Clinical Impact of Prognostic Nutrition Index for Advanced Gastric Cancer Patients with Peritoneal Metastases Treated Nivolumab Monotherapy

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Although nivolumab shows survival benefits for patients with advanced gastric cancer (AGC), predictive biomarkers for nivolumab treatment in AGC remain unclear, especially in the case of peritoneal metastases. This study investigated the clinical significance of the prognostic nutrition index (PNI), reflecting the host nutritional status and immunity, in AGC patients undergoing nivolumab monotherapy. This study retrospectively analyzed 53 AGC patients who received nivolumab between October 2017 and February 2021. Among them, 35 patients with peritoneal metastases were reviewed to investigate the relationship between the PNI and oncological outcomes. The PNI was calculated as 10×serum albumin level (g/dl)+0.005×total lymphocyte count (per mm^3) at the first administration of nivolumab. With a median follow-up duration of 2.0 (0.3-13.5) months, the median overall survival (OS) was 2.0 months. The overall response and disease-control rates were 0.0% and 20.0%, respectively. Among the 35 patients, 13 patients were identified as a high-PNI group. In the univariate analysis, the high-PNI group showed a significantly longer PFS and OS than the low-PNI group. In the multivariate analysis, the high-PNI was independently associated with a longer PFS (p=0.021) and OS (p=0.022). The PNI can be useful for predicting PFS and OS in AGC patients with peritoneal metastases. However, further studies are required to validate these results in AGC and new strategies are needed to improve the outcome for AGC patients with peritoneal metastases.

Key Words: *Stomach Neoplasms; Nivolumab; Peritoneal Neoplasms*

INTRODUCTION

Despite improved outcomes for advanced gastric cancer (AGC) via the introduction of several effective combination chemotherapies and identification of immune checkpoint inhibitors (ICIs), distant metastases remain frequent and are associated with a dismal prognosis, where peritoneal implantation is the most common metastatic site, with an incidence of 53.5%.[1,2] Since peritoneal metastases exhibit aggressive behavior and biological resistance to chemotherapy, the treatment of patients with peritoneal meta-

stases is rarely successful with only a 2% five-year survival rate.[3] Thus, novel approaches are needed to overcome the limitations of conventional cytotoxic chemotherapy for AGC patients with peritoneal metastases.

ICIs are already recognized standard treatments for patients with recurrent or metastatic AGC.[4] For example, a phase III (ATTRACTION-2) trial that compared nivolumab targeting the programmed cell death protein-1 (PD-1) with a placebo in 493 Asian patients showed a survival benefit in third- or later line treatment.[5] Moreover, a recent global phase III (CheckMate 649) trial found that nivolumab in

combination with chemotherapy was the first PD-1 inhibitor to demonstrate superior overall survival (OS) and progression-free survival (PFS) as a first-line treatment.[6] Plus, a phase II/III (ATTRACTION-4) trial conducted in Asia reported significantly improved PFS.[7] Notwithstanding, subgroup analyses of this data have shown disappointing results for peritoneal metastases, although there have been a few case reports of successful treatment when using nivolumab for AGC with peritoneal metastases.[8] Yet, the effects of ICIs seem to vary depending on the tumor biology, with various clinical factors also influencing the response to ICIs.[4] Thus, evaluating the clinical features and treatment outcomes for peritoneal metastases treated with nivolumab may help to provide more effective therapeutic strategies for AGC patients.

The prognostic nutrition index (PNI) is calculated based on the serum albumin level and peripheral blood lymphocyte count and was originally developed to predict the risk of postoperative complications mainly in surgical patients by assessing the preoperative nutritional status.[9] Notably, the total lymphocyte count can have a favorable impact on the tumor inhibiting effects of ICIs and be used as an index for evaluating the host immunity and response to ICIs.[10] Meanwhile, the serum albumin level can reflect the host immunologic status in AGC patients with peritoneal metastases, where cancer progression in the diminished the oral intake, leading to downregulation of the nutritional status of the patient.[11] Thus, there is increasing evidence that the PNI can be an effective prognostic marker, as well as a predictive indicator related to ICIs for various solid tumors.[12-14] Accordingly, this study investigated the clinical significance of the PNI for predicting the therapeutic effects of AGC patients with peritoneal metastases treated nivolumab monotherapy.

MATERIALS AND METHODS

1. Study design and patients

This study retrospectively examined the medical records of all patients with unresectable advanced or recurrent gastric cancer who received nivolumab treatment at Kyungpook National University Chilgok Hospital (KNUCH) between October 2017 and February 2021. The clinical parameters, such as age, sex, performance status, histology, number of organs with metastases, and laboratory findings at the time of the first nivolumab administration were reviewed from the hospital database. Nivolumab was administered by intravenous infusion at a dose of 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The study was approved by the Institutional Review Board of KNUCH (IRB No: KNUH 2021-11-009).

2. Definition of PNI

The PNI was calculated as 10×serum albumin level (g/dl)+0.005×total lymphocyte count (per mm^3) at the first administration of nivolumab. The patients were classified as either low (<40) or high (≥40) as the reference.[15]

3. Statistical analysis

PFS was measured from the time of commencing treatment to disease progression or death. OS was estimated from the date of diagnosis to death from any cause. The tumor response was evaluated according to the response evaluation criteria in solid tumors (RECIST) version 1.1. The survival analysis used the Kaplan–Meier method with a log-rank test. A multivariate analysis was performed using variables in the previous study of Hagi et al.[16] using Cox's proportional hazards model to derive a potentially suitable set of predictors. Two-sided p-values of <0.05 were considered significant. The statistical analyses were performed using SPSS software version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

1. Patients

A total of 35 patients with peritoneal metastases were analyzed and their characteristics are summarized in Table 1. The median age was 54.5 years (range=25-71

TABLE 1. Baseline patient characteristics

Characteristic	Total (n=35) n (%)
Age, years	
Median (range)	54.5 (25.0-71.0)
Gender	
Male	19 (54.2)
Female	16 (45.7)
ECOG performance status	
0 or 1	15 (42.9)
2	19 (54.2)
3	1 (2.9)
Histologic differentiation	
Well differentiated	3 (8.6)
Moderate differentiated	4 (11.4)
Poorly differentiated	6 (17.1)
Poorly cohesive carcinoma	15 (42.9)
Mixed type	7 (20.0)
Treatment before nivolumab	
0	1 (2.9)
1	0 (0.0)
2	18 (51.4)
3	16 (45.7)
Number of metastases	
1	1 (2.9)
2	10 (28.6)
≥3	24 (68.6)
Previous history of surgical resection	
Curative	9 (25.7)
Palliative	10 (28.6)
Not done	16 (45.7)
Nivolumab cycle	
1	13 (37.1)
2	8 (22.9)
≥3	14 (40.0)

years) and 54.2% were male. Most of the patients had an ECOG performance status of 2 (54.2%). The histologic differentiations were as follows: well differentiated (n=3, 8.6%), moderately differentiated (n=4, 11.4%) and poorly differentiated (n=6, 17.1%). The liver (n=7, 20.0%), lung (n=7, 20.0%) and distant lymph nodes (n=16, 45.7%) were the most common sites of metastases. Before chemotherapy, 9 (25.7%) patients underwent curative surgical resection, and 10 (28.6%) underwent palliative surgical resection. Among the 35 patients, 22 and 13 patients were classified in the low-PNI and high-PNI group, respectively.

2. Response and survival outcomes for nivolumab

No patient exhibited a complete response or partial response. 7 patients showed stable disease, giving a disease control rate of 20.0%. At the last follow-up, the median follow-up duration was 2.0 (0.0-13.5) months. During the analyses, 31 (88.6%) patients experienced progression and 33 (94.3%) patients died. The median PFS was 1.1 months and the median OS was 2.0 months (Fig. 1).

3. Relationship between PNI and survival outcome

In the univariate analysis, the high-PNI group showed a significantly longer PFS and OS than the low-PNI group (Fig. 2). In the multivariate analysis using a Cox proportional hazard model adjusted for age, histologic differentiation, and ECOG, the high-PNI group was independently associated with a longer PFS (hazard ratio=0.366, 95% confidence interval (CI)=0.155-0.861, p=0.021) and OS (Hazard ratio=0.349, 95% CI=0.142-0.860, p=0.022) (Table 2).

DISCUSSION

The clinical significance of the PNI was investigated in 35 patients with metastatic AGC who underwent nivolumab mostly as second- or third-line therapy. As a result, the PNI was identified as an independent predictive factor of PFS and OS, suggesting that the PNI may be a useful biomarker to predict the response of AGC patients with peritoneal metastases treated with ICIs.

The molecular mechanisms by which AGC undergoes peritoneal metastases are not completely clear and consid-
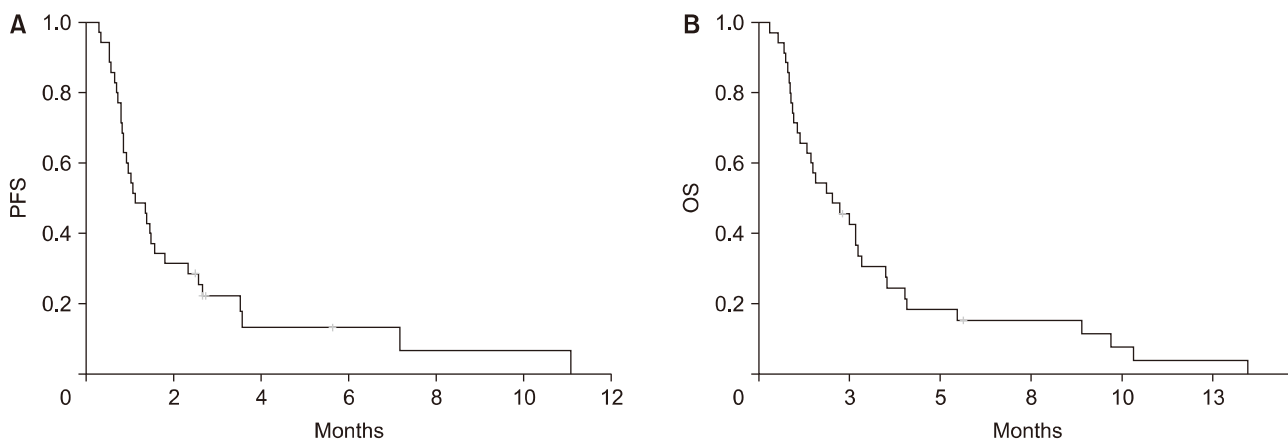

FIG. 1. Kaplan-Meier survival curves for progression-free survival (PFS) (A) and overall survival (OS) of 35 patients according to peritoneal metastasis (B).
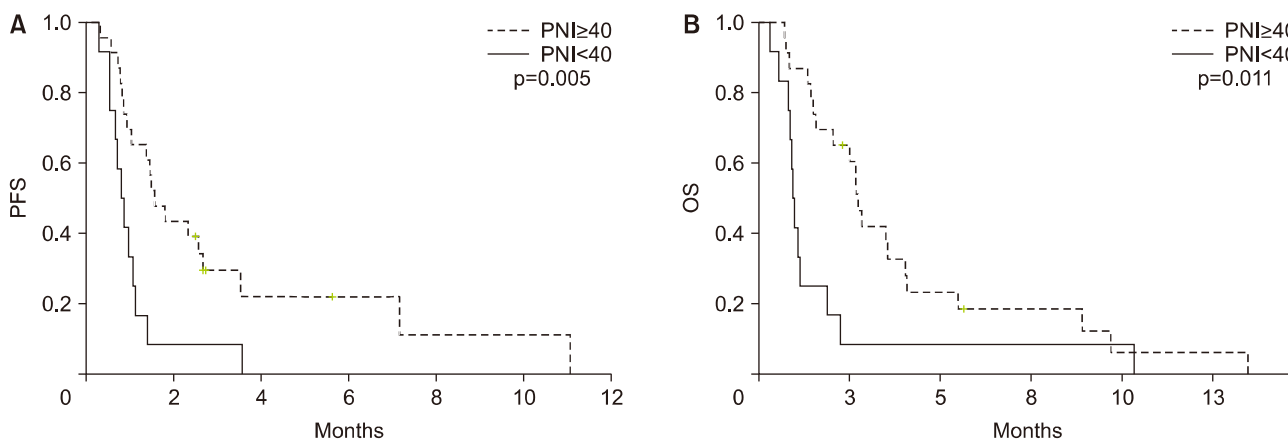

FIG. 2. Kaplan-Meier survival curves for progression-free survival (PFS) (A) and overall survival (OS) of 35 patients according to PNI (B).

TABLE 2. Multivariate analyses for progression-free survival and overall survival

Variables	Category	Progression-free survival			Overall survival		
		p-value	HR	95% CI	p-value	HR	95% CI
Age, years	≥55 vs. <55	0.524	1.287	0.592-2.794	0.875	1.062	0.502-2.244
Histologic differentiation	WD & MD vs. PD & others	0.775	0.872	0.340-2.235	0.156	0.486	0.180-1.316
ECOG PS	≥2 vs. <2	0.075	2.136	0.927-4.922	0.140	1.885	0.812-4.379
PNI	≥40 vs. <40	0.021	0.366	0.155-0.861	0.022	0.349	0.142-0.860
Nivolumab cycle	≥3 vs. <3	0.012	0.312	0.126-0.776	<0.001	0.081	0.023-0.285

WD: well differentiated, MD: moderate differentiated, PD: poorly differentiated, ECOG PS: Eastern Cooperative Oncology Group Performance Status, PNI: Prognostic Nutrition Index.

ered as a multistep process, including the detachment of cancer cells from the primary tumor, survival in the free abdominal cavity, attachment to the distant peritoneum, invasion into the subperitoneal space, and proliferation with angiogenesis.[17] In particular, various molecules, such as E-cadherin, chemokines, growth factor receptors/ligands, immune cells, and extracellular matrix, broadly contribute during the invasion of the gastric wall and migration of the cancer cells.[18] These factors all play an essential role in the progression and chemoresistance of peritoneal metastases.[19] Although recent studies of AGC patients with peritoneal metastases have attempted to demonstrate improved survival with systemic chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC)/peritonectomy, the long-term outcomes remain dismal.[20] In the present study, peritoneal metastases showed poor outcomes even after treatment with nivolumab, as consistent with previous study results. Subgroup analyses of the ATTRACTION-2 trial found no significant benefit from nivolumab in patients with peritoneal metastases. Similarly, Aarnink et al.[21] reported that ICIs used in non-small cell lung cancer (NSCLC) patients with peritoneal metastasis were associated with poor PFS and OS. Recent studies also showed that diffuse and signet ring cell histologies had poor outcomes with nivolumab treatment, indicating that these types seemingly promote AGC cell migration, invasion, and enhanced peritoneal metastases.[6,22-24] Therefore, since these findings and the current results suggest that peritoneal metastases have a relatively limited response to ICIs, the role of ICIs in AGC with peritoneal metastases requires further clarification.

Recent research has been focused on identifying robust predictive biomarkers for AGC treated with ICIs. The PNI, first reported by Onodera et al., is a well-known inflammatory prognostic marker for several solid tumors.[25] The PNI includes the serum lymphocyte and albumin levels. There is increasing evidence that the lymphocyte ratio can be an effective predictive indicator related to ICIs for various solid tumors, having a favorable effect on their tumor inhibiting properties.[4] Moreover, albumin is an acute-phase protein and decreases in response to inflammation.[26] Thus, low levels of albumin may reflect cancer-induced malnutrition and have a negative impact on prognosis. Therefore, indicating a poor diet in the case of AGC with peritoneal

metastases, these factors may help to determine the predictive value of ICIs including nivolumab in these patients. Several studies covering a variety of cancers: gastric cancer, colorectal cancer, NSCLC, and genitourinary cancer treated with ICIs found that a low PNI resulted in worse OS and PFS across various types of malignancies, which is consistent with the current study results.[9,12,27,28] However, these studies were featured with heterogeneous characteristics bewteen PNI-high and PNI-low groups. These imbalanced baselines might influence the outcomes of patients. Recently, another study showed a statistically significant outcome with a large number of gastric cancer patients. Mohri et al.[9] analyzed 365 CRC patients who underwent curative resection, and reported that a PNI <45 independently affected OS. This particular parameter also has demonstrated several advantages for daily clinical practice, including being ready to use, easily measurable, repeatable, and relatively economical to evaluate.[4] Thus, considering its recognized influence on host nutritional status, immunity, and cancer, the PNI can be effectively used to predict the therapeutic effects of nivolumab in AGC patients with peritoneal metastases.

Although the present data identified a significant prognostic role of PNI in AGC patients with peritoneal metastases treated with nivolumab, there are several potential limitations. First, the sample size was too small to compare between two groups. Plus, the current study was a retrospective evaluation and follow-up duration was relatively short. Third, various environmental factors including albumin, body mass index, malnutrition, and the timing of PNI assessment could also affect the value of PNI and no detailed information was provided on the actual condition of each patient. Moreover, the cutoff values will need to be standardized. However, considering the homogeneous disease and treatment, any potential confounding effect due to patient populations was comparably small in the present study.

In summary, the PNI can be useful for predicting PFS and OS in AGC patients with peritoneal metastases treated with nivolumab. Therefore, further large-scale prospective studies are required to validate the improved results in the PNI-high group and new strategies are also needed to overcome the worse outcome in the PNI-low group in AGC patients with peritoneal metastases treated ICIs.

CONFLICT OF INTEREST STATEMENT

None declared.

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