ORIGINAL ARTICLE

Low pre-treatment nutritional index is significantly related to poor outcomes in small cell lung cancer

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Abstract

Background: The importance of nutritional status and chronic inflammation has been emphasized in cancer. We investigated the impact of Onodera's prognostic nutritional index (OPNI) on clinical outcomes in small cell lung cancer (SCLC) patients.

Methods: Data from 220 SCLC patients treated with first-line platinum-based chemotherapy from 2006 to 2017 were retrospectively reviewed. The OPNI was calculated as $10 \times$ serum albumin level (g/dL) $+ 0.005 \times$ absolute lymphocyte count (/mm^3). Patients with an OPNI of > 45, 40–45, or < 40 were categorized in high, intermediate, or low OPNI groups, respectively.

Results: The proportion of non-responders to first-line therapy increased as the OPNI decreased (high, intermediate, low OPNI groups: 6.7%, 18.0%, and 30.8%, respectively; $P < 0.001$). Early discontinuation of first-line therapy because of treatment toxicity occurred more frequently in the lower OPNI groups (high, intermediate, low OPNI groups: 5.8%, 21.3%, and 25.6%, respectively; $P < 0.001$). The one-year progression-free and overall survival rates in the high, intermediate, and low OPNI groups were 29%, 19%, and 3%, and 61%, 46%, and 23%, respectively. In multivariate analyses, the low OPNI group was independently associated with poor progression-free (hazard ratio 1.592; 95% confidence interval 1.009–2.511; $P = 0.046$) and overall (hazard ratio 1.911; 95% confidence interval 1.208–3.024; $P = 0.006$) survival compared to the high OPNI group.

Conclusion: SCLC patients with an OPNI < 40 showed a low tolerance to chemotherapy and a poor prognosis. Further evaluation is needed to validate these findings.

Introduction

Small cell lung cancer (SCLC), characterized by rapid growth, early widespread metastasis, and frequent paraneoplastic syndromes,[1] accounts for approximately 13% of all lung cancers.[2] Over the last 30 years, platinum-based doublet chemotherapy with and without concurrent thoracic radiotherapy has been the standard first-line therapy for limited-stage (LD) and extensive-stage (ED) SCLC, respectively.[3,4] Traditionally, a poor performance status (PS), ED,

old age, and an elevated serum lactate dehydrogenase (LDH) level are associated with a poor prognosis in SCLC patients.[5,6] However, novel pre-treatment prognostic factors are still required to identify those patients who will benefit from first-line therapy and those who require adjustment of their chemotherapy dose.

The importance of nutritional status has been emphasized in cancer. A number of studies have indicated that malnutrition is associated with intolerance to chemotherapy, decreased quality of life, greater psychological distress,

and poor survival in patients with cancer.[7–9] Among several markers of nutritional status, Onodera's prognostic nutritional index (OPNI) has recently been considered useful because of its simplicity and clinical implications. The OPNI was initially designed to assess the risk of postoperative complications in gastrointestinal surgical patients using the serum albumin level and absolute lymphocyte count.[10] Researchers have since reported relationships between the OPNI and clinical outcomes of patients with various types of cancer.[11–14] One study reported that the risk of death in SCLC patients with a low OPNI was increased by 40% compared to those with a high OPNI.[15] However, the authors only reported associations of the OPNI with baseline clinicopathologic factors and overall survival (OS).

In the present study, we investigated the prognostic value of the OPNI in patients with SCLC treated with first-line platinum-based chemotherapy. To understand how the OPNI affects the prognosis of these patients, we assessed their response to first-line therapy, treatment-related toxicities, and treatment compliance.

Methods

Patients

After the institutional review board approved this study, we retrospectively reviewed the data of all consecutive SCLC patients recorded in the electronic medical record system between July 2006 and February 2017 at the Gyeongsang National University Hospital. Among them, 238 patients treated with platinum-based chemotherapy as first-line regimen without active infection at the time of chemotherapy initiation were screened. Eighteen patients were excluded from the study for the following reasons: chemotherapy commenced at another hospital ($n = 11$), inconsistent histology results ($n = 3$), a lack of clinical information ($n = 2$), and either no treatment or treatment with a non-platinum-based regimen ($n = 2$). Finally, a total of 220 patients were included in the study.

Assessments

Baseline assessments included demographics, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), tumor stage, treatment history, complete blood count (CBC), and serum chemistry including albumin and LDH levels. The baseline laboratory values measured closest to the date of chemotherapy initiation were recorded. The mean interval from the measurement of the CBC and serum albumin level to the initiation of chemotherapy was 1.7 ± 1.9 days (median 1 day; range: 0–12 days). Serum LDH was not measured in 63 patients

within two weeks before chemotherapy initiation, and thus their LDH baseline values were considered missing. Response Evaluation Criteria in Solid Tumors version 1.1 via computed tomography was used to assess tumor response to the first-line regimen. Grade ≥ 3 adverse events resulting from the first-line chemotherapy were evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Treatment-related mortality (TRM) was defined as death as a probable or possible result of chemotherapy-related toxicity during the treatment period or within 30 days of the last dose of chemotherapy. Premature cessation of the scheduled treatment because of chemotherapy-related toxicity was referred to as early discontinuation of treatment. Additional dose reductions because of chemotherapy-related toxicity were also reviewed. The OPNI was calculated as follows: OPNI = 10 × serum albumin level (g/dL) + 0.005 × absolute lymphocyte count (/mm^3). As originally designed, patients with an OPNI of > 45, 40–45, or < 40 were categorized in the high, intermediate, or low OPNI groups, respectively.[10]

Statistical analysis

The chi-squared test for trend and Spearman's rank correlation were used to assess the relationships between the OPNI group and categorical variables and between the OPNI group and continuous variables, respectively. The reverse Kaplan–Meier method was used to estimate the median follow-up duration. Progression-free survival (PFS) was defined as the interval from chemotherapy initiation to either the first progression, death from any cause, or the final follow-up. OS was defined as the interval from chemotherapy initiation to either death from any cause or the final follow-up. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. All variables with a *P* value < 0.20 in univariate analyses were included in multivariate analysis, using the Cox regression model and the enter selection method. Variables with a missing value were excluded from multivariate analyses. A *P* value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using Stata version 14.1 (Stata Corp., College Station, TX, USA).

Results

Study population

Of the 220 total patients, 120 were assigned to the high OPNI group, 61 to the intermediate, and 39 to the low. The OPNI ranged from 28.0 to 65.2. The patient characteristics according to the OPNI are described in Table 1. The overall median age was 68 years (range: 43–86). The

Table 1 Patient characteristics and treatment response

Factor	OPNI > 45 (n = 120)	OPNI 40–45 (n = 61)	OPNI < 40 (n = 39)	P
OPNI				
Median	49.0	43.2	37.2	
Mean (± std dev)	50.5 (± 4.4)	42.9 (± 1.5)	37.1 (± 2.4)	**< 0.001**
Range	45.2–65.2	40.0–45.0	28.0–39.9	
Age, years				
Median	68	70	66	
Mean (± SD)	66.4 (± 8.4)	68.9 (± 7.7)	66.6 (±7.3)	0.475
Range	43–85	48–86	49–82	
Sex				0.292
Male	109 (90.8)	50 (82.0)	34 (87.2)	
Female	11 (9.2)	11 (18.0)	5 (12.8)	
Smoking				0.142
Non-smoker	2 (1.7)	5 (8.2)	2 (5.1)	
Smoker	118 (98.3)	56 (91.8)	37 (94.9)	
ECOG PS				**< 0.001**
0–1	99 (82.5)	35 (57.4)	19 (48.7)	
2–3	21 (17.5)	26 (42.6)	20 (51.3)	
Stage				**< 0.001**
LD	62 (51.7)	22 (36.1)	6 (15.4)	
ED	58 (48.3)	39 (63.9)	33 (84.6)	
LDH, U/L (n = 157)				
Median	227	269	309	
Mean ± std dev	289 ±255	298 ±136	478 ±443	**< 0.001**
Elevated	45 (51.7)	24 (63.2)	24 (75.0)	**0.019**
First-line regimen				**0.005**
EP	93 (77.5)	39 (63.9)	22 (56.4)	
EC	21 (17.5)	18 (29.5)	12 (30.8)	
IP	6 (5.0)	4 (6.6)	5 (12.8)	
Thoracic RT				**< 0.001**
Yes	65 (54.2)	20 (32.8)	5 (12.8)	
No	55 (45.8)	41 (67.2)	34 (87.2)	
Prophylactic cranial irradiation				**< 0.001**
Yes	57 (47.5)	23 (37.7)	4 (10.3)	
No	63 (52.5)	38 (62.3)	35 (89.7)	
Response to first-line regimen (Total / in LD / in ED)				**< 0.001/0.004/0.022**
CR	20 (16.7) / 19 (30.7) / 1 (1.7)	3 (4.9) / 3 (13.6) / 0 (0.0)	0 (0.0) / 0 (0.0) / 0 (0.0)	
PR	92 (76.7) / 42 (67.7) / 50 (86.2)	47 (77.1) / 18 (81.8) / 29 (74.4)	27 (69.2) / 4 (66.7) / 23 (69.7)	
SD, PD, and NA	8 (6.7) / 1 (1.6) / 7 (12.1)	11 (18.0) / 1 (4.6) / 10 (25.6)	12 (30.8) / 2 (33.3) / 10 (30.3)	

Bold font indicates significant *P* values. Categorical variables are presented as number of patients (%). CR, complete response; EC, etoposide/carboplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; ED, extensive-stage; EP, etoposide/cisplatin; IP, irinotecan/cisplatin; LD, limited-stage; LDH, lactate dehydrogenase; NA, not available; OPNI, Onodera's Prognostic Nutritional Index; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease; std dev, standard deviation.

majority of patients were male and smokers, without significant differences among the three OPNI groups. A higher OPNI level was significantly associated with a poor ECOG PS, advanced stage, and high LDH level (all *P* < 0.001). The most commonly used regimen was etoposide/cisplatin. The low OPNI group more frequently received alternative regimens, such as etoposide/carboplatin and irinotecan/cisplatin, compared to the high OPNI group (*P* = 0.005). The treatment response to the first-line regimen was worse as the OPNI decreased, regardless of tumor stage (*P* < 0.001, *P* = 0.004, and *P* = 0.022 in total, LD, and ED, respectively). None of the patients in the low OPNI group showed a complete response and 30.8% (12/39) did not achieve an objective response. After excluding the patients prematurely withdrawn from treatment because of treatment toxicity (*n* = 30) and those who

Table 2 Toxicities and treatment compliance

Factor	Grade	OPNI > 45 (*n* = 120)	OPNI 40–45 (*n* = 61)	OPNI < 40 (*n* = 39)	*P*
Any hematologic toxicity	G3/4	109 (90.8)	57 (93.4)	32 (82.1)	0.230
	G4	81 (67.5)	37 (60.7)	23 (59.0)	0.265
Anemia	G3	21 (17.5)	12 (19.7)	9 (23.1)	0.439
Thrombocytopenia	G3/4	23 (19.2)	17 (27.9)	14 (35.9)	**0.026**
	G4	3 (2.5)	7 (11.5)	7 (18.0)	**0.001**
Neutropenia	G3/4	108 (90.0)	56 (91.8)	31 (79.5)	0.150
	G4	80 (66.7)	37 (60.7)	22 (56.4)	0.214
Febrile neutropenia	G3/4/5	18 (15.0)	15 (24.6)	9 (23.1)	0.149
	G4/5	7 (5.8)	7 (11.5)	3 (7.7)	0.458
Any non-hematologic toxicity	G3/4/5	38 (31.7)	23 (37.7)	17 (43.6)	0.157
	G4/5	14 (11.7)	10 (16.4)	8 (20.5)	0.150
Treatment-related mortality		6 (5.0)	4 (6.6)	3 (7.7)	0.506
Early discontinuation of treatment		7 (5.8)	13 (21.3)	10 (25.6)	**< 0.001**
Additional dose reduction		41 (34.2)	24 (39.3)	9 (23.1)	0.377

Bold font indicates significant *P* values. Categorical variables are presented as number of patients (%). OPNI, Onodera's Prognostic Nutritional Index.

declined further treatment (*n* = 13), the proportion of patients who did not respond to the first-line regimen was highest in the low OPNI group (high, intermediate, and low OPNI groups: 5.6%, 13.6%, and 26.9%, respectively; *P* < 0.001). Given the advanced stage and worse treatment response, the low thoracic radiotherapy and prophylactic cranial irradiation rates seen in the low OPNI group might be expected.

Treatment-related toxicity and compliance

Table 2 presents the details of the treatment-related toxicities and compliance with the first-line regimen according to the OPNI. As the OPNI decreased, the incidences of grade 3/4 and grade 4 thrombocytopenia increased (high, intermediate, and low OPNI groups: 19.2% and 2.5%, 27.9% and 11.5%, and 35.9% and 18.0%, respectively; *P* = 0.026 and *P* = 0.001). Otherwise, no differences in anemia, neutropenia, febrile neutropenia, or non-hematologic toxicities were observed among the three OPNI groups. TRM occurred in 5.9% (13/220) of the total patients, without a significant difference among the three groups.

In terms of treatment compliance, the lower OPNI groups were associated more frequently with early discontinuation of treatment. While only 5.8% (7/120) of the high OPNI group discontinued treatment prematurely because of treatment toxicity, 21.3% (13/61) and 25.6% (10/39) discontinued in the intermediate and low OPNI groups, respectively (*P* < 0.001). There was no difference in the incidence of an additional dose adjustment among the three groups.

Survival

The median follow-up duration was 4.1 years in all patients, and 178 deaths had occurred at the time of

analysis. In the entire cohort, the median PFS and OS rates were 6.5 (95% confidence interval [CI] 6.2–6.9) and 11.7 (95% CI 9.8–13.6) months, respectively. The median PFS rates of the high, intermediate, and low OPNI groups were 6.9 (95% CI 6.3–8.1), 6.6 (95% CI 6.2–8.4), and 4.5 (95% CI 2.9–5.6) months, respectively (Fig 1a). The one-year PFS rates of the high, intermediate, and low OPNI groups were 29% (95% CI 21–37%), 19% (95% CI 10–30%), and 3% (95% CI 0–13%), respectively. There were significant differences in PFS between the low and high OPNI groups (*P* < 0.001) and between the low and intermediate OPNI groups (*P* < 0.001), but not between the intermediate and high OPNI groups (*P* = 0.268). In patients with LD, the low OPNI group had poorer PFS (median 2.9 months, 95% CI 0.1–not reached) than the intermediate (median 9.3 months, 95% CI 1.6–6.7; *P* < 0.001) and high (median 11.1 months, 95% CI 6.8–15.9; *P* < 0.001) OPNI groups (Fig 1c). In patients with ED, there was a trend toward worse PFS in the low OPNI group (median 4.5 months, 95% CI 2.9–5.6) compared to the high OPNI group (median 6.2 months, 95% CI 5.4–6.9; *P* = 0.057) (Fig 1e).

Similar results were observed for OS. The median OS rates of the high, intermediate, and low OPNI groups were 14.9 (95% CI 12.2–17.2), 9.8 (95% CI 8.3–14.2), and 8.0 (95% CI 5.3–9.3) months, respectively (Fig 1b). The one-year OS rates of the high, intermediate, and low OPNI groups were 61% (95% CI 51–69%), 46% (95% CI 32–58%), and 23% (95% CI 11–38%), respectively. There were significant differences in OS among all three groups (Fig 1b). In patients with LD, the low OPNI group had poorer OS (median 2.9 months, 95% CI 0.1–not reached) than the intermediate (median 16.8 months, 95% CI 8.3–27.5; *P* < 0.001) and high (median 18.9 months, 95% CI 12.8–30.9; *P* < 0.001) OPNI groups (Fig 1d). In patients
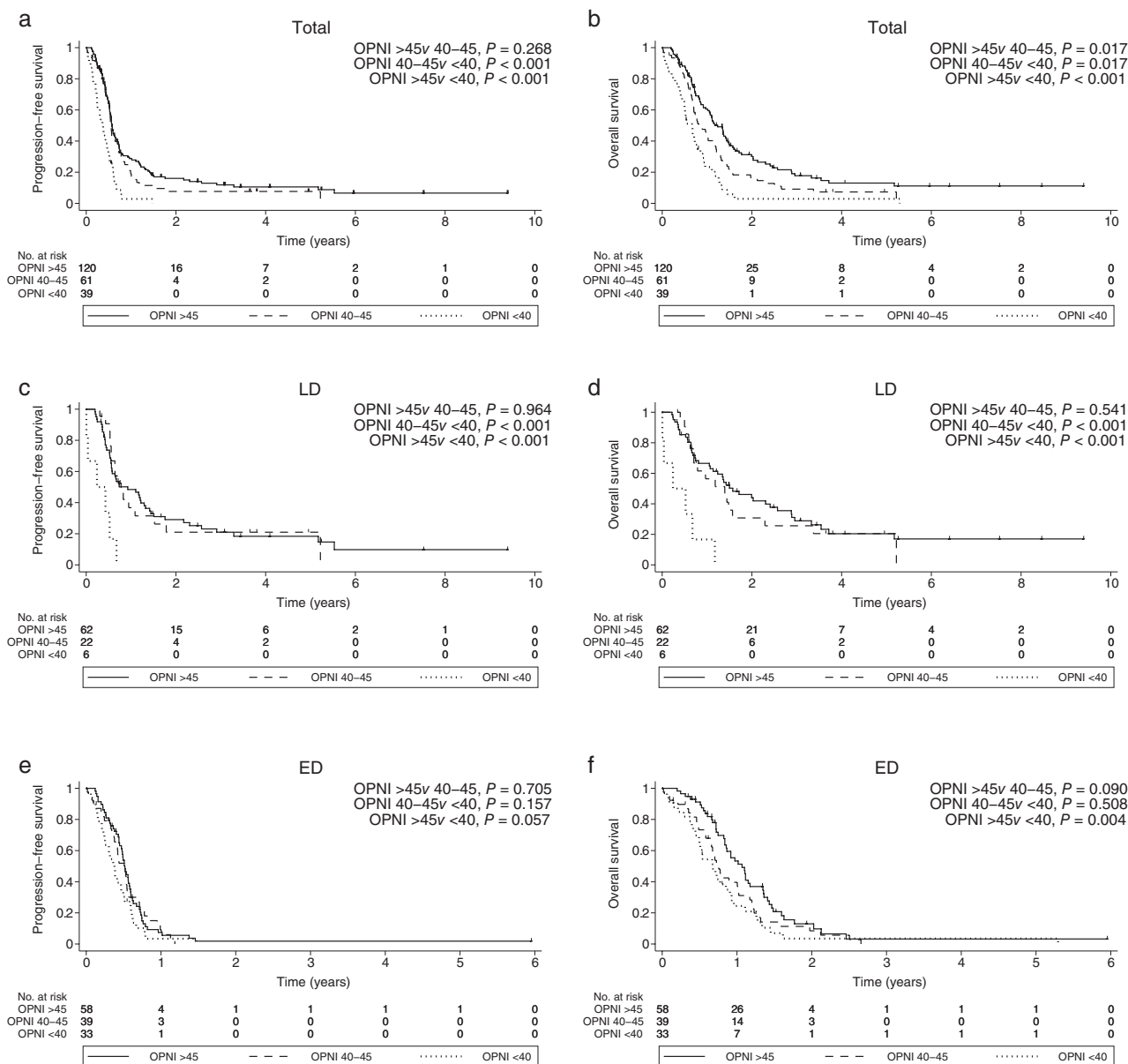
Figure 1 Progression-free survival in (**a**) all patients, (**c**) patients with limited-stage (LD), and (**e**) patients with extensive-stage (ED). Overall survival in (**b**) all patients, (**d**) patients with LD, and (**f**) patients with ED. OPNI, Onodera's Prognostic Nutritional Index.

with ED, OS was significantly worse in the low OPNI group (median 8.1 months, 95% CI 5.9–10.9) than in the high OPNI group (median 12.8 months, 95% CI 10.1–16.2; *P* = 0.004) (Fig 1f).

After adjusting for potential confounding variables such as age, ECOG PS, stage, and chemotherapy regimen, the low OPNI group was found to be independently associated with a poor PFS relative to the high OPNI group (hazard ratio 1.592, 95% CI 1.009–2.511; *P* = 0.046) (Table 3). The low OPNI group was also associated with poor OS compared to the high OPNI group in multivariate analysis

(hazard ratio 1.911, 95% CI 1.208–3.024; *P* = 0.006). There were no significant differences in PFS (*P* = 0.403) or OS (*P* = 0.909) between the high and intermediate OPNI groups in multivariate analyses.

Discussion

We demonstrated the prognostic value of the OPNI in SCLC patients receiving first-line chemotherapy. The lower OPNI group exhibited a higher tumor burden (stage and serum LDH) and poorer PS. In addition, the highest

Table 3 Cox regression for PFS and OS

| | PFS | | | | | | OS | | | | | |
| | Univariate | | | Multivariate | | | Univariate | | | Multivariate | | |
Factor	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age, years												
≤ 65	Ref.			Ref.			Ref.			Ref.		
> 65	1.271	0.949–1.704	0.108	1.340	0.964–1.862	0.081	1.434	1.057–1.946	0.021	1.575	1.113–2.229	**0.010**
Gender												
Male	Ref.						Ref.					
Female	0.815	0.522–1.272	0.368				0.877	0.550–1.397	0.580			
ECOG PS												
0–1	Ref.			Ref.			Ref.			Ref.		
2	1.965	1.444–2.673	< 0.001	1.634	1.134–2.355	**0.008**	2.582	1.871–3.563	< 0.001	2.045	1.419–2.948	**< 0.001**
Stage												
LD	Ref.			Ref.			Ref.			Ref.		
ED	2.701	1.971–3.699	< 0.001	2.536	1.815–3.545	**< 0.001**	2.114	1.534–2.913	< 0.001	2.043	1.431–2.917	**< 0.001**
Regimen												
EP	Ref.			Ref.			Ref.			Ref.		
EC	1.412	1.013–1.968	0.041	1.255	0.883–1.786	0.206	1.541	1.092–2.176	0.014	1.135	0.791–1.628	0.492
IP	1.517	0.887–2.594	0.128	1.024	0.571–1.835	0.937	1.247	0.716–2.171	0.436	0.827	0.451–1.518	0.540
OPNI												
> 45	Ref.			Ref.			Ref.			Ref.		
40–45	1.202	0.861–1.678	0.279	0.854	0.590–1.236	0.403	1.516	1.077–2.134	0.017	1.022	0.701–1.491	0.909
< 40	2.680	1.825–3.937	< 0.001	1.592	1.009–2.511	**0.046**	2.697	1.823–3.992	< 0.001	1.911	1.208–3.024	**0.006**

Bold font indicates significant *P* values. CI, confidence interval; EC, etoposide/carboplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; ED, extensive-stage; EP, etoposide/cisplatin; HR, hazard ratio; IP, irinotecan/cisplatin; LD, limited-stage; OPNI, Onodera's Prognostic Nutritional Index; OS, overall survival; PFS, progression-free survival.

proportions of patients refractory (30.8%) or intolerant to (25.6%) first-line chemotherapy were found in the low OPNI group. The low OPNI group was associated with a poor prognosis, with median PFS and OS of only 4.5 and 8 months, respectively.

Cancer cachexia is defined as a multifactorial syndrome with ongoing loss of muscle mass with or without loss of fat mass that cannot be fully reversed by conventional nutritional support and is associated with reduced survival.[16] Chronic inflammation has been demonstrated as one of the main contributors involved in cancer cachexia.[17,18] Pro-inflammatory cytokines derived from tumor or immune cells activate the altered metabolic pathways associated with skeletal muscle wasting.[18] For example, IL-6 regulates altered mitochondrial biogenesis, which precedes the decrease in muscle mitochondrial content.[19] Tumor necrosis factor-alpha is involved in proteolysis, increased gluconeogenesis, and loss of adipose tissue.[20] IL-1 increases the plasma levels of tryptophan and serotonin, which lead to anorexia.[21] However, the relationship between cancer cachexia and inflammation may not be explained solely by the cytokine alone because cancer cachexia develops from a complex interaction of factors.[21] Rather, the acute-phase proteins (APP), which are increased in up to 50% of cancer patients, may better explain the general inflammatory condition in cachectic cancer patients.[20,22] Among the APPs, albumin is a good indicator of the extent of cachexia, because it is also associated with body cell mass, as well as systemic inflammation.[23] In SCLC, the C-reactive protein/albumin ratio and albumin/globulin ratio were reported to be associated with patient prognosis.[24,25] Another contributor involved in cancer cachexia is impaired immune function. It was reported that immune suppression occurs as early as the pre-cachectic state[26] and may induce cancer cachexia via the STAT3 signaling pathway.[27] Lymphocytes have been largely studied with respect to the relationship between the immune system and cancer.[28,29] In addition, the absolute lymphocyte count is reported to decrease as the severity of malnutrition increases.[30] Given that albumin and lymphocytes reflect chronic inflammation and immune function, which are closely related to cancer cachexia, as well as nutritional status, the OPNI may be an excellent biomarker of cancer cachexia. Consequently, our study confirmed the negative impact of cancer cachexia on the prognosis of cancer patients.

Another negative impact of cancer cachexia is intolerance to anticancer therapy.[16] Sarcopenia, one component of the diagnostic criteria for cancer cachexia, is associated with frequent dose-limiting toxicities, TRM, and early discontinuation of treatment in cancer patients treated with chemotherapy.[31–33] In previous studies of gastrointestinal

cancer and non-small cell lung cancer (NSCLC), patients with self-reported weight loss experienced severe stomatitis and plantar-palmar syndrome[34] and failed to complete the scheduled chemotherapy,[35] respectively, more frequently compared to patients that did not experience weight loss. Malnutrition and hypoalbuminemia are associated with major chemotherapy-induced toxicities in NSCLC.[36] In our study, the SCLC patients with a lower OPNI experienced early discontinuation of treatment and grade 3/4 thrombocytopenia more frequently than those with a higher OPNI. This finding is the first observation to show the relationship between the OPNI and chemotherapy-related toxicity in SCLC patients and supports the adverse effects of cancer cachexia on the tolerance to anticancer therapy. Given the retrospective nature of this study, specific adverse events caused by chemotherapy (non-hematologic toxicity in particular) may have been underreported in this study. Therefore, a prospective study is needed to evaluate the association between the OPNI and treatment-related toxicity in SCLC.

The cutoff values of the OPNI varied among previous studies. The following two OPNI cutoff values are commonly used for cancer patients: 40 (applied in our study), originally defined by Onodera *et al.*;[10,37–39] and a range of 45–51, determined by receiver operating characteristic curve analyses.[11,13,40–42] A pre-defined OPNI cutoff value of 40 is the most conservative approach used to dichotomize or categorize continuous variables. A possible disadvantage of using this value is that it can result in unequally sized study groups and therefore reduce the statistical power of the test.[43] The 45–51 value range, determined from an outcome-oriented approach, has also been widely used to dichotomize continuous variables in clinical studies. However, applying this range to survival data is problematic because of the presence of censored observations and potential competing risks.[44] The only previous study that applied the OPNI to SCLC defined a cutoff value of 52.48 using the minimal *P* value approach,[15] which can inflate the type I error rate.[45] We suggest using a predefined OPNI of 40 as the cutoff to perform reasonable comparisons among studies and to reduce the bias caused by the data-driven technique.

The main limitation of this study is its retrospective nature. This resulted in the potential underestimation of some clinical data, as well as selection bias. As described above, non-treatment-related hematologic toxicities could not be investigated thoroughly. In addition, there were missing values for the serum LDH level and self-reported weight loss, which are important in the study of SCLC and cancer cachexia.

In conclusion, this study showed that a low OPNI was associated with intolerance to first-line platinum-based chemotherapy and poor prognosis in SCLC patients. We suggest that intensive supportive care may be required to improve treatment response and prognosis in those with a low OPNI. Additionally, we hope that the OPNI will be useful as a surrogate marker of cancer cachexia in future studies.

Acknowledgment

Disclosure

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