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Neuron - specific enolase predicts the prognosis in advanced small cell lung cancer patients treated with first-line PD-1/PD-L1 inhibitors

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Abstract

There has been no effective biomarker for small cell lung cancer (SCLC) patients with first-line immune checkpoint inhibitors (ICIs) treatment. The predictive value of neuron-specific enolase (NSE) in this cohort remains unclear.

The medical records of 254 consecutive SCLC patients receiving programmed cell death receptor-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors were compiled from January 2015 to October 2020 in Chinese PLA General Hospital. Survival analysis was performed to explore the prognostic role of NSE at baseline and 3 weeks post treatment.

One hundred two advanced SCLC patients treated with first-line PD-1/PD-L1 inhibitors were enrolled in this study. Normal baseline NSE levels were correlated with significantly prolonged progression-free survival (PFS, median: 8.7 vs 4.7 months, $P = .006$) and overall survival (OS, median: 23.8 vs 15.2 months, $P = .014$) compared with elevated baseline NSE levels, so as for normal NSE levels at 3 weeks with prolonged PFS (median PFS: 8.4 vs 4.5 months, $P = .0002$) and OS (median OS: 23.3 vs 7.4 months, $P < .0001$). Intriguingly, elevated NSE levels at 3 weeks were associated with shorter PFS (median PFS: 4.5 vs 5.8 months, $P = .04$) and OS (median OS: 5.5 vs 14.7 months, $P < .0001$) compared with normal NSE levels in the elevated baseline NSE subgroup. Most subgroup analyses stratified by clinical characteristics confirmed the prognostic value of baseline NSE level.

Elevated NSE levels at baseline and 3 weeks were associated with worse prognosis in advanced SCLC patients receiving first-line ICIs treatment. NSE level might be applied as a useful prognostic tool for SCLC patients with immunotherapy.

Abbreviations: CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group Performance Status, ED = extensive disease, HR = hazard ratio, ICIs = immune checkpoint inhibitors, LD = limited disease, NSCLC = non-small cell lung cancer, NSE = neuron-specific enolase, OS = overall survival, PD = progressive disease, PD-1 = programmed cell death receptor-1, PD-L1 = programmed cell death-ligand 1, PFS = progression-free survival, SCLC = small cell lung cancer, TMB = tumor mutational burden.

Keywords: first-line, immune checkpoint inhibitor, neuron-specific enolase, prognosis, small cell lung cancer

1. Introduction

Lung cancer is still the leading cause of cancer-related morbidity and mortality worldwide.[1] Small cell lung cancer (SCLC) constitutes a relatively uncommon type (approximately 15%) of lung cancer, characterized by vigorous growth, early metastasis and dismal prognosis.[2,3] SCLC can be stratified into limited disease (LD) and extensive disease (ED) according to the Veteran's Administration Lung Cancer Study Group Staging System, which account for about one-third and two-thirds, respectively.[2,4]

Unlike non-small lung cancer (NSCLC), the options for treating SCLC remain limited. Surgical approach can be

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Informed consent was obtained from all individual participants included in the study.

All the authors and participants agree to publish the data.

The ethics approval was waived, as this is a retrospective study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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proposed in only a small fraction (5%) of SCLC patients, which present with early stage.[5,6] Other unrespectable patients have to receive chemotherapy with or without radiotherapy.[7–9] Despite highly sensitive to traditional chemotherapy and radiotherapy, most patients relapse after several months. The median overall survival (OS) is approximately 10 to 12 months for ED-SCLC and 15 to 20 months for LD-SCLC, respectively.[10–12] As the driver genes of SCLC are still unclear, there have been few advances in the treatment of SCLC until the application of immune checkpoint inhibitors (ICIs) in SCLC patients.

Programmed cell death receptor-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors, as the representation of ICIs, have been demonstrated to improve the prognosis of NSCLC, melanoma, head and neck cancers and other malignancies.[13–16] In recent years, several clinical trials, including IMpower133, CASPIAN and ECOG-ACRIN EA5161, have shown the first-line PD-1/PD-L1 inhibitors treatment could significantly improve progression-free survival (PFS) and OS compared with chemotherapy alone in ED-SCLC.[17–19] These trials demonstrated the patients with ED-SCLC could benefit fromPD-1/PD-L1 inhibitors. Despite the promising results, the high expenditure and potential risk of immunotherapy cannot be neglected. Hence, it is of crucial importance to explore biomarkers to identify SCLC patients getting benefit from PD-1/PD-L1 inhibitors.

PD-L1 expression and tumor mutational burden (TMB) are commonly used biomarkers for patients with PD-1/PD-L1 inhibitors treatment.[20] However, previous studies indicated that only about 10% of SCLC patients were positive with a PD-L1 expression when the cutoff value was 1%.[21,22] In the CheckMate-032 study, the PD-L1 expression was not related to the response of SCLC patients.[19] Although a previous study indicated that TMB might be a biomarker for SCLC treated with nivolumab,[23] the prognostic role of TMB remains unclear in SCLC patients with ICIs treatment. Summarily, up to now, there have been no effective biomarkers that could guide the application of PD-1/PD-L1 inhibitors in SCLC patients. Hence, there is an urgent need to explore effective biomarkers in clinical practice.

Neuron-specific enolase (NSE) is an important neuroendocrine tumor marker routinely used for diagnosis and therapeutic monitoring in SCLC patients. However, the prognostic role of NSE in SCLC remains controversial in previous studies.[24] In addition, there has been no study evaluating the prognostic value of NSE level in SCLC patients treated with first-line PD-1/PD-L1 inhibitors. A previous study indicated that approximately 30% of SCLC patients had a normal NSE level at diagnosis.[25] In this study, we investigated whether NSE level could serve as an effective biomarker to identify SCLC patients getting benefit from the ICIs plus chemotherapy in first-line treatment, which would be easily attainable and cost-effective.

2. Methods

2.1. Study design and patients

This retrospective study was conducted in the First Medical Center of Chinese PLA General Hospital in the real clinical practice setting. The ethical approval was waived as it was a retrospective study without patients' privacy information. The medical records of 254 consecutive SCLC patients (Stage IIB-IV) receiving PD-1/PD-L1 inhibitors were compiled from January 1, 2015 to October 31, 2020. Among these patients, 102 patients met the including criteria:

1. patients were pathologically diagnosed as SCLC;
2. PD-1/PD-L1 inhibitors combined with chemotherapy were used at first-line treatment;
3. at least 2 cycles of PD-1/PD-L1 inhibitors treatment (generally 6 weeks);
4. serum NSE was measured at baseline (around 5 days);
5. tumor assessment was performed at baseline and 3 weeks later.

2.2. Data collection

Serum NSE levels at baseline and 3 weeks were measured with Access NSE test kits (Roche, Inc, Switzerland) of E601 Immunoassay System with the normal upper limit of 24 ng/mL. Patients' characteristics at baseline including age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), stage, smoking history and the presence of brain, liver, and bone metastasis were recorded. Treatment response was evaluated every 6 to 8 weeks by 2 investigators (YH and ZZ) independently according to Response Evaluation Criteria in Solid Tumors criteria version 1.1,[26] including complete response, partial response, stable disease (SD), and progressive disease (PD). PFS was referred to the interval time from the start of PD-1/PD-L1 inhibitors until PD, death, or the last follow-up (censored). OS was referred to the interval time from PD-1/PD-L1 inhibitors initiation until death or the last follow-up (censored). All patients were followed up by counseling telephone and searching electronic medical records with the cut-off date of March 20, 2021.

2.3. Statistical analysis

Statistical analysis was performed with IBM SPSS 23.0, and graphs were drawn with GraphPad Prism 8.0. The cohort was divided into 2 groups according to NSE level with a cutoff value of 24 ng/mL. Categorical variables were compared by the Chi-Squared test. Survival estimates were calculated by the Kaplan–Meier method, and group differences were compared by log-rank test. Univariate and multivariate analyses were applied for identifying independent variables. Hazard ratio (HR) with its 95% confidence interval (CI) was determined by Cox proportional hazard regression model. All statistical tests were two-sided, and P values $<.05$ were considered as statistically significant.

3. Results

3.1. Patient characteristics

A total of 102 advanced SCLC with first-line ICIs treatment were included in this study. The detailed information was displayed in Table 1, the median age was 60 years with a range of 32 to 82 years; about 90% were male and 80% had a smoking history; most of the patients (96%) had an ECOG PS of 0 to 1; 75 patients (73.5%) had extensive-stage disease (ED), and 66 patients (64.7%) received PD-1 inhibitors; the presence of brain metastasis, liver metastasis, and bone metastasis accounted for 21.6%, 23.5% and 28.4%, respectively; more than half of patients (59.8%) were evaluated as partial response, 31.4% were SD, and 8.8% were PD; 52.9% of patients had elevated NSE levels (NSE $\geq$ 24ng/mL) at baseline, and 22.5% still had elevated

Table 1

Characteristics of patients with advanced SCLC.

Characteristics	No. of patients (n = 102)	Percentage (%)
Age (yr), median (range)	60 (32–82)	
<60	50	49.0
≥60	52	51.0
Sex		
Male	90	88.2
Female	12	11.8
ECOG PS		
0–1	96	94.1
≥2	6	5.9
Stage		
LD	27	26.5
ED	75	73.5
Smoking history		
Never smoke	21	20.6
Smoke	81	79.4
ICIs		
PD-1 inhibitors	66	64.7
PD-L1 inhibitors	36	35.3
Brain metastasis		
Yes	22	21.6
No	80	78.4
Liver metastasis		
Yes	24	23.5
No	78	76.5
Bone metastasis		
Yes	29	28.4
No	73	71.6
Best response		
PR	61	59.8
SD	32	31.4
PD	9	8.8
NSE at baseline (ng/mL)		
Median (range)	29.5 (5.9–1333.0)	
Normal (<24)	48	47.1
Elevated (≥24)	54	52.9
NSE levels at 3 weeks (ng/mL)		
Median (range)	15.0 (5.9–694.1)	
Normal (<24)	70	68.6
Elevated (≥24)	23	22.5
Unknown	9	8.8

ECOG PS = Eastern Cooperative Oncology Group Performance Status, ED = extensive disease, ICI = immune checkpoint inhibitor, LD = limited disease, NSE = neuron-specific enolase, PD = progressive disease, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand 1, PR = partial response, SD = steady disease.

Table 3

The differences of patients' characteristics between normal and elevated baseline NSE levels.

Characteristics	Baseline NSE levels		X^2	*P* value
	Normal	Elevated		
Age (yr)				
<60	28	22	3.15	0.11
≥60	20	32		
Sex				
Male	40	50	2.10	0.22
Female	8	4		
ECOG PS				
0–1	47	49	2.36	0.21
≥ 2	1	5		
Stage				
LD	16	11	2.19	0.18
ED	32	43		
Smoke				
Never smoke	9	12	0.19	0.81
Smoke	39	42		
ICIs				
PD-1 inhibitors	34	32	1.49	0.30
PD-L1 inhibitors	14	22		
Brain metastasis				
Yes	11	11	0.10	0.81
No	37	43		
Liver metastasis				
Yes	8	16	2.37	0.16
No	40	38		
Bone metastasis				
Yes	9	20	4.18	0.05
No	39	34		

CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group Performance Status, ED = extensive disease, HR = hazard ratio, ICI = immune checkpoint inhibitor, LD = limited disease, NSE = neuron-specific enolase, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand 1.

NSE levels at 3 weeks after the first ICIs treatment. The median level of baseline NSE was 29.5 ng/mL with a range of 5.9 to 1333.0 ng/mL. The median follow-up time was 19.2 months with 95%CI of 13.7 to 24.7 months.

3.2. Univariate and multivariate analysis of progression-free survival and overall survival

In terms of PFS, the univariate analysis indicated that ECOG PS ≥2, the presence of bone metastasis and elevated baseline NSE

Table 2

Univariate and Multivariate Analysis for PFS and OS.

Variable	Category	PFS				OS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95%CI)	*P* value	HR (95% CI)	*P* value
Age (yr)	≥60 vs < 60	1.12 (0.70, 1.80)	.63			1.24 (0.66, 2.32)	.507		
Sex	Female vs Male	1.26 (0.63, 2.55)	.52			0.34 (0.08, 1.40)	.133		
Smoking history	Yes vs No	0.58 (0.33, 1.03)	.06			1.73 (0.67, 4.42)	.255		
Agent	PD-L1 inhibitors vs PD-1 inhibitors	1.29 (0.79, 2.10)	.31			1.97 (1.01, 3.84)	.048	2.01 (0.95, 4.23)	.066
Stage	ED vs LD	1.05 (0.61, 1.79)	.87			3.49 (1.24, 9.84)	.018	1.33 (0.41, 4.33)	.639
ECOG PS	≥ 2 vs 0–1	2.74 (1.17, 6.39)	.02	2.66 (1.13, 6.24)	0.025	6.29 (2.59, 15.30)	<.001	6.06 (1.99, 18.44)	.002
Brain metastasis	Yes vs No	1.13 (0.64, 1.97)	.68			1.84 (0.91, 3.71)	.089		
Liver metastasis	Yes vs No	1.57 (0.92, 2.69)	.10			4.62 (2.43, 8.80)	<.001	2.92 (1.30, 6.59)	.01
Bone metastasis	Yes vs No	2.86 (1.70, 4.80)	<.001	2.75 (1.62, 4.67)	<0.001	5.53 (2.86, 10.68)	<.001	4.59 (2.06, 10.22)	<.001
Baseline NSE (ng/mL)	≥24 vs <24	1.95 (1.20, 3.16)	.007	1.93 (1.18, 3.17)	0.009	2.19 (1.15, 4.16)	.017	2.41 (1.14, 5.10)	.021

CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group Performance Status, ED = extensive disease, HR = hazard ratio, ICI = immune checkpoint inhibitor, LD = limited disease, NSE = neuron-specific enolase, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand 1.

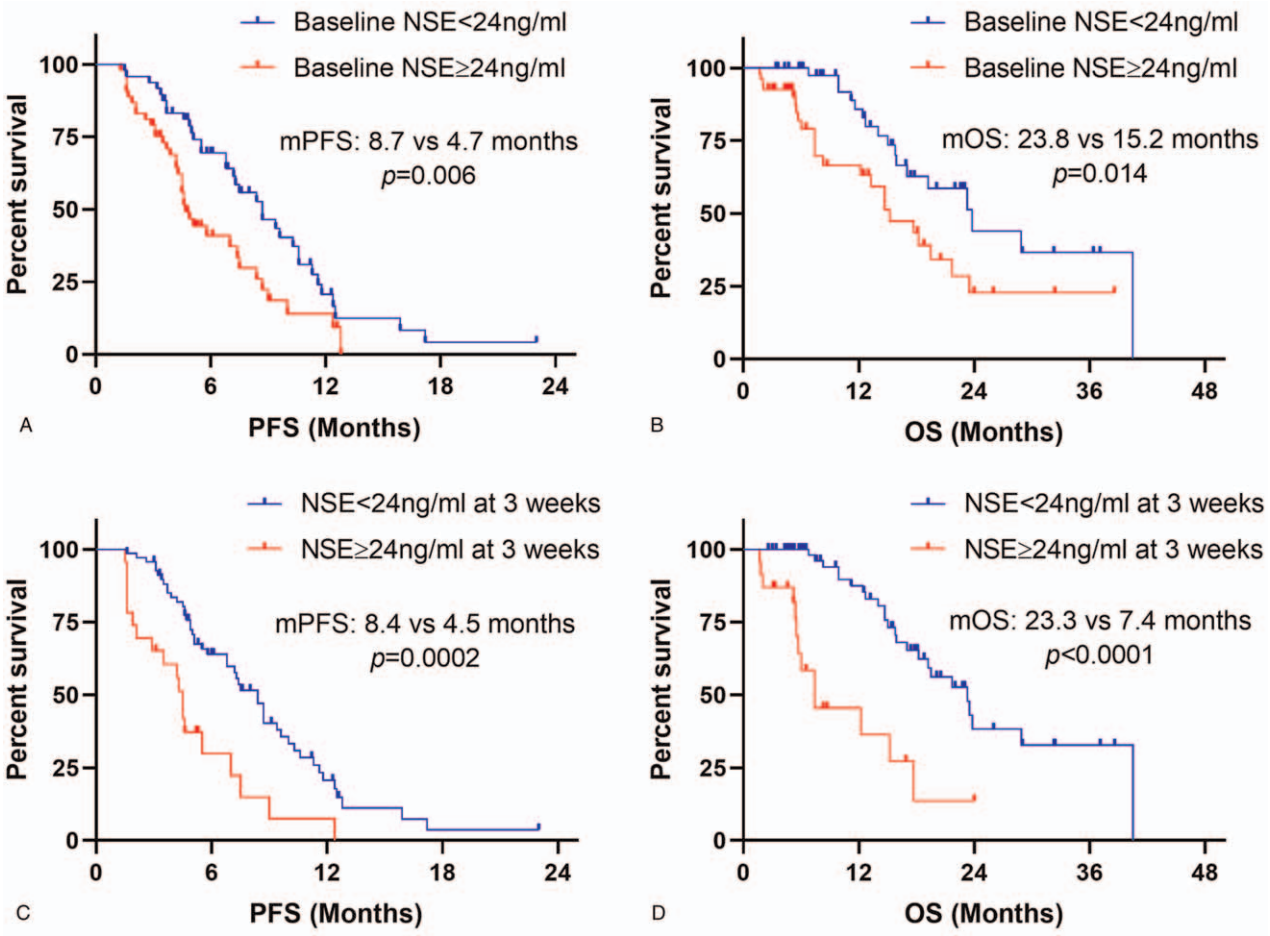

Figure 1. NSE levels at baseline and 3 weeks associated with PFS and OS in SCLC patients receiving first-line PD-1/PD-L1 inhibitors. NSE levels at baseline were associated with PFS (a) and OS (b). NSE levels at 3 weeks were associated with PFS (c) and OS (d). NSE = neuron-specific enolase, PFS = progression-free survival, OS = overall survival.

levels were correlated with shorter PFS with all $P < .05$, and the multivariate analysis showed that ECOG PS ≥2 (HR: 2.66; 95% CI, 1.13–6.24; $P = .025$), bone metastasis (HR: 2.75; 95% CI, 1.62–4.67; $P < .001$) and elevated baseline NSE levels (HR: 1.93; 95%CI, 1.18–3.17; $P = .009$) were independently associated with worse PFS (Table 2). In terms of OS, the univariate analysis showed that ECOG PS 0–1, LD, PD-1 inhibitors, liver metastasis, bone metastasis and normal baseline NSE levels were correlated with better OS with all $P < .05$, and multivariate analysis demonstrated that ECOG PS ≥ 2 (HR: 6.06; 95% CI, 1.99–18.44; $P = .002$), liver metastasis (HR: 2.92; 95% CI, 1.30–6.59; $P = .01$), bone metastasis (HR: 4.59; 95%CI, 2.06–10.22; $P < .001$) and elevated NSE levels (HR: 2.41; 95% CI, 1.14–5.10; $P = .021$) were independent risk factors for OS (Table 2). In summary, elevated baseline NSE level was an independent risk factor for PFS (HR: 1.93) and OS (HR: 2.41) with all $P < .05$.

3.3. Association of neuron-specific enolase levels at baseline and 3 weeks with progression-free survival and overall survival

A total of 102 patients were included for baseline NSE analysis. There was no statistically significant difference in patients' characteristics between the normal baseline NSE group and elevated NSE group with all $P > .05$ (Table 3). The results of Kaplan–Meier survival curves showed that normal baseline NSE levels were correlated with significantly prolonged PFS (median PFS: 8.7 vs 4.7 months, $P = .006$) and OS (median OS: 23.8 vs 15.2 months, $P = .014$) compared with elevated baseline NSE levels (Fig. 1a - b). After 3 weeks' ICIs treatment, 93 patients (91.2%) examined the blood tests of NSE levels. Kaplan–Meier survival curves demonstrated that normal NSE levels at 3 weeks were also correlated with significantly prolonged PFS (median PFS: 8.4 vs 4.5 months, $P = .0002$) and OS (median OS: 23.3 vs 7.4 months, $P < .0001$) compared with elevated NSE levels (Fig. 1c-d). Further, we conducted subgroup analysis in patients with elevated baseline NSE levels. The results showed that patients with elevated NSE levels at 3 weeks had shorter PFS (median PFS: 4.5 vs 5.8 months, $P = .04$) and OS (median OS: 5.5 vs 14.7 months, $P < .0001$) than those with normal NSE levels in the elevated baseline NSE subgroup (Fig. 2a-b).

3.4. Subgroup analysis of association between baseline neuron-specific enolase and survival time

To further evaluate the prognostic value of baseline NSE, we conducted subgroup analysis stratified by patients' characteristics. As shown in Figure 3, the results demonstrated that

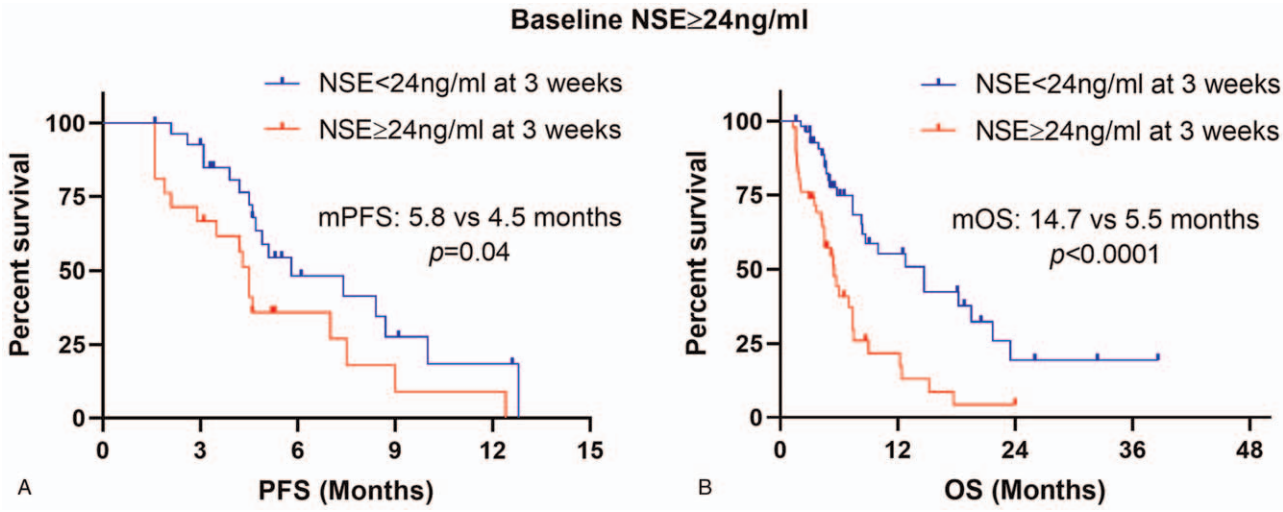

Figure 2. NSE levels at 3 weeks associated with PFS (a) and OS (b) in elevated baseline NSE subgroup. NSE = neuron-specific enolase, PFS = progression-free survival, OS = overall survival.

PFS subgroup	No. of patients	Baseline NSE levels		HR (95 % CI)	*p-value*
		High	Normal		
Overall	102	54	48	1.95 (1.20—3.16)	0.01
Age (year)					
< 60	50	22	28	1.81 (0.89—3.69)	0.10
≥ 60	52	32	20	2.24 (1.06—4.75)	0.04
Sex					
Male	90	50	40	2.05 (1.22—3.46)	0.01
Female	12	4	8	1.75 (0.39—7.97)	0.47
ECOG PS					
0–1	96	49	47	1.75 (1.06—2.89)	0.03
≥ 2	6	5	1	40 (0—166756)	0.39
Stage					
LD	27	11	16	2.94 (0.93—9.31)	0.07
ED	75	43	32	1.83 (1.05—3.21)	0.03
ICIs					
PD-1 inhibitors	66	32	34	2.83 (1.49—5.37)	0.00
PD-L1 inhibitors	36	22	14	1.16 (0.52—2.58)	0.72
Smoke					
Never smoke	21	12	9	1.42 (0.49—4.13)	0.52
Smoke	81	42	39	2.06 (1.19—3.58)	0.01
Brain metastasis					
Yes	22	11	11	6.70 (1.72—26.17)	0.01
No	80	43	37	1.61 (0.93—2.77)	0.09
Liver metastasis					
Yes	24	16	8	12.50 (1.56—100)	0.02
No	78	38	40	1.63 (0.93—2.86)	0.09
Bone metastasis					
Yes	29	20	9	3.79 (1.41—10.2)	0.01
No	73	34	39	1.57 (0.86—2.88)	0.14

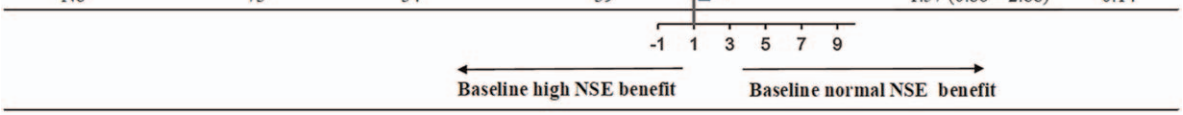

Figure 3. Subgroup analysis of association between baseline NSE and PFS. NSE = neuron-specific enolase, PFS = progression-free survival.

OS subgroup	No. of patients	Baseline NSE levels		HR (95 % CI)	*p-value*
		High	Normal		
Overall	102	54	48	2.19 (1.15—4.16)	0.02
Age (year)					
< 60	50	22	28	1.85 (0.70—4.88)	0.21
≥ 60	52	32	20	2.57 (0.85—7.74)	0.09
Sex					
Male	90	50	40	1.95 (1.01—3.75)	0.046
Female	12	4	8	105 (0—13651960)	0.44
ECOG PS					
0–1	96	49	47	1.86 (0.93—3.69)	0.08
≥2	6	5	1	40 (0—166757)	0.39
Stage					
LD	27	11	16	0.44 (0.05—4.22)	0.48
ED	75	43	32	2.75 (1.37—5.50)	0.004
ICIs					
PD-1 inhibitors	66	32	34	2.33 (1.04—5.24)	0.04
PD-L1 inhibitors	36	22	14	1.28 (0.42—3.91)	0.66
Smoke					
Never smoke	21	12	9	5.04 (0.55—46.16)	0.15
Smoke	81	42	39	1.87 (0.95—3.68)	0.07
Brain metastasis					
Yes	22	11	11	2.61 (0.73—9.39)	0.14
No	80	43	37	2.18 (1.02—4.67)	0.045
Liver metastasis					
Yes	24	16	8	17.43 (2.10—144.51)	0.01
No	78	38	40	1.64 (0.71—3.79)	0.25
Bone metastasis					
Yes	29	20	9	2.43 (0.93—6.34)	0.07
No	73	34	39	1.41 (0.54—3.68)	0.48

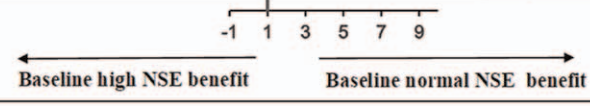

Figure 4. Subgroup analysis of association between baseline NSE and OS. NSE = neuron-specific enolase, OS = overall survival.

baseline normal NSE was associated with prolonged PFS compared with baseline elevated NSE in most of subgroups, including age ≥60 years, male, ECOG PS 0–1, ED, PD-1 inhibitors, smokers, and the presence of brain, liver, and bone metastasis with all $P < .05$. For OS, the results showed that baseline normal NSE was correlated with better OS in subgroups of male, ED, PD-1 inhibitors, no brain metastasis and the presence of liver metastasis with all $P < .05$ (Fig. 4).

4. Discussion

The treatment advances for SCLC patients were stagnant for nearly 3 decades until the application of PD-1/PD-L1 inhibitors brought new hope to advanced SCLC patients.[27] However, not all SCLC patients could get benefit from the first-line ICIs treatment. Disappointingly, there has been no effective biomarker to identify SCLC patients likely to get benefit from ICIs. The prognostic role of PD-L1 expression and TMB in SCLC patients receiving ICIs treatment remains unclear. Therefore, it is urgently needed to explore additional prognostic biomarkers for these patients in the clinical practice.

The detection of serum tumor markers is routinely used in the clinic, which is more convenient and affordable compared with PD-L1 expression and TMB. As a relatively specific tumor marker for SCLC patients, NSE was reported previously to be an independent prognostic indicator for OS in both LD-SCLC patients and ED-SCLC patients.[28,29] However, there has been no research investigating its prognostic value in SCLC patients with first-line ICIs treatment. Hence, we conducted this study to determine whether NSE level could predict the prognosis of SCLC patients with first-line ICIs treatment.

Our data showed that elevated NSE level at baseline was correlated with worse PFS and OS in SCLC patients with first-line ICIs treatment. Previous studies also indicated that high NSE level was correlated with shorter OS in SCLC patients receiving traditional chemotherapy with or without radiotherapy.[28–34] Although the definite underlying mechanisms of the relationship between high NSE level and poor prognosis remain unclear, an experimental study demonstrated that the knockdown of NSE restrained the migration and proliferation of SCLC cells with downregulated pro-metastatic gene vascular endothelial growth factor and upregulated metastasis suppressor genes.[35] We

speculated that there might be a difference in the tumor immune microenvironment or transcriptome between SCLC patients with elevated NSE levels and normal NSE levels. Therefore, related research needs to be conducted in the future to figure out the mechanisms for the relationship between high NSE levels and poor prognosis. Multivariate analysis of OS also demonstrated that elevated NSE level was an independent risk factor in addition to ECOG PS ≥2, liver metastasis, and bone metastasis. Optimization-based method or propensity score matching was intended to be used like our previous study to balance the baseline covariates between the elevated NSE group and normal NSE group.[36,37] However, as the baseline covariates were comparable between the 2 groups, these methods were waived. Taken together, elevated NSE level at baseline was associated with dismal prognosis of SCLC patients with first-line ICIs treatment.

We explored the predictive value of baseline NSE level by subgroup analysis. PFS and OS between baseline NSE high group and normal group were statistically significant different in the PD-1 subgroup, but not for the PD-L1 subgroup. Several reasons should be taken into consideration. Firstly, for the retrospective nature, it is inevitable to have selective bias. Secondly, the sample size of the PD-L1 subgroup was relatively small, which only have 36 patients. Lastly, anti-tumor mechanisms of PD-1 inhibitor and PD-L1 inhibitor were different, which may lead to the different anti-tumor effect.

We also investigated the prognostic role of the NSE level at 3 weeks post initial treatment. Most patients had a decreased NSE level at 3 weeks than the baseline value. Elevated NSE level at 3 weeks was also correlated with shorter PFS and OS compared with normal NSE level. Intriguingly, we wondered if there was a survival difference between patients with high NSE level at 3 weeks and patients with normal NSE level at 3 weeks in the baseline elevated NSE subgroup. Surprisingly, there was a significant difference in PFS and OS between these 2 groups, suggesting the strong prognostic power of NSE level in the SCLC patients. We did not perform the survival analysis in the baseline NSE normal subgroup, as there was only one patient who had an elevated NSE level at 3 weeks in the baseline NSE normal group. Summarily, the NSE levels at 3 weeks were also correlated with worse PFS and OS, and the patients with elevated baseline NSE level could still benefit from the ICIs treatment if serum NSE decreased to normal level at 3 weeks.

To our knowledge, this is the first study to provide survival data of SCLC patients receiving first-line ICIs treatment in the real world and thoroughly examine the prognostic role of NSE level. However, there remain some limitations in this study. Firstly, for a single-center retrospective study with limited cases, these results need to be validated in the multi-center prospective study. Secondly, the cutoff value of NSE level in survival analysis was set at 24 ng/mL (normal upper limit of the reference range), which might be not optimal. Last but not least, related research still needs to be performed in the future to explain the definite reasons for the relationship between high NSE levels and poor prognosis. However, we proposed a simple and effective tool for physicians to guide the application of first-line PD-1/PD-L1 inhibitors in advanced SCLC patients.

5. Conclusions

Our study showed that elevated NSE levels at baseline and 3 weeks were correlated with worse clinical outcomes in advanced SCLC patients receiving PD-1/PD-L1 inhibitors at first-line treatment. NSE level might serve as a useful prognostic factor for patients with immunotherapy.

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