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ORIGINAL ARTICLE

Discrepancy between the NCI-CTCAE and DEB-NTC scales in the evaluation of oxaliplatin-related neurotoxicity in patients with metastatic colorectal cancer

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Abstract
Background Several oxaliplatin-specific scales have been proposed in clinical practice to evaluate oxaliplatin-related neurotoxicity. We investigated whether there might be a discrepancy between the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) and the Neurotoxicity Criteria of Debiopharm (DEB-NTC), the commonly used oxaliplatin-specific scales, in the evaluation of peripheral neurotoxicity.
Patients and methods The subjects were 42 patients with metastatic colorectal cancer who received more than 6 cycles of first-line therapy with modified FOLFOX6 and more than 6 cycles of second-line therapy with FOLFIRI. The median number and cumulative dose of oxaliplatin administrations were 10.5 (range 6–22) and 889.4 mg/m^2 (range 484.5–1875.0 mg/m^2), respectively. The peripheral neurotoxicity was evaluated during mFOLFOX6 therapy and after its discontinuation using NCI-CTCAE ver. 3.0 and DEB-NTC. Data were collected prospectively and analyzed retrospectively.
Results The concordance rate of the peripheral neurotoxicity grade determined by these criteria was low: 48.8% during mFOLFOX6 and 47.3% after discontinuation of therapy. The cumulative dose of oxaliplatin-related peripheral neurotoxicity in 50% of the patients was lower when evaluated by DEB-NTC for both grades 1 ($P = 0.09$) and 2 ($P < 0.001$). The cumulative rate of improvement from grade 2 to 1 ($P < 0.001$) and from grade 2 to 0 ($P < 0.05$) after discontinuation of mFOLFOX6 therapy was higher when NCI-CTCAE was used for the evaluation.
Conclusion We found a discrepancy between the NCI-CTCAE and DEB-NTC scales in the evaluation of oxaliplatin-related neurotoxicity and suggest that the concomitant use of NCI-CTCAE and DEB-NTC would be useful to maintain oxaliplatin-based chemotherapy at higher quality.

Keywords Colorectal cancer · Oxaliplatin · Peripheral neurotoxicity · NCI-CTCAE · DEB-NTC

Introduction

Oxaliplatin-based chemotherapy has improved the outcomes of metastatic colorectal cancer patients [1, 2], and its efficacy as adjuvant chemotherapy for colon cancer has recently been reported [3, 4]. One of the important problems associated with oxaliplatin-based chemotherapy is its peripheral neurotoxicity, occurring mainly in the distal extremities, larynx, and the perilabial areas. This peripheral neurotoxicity includes acute toxicity, occurring during or within several hours of administration of oxaliplatin, and cumulative (chronic) toxicity, occurring with repeated administrations of oxaliplatin [2, 5–11]. The former is transient and is likely to be induced by cold stimulation; it is reported to occur in about 85–95% of the patients treated with the drug [2, 8–11]. The latter is one of the important reasons for discontinuation of oxaliplatin therapy, along with disease progression and hypersensitivity reaction [12, 13]. Cumulative (chronic) toxicity persists for a

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prolonged period, even after discontinuation of oxaliplatin therapy. Although various methods to reduce oxaliplatin-related neurotoxicity have been proposed in recent years, no definitive method other than discontinuation of oxaliplatin has been established to date [5, 10, 14–19].

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) [20] scale has generally been used for the evaluation of adverse events related to anticancer drug treatment. The scale has also been commonly used for evaluation of the peripheral neurotoxicity associated with anticancer drugs. In addition, some other oxaliplatin-specific scales have also been proposed for evaluation of oxaliplatin neurotoxicity. However, to the best of our knowledge, there has been no report of a close comparison of the results of evaluation by NCI-CTCAE and such oxaliplatin-specific scales. One of the commonly used oxaliplatin-specific scales is the Neurotoxicity Criteria of Debiopharm (DEB-NTC) [21–23]. Peripheral neurotoxicity is classified into 5 grades (including death) in the NCI-CTCAE, but into 3 grades in the DEB-NTC. While grade 3 neurotoxicity is defined as peripheral neuropathy accompanied by functional impairment that interferes with daily living in both the NCI-CTCAE and DEB-NTC scales, the definitions of grade 1 and grade 2 neurotoxicities differ between the two scales. NCI-CTCAE places major emphasis on the severity of a range of objective neuropathies which exert no influence on daily living, whereas DEB-NTC places importance on the duration of the peripheral neurotoxicity (Table 1). The present study was aimed at evaluating the neurotoxicity of oxaliplatin using the two scales in patients receiving FOLFOX therapy for the treatment of colorectal cancer, determining the discrepancy between these scales, and examining the clinical significance of the two sets of evaluation criteria.

Table 1 Criteria of neurotoxicity according to the NCI-CTCAE ver. 3.0 and DEB-NTC scales

Grade	NCI-CTCAE	DEB-NTC
1	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling), but not interfering with function	Within 7 days
2	Sensory alteration or paresthesia (including tingling) interfering with function, but not interfering with ADL	More than 7 days
3	Sensory alteration or paresthesia interfering with ADL	Functional impairment interfering with ADL
4	Disability	–
5	Death	

ADL activities of daily living

Patients and methods

Patients

Severe neurotoxicity by oxaliplatin is generally associated with the cumulative dose of oxaliplatin. We therefore analyzed 42 patients with metastatic colorectal cancer who received more than 6 cycles of first-line therapy with modified FOLFOX6 (mFOLFOX6) [24] and more than 6 cycles of second-line therapy with FOLFIRI [18] after failure of mFOLFOX6 at our institute between October 2006 and June 2009 (Table 2). The male:female ratio was 23:19, and the median age of the patients was 63 years (range 32–79 years). Performance status (PS) determined according to the method of the Eastern Cooperative Oncology Group (ECOG) was PS 0 in 36 patients and PS 1 in 6 patients. The median number of oxaliplatin administrations was 10.5 (range 6–22), and the median total dose of oxaliplatin was 889.4 mg/m^2 (range 484.5–1875.0 mg/m^2). The primary site was the colon in 22 patients and the rectum in 20 patients. The target lesions were located in the liver in 22 patients, lung in 18 patients, peritoneum in 11 patients, lymph nodes in 11 patients, and adrenal gland in 1 patient. The objective tumor response was rated as complete response in one patient, partial response in 14 patients, stable disease in

Table 2 Patient characteristics

Male:female	23:19
Age (years)[a]	63 (32–79)
Number of oxaliplatin administrations[a]	10.5 (6–22)
Total dose of oxaliplatin (mg/m^2)[a]	889.4 (484.5–1875.0)
ECOG performance status (0:1)	36:6
Primary site	
Colon	22
Rectum	20
Target lesions[b]	
Liver	22
Lung	18
Peritoneum	11
Lymph node	11
Adrenal gland	1
Calcium/magnesium therapy	
Randomized controlled trial	17
Clinical practice	4
Reason for the discontinuation of mFOLFOX6	
Disease progression	20
Hypersensitivity reaction	12
Peripheral neurotoxicity	10

[a] Median (range)

[b] The subjects include overlapping cases

23 patients, and progressive disease in 4 patients. The reason for the discontinuation of mFOLFOX6 therapy was disease progression in 20 patients, hypersensitivity reactions in 12 patients, and peripheral neurotoxicity in 10 patients. Calcium/magnesium therapy was given before and after oxaliplatin therapy in a total of 21 (50%) patients. Of these, 17 patients received calcium/magnesium therapy in the clinical trial [25], and 4 received it in clinical practice.

mFOLFOX6 therapy

Oxaliplatin 85 mg/m^2 and levofolinate calcium 200 mg/m^2 were given concomitantly by drip infusion over 2 h, followed by rapid intravenous infusion of 5-fluorouracil (FU) at 400 mg/m^2. Thereafter, 5-fluorouracil was given at 2400 mg/m^2 as a continuous drip infusion over 46 h. The above procedure represented one cycle of treatment, and the treatment cycles were repeated every 2 weeks. The drugs were administered into the central vein via a subcutaneous indwelling port. Patients were hospitalized for the initial treatment, whereas the subsequent cycles were given in an outpatient chemotherapy clinic. Treatment was discontinued when evidence of disease progression (progressive disease, PD) was noted according to the Response Evaluation Criteria in Solid Tumors ver. 1.0 (RECIST) [26], or when there were intolerable adverse events. When an adverse event(s) of grade 3 or greater severity according to NCI-CTCAE ver. 3.0 occurred, the mFOLFOX6 therapy was suspended until the severity of the reaction improved to grade 2 or lower severity, and when mFOLFOX6 therapy was resumed, the dose of oxaliplatin was reduced to 70–80% of the initial dose level. 5-FU/LV therapy not combined oxaliplatin therapy was not adopted in any of the patients of this series. When calcium/magnesium was given to the patients, calcium gluconate hydrate 10 mL and 0.5 M magnesium sulfate 10 mL were dissolved together in 5% dextrose solution 100 mL, and given by intravenous drip infusion before and after the administration of oxaliplatin. FOLFIRI therapy was begun after a drug-free period of 4 weeks following the end of mFOLFOX6 therapy. FOLFIRI therapy was given a median 12 times (range 6–33).

Evaluation of neurotoxicity

On every visit of the patients to the clinic for chemotherapy, the patient's history was obtained by a nurse, pharmacist or physician in-charge at the outpatient chemotherapy clinic to determine the severity and duration of neurotoxicity according to both the NCI-CTCAE ver. 3.0 and DEB-NTC scales. The data were recorded prospectively in the medical charts, and later analyzed retrospectively.

Statistical analysis

The statistical software StatFlex ver. 6.0 (Artec, Osaka, Japan) was used for the statistical analysis. The κ statistic [27] was obtained to determine the rates of concordance of the neurotoxicity grades determined by the two sets of criteria. More specifically, the concordance was rated as follows: poor, $\kappa \leq 0.0$; slight, $0.0 < \kappa \leq 0.2$; fair, $0.2 < \kappa \leq 0.4$; moderate, $0.4 < \kappa \leq 0.6$; substantial, $0.6 < \kappa \leq 0.8$; almost perfect, $0.8 < \kappa \leq 1.0$. Curves of cumulative incidence and cumulative improvement of peripheral neurotoxicity were drawn by the Kaplan–Meier method, and the log-rank test was used for comparison of the curves. The results were regarded as statistically significant at $P < 0.05$.

Results

The median duration of mFOLFOX6 therapy was 181 days (range 91–422 days). Grade 0–2 peripheral neurotoxicity was recorded a total of 472 times during this period. The rate of concordance of grade 0–2 peripheral neurotoxicity as evaluated by the two sets of criteria was 48.8%, with $\kappa = 0.26$ (95% confidence interval 0.21–0.32) (Table 3). The median observation period after discontinuation of oxaliplatin, i.e., the median duration of FOLFIRI therapy, was 244 days (range 84–728 days). During this period, evaluation of neurotoxicity was carried out a total of 573 times. The rate of concordance of grade 0 to grade 2 peripheral neurotoxicity as evaluated by the two sets of criteria was again low, at 47.3%, with $\kappa = 0.18$ (95% confidence interval 0.13–0.22) (Table 4).

Figure 1a, b shows the cumulative incidence rates of grades 1 and 2 peripheral neurotoxicity during mFOLFOX6 therapy. According to both NCI-CTCAE ver. 3.0 and DEB-NTC, neurotoxicity of grade 1 or greater severity occurred in 41 of the 42 patients. There was a tendency for grade 1 neurotoxicity to be detected at a lower total dose of oxaliplatin when the evaluation was based on DEB-NTC

Table 3 Concordance rate of the peripheral neurotoxicity grade evaluated by NCI-CTCAE and DEB-NTC scales during mFOLFOX6 therapy

	DEB-NTC			
	Grade	0	1	2
NCI-CTCAE	0	103	73	24
	1	15	71	124
	2	3	8	61

Concordance rate 48.8%, κ 0.26 (95% confidence interval 0.21–0.32), $P < 0.001$

Table 4 Concordance rate of the peripheral neurotoxicity grade evaluated by NCI-CTCAE and DEB-NTC scales during FOLFIRI therapy

	DEB-NTC			
	Grade	0	1	2
NCI-CTCAE	0	23	24	49
	1	1	57	204
	2	0	10	178

Concordance rate 47.3%, κ 0.18 (95% confidence interval 0.21–0.32), $P < 0.001$

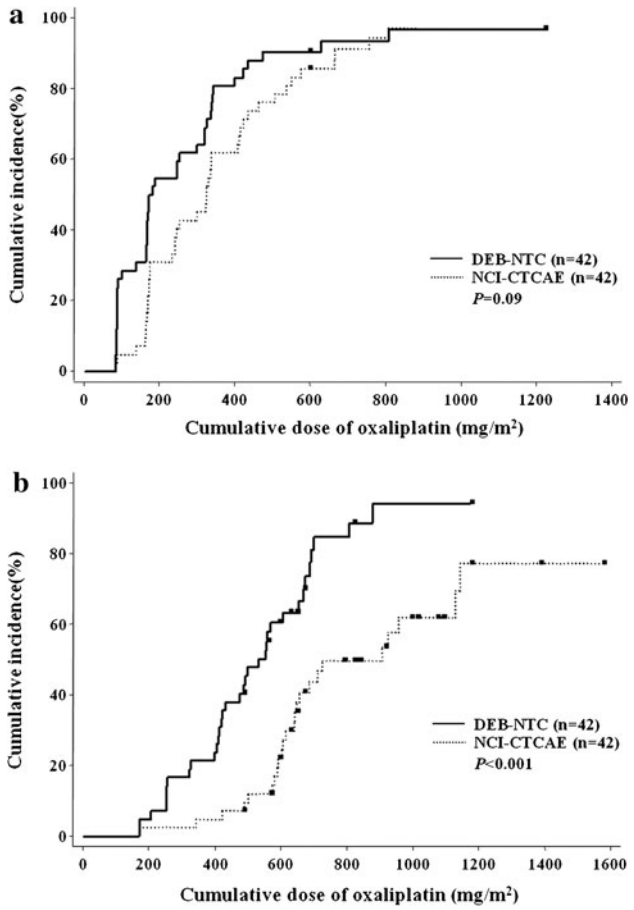

Fig. 1 **a** Cumulative incidence of grade 1, **b** cumulative incidence of grade 2 during mFOLFOX6 therapy

than when it was based on NCI-CTCAE ver. 3.0 ($P = 0.09$) (Fig. 1a). The total dose of oxaliplatin at which the incidence of grade 2 neurotoxicity reached 50% was 480 mg/m^2 when the evaluation was based on DEB-NTC and 627 mg/m^2 when the evaluation was based on NCI-CTCAE ver. 3.0; the total dose of oxaliplatin until the occurrence of grade 2 neurotoxicity was significantly lower when the evaluation was based on DEB-NTC ($P < 0.001$) (Fig. 1b). The cumulative dose between the occurrence of grade 1 neurotoxicity and increase in its severity to grade 2 was about 300 mg/m^2 according to evaluation by both DEB-NTC and NCI-CTCAE ver. 3.0. Grade 3 neurotoxicity (according to both NCI-CTCAE and DEB-NTC) occurred in 7 patients (16.7%).

Figure 2a–d shows the cumulative improvement of peripheral neurotoxicity during FOLFIRI therapy. Grade 3 peripheral neurotoxicity was found in 7 patients according to NCI-CTCAE ver. 3.0, and improved to grade 2 in 6 of these patients during the observation period. There was no difference in the improvement curves between the two sets of criteria ($P = 0.35$) (Fig. 2a). When the evaluation was based on NCI-CTCAE ver 3.0, improvement from grade 2 to grade 1 was found in 50% of the patients by 200 days after discontinuation of oxaliplatin, whereas when it was based on DEB-NTC, the rate of improvement within the observation period remained at 5% ($P < 0.001$) (Fig. 2b). In regard to the improvement from grade 2 to grade 0, the cumulative improvement reached a plateau at 40% during the observation period when the evaluation was based on NCI-CTCAE ver. 3.0, whereas when the evaluation was based on DEB-NTC, the cumulative improvement was determined to be only 5% ($P < 0.05$) (Fig. 2c). There was no significant difference in the curve of cumulative improvement from grade 1 to grade 0 between the two sets of criteria ($P = 0.19$) (Fig. 2d). However, a cumulative improvement of 45% was obtained during the observation period when the evaluation was based on NCI-CTCAE ver. 3.0, whereas the corresponding rate obtained was only 20% when the evaluation was based on the DEB-NTC scale.

Discussion

The present study revealed a discrepancy between the NCI-CTCAE ver. 3.0 and DEB-NTC scales in the evaluation of peripheral neurotoxicity associated with oxaliplatin-based chemotherapy for metastatic colorectal cancer. Specifically, it appears that grade 1 or grade 2 peripheral neurotoxicity after the start of mFOLFOX6 therapy can be detected earlier when the evaluation was based on DEB-NTC than when it was based on NCI-CTCAE ver. 3.0. With respect to evaluation of improvement in the peripheral neurotoxicity after discontinuation of oxaliplatin, grade 1 or grade 2 neurotoxicity persisted for longer when the evaluation was based on the DEB-NTC scale. In particular, it is noteworthy that scarcely any improvement of neuropathy was found during the observation period after discontinuation of oxaliplatin (84–728 days, median 240 days) in patients with grade 2 symptoms, i.e., those who had peripheral neuropathy persisting for at least 14 days. There was no close relationship between the grade of paresthesia and the duration of peripheral neurotoxicity.

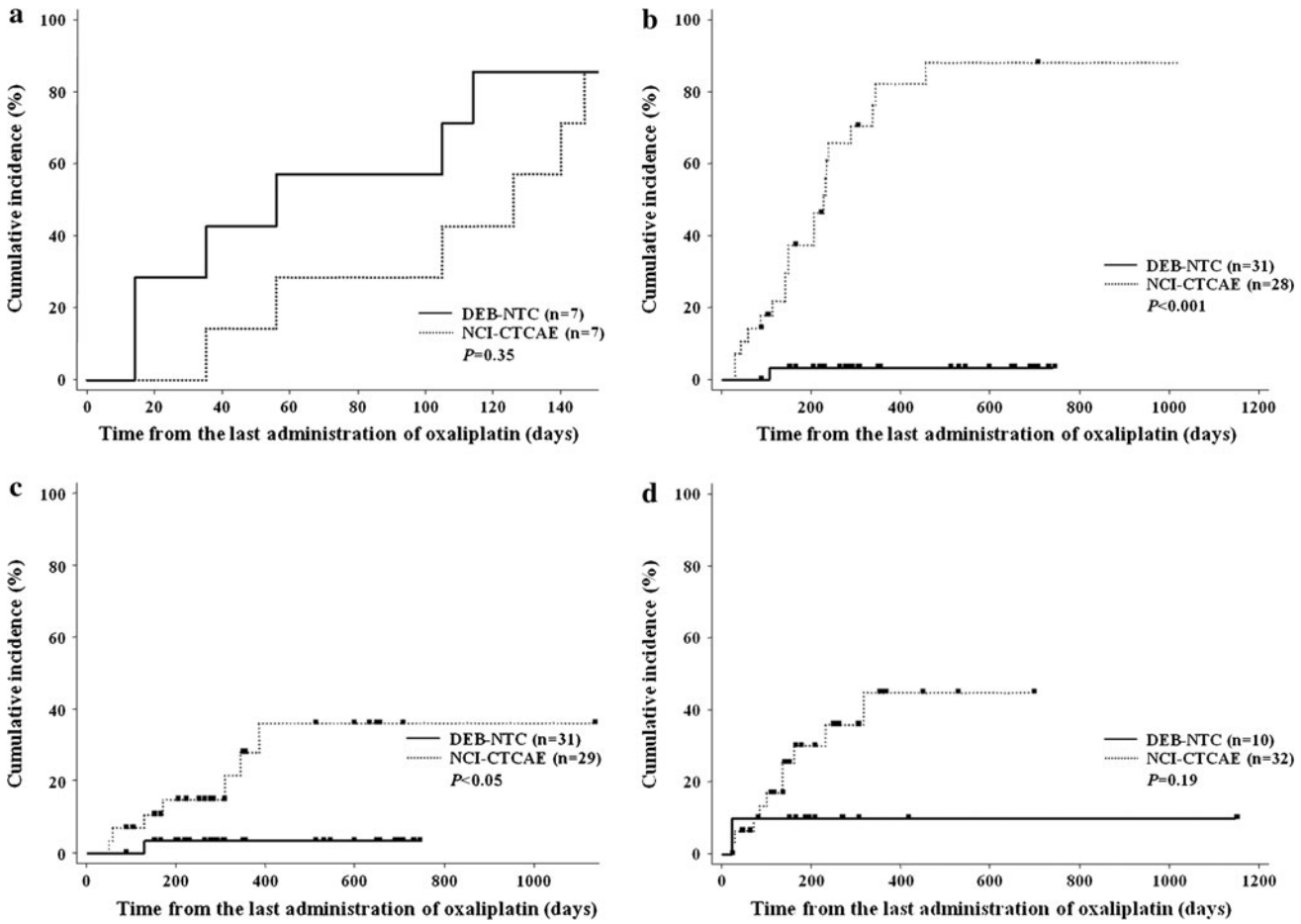

Fig. 2 **a** Cumulative improvement from grade 3 to grade 2, **b** cumulative improvement from grade 2 to grade 1, **c** cumulative improvement from grade 2 to grade 0, **d** cumulative improvement from grade 1 to grade 0 during FOLFIRI therapy

Therefore, we speculated that this discrepancy between the evaluations by NCI-CTCAE ver. 3.0 and DEB-NTC arose from the criteria used for toxicity up to grade 2, because the former criteria place stress on the grade of paresthesia, whereas the latter attach more importance to the duration of peripheral neurotoxicity.

How to apply these findings to practical oxaliplatin-based chemotherapy is an important issue. A key point in oxaliplatin-based chemotherapy is to prevent the appearance of grade 3 peripheral neuropathy. In patients with paraesthesias associated with pain or functional impairment persisting until the next cycle, oxaliplatin should be permanently discontinued [28]. Therefore, it is crucial to predict the development of grade 3 neuropathy as early as possible. The present study revealed that peripheral neuropathy persisting for at least 14 days, i.e., grade 2 neuropathy, was detected earlier, at an oxaliplatin dose 150 mg/m^2 lower, when the evaluation was based on DEB-NTC than when it was based on NCI-CTCAE ver. 3.0. Therefore, it is important to ask the patient carefully about the duration of neuropathy. When DEB-NTC is used for the evaluation of neuropathy in daily clinical practice, continuation of treatment should be considered as long as there is no interference with the patient's daily activities. However, there may be criticism that if a physician decides to discontinue or restart the chemotherapy according to the DEB-NTC scale, the total dose of oxaliplatin, which may affect the survival period, would be lower than that with the use of the NCI-CTCAE scale. We cannot address this issue exactly, but it deserves further investigation in future clinical trials or accumulated cases in clinical practice.

The usefulness of FOLFOX4 [2] and FLOX [4] as adjuvant chemotherapy for colon cancer has been reported. However, a follow-up study of the MOSAIC trial [3] showed that peripheral neuropathy was persistent in 15.4% of the surviving patients who were followed up for at least 4 years after adjuvant chemotherapy with FOLFOX4. In the MOSAIC study, peripheral neuropathy was evaluated by NCI-CTCAE ver. 1.0. It would be interesting to speculate on what results might have been obtained if the evaluation had been based on DEB-NTC, since even more delayed improvement of neuropathy tends to be obtained

when the evaluation is based on DEB-NTC than when it is based on NCI-CTCAE. If clinical trials aimed at reducing peripheral neuropathy in patients receiving oxaliplatin-based chemotherapy in the adjuvant setting are planned in the future, the use of DEB-NTC together with NCI-CTCAE is recommended for the evaluation of neuropathy. Although it would be ideal for specific scales to be designed for the evaluation of acute and chronic peripheral neuropathy, no such scales are available at present.

Some oxaliplatin-specific scales other than DEB-NTC have been proposed. In the NSABP C-07 study, Stephanie et al. [4] evaluated pain during oxaliplatin therapy by means of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Oxaliplatin-Specific Neurotoxicity Scale (NTX-12) and NCI-Sanofi grade. A questionnaire evaluation of the quality of life (QOL) of patients was also carried out in the N04C7 study [29]. In addition, de Gramont et al. [2] evaluated peripheral neurotoxicity as a factor affecting the patient's QOL using QOL scores. A patient-oriented survey technique based on the Patient Neurotoxicity Questionnaire (PNQ): oxaliplatin has also been reported. From this point of view, evaluation of the duration of peripheral neuropathy, a subjective variable that can only be described by the patients themselves, by DEB-NTC might be able to contribute to QOL improvement of the patients given oxaliplatin-based chemotherapy.

When evaluating the grade of peripheral neurotoxicity in patients examined in previous clinical trials or treated in clinical practice, attention should be paid to which set of criteria was used: NCI-CTCAE ver. 3.0 or other oxaliplatin-specific scales. At present, NCI-CTCAE is used commonly in many medical institutions for the evaluation of adverse events during anticancer drug treatment. When the grade was different between these scales, we preferred the evaluation using the NCI-CTCAE scale because NCI-CTCAE is believed to be a global standard. However, it would appear that the addition of DEB-NTC to NCI-CTCAE for the evaluation of adverse events in patients receiving oxaliplatin may contribute to the formulation of better treatment plans from the aspects of reduction, discontinuation, or even resumption of oxaliplatin therapy in the future.

In order to maintain comparability among the results of different trials, neurotoxicity should be always graded according to the NCI-CTCAE scale, and use of any oxaliplatin-specific scales should be regarded as supplemental. However, all physician-based assessment tools used to grade subjective toxicity phenomena, such as neurotoxicity, have shown dramatic disagreements between physician-reported and patient-reported severity of symptoms [30].

In the future, patient-based assessment of neurotoxicity could provide more reliable and more accurate information about the incidence and severity of oxaliplatin-induced neurotoxicity.

Conflict of interest No author has any conflict of interest.

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