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Changes in Chemotherapeutic Strategies and Their Prognostic Impact in Patients With Advanced Gastric Cancer

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Abstract. *Background/Aim: To investigate changes in post-progression chemotherapy (PPC) before and after nivolumab approval and determine their prognostic impact. Patients and Methods: A total of 146 patients with unresectable gastric cancer who had at least progressive disease after first- and/or second-line chemotherapy were retrospectively enrolled. Results: Among the 146 patients, 46 and 23 received ramucirumab and nivolumab, respectively. Moreover, 95 and 62 patients received PPC after first- and second-line chemotherapy, respectively. Group B (i.e., at least chemotherapy after nivolumab approval) had significantly higher proportions of patients receiving ramucirumab therapy, nivolumab therapy, and PPC after first- or second-line chemotherapy compared to group A (i.e., termination of chemotherapy before nivolumab approval). Group A had significantly poorer prognosis than group B. Multivariate analysis showed that age, number of distant metastatic sites, and ramucirumab therapy were independent prognostic factors. Conclusion: Changes in chemotherapeutic strategies, including PPC, might contribute to improved prognosis in patients with advanced gastric cancer.*

Studies have shown that patients with stage IV gastric cancer have poor prognosis, with reported 5-year survival rates ranging from 8.8% to 14.9% (1, 2). As such, several investigators have focused on the recent advancements in chemotherapy for patients with advanced gastric cancer (3, 4). Accordingly, the ToGA trial indicated the clinical utility of trastuzumab as a first-line treatment for patients with human epidermal growth factor receptor 2-positive advanced gastric cancer (5). Moreover, the RAINBOW trial showed that ramucirumab demonstrated additional effects as a second-line treatment (6). The aforementioned trials suggest the potential clinical benefits of molecular targeted drugs for patients with unresectable advanced or recurrent gastric cancer. Consequently, the Japanese Gastric Cancer Treatment Guidelines 2018 has recommended the combination of ramucirumab and paclitaxel as a second-line treatment (7).

Recently, immune therapy using immune checkpoint blockade has been highlighted as a promising approach for patients with various malignancies, including gastric cancer (8, 9). Nivolumab, an anti-programmed cell death protein 1 antibody, is an immune checkpoint inhibitor that demonstrated clinical efficacy in the ATTRACTION-2 trial as a third-line treatment for patients with advanced gastric or gastroesophageal junction cancer who had previously undergone two or more chemotherapy regimens (10). Consequently, nivolumab had been approved for use in Japan and has been recommended as a third-line treatment in the Japanese Gastric Cancer Treatment Guidelines 2018 (7). The aforementioned findings suggest the need to establish recommended regimens for later-line treatments after first-line chemotherapy. As such, the approval of nivolumab may change the chemotherapeutic strategy for the clinical management of patients with advanced gastric cancer. However, the prognostic impact of chemotherapeutic changes remains unclear, with only a few studies comparing post-progression chemotherapy (PPC) between patients receiving chemotherapy before and after nivolumab approval.

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Therefore, the present study aimed to compare the clinicopathological factors, PPC, and prognosis between patients receiving chemotherapy before and after nivolumab approval and assess the prognostic significance of chemotherapeutic changes, including PPC, in patients with advanced gastric cancer.

Patients and Methods

Patients. A total of 146 patients (92 men and 54 women; age range=30-90 years; median age=69.5 years) with unresectable gastric cancer who had at least progressive disease (PD) after first- and/or second-line chemotherapy at Kagoshima University Hospital (Kagoshima, Japan) between June 2007 and October 2019 were retrospectively reviewed. Patients with synchronous or metachronous malignancies in other organs and disease recurrence were excluded. All patients were categorized and staged based on the TNM classification for gastric carcinoma (11). This retrospective study was approved by the Ethics Committee of Kagoshima University in accordance with the Declaration of Helsinki (approval number: 200182). Written informed consent was obtained from all patients.

Assessment of tumor response and post-progression chemotherapy. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (12). PPC was clinically indicated for patients with a performance status of at least 0-2, preserved major organ function, and PD after first- or second-line chemotherapy. Moreover, PPC was comprehensively determined based on the patient's conditions, serum levels of carcinoembryonic antigen or carbohydrate antigen 19-9, and physician's selection of patients with non-measurable lesions.

Statistical analysis. The relationship between nivolumab approval status and clinicopathological factors, including PPC after first- or second-line chemotherapy, was assessed using the chi-square test, Fisher's exact test, or Wilcoxon rank-sum test. Overall survival (OS) was defined as period from first-line chemotherapy initiation to death or last follow-up. Kaplan-Meier survival curves were generated, while prognostic differences were determined using the log-rank test. Prognostic factors were assessed using univariate and multivariate analyses (Cox proportional hazard regression model). All data were analyzed using JMP14 (SAS Institute Inc., Cary, NC, USA), with a p-value of <0.05 indicating statistical significance.

Results

Patient characteristics. Patients' clinicopathological factors are summarized in Table I. Among the 146 patients, 1, 15, and 130 had clinical T2, T3, and T4 tumors, respectively. Moreover, 24, 29, 41, and 52 patients had a clinical lymph node status of N0, N1, N2, and N3, respectively. All patients had distant metastasis, including peritoneal dissemination (n=99), liver metastasis (n=31), lung metastasis (n=3), and distant lymph node metastasis (n=40), with 112 and 34 patients having one and more than two distant metastatic sites, respectively. Among the patients enrolled herein, 46 and 23 received ramucirumab therapy after first- or later-line treatments and nivolumab therapy after second- or later-line treatments, respectively. Furthermore, 95 and 62 patients underwent PPC after first- and second-line chemotherapy, respectively.

Table I. *Clinicopathological features (n=146).*

Factor		n (%)
Gender	Male	92 (63.0)
	Female	54 (37.0)
Median age (range), years		69.5 (30-90)
Tumor location	Whole	30 (20.5)
	Upper	57 (39.0)
	Middle	25 (17.1)
	Lower	34 (23.3)
Macroscopic type	Type 1	3 (2.1)
	Type 2	11 (7.5)
	Type 3	81 (55.5)
	Type 4	49 (33.6)
	Type 5	2 (1.4)
Depth of tumor invasion	cT2	1 (0.7)
	cT3	15 (10.3)
	cT4	130 (89.0)
Lymph node metastasis	cN0	24 (16.4)
	cN1	29 (19.9)
	cN2	41 (28.1)
	cN3	52 (35.6)
Distant metastasis	M0	0 (0.0)
	M1	146 (100.0)
Number of distant metastatic sites	1	112 (76.7)
	2	26 (17.8)
	3	7 (4.8)
	4	1 (0.7)
Peritoneal dissemination	Absence	47 (32.2)
	Presence	99 (67.8)
Liver metastasis	Absence	115 (78.8)
	Presence	31 (21.2)
Lung metastasis	Absence	143 (97.9)
	Presence	3 (2.1)
Distant lymph node metastasis	Absence	106 (72.6)
	Presence	40 (27.4)
Histological type	Differentiated	32 (21.9)
	Undifferentiated	114 (78.1)
Ramucirumab treatment	Absence	100 (68.5)
	Presence	46 (31.5)
Nivolumab treatment	Absence	123 (84.2)
	Presence	23 (15.8)
Post-progression chemotherapy after first-line chemotherapy	Absence	51 (34.9)
	Presence	95 (65.1)
Post-progression chemotherapy after second-line chemotherapy	Absence	84 (57.5)
	Presence	62 (42.5)

Given that nivolumab was approved for use in Japan on September 22, 2017, patients were subsequently divided into the following two groups based on the nivolumab approval date for further analysis: Group A (those who terminated chemotherapy before nivolumab approval) and group B (those receiving at least chemotherapy after nivolumab

Table II. *Relationship between nivolumab approval status and clinicopathological findings.*

Factor	Therapeutic period, n (%)		*p*-Value
	Group A (Before nivolumab approval, n=98)	Group B (After nivolumab approval, n=48)	
Gender			0.8562
Male	61 (62.2)	31 (64.6)	
Female	37 (37.8)	17 (35.4)	
Mean age, years	67.7±10.8	63.8±15.0	0.2490
Tumor location			1.0000
Whole/upper	58 (59.2)	29 (60.4)	
Middle/lower	40 (40.8)	19 (39.6)	
Macroscopic type			1.0000
Type non-4	65 (66.3)	32 (66.7)	
Type 4	33 (33.7)	16 (33.3)	
Depth of tumor invasion			1.0000
cT2	1 (1.0)	0 (0.0)	
cT3-4	97 (99.0)	48 (100.0)	
Lymph node metastasis			0.8542
cN0-2	64 (65.3)	30 (62.5)	
cN3	34 (34.7)	18 (37.5)	
Number of distant metastatic sites			0.8352
1	76 (77.6)	36 (75.0)	
≥2	22 (22.4)	12 (25.0)	
Peritoneal dissemination			0.2580
Absence	35 (35.7)	12 (25.0)	
Presence	63 (64.3)	36 (75.0)	
Liver metastasis			0.3953
Absence	75 (76.5)	40 (83.3)	
Presence	23 (23.5)	8 (16.7)	
Lung metastasis			1.0000
Absence	96 (98.0)	47 (97.9)	
Presence	2 (2.0)	1 (2.1)	
Distant lymph node metastasis			0.2412
Absence	68 (69.4)	38 (79.2)	
Presence	30 (30.6)	10 (20.8)	
Histological type			0.5303
Differentiated	20 (20.4)	12 (25.0)	
Undifferentiated	78 (79.6)	36 (75.0)	
Ramucirumab treatment			<0.0001
Absence	82 (83.7)	18 (37.5)	
Presence	16 (16.3)	30 (62.5)	
Nivolumab treatment			<0.0001
Absence	98 (100.0)	25 (52.1)	
Presence	0 (0.0)	23 (47.9)	

approval). Accordingly, 98 and 48 patients were classified into groups A and B, respectively.

Relationship between nivolumab approval status and clinicopathological factors. A total of 16 (16.3%) and 30 (62.5%) patients underwent ramucirumab therapy in groups A and B, respectively. Accordingly, a significant correlation was observed between nivolumab approval status and the presence or absence of ramucirumab therapy ($p<0.0001$) (Table II). Unsurprisingly, none of those in group A underwent nivolumab therapy, whereas 23 (47.9%) patients in group B underwent nivolumab therapy ($p<0.0001$) (Table II). No significant relationships between nivolumab approval status and other clinicopathological findings, such as age, depth of tumor invasion, lymph node metastasis, and number of distant metastatic sites were noted (all $p>0.05$) (Table II).

Relationship between nivolumab approval status and post-progression chemotherapy. A total of 53 (54.1%) and 42 (87.5%) patients received PPC after first-line chemotherapy (Figure 1), whereas 26 (26.5%) and 36 (75.0%) patients received PPC after second-line chemotherapy in groups A and

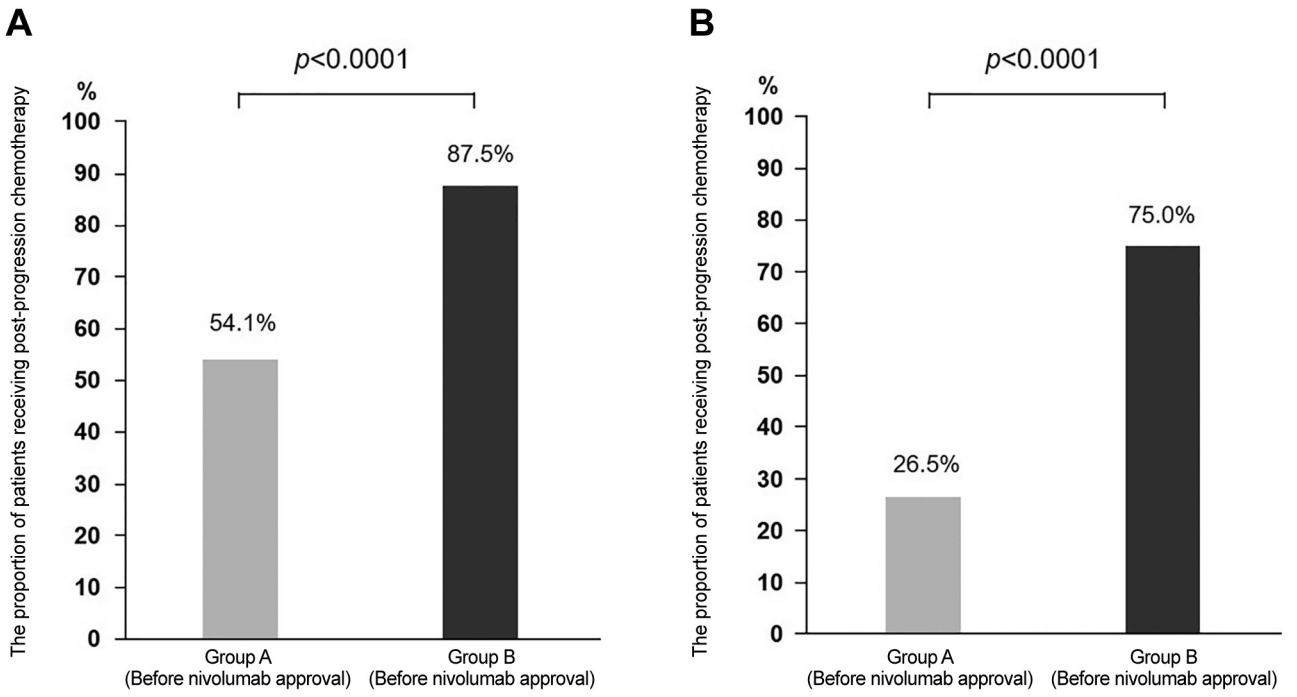

Figure 1. *The proportion of patients receiving post-progression chemotherapy after first- or second-line chemotherapy. A) after first-line chemotherapy. B) after second-line chemotherapy.*

B, respectively (Figure 1). Consequently, nivolumab approval status was significantly associated with PPC after first- and second-line chemotherapy (all $p<0.0001$) (Figure 1).

Prognostic analysis based on nivolumab approval status. Groups A and B had a median survival time of 412 and 669 days, respectively (Figure 2). Accordingly, group A had significantly worse prognosis than group B ($p=0.0002$) (Figure 2).

Univariate analysis showed that age (<70 *vs.* ³70), number of distant metastatic sites (1 *vs.* ³2), ramucirumab therapy, and nivolumab therapy were significantly correlated with survival ($p=0.0427$, $p=0.0253$, $p=0.0005$, and $p=0.0025$, respectively) (Table III). Multivariate analysis identified age, number of distant metastatic sites, and ramucirumab therapy as independent prognostic factors ($p=0.0252$, $p=0.0036$, and $p=0.0076$, respectively) (Table III).

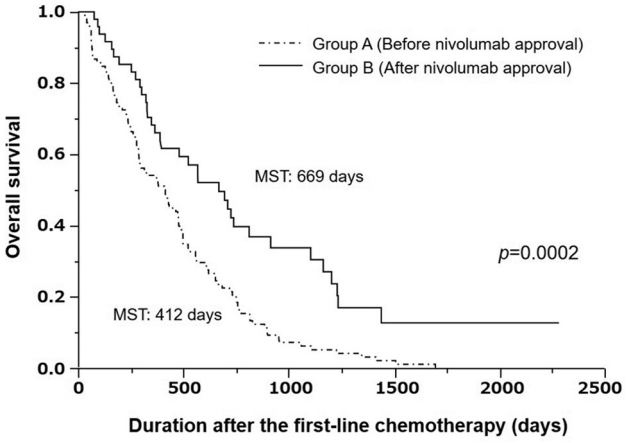

Figure 2. *Kaplan-Meier survival curves according to nivolumab approval status.*

Discussion

Recent advancements in chemotherapy have prompted the Japanese Gastric Cancer Treatment Guidelines 2018 to establish recommended regimens for each line. In particular, the aforementioned guidelines have considered molecular targeted drugs, such as trastuzumab and ramucirumab, as potential agents for first- or second-line treatments, while recommending nivolumab for third-line treatment (7). Given that establishing recommended regimens for each line supports the selection of anti-cancer agents, administering PPC after first- or second-line treatments may be clinically straightforward. To our knowledge, no clinical study has yet assessed the prognostic significance of chemotherapeutic changes,

Table III. *Univariate and multivariate analyses of survival.*

	Univariate analysis			Multivariate analysis		
Independent factor	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Gender			0.0774			
Female	1.000	Reference				
Male	1.379	0.965-1.971				
Age (years)			0.0427			0.0252
<70	1.000	Reference		1.000	Reference	
≥70	1.436	1.012-2.037		1.498	1.052-2.133	
Tumor location			0.6418			
Middle/lower	1.000	Reference				
Whole/upper	1.086	0.766-1.540				
Macroscopic type			0.7824			
Type non–T4	1.000	Reference				
Type 4	0.950	0.663-1.363				
Depth of tumor invasion			0.8803			
cT2-3	1.000	Reference				
cT4	1.043	0.602-1.807				
Lymph node metastasis			0.1418			
cN0-2	1.000	Reference				
cN3	1.306	0.915-1.865				
Number of distant metastatic sites			0.0253			0.0036
1	1.000	Reference		1.000	Reference	
≥2	1.595	1.060-2.402		1.860	1.225-2.824	
Histological type			0.3998			
Differentiated	1.000	Reference				
Undifferentiated	1.207	0.779-1.870				
Ramucirumab treatment			0.0005			0.0076
Absence	1.000	Reference		1.000	Reference	
Presence	0.501	0.338-0.741		0.555	0.360-0.855	
Nivolumab treatment			0.0025			0.0572
Absence	1.000	Reference		1.000	Reference	
Presence	0.423	0.242-0.739		0.553	0.300-1.018	

CI: Confidence interval.

including PPC, in patients with unresectable advanced gastric cancer. Taken together, the current study has been the first to examine the association between prognosis and chemotherapeutic changes after nivolumab approval.

Ramucirumab had been approved for use in Japan on March, 2015 for the treatment of unresectable advanced or recurrent gastric cancer. Consequently, group A used ramucirumab between March 2015 and September 2017. This study found that 16 (16.3%) and 30 (62.5%) patients received ramucirumab in groups A and B, respectively. Furthermore, 0 (0%) and 23 (47.9%) patients received nivolumab in groups A and B, respectively. The aforementioned results indicate that group B had higher utilization rates of ramucirumab and nivolumab than group A, suggesting variations in chemotherapeutic regimens due to the advent of new anti-cancer agents, such as molecular targeted drugs and immune checkpoint inhibitors.

The current study demonstrated that group B had a higher proportion of patients receiving PPC after first- or second-line chemotherapy compared to group A. In particular, PPC initiation rates after second-line chemotherapy differed dramatically between both groups (26.5% *vs*. 75.0%). The Japanese Gastric Cancer Treatment Guidelines 2018 recommends nivolumab or irinotecan monotherapy as third-line chemotherapy (7). Moreover, the Japanese Gastric Cancer Association recommends trifluridine/tipiracil for third-line chemotherapy based on the results of the TAGS trial (13). Collectively, the development of recommended regimens for later-line chemotherapy may lead to increased PPC initiation rates after first- or second-line chemotherapy through active physician involvement. Furthermore, Takashima *et al*. reported that 69%-85% and 11%-59% of patients in Japanese and non-Japanese clinical trials received second-line chemotherapy after first-line chemotherapy failure, respectively (14). These findings suggest intercountry differences in PPC initiation, with Japanese trials, including our retrospective study, administering PPC initiation after first- or second-line chemotherapy.

The present study observed a significant difference in prognosis between both groups (p=0.0002). Additionally, multivariate analysis identified ramucirumab therapy as an independent prognostic factor. Unfortunately, although univariate analysis identified nivolumab therapy as an independent prognostic factor (p=0.0025), multivariate analysis did not (p=0.0572). Our sample size may be small for the evidence of valid differences in multivariate analysis. However, the objective response rate and disease control rate to nivolumab in patients with target lesions were 27.3% (3/11) and 63.6% (7/11), respectively. Interestingly, several investigators have shown that nivolumab exposure may promote subsequent chemosensitivity in patients with advanced gastric cancer (15, 16). Indeed, Kato *et al*. reported an overall response rate of 31% and 10% in patients receiving subsequent cytotoxic chemotherapy after immunotherapy and third-line treatment without previous immunotherapy, respectively (16). These results suggest that novel anti-cancer agents, such as ramucirumab or nivolumab, show promise in improving the prognosis of patients with unresectable advanced gastric cancer. Furthermore, Iizumi *et al*. reported that higher PPC initiation rates after first- and second-line chemotherapy were correlated with longer OS and post-progression survival in patients with advanced gastric cancer, suggesting that second- and third-line chemotherapy might improve survival (17). The current study found that group B had higher PPC initiation rates after first- and second-line chemotherapy and better prognosis than group A, indicating a close relationship between PPC and prognosis in patients with advanced gastric cancer receiving chemotherapy.

The present study has several limitations worth noting. First, this was a single-center retrospective study consisting of a small population (n=146). Second, chemotherapy regimens for each line were clinically selected based on the Japanese Gastric Cancer Treatment Guidelines. However, varying chemotherapy regimens had been administered considering clinical trial registration, patient conditions, or physician discretion. These limitations might have resulted in bias, which could adversely influence our results. For such reasons, larger studies are warranted to strengthen the conclusions presented herein.

In conclusion, our retrospective study suggested that changes in chemotherapeutic strategy might contribute to improved prognosis in patients with advanced gastric cancer.

Conflicts of Interest

All Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

T.A., D.M., K.O., T.T., K.S., Y.T., Y.K., S.M., H.K., Y.U., and T.O. contributed to the study design. T.A., D.M., K.O., T.T., K.S., and Y.T. were involved in data collection and data interpretation. T.A., Y.K., S.M., H.K., Y.U., and T.O. contributed to the statistical analyses. T.A. wrote the manuscript. All Authors have read and approved the final manuscript.

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