#6619

Prospective assessment of chemotherapy-induced neurotoxicity in breast cancer (HOR 02) and questionnaire survey of physicians' perspectives

K. Kuroi[1], K. Shimozuma[2,3], Y. Ohashi[2,4], A. Takeuchi[2], T. Aranishi[2], S. Morita[5], S. Ohsumi[6], H. Makino[7], T. Watanabe[8], F. H. Hausheer[9]

1 Tokyo Metropolitan Komagome Hospital, Tokyo, Japan
2 Public Health Rsrch Foundation, Tokyo, Japan
3 Univ. of Tokyo, Tokyo, Japan; Ritsumeikan University, Shiga, Japan
4 Univ of Tokyo, Tokyo, Japan
5 Nagoya Univ, Nagoya, Japan
6 National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan
7 Niigata City General Hospital, Niigata, Japan
8 Hamamatsu Oncology Center, Hamamatsu, Japan
9 BioNumerik Pharmaceuticals, San Antonio, USA

CSP-HOR (Comprehensive Support Project for Health Outcomes Research)
CSPOR (Comprehensive Support Project for Oncological Research)

Background

- Chemotherapy-induced peripheral neuropathy (CIPN) commonly occurs during taxane chemotherapy.
- There is no standardized approach used in the assessment of CIPN.
- Physician-based instruments (e.g., NCI-CTC) are widely used to assess CIPN.
- However, current evidence suggests that physician-based assessments under-report the incidence and severity of CIPN.
- To overcome this limitation, a patient-based questionnaire, Patient Neurotoxicity Questionnaire (PNQ) was developed, and a phase III randomized adjuvant trial of breast cancer (N-SAS BC 02; AC followed by PAC/DOC vs. PAC/DOC alone) has demonstrated that PNQ is reliable and sensitive and responsive instrument to assess CIPN (Shimozuma et al., SABCS 2004; #6037).

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 with review by several oncologists, neurological physicians, and linguistic experts who are fluent both in English and Japanese.

PNQ

Item	☐ A	☐ B	☐ C	☐ D*	☐ E*
1.	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.
2.	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 weakness in my arms or legs. It completely prevents me from doing most activities.

*Patients answering D or E provided additional information on specific Activities of Daily Living (ADL's) that were affected.

Purpose

Part I

To evaluate the reliability and sensitivity of PNQ in advanced or metastatic breast cancer treated by weekly administration of paclitaxel (HOR 02).

Part II

To know physicians' perspectives regarding the assessment of CPIN in Japan (Questionnaire survey)

Part I

Prospective evaluation of the reliability and sensitivity of PNQ in advanced or metastatic breast cancer treated by weekly administration of paclitaxel (HOR 02).

Patients and Methods

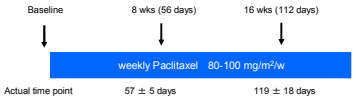
- CIPN and QOL were prospectively assessed in thirty-five patients with advanced or metastatic breast cancer who received weekly paclitaxel (80-100 mg/m^2/w).
- PNQ and FACT-Ntx were compared to NCI-CTC. Assessments were conducted at baseline, 8wks, 16wks after starting treatments.

CIPN and HRQOL Instruments

Patient-based	Physician-based
PNQ* (Patient Neurotoxicity Questionnaire)	NCI-CTC (Version 2.0) (Neuro-sensory & Neuro-motor)
FACT/G-Taxane (Functional Assessment of Cancer Therapy/general-Neurotoxicity)	PNEF** (Physician Neurotoxicity Examination Form)

* Hausheer, et al., Semin Oncol 2006, Shimozuma, et al., 2004 SABCS, 2006 ASCO.
** Developed by Hausheer, et al.

Schedule of CIPN and HRQOL assessments



Actual time point	57 ± 5 days	119 ± 18 days
Cummulative dose	520 ± 122 mg	929 ± 180 mg

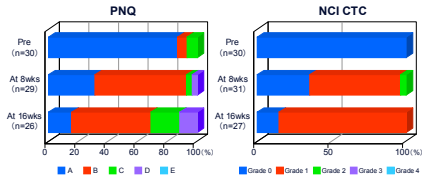
Patient Characteristics

Variables	
Age Mean (SD)	54 (36-67)
Performance status	
0	26
1	6
2	1
Disease	
Advanced / primary	13
Metastatic breast cancer	19
unknown	1
Disease site	
None	1
Single: Soft tissue / breast	16
Lung	1

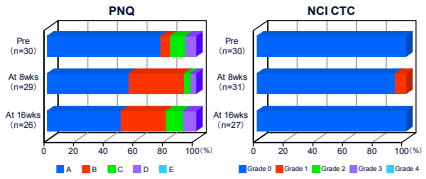
Variables	
Liver	1
Bone	0
Multiple	11
Other / unknown	3
Previous therapy	
No	8
Yes	24
Chemotherapy*	22
Endocrine therapy*	14
Radiation*	4
Unknown	1

(n=35, Data from 2 patients were missing)
* with overlapped account

Change of sensory disturbance



Change of motor disturbance



Correlation matrix of five instruments

	NCI CTC sensory	NCI CTC motor	PNQ sensory	PNQ motor	FACT-Ntx
NCI CTC sensory	1	0.15	0.58	0.08	0.3
NCI CTC-motor		1	*	*	*
PNQ-sensory			1	0.39	0.51
PNQ-motor				1	0.57
FACT-Ntx					1

Spearman's correlation coefficient (overall)
*: The narrow distribution of grade of NCI CTC motor did not allow the calculation

Results (HOR 02)

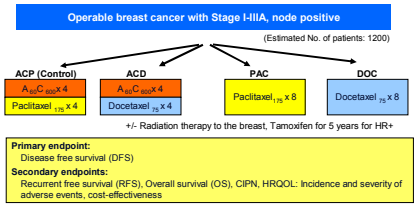
- Compliance: average response rate was 88.9%.
- Sensory PNQ scores correlated with sensory FACT-Ntx scores (r=0.51), and NCI-CTC scores (r=0.58).
- NCI-CTC scores mainly distributed between 0 and 1, while PNQ scores widely distributed.
- Follow-up study revealed that sensory CIPN assessed by PNQ appeared to be sensitive as compared to NCI-CTC.

Part II

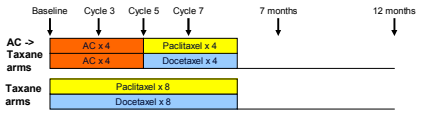
A questionnaire survey on physician perspectives regarding the assessment of CIPN in Japan.

A questionnaire was sent to 67 physicians who have participated in N-SAS BC 02 to clarify their perspectives regarding the CIPN.

Study Schema of N-SAS BC 02



Schedule of CIPN and HRQOL Assessments in NSAS BC02



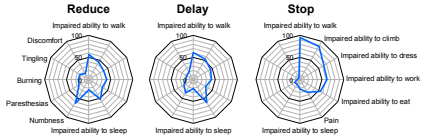
Responder's Characteristics

	No.	%
Age, years (mean)	47 (34-66)	
Sex M / F	43 / 3	94 / 6
Oncology experience, years (mean)	15 (2-30)	
Practice setting		
Cancer center / General / University	22 / 17 / 7	48 / 37 / 15
Specialty		
Surgery /Internal medicine / Others	38 / 4 / 4	82/ 9 / 9
Qualification (Breast oncology)		
Board certified / None	31 / 15	67 / 33
On-site neurologist		
Exist / None	18 / 28	39 / 61
Diagnosis and management of CIPN		
Confident / Insecure	4 / 42	9 / 91

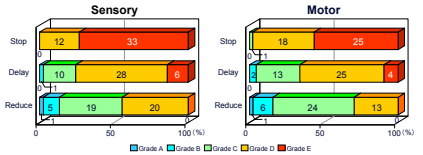
( ) : range

What are the conclusive symptom for diagnosis of CIPN?

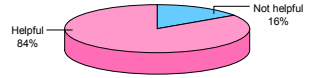
Physicians' Treatment Policy by CIPN Symptom



Physicians' Treatment Policy by PNQ Grade



Physician's view of PNQ



Results (Questionnaire survey)

- 47 out of 61 physicians (70%) responded.
- Majority of them considered neurosensory symptoms as diagnostic hallmark for CIPN.
- However, for the justification for treatment delay, dose modification, or treatment cessation, most laid weight on functional impairment in patients with CIPN.
- Most (84%) rated PNQ is helpful in management of patients at risk for CIPN.

Conclusion

Physicians tended to underestimate CIPN, and PNQ was a more reliable and valid instrument to assess CIPN with high acceptability in physicians.