Efficacy of ramucirumab and subsequent nivolumab therapy in patients with advanced gastric cancer: A retrospective study

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Abstract. Nivolumab monotherapy is a standard treatment of metastatic gastric cancer, and this type of cancer involves vascular endothelial growth factor (VEGF) signaling in the tumor immunological environment. The subgroup analysis of the ATTRACTION-2 trial revealed that prior treatment with ramucirumab (RAM), a VEGF inhibitor, affected the therapeutic effect of nivolumab. The present retrospective study aimed to review patients with metastatic gastric cancer who were treated with paclitaxel (PTX) and RAM followed by nivolumab. A total of 29 patients with metastatic gastric cancer were treated with PTX + RAM as second-line treatment, followed by nivolumab monotherapy as third-line treatment. The therapeutic efficacy of nivolumab was compared in 13 patients with progression-free survival (PFS) of <5 months and 16 patients with PFS ≥5 months after PTX + RAM therapy. The present study included 22 male and seven female patients, with a median age of 68 years (range, 45-82 years). Human epidermal growth factor receptor 2 positivity was observed in six patients. The disease control rate was 62.1%. The PFS and overall survival (OS) were 4.4 and 11.9 months, respectively. Patients with PFS ≥5 months after PTX + RAM therapy showed better outcome in both PFS (5.3 months vs. 2.8 months, P=0.039) and OS (6.9 months vs. 15.2 months, P=0.066) after nivolumab treatment than patients with PFS of <5 months after PTX + RAM therapy. However, no significant relationship was observed between the outcome of first-line treatment and nivolumab. The therapeutic effect of nivolumab was associated with prior PTX + RAM treatment in advanced gastric cancer.

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Abbreviations: VEGF, vascular endothelial growth factor; RAM, ramucirumab; PTX, paclitaxel; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; MSI, microsatellite instability; 5FU, fluorouracil; ICI, immune checkpoint inhibitor; NE, no evaluation

Key words: nivolumab, PTX, RAM, metastatic gastric cancer, PFS, OS

Introduction

According to World Health Organization cancer statistics, gastric cancer is the second most common malignancy and the fourth most common cause of cancer mortality worldwide (1). Prognosis has gradually improved because of advances in chemotherapy regimens, but is not yet satisfactory, and a permanent cure is rarely achieved.

Currently, the standard treatment for unresectable or metastatic gastric cancer is systemic chemotherapy. In Japan, combined induction chemotherapy with fluorouracil (5FU) and platinum is the current first-line standard therapy for unresectable or metastatic gastric cancer (2-5). For second-line therapy, the fourth edition of the Gastric Cancer Treatment Guidelines recommends three anticancer monotherapies, viz. paclitaxel (PTX), irinotecan, and docetaxel, as second-line therapy (6). PTX plus ramucirumab (RAM) showed additional efficacy compared with PTX monotherapy in the RAINBOW trial (7), making it the standard of care in the fifth edition of the Gastric Cancer Treatment Guidelines (8).

Chemotherapy has been shown to prolong survival in patients who received first- and second-line treatments for unresectable advanced/recurrent gastric cancer; however, no treatment has shown sufficient efficacy after third-line therapy. Previously, PTX and irinotecan as monotherapy were recommended for second- line therapy based on the results of the WJOG4007 trial (9). The recommended third-line regimen include nivolumab and irinotecan monotherapies (8). However, since PTX + RAM has become the standard of care for second-line therapy, irinotecan has been used as third-line treatment. Currently, no trials comparing irinotecan and nivolumab exist; therefore, it is unclear which drug should be administered first.

Nivolumab, a human IgG4 monoclonal antibody against the immune checkpoint molecule, programmed cell death-1 receptor, has shown efficacy and safety in various cancer types. It significantly prolonged survival compared with placebo in patients with unresectable advanced or recurrent

gastric cancer, who were treated with two or more chemotherapy regimens in the phase III ATTRACTION-2 trial (10). The subgroup analysis of this trial revealed that prior treatment with RAM, a vascular endothelial growth factor (VEGF) inhibitor, affected the therapeutic effect of nivolumab (11). VEGF signaling alters the tumor microenvironment and may affect the efficacy of immunotherapy (12-14).

Therefore, this study reviewed patients with unresectable or metastatic gastric cancer who were treated with second-line chemotherapy using PTX + RAM followed by nivolumab. Furthermore, we evaluated the outcomes of nivolumab treatment in selected patients who responded well to PTX + RAM treatment.

Patients and methods

Patients. Twenty-nine patients with metastatic gastric cancer were recruited for the present retrospective study. They were treated with PTX (80 mg/m^2) + RAM (8 mg/m^2) as second-line treatment, followed by nivolumab monotherapy (240 mg/body) as third-line treatment between January 2017 and October 2020 at the Saitama Medical Center, Jichi Medical University, Japan. The patients were >18 years old, and their Eastern Cooperative Oncology Group performance status (ECOG PS) was 0, 1, or 2. This study was approved by the Research Ethics Committee of Jichi Medical University (GC07-13). Written informed consent was obtained from all patients before receiving chemotherapy according to the Institutional Review Board instructions of Jichi Medical University. In addition to the ethical approval and informed consents, all methods were performed in accordance with the Declaration of Helsinki on ethical principles in conducting human research.

Efficacy and safety assessment. The incidences of adverse events, progression-free survival (PFS), and overall survival (OS) were assessed. PFS was defined as the time from the start of nivolumab therapy to either disease progression or death. OS was defined as the time from the start of nivolumab therapy to death from any cause. Tumors were evaluated every 2 or 3 months using computed tomography (CT) or positron emission tomography/CT imaging that was initially used to stage the tumor. Tumor response and progression were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0. Treatment was continued until disease progression, unacceptable toxicity, deterioration of the ECOG PS to >2, or withdrawal of patient consent.

Response criteria for target lesions. Response was assessed after two cycles of chemotherapy. Measurable tumors were evaluated according to the RECIST. Complete response (CR) was defined as the disappearance of all non-nodal target lesions, with each nodal target lesion having a reduction in the short axis of <10 mm. When nodal target lesions are selected at baseline, the sum of the diameters may not be 0 mm, even if the target lesion response is CR. Partial response (PR) was defined as a decrease of at least 30% in the sum of target lesion diameters, taking the baseline sum of diameters as reference. Progressive disease (PD) was defined as an increase of at least 20% in the sum of target lesion diameters, taking the smallest sum of diameters as reference (this includes the baseline sum if that is the smallest in the study). Stable disease (SD) was defined as insufficient tumor shrinkage to qualify as PR and insufficient tumor growth relative to the sum of the smallest longest diameters to qualify as PD. Owing to the absence of measurable lesions, no evaluation (NE) is difficult to determine. The sum of the diameters must demonstrate an absolute increase of at least 5 mm.

Statistical analysis. Statistical analyses were performed using StatView 5.0.1 (SAS Institute Inc., NC, USA). The OS and PFS curves were analyzed using the Kaplan-Meier method, and the differences between the groups were compared using the log-rank test. Prognostic factors, including, age, sex, ECOG PS, site of metastasis, previous gastrectomy, HER2 and MSI status, first-line chemotherapy, and PTX + RAM and nivolumab response, were analyzed for survival by multivariate analysis using the Cox proportional hazards model. All reported P-values were two-sided, and $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Baseline patient characteristics.

Characteristic	Value
Median age, years (range)	68 (45-82)
Sex (Male/Female)	22/7
ECOG PS (0/1/2/3)	8/17/4/0
Site of metastases	
Lymph node	3
Peritoneum	14
Liver	6
Lung	1
Pleura	0
Bone	1
Other	1
Previous gastrectomy	
No	17
Yes	12
HER2	
Positive	6
Negative	23
MSI	
High	2
Low	27
Previous treatment	
Any	29
Pyrimidine analogs	28
Platinum	27
Taxane	1
Trastuzumab	6

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability.

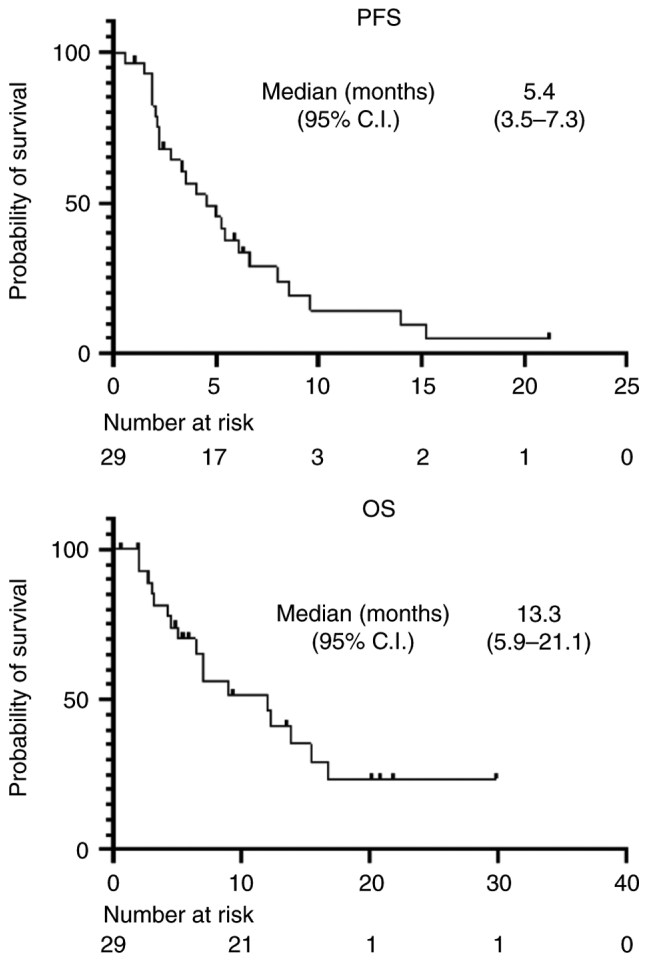

Figure 1. Kaplan-Meier curve analysis of PFS and OS. C.I., confidence interval; OS, overall survival; PFS, progression-free survival.

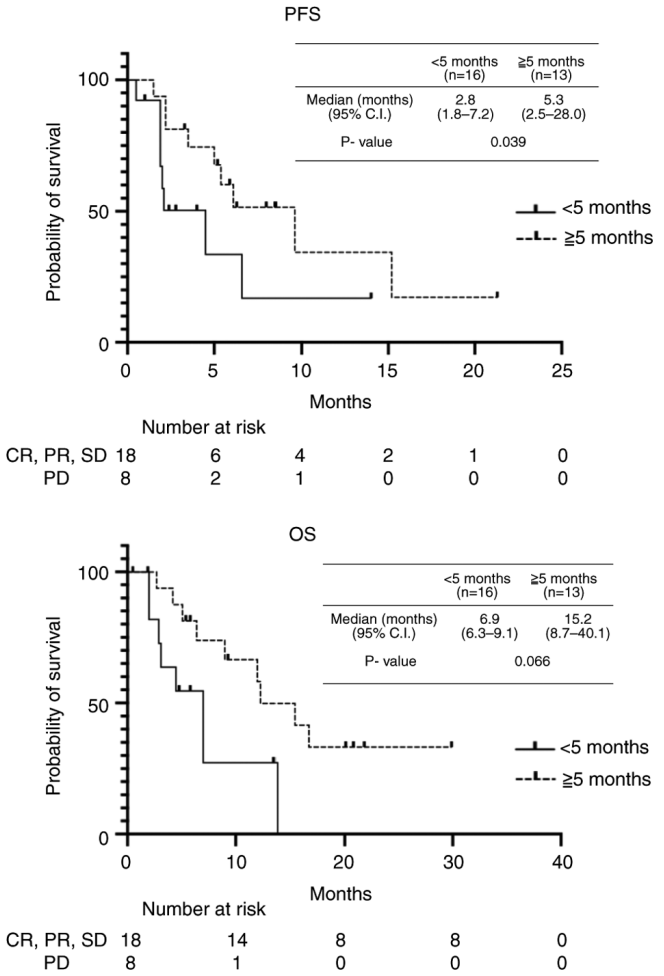

Figure 2. Kaplan-Meier curve analysis of PFS and OS by paclitaxel + ramucirumab response. C.I., confidence interval; CR, complete response; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

Results

Patient characteristics. The characteristics of the 29 patients (22 males and 7 females) are detailed in Table I. The median age of the patients was 68 years (range 45-82 years). ECOG PS 0, 1, and 2 were observed in eight, 17, and four patients, respectively. Gastrectomy was performed in 12 patients. Human epidermal growth factor receptor 2 (HER2) positivity was identified in six patients. High microsatellite instability (MSI-H) was observed in two patients. All patients were treated with a single regimen prior to PTX + RAM. All HER2-positive patients received combination therapy with trastuzumab. Approximately all HER2-negative patients received 5FU and platinum anti-tumor agents.

Efficacy. Nivolumab treatment showed CR, PR, SD, PD, and NE in 2 (7.0%), 4 (13.8%), 12 (41.4%), 8 (27.6%), and 3 patients (10.3%), respectively. The objective response rate (CR + PR) was 20.7%, and the disease control rate (CR + PR + SD) was 62.1%. The median PFS and OS were 4.4 months (3.3-7.1) and 14.9 months (9.9-24.0), respectively (Fig. 1).

The median PFS in patients after PTX + RAM treatment was 5.1 months (0.5-19.6); we analyzed the therapeutic effect of nivolumab in two groups: poor response (PFS <5 months after PTX + RAM therapy) and good response (PFS >5 months after PTX + RAM therapy) groups. The poor and good response groups included 13 and 16 patients, respectively. The good response group showed better outcome in both PFS and OS after nivolumab treatment than the poor response group (PFS: 5.3 vs. 2.8 months, P=0.039; OS: 15.2 vs. 6.9 months, P=0.066) (Fig. 2). In addition, we analyzed the therapeutic effect of nivolumab in two groups; poor response and good response to the first-line chemotherapy (PFS <9 months vs. PFS >9 months). The median PFS during first-line chemotherapy was 9.1 months (0.9-35.9) and the poor and good response groups included 14 and 15 patients, respectively. No difference in OS after nivolumab treatment was seen between the poor and good response group (10.1. vs. 11.6 months, P=0.566), which indicated that the first-line chemotherapy was not involved in the therapeutic effect of nivolumab.

Multivariate analyses showed a good response to PTX + RAM [hazard ratio (HR) 0.116, 95% confidence interval (CI) 0.037-0.742, P=0.019] as an independent prognostic factor for survival (Table II). Age, sex, ECOG PS, metastatic site, previous gastrectomy, HER2 status, MSI status, first-line chemotherapy, and nivolumab were not significantly associated with survival.

Table II. Results of multivariate analyses of associations between patient characteristics and survival.

Variable	P-value
PTX + RAM response (+/-)	0.019
Age (≤59/≥60 years)	0.990
Sex (male/female)	0.711
ECOG PS (0/1/2/3)	0.348
Site of metastases (peritoneum/others)	0.665
Previous gastrectomy (+/-)	0.816
HER2 (positive/negative)	0.278
MSI (high/low)	0.761
Response of first-line chemotherapy (response/no response)	0.543

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; MSI; microsatellite instability; PTX + RAM, paclitaxel + ramucirumab.

Discussion

In this study, the efficacy of nivolumab as a third-line treatment option was associated with the efficacy of prior PTX + RAM treatment in patients with advanced gastric cancer. The longer the PFS after pretreatment with PTX + RAM, the better the therapeutic effect of nivolumab. To our knowledge, this retrospective analysis is the first to show a therapeutic association between second-line PTX + RAM and third-line nivolumab treatment. This study on the therapeutic effect of PTX + RAM is a useful tool in actual clinical practice. Currently, the Japanese guidelines recommend nivolumab, CPT-11, and trastuzumab deruxtecan as third-line therapies for HER2-positive patients (8). Therefore, patients with HER2-positive gastric cancer were excluded from this study.

In the Japanese subgroup analysis of the ATTRACTION-2 trial, the overall PFS and OS were 1.7 and 5.4 months, respectively (11). In contrast, in this study, the overall PFS and OS were 4.4 and 14.9 months, respectively. Although a simple comparison could not be made, the PFS in the present study was more than twice the PFS observed in the Japanese subgroup analysis. Herein, all patients were treated with RAM + PTX as second-line treatment, followed by nivolumab monotherapy as third-line treatment. In contrast, in the above-mentioned Japanese subgroup analysis, several patients in the RAM + PTX group received nivolumab after treatment with irinotecan or other drugs. This may have affected the results. For those who respond well to PTX + RAM, nivolumab consecutively before using irinotecan may be valuable.

Recently, several trials including CheckMate 649 and ATTRACTION-4 demonstrated the benefit of first-line chemotherapy with nivolumab and cytotoxic anticancer drugs in patients without HER amplification (12,13). These findings led to an increase in the use of combination therapy with nivolumab in first-line chemotherapy, resulting in a decrease in the use of nivolumab monotherapy in third-line chemotherapy. However, patients who received first-line chemotherapy without nivolumab would be good candidates for third-line nivolumab monotherapy if they responded well to RAM + PTX during the second-line chemotherapy.

The development and clinical application of immune checkpoint inhibitors (ICIs), such as nivolumab and pembrolizumab, have dramatically improved the outcome of cancer chemotherapy. In addition, as the analysis of tumor immunity has progressed, attention has focused on the dynamic and complex mutual involvement of many protein molecules in the biological processes of angiogenesis and tumor immunity. Previous reports have provided information on the relationship between angiogenesis and tumor immunity (14-19). VEGF suppresses dendritic cell maturation and T-cell function and migration and promotes suppressive T-cell activation, all of which promote tumor immune responses (14,17). RAM is a monoclonal antibody that binds to the VEGF receptor (VEGFR)-2 and primarily inhibits the VEGF-A/VEGFR-2-mediated angiogenic signaling cascade. Moreover, angiogenesis inhibitors such as ramucirumab are expected to promote anti-tumor immune responses by regulating immunosuppressive activity. This suggests that the combined use of angiogenesis inhibitors and immunotherapies, including ICIs, may exhibit synergistic antitumor effects. Various reports exist on predicting nivolumab efficacy; however, no biomarkers have been identified that can be used in all cases. Programmed death-ligand 1 expression is a promising biomarker. In our study, we postulated that RAM reactivated the tumor immune response and enhanced nivolumab efficacy. The enhanced effect of an ICI in combination with angiogenesis inhibitors has already been reported in lung, renal, and hepatocellular carcinomas (18,19).

In the near future, we may narrow down the characteristics of the patient group that can benefit from this combination therapy and obtain important information on the appropriate timing and dosage of the combination therapy. This may generate significant evidence for combination therapy with a cytotoxic anticancer drug + an angiogenesis inhibitor + an ICI. Currently, a clinical trial of nivolumab combined with PTX + RAM as second-line treatment for gastric cancer is being conducted (20).

Several limitations of the present study should be acknowledged. First, the study was conducted with a retrospective design at a single center. Second, all enrolled patients with advanced gastric cancer were Japanese, and the sample size was small. Therefore, confirmation in a large-scale prospective study is required.

In conclusion, RAM may enhance nivolumab efficacy as the therapeutic effect of nivolumab was found to be associated with PTX + RAM pretreatment.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MS acted as a guarantor of the integrity of the study, conceived the study concept AND designed the study. ST, YE and FW performed the literature research. ST, YE, FW, YK and IA performed data acquisition, data analysis and statistical analysis, and prepared and edited the manuscript. KS and TR reviewed the manuscript. MS, TR and KS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of Jichi Medical University (approval no. GC07-13). Written informed consent was obtained from all patients before receiving chemotherapy.

Patient consent for publication

Written informed consent was obtained from all patients for publication of this paper. In addition, all methods were performed in accordance with the Declaration of Helsinki on ethical principles in conducting human research.

Competing interests

The authors declare that they have no competing interests.

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