version of the FACT-An was created through the standard procedure reported before, and it was demonstrated that detailed efforts were needed in this process. In the second step, the evaluation using psychometric testing, factor analysis was considered to be a good tool in cross-cultural comparison, and indicated that both the Fatigue subscale and the Anemia subscales were cross-culturally equivalent QOL subscales. The next step of FACT-An development will be longitudinally clinical validity with hemoglobin values and norming in a clinical trial.

Acknowledgments: The authors thank all the patients who participated in this study. This study was supported by grants from Japan Research Foundation for Clinical Pharmacology and Eli Lilly Japan.

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(Received, June 2, 2004)
(Accepted, July 22, 2004)