Post-treatment Glasgow Prognostic Score Predicts Efficacy in Advanced Non-small-cell Lung Cancer Treated With Anti-PD1

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Abstract. *Background/Aim:* No definitive biomarker exists for predicting treatment efficacy or response to therapy with antibody to programmed cell death-1 (PD1) for patients with advanced non-small cell lung cancer (NSCLC). Hence, we investigated whether the Glasgow prognostic score (GPS) predicted anti-PD1 treatment response for advanced NSCLC. *Patients and Methods:* This study retrospectively identified 47 patients with NSCLC treated with anti-PD1 and assessed the prognostic value of the GPS. The GPS was calculated using C-reactive protein and albumin concentrations 1 month after starting anti-PD1 treatment. Kaplan–Meier method and Cox proportional hazard models were used to examine differences in progression-free (PFS) and overall (OS) survival, and clinical response. *Results:* The post-treatment GPS independently predicted anti-PD1 treatment efficacy, as a good post-treatment GPS (GPS 0-1) was significantly associated with improved PFS. Intra-treatment GPS change was associated with clinical response. *Conclusion:* The post-treatment GPS independently predicted efficacy of anti-PD1 treatment for NSCLC.

Lung cancer is the leading cause of cancer-related mortality worldwide (1); most cases are diagnosed at advanced or inoperable stages. Advanced cases often involve weight loss

and inflammatory response, with the magnitude of the systemic inflammatory response (SIR) predicting progression and survival in many cancer types (2-4). Thus, cancer-related prognosis is routinely examined using various SIR-based scoring systems, such as the neutrophil-to-lymphocyte ratio (NLR). The Glasgow prognostic score (GPS) is another SIR-based scoring system combining serum C-reactive protein (CRP) and albumin concentrations (5). The GPS is also an independent prognostic marker for advanced non-small cell lung cancer (NSCLC) (6-13).

Immune checkpoint inhibitors, such as antibodies to programmed cell death-1 (PD1) and programmed cell death ligand-1 (PD-L1) proteins, exhibit high clinical efficacy in several cancer types. Nivolumab and pembrolizumab are clinically approved antibodies targeting PD1; they are widely used for NSCLC treatment (14-17). Although immunohistochemistry-based tumor cell expression of PD-L1 is used to predict responses to anti-PD1/PD-L1 treatment, some patients respond to these treatments despite having low or no PD-L1 expression (14, 15). Moreover, anti-PD1/PD-L1 treatment is expensive and carries a risk of severe immune-related adverse events (18). Thus, early identification of patients who would respond to this treatment could help reduce the treatment cost and the risk of severe adverse outcomes. SIR-based markers can predict the response to immune checkpoint inhibitors, with the NLR predicting the response to immune checkpoint inhibitors in melanoma (19-21), renal cell carcinoma (22), and NSCLC (23-25). However, there is little information regarding the association between the GPS and the response to anti-PD1 treatment. Therefore, we investigated whether the post-treatment GPS is able to predict the response to anti-PD1 treatment in patients with advanced NSCLC.

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Table I. Patient characteristics.

Characteristic	Subgroup	All patients N=47	Post-treatment GPS			
			0 (N=24)	1 (N=6)	2 (N=17)	p-Value
Age	<65/≥65 years	14/33	9/15	1/5	4/13	0.4736
Gender	M/F	37/10	18/6	4/2	15/2	0.4409
Stage	I-II/III-IV	4/43	2/22	0/6	2/15	0.6736
Smoke	Ever/never	42/5	20/4	5/1	17/0	0.2049
Pre-treatment, ECOG-PS	0-1/2	44/3	22/2	6/0	16/1	0.7524
Post-treatment, ECOG-PS	0-1/2-4	36/11	20/4	6/0	10/7	0.0660
Histology	Sq/non-Sq	12/35	1/23	2/4	9/8	0.0018
Line of anti-PD1, therapy	1-2/≥3	33/14	16/8	5/1	12/5	0.7264
Anti-PD1 treatment	Nivolumab/pembrolizumab	36/11	18/6	5/1	13/4	0.9111
PD-L1 expression	≥50/<50/unknown	11/15/21	6/6/12	1/3/2	4/6/7	0.8178
Radiation therapy	Yes/no	27/20	15/9	4/2	8/9	0.5461

GPS: Glasgow prognostic score; N: number of patients; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Sq: squamous cell carcinoma; PD1: programmed cell death-1; PD-L1: programmed cell death ligand-1.

Patients and Methods

Patients. This retrospective study evaluated consecutive patients with histologically or cytologically diagnosed NSCLC who had received anti-PD1 treatment (nivolumab or pembrolizumab) at Gunma University Hospital between January 2016 and June 2018. Serum CRP and albumin concentrations were measured before and 1 month after treatment initiation. The GPS was defined as: 0: CRP <10 mg/l and albumin >35 g/l; 1: CRP ≥10 mg/l or albumin <35 g/l; or 2: CRP >10 mg/l and albumin <35 g/l. The NLR was defined as the ratio of absolute neutrophil and absolute lymphocyte counts; the NLR cut-off value was set at 5 (23, 26).

The study protocol was approved by the Institutional Review Board of Gunma University Hospital (2018-186), and followed the guidelines of the Helsinki Declaration. Adverse events were graded using the Common Terminology Criteria for Adverse Events (version 4.0) (27). Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1) (28). For immunohistochemical analysis, PD-L1 expression was studied using an antibody against PD-L1 protein (22C3 pharmDx; Dako, Glostrup, Denmark). The follow-up duration for censored cases was 4.13-31.8 months (median=14.7 months).

Statistical analysis. Continuous and categorical variables were analyzed using Student's *t*-test and chi-squared test, respectively. The relationships between different variables or matched pairs were examined using the non-parametric Spearman rank test or Wilcoxon signed-rank test, as appropriate. The Kaplan–Meier method and log-rank test were used to compare differences in patient survival. Progression-free survival (PFS) was recorded as the time between initiation of anti-PD1 treatment to the first instance of disease relapse, death, or the last follow-up visit with no evidence of relapse. Overall survival (OS) was measured as the interval from anti-PD1 treatment initiation to death from any cause. Univariate and multivariate analyses were performed using Cox's proportional hazard models for survival. Differences were considered significant at *p*-values of less than 0.05; all analyses were performed using JMP Pro software (version 12.0; SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics. The present study included 47 patients with advanced NSCLC (37 men; 10 women); their demographic characteristics are shown in Table I. At anti-PD1 treatment initiation, the median age was 69 years (range=48-81 years); 42 patients were smokers. The study group included 31 patients with adenocarcinoma, 12 with squamous cell carcinoma, three with poorly differentiated carcinoma, and one with adenosquamous carcinoma. Prior to anti-PD1 treatment, 27 patients received radiation therapy. Two patients had epidermal growth factor receptor mutations, and one patient showed anaplastic lymphoma kinase rearrangements. All patients received single-agent immunotherapy, with 36 patients receiving nivolumab (median=6 cycles, range=1-60 cycles) and 11 patients receiving pembrolizumab (median=3 cycles, range=1-22 cycles). After 1 month of PD1 treatment, the GPS was 0, 1, and 2 for 24, 6, and 17 patients, respectively; the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of patients was 0-1 in 36 patients, 2 in six patients, 3 in three patients, and 4 in two patients.

Association between the GPS and response to anti-PD1 treatment. The median PFS for the whole patient cohort was 4.9 months (95% confidence interval (CI)=1.9-7.6 months); 34 patients experienced disease progression. Tables II-IV show the results of univariate and multivariate analyses for PFS, OS, and clinical response. Univariate analyses revealed significant differences in PFS according to the post-treatment ECOG-PS, GPS, and NLR. However, multivariate analyses revealed that the post-treatment GPS was the sole independent predictor of a short PFS (hazard ratio (HR)=0.45, *p*=0.04) (Table II). The Kaplan–Meier curves for PFS according to post-treatment GPS

Table II. Analysis of factors for association with progression-free survival (PFS) after anti-programmed cell death-1 (PD1) therapy.

Characteristic	Subgroup	HR for PFS (95% CI)			
		Univariate	<i>p</i> -Value	Multivariate	<i>p</i> -Value
Age	<65/≥65 years	1.04 (0.49-2.09)	0.92		
Gender	M/F	0.61 (0.29-1.38)	0.22		
Smoke	Ever/never	0.53 (0.22-1.57)	0.23		
Histology	Sq/nonSq	0.94 (0.37-2.06)	0.88		
Line of therapy	1-2/≥3	0.50 (0.25-1.04)	0.06		
Radiation therapy	Yes/no	0.73 (0.37-1.45)	0.36		
Pre-ECOG-PS	0-1/2-4	0.55 (0.19-2.31)	0.36		
Pre-GPS	0-1/2	0.81 (0.40-1.74)	0.57		
Pre-NLR	High/low	0.80 (0.40-1.57)	0.52		
Post-ECOG-PS	0-1/2-4	0.42 (0.20-0.92)	0.03	0.55 (0.25-1.29)	0.16
Post-GPS	0-1/2	0.36 (0.18-0.75)	<0.01	0.45 (0.21-0.99)	0.04
Post-NLR	High/low	3.30 (1.46-7.26)	<0.01	2.12 (0.85-5.13)	0.11

HR: Hazard ratio; Sq: squamous cell carcinoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GPS: Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; Pre: before anti-PD1 therapy; Post: after anti-PD1 therapy.

are shown in Figure 1, with a GPS of 0-1 being associated with significantly longer PFS than a GPS of 2 ($p<0.01$). The median OS for the whole patient cohort was 19.7 months (95% CI=10.0 months to not reached); 22 patients eventually died. Based on the post-treatment ECOG-PS and GPS, univariate analyses revealed significant differences in OS. Multivariate analyses showed that both these markers independently predicted a short OS (HR=0.15, $p<0.01$; HR=0.18, $p<0.01$, respectively; Table III). The Kaplan–Meier curves for OS according to post-treatment GPS are presented in Figure 1, showing a GPS of 0–1 to be associated with significantly longer OS than GPS of 2 ($p<0.01$).

Twelve out of the 47 patients (33.3%) exhibited an objective clinical response to anti-PD1 treatment. Univariate analyses revealed that treatment response was associated with a low post-treatment GPS and low post-treatment NLR (Table IV). Although the post-treatment GPS was marginally associated with treatment response, only the post-treatment NLR was a significant predictor of treatment response (odds ratio=0.16, $p=0.05$) (Table IV); it was not possible to calculate the HR because none of the patients with a high NLR exhibited a clinical response. The pre-treatment PS, pre-treatment GPS, and pre-treatment NLR values were not associated with PFS, OS, or clinical response (Tables II-IV).

Changes in GPS during anti-PD1 treatment. Figure 2 shows the changes in GPS during anti-PD1 treatment. Among 12 patients with an objective clinical response, six patients (50%) showed an improved GPS, six (50%) maintained a stable GPS, and there were no patients whose GPS deteriorated ($p=0.03$). Among 20 patients who experienced disease progression, we found one patient with improved GPS (5%), 12 with a stable GPS (60%), and seven with a

worsened GPS (35%) ($p=0.04$). Patients with stable disease did not exhibit a significant change in their GPS ($p=0.48$).

Discussion

To the best of our knowledge, this is the first study examining the relationship between GPS and efficacy of anti-PD1 treatment. One month after starting anti-PD1 treatment, the GPS was significantly associated with both PFS and OS, while the post-treatment GPS was marginally associated with response to anti-PD1 treatment. Thus, the post-treatment GPS may be useful for early prediction of a patient's response to anti-PD1 treatment and their subsequent prognosis.

The GPS has prognostic value in lung cancer, independently of tumor stage and conventional prognostic markers (6-13). The GPS is also associated with elevated cytokine and adipokine levels, drug metabolism, weight and muscle loss, and poor PS (4, 29-35). These factors are associated with the host immune status and may influence the efficacy of anti-PD1 treatment. Furthermore, the GPS is calculated using serum CRP and albumin concentrations; this test is feasible and associated with a minimal cost at most institutions. Moreover, the assessment of the GPS is more objective compared to the conventional prognostic factor ECOG-PS (36). Therefore, it appears reasonable to consider the use of the GPS in clinical practice.

Several studies have investigated biomarkers that can predict the response to immune checkpoint inhibitors (37). For example, the pre-treatment NLR may predict the prognosis of patients with NSCLC treated with nivolumab (23); however, the present study revealed that the pre-treatment GPS and NLR values were not associated with the efficacy of anti-PD1 treatment (Table II). Previously, the post-treatment not the pre-treatment NLR was associated with the efficacy of anti-PD1

Table III. Analysis of factors for association with overall (OS) survival after anti-programmed cell death-1 (PD1) therapy.

Characteristic	Subgroup	HR for OS (95% CI)			
		Univariate	p-Value	Multivariate	p-Value
Age	<65/≥65 years	1.28 (0.51-3.03)	0.59		
Gender	M/F	0.93 (0.34-3.24)	0.89		
Smoke	Ever/never	1.08 (0.31-6.81)	0.91		
Histology	Sq/nonSq	2.53 (0.93-6.37)	0.07		
Line of therapy	1-2/≥3	0.52 (0.22-1.28)	0.15		
Radiation therapy	Yes/no	1.20 (0.51-2.92)	0.68		
Pre-ECOG-PS	0-1/2-4	0.33 (0.11-1.44)	0.12		
Pre-GPS	0-1/2	0.43 (0.18-1.02)	0.05		
Pre-NLR	High/low	1.82 (0.72-4.67)	0.18		
Post-ECOG-PS	0-1/2-4	0.16 (0.07-0.42)	<0.01	0.15 (0.06-0.42)	<0.01
Post-GPS	0-1/2	0.19 (0.07-0.47)	<0.01	0.18 (0.06-0.48)	<0.01
Post-NLR	High/low	2.94 (0.99-7.92)	0.05		

HR: Hazard ratio; Sq: squamous cell carcinoma; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; GPS: Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; Pre: before anti-PD1 therapy; Post: after anti-PD1 therapy.

Table IV. Analysis of factors for association with response to anti-programmed cell death-1 (PD1) therapy.

Characteristic	Subgroups	OR for response (95% CI)			
		Univariate	p-Value	Multivariate	p-Value
Age	<65/≥65 years	1.38 (0.33-7.10)	0.67		
Gender	M /F	0.68 (0.09-3.29)	0.64		
Smoke	Ever/never	<0.01 (<0.01-1.28)	0.08		
Histology	Sq/nonSq	5.04 (0.81-97.94)	0.09		
Line of therapy	1-2/≥3	0.38 (0.05-1.76)	0.23		
Radiation therapy	Yes/No	0.95 (0.24-3.58)	0.94		
Pre-ECOG-PS	0-1/2-4	1.5 (0.07-17.19)	0.76		
Pre-GPS	0-1/2	1.79 (0.44-7.01)	0.41		
Pre-NLR	High/low	0.79 (0.18-4.24)	0.77		
Post-ECOG-PS	0-1/2-4	0.58 (0.08-2.76)	0.51		
Post-GPS	0-1/2	0.11 (<0.01-0.65)	0.01	0.16 (<0.01-1.03)	0.05
Post-NLR	High/low	-	<0.01	-	0.02

OR: Odds ratio; Sq: squamous cell carcinoma; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; GPS: Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; Pre: before anti-PD1 therapy; Post: after anti-PD1 therapy.

treatment (24); this highlights the challenges associated with early identification of patients who will respond better to anti-PD1 treatment. Nevertheless, the present study revealed that early evaluation of post-treatment GPS (after 1 month of treatment) was able to predict the efficacy of anti-PD1 treatment; furthermore, multivariate analyses demonstrated that the post-treatment GPS was better than the post-treatment NLR to predict PFS due to anti-PD1 treatment. Moreover, the current study revealed significant changes in the GPS during treatment of patients who had experienced a partial response or disease progression (Figure 2). Therefore, early evaluation of any change in the GPS may help in distinguishing between patients who will experience a clinical response, have stable

disease, or experience true disease progression. However, further studies are needed to examine the predictive value of the post-treatment GPS in clinical settings.

This study has several limitations. Firstly, the study used a single-center retrospective protocol, prone to institutional biases and differences in the timing of evaluations made by clinicians. Secondly, the sample size was small; it was difficult to address this because of i) the relatively recent approval of anti-PD1 therapy; and ii) the single-center retrospective nature of this study. Lastly, almost half of the patients did not undergo PD-L1 testing (21/47, 45%); this was owing to the lack of routine PD-L1 testing for patients with NSCLC at our institution, resulting in the exclusion of

Figure 1. Kaplan-Meier curves for progression-free (PFS) and overall (OS) survival of all patients (A and B, respectively) and according to the post-treatment Glasgow prognostic score (GPS) (C and D, respectively).

Figure 2. Changes in the Glasgow prognostic score (GPS) during treatment with an antibody to programmed cell death-1 (PD1). The changes from the pre-treatment GPS to post-treatment GPS are shown for patients with a partial response (PR, panel A), stable disease (SD, panel B) and progressive disease (PD, panel C). p -Values were calculated using the Wilcoxon signed-rank test.

this variable from our analyses. Hence, well-designed prospective studies are needed.

In conclusion, the post-treatment GPS at 1 month was able to predict both the efficacy and clinical response to anti-PD1 treatment in patients with NSCLC. Although further studies are warranted to validate these findings, our results suggest that determination of early post-treatment GPS may help in better managing patients with NSCLC receiving anti-PD1 treatment.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this study.

Authors' Contributions

NK designed the study and wrote the article. NS, TY, and TA helped design the study. YT, YM, RS, SK, KK, AM, and TM contributed to the clinical treatment. TH takes responsibility for accuracy of this study.

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