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Symposium 1 ● Biostatistics：Quality of Life in Clinical Trials and Economic Evaluation

Development Program for the Japanese Version of the PRO-CTCAE

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ABSTRACT

Background The US National Cancer Institute（NCI）-Common Terminology Criteria for Adverse Events（CTCAE）is a longstanding empirically developed grading system designed for use in cancer clinical trials to aid clinicians in detecting and documenting an array of adverse events（AEs）commonly encountered in oncology. There is growing awareness that collecting symptom data directly from patients using patient-reported outcome（PRO）tools can improve the accuracy and efficiency of symptomatic AE data collection. The purpose of the NCI Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events（PRO-CTCAE）project is to develop a patient-reported outcomes measurement system to allow patients to self-report the symptomatic adverse events listed in the CTCAE, thus improving the accuracy and precision of grading symptomatic AEs. The development of a translation of the NCI PRO-CTCAE into Japanese serves an important role by enabling collection of symptomatic AE information from Japanese speakers. A project team（the PRO-CTCAE-J Working Group）was formed to accomplish the translation and Japanese linguistic validation, and to explore the feasibility and acceptability of using the NCI PRO-CTCAE-J in the Japanese clinical trials context. A material transfer agreement was established between Japanese investigators and the US NCI in order to conduct this work.

Methods and Results Forward and back translations were performed and an independent review was performed by the Japan Clinical Oncology Group（JCOG）Executive Committee. We conducted cognitive interviews in a range of treatment settings among diverse groups of

PRO-CTCAE の日本語版開発

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cancer patients. Participants were asked to self-complete the PRO-CTCAE and then were interviewed using semi-structured scripts and predetermined probes to determine whether any items were difficult to comprehend and/or not relevant to their symptoms. We are currently analyzing results of the interviews. PRO-CTCAE is being administered in an international randomized controlled trial（NCCTG0949/JCOG1018）. Before JCOG1018 opened, we conducted a feasibility evaluation in 16 patients, to assure that patients were willing and able to report this information in a timely manner. There were no missing data and feasibility of the measurement was confirmed. The physicians' reports tended to underestimate than the patients' reports as previously published elsewhere. We are currently planning a validation study to examine the reliability and validity of the Japanese language translation of the PRO-CTCAE.

Conclusion We are continuing the development process under the provisions of a material transfer agreement with the US NCI and plan to have a translated and linguistically validated NCI PRO-CTCAE-J（Japanese language）available for use in Japanese clinical trials settings.
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KEY WORDS Patient-Reported Outcome（PRO）, NCI Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events（PRO-CTCAE）, NCI PRO-CTCAE-J（Japanese language）

BACKGROUND

The US National Cancer Institute（NCI）-Common Terminology Criteria for Adverse Events（CTCAE）is a longstanding empirically developed grading system designed for use in cancer clinical trials to aid clinicians in detecting and documenting an array of adverse events（AEs）commonly encountered in oncology. There is growing awareness that collecting symptom data directly from patients using patient-reported outcome（PRO）tools can improve the accuracy and efficiency of symptomatic AE data collection[1)]. The purpose of the NCI Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events（PRO-CTCAE）project is to develop a patient-reported outcomes measurement system to allow patients to self-report the symptomatic adverse events listed in the CTCAE, thus improving the accuracy and precision of grading symptomatic AEs[2,3)]. The accurate reporting of AEs that patients experience during clinical trials is a requirement that facilitates evaluation of new therapies and determination of treatment tolerability and safety. The development of a translation of the NCI PRO-CTCAE into Japanese serves an important role by enabling collection of symptomatic AE information from Japanese speakers. A project team（the PRO-CTCAE-J Working Group）was formed to accomplish the translation and Japanese linguistic validation, and to explore the feasibility and acceptability of using the NCI PRO-CTCAE-J in the Japanese clinical trials context. A material transfer agreement was established between Japanese investigators and the US NCI in order to conduct this work.

METHODS and RESULTS

Task 1：Developing the Japanese language translation of PRO-CTCAE

The task was accomplished as follows：

Step 1. Forward translation（FWT1, FWT2）
- Two native speakers of Japanese
- Knowledge of medical/health/psychological concepts

Step 2. Reconciliation of forward translation（FWT1＋2）
- Native speaker of Japanese
- Knowledge of medical/health/psychological concepts
- Resolve any discrepancies
- Provide alternative translation, if necessary
- Ensure linguistic compatibility with all dialects, if applicable

Step 3. Back translation of reconciled version（BWT1, BWT2）
- Two native English speakers
- Fluent in Japanese
- Not involved in previous steps（step 1-2）
- Knowledge of medical/health/psychological concepts
- Capture the meaning of the item；if there is more than one meaning, list them all

Step 4. Independent reviews by Japan Clinical Oncology Group（JCOG）
- Each expert performs an independent review and completes the review forms supplied by the PRO-CTCAE-J Working Group
- Provide alternative translation, if appropriate

Step 5. Finalization by PRO-CTCAE-J Working Group, including consultation with language coordinator as needed
- Finalize and choose best translations where necessary
- Develop testing documents
- US NCI PRO-CTCAE-Japanese version prepared by Tohoku University/The University of Tokyo/JCOG

Step 6. The finalized version of the NCI PRO-CTCAE Japanese translation was reviewed and approved by bilingual scientific staff at the US NCI

Task 2：Pilot testing

Cognitive interviewing

We conducted cognitive interviews in a range of treatment settings among diverse groups of cancer patients. Participants were asked to self-complete the PRO-CTCAE and then were interviewed using semi-structured scripts and predetermined probes to determine whether any items were difficult to comprehend and/or not relevant to their symptoms. Twenty-one patients participated at Kansai Medical University Hirakata Hospital and at the University of Tokyo Hospital between 2011-2012, with the following baseline characteristics：

Cancer type：Breast 10, Lung 7, Pancreas 3, Esophageal 1
Gender：Male 6, Female 15
Age：Median 65（range 40-80）years-old
ECOG Performance Status（PS）：score 0：6, score 1：9, score 2：4, score 3：2
Local disease only：3, Metastatic disease：18
Treatment：Chemotherapy 20, Hormonal therapy 1

We are currently analyzing results of the interviews.

NCCTG0949/JCOG1018 and feasibility assessment of the PRO-CTCAE-J

PRO-CTCAE is being administered in an international randomized controlled trial（NCCTG0949/JCOG1018）. At North American sites, the PRO-CTCAE is available in English and Spanish, and at Japanese sites the PRO-CTCAE-J is available. In this trial, mFOLFOX7 plus bevacizumab is being compared to fluoropyrimidine-based therapy（i. e., 5-FU or capecitabine）plus bevacizumab, in elderly patients with metastatic colorectal adenocarcinoma, with a survival primary endpoint. All participating patients are asked to complete a subset of nine PRO-CTCAE items related to the expected AEs in this trial（neuropathy, nausea, diarrhea, hand/foot syndrome, fatigue）. These questions are anticipated to take no longer than 5 minutes to complete and are included in the patient case report forms（CRFs）. Total expected accrual is 380 at Japanese sites. The PRO-CTCAE items will be summarized descriptively to identify the number of patients who report symptomatic AEs with comparison to the proportion of patients for whom clinicians identify an AE for the same symptoms. Before JCOG1018 opened, we conducted a feasibility evaluation in 16 patients, to assure that patients were willing and able to report this information in a timely manner. Characteristics of these patients were as follows：

Age：65±10（mean±SD）range 45-79 years-old
Gender：Male 8, Female 8
ECOG PS：score 0：4, score 1：11, score 2：1
Stage：Ⅲ：3, Ⅳ：6, Recurrence：7
Treatment：FOLFOX：5, FOLFOX+Bevacizumab：11

There were no missing data and feasibility of the measurement was confirmed. In an exploratory analysis, The physicians' reports tended to underestimate than the patients' reports as previously published elsewhere.

Task 3：Validation study

We are currently planning a validation study to examine the reliability and validity of the Japanese language translation of the PRO-CTCAE. This study will evaluate the validity, reliability, sensitivity, and clinical meaningfulness of score changes for individual PRO-CTCAE items. These are essential properties of any PRO measure to be used widely in the clinical research setting. There are 78 individual symptomatic AEs developed in the PRO-CTCAE, among which a subset has been identified as "core" based on incidence in prior NCI-sponsored trials and general applicability across diseases. All patients will be asked to complete all core and selected non-core PRO-CTCAE items at a minimum of two time points as well as the EORTC QLQ-C30（two time points）and Global Impression of Change items（final time point only）. Clinical data including the clinician-reported ECOG performance status（PS）will also be

obtained for each patient over the course of the study via case report forms. For each symptom item, we will correlate its responses to various anchor measures to assess validity（criterion and content）and examine its sensitivity and ability to detect change over time. Our overall objective is to assess the psychometric properties of the PRO-CTCAE.

Task 4：Technology development
Task 5：Educational materials
An electronic-based system（such as using iPad）will be developed to provide interfaces to investigators, clinicians, and patients to collect and report patient-reported symptom data. Educational materials for using the system will be prepared as well.

CONCLUSION

We are continuing the development process under the provisions of a material transfer agreement with the US NCI and plan to have a translated and linguistically validated NCI PRO-CTCAE-J（Japanese language）available for use in Japanese clinical trials settings.

抄　　録

1　背　景

がん臨床試験における有害事象の報告に用いられる重症度基準として NCI-CTCAE（National Cancer Institute-Common Terminology Criteria for Adverse Events）が長年にわたり広く用いられているが，グレーディングは担当医師の判断によることから，特に主観的な側面が含まれる判断については患者の状態を正確に評価できない可能性が指摘されている（Basch E, N Engl J Med 2010 など）。近年，医療者による評価だけではなく患者の主観の評価，すなわち Patient-Reported Outcomes（PRO）の重要性が認識されてきた（FDA's Guidance on Patient Reported Outcomes in Clinical Research 2009 など）。

この考え方を有害事象の報告の際に役立て，より正確度と精度の高いグレーディングを可能としようとする試みから PRO-CTCAE は NCI の研究班によって作成された（http://outcomes.cancer.gov/tools/pro-ctcae.html）。同研究班では，既存の CTCAE を生かしつつ PRO の要素を導入して，患者の評価に基づく有害事象のデータを測定できるようなシステムツールを作成した。具体的には，有害事象項目のグレーディングの評価基準を，より患者が理解できるような文書で置き換えて，患者自身が評価を行うものである。

2　目　的

われわれは数年前より米国 NCI 研究班の Dr. Basch らと交流を深め，PRO-CTCAE 日本語版の開発に着手した。

3　方法・結果

NCI が作成した原版を，順翻訳，逆翻訳，翻訳の統一の手続きで日本語に翻訳し，CTCAE 日本語版を作成している JCOG（Japan Clinical Oncology Group）と共同で，2012 年 8 月に PRO-CTCAE 日本語訳 東北大学/東京大学/JCOG 版を作成した。2012 年 9 月から同版を用いて 21 人のがん患者（乳癌 10 人，肺癌 7 人，肝臓癌 3 人，食道癌 1 人）にインタビュー調査を実施した。また，現在 JCOG と米国 NCCTG（North Central Cancer Treatment Group）とが共同で実施する大腸がん臨床試験 JCOG1018 で試行的に同版の特定の項目を測定している。これらの結果を踏まえ NCI と協議のうえ必要に応じて修正を加え，尺度の妥当性と信頼性の調査を実施し日本語版を確定するなど，さらなる開発を進めていく予定である。

4　結　論

PRO-CTCAE の日本語版の開発を早急に進めるとともに，携帯情報端末での利用可能性などについて検討する予定である。

REFERENCES

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