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Potential Role of pNF-H, a Biomarker of Axonal Damage in the Central Nervous System, as a Predictive Marker of Chemotherapy-Induced Cognitive Impairment

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Abstract

Purpose: Chemotherapy-induced cognitive impairment (CICI) is a clinically significant problem. Previous studies using magnetic resonance imaging indicated structural changes in the cerebral white matter of patients with CICI. Phosphorylated neurofilament heavy subunit (pNF-H), a major structural protein in axons, was recently reported to be elevated in the serum of patients with some central nervous system disorders. We performed a cross-sectional analysis of neuropsychological test results and serum pNF-H levels in patients undergoing adjuvant chemotherapy for breast cancer. Our hypothesis was that CICI is accompanied by axonal damage that can be detected by elevated serum pNF-H levels.

Experimental Design: Seventy-six patients with early breast cancer in various phases of treatment (naïve to chemotherapy; after one, three, or seven cycles of chemotherapy; or with a history of chemotherapy) were assessed by self-administered neuropsychological tests and a single pNF-H measurement. The χ^2 and Mann–Whitney tests were used for statistical analysis.

Results: Increased pNF-H levels were observed in 28.8% of the patients who underwent chemotherapy, but in none of the chemotherapy-naïve patients or patients with a history of chemotherapy. The pNF-H–positive rate increased significantly in proportion to the number of chemotherapy cycles (one cycle, 5.0%; three cycles, 31.6%; seven cycles, 55.0%; $P < 0.05$). No significant differences in neuropsychological test results were observed among the groups.

Conclusions: The serum pNF-H level in patients undergoing chemotherapy for breast cancer increased in a cumulative dose-dependent manner, suggesting its potential application as a biomarker of neural damage after chemotherapy. *Clin Cancer Res; 21(6); 1348–52. ©2015 AACR.*

Introduction

Chemotherapy can offer long-term survival for patients with cancer, especially patients with breast cancer and blood cancer. However, several recent reports (1–3) have revealed that chemotherapy may induce cognitive dysfunction such as deficits in attention, concentration, executive function, verbal or visual learning, and processing speed (4, 5) For example, one study showed that patients' attention and memory task abilities were worse after than before chemotherapy. However, healthy subjects exhibited progressive improvement in these abilities with task repetition (6). Although the cognitive dysfunction following chemotherapy is usually less severe, it sometimes impairs activities of daily living and quality of life to the point of debilitation. Recently, such chemotherapy-induced cognitive impairment (CICI) has been recognized as a clinically significant issue in patients treated with chemotherapy and cancer survivors with a history of chemotherapy (1–3, 7–9). Elucidation of the mechanisms of and diagnostic and therapeutic measures for CICI is urgently required.

One proposed mechanism of CICI is direct neurotoxicity by chemotherapy itself (7). Magnetic resonance imaging studies have demonstrated lower integrity of cerebral white matter (location of myelinated axons) rather than gray matter (location of neuronal cell bodies) in patients with CICI than in healthy subjects (10–12). However, these findings do not directly indicate whether the decreased integrity of the cerebral white matter is caused by damage to axons themselves, which are the main components of white matter, or by Wallerian axonal degeneration following neuronal damage.

Various tissues in the central nervous system (CNS), including neurons, axons, and glia, release several lines of proteins into the cerebral spinal fluid and/or peripheral blood flow when damaged (13–17). The use of some of these proteins in the cerebral spinal fluid and/or blood has been explored as objective biomarkers of the severity of neuronal damage. Increased levels of the circulating phosphorylated form of the high-molecular-weight neurofilament subunit (pNF-H), a major structural protein in central and

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Translational Relevance

Chemotherapy-induced cognitive impairment (CICI) has been recognized as a clinically significant issue in patients treated with chemotherapy and cancer survivors with a history of chemotherapy. Elucidation of the mechanisms of and diagnostic and therapeutic measures for CICI is urgently required. This study investigated CICI with a particular focus on the phosphorylated form of the high-molecular-weight neurofilament heavy subunit NF-H (pNF-H), a major structural protein in axons, as a predictive maker of CICI. We found that the serum pNF-H level in patients undergoing chemotherapy for breast cancer increased in a cumulative dose-dependent manner, suggesting the potential application of pNF-H as a biomarker of neural damage after chemotherapy. It might be useful to investigate the mechanisms and severity indexes of CICI and neuronal toxicity of chemotherapy on the CNS by using pNF-H as a surrogate marker, rather than subjective cognitive test batteries.

peripheral axons, were recently reported in a rodent model of spinal cord injury (17). The pNF-H level is associated with the severity of spinal cord injury (18) and may have adequate sensitivity to serve as a biomarker of treatment efficacy in patients with spinal cord injury (19). Increased pNF-H levels are also observed in patients with supraspinal CNS damage, such as that caused by multiple sclerosis (20), febrile seizures (21), hypoxic-ischemic encephalopathy (22), acute intracerebral hemorrhage, and other conditions. Thus, pNF-H has potential as an effective biomarker of CNS damage caused by either neuronal or axonal injury.

The purpose of the present study was to evaluate the potential role of pNF-H as a predictive marker of CICI. We performed a cross-sectional analysis of the results of neuropsychological tests, which can be conducted in the clinical setting and serum pNF-H levels in patients with breast cancer undergoing adjuvant chemotherapy.

Patients and Methods

Patients

Patients were eligible if they had histologic proof of early breast cancer. Patients were ineligible if they were <18 or >70 years of age, had a psychiatric disorder, or had a history of chemotherapy for another malignancy. The patients were assigned to various phases of treatment (before chemotherapy, after one cycle of chemotherapy, after three cycles of chemotherapy, after seven cycles of chemotherapy, and survivors who had undergone previous chemotherapy). Both neoadjuvant and adjuvant chemotherapy were eligible for inclusion. Various chemotherapy regimens were acceptable. The use of hormone agents was permitted in the group of patients who had undergone previous chemotherapy. These hormone agents including both tamoxifen and aromatase inhibitors were applied to the patients according to their menopausal status. Written informed consent was obtained from all participants. This study was approved by the institutional review board of our hospital and supported by Health Labour Sciences Research Grant from the Japanese Ministry of Health, Labour and Welfare (H24-Ganrinsho-ippan-011 and H26-Kakushinntekigan-ippan-060).

Methods

All patients underwent self-administered neuropsychological tests and pNF-H level measurements at once when they were assigned. The EuroQOL-5 Dimension questionnaire (EQ-5D), Hospital Anxiety and Depression Scale (HAD), State-Trait Anxiety Inventory (STAI), PainDETECT questionnaire, Epworth Sleepiness Scale (ESS), Raven's Colored Progressive Matrices (RCPM), Cognitive Failure Questionnaire (CFQ), Japanese version of the Brief Fatigue Inventory (BFI-J), Japanese version of the Newest Vital Sign (NVS-J), and Japanese Adult Reading Test (JART) were used. The EQ-5D is a scale of health-related quality of life (23), and the HAD is a self-assessment scale of anxiety and depression in the setting of an outpatient clinic of a medical hospital (24). The STAI is a 40-item instrument that measures transient and enduring levels of anxiety (25). PainDETECT is a screening questionnaire used to identify peripheral neuropathy and neuropathic pain (26). The ESS is a scale of subjective sleepiness (27). The RCPM is a standardized test designed to measure nonverbal intellectual capacity (28). The CFQ assesses self-reported cognitive functioning (29). The BFI-J is a nine-item questionnaire designed to assess fatigue in patients with cancer (30, 31). The NVS-J measures health literacy in Japanese adults (32). The JART evaluates the premorbid intelligence quotient (33). The serum pNF-H level was determined with a commercially available enzyme-linked immunosorbent assay kit (Human Phosphorylated Neurofilament H ELISA; BioVendor), following the manufacturer's protocol. The serum samples were diluted 3-fold before the analysis. pNF-H levels of >70.5 pg/mL were considered to be positive (18).

All statistical analyses were performed using SPSS software. The χ^2 and Mann–Whitney tests were used to compare data. Statistical significance was assessed at $P < 0.05$.

Results

A total of 76 patients participated in this study. Five patients were naïve to chemotherapy; 20 had completed 1 cycle of chemotherapy, 20 had completed 3 cycles of chemotherapy, 19 had completed 7 cycles of chemotherapy, and 12 had completed chemotherapy at least 24 months before this study. The patients' demographic data and neuropsychological test results are summarized in Tables 1 and 2. An increased pNF-H level was observed in 28.8% of the patients who underwent chemotherapy, but in none of the chemotherapy-naïve patients or patients who had undergone previous chemotherapy. The pNF-H–positive rate in each patient group treated with chemotherapy increased significantly in proportion to the number of chemotherapy cycles (one cycle, 5.0%; three cycles, 31.6%; seven cycles, 55.0%; $P < 0.05$; Fig. 1). The average pain intensity in each group according to the PainDETECT was 3.0 ± 2.3, 1.8 ± 1.8, 1.7 ± 2.0, 1.6 ± 1.6, and 1.6 ± 1.9 (naïve to chemotherapy, after one cycle of chemotherapy, after three cycles of chemotherapy, after seven cycles of chemotherapy, and previously treated by chemotherapy, respectively; $P = 0.65$). The PainDETECT numbness scores in each group were 2.2 ± 1.3, 1.2 ± 0.4, 2.0 ± 1.0, 1.6 ± 1.1, and 1.8 ± 0.8, respectively ($P = 0.14$). Symptoms of peripheral neuropathy in the patients with increasing pNF-H levels were not salient and were comparable with those in pNF-H–negative patients. The average PainDETECT pain intensity and numbness scores in the pNF-H–positive versus pNF-H–negative patients were 1.6 ± 1.8 versus 1.8 ± 1.8 ($P = 0.62$) and $1.5 \pm$

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Table 1. Patient demographics

	Chemotherapy naïve (*N* = 5)	After 1 cycle of chemotherapy (*N* = 20)	After 3 cycles of chemotherapy (*N* = 20)	After 7 cycles of chemotherapy (*N* = 19)	Patients with a history of previous chemotherapy (*N* = 12)
Age (median), y	49	45.5	45	50	46
Postmenopausal, *n* (%)	3 (60)	3 (15)	9 (45)	7 (35)	6 (50)
Hormonal therapy, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	9 (75)
Chemotherapy regimen, *n* (%)					
FEC	N/A	1 (5)	4 (20)	N/A	N/A
AC	N/A	15 (75)	9 (45)	N/A	N/A
DOC	N/A	4 (20)	7 (35)	N/A	N/A
FEC-DOC	N/A	N/A	N/A	15 (79)	8 (67)
AC-DOC	N/A	N/A	N/A	3 (16)	0 (0)
Other	N/A	N/A	N/A	1 (5)	4 (33)
Days from first chemotherapy (median)	N/A	21	63	154	944

Abbreviations: AC, adriamycin and cyclophosphamide; DOC, docetaxel; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; N/A, not applicable.

1.1 versus 1.7 ± 0.9 ($P = 0.18$), respectively. No significant differences were observed in the neuropsychological test results among the patient groups (Table 3).

Discussion

In the present study, some of the patients treated with chemotherapy showed increased serum pNF-H levels, and the chemotherapy-associated pNF-H positivity rate increased in a cumulative dose-dependent manner. These findings indicate that the serum pNF-H level in patients treated with chemotherapy is probably derived from axon degeneration in the CNS and that neuronal toxicity by chemotherapy operates temporally because none of the patients who had completed chemotherapy at least 24 months before the study showed increasing pNF-H levels. These results suggest a potential application of pNF-H as a biomarker of neural damage in the CNS after chemotherapy. In patients with chemotherapy-induced peripheral neuropathy, it is already known that chemotherapy impairs function of the peripheral nervous system in a cumulative dose-dependent manner (34, 35). However, among the present study participants, few patients showed peripheral neuropathy and neuropathic pain, and cumulative dose-dependent development of neuropathy was not observed. Furthermore, although pNF-H is certainly included in the peripheral nerve axon and oxaliplatin can lead to loss of pNF-H immunoreactivity in the dorsal root ganglion (36), symptoms of peripheral neuropathy with increasing pNF-H levels were not salient in the present patients, as in pNF-H–negative patients.

We found no differences in the neuropsychological test results between patients with and without increasing pNF-H levels. These tests failed to detect cognitive decline from the pretreatment to posttreatment period in almost all of the patients who still scored within the normal range in the posttreatment period, possibly because of high premorbid cognitive function. Previous studies (6, 10, 11) used more dedicated cognitive test batteries assessed by an experimenter, and the tests were applied much later than in the present study. The time points at which the patients were assessed by neuropsychological tests vary among previous studies, but many tests were conducted from 1 month to 1 year after

Table 2. Results of neuropsychological tests among groups sorted by treatment phase

	Chemotherapy naïve (*N* = 5)	After 1 cycle of chemotherapy (*N* = 20)	After 3 cycles of chemotherapy (*N* = 20)	After 7 cycles of chemotherapy (*N* = 19)	Patients with a history of previous chemotherapy (*N* = 12)
pNF-H–positive, *n* (%)	0 (0)	1 (5)	6 (30)	11 (57.8)	0 (0)
CFQ[a] (mean, SD)	21.5 ± 8.3	19.4 ± 11.0	17.5 ± 10.8	18.4 ± 11.4	25.6 ± 10.9
HADS[b]					
Anxiety subscale (mean, SD)	5.0 ± 2.9	5.5 ± 2.8	3.7 ± 2.8	5.0 ± 2.9	4.3 ± 2.9
Depression subscale (mean, SD)	3.4 ± 4.0	4.7 ± 3.4	3.9 ± 3.4	4.0 ± 3.6	2.8 ± 3.4
STAI[b]					
State anxiety (mean, SD)	41.6 ± 11.6	43.3 ± 11.1	38.3 ± 11.4	42.0 ± 11.9	36.9 ± 11.2
Trait anxiety (mean, SD)	45 ± 9.8	44.9 ± 11.4	35.0 ± 11.4	42.7 ± 11.9	38.1 ± 11.2
ESS[b] (mean, SD)	6.6 ± 4.0	10.5 ± 4.2	9.2 ± 4.1	8.0 ± 3.8	8.8 ± 3.8
BFI-J[b] (mean, SD)	34.5 ± 17.5	16 ± 14.8	16.3 ± 14.7	17.3 ± 15.8	21.9 ± 15.7
NVS[a] (mean, SD)	4.6 ± 0.7	4.2 ± 1.1	4.5 ± 1.1	4.6 ± 1.2	4.2 ± 1.1
JART[a] (mean, SD)					
Full-scale IQ	109.6 ± 7.5	106.7 ± 9.4	110.5 ± 9.2	110.2 ± 10.0	110.9 ± 9.6
Verbal IQ	111.4 ± 8.6	108.1 ± 10.6	112.4 ± 10.5	112.1 ± 11.3	112.8 ± 10.9
Performance IQ	106.3 ± 5.5	104.2 ± 6.9	107.0 ± 6.8	106.8 ± 7.3	107.2 ± 7.1
RCPM[a] (mean, SD)	36.0 ± 1.3	36.0 ± 0.7	35.8 ± 0.7	35.8 ± 0.8	35.5 ± 0.7
PainDETECT[b] (mean, SD)	4.1 ± 4.7	4.0 ± 4.8	3.7 ± 4.7	4.2 ± 5.0	4.2 ± 4.7
EQ5D[a] (mean, SD)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1

Abbreviations: CFQ, cognitive failure questionnaire; EQ5D, EuroQOL-5 Dimension questionnaire; HADS, Hospital Anxiety and Depression Scale; IQ, intelligence quotient; pNF-H, phosphorylated form of the high-molecular-weight neurofilament subunit.

[a]The score would decrease when the function declines.

[b]The score would increase when the function declines.

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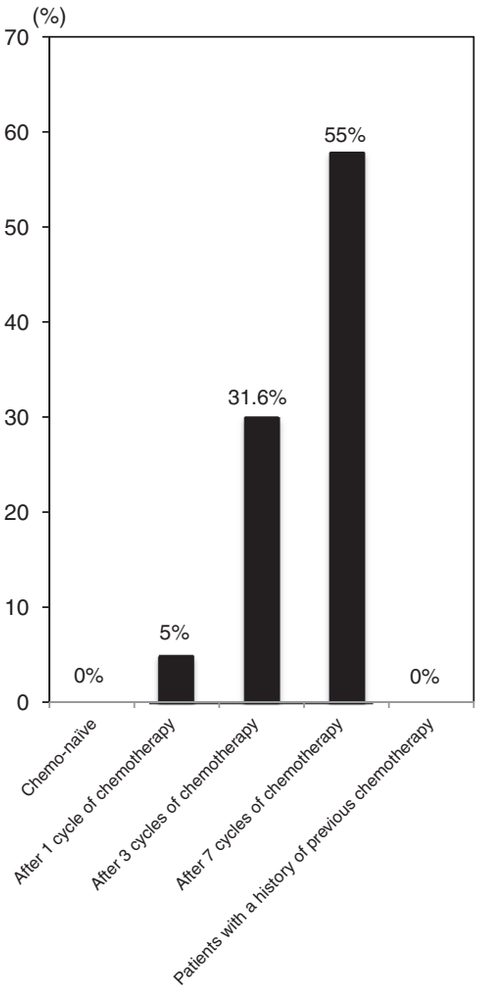

Figure 1.
Rate of pNF-H positivity in each patient group treated with chemotherapy. pNF-H, phosphorylated form of the high-molecular-weight neurofilament subunit.

chemotherapy (3, 10–12, 37). We used self-administered neuropsychological tests to screen CICI in common clinical settings using simple cognitive test batteries. However, such tests might not be sensitive enough to detect subtle changes in CICI. Whether intimate relationships exist between the pNF-H level and dedicated cognitive test batteries requires further assessment. Subjective complaints regarding cognitive decline after chemotherapy and other cancer treatments might be associated with depression, anxiety, and fatigue (2, 3). Most of the participants in the present study showed no depression or anxiety. Moreover, the cognitive decline was not found among the patients who went into menopause or used some hormonal therapy, although menopausal status and hormone therapy might affect the cognitive function (38). These may have been related to the fact that the neuropsychological test results did not detect cognitive decline. It might be useful to investigate the mechanisms and severity indices of CICI and neural toxicity of chemotherapy on the CNS using pNF-H as a surrogate marker rather than subjective cognitive test batteries.

Table 3. Results of neuropsychological tests among groups sorted by pNF-H level

	pNF-H–positive ($N = 18$)	pNF-H–negative ($N = 56$)	*P*
CFQ[a] (mean, SD)	18.8 ± 11.2	21.1 ± 10.6	0.77
HADS[b]			
Anxiety subscale (mean, SD)	4.3 ± 2.8	4.9 ± 2.8	0.35
Depression subscale (mean, SD)	4.5 ± 3.5	3.9 ± 3.3	0.83
STAI[b]			
State anxiety (mean, SD)	40.1 ± 11.2	42.8 ± 10.9	0.79
Trait anxiety (mean, SD)	40.2 ± 11.3	43.1 ± 11.2	0.41
ESS[b] (mean, SD)	8.5 ± 4.2	9.5 ± 4.1	0.26
BFI-J[b] (mean, SD)	18.1 ± 14.4	19.1 ± 14.9	0.74
NVS[a] (mean, SD)	4.8 ± 1.2	4.5 ± 1.1	0.18
JART[a]			
Full-scale IQ (mean, SD)	110.4 ± 9.3	113.4 ± 9.3	0.79
Verbal IQ (mean, SD)	112.3 ± 10.6	115.2 ± 10.6	0.79
Performance IQ (mean, SD)	107.0 ± 6.8	110.1 ± 6.8	0.79
RCPM[a] (mean, SD)	35.9 ± 0.7	37.0 ± 0.7	0.37
PainDETECT[b] (mean, SD)	4.2 ± 4.9	4.1 ± 4.7	0.26
EQ5D[b] (mean, SD)	0.8 ± 0.1	0.8 ± 0.1	0.87

Abbreviations: CFQ, cognitive failure questionnaire; EQ5D, EuroQOL-5 Dimension questionnaire; HADS, Hospital Anxiety and Depression Scale; IQ, intelligence quotient; pNF-H, phosphorylated form of the high-molecular-weight neurofilament subunit.
[a]The score would decrease when the function declines.
[b]The score would increase when the function declines.

Conclusions

The serum pNF-H level in patients with breast cancer treated with chemotherapy increased in a cumulative dose-dependent manner. Axonal damage in the CNS can be cumulatively caused by chemotherapy, which might eventually lead to CICI. The present findings suggest a potential application of pNF-H as a biomarker of CNS damage after chemotherapy. However, the self-administered neuropsychological tests used in this study did not demonstrate significant cognitive impairment. A prospective cohort study is needed to validate the usefulness of pNF-H for assessment of CICI.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A. Natori, M. Sumitani, T. Yamauchi, H. Yamauchi
Development of methodology: A. Natori, T. Ogata, T. Kogure, T. Yamauchi, H. Yamauchi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Natori, T. Ogata, T. Yamauchi, H. Yamauchi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Natori, M. Sumitani, T. Kogure, T. Yamauchi, H. Yamauchi
Writing, review, and/or revision of the manuscript: A. Natori, T. Kogure, T. Yamauchi, H. Yamauchi
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Natori, T. Yamauchi, H. Yamauchi
Study supervision: H. Yamauchi

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