Validation of the Patient Neurotoxicity Questionnaire (PNQ) During Taxane Chemotherapy in a Phase III Randomized Trial in Patients with Breast Cancer: N-SAS BC 02

Kojiro Shimozuma, MD, PhD[1,2], Yasuo Ohashi, PhD[2,3], Ayano Takeuchi[3], Satoshi Morita, PhD[2,3], Shozo Ohsumi, MD, PhD[2,5], Yoshihide Sunada, MD, PhD[6], Katsumasa Kuroi, MD, PhD[2,7], Haruhiko Makino, MD, PhD[2,8], Toru Watanabe, MD, PhD[2,9] and Frederick H Hausheer, MD, FACP[10]

1 University of Marketing and Distribution Sciences, Kobe, Japan;
2 Public Health Research Foundation, Tokyo, Japan; 3 University of Tokyo, Tokyo, Japan;
4 Kyoto University, Kyoto, Japan; 5 National Shikoku Cancer Center, Matsuyama, Japan;
6 Kawasaki Medical School, Kurashiki, Japan; 7 Showa University Toyosu Hospital, Tokyo, Japan;
8 Niigata Prefectural Sakamachi Hospital, Niigata, Japan;
9 International University of Health and Welfare, Tokyo, Japan;
10 BioNumerik Pharmaceuticals, Inc. San Antonio, United States

Background

- Taxanes (paclitaxel, docetaxel) have become standard chemotherapies for the treatment of patients with node positive breast cancer (BC).
- Chemotherapy-induced peripheral neuropathy (CIPN) is a common and serious clinical problem that occurs during taxane therapy.
- CIPN can be dose-limiting and result in treatment delays, dose modifications, and in severe cases, treatment discontinuation.
- The most widely used method for the assessment of CIPN is the National Cancer Institute – Common Toxicity Criteria (NCI-CTC), a physician-based instrument which is currently not validated.
- Symptoms of CIPN are subjective in nature, very similar to the symptoms of pain or nausea.
- Reports in the medical literature demonstrate that physician-based scales, including the NCI-CTC, under-report both the incidence and severity of CIPN.
- Objective measurements (e.g., nerve conduction velocity, NCV; vibration perception threshold, VPT; electromyography, EMG) are not diagnostically reliable in the assessment of CIPN.

Objectives for Instrument Validation

- To prospectively characterize the psychometric properties and diagnostic reliability of a new patient-based instrument called the Patient Neurotoxicity Questionnaire (PNQ) in a large randomized Phase III study in cancer patients receiving neurotoxic chemotherapy.
- To prospectively compare the PNQ with other instruments that are available for the assessment of CIPN, including both patient-based (FACT-Ntx, recently validated) and physician-based methods (NCI-CTC).

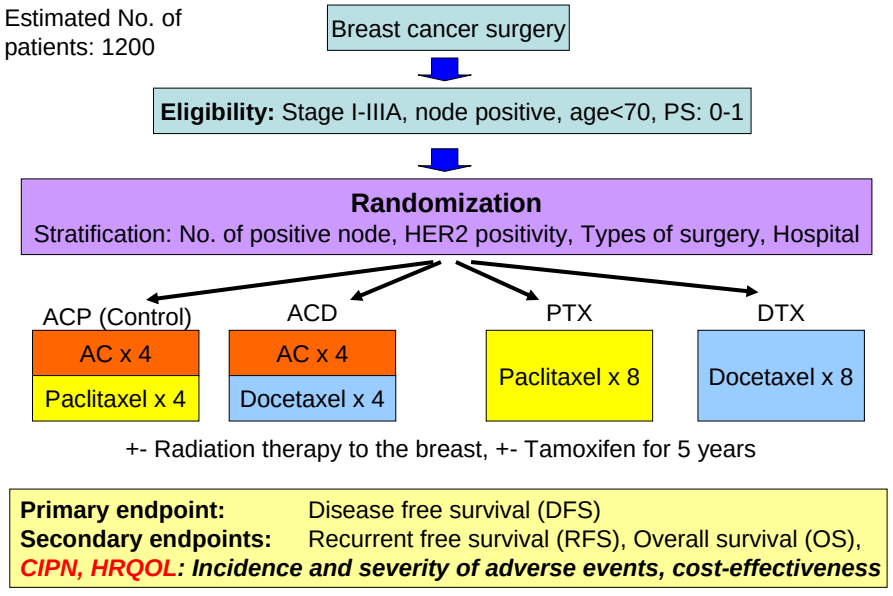
Patients and Main Eligibility Criteria

- Patients
  - 300 patients (Nov. 2001 – May. 2003)
    - who were enrolled in the National Surgical Adjuvant Study of Breast Cancer 02 (N-SAS BC 02)
- Main Eligibility Criteria for N-SAS BC 02
  - Females with pathologically proven breast cancer
  - Clinical stage: I – IIIA
  - Axillary lymph node positive
  - Age: 18 - 70
  - Performance status (ECOG): 0, 1

N-SAS BC 02: Design & Purpose

- A Phase III randomized trial comparing four treatment arms of different adjuvant chemotherapy regimens in BC patients (please see schema).
- The primary objective of the N-SAS BC 02 is to assess the non-inferiority of the standard regimen (AC x 4 cycles followed by taxane x 4 cycles) compared to the new regimen (taxane x 4 cycles) using disease free survival (DFS) as the primary endpoint.
- The prospective assessment of the incidence and severity of CIPN and health-related quality-of-life (HRQOL) are included as clinically important secondary endpoints in this study.

N-SAS BC 02



Treatment Regimens

- ACP (AC => Paclitaxel) (Control arm)

Doxorubicin (or Epirubicin)	60 mg/m^2 (or 75 mg/m^2)	q3wks x 4
Cyclophosphamide	600 mg/m^2	
Paclitaxel	175 mg/m^2	q3wks x 4

- ACD (AC => Docetaxel)

Doxorubicin (or Epirubicin)	60 mg/m^2 (or 75 mg/m^2)	q3wks x 4
Cyclophosphamide	600 mg/m^2	
Docetaxel	75 mg/m^2	q3wks x 4

- PTX

Paclitaxel	175 mg/m^2	q3wks x 8

- DTX

Docetaxel	75 mg/m^2	q3wks x 8

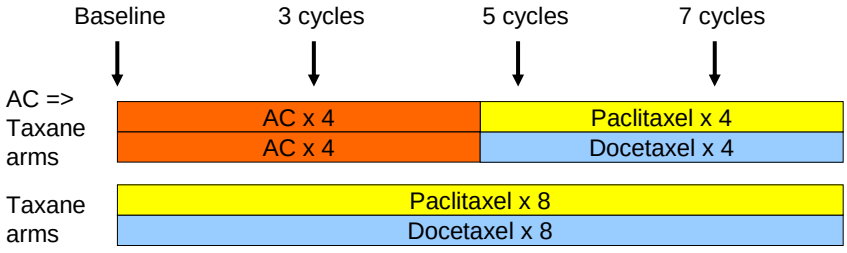
Patients Characteristics

Variables	
Age Mean (SD)	**51.7 (8.9)**
Type of surgery (%)	
Breast conservation	**173 (57.7)**
Mastectomy	**127 (42.3)**
No. Positive lymph node(s) (%)	
1 - 3	**165 (55.0)**
4 - 9	**80 (26.7)**
≥10	**55 (18.3)**

Instruments Evaluated

Patient-based	Physician-based
PNQ (Patient Neurotoxicity Questionnaire)	**NCI-CTC (Version 2.0)** (Neuro-sensory & Neuro-motor)
FACT/GOG-Ntx* (Functional Assessment of Cancer Therapy-Neurotoxicity) *Validated (Calhoun. et al., 2004)	**PNEF** (Physician Neurotoxicity Evaluation Form)

Timing of CIPN and HRQOL Assessments



- Assessments were obtained at baseline, 3rd, 5th & 7th cycle after starting adjuvant treatment.
- Baseline CIPN and HRQOL assessments were on average obtained at 38.2 days after the initial surgery.

Patient Neurotoxicity Questionnaire (PNQ)

Background & Development Rationale

- Purpose: define a clinically meaningful & reliable diagnostic endpoint for use in the assessment of the incidence & severity of CIPN in clinical trials.
- Designed to obtain clinically relevant and quantifiable CIPN diagnostic information directly from the patient regarding subjective symptoms (e.g. tingling, pain and numbness).
- PNQ is a simple self-administered instrument designed and developed by BioNumerik Pharmaceuticals, Inc. with input from the Food and Drug Administration (FDA).

PNQ Characteristics

- PNQ is comprised of specific questions that are designed to obtain clinically relevant information directly from the patient by eliciting and grading the subjective symptoms of CIPN impairment in the activities of daily living (ADL).
- The PNQ has a clear demarcation for ADL interference as well as defined ADL; these permit assessment of CIPN as a clinical endpoint.

Japanese translation (from original English)

- Developed using forward and backward translation procedures by several oncologists, neurological physicians, and linguistic experts who are fluent both in English and Japanese.

Patient Neurotoxicity Questionnaire (PNQ)

Item 1.	☐ A	☐ B	☐ C	☐ D*	☐ E*
	I have no numbness, pain, or tingling in my hands or feet.	I have mild tingling, pain or numbness in my hands or feet. This does not interfere with my activities.	I have moderate tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate to severe tingling, pain or numbness in my hands or feet. This interferes with my activities of daily living.	I have severe tingling, pain or numbness in my hands or feet. It completely prevents me from doing most activities.
Item 2.	☐ A	☐ B	☐ C	☐ D*	☐ E*
	I have no weakness in my arms or legs	I have mild weakness in my arms or legs. This does not interfere with my activities.	I have moderate weakness in my arms or legs. This does not interfere of my activities of daily living.	I have moderate to severe weakness in my arms or legs. This interferes with my activities of daily living.	I have severe in my arms or legs. It completely prevents me from doing most activities.

Examples of Activities of Daily Living for PNQ

** Please indicate by placing an X in the box or writing in the space provided which activity or activities have been interfered with as a result of therapy. If the item does not pertain to you, leave the box blank.*

- ☐ **Button clothes**
- ☐ **Use a spoon**
- ☐ **Use a knife**
- ☐ **Use a fork**
- ☐ **Other eating utensils**
- ☐ **Open doors**
- ☐ **Put in or remove contact lenses**
- ☐ **Dial or use a touch tone telephone**
- ☐ **Operation of remote controls**
- ☐ **Perform activities of importance to me**
- ☐ **Fasten Buckles**
- ☐ **Sleep**
- ☐ **Climb stairs**
- ☐ **Type on a keyboard**
- ☐ **Write**
- ☐ **Walk**
- ☐ **Put on jewelry**
- ☐ **Knit**
- ☐ **Sew**
- ☐ **Work**
- ☐ **Tie shoes**
- ☐ **Other, please indicate**

Properties Evaluated

- Acceptability and Compliance
  - Completion rate comparison of the instruments (Table 1)
- Sensitivity
- Concordance
- Validity
  - Criterion validity
    - Correlation of the PNQ score with the FACT score (Table 2) and the physician-based NCI-CTC (Table 4) and PNEF scores (not shown) .
    - Correlation of the FACT score with NCI-CTC score (Table 3).
  - Construct validity
    - Comparison of the score distribution between the PNQ and the physician-based NCI-CTC and PNEF (not shown).
  - Clinical validity (responsiveness)
    - Change of the scores of all the four instruments over time with cumulative taxane exposure (Fig. 1)
    - Specificity: incidence and severity of reported CIPN during non-neurotoxic treatment vs. during taxane treatment (not shown)

Table 1: Results
- Physician & Patient Compliance -

		Baseline	3 cycles	5 cycles	7 cycles
No. Patients		300	294	288	272
Response rate (%)	Patient-based PNQ and FACT	97.7	97.6	97.6	96.3
	Physician-based NCI-CTC and PNEF	97.7	98.0	97.7	96.3

- In this study, high compliance was noted for both patient-based and physician-based instruments. Physicians were required to use a standardized neurological examination form in this study.
- High compliance with both patient-based and physician-based instruments was maintained over all cycles of treatment.

Table 2: Results
- Correlation: PNQ & FACT-Ntx -

Spearman's correlation coefficient; Overall Cycles

		FACT- Ntx
PNQ	Sensory	0.70
	Muscle strength	0.58

- Note that a higher CIPN score for both the PNQ and FACT-Ntx subscale indicates greater (worse) neurotoxicity.
- The FACT-Ntx was recently validated as a sensitive and reliable instrument for the assessment of taxane neuropathy (Calhoun, 2004).
- The newly developed PNQ correlates well (0.70) with the FACT-Ntx (validated) particularly the sensory component which is an expected result based on the known clinical features of CIPN.
- The intra-cycle correlation values calculated for baseline, Cycle 3, Cycle 5 & Cycle 7 showed similar results to the overall correlation values above.

Table 3: Results

- Correlation: NCI-CTC & FACT-Ntx -

Spearman's correlation coefficient; Overall Cycles

		FACT- Ntx
NCI - CTC	Sensory	0.48
	Motor	0.27

- **Note that a higher score for both the NCI-CTC and FACT-Ntx subscale indicates greater (worse) neurotoxicity.**
- **Studies reported in the literature demonstrate that physician-based instruments under-report subjective symptoms including neuropathy (e.g., numbness, tingling).**
- **As noted in the table above, it appears that the physician-based NCI-CTC does not correlate well with the validated patient-based FACT-Ntx.**
- **The intra-cycle correlation values calculated for baseline, Cycle 3, Cycle 5 & Cycle 7 showed similar results to the overall correlation values above.**

Table 4: Results

- Correlation: PNQ & NCI-CTC -

Spearman's correlation coefficient; Overall Cycles

		NCI-CTC	
		Sensory	Motor
PNQ	Sensory	0.45	0.24
	Muscle strength	0.21	0.13

- **Note that a higher score for both the PNQ and NCI-CTC indicates greater (worse) neurotoxicity.**
- **Studies reported in the literature show that patients provide information not provided by physicians (Savage 2002) and that there is increasing disagreement with increasing symptom severity (Stephens 1997).**
- **As noted in the table above, it appears that the physician-based NCI-CTC does not correlate well with the patient-based PNQ.**
- **The intra-cycle correlation values calculated for baseline, Cycle 3, Cycle 5 & Cycle 7 showed similar results to the overall correlation values above.**

Results (5)

- Summary of Correlation Values -

Spearman's correlation coefficient

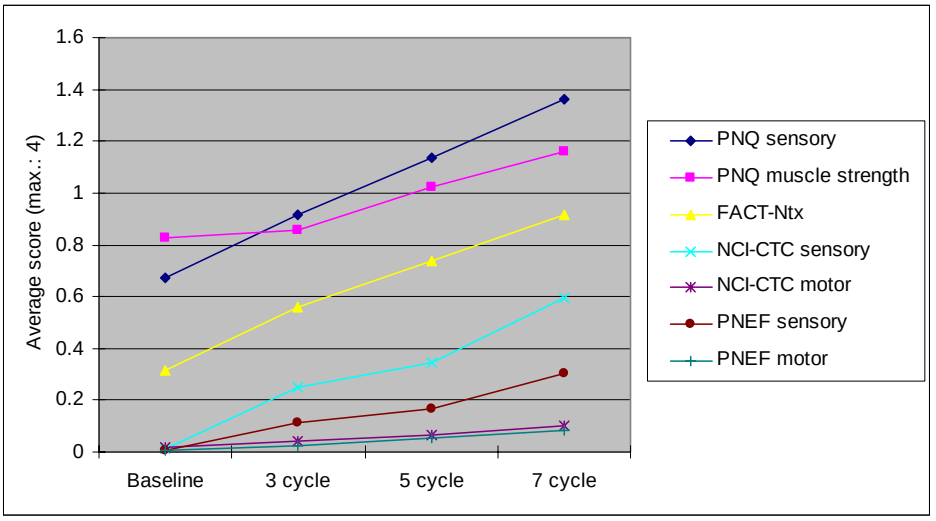
Sensory component	PNQ	NCI-CTC	FACT-Ntx
PNQ	1.0	0.45	0.70
NCI-CTC	-	1.0	0.48
FACT-Ntx	-	-	1.0

Spearman's correlation coefficient

Motor component	PNQ	NCI-CTC	FACT-Ntx
PNQ	1.0	0.13	0.58
NCI-CTC	-	1.0	0.27
FACT-Ntx	-	-	1.0

Fig. 1: Results

- Change of the scores over time -



- **Higher score always indicates greater (worse) neurotoxicity in this figure.**

Summary of Results

- Patient and physician compliance for the four instruments was excellent; 96.3% to 98.0%. No significant difference was observed in compliance between patient-based and physician-based instruments.
- The newly developed patient-based PNQ correlated well with the validated FACT-Ntx (0.70, sensory), whereas neither patient-based instrument (PNQ and FACT-Ntx) appeared to correlate well with the physician-based NCI-CTC (<0.48, sensory).
- The motor PNQ correlations obtained were lower (0.13 to 0.58) than the sensory PNQ correlations (0.45 to 0.7); this is consistent with the medical literature where CIPN is predominantly sensory in nature and rarely includes a motor component.
- At baseline assessments, physicians using the NCI-CTC and PNEF instruments rarely recorded evidence of CIPN in contrast to a large proportion of patients who reported CIPN using the PNQ; physicians rarely reported higher grades of CIPN as compared to patients who often reported a higher incidence of more severe grades of CIPN.

Conclusions

- **The PNQ is a simple, easily administered instrument that is completed with high compliance in the assessment of the incidence and severity of taxane neuropathy.**
- **Patient-based methods (PNQ and FACT-Ntx) appear to be more sensitive, responsive, valid and clinically relevant for the assessment and quantification of CIPN.**
- **Consistent with studies reported in the medical literature, the results from this study demonstrate that physician-based instruments often under-report the incidence and severity of CIPN as compared with patient-based instruments.**
- **The motor component of CIPN is not reliably detected by the NCI-CTC, however, the CIPN motor component is a substantially less prominent feature as compared to the sensory component. This is expected and is consistent with the clinical diagnostic features of CIPN.**
- **The PNQ and FACT-NTX were similar in terms of responsiveness, however, the PNQ appears to be superior to the FACT-Ntx (validated) in specificity and sensitivity; the PNQ more frequently identified higher grades of sensory neuropathy in the same patients.**
- **The results of this study clearly demonstrate that the PNQ is a valid instrument for the assessment of CIPN in clinical trials.**

References

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