Early-onset Neutropenia during Perioperative Chemotherapy Is Predictive of Increased Survival in Patients with Completely Resected Non-small Cell Lung Cancer: A Retrospective Analysis

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Abstract. *Background: Chemotherapy-induced neutropenia (CIN) has been found to be predictive of better therapeutic outcomes in studies of patients with various tumors. This study investigated whether CIN occurring during perioperative chemotherapy cycles 1 or 2 is a prognostic indicator in patients with completely resected non-small cell lung cancer (NSCLC). Patients and Methods: The records of patients with completely resected NSCLC receiving at least two cycles of perioperative platinum-based doublet chemotherapy were reviewed retrospectively. Early-onset CIN was defined as a neutrophil count $<2.0\times10^9$/l during chemotherapy cycles 1 or 2. Subjects were stratified into two groups: presence or absence of early-onset CIN. Results: A total of 93 patients were included in this analysis. Early-onset CIN developed in 54.8% (51/93) cases. The median overall survival (OS) of patients developing early-onset CIN was significantly longer than the survival of patients without early-onset CIN (92.4 vs. 35.8 months, p=0.022), and the median disease-free survival (DFS) of patients with early-onset CIN was also longer, although the difference was not significant (48.3 vs. 18.6 months, p=0.138). Multivariate analysis demonstrated that early-onset CIN was an independent prognostic indicator for OS [hazard ratio (HR) for death=0.422, 95% confidence interval (CI)=0.201-0.884; p=0.022] and DFS (HR for recurrence=0.482, 95% CI=0.247-0.943; p=0.033). Conclusion: Early-onset CIN during perioperative chemotherapy is predictive of better OS and DFS in patients with completely resected NSCLC.*

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in many countries (1). Radical resection is the cornerstone for the best chance of cure, even though chemotherapy and radiotherapy have also led to improved outcomes. However, only approximately 30% of patients with NSCLC are surgical candidates at-diagnosis because the symptoms associated with lung cancer, for which patients seek treatment, usually occur when the disease is advanced. Reported 5-year survival rates of patients with pathological stage IA, IIA, and IIIA NSCLC are 73%, 46%, and 24%, respectively, largely because of postoperative recurrence (2). Several studies have demonstrated that cisplatin-based adjuvant chemotherapy for patients with resected NSCLC improved overall survival (OS) compared with surgery-alone; thus it has been adopted as the standard-of-care for patients with stage IB NSCLC and higher (3-5). Although neoadjuvant chemotherapy failed to show improved survival of patients with completely resected NSCLC in three large-scale clinical trials (6-8), the results of two meta-analyses have indicated that neoadjuvant chemotherapy can also improve survival to the same degree as adjuvant chemotherapy (9, 10).

Although hematological toxicity is a very common and dose-limiting side-effect of most cytotoxic chemotherapy agents, there have been several studies showing that chemotherapy-induced neutropenia (CIN) predicted improved clinical outcomes in patients with various types of advanced-stage cancer, including ovarian (11), gastric (12), as well as small-cell lung cancer (13) and NSCLC (14-16). Chemotherapy-induced myelosuppression was also found to be a prognostic indicator for improved survival in patients with breast cancer who received adjuvant chemotherapy (17, 18). We have recently shown that the time of onset of CIN is

a prognostic factor in patients with metastatic NSCLC; patients with early-onset CIN had better outcomes than patients with late-onset or lack of CIN altogether (19).

To date, the effect of perioperative CIN (occurring in the setting of neoadjuvant or adjuvant chemotherapy) on the outcomes of patients with completely resected NSCLC has not been investigated. The purpose of this retrospective study was to evaluate the prognostic significance of perioperative early-onset CIN for survival in patients with NSCLC who underwent complete resection.

Patients and Methods

Patients. This analysis included patients with completely resected NSCLC who were treated with perioperative platinum-based doublet chemotherapy for at least two cycles. Patients undergoing radiotherapy for the main primary lesion prior to completion of perioperative chemotherapy were excluded. The patients were followed up after surgery generally at intervals of 3-6 months for at least two years, and thereafter at 6-month intervals for at least five years. All study patients were restaged according to the 7th edition of the TNM staging system for lung cancer (20). The clinical data were retrospectively retrieved from the electronic medical records of the five hospitals comprising Hallym University Medical Center. The study proposal was approved by the Institutional Ethics Committee (2011-I059).

Chemotherapy and dose intensity. Chemotherapy was administered in the neoadjuvant and/or adjuvant setting at the physician's discretion. It was administered for two to six cycles every three weeks unless there was progression of disease. Chemotherapy was postponed for one week if hematological toxicity was grade 2 or more on the day of drug infusion. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not prescribed. However, G-CSF was allowed for patients with febrile neutropenia. Dexamethasone was allowed for the prevention of emesis, at the discretion of the treating physician.

The relative dose intensity was defined as the delivered dose divided by the planned dose per unit of time, as indicated by the protocol. Individual values were calculated for each agent of the platinum doublet, although to simplify analysis, the percentage relative dose intensity of the platinum agents (cisplatin and carboplatin) were combined as was that for the drug pairing with platinum.

Assessment of neutropenia. A complete blood cell (CBC) count with differential was performed before each administration of chemotherapeutic agent and when clinically indicated for managing toxicities such as febrile neutropenia. The worst grade of neutropenia for each cycle of chemotherapy was used for analysis. Absolute neutrophil counts (ANCs) were determined by multiplying the white blood cell count by the total percentage of neutrophils. CIN was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (21), as follows: Grade 1, 1.5×10^9/l≤ANC<2.0×10^9/l; grade 2, 1.0×10^9/l≤ANC<1.5×10^9/l; grade 3, 0.5×10^9/l≤ANC<1.0×10^9/l; grade 4, ANC<0.5×10^9/l. Early-onset CIN was defined as ANC <2.0×10^9/l during chemotherapy cycle 1 or 2.

Table I. *Distribution of patients according to the perioperative chemotherapy regimen*.

Drug combined with platinum	Number of patients (%)	
	Cisplatin at 60 mg/m^2 on day 1	Carboplatin 5 AUC on day 1
Vinorelbine, 25 mg/m^2 on days 1, 8	37 (39.8)	13 (14.0)
Gemcitabine, 1250 mg/m^2 on days 1, 8	14 (15.1)	6 (6.5)
Paclitaxel, 175 mg/m^2 on day 1	9 (9.7)	8 (8.6)
Docetaxel, 60 mg/m^2 on day 1	3 (3.2)	0 (0.0)
Pemetrexed, 500 mg/m^2 on day 1	1 (1.1)	0 (0.0)
Etoposide, 100 mg/m^2 on days 1-3	2 (2.2)	0 (0.0)

AUC: Total area under the plasma concentration–time curve from time zero to time infinity.

Statistical analysis. OS was the primary endpoint of this analysis, and disease-free survival (DFS) was the secondary endpoint. Survival curves were derived using the Kaplan–Meier method and were compared using the log-rank test. OS was determined from the date of initiating chemotherapy or surgery, whichever came first, to the date of death by any cause. DFS was determined from the date of surgery to the date of the first evidence of disease recurrence or to the date of death. Multivariate analysis was performed using the Cox proportional hazards regression model. Multivariate Cox proportional hazards modeling was stratified according to sex, age (<65 *vs.* ≥65 years), performance status (0 *vs.* 1), histological subtype (adenocarcinoma *vs.* others), postoperative pathological stage (I *vs.* II *vs.* III), type of surgery (lobectomy or bilobectomy *vs.* pneumonectomy), timing of chemotherapy (neoadjuvant only or plus adjuvant *vs.* adjuvant), early-onset CIN (present *vs.* absent), and adjuvant radiotherapy (yes *vs.* no) as covariates. This study used the Pearson chi-square test for comparison of categorical variables between groups. The SPSS software version 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Patients' characteristics. A total of 93 patients between January 2000 and July 2011 were included in this retrospective analysis. The median number of chemotherapy cycles was four (range 2-6). Neoadjuvant chemotherapy was administered to 9.7% (9/93), neoadjuvant and adjuvant to 10.8% (10/93), and adjuvant to 79.6% (74/93) of patients. All the patients receiving neoadjuvant with or without adjuvant chemotherapy received 2-4 cycles before surgery; therefore, early-onset CIN developing in these patients was identified preoperatively, whereas it was identified postoperatively in patients receiving adjuvant-only chemotherapy. Vinorelbine–platinum was the most frequent doublet administered to patients [53.8% (50/93)]. The chemotherapy regimens are shown in Table I.

Table II. *Characteristics of patients grouped according to timing of neutropenia during perioperative chemotherapy.*

	Early-onset neutropenia†		
	Present	Absent	*p*-Value
Number (%)	51 (54.8)	42 (45.2)	
Median age, years (range)	64 (43-76)	63 (36-80)	0.789
Gender, male:female	40:11	28:14	0.203
Performance status, n (%)			0.073
0	45 (88.2)	31 (73.8)	
1	6 (11.8)	11 (26.2)	
Histology, n (%)			0.384
Adenocarcinoma	27 (52.9)	18 (42.9)	
Squamous	23 (45.1)	21 (50.0)	
Large cell	1 (2.0)	1 (2.4)	
Pleomorphic	0 (0.0)	2 (4.8)	
Postoperative stage, n (%)			0.160
IA	1 (2.0)	1 (2.4)	
IB	13 (25.5)	10 (23.8)	
IIA	12 (23.5)	3 (7.1)	
IIB	8 (15.7)	5 (11.9)	
IIIA	17 (33.3)	23 (54.8)	
Type of surgery, n (%)			0.552
Lobectomy or bilobectomy	40 (78.4)	35 (83.3)	
Pneumonectomy	11 (21.6)	7 (16.7)	
Timing of chemotherapy, n (%)			0.742
Neoadjuvant	4 (7.8)	5 (11.9)	
Neoadjuvant and adjuvant	5 (9.8)	5 (11.9)	
Adjuvant	42 (82.4)	32 (76.2)	
Chemotherapy cycles, mean±SD	3.9±1.1	3.9±1.4	0.923
Relative dose intensity in cycle 1-2, mean±SD (%)			
Platinum	83.7±13.8	91.5±11.2	0.004
Drug combined with platinum	80.8±17.1	89.9±12.6	0.005
Grade of neutropenia‡, n (%)			<0.001
0	0 (0.0)	26 (61.9)	
1-2	22 (43.1)	10 (23.8)	
3-4	29 (56.9)	6 (14.3)	
Adjuvant radiotherapy, n (%)	2 (3.9)	2 (4.8)	0.842

†Neutrophil count in cycle 1 or 2 $<2.0\times10^9$/l. ‡The most severe grade of neutropenia occurring during perioperative chemotherapy.

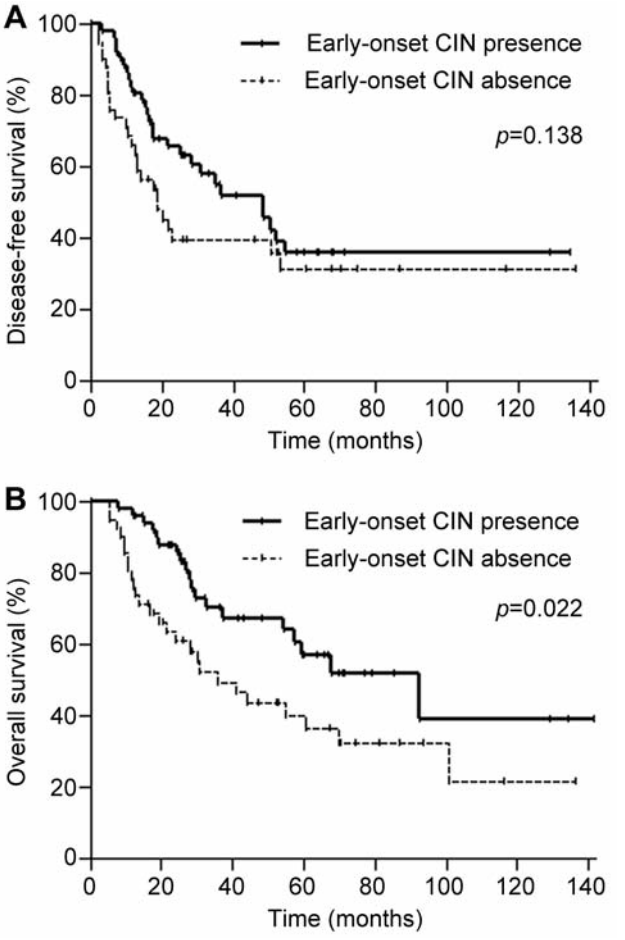

Figure 1. *Kaplan–Meier estimates of disease-free survival (A) and overall survival (B) according to early-onset chemotherapy-induced neutropenia (CIN) during perioperative chemotherapy in patients with completely resected non-small cell lung cancer. Early-onset neutropenia was defined as a neutrophil count $<2.0\times10^9$/l in cycle 1 or 2. p: Log-rank test.*

Early-onset CIN developed in 54.8% (51/93) of patients. Grade 1-2 early-onset CIN was found in 43.1% (22/51) and grade 3-4 early-onset CIN in 56.9% (29/51) of patients. There were no significant differences between patients developing or not developing early-onset CIN for age, sex ratio, performance status, histological subtype, postoperative pathological stage, type of surgery, timing of chemotherapy, number of chemotherapy cycles given, or adjuvant radiotherapy (Table II). However, the patients with early-onset CIN received significantly lower mean relative dose intensities of platinum (83.7% *vs*. 91.5%, $p=0.004$) and the drug combined with platinum (80.8% *vs*. 89.9%, $p=0.005$) during cycles 1-2 than did patients without.

Treatment outcomes. Kaplan–Meier analysis found a significant association between CIN and survival. Although the difference for DFS between patients with early-onset CIN and those without was not significant (48.3 *vs*. 18.6 months, $p=0.138$) (Figure 1A), OS was significantly longer in patients with early-onset CIN than those without (92.4 *vs*. 35.8 months, $p=0.022$) (Figure 1B). Patients who underwent lobectomy or bilobectomy had longer OS than those who underwent pneumonectomy ($p=0.030$). Patients with a performance status of 0 and postoperative stage I disease tended to have longer OS, but statistical significance was not achieved (both $p=0.059$). Performance status 1, postoperative stage II and III disease, pneumonectomy, and adjuvant radiotherapy were significantly-associated with shorter DFS (Table III).

Table III. *Kaplan–Meier estimates of disease-free and overall survival.*

	Disease-free survival (months)			Overall survival (months)		
	Median	95% CI	*p*-Value†	Median	95% CI	*p*-Value†
Gender						
Female	48.3	0.0-101.3	0.816	92.4	45.3-139.5	0.212
Male	30.7	4.4-57.0		54.8	33.5-76.1	
Age, years						
<65	25.0	12.0-38.0	0.896	57.4	17.2-97.6	0.802
≥65	48.3	16.6-80.0		60.6	40.1-81.2	
Performance status						
0	48.7	26.3-71.1	0.045	67.8	36.4-99.2	0.059
1	17.5	15.4-19.6		35.8	16.4-55.2	
Histology						
Adenocarcinoma	28.3	16.1-40.5	0.609	92.4	43.6-141.2	0.267
Other	48.7	12.9-84.5		54.4	31.9-76.9	
Postoperative stage						
I	Not reached		0.002	Not reached		0.059
II	30.7	0.9-60.5		57.4	34.6-80.2	
III	17.7	12.3-23.1		35.8	17.3-54.3	
Type of surgery						
Lobectomy or bilobectomy	36.5	10.1-62.9	0.038	92.4	52.2-132.6	0.030
Pneumonectomy	16.4	10.6-22.2		32.8	18.6-47.0	
Timing of chemotherapy						
Neoadjuvant (alone or plus adjuvant)	53.0	1.7-104.3	0.814	54.8	24.2-85.4	0.357
Adjuvant	30.7	4.2-57.2		60.6	24.2-97.0	
Early-onset neutropenia‡						
Present	48.3	30.0-66.6	0.138	92.4	45.7-139.1	0.022
Absent	18.6	9.6-27.6		35.8	16.6-55.0	
Adjuvant radiotherapy						
Yes	3.2	0.0-12.5	0.012	9.6		0.458
No	35.3	9.6-61.0		59.4	44.8-74.0	

†Log-rank test. ‡Neutrophil count in cycle 1 or 2: $<2.0\times10^9$/l.

Multivariate analysis also demonstrated that early-onset CIN was an independent prognostic indicator for longer OS [hazard ratio (HR) for death=0.422, 95% confidence interval (CI)=0.201-0.884; $p=0.022$] and DFS (HR for recurrence=0.482, 95% CI=0.247-0.943; $p=0.033$). Lobectomy or bilobectomy and postoperative stage I disease were also prognostic for longer OS. Non-adenocarcinoma cell type, postoperative stage I, and lobectomy or bilobectomy were significantly associated with a low risk of recurrence. Male patients and patients undergoing adjuvant radiotherapy tended to have a higher risk of recurrence (Table IV).

A subgroup analysis of the patients given neoadjuvant-alone or neoadjuvant-plus-adjuvant chemotherapy found that early-onset CIN developed in 47.4% (9/19) of patients. There was no difference in the baseline clinical variables of patients with early-onset CIN compared with the patients not developing early-onset CIN. The response rate after two cycles of preoperative chemotherapy was 88.9% (8/9) *vs.* 80.0% (8/10), respectively ($p=0.596$).

Treatment outcomes: CIN timing and severity. CIN of grade 1 or more during any chemotherapy cycle occurred in 72.0% (67/93) of patients. The median OS of the patients developing CIN during any cycle was significantly longer than that for patients not developing CIN, by Kaplan–Meier analysis (69.8 months, range=42.2-97.4 months *vs.* 24.2 months, range=0.0-49.7 months, respectively; $p=0.030$). The median DFS was also longer in patients developing CIN during any cycle than that for the patients not developing CIN, but the difference was not significant (36.5 months, range=14.0-59.0 months *vs.* 18.4 months, range=9.6-27.2 months, respectively; $p=0.300$). On multivariate analysis, CIN during any cycle was also an independent prognostic factor for longer OS (HR for death=0.415, 95% CI=0.193-0.890; $p=0.024$) but not for DFS (HR for recurrence=0.574, 95% CI=0.279-1.182; $p=0.132$).

The severity of early-onset CIN did not significantly affect OS or DFS. On multivariate analysis, the HR for death of patients with grade 3-4 CIN was 0.612 (95% CI=0.196-1.908, $p=0.397$), compared with the patients with grade 1-2

Table IV. *Multivariate analysis: disease-free and overall survival.*

	Recurrence			Death		
	HR†	95% CI	*p*-Value	HR†	95% CI	*p*-Value
Gender						
Female	0.463	0.199-1.080	0.075	0.447	0.159-1.252	0.125
Male	1			1		
Age, years						
<65	0.945	0.518-1.724	0.854	1.280	0.657-2.494	0.468
≥65	1			1		
Performance						
0	0.640	0.306-1.339	0.236	0.832	0.370-1.870	0.656
1	1			1		
Histology						
Adenocarcinoma	2.411	1.099-5.286	0.028	1.466	0.606-3.550	0.396
Other	1			1		
Postoperative stage						
I	0.224	0.083-0.608	0.003	0.366	0.129-1.032	0.057
II	0.798	0.392-1.625	0.535	0.988	0.455-2.146	0.975
III	1			1		
Type of surgery						
Lobectomy or bilobectomy	0.303	0.145-0.633	0.001	0.388	0.184-0.817	0.013
Pneumonectomy	1			1		
Timing of chemotherapy						
Neoadjuvant (alone or plus adjuvant)	1.595	0.570-4.458	0.374	2.193	0.819-5.868	0.118
Adjuvant	1			1		
Early-onset neutropenia‡						
Present	0.482	0.247-0.943	0.033	0.422	0.201-0.884	0.022
Absent	1			1		
Adjuvant radiotherapy						
Yes	4.337	0.832-22.595	0.081	1.987	0.313-12.609	0.466
No	1			1		

†Hazard ratio after adjustment for the other clinical variables in the Cox proportional hazard regression analysis. ‡Neutrophil count in cycle 1 or 2: $<2.0\times10^9$/l. CI: Confidence interval.

CIN; and the HR for recurrence was 0.562 (95% CI=0.223-1.416, p=0.222). The severity of CIN during any cycle was also not significant for OS or DFS. On multivariate analysis, the HR for death of patients with grade 3-4 CIN (52.2%, 35/67) during any cycle was 0.740 (95% CI=0.311-1.763, p=0.497) compared with patients with grade 1-2 CIN (47.8%, 32/67) during any cycle; and the HR for recurrence was 0.572 (95% CI=0.282-1.160, p=0.121).

Discussion

Neutropenia due to cytotoxic chemotherapy is a common adverse event. We previously found an association between early-onset CIN and both progression-free survival and OS in patients with metastatic NSCLC who were treated with gemcitabine–platinum doublet chemotherapy as first-line chemotherapy (19). To our knowledge, there are no published studies on the effect of CIN in patients with NSCLC undergoing complete surgical resection and perioperative chemotherapy. Therefore, this is the first study showing the association of early-onset CIN with better outcomes in patients with NSCLC who underwent complete surgical resection and perioperative chemotherapy. A unique feature of our study was the introduction of the concept of the timing of the onset of CIN in patients with NSCLC. Early-onset CIN was found to be an independent prognostic factor for OS and DFS, suggesting that early-onset CIN may be a surrogate marker that predicts a favorable outcome in patients undergoing perioperative chemotherapy. CIN occurring during any chemotherapy cycle was also an independent prognostic factor for OS, but not for DFS, suggesting that early-onset CIN may be clinically more useful for predicting prognosis; and it is also advantageous, because it can be identified earlier in the chemotherapy regimen.

CIN may predict increased survival time. Several clinical studies have described the positive impact of CIN on the survival of patients with various types of advanced cancer. Di

Maio *et al*. investigated the impact on survival of patients with advanced NSCLC according to whether or not CIN occurred (14). They evaluated three randomized trials, examining chemotherapy-induced hematological toxicities in patients who received all six planned chemotherapy cycles and who were still alive 180 days after randomization. They found that neutropenia during chemotherapy was associated with longer patient survival. In another study that confirmed the prognostic value of CIN for OS, Kishida *et al*. evaluated chemotherapy-naïve patients with advanced NSCLC who received chemotherapy in a randomized controlled trial and found that CIN was a predictor of improved patient survival (15).

Regarding the severity of neutropenia, some studies have suggested that moderate neutropenia was associated with better drug efficacy and longer survival than no or severe neutropenia, especially in patients with early breast or advanced gastric cancer (12, 22). A few breast cancer studies have shown that under-dosing was associated with unfavorable survival outcomes (23-25). However, this does not justify the use of high-dose chemotherapy for NSCLC because there is still no clinical evidence to support this treatment for NSCLC. Our study failed to demonstrate an association between the grade of early-onset CIN and survival outcome. The severity of CIN was not associated with OS or DFS in our study patients, and these findings are consistent with other studies which included patients with NSCLC (14-16, 19).

Early-onset neutropenia during perioperative chemotherapy is predictive of better OS, but it is not fully understood why such a relationship exists. It may be a result of the effective killing of microscopic residual cancer cells or cancer stem cells. Early-onset CIN may also be a surrogate marker indicating the efficacy of subsequent chemotherapeutic agents in the case of recurrence (19). Potential variables associated with chemosensitivity may include genetic factors, concentration of drug within the tumor, metabolism of the drug, microenvironment of tumor cells, or interactions between some or all of these variables. The impact of single-nucleotide polymorphisms (SNPs) on the survival in patients with solid tumors has been studied. SNPs in DNA repair genes may augment response to cytotoxic agents. This hypothetical mechanism could explain the relationship between CIN and survival. However, a large retrospective analysis of patients with advanced NSCLC failed to show a significant association between CIN and candidate SNPs in excision repair cross complimentary group-1 (ERCC1), X-ray cross-complementing group-3 (XRCC3), xeroderma pigmentosum group D-23 (XPD-23), and XPD-10, or between SNPs and survival (26).

This study has several limitations. It was a retrospective study of a small cohort that only included a Korean population. It evaluated postoperative pathological stages, even in patients administered neoadjuvant chemotherapy. It is unclear whether the neutrophil counts performed on the day each patient received chemotherapy actually represented the nadir for that patient during that cycle. This study included patients on heterogeneous chemotherapy regimens. Despite these drawbacks, we believe that our study results provide information applicable to routine clinical practice.

Early-onset CIN may be a clinically valuable surrogate prognostic marker for patients with NSCLC who undergo complete lung resection and perioperative chemotherapy. It may predict the outcome of patients within two cycles of chemotherapy, that is, within six weeks. When early-onset CIN is compared to CIN occurring during any cycle, the former may be more valuable because it enables the early prediction of DFS and OS, whereas the latter may only predict OS. The results of this study and our previous study of patients with advanced NSCLC suggest that early-onset CIN may be a prognostic factor applicable to both operable and advanced NSCLC. In conclusion, early-onset neutropenia during perioperative chemotherapy is predictive of better OS, regardless of its severity, in patients with NSCLC who have undergone complete resection and perioperative chemotherapy.

Conflicts of Interest

The Authors declare that they have no conflicts of interest

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