ORIGINAL

Ability of the Glasgow Prognostic Score to predict the tolerability and efficacy of platinum-combination chemotherapy among elderly patients with advanced non-small cell lung cancer

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Abstract : *Background* : Although platinum-combination chemotherapy is widely used to treat advanced non-small cell lung cancer (NSCLC), not all elderly patients benefit from this regimen. In this retrospective study, we aimed to evaluate whether the Glasgow Prognostic Score (GPS), an indicator of systemic inflammation and malnutrition, could predict the tolerability and efficacy of platinum-combination chemotherapy among elderly patients with NSCLC. *Methods* : The eligibility criteria included patients aged ≥70 years with NSCLC treated with first-line platinum-combination chemotherapy at Shimane University Hospital between January 2015 and December 2018. *Results* : Thirty-two patients with NSCLC (median age, 74 years) were included. The GPS scores were 0–1 for 19 patients and 2 for 13 patients. Four chemotherapy cycles were completed by 57.9% and 30.8% of patients in the GPS 0–1 and GPS 2 groups, respectively. The GPS 0–1 group experienced better outcomes than the GPS 2 group (response rate : 26% vs. 15%, *P* = 0.67 ; median progression-free survival : 4.1 vs. 2.1 months, *P* = 0.0026 ; median overall survival : 22.8 vs. 9.6 months, *P* = 0.0092). *Conclusions* : Platinum-combination chemotherapy demonstrated promising efficacy among elderly NSCLC patients with a GPS 0–1. Therefore, GPS may be crucial in determining whether treatments recommended for younger patients are suitable for older patients with NSCLC. J. Med. Invest. 68 : 260-264, August, 2021

Keywords : *non-small cell lung cancer, platinum-combination chemotherapy, Glasgow Prognostic Score, elderly patients*

INTRODUCTION

Platinum-combination chemotherapy is a widely used standard treatment for advanced non-small cell lung cancer (NSCLC) (1). The recent development of reduced toxicity in platinum-combinations has broadened its scope by including elderly patients (2-5). However, elderly patients experience age-related changes along with the development of comorbidities, implying that not all elderly patients benefit from platinum-combination chemotherapy. For example, although a subset analysis of the CA031 study data demonstrated that carboplatin plus nanoparticle albumin-bound paclitaxel is safe and effective among elderly patients, a phase II study to assess the efficacy and safety of the treatment regimen was interrupted because of treatment-related mortality and serious adverse events among elderly patients with NSCLC (4, 6).

The Glasgow Prognostic Score (GPS) is an indicator of systemic inflammation and malnutrition (7, 8). Fujio *et al.* retrospectively demonstrated that among patients with advanced NSCLC and an Eastern Cooperative Oncology Group performance status (PS) of 2, a high GPS was associated with poorer outcomes than a low GPS (9). Thus, the GPS may be useful for identifying elderly patients with NSCLC who are likely to benefit from

platinum-combination chemotherapy. The present study aimed to evaluate whether the GPS could predict the tolerability and efficacy of platinum-combination chemotherapy in elderly patients with NSCLC.

PATIENTS AND METHODS

Patients

We retrospectively reviewed elderly patients with NSCLC who received platinum-combination chemotherapy as first-line treatment at the Shimane University Hospital between January 2015 and December 2018. The study's retrospective protocol was approved by our Institutional Review Board (approval number : 4654, approval date : June 4, 2020), which also waived the requirement for informed consent. Based on several previous studies, "elderly" patients were defined as being aged ≥70 years (2, 4, 6). Patients were excluded from this study if they had epidermal growth factor receptor gene mutations or anaplastic lymphoma kinase fusion genes.

Assessments

Blood tests were conducted for all patients to determine their pretreatment serum concentrations of serum albumin (Alb) and C-reactive protein (CRP). Those findings were used to determine the GPS scores (7, 8) : a GPS of 0 was defined as patients with CRP concentration of < 1.0 mg/dL and Alb concentration of ≥3.5 mg/dL ; a GPS of 1 was defined as patients with CRP concentration of ≥1.0 mg/dL or Alb concentration of < 3.5 mg/dL ; and a GPS of 2 as patients with CRP concentration of ≥1.0 mg/dL and

Alb concentration of < 3.5 mg/dL. In a retrospective study for advanced patients with NSCLC with a PS of 2, Fujio *et al.* compared the outcomes to a GPS 0–1 group or a GPS 2 group (9). Similarly, in our study, the patients were assigned to a GPS 0–1 group or a GPS 2 group for the analyses to compare the tolerability and efficacy of platinum-combination chemotherapy. Treatment responses were retrospectively assessed using version 1.1 of the Response Evaluation Criteria in Solid Tumors. Adverse events were evaluated using version 5.0 of the Common Terminology Criteria for Adverse Events.

Statistical methods

Progression-free survival (PFS) and overall survival (OS) outcomes were evaluated using the Kaplan-Meier method and log-rank test. All other analyses were performed using Fisher's exact test. Differences were considered statistically significant at P-values of < 0.05. The analyses were performed using JMP software (version 10.0 ; SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

The study included 32 patients (29 men and 3 women) with a median age of 74 years, and their characteristics are listed in Table 1. The GPS 0–1 group included 19 patients (GPS 0 included

Table 1. Patient characteristics

		GPS 0–1 (n = 19)	GPS 2 (n = 13)
Age, years	Median (range)	74 (70–84)	74 (70–82)
Sex, n (%)	Female	3 (15.8%)	0 (0%)
Histology, n (%)	Non-SCC	11 (57.9%)	6 (46.2%)
	SCC	8 (42.1%)	7 (53.8%)
Stage, n (%)	III	4 (21.0%)	2 (15.4%)
	IV	15 (78.9%)	11 (84.6%)
PS, n (%)	0	6 (31.6%)	0 (0%)
	1	11 (57.9%)	13 (100%)
	2	2 (10.5%)	0 (0%)
Comorbidities, n (%)	COPD	8 (42.1%)	5 (38.5%)
	DM	6 (31.6%)	6 (46.2%)
	Heart disease	6 (31.6%)	4 (30.8%)
	Other cancer	7 (36.8%)	1 (7.7%)
	ILD	6 (31.6%)	1 (7.7%)
	Cerebrovascular disease	4 (21.0%)	2 (15.4%)
	Hepatic disease	3 (15.8%)	2 (15.4%)
Platinum agent, n (%)	CBDCA	16 (84.2%)	12 (92.3%)
	CDDP	3 (15.8%)	1 (7.7%)
Additional drugs, n (%)	PEM	5 (26.3%)	5 (38.5%)
	Nab-PTX	3 (15.8%)	4 (30.8%)
	TS-1	4 (21.0%)	3 (23.1%)
	PEM + Bev	4 (21.0%)	0 (0%)
	PTX	2 (10.5%)	0 (0%)
	GEM	1 (5.3%)	1 (7.7%)

GPS, Glasgow Prognostic Score ; SCC, squamous cell carcinoma ; PS, performance status ; COPD, chronic obstructive pulmonary disease ; DM, diabetes mellitus ; ILD, interstitial lung disease ; CBDCA, carboplatin ; CDDP, cisplatin ; PEM, pemetrexed ; nab-PTX, nanoparticle albumin-bound paclitaxel ; TS-1, tegafur/gimeracil/oteracil ; BEV, bevacizumab ; PTX, paclitaxel ; GEM, gemcitabine.

14 patients and GPS 1 included 5 patients), and the GPS 2 group included 13 patients. The GPS 0–1 group included 6 patients with a PS of 0, 11 with a PS of 1, and 2 with a PS of 2. All 13 patients in the GPS 2 group had a PS of 1. Chronic obstructive pulmonary disease, diabetes mellitus, and heart disease were common comorbidities. Most patients received carboplatin as the platinum agent. Although there were no significant differences in the baseline characteristics of the two groups, the GPS 0–1 group had higher proportions of female patients, presence of other cancers, and interstitial lung disease.

Treatment parameters

The treatment parameters are shown in Table 2. The median number of chemotherapy cycles was 4 cycles (range : 1–11 cycles) in the GPS 0–1 group and 2 (range : 1–4 cycles) in the GPS 2 group. Four chemotherapy cycles were completed by 57.9% of patients in the GPS 0–1 group and 30.8% in the GPS 2 group. The main cause of treatment discontinuation was disease progression, which was relatively common in the GPS 2 group (7 patients, 53.4%).

Table 2. Treatment parameters

	GPS 0–1 (n = 19)	GPS 2 (n = 13)
Median chemotherapy cycles (range)	4 (1–11)	2 (1–4)
Patients who completed 4 cycles, n (%)	11 (57.9%)	4 (30.8%)
Causes of discontinuation		
Disease progression, n (%)	4 (21.0%)	7 (53.4%)
Toxicity, n (%)	2 (10.5%)	2 (15.4%)
PS worsening, n (%)	2 (10.5%)	0 (0%)

GPS, Glasgow Prognostic Score ; PS, performance status.

Efficacy

Table 3 shows the tumor responses. The overall response rates (ORRs) were 26.3% in the GPS 0–1 group and 15.4% in the GPS 2 group ; however, the difference was not significant (*P* = 0.67). The disease control rates were 68.4% in the GPS 0–1 group and 23.1% in the GPS 2 group, and most patients in the GPS 2 group developed progressive disease (10 patients, 76.9%). The survival curves are shown in Figures 1 and 2. Patients in the GPS 0–1 group had significantly longer median values for PFS (4.1 months [95% confidence interval : 2.2-7.4 months] vs. 2.1 months [95% confidence interval : 0.8-2.7 months], *P* = 0.0026) and OS (22.8 months [95% confidence interval : 8.2-NA months] vs. 9.6 months [95% confidence interval : 2.6-14.8 months], *P* = 0.0092). In a subgroup analysis including patients aged ≥75 years (n = 15), the median PFS in the GPS 0–1 group and the GPS 2 group was 3.2 and 2.1 months (*P* = 0.11), respectively, and

Table 3. Tumor responses

	GPS 0–1 (n = 19)	GPS 2 (n = 13)	P
CR, n (%)	0 (0%)	0 (0%)	
PR, n (%)	5 (26.3%)	2 (15.4%)	
SD, n (%)	8 (42.1%)	1 (7.7%)	
PD, n (%)	6 (31.6%)	10 (76.9%)	
ORR	26.3%	15.4%	0.67
DCR	68.4%	23.1%	0.29

CR, complete response ; PR, partial response ; SD, stable disease ; PD, progressive disease ; ORR, overall response rate ; DCR, disease control rate.
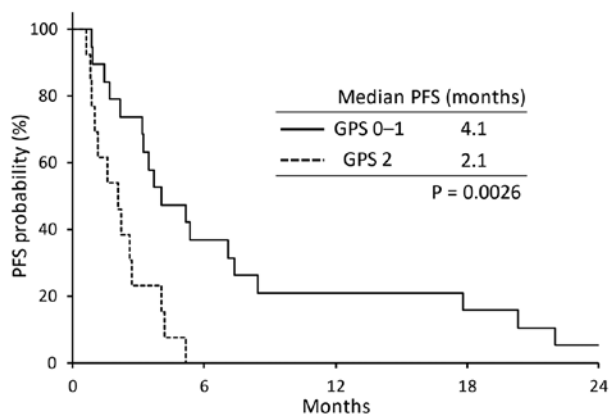
Figure 1. Kaplan-Meier curves for progression-free survival (PFS) according to the Glasgow prognostic score (GPS).
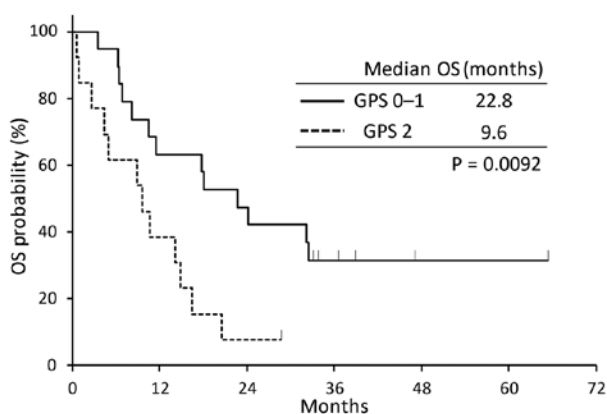

Figure 2. Kaplan-Meier curves for overall survival (OS) according to the Glasgow prognostic score (GPS).

Table 4. Toxicities

	GPS 0–1 (n = 19)		GPS 2 (n = 13)	
Hematological	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Anemia	19 (100%)	3 (15.8%)	13 (100%)	5 (38.5%)
Thrombocytopenia	12 (63.2%)	4 (21.0%)	10 (76.9%)	3 (23.1%)
Neutropenia	12 (63.2%)	6 (31.6%)	9 (69.2%)	2 (15.4%)
Leukopenia	11 (57.9%)	3 (15.8%)	9 (69.2%)	3 (23.1%)
Non-hematological	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Anorexia	14 (73.7%)	0 (0%)	8 (61.5%)	1 (7.7%)
Constipation	12 (63.2%)	0 (0%)	9 (69.2%)	0 (0%)
Fatigue	11 (57.9%)	0 (0%)	10 (76.9%)	0 (0%)
Nausea	6 (31.6%)	0 (0%)	4 (30.8%)	1 (7.7%)
AST	5 (26.3%)	0 (0%)	5 (38.5%)	0 (0%)
ALT	4 (21.0%)	0 (0%)	3 (23.1%)	0 (0%)
Creatinine	2 (10.5%)	0 (0%)	3 (23.1%)	1 (7.7%)
Rash	2 (10.5%)	0 (0%)	2 (15.4%)	1 (7.7%)

GPS, Glasgow prognostic score ; AST, aspartate transaminase ; ALT, alanine transaminase.

DISCUSSION

This retrospective study evaluated whether the GPS could efficiently predict the tolerability and efficacy of platinum-combination chemotherapy among elderly Japanese patients with NSCLC. The results revealed that the GPS 0–1 group had an ORR of 26.3%, a median PFS of 4.1 months, and a median OS of 22.8 months. These results were comparable to the reported efficacy of platinum-combination chemotherapy among all patients with NSCLC, including young patients (3, 10-12). The present study revealed that the GPS 2 group had a higher disease progression rate and shorter PFS and OS intervals than the GPS 0–1 group. Similarly, in a subgroup analysis of patients aged ≥75 years, the median PFS and OS of the GPS 0–1 group tended to be longer than those of the GPS 2 group (3.2 vs 2.1 months and 32.5 vs 9.8 months, respectively). There were no significant differences observed with regard to adverse events between the two groups, and only a few patients experienced febrile neutropenia or grade 3 non-hematological adverse events. Moreover, in the GPS 2 group, the main cause of treatment discontinuation was disease progression, as opposed to toxicity. Thus, platinum-combination chemotherapy might be less effective, but not intolerable, for elderly patients with NSCLC and a GPS of 2.

Although in our study, all patients in the GPS 2 group possessed a good PS (PS = 1), they experienced poor response to treatment and had a poor prognosis. Therefore, for elderly patients, assessment using the PS alone may be insufficient, and the GPS could be a valuable marker for predicting the tolerability, efficacy, and prognosis after various treatments for NSCLC (7, 8, 13-16). Furthermore, Fujio *et al.* reported that among patients with advanced NSCLC and a PS of 2, a GPS of 2 was associated with poorer outcomes than a GPS of 0–1 (9). Based on the results of our study and that conducted by Fujio *et al.*, it appears that patients with NSCLC with a GPS of 0–1 might benefit from standard treatment that is recommended for younger patients or patients with a good PS, even if the patient is in a high-risk group (older aged or poorer PS). Thus, the GPS might be a helpful tool to guide treatment selection for NSCLC among patients with higher risk factors. Additionally, the combination of platinum-based chemotherapy and ICIs has recently become

the median OS in the GPS 0–1 group and the GPS 2 group was 32.5 and 9.8 months (p = 0.11), respectively.

Additional chemotherapy regimens were administered to 14 patients (73.7%) in the GPS 0–1 group and 8 (61.5%) in the GPS 2 group. Immune checkpoint inhibitors (ICIs) were administered to 9 patients (47.4%) (programmed death-ligand 1 tumor proportion score was 0% in 3 patients, 1-49% in 2 patients, ≥50% in 1 patient, and unknown in 3 patients) in the GPS 0–1 group and 6 patients (46.2%) (programmed death-ligand 1 tumor proportion score was 0% in 2 patients, 1-49% in 2 patients, and unknown in 2 patients) in the GPS 2 group. In the GPS 0–1 group, ORR of ICIs was 22% and 3 patients experienced PFS for more than 1 year by ICIs. In the GPS 2 group, ORR of ICIs was 0% and 1 patient experienced PFS for more than 1 year by ICIs.

Toxicity

The most common adverse events are shown in Table 4. No significant inter-group differences were observed for all grades of adverse events. However, both groups had relatively high rates of hematological adverse events, except febrile neutropenia, with incidences of 15–40% for grade 3–4 hematological adverse events. One patient in the GPS 0–1 group experienced febrile neutropenia. Although anorexia, constipation, and fatigue were common events, few cases involved grade 3 events. No grade 4 non-hematological adverse events were observed in either of the two groups. However, 1 treatment-related death caused by grade 5 acute kidney injury occurred in the GPS 2 group.

standard therapy for advanced NSCLC (17-19). Therefore, we further intend to verify whether the GPS can predict the tolerability and efficacy of platinum-based chemotherapy plus ICIs among elderly patients with NSCLC.

The present study has several limitations. First, the retrospective design and small sample size are potential sources of bias. Second, the patients were treated using various chemotherapy regimens, and the small sample size precluded treatment-specific sub-analyses. Third, CRP and Alb concentrations are non-specific markers, and comorbidities can also influence the GPS. Therefore, the GPS may not always accurately reflect the condition of elderly patients with NSCLC. Fourth, additional therapy with ICIs might affect the result for OS. The efficacy of ICIs was better in the GPS 0–1 group than in the GPS 2 group.

In conclusion, platinum-combination chemotherapy provided promising efficacy for elderly patients with NSCLC and a GPS of 0–1. Thus, elderly patients with NSCLC and a GPS of 0–1 may benefit from standard treatment regimens that are generally recommended for younger patients.

FUNDING

CONFLICTS OF INTEREST

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