Objective: Since there is now growing interest in the incorporation of patient-reported outcome measures in cancer clinical trials, a patient-based questionnaire, the Patient Neurotoxicity Questionnaire (PNQ) was developed to quantify the symptoms and severity of chemotherapy-induced peripheral neuropathy (CIPN). The aim of this study was to evaluate the physicians’ perspectives regarding the utility and diagnostic value of PNQ.

Methods: A questionnaire was sent to 61 physicians who participated in a Phase III randomized trial of adjuvant chemotherapy in breast cancer (AC followed by taxane versus taxane alone) that used the PNQ to assess CIPN.

Results: Forty-seven out of 61 physicians (77%) responded. The majority considered neurosensory symptoms the diagnostic hallmark for CIPN and most regarded interference with activities of daily living (ADLs) as definite justification for treatment modifications. For neurosensory disturbance, the majority of physicians indicated that Grade D severity (moderate to severe symptoms interfering with ADLs) should result in treatment postponement and Grade E severity (severe symptoms preventing most ADLs) should result in treatment discontinuation. Similarly, for neuromotor disturbance, over half of the physicians replied that Grade C (moderate symptoms not interfering with ADLs), D and E severity should result in dose reduction, treatment postponement and treatment discontinuation, respectively. Eighty-four percentage of the physicians reported that the use of the PNQ was helpful in the diagnosis and assessment of patients at risk of CIPN.

Conclusions: The PNQ appears to be a useful instrument for the diagnosis and grading of CIPN, as well as for clinical decision-making regarding treatment modifications secondary to CIPN.

Key words: neuropathy – chemotherapy – patient-reported outcome – questionnaire – breast cancer

INTRODUCTION
Chemotherapy-induced peripheral neuropathy (CIPN) is a common and serious clinical problem that affects many patients receiving chemotherapy with agents such as platinum compounds, taxanes and vinca alkaloids (1–3). Besides compromising a patient’s quality of life (QOL), it can result in chemotherapy dose reduction, treatment postponement or treatment discontinuation, as no standard therapy exists for the prevention and treatment of CIPN (2–4). Until now, physician-based instruments such as the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI-CTCAE) or the World Health...
Organization (WHO) classification have been most widely
used to assess CIPN (2,5–7). However, the symptoms and
severity of CIPN are largely subjective in nature, so that
diagnosis and grading are not always straightforward.
Furthermore, the absence of a universally recognized stan-
dard for quantifying CIPN symptoms makes comparisons
among published studies of CIPN difficult. More impor-
tantly, current evidence suggests that physician-based assess-
ments under-report the incidence and severity of CIPN (8–
10). Therefore, the development of a new and reliable
method for the assessment of CIPN would represent an
important medical advancement not only for cancer patients
but also for health-care providers involved in its diagnosis
and management.

Given the foregoing, there is now growing interest in the
incorporation of patient-reported outcome (PRO) measures
in cancer clinical trials (11), and recently a patient-based
questionnaire, the Patient Neurotoxicity Questionnaire (PNQ)
was developed to quantify the symptoms and severity of
CIPN (2). A Phase III randomized trial of adjuvant chemo-
therapy in breast cancer, the National Surgical Adjuvant
Study of Breast Cancer (N-SAS BC) 02 (AC followed by
taxane versus taxane alone), demonstrated that the PNQ is a
reliable, sensitive and responsive instrument for assessing
CIPN (9,12,13). In this survey, we aimed to obtain and
evaluate the perspectives of the physicians who participated
in the study mentioned, regarding their experience with the
PNQ in Japan, using a questionnaire.

PATIENTS AND METHODS

PATIENT NEUROTOXICITY QUESTIONNAIRE

The PNQ is a simple self-administered instrument designed
and developed by BioNumerik Pharmaceuticals, Inc. with
input from the US Food and Drug Administration (FDA). It
comprises specific questions designed to obtain clinically
relevant and quantifiable CIPN diagnostic information
directly from the patient, regarding the incidence and sever-
ity of subjective CIPN symptoms (e.g. tingling, pain and
numbness) (2) (Table 1). It is also designed to make a clear
delineation between no interference and interference with
declned activities of daily living (ADLs). This demarcation
falls between Grades C and D, and corresponds to the
absence (Grade C or less) or presence (Grade D or higher)
of neurosensory or neuromotor symptoms that interfere with
ADLs. In addition, patients with Grades D or E are asked to
identify which activity or activities are interfered with as a
result of therapy.

A Japanese translation (from the original English) has
been developed using forward and backward translation with
review by several oncologists, neurologists and linguistic
experts who are fluent in both English and Japanese (9).

SURVEY QUESTIONNAIRE

The questionnaire (available from the Comprehensive
Support Project for Oncology Research, CSPOR and
Comprehensive Support Project for Health Outcomes
Research, CSP-HOR, http://www.csp.or.jp/) was developed
during discussions with an expert panel that included
experienced breast oncologists and social scientists. First,
each respondent was asked to check or otherwise indicate all
specific patient-reported symptoms that he/she, as a clinician,
believed were conclusive for the diagnosis of CIPN. These
symptoms included numbness, tingling, burning pain, pain,
discomfort, pins and needles. The respondents were then
asked to identify the patient-reported PNQ grade and
physician-reported NCI-CTCAE grade that would lead them
to a decision to continue, postpone, discontinue or modify
the dose of chemotherapy. They were also asked whether
they considered Grade C neurotoxicity clinically significant,
whether the PNQ would be helpful in the management of
patients at risk of CIPN, and whether the list of ADLs located in the bottom portion of the PNQ was adequate.
Finally, the characteristics of the respondents were assessed
by 11 questions about age, gender, specialty, board certifica-
tion, clinical experience as a breast oncologist, number of
breast cancer patients diagnosed in the hospital per year,

Table 1. Patient neurotoxicity questionnaire

<table>
<thead>
<tr>
<th>Item 1</th>
<th>Item 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>I have no numbness, pain, or tingling in my hands or feet.</td>
<td>I have mild tingling, pain or numbness in my hands or feet. This does not interfere with my activities.</td>
</tr>
<tr>
<td>I have no weakness in my arms or legs.</td>
<td>I have mild weakness in my arms or legs. This does not interfere with my activities.</td>
</tr>
</tbody>
</table>

Additional information on specific activities of daily living that were affected in patients answering D or E: 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 telephones, operate a remote control, fasten buckles, sleep, climb stairs, type on a keyboard, write, walk, put on jewelry, knit, sew, work, tie shoes, drive. The patient was requested to specify in the space, if activities of importance to her/him have been interfered as a result of therapy.
clinical experience of CIPN, clinical experience of neurological disorders other than CIPN, availability of an on-site neurologist, the cooperative framework of the neurologist and confidence with CIPN management.

PARTICIPANTS
We selected 61 higher accrues who participated and actually treated patients in N-SAS BC 02 as potential respondents. The endpoints of N-SAS BC 02 included the prospective assessment of health-related QOL as well as validation of the PNQ in breast cancer patients receiving neurotoxic and non-neurotoxic treatment (9,12,13). The assessment was made at baseline, 3, 5, 7 and 12 months after starting adjuvant chemotherapy in the first 300 patients enrolled, and the instruments were directly sent to CSPOR data center by the patient without checking by her physician and nurses. The clinical research coordinator could check the omission of recording, however, the result of these assessments was kept from the physician. In N-SAS BC 02, the questionnaire completion rate was more than 90% at any assessment point (12,13).

In June 2006, the questionnaire was mailed with a covering letter explaining that this survey was confidential and anonymous. Consent to participate was indicated by the completion and return of the questionnaire. A second survey was mailed to physicians who had not returned the questionnaire within 2 weeks of the initial mailing. This study was performed according to the ethical guidelines for epidemiological research (http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/sisin2.html).

DATA ANALYSIS
The chi-squared test, Fisher’s exact test and the Kruskal–Wallis test were performed using JMP7, and P values less than 0.05 were considered statistically significant.

RESULTS
SURVEY PARTICIPANTS
Forty-seven of the 61 physicians (77%) responded (36% at first survey, 64% after second survey) (Table 2). The median age of the respondents was 47 years (range, 34–66). The majority was surgeons working at a cancer center or core hospital and was also experienced breast oncologists. The median duration of experience in breast oncology was 15 years (more than 10 years in 53% of respondents), and 67% were specialists certified by the Japanese Breast Cancer Society. All physicians had experience in the diagnosis and management of CIPN, and half of them had experience with peripheral neuropathy of differing etiologies. There was no full-time neurologist in 61% of the hospitals, and 91% of physicians felt insecure about the diagnosis and management of CIPN.

Table 2. Responders’ characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Age, years (mean)</td>
<td>46 (34–66)</td>
</tr>
<tr>
<td>Sex</td>
<td>M/F</td>
</tr>
<tr>
<td>Breast oncology experience, years (mean)</td>
<td>15 (2–30)</td>
</tr>
<tr>
<td>Practice setting</td>
<td>Cancer center/general/university</td>
</tr>
<tr>
<td>Specialty</td>
<td>Surgery/internal medicine/others</td>
</tr>
<tr>
<td>Board certification by Japanese Breast Cancer Society</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Experience of CIPNa</td>
<td>Yes/none</td>
</tr>
<tr>
<td>Experience of PN by the other causea</td>
<td>Yes/none</td>
</tr>
<tr>
<td>Availability of on-site neurologistb</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Diagnosis and management of CIPNb</td>
<td>Confident/Insecure</td>
</tr>
</tbody>
</table>

CIPN, chemotherapy-induced peripheral neuropathy; PN, peripheral neuropathy; M/F, male/female.

ANSWERS REGARDING SYMPTOMS OF CIPN
As shown in Fig. 1, numbness (100%), tingling (74%), pain (58%) and weakness (65%) were rated as symptoms conclusive for the diagnosis of CIPN by the majority of physicians. Other symptoms such as burning (39%), discomfort (22%) and pins and needles (30%) were considered less significant. The majority of physicians selected numbness (61%),

Figure 1. Symptoms considered conclusive for a diagnosis of chemotherapy-induced peripheral neuropathy (CIPN) (n = 46). Respondents were able to choose more than one answer.
impaired ability to walk (57%) or pain (52%) as reasons for a dose reduction (Fig. 2). Similarly, the majority of physicians indicated that they would postpone chemotherapy if patients had impaired ability to walk (61%), pain (61%) or impaired ability to climb stairs (54%). As reasons for treatment discontinuation, almost all selected impaired ability to walk (96%) and climb stairs (87%); and the majority of physicians selected impaired ability to dress (63%), work (61%) or eat (52%).

DEcisions Regarding Treatment Modifications According to the Severity of CIPN

When asked about the treatment modifications according to the PNQ grade for neurosensory or neuromotor disturbance, no physician considered continuation of treatment without modification acceptable at Grade D or E (Figs 3 and 4). For neurosensory disturbance, opinions as to when to reduce the dose were divided between Grades C (42%) and D (44%), while the majority of physicians indicated that Grade D severity should result in treatment postponement (62%) and Grade E severity should result in treatment discontinuation (73%). Similarly, for neuromotor disturbance, over half of the physicians replied that Grades C (54%), D (57%) and E (57%) severity should result in dose reduction, treatment postponement and treatment discontinuation, respectively. These results were not significantly affected by board certification or by duration of breast oncology experience, except for discontinuing of treatment by severity of neuromotor disturbance. When the correlation between the PNQ grade of neuromotor disturbance and the decision to discontinue treatment was analyzed in terms of duration of oncology experience, a significantly higher proportion of physicians who had more than 10 years experience in breast oncology selected Grade E compared with those with less experience (Grades C, D and E: 4, 25 and 70% among the former; 0, 63 and 37% among the latter, respectively, \( P < 0.05 \)).

Regarding NCI-CTCAE grades, all physicians considered it appropriate to continue treatment if the severity of sensory or motor neuropathy was Grade 1, and none opted to discontinue treatment when the severity of sensory or motor neuropathy was Grade 1, or 2 (Fig. 5). When the severity of sensory or motor neuropathy was Grade 3, 57% of physicians chose to postpone treatment, and when it was Grade 4, the majority selected to discontinue treatment (87% in sensory neuropathy and 91% in motor neuropathy). These results were not significantly affected by board certification, or by duration of breast oncology experience (data not shown).
PHYSICIANS’ PERCEPTIONS REGARDING THE PNQ

Regarding the utility of the PNQ, 42% of physicians considered Grade C as clinically significant, 84% of physicians rated the PNQ as helpful in management of patients at risk of CIPN and 93% considered the list of ADLs sufficient. In addition, some of respondents indicated that Grade C would predict the occurrence of more severe CIPN.

DISCUSSION

This survey demonstrated that a large proportion of physicians were not confident about the diagnosis and management of CIPN, despite the fact that the majority of them was specialist breast oncologists, and all had experience in the diagnosis and management of CIPN. This might be associated not only with the absence of support by on-site neurologists in many cases, but also with the lack of standardized assessment methods for CIPN.

In general, the most common features of CIPN are predominantly sensory distal neuropathic symptoms, including a mixture of paresthesia and dysesthesia, and complaints described as burning, numbness, tingling and shooting pains, typically in a glove-and-stocking distribution. Motor neuropathy is not well recognized and is believed to be much less common than sensory neuropathy (1,14). The majority of physicians involved in this survey considered neurosensory symptoms to be the diagnostic hallmark for CIPN. In addition, decisions in favor of dose reduction, treatment postponement or treatment discontinuation were predominantly due to the presence of impaired ability to perform ADLs such as walking, climbing stairs, dressing, working and eating. These results support the appropriateness of using interference with ADLs as the demarcation between PNQ Grades C and D, and demonstrate the important role a patient-based instrument can play in the diagnosis and assessment of the severity of CIPN as well as in treatment decision-making.

Until now, one of the most widely recognized physician-based approaches used to assess CIPN has been the NCI-CTCAE (2,10,15). However, this approach requires both patient cooperation and skill on the part of physicians to obtain essential diagnostic information regarding CIPN. From the viewpoint of the treating physician, the grading scheme should be clinically meaningful, and sufficiently sensitive, specific and reliable to detect CIPN. In this survey, all physicians chose to continue treatment with or without dose modification if the PNQ grade was Grade C or lower, i.e. if neurosensory or neuromotor symptoms did not interfere

Figure 4. Treatment decisions according to PNQ grades for neuromotor symptoms. The highest grade leading to a decision to continue and the lowest grade leading to a decision to reduce the dose or to postpone or discontinue treatment was recorded where multiple responses were obtained. Continue, continue treatment without postponement or modification of the chemotherapy dose level; Reduce, continue treatment, however, reduce the chemotherapy dose level; Postpone, postpone treatment until the patient’s symptoms improve; Discontinue, discontinue treatment.

Figure 5. Treatment decisions according to National Cancer Institute’s Common Terminology Criteria for Adverse Events grades. Continue, continue treatment without postponement or modification of the chemotherapy dose level; Reduce, continue treatment, however, reduce the chemotherapy dose level; Postpone, postpone treatment until the patient’s symptoms improve; Discontinue, discontinue treatment.
with ADLs. In contrast, they selected treatment modifications such as reducing the dose, or postponing or discontinuing treatment, if the patient’s PNQ score was Grade D or E; the grades correspond to the presence of neurosensory or neuromotor symptoms that interfere with ADLs, or that completely prevent ADLs, respectively. It is also important to note that decision-making regarding treatment modifications by PNQ grade was not affected by board certification or duration of breast oncology experience, barring one exception. In this survey, the decision to discontinue treatment due to neuromotor disturbance varied by duration of breast oncology experience. Although we could not determine whether this was due to the experience level itself or other factors, these results agree with the main purpose behind the development of the PNQ, which was designed to allow adequate assessment of both the severity of symptoms and the degree of functional impairment in patients at risk of CIPN. In this respect, the PNQ appears to be suitable for use in decision-making regarding treatment postponement, dose modification and treatment discontinuation.

In the questions regarding making decisions about treatment modifications based on NCI-CTCAE grading, the results were similar to those obtained with the PNQ. Most physicians chose to postpone or discontinue treatment if sensory or motor neuropathy was Grade 3, and the great majority of them selected to discontinue treatment if the severity was Grade 4. The NCI-CTCAE neuropathy categories range from Grade 0 (which includes the normal range) to Grade 5 (death), where Grade 4 means life-threatening or disabling. It is important to note, however, that no specific ADLs are defined in the NCI-CTCAE grading, and the diagnostic criterion of ‘interfering with function, but not interfering with ADLs’ is ambiguous and may be interpreted inconsistently by physicians (2). Moreover, the specific activities and levels of function that are compromised are neither defined nor captured as part of the NCI-CTCAE grading system. Interestingly, when several grading scales for the assessment of CIPN were compared by Postma et al. (5), interobserver agreement for the National Cancer Institute of Canada-Common Toxicity Criteria (NCIC-CTC) was the lowest. These investigators compared four different grading scales (the NCIC-CTC, Eastern Cooperative Oncology Group, WHO and Ajani scales), and found disagreement between two neurologists on at least one of these scales in 80% of the patient evaluations (i.e. complete agreement on all grades of all scales was noted in only 20% of patients). The overall percentage of interobserver agreement on all CIPN grades ranged from 46 to 84%. Moreover, exact agreement on severe (Grade 3) neuropathy using the NCIC-CTC was only 42%, indicating that the evaluation criteria and scoring are not interpreted in the same manner by different examiners. The variability in determining CIPN grades using these scales indicates that physician-based instruments can lead to ambiguities when deciding upon treatment modifications. NCIC-CTC is a grading scale similar to NCI-CTCAE, and thus, NCI-CTCAE may be subject to the same variability and resulting disadvantages.

The other available patient-based questionnaires might include Functional Assessment of Cancer Therapy (FACT)-Taxane, FACT&GOG-Ntx (16,17). These instruments are more discerning but contain questions that are not specific for the assessment of CIPN. Moreover, they report an overall numerical score that is the sum of several subscores, including neurosensory, neuromotor and autonomic symptoms, and do not define the demarcation or scoring of clinically important functional impairment of ADLs (2). In addition, no medical interpretation of functional impairment of ADLs is provided by these instruments. Importantly, CIPN assessment should be practical and convenient for both patients and health-care providers, and should not require any invasive procedures or large amounts of time and resources to perform (2,3,15). In this respect, the PNQ with its defined list of ADLs appears to fulfill these criteria. It also appears to be acceptable to health-care providers, as most of the physicians involved in this survey considered it helpful in the management of patients at risk of CIPN. However, further studies will be needed to address the question of whether PNQ Grade C can predict the occurrence of more severe CIPN.

CONCLUSION

It is currently not standard practice in routine cancer care or clinical trials to directly collect PROs including symptoms of CIPN, or to use these data as a basis for clinical decision-making, research conclusions or drug approval. However, the PNQ appears to be a useful instrument with high acceptability by physicians, not only for collecting information about the symptoms and severity of CIPN, but also in making decision regarding treatment modifications.

Acknowledgments

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Conflict of interest statement

The author, Frederick H. Hausheer, is the Chairman & Chief Executive Officer, a substantial shareholder and a holder of
stock options of BioNumerik Pharmaceuticals, Inc. The author, Stacey Bain, is an officer and a holder of stock options of BioNumerik Pharmaceuticals, Inc.

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