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Assessment and quantification of taxane-induced neurotoxicity in a phase III randomized trial of patients with breast cancer (AC followed by PAC/DOC vs. PAC/DOC alone): N-SAS BC 02

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Comprehensive Support Project

Background

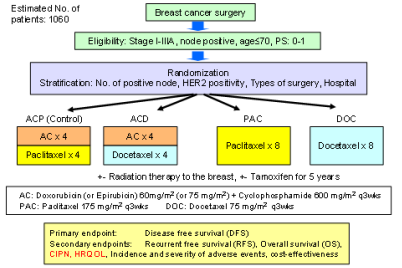
- Chemotherapy-induced peripheral neuropathy (CIPN) commonly occurs during taxane chemotherapy (Tx).
- There is no standardized approach used in the assessment of CIPN.
- Physician-based instruments (e.g., NCI-CTC) are widely used for this purpose, but are associated with several important limitations.
- Current medical evidence suggests that physician-based assessments under-report the incidence and severity of subjective symptoms, and often do not reliably or accurately assess symptoms of CIPN.
- We prospectively assessed CIPN during Tx in a phase III randomized trial to evaluate the reliability and sensitivity of patient based and physician based approaches.

Methods

Design & Purpose

- **Prospective assessment**
  - Chemotherapy-induced peripheral neuropathy (CIPN) and health-related quality of life (HRQOL)
    - The first 300* patients were recruited (Nov. 2001 – May 2003) in a phase III randomized trial (N-SAS BC 02) (see schema) of breast cancer using taxane chemotherapy (Tx).
      - *300 patients were estimated to be an adequate sample size to accurately assess CIPN and HRQOL, while 1060 patients were recruited for N-SAS BC 02.
- **To evaluate the Patient Neurotoxicity Questionnaire (PNQ)**
  - Feasibility
    - Completion rate comparison of the instruments
  - Criterion validity
    - Correlation (-sensory, -motor) with FACT (-Ntx, -G) and NCI-CTC (-sensory, -motor)
  - Clinical validity
    - Sensitivity
      - Comparison of score distribution with NCI-CTC
    - Specificity
      - Incidence and severity of reported CIPN during non-neurotoxic treatment (AC) vs. neurotoxic taxane treatment (PAC/DOC)
    - Responsiveness
      - Comparison (-sensory, -motor) with FACT (-Ntx, -G) over time among treatment arms

Study Schema of N-SAS BC 02

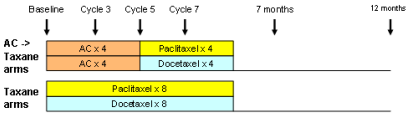


CIPN and HRQOL Instruments

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)	PNEP*** (Physician Neurotoxicity Examination Form)

* Hausheer, et al., Semin Oncol 2006, Shimozuma, et al., 2004 SABCS
** Calhoun, et al., Int J Gynecol Cancer 2003
*** Developed by Hausheer, et al

Timing of CIPN and HRQOL Assessments



- CIPN and HRQOL assessments were obtained at baseline, 3rd, 5th & 7th cycle, and 7 and 12 months after starting adjuvant treatment.

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).
- Simple self-administered instrument designed and developed by BioNumerik Pharmaceuticals, Inc. with input from the Food and Drug Administration (FDA).

PNQ Characteristics

- 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).
- Has a clear demarcation for ADL interference and 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.

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 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 (ADLs) that were affected.

Results

Patient Characteristics N=300

Variables		Variables	
Age Mean (SD)	51.7 (8.9)	ER (%)	
Type of surgery (%)		negative	224 (74.7)
Breast conservation	173 (57.7)	positive	76 (25.3)
Mastectomy	127 (42.3)	PR (%)	
No. Positive lymph node(s) (%)		negative	40 (13.3)
1 - 3	165 (55.0)	positive	258 (86.0)
4 - 9	80 (26.7)	unknown	2 (0.7)
≥ 10	55 (18.3)	HER2 (%)	
Radiation therapy (after finishing the protocol treatments)		negative	82 (27.4)
		positive	124 (41.3)
No	143 (47.7)	1+/2+/3+	50/18/56
Yes	157 (52.3)	unknown	94 (31.3)

No significant differences were observed in the distribution among the four treatment arms.

Patient & Physician Compliance

- High compliance was noted for both patient-based (85.7-96.2%) and physician-based instruments (85.3-98.0%) during the first year of this study.

Criterion validity

- Correlation matrix of the four instruments -

Spearman's correlation coefficient; Overall Cycles

	PNQ-motor	FACT-Ntx subscale	NCI-CTC-sensory	NCI-CTC-motor	FACT-G
PNQ sensory	0.48	0.66	0.44	0.19	0.29
PNQ-motor		0.51	0.22	0.16	0.39
FACT-Ntx subscale			0.45	0.23	0.43
NCI-CTC-sensory				0.26	0.09
NCI-CTC-motor					0.11

- Patient-based PNQ-sensory scores strongly correlated with FACT-Ntx scores (r=0.66), and weakly correlated with clinician-based NCI-CTC-sensory scores (r=0.44).
- A higher correlation was noted between PNQ-sensory and FACT-Ntx (r=0.70) if the 5 items* not diagnostic of taxane-induced CIPN were excluded (data not shown in the table) from FACT-Ntx.

* (1)joint pain/muscle cramps, (2)feel weak all over, (3)trouble hearing, (4)ringing in ears, (5)trouble feeling the shape of small objects

Sensitivity

- Distribution of the scores (PNQ vs. NCI-CTC) -

NCI-CTC-sensory

PNQ-sensory	0	1	2	3	4
A/0	489	38	0	0	0
B/1	432	252	4	0	0
C/2	113	171	5	0	0
D/3	44	66	11	3	1
E/4	9	1	0	0	0

Kappa=0.16

NCI-CTC-motor

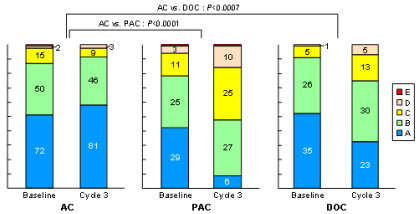
PNQ-motor	0	1	2	3	4
A/0	492	5	1	0	0
B/1	701	37	2	0	0
C/2	231	17	3	0	0
D/3	62	10	5	1	0
E/4	9	0	0	0	0

Kappa=0.02

- **PNQ scores distributed between A and E (full range), while NCI-CTC scores mainly distributed between 0 and 1.**
- Sensitivity of NCI-CTC, when PNQ scores are regarded as to be true.
  - AB/CDE and 01/234: Sensitivity=0.047 (sensory), 0.027 (motor)
  - ABC/DE and 012/34: Sensitivity=0.030 (sensory), 0.011 (motor)
- Specificity distributed between 0.996 and 1.

Specificity

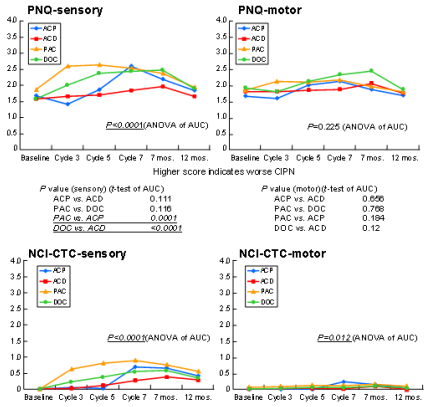
- Comparison of PNQ sensory scores during the first 3 cycles (non-neurotoxic AC vs. neurotoxic PAC/DOC) -



- Comparison of CIPN during the first 3 cycles showed that significantly higher overall incidence of sensory disturbance was observed in Tx compared with AC as assessed by PNQ (PAC, P<0.0001; DOC, P<0.001).

Responsiveness

- PNQ, NCI-CTC and FACT scores during the first year -



P value (sensory) (t-test of AUC)

ACP vs. ACD	0.111
PAC vs. DOC	0.116
PAC vs. ACP	0.0001
DOC vs. ACD	<0.0001

P value (motor) (t-test of AUC)

ACP vs. ACD	0.656
PAC vs. DOC	0.766
PAC vs. ACP	0.194
DOC vs. ACD	0.12

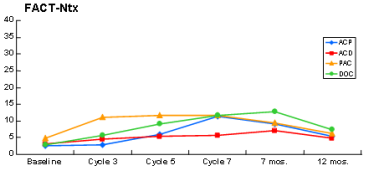
P value (sensory) (t-test of AUC)

ACP vs. ACD	0.0003
PAC vs. DOC	<0.0001
PAC vs. ACP	<0.0001
DOC vs. ACD	<0.0001

P value (motor) (t-test of AUC)

ACP vs. ACD	0.015
PAC vs. DOC	0.059
PAC vs. ACP	0.172
DOC vs. ACD	0.171

FACT-Ntx



- **No statistically significant difference was observed among the four treatment arms as assessed both by FACT-Ntx and by FACT-G (data not shown).**

Summary of Results

- **Acceptability and compliance**
  - –High compliance was noted for both patient-based (85.7-96.2%) and physician-based (85.3-98.0%) instruments during the first year of this study.
- **Criterion validity**
  - –The newly developed patient-based PNQ scores strongly correlated with FACT-Ntx scores (r=0.66-0.70 [Ntx without 5 items]) while they weakly correlated with clinician-based NCI-CTC-sensory scores (r=0.44).
- **Clinical validity**
  - –PNQ was more sensitive than NCI-CTC in detecting CIPN.
  - –Significant difference was noted in PNQ scores between non-neurotoxic treatment (AC) phase and neurotoxic Tx phase.
  - –Significant difference was observed in CIPN assessed both by PNQ and by NCI-CTC among the four treatment arms during the study period.
    - ACD and ACP tend to have less CIPN than taxane monotherapy as assessed by PNQ.
    - As assessed by NCI-CTC, ACD tends to have the least CIPN.

Conclusions

- This study confirmed that physicians tend to underestimate CIPN.
- Patient-based PNQ is more reliable and valid than other instruments that assess CIPN.
- New and reliable CIPN assessment methods can provide data that should contribute to the treatment decision process of cancer patients and their physicians.

References

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