Assessment of Systemic Inflammatory Response and Nutritional Markers in Patients With Trastuzumab-treated Unresectable Advanced Gastric Cancer

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Abstract. *Aim: To determine whether markers of systemic inflammatory response and nutrition are a predictor of treatment response in patients with trastuzumab-treated unresectable advanced gastric cancer. Patients and Methods: Twenty-one patients who received chemotherapy for unresectable advanced gastric cancer at Kochi Medical School from 2013 to 2020 were enrolled. Clinicopathological information and systemic inflammatory response data were obtained retrospectively to investigate associations between baseline cancer-related prognostic variables and survival outcomes. Results: The median overall survival (OS) and progression-free survival (PFS) for the whole cohort were 24.5 (range=1.9-88.4) months and 7.0 (range=2.0-23.4) months, respectively. The objective response rate and disease control rate were 52.4% and 81.0%, respectively. The median PFS for patients with a neutrophil to lymphocyte ratio (NLR) <2.8 was significantly longer than that for those with NLR ≥2.8 (8.9 vs. 6.0 months; $p=0.048$). Although the median OS also tended to be longer for patients with NLR <2.8, the difference was not statistically significant. No significant differences in median OS and PFS were observed between patients with a prognostic nutrition index (PNI) <41.6 and those with PNI ≥41.6. Conclusion: An NLR ≥2.8 is a predictor of poorer prognosis in patients receiving systemic*

treatment with trastuzumab and chemotherapy for unresectable advanced or recurrent gastric cancer.

Gastric cancer is one of the most common malignant tumors and the seventh leading cause of cancer-related deaths worldwide; it is also the second-most frequent cause of cancer-related deaths in Japan (1-3). Systemic anti-neoplastic treatment including chemotherapy or molecular-targeted drug therapy improves survival and possibly provides significant palliation of symptoms compared with best supportive care alone, which is recommended as the standard treatment in patients with unresectable advanced or recurrent gastric cancer (4).

Human epidermal growth factor receptor 2 (HER2), which is associated with cell proliferation, apoptosis and differentiation, is used in clinical practice for targeted therapy. According to the randomized phase III ToGA trial, HER2 expression was predictive for the success of treatment with trastuzumab, a monoclonal antibody against HER2, in advanced gastric cancer (5). Treatment with trastuzumab with adjunct chemotherapy consisting of capecitabine plus cisplatin has been shown to yield promising results in patients with HER2-positive first-line metastatic advanced gastric cancer (5, 6).

Recent studies have identified the prognostic impact of inflammatory response and nutritional status on the survival of patients with many types of malignant solid tumors, as demonstrated by indices such as the Glasgow prognostic score (GPS), prognostic nutrition index (PNI), and neutrophil to lymphocyte ratio (NLR) (7-10). However, information regarding the prognostic significance of these inflammatory response and nutritional markers for patients with unresectable advanced or recurrent gastric cancer receiving systemic treatment with trastuzumab and chemotherapy is lacking. Therefore, in the present study, we retrospectively analyzed a range of clinicopathological factors including the

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Key Words: Gastric cancer, Glasgow prognostic score, neutrophil to lymphocyte ratio, prognostic nutrition index, prognostic value, survival.

GPS, PNI, and NLR for any association between these factors and the prognosis of such patients.

Patients and Methods

Patients. Twenty-one patients with unresectable advanced gastric cancer who were treated with trastuzumab at the Kochi Medical School during the period from January 2013 to December 2020 were identified from a medical information database. Gastric cancer diagnoses were determined by esophagogastroduodenoscopy, biopsy specimen analysis, computed tomography, magnetic resonance imaging, ultrasonography of the abdomen, and positron-emission tomography.

Patients with gastric cancer were treated with trastuzumab plus chemotherapy as first-line therapy when their tumor samples were scored as 3+ for HER2 by immunohistochemistry, or if their tumor samples were scored 2+ and were positive by fluorescent *in situ* hybridization analysis.

Blood samples were collected for analysis of serum concentrations of albumin and C-reactive protein (CRP), and for neutrophil and lymphocyte cell counts. Tumor histology was categorized as intestinal type (well-differentiated, moderately differentiated, and papillary adenocarcinoma) or diffuse type (poorly differentiated, mucinous adenocarcinoma, and signet ring cell carcinoma) according to Lauren's classification (11).

Objective tumor response was evaluated in patients with target lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (12), and the assessment was repeated every 6 to 8 weeks after initiation of trastuzumab therapy using computed tomography.

The overall survival (OS) and progression free survival (PFS) after treatment were both determined as described below (Statistical analyses section). OS was calculated from the initiation of systemic anti-neoplastic treatment until death or the last follow-up consultation. PFS was defined as the time from trastuzumab treatment initiation as first-line therapy to objective disease progression.

The study was approved by the Institutional Review Board at the Kochi Medical School Hospital (approval number: 2020-6) and was conducted in accordance with the Declaration of Helsinki and the Japanese Good Clinical Practice Guidelines. Informed consent was obtained from all participants in the study.

Measurement of systemic inflammation and nutrition-related variables. Venous blood samples were taken at the time of diagnosis and during trastuzumab treatment, and the percentages of each type of blood cell were determined from blood smears stained with Giemsa's reagent. The systemic inflammatory response and nutrition status, as determined by the NLR, PNI, and GPS, were calculated.

NLR was defined as the neutrophil count divided by the lymphocyte count. The GPS and PNI were constructed as previously described to evaluate inflammatory status prior to chemotherapy, and to determine which of the two scores demonstrated a better correlation with prognosis in patients with gastric cancer (7, 13). GPS was determined as follows: Patients with elevated CRP (>1.0 mg/dl) and hypoalbuminemia (<3.5 g/dl) were allocated a score of 2; patients with only one of these biochemical abnormalities were allocated a score of 1; and patients with neither of these abnormalities were allocated a score of 0 (8). PNI was calculated

Table I. Clinical characteristics of patients (n=21) who underwent trastuzumab therapy for unresectable gastric cancer.

Age, years	Median (range)	68 (36-83)
Gender, n	Male	16
	Female	5
Histology, n	Intestinal type	15
	Diffuse type	6
Metastasis site, n	Hematogenous	13
	(liver, lung, bone)	
	Peritoneum	5
	Lymph node	3
Disease status, n	Initially metastatic	15
	Recurrent after curative	6
Laboratory examinations		
Albumin (mg/dl)	Median (range)	4.1 (2.7-4.9)
C-Reactive protein, mg/dl	Median (range)	0.4 (0.05-5.9)
White blood cell count, n/mm ³	Median (range)	6,900 (3,200-12,200)
Neutrophil count, n/mm ³	Median (range)	4,540 (1,710-10,180)
Lymphocyte count, n/mm ³	Median (range)	1,560 (970-3,230)
Serum tumor markers		
CEA, ng/ml	Median (range)	8.9 (0.9-671.1)
CA19-9, U/ml	Median (range)	27.6 (4.1-891.3)
CA125, U/ml	Median (range)	18.7 (7.0-308.8)
Inflammatory response and nutritional biomarkers		
GPS, n	0	17
	1	3
	2	1
NLR	Median (range)	2.8 (1.1-9.2)
PNI	Median (range)	41.1 (27.1-49.1)

CA: Carbohydrate antigen; CEA: carcinoembryonic antigen; GPS: Glasgow prognostic score; NLR: neutrophil to lymphocyte ratio; PNI: prognostic nutrition index.

using the following formula: PNI=[serum albumin level (g/l)+[5×total lymphocyte count (n/l)] (14).

Statistical analyses. We tested differences in mean values between groups of patients for significance using a Mann-Whitney *U*-test for continuous variables and Pearson's chi-squared test for categorical variables. The Kaplan-Meier method was used to generate cumulative survival rates and compared them using the log-rank test to evaluate significant differences. Statistical analyses were performed using SPSS for Windows, version 22.0 (IBM, Armonk, NY, USA). A multivariate Cox proportional hazards regression analysis was used to identify factors independently associated with survival. For the subgroup analysis of OS, hazard ratio (HR) and 95% confidence interval (CI) within each subgroup were summarized. When the various factors were considered in a multivariate analysis, all were dichotomized according to the univariate analysis.

Results

Patient characteristics. Table I summarizes the clinical characteristics of patients with unresectable advanced gastric

Figure 1. Kaplan-Meier survival analysis for patients overall. Kaplan-Meier estimates of overall (A) and progression-free (B) survival in patients with unresectable advanced gastric cancer who were treated with trastuzumab and chemotherapy. Median overall survival was 24.5 (range=1.9-88.4) months and median progression-free survival was 7.0 (range=2.0-23.4) months.

cancer included in the present study. The study cohort comprised 16 men and five women, with a median age of 68 years (range=36-83 years). Of these 21 patients, 15 had intestinal type tumor and 6 diffuse type tumor. Metastasis was mainly hematogenous (13 patients). At diagnosis, 15 patients were classified as having metastatic cancer and six were classified as having recurrent cancer, following curative resection of gastric cancer. Eastern Cooperative Oncology Group performance status was 0 in 20 patients, 1 in one patient, and the median follow-up period for survivors was 22.8 months. Among the 21 patients for whom the response assessment using target lesions was evaluable, a complete response (CR) was observed in 0 patients, a partial response (PR) in 11 patients (52.4%), stable disease (SD) in 6 patients (28.6%), and progressive disease (PD) in 4 patients (19.0%), resulting in an objective response rate (ORR) of 52.4% and a disease control rate of 81.0%.

All patients were shifted to second-line chemotherapy using taxanes with or without ramucirumab, or irinotecan after evidence of disease progression. The median OS for the whole cohort was 24.5 (range=1.9-88.4) months and the OS rate at 1, 2, and 3 years after therapy was 89.5%, 48.9% and 29.3%, respectively (Figure 1A). The median PFS for the whole cohort was 7.0 (range=2.0-23.4) months (Figure 1B).

The median pretreatment NLR and PNI values for the whole cohort were 2.8 (range=1.1-9.2) and 41.1 (range=27.1-49.1), respectively. There was no significant influence on OS and PFS by age, gender, disease status, metastatic site, or time to recurrence, according to the results of the univariate analysis (Table II).

Association of systemic inflammatory markers and patient survival. Because the median pretreatment NLR for the whole cohort was 2.8, patients were divided into two groups based on their pretreatment NLR, *i.e.* NLR <2.8 and ≥ 2.8 . Similarly, as the median pretreatment PNI was 41.1, patients were divided into two groups based on their pretreatment PNI (PNI <41.1 and PNI ≥ 41.1). The median OS for patients with NLR <2.8 was 28.5 months, which was longer than that for those with NLR ≥ 2.8 (22.9 months), although the difference did not reach statistical significance ($p=0.119$; Figure 2A). The median PFS for patients with NLR <2.8 was 8.9 months and was significantly longer than the that for those with NLR ≥ 2.8 (6.0 months; $p=0.048$; Figure 2B). No significant difference was observed in median OS (21.6 *vs.* 22.9 months; $p=0.731$) or PFS (8.9 *vs.* 12.1 months; $p=0.814$) between patients with a PNI <41.6 and those with a PNI ≥ 41.6 (Figure 3).

Discussion

We found that NLR ≥ 2.8 predicted poor prognosis in patients with unresectable advanced or recurrent gastric cancer who received systemic treatment with trastuzumab and chemotherapy. Thus, a high NLR score may have important implications in clinical practice.

Although trastuzumab in combination with platinum-based chemotherapy is the standard first-line regimen in HER2-positive advanced gastric cancer, predictive markers of treatment have not been established (5, 6). To the best of our knowledge, this is the first study to demonstrate a

Table II. Overall and progression free survival of patients treated with trastuzumab for unresectable or recurrent gastric cancer using univariate analysis.

Variable		Overall survival		Progression-free survival	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age group	<68 Years	1		1	
	≥68 Years	1.119 (0.390-3.209)	0.834	1.262 (0.420-3.794)	0.678
Gender	Male	1		1	
	Female	1.512 (0.398-5.747)	0.544	1.443 (0.379-5.499)	0.591
Histological type	Intestinal type	1		1	
	Diffuse type	0.654 (0.199-2.149)	0.485	1.471 (0.427-5.062)	0.541
Metastasis site	Hematogenous (liver, lung, bone)	1		1	
	Peritoneum	2.241 (0.443-11.340)	0.329	3.311 (0.403-27.194)	0.265
	Lymph node	4.485 (0.657-30.612)	0.126	5.368 (0.565-51.031)	0.144
Disease status	Initially metastatic	1		1	
	Recurrent after curative	2.298 (0.665-7.938)	0.188	1.251 (0.377-4.158)	0.714
GPS	0	1		1	
	1 or 2	2.605 (0.503-13.500)	0.254	1.340 (0.287-6.248)	0.709
NLR	<2.8	1		1	
	≥2.8	2.576 (0.784-8.465)	0.119	3.777 (1.012-14.095)	0.048
PNI	<41.1	1		1	
	≥41.1	0.828 (0.282-2.431)	0.731	0.869 (0.271-2.790)	0.814

CI: Confidence interval; GPS: Glasgow prognostic score; HR: hazard ratio; NLR: neutrophil to lymphocyte ratio; PNI: prognostic nutrition index.

relationship between inflammatory response and prognosis in patients with unresectable advanced or recurrent gastric cancer who had received trastuzumab with chemotherapy.

Previous studies have reported that the HER2 overexpression rate in patients with gastric cancer was 17-18% and was significantly associated with a high grade, advanced stage, and a high Ki-67 labeling index (15-17). Kurokawa *et al.* evaluated 1, 148 patients with gastric cancer who underwent gastrectomy to investigate the prognostic impact of HER2 expression, demonstrating HER2 overexpression to be an independent prognostic factor in patients with any stage of gastric cancer (18). In the present study, the median OS and PFS were 24.5 months and 7.0 months, respectively; both values are relatively longer compared to survival times of patients with common type unresectable gastric cancer, despite the unfavorable prognostic factor of HER2 overexpression. Thus, patients with HER2 overexpression who undergo trastuzumab treatment with chemotherapy may be expected to benefit from longer survival times.

Recently, Hwang *et al.* reported that a high NLR was associated with a shorter PFS and OS in trastuzumab-treated patients with HER2-positive gastric cancer, when the cut-off value of NLR was set to 3.0 (19). In the present study, although patients with an NLR ≥2.8 tended to have poorer prognosis than those with an NLR <2.8 (median OS: 22.9 vs. 28.5 months, respectively), the difference was not significant ($p=0.119$). The recent development of second- and further-line treatments for unresectable advanced gastric cancer, including ramucirumab, nivolumab, and trifluridine/tipiracil,

has improved OS and quality of life (20-23). Therefore, improvement in post-progression survival after first-line treatment using trastuzumab may result in the loss of prognostic significance in OS.

Although the mechanism by which systemic inflammatory response markers influence cancer survival in these patients remain unclear, it is possible that pretreatment neutrophil and lymphocyte numbers reflect the level of inflammation within the tumor (24). Evidence is accumulating that cancer progression is influenced by the systemic inflammatory response (10, 24, 25). Furthermore, cytokines generated by neutrophils may establish a microenvironment that promotes angiogenesis, and thus promotes tumor growth and metastasis (25). An oncogenic change induces an inflammatory microenvironment that promotes the development of tumors, aids in the proliferation and survival of malignant cells, promotes angiogenesis and metastasis, subverts adaptive immune responses, and alters responses to hormones and chemotherapeutic agents (26).

Previous research from several laboratories has demonstrated that GPS and PNI, in addition to NLR, are predictors of oncological outcome in gastric cancer (8, 27-29). The current study demonstrated that the median OS and PFS of patients with a high PNI tended to be prolonged (compared to those of patients with a low PNI), although the difference was not significant. A similar trend was found in GPS 0 compared to GPS 1 or 2. Recent randomized phase III trial data demonstrated the superior predictive value (compared to traditional inflammatory indices) of a

Figure 2. Kaplan-Meier survival analysis according to the neutrophil to lymphocyte ratio (NLR). Kaplan-Meier estimates of overall (A) and progression-free (B) survival according to NLR for patients with unresectable gastric cancer who were treated with trastuzumab and chemotherapy. No significant difference in overall survival was observed between patients with NLR <2.8 and those with NLR ≥2.8 (28.5 vs. 22.9 months, hazard ratio=2.58, 95% confidence interval=0.78-8.47; $p=0.119$). The median progression-free survival was significantly higher for patients with NLR <2.8 (8.9 vs. 6.0 months, hazard ratio=3.78, 95% confidence interval=1.01-14.1; $p=0.048$).

Figure 3. Kaplan-Meier survival analysis according to the prognostic nutrition index (PNI). Kaplan-Meier estimates of overall (A) and progression-free (B) survival according to PNI for patients with unresectable gastric cancer who were treated with trastuzumab and chemotherapy. No significant differences in overall and progression-free survival were observed between patients with a PNI <41.1 and those with a PNI ≥41.1 (21.6 vs. 22.9 months, hazard ratio=0.83, 95% confidence interval=0.28-2.43; $p=0.731$; 8.9 vs. 12.1 months, hazard ratio=0.87, 95% confidence interval=0.27-2.79; $p=0.814$, respectively).

combination of C-reactive protein and serum albumin or pre-albumin levels (30, 31). Accordingly, the development of a novel grading system based on previous systemic inflammatory responses and nutrition status may be expected to provide a more accurate prediction of patient survival.

There were several limitations in the present study. Firstly, due to the retrospective nature of this study, it is possible that selection bias may have influenced survival data. Secondly, this study was conducted at a single institution with a relatively small number of patients, which may also affect patient selection bias. Therefore, the results of this study should be interpreted cautiously. Accordingly, further well-designed, prospective, multicenter validation studies with adequate statistical power and a larger number of patient subgroups are warranted to confirm our results.

In conclusion, a high NLR is associated with poorer survival times in patients with unresectable advanced or recurrent gastric cancer who received systemic treatment with trastuzumab and chemotherapy. Thus, NLR, a marker of inflammatory response, may serve as a useful biomarker for the prediction of patient prognosis. Further studies are needed to determine the reliability and accuracy of using NLR as a prognostic tool during trastuzumab treatment.

Conflicts of Interest

None.

Authors' Contributions

Study conception and design: Tsutomu Namikawa and Michiya Kobayashi. Acquisition of data: Tsutomu Namikawa, Masahiro Maeda, Keiichi Yokota, Nobuhisa Tanioka, Jun Iwabu, Masaya Munekage, Sunao Uemura and Hiroyuki Kitagawa. Analysis and interpretation of data: Tsutomu Namikawa and Hiromichi Maeda. Drafting of manuscript: Tsutomu Namikawa. Critical revision of manuscript: Tsutomu Namikawa and Kazuhiro Hanazaki.

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