



# Delivery rate of patients with advanced gastric cancer to third-line chemotherapy and those patients' characteristics: an analysis in real-world setting

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**Background:** Nivolumab has recently become available for third-line chemotherapy of advanced gastric cancer in Japan. The drug is expected to provide long-term survival in some patients. However, not all patients receive third-line therapy. In this study, we investigated the frequency of prescribing and the predictive factors for prescribing of third-line chemotherapy for patients with advanced gastric cancer.

**Methods:** We retrospectively analyzed the medical records of 271 patients with unresected advanced gastric cancer who had started chemotherapy between January 2006 and June 2017 at Kurashiki Central Hospital. Patients' median age was 68 years, and 190 patients were male. We compared baseline characteristics of patients who did or did not receive third-line chemotherapy and, through multivariate logistic-regression analysis, identified potential predictive factors for receiving third-line chemotherapy.

**Results:** Among the 271 patients, 71 (26.2%) received third-line chemotherapy. In the univariate analysis, the rate of receiving this care was significantly related to patients' performance status, cancer histology, and several laboratory variables at baseline. Multivariate analysis revealed that performance status 0 and serum C-reactive protein levels  $\leq 0.6$  mg/dL were independent and significant predictive factors for administration of the third-line chemotherapy; adjusted odds ratios of the two factors were 4.17 (95% confidence interval, 2.13–8.15) and 2.46 (1.19–5.08), respectively.

**Conclusions:** In this real-world study, only 26.2% of patients received third-line chemotherapy. Poor performance status and high serum C-reactive protein value at the start of first-line chemotherapy were significantly associated with lower frequency of administration of third-line chemotherapy.

**Keywords:** Gastric cancer; third-line chemotherapy; performance status (PS); C-reactive protein (CRP)

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## Introduction

Gastric cancer is the fifth most common cancer and the third most common cause of cancer mortality worldwide (1). In Japan, nearly 45,000 people die from gastric cancer annually (2). Efforts to improve the outcome of gastric cancer remain a major medical issue. Since ipilimumab, an anti-CTLA-4 antibody, improved overall survival of

patients with metastatic melanoma (3), immune checkpoint inhibitors (ICIs) have been spotlighted for treatment of various types of cancers (3–8).

A recent study has found a significant survival benefit of nivolumab, an anti-PD-1 ICI, for patients with advanced gastric cancer (AGC) who had received two or more previous chemotherapy regimens (9). The results of that

**Table 1** Patients' baseline characteristics

Characteristics	Total, n=271
Age, median [IQR], years	68 [62–74]
Sex, n (%)	
Male	190 (70.1)
Female	81 (29.9)
BMI, median (IQR), kg/m <sup>2</sup>	21.3 (18.9–23.6)
ECOG PS, median [IQR]	1 [0–1]
Tumor site, n (%)	
Esophagogastric junction	22 (8.1)
Stomach	249 (91.9)
Histology, n (%)	
Intestinal	83 (30.6)
Diffuse	179 (66.1)
Indeterminable	9 (3.3)
HER2 status, n (%)	
Positive	17 (6.3)
Negative	92 (33.9)
Unknown	162 (59.8)
Ascites, n (%)	
Presence	142 (52.4)
Absence	124 (45.8)
Unknown	5 (1.8)
Number of organs with metastases, median [IQR]	2 [1–2]

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; HER2, human epidermal growth factor receptor type 2; IQR, interquartile range.

study led to approval of nivolumab for treatment of third-line chemotherapy for AGC in some countries, including Japan. Before that, irinotecan or other cytotoxic agents had been used for third-line treatment, but long-term survival was difficult to achieve with those drugs (10–14). Nivolumab has provided longer survival time in some patients with AGC (9), thus increasing expectations of benefits with this third-line chemotherapy. However, no reports have focused on the rate of AGC patients receiving this drug or on predictors for the possibility of their receiving it in the real-world setting. Thus, we addressed these issues in the

present study conducted in a community hospital in Japan.

## Methods

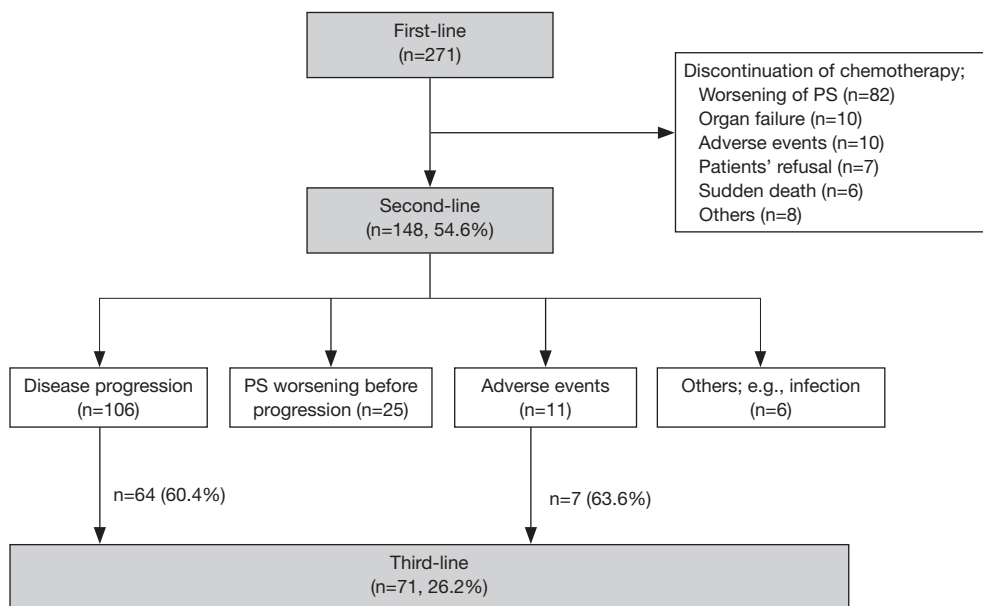
We retrospectively reviewed medical records of patients with locally unresectable gastric cancer or with distant metastasis who had been treated in Kurashiki Central Hospital. Eligible patients had histologically diagnosed gastric cancer, including adenocarcinoma at the esophagogastric junction. They had started chemotherapy between January 2006 and June 2017. Patients with recurrent gastric cancer after radical surgery and those who were still receiving chemotherapy on March 2018 were excluded.

Chemotherapy regimens were decided according to the latest national guidelines in Japan at the time of treatment (15–18). The following changes of regimen were not considered changes of the treatment line: (I) addition of trastuzumab at identification of HER2 overexpression, and (II) withdrawal of one of the agents in combined chemotherapy due to adverse events, e.g., from S-1 (tegafur, gimeracil and oteracil potassium) plus cisplatin to S-1 monotherapy.

Baseline patients' clinicopathologic and laboratory data were compared between the two groups: those who had proceeded to the third-line chemotherapy and those had not. In this study, the term "baseline" means the moment of the starting of the first-line chemotherapy. Continuous variables, expressed as median (interquartile range) or means  $\pm$  standard deviation, were compared using the Mann-Whitney U test or Student's *t*-test. Categorical variables, expressed as numbers (percentages), were compared using Chi-square test. Univariate analysis was conducted to identify potential predictive factors for the delivery of the third-line treatment. Factors with P values  $<0.05$  were then taken to a multivariate logistic-regression analysis. All statistical analyses were performed with the EZR software program (Saitama Medical Center, Saitama, Japan) (19).

## Results

Two hundred seventy-one patients were included in this study. Their baseline clinicopathologic characteristics are listed in *Table 1*. One hundred forty-eight patients (54.6%) received second-line chemotherapy. Among them, 71 (26.2%) in total proceeded to third-line chemotherapy;



**Figure 1** Patients flow. PS, performance status.

64 patients (60.4%) of 106 patients with disease progression and 7 (63.6%) of 11 patients with adverse events (Figure 1). The reasons for not proceeding to third-line chemotherapy after disease progression were performance status (PS) deterioration (37 patients), organ function inadequate for further chemotherapy (3 patients), infection (1 patient), and patient's refusal (1 patient).

The chemotherapy regimens and median survival time from the start of each line of chemotherapy are listed in Table 2. S-1 plus cisplatin, paclitaxel monotherapy, and irinotecan monotherapy were the most frequently used regimen for the first, second, and third-line treatment, respectively. The median survival time from the start of third-line treatment was approximately 5 months.

Characteristics of patients who received the third-line chemotherapy (n=71) and those who did not (n=200) were compared (Table 3). There were significant differences between the two populations in Eastern Cooperative Oncology Group (ECOG) PS, tumor histology, and these laboratory markers: hemoglobin, percentages of peripheral blood lymphocytes, total protein, albumin, blood urea nitrogen, and C-reactive protein (CRP). The two populations were not significantly different in age, gender, body mass index, tumor site, HER2 status, ascites status, numbers of organs with metastases, the serum tumor markers carcinoembryonic antigen and carbohydrate antigen 19-9, and several routine laboratory blood tests

(white blood cell count, platelet count, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, lactic dehydrogenase, alkaline phosphatase, blood urea nitrogen, and serum creatinine).

The factors mentioned above with significant differences between the two patient groups were analyzed to determine predictive variables for the administration of third-line chemotherapy; cut-off values of continuous variables were determined by creating receiver operating characteristics curves (Table 4). Hemoglobin, which had no appropriate cut-off value, was not included in the analysis. In the univariate analysis, ECOG PS 0, intestinal-type tumor histology, peripheral blood lymphocytes  $\geq 19\%$ , total serum protein  $\geq 6.4$  g/dL, serum albumin  $\geq 3.3$  g/dL, blood urea nitrogen  $\leq 14$  mg/dL, and CRP  $\leq 0.6$  mg/dL were significantly associated with the administration of third-line chemotherapy. In the multivariate logistic-regression analysis, ECOG PS 0 (odds ratio, 4.17; 95% CI, 2.13–8.15) and CRP  $\leq 0.6$  mg/dL (odds ratio, 2.46; 95% CI, 1.19–5.08) were the significant and independent predictors for the administration of the third-line chemotherapy.

The number and percentages of patients who received third-line chemotherapy, according to ECOG PS and serum CRP values, are illustrated in Figure 2. The percentage of third-line chemotherapy was 55.0% when patients had good PS (0) and serum CRP values  $\leq 0.6$  mg/dL, whereas the rate was only 5.1% when patients had poor

**Table 2** Chemotherapy regimens and median survival time from the start of each line of chemotherapy

Variables	Total, n=271
First-line regimen, n (%)	
S-1 + cisplatin	144 (53.1)
S-1 + oxaliplatin	24 (8.9)
S-1 monotherapy	73 (26.9)
Trastuzumab containing regimen	7 (2.6)
Others	23 (8.5)
Second-line regimen, n (%)	
Paclitaxel + ramucirumab	12 (8.1)
Paclitaxel or docetaxel monotherapy	77 (52.0)
Irinotecan monotherapy	35 (23.6)
Others	24 (16.2)
Third-line regimen, n (%)	
Irinotecan monotherapy	35 (49.3)
Paclitaxel or docetaxel monotherapy	23 (32.4)
Nivolumab	1 (1.4)
Others	12 (16.9)
Survival time from the start of the first line, median [IQR], days	234 [133–486]
Survival time from the start of the second line, median [IQR], days	166 [102–323]
Survival time from the start of the third line, median [IQR], days	151 [87–239]

IQR, interquartile range.

PS ( $\geq 1$ ) and CRP values  $>0.6$  mg/dL.

## Discussion

In this study, we found that only a quarter of AGC patients received third-line chemotherapy in a real-world practice in Japan. Most reported studies on third-line chemotherapy in AGC have been in trial settings. We found also that patients' baseline ECOG PS and serum CRP values at the start of first-line chemotherapy were significantly associated with the administration of third-line chemotherapy.

To the best of our knowledge, this is the first study that focused on the frequency of AGC patients receiving third-line chemotherapy. In clinical trials, rates of advancing chemotherapy from first-line to second-line

therapy were 38–75% (20–22) and from second to third-line 45–48% (23). Corresponding rates in our study were similar—54.6% and 48.0%, which means that only 26.2% of our AGC patients received third-line chemotherapy. This relatively low rate has prompted us to consider ways in which the frequency of treating AGC patients with third-line therapy can be improved, e.g., starting third-line therapy earlier in the progression of chemotherapy regimens. However, studies with pembrolizumab, an anti-PD-1 ICI, for second-line treatment (24) and with avelumab, an anti-PD-L1 ICI for third-line treatment (25), did not find superiority of these ICIs over conventional cytotoxic agents; thus, earlier administration of these drugs may not be advantageous. Nivolumab, though, has been reported to have survival benefits as well as other important features not seen with other cytotoxic agents, such as long-lasting effects and excellent safety profile in heavily pretreated AGC patients. Thus, earlier start of nivolumab and related drugs may be considered in some situations.

We found that patients' ECOG PS and serum CRP levels at baseline were significantly associated with the administration of third-line chemotherapy. ECOG PS and CRP are reported to predict prognosis of patients with metastatic gastric cancer (26,27). In our study, the delivery of third-line therapy was well stratified according to the two factors. Validation of this simple approach to predict the possibility for AGC patients to proceed to third-line chemotherapy is warranted in future study. Tumor histology, known as another prognostic factor for AGC patients (28), tended to be associated with the administration of third-line therapy ( $P=0.066$ ), but did not reach statistical significance.

It is also important to determine whether nivolumab should be used earlier in lines of therapy, i.e., in second or even in first-line therapy. Currently, several phase III randomized controlled trials are evaluating the efficacy of ICIs in first-line therapy for AGC. If those trials meet the primary endpoints, the chance to use this ICI for AGC patients will increase.

Limitations of this study are: first, it is a retrospective, single-center study. Second, the study did not include patients with recurrent gastric cancer after radical surgery. Third, the study covered more than ten years, and treatment strategies for AGC changed significantly during the period. Only 8.1% of AGC patients had received ramucirumab plus paclitaxel for second-line therapy, which is the most-recommended regimen in the current guidelines in Japan (18); such changes could have influenced our findings.

**Table 3** Baseline characteristics of patients who did or did not receive third-line chemotherapy

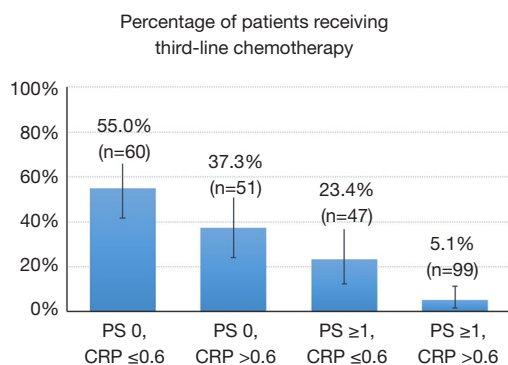
Characteristics	3rd-line therapy (n=71)	No 3rd-line (n=200)	P value
Age, median (IQR), years	66.0 (62.0–73.5)	69.0 (62.8–74.3)	0.151
Sex, n (%)			1
Male	50 (70.4)	140 (70.0)	
Female	21 (29.6)	60 (30.0)	
BMI, median (IQR), kg/m <sup>2</sup>	21.5 (19.3–23.7)	21.1 (18.6–23.5)	0.462
ECOG PS, median [IQR]	0 [0–1]	1 [0–1]	<0.001
Tumor site, n (%)			1
Esophagogastric junction	6 (8.5)	16 (8.0)	
Stomach	65 (91.5)	184 (92.0)	
Histology, n (%)			0.02
Intestinal	29 (40.8)	54 (27.0)	
Diffuse	37 (52.1)	142 (71.0)	
Indeterminable	5 (7.0)	4 (2.0)	
HER2 status, n (%)			0.428
Positive	2 (2.8)	15 (7.5)	
Negative	22 (31.0)	70 (35.0)	
Unknown	47 (66.2)	115 (57.5)	
Ascites, n (%)			0.101
Presence	31 (43.7)	111 (55.5)	
Absence	39 (54.9)	85 (42.5)	
Unknown	1 (1.4)	4 (2.0)	
Number of metastatic organs, median [IQR]	2 [1–2]	2 [1–2]	0.204
Hb, mean ± SD (g/dL)	11.4±2.3	10.7±2.3	0.022
WBC, median (IQR) (/μL)	6,400 (5,600–8,100)	7,100 (5,600–8,900)	0.117
Lym, median (IQR) (%)	19.8 (16.2–27.2)	18.0 (12.9–25.1)	0.013
TP, mean ± SD (g/dL)	6.4±0.6	6.1±0.7	0.002
ALB, median (IQR) (g/dL)	3.5 (3.1–3.8)	3.1 (2.7–3.5)	<0.001
BUN, median [IQR] (mg/dL)	13 [11–15]	14 [11–19]	0.03
CRP, median (IQR) (mg/dL)	0.40 (0.12–1.37)	1.09 (0.34–3.97)	<0.001
CEA, median (IQR) (ng/mL)	5.5 (2.8–40.3)	5.4 (2.4–42.4)	0.945
CA19-9, median (IQR) (U/mL)	31.7 (11.4–807)	55.4 (7.7–607)	0.788

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; HER2, human epidermal growth factor receptor type2; Hb, hemoglobin; WBC, white blood cells; Lym, lymphocytes; TP, total protein; ALB, albumin; BUN, blood urea nitrogen; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

**Table 4** Univariate and multivariate analyses of predictors for treatment with third-line chemotherapy

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
ECOG PS (0 vs. $\geq 1$ )	6.39 (3.48–11.70)	<0.001	4.17 (2.13–8.15)	<0.001
Histology (intestinal vs. diffuse)	2.06 (1.16–3.68)	0.014	1.88 (0.96–3.68)	0.066
Hb, g/dL ( $\geq 11$ vs. <11)	1.57 (0.91–2.72)	0.105	–	–
Lym, % ( $\geq 19$ vs. <19)	1.87 (1.08–3.24)	0.026	0.84 (0.42–1.70)	0.633
TP, g/dL ( $\geq 6.4$ vs. <6.4)	2.20 (1.27–3.81)	0.005	1.84 (0.90–3.74)	0.093
Alb, g/dL ( $\geq 3.3$ vs. <3.3)	3.88 (2.18–6.89)	<0.001	1.83 (0.84–3.99)	0.130
BUN, mg/dL ( $\leq 13$ vs. >13)	1.85 (1.05–3.27)	0.034	1.84 (0.94–3.63)	0.076
CRP, mg/dL ( $\leq 0.6$ vs. >0.6)	3.65 (2.07–6.46)	<0.001	2.46 (1.19–5.08)	0.015

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; Hb, hemoglobin; Lym, lymphocytes; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; CRP, C-reactive protein.



**Figure 2** The number and percentage of patients who received third-line chemotherapy, according to ECOG PS and serum CRP values. The bars represent the percentages of third-line chemotherapy received, and the whiskers represent 95% confidence intervals. ECOG, Eastern Cooperative Oncology Group; PS, performance status; CRP, C-reactive protein.

In conclusion, the present study showed that only 26.2% of patients received third-line chemotherapy and that their baseline PS and serum CRP levels were associated with the delivery to the therapy. How we raise the chance for AGC patients to receive therapy with expected effect such as nivolumab needs further study.

### Acknowledgments

None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statements:* All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Kurashiki Central Hospital Ethics Committee reviewed and approved this study (No. 2872). In this study, patient data were retrieved from hospital medical record system. Therefore, informed consent was obtained in an opt-out system. The authors expect that the study outcomes will affect the future management of the patients and they declare that the patients' personal data have been secured.

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