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Clinical usefulness of ramucirumab plus paclitaxel for unresectable and recurrent gastric cancer

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Abstract

Introduction

Recently in Japan, Ramucirumab (RAM) became the first anti-angiogenic agent to be approved for second-line treatment of gastric cancer. In the present study, we aimed to evaluate the efficacy and safety of RAM plus paclitaxel (PTX) in patients with unresectable and recurrent gastric cancer in our institution.

Patients and Methods

The subjects were 11 patients with unresectable and recurrent gastric cancer who received RAM plus PTX as a second- or later-line treatment at our hospital between June 2015 and September 2017, after the failure of previously-attempted treatments. We assessed the efficacy and safety of RAM plus PTX, and also compared them between patients aged <75 years (n=6) and those aged ≥75 (n=5), by performing a retrospective analysis based on the data obtained from daily clinical practice for gastric cancer treatment.

Results

Objective tumor response was observed in one of the 11 patients (9.1%) with partial response, and disease control was seen in the remaining 10 (90.9%). The median overall survival (OS) and progression-free survival (PFS) of the patients were 20.8 months (95% CI 7.8-NA (not applicable)) and 11.3 months (95% CI 6.5-NA), respectively. There were no serious adverse events.

The median OS for the <75 years group and ≥75 years group was NA (due to short follow-up period) and 20.8 months (p = 0.336), respectively, and their respective median PFS rates were 9.4 and 11.3 months (p = 0.492). The difference of rate of adverse events was not significant between the two age groups in the present study, though the number of adverse events was not sufficient.

Conclusion

The results of the present study suggest that the combination chemotherapy of RAM and PTX was effective in unresectable and recurrent gastric cancer patients as a second- or later-line therapy, and has been shown to be safe and feasible in elderly patients.

Key words : ramucirumab, paclitaxel, elderly, chemotherapy, advanced gastric cancer

Introduction

Gastric cancer is the fifth most common cancer worldwide, with a high incidence in East Asia[1]. Survival can be improved by aggressive surgical resection and postoperative adjuvant therapy when the cancer is detected at early stage ; however, the prognosis of unresectable and recurrent gastric cancer has been grim. In such situations, various kinds of molecularly targeted agents have been used in gastrointestinal areas. For instance, a number of molecularly targeted agents are clinically used for

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colorectal cancer, including bevacizumab, panitumumab, cetuximab and trastuzumab. However, except for trastuzumab, which is a human epidermal growth factor receptor 2 (HER2)-targeted monoclonal antibody, these agents' effectiveness for treating unresectable and recurrent gastric cancer has been reported to be negative[2-4]. Ramucirumab (RAM), a human IgG1 monoclonal antibody vascular endothelial growth factor-2 (VEGFR-2) antagonist, is the first anti-angiogenic agent in Japan to be approved for second-line treatment of gastric cancer. This antagonist prevents ligand binding and receptor-mediated pathway activation in endothelial cells[5], inhibits tumor angiogenesis and has an anti-tumor effect. In a recent study, the efficacy of RAM alone or combined with paclitaxel (PTX) for the treatment of unresectable and recurrent gastric cancer was reported. These therapies significantly improve overall survival (OS) compared with placebo plus PTX or placebo alone, although several kinds of severe adverse events have been reported[6,7]. Currently, these therapies are used for second-line chemotherapy.

Recently, the number of elderly patients with gastric cancer has been increasing due to the aging Japanese population. Accordingly, the opportunities for more elderly gastric cancer patients receiving chemotherapy seems to be increasing. In the RAINBOW trial[6], subgroup analysis of progression-free survival (PFS) was performed for patients aged <65 years and patients aged ≥65 years. The analysis showed that the PFS for the patients who were receiving RAM plus PTX was longer than that of the patients receiving placebo plus PTX in both age groups.

In the current report, we aimed to evaluate the efficacy and safety of RAM plus PTX for unresectable and recurrent gastric cancer, and compare them between patients aged <75 years and elderly patients with age ≥75 in our institution.

Materials and Methods

Study design and patients

The present study is a retrospective analysis based on data from daily clinical practice for gastric cancer treatment. The subjects were 11 patients with unresectable and recurrent gastric cancer who received RAM plus PTX as a second- or later-line treatment at our hospital between June 2015 and September 2017, after the failure of previous treatments.

Procedures

Patients received a 28-day cycle of RAM 8 mg/kg intravenously on days 1 and 15, plus PTX 80 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle. They received the treatment until disease progression or unacceptable toxicity occurred. Computed tomography scans were done every 12 weeks to determine the overall response. Disease progression and tumor response were assessed in accordance with RECIST 1.1. We defined stable disease (SD) or partial response (PR) lasting for 6 months as best overall response.

We assessed the safety and efficacy of RAM plus PTX retrospectively. Adverse Events were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE ; version 4.0). OS, defined as the time from the first administration of RAM plus PTX to death from any cause, and PFS, defined as time from the first administration of RAM plus PTX to radiographic progression. Objective tumor response was defined as the proportion of patients who had a best response of complete response (CR) or PR. Disease control was defined as the proportion of patients who had a best response of CR, PR, or SD.

Statistical analysis

Estimations of time-to-event curves were generated using the Kaplan-Meier method. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[8].

Results

Table 1 shows the background characteristics of the 11 patients. The median number of courses of RAM plus PTX was 10 (range : 2-21).

Regarding RAM plus PTX treatment, as shown in Fig. 1, 11 patients started RAM plus PTX treatment at full dose, however, seven received dose reduction, four of whom had PTX reduction, and the remaining three had reduction of both RAM and PTX. As for dosing interval, five patients changed treatment frequency during the course and received both RAM and PTX every other week and one of them started to receive RAM only in the middle of the course. The collection of the 11 patients' data , with a median duration of OS follow-up of 15.9

Table 1. Patient characteristics

	(*N*=11)
Age(years)	
Median (range)	68 (42-83)
<75	6 (54.5%)
≥75	5 (45.5%)
Sex	
Male	8
Female	3
State of cancer	
recurrence after curative resection	7
non-curative resection	2
unresectable	2
Previous surgery for gastric cancer	
Yes	9
Total gastrectomy	4
Partial gastrectomy	5
No	2
HER2 status	
Positive	1
Negative	10

	(*N*=11)
Previous treatment regimens	
1	6
2	2
3	2
4	1
Tissue type	
pap	0
tub1	2
tub2	2
por1	2
por2	4
sig	0
muc	1
Peritoneal metastasis	
Yes	4
No	7

pap, Papillary adenocarcinoma ; tub, Tubular adenocarcinoma ; tub1, well differentiated ; tub2 moderately differentiated ; por, poorly differentiated adenocarcinoma ; por1, solid type ; por2, non-solid type ; sig, Signet-ring cell carcinoma ; muc, Mucinous adenocarcinoma

months (interquartile range 7.7-17.9), revealed that three (27.3%) patients had died, and administration of RAM plus PTX had been withheld in six patients due to disease progression. Treatment was still continuing in the remaining five patients. As for the best overall response, objective tumor response was observed in one patient (9.1%) with PR, and disease control was seen in the other 10 (90.9%) (Fig. 1). The median OS was 20.8 months (95% CI 7.8-NA (not applicable)). The median PFS was 11.3 months (95% CI 6.5-NA) (Fig. 2). The most common grade 3 or 4 adverse events due to the treatment with RAM plus PTX was neutropenia, which accounted for 72.7%. This was followed by hypertension, which accounted for 27.3%, febrile neutropenia, anemia, and proteinuria, each of which accounted for 9.1%. On the other hand, there were no serious adverse events, such as gastrointestinal perforation / hemorrhage. The most common less than grade 3 adverse events were neuropathy and fatigue, both of which accounted for 72.7% (Table. 2).

The median age of the patients was 68 years, and five patients were aged 75 or older (Table. 1). The median ages of patients aged <75 and those aged ≥75 were 63 (range, 42-68) and 76 (range, 75-83), respectively, and their median OS was NA (due to short follow-up period) and 20.8 months ($p = 0.336$), respectively (Fig. 3A). The median PFS was 9.4 months for the <75 group and 11.3 months for the ≥75 group ($p = 0.492$) (Fig. 3B). The difference of rate of adverse events was

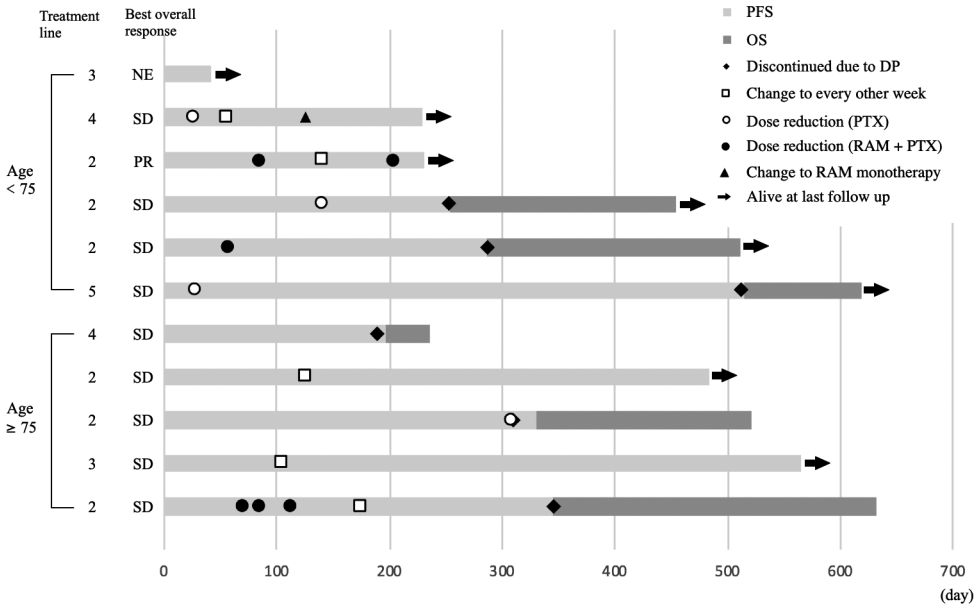

Fig. 1. Swimmers plot detailing progression-free survival (PFS), overall survival (OS) and dose / interval adjustment of RAM plus PTX.
Swimmers plot illustrating PFS, OS and dose / interval adjustment of RAM plus PTX of all individual patients in this study. The age of patients, treatment line and best overall response of RAM plus PTX : PFS (gray) and OS (black). NE (Not Evaluable), SD (Stable Disease), PR (Partial Response), DP (Disease Progression).

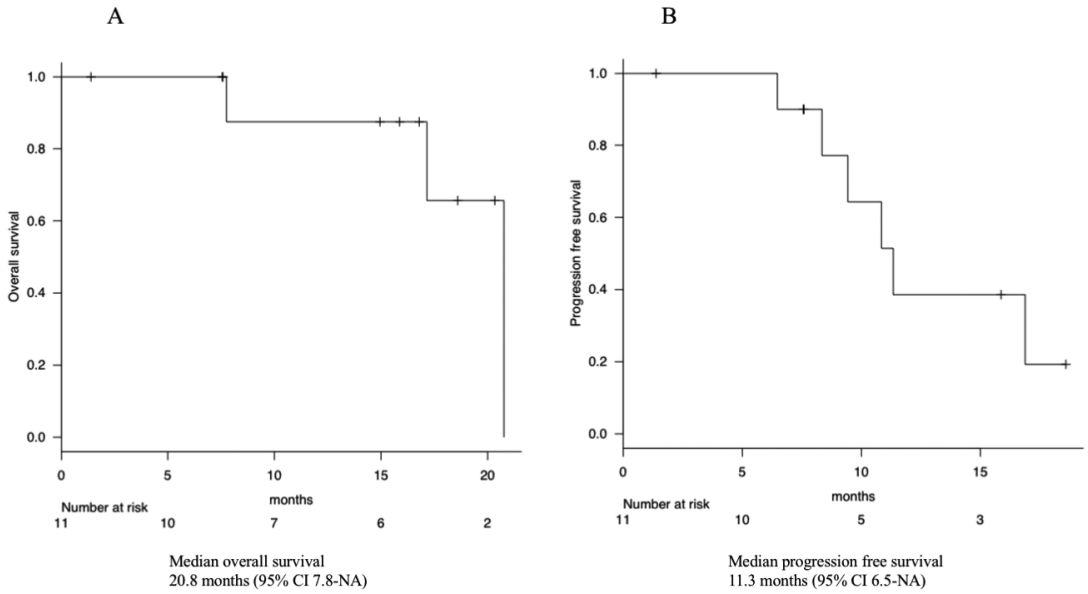

Fig. 2. Overall survival (OS) and progression-free survival (PFS) analysis of the patients receiving RAM plus PTX.
Kaplan-Meier curves for OS (A) and PFS (B).

not significant between age <75 and ≥75 in this study, though the number of adverse events was not sufficient (Table. 2). These results suggest that RAM plus PTX could show promise as a treatment for even elderly patients aged ≥75, even though the OS was not fully evaluated because of the relatively short follow-up period.

Discussion

Our results indicate that chemotherapy using RAM plus PTX was effective in unresectable and recurrent gastric cancer patients as a second- or later-line therapy, and is safe and feasible even in elderly patients aged ≥75 at reduced doses and/or when the dosing interval is extended.

Table 2. Adverse events occurring in patients on RAM plus PTX

	Grade 1 or 2	(<75 : ≧75)	Grade 3 or 4	(<75 : ≧75)
Neutropenia	2 (18.2%)	(2 : 0)	8 (72.7%)	(4 : 4)
Febrile neutropenia	0		1 (9.1%)	(0 : 1)
Anemia	0		1 (9.1%)	(0 : 1)
Platelet count decreased	2 (18.2%)	(1 : 1)	0	
Neuropathy	8 (72.7%)	(4 : 4)	0	
Nausea	2 (18.2%)	(1 : 1)	0	
Vomiting	0		0	
Diarrhea	5 (45.5%)	(3 : 2)	0	
Proteinuria	1 (9.1%)	(1 : 0)	1 (9.1%)	(0 : 1)
Hypertension	6 (54.5%)	(4 : 2)	3 (27.3%)	(1 : 2)
Epistaxis	4 (36.4%)	(3 : 1)	0	
Dysgeusia	3 (27.3%)	(0 : 3)	0	
Infusion-related reaction	0		0	
Gastrointestinal perforation/hemorrhage	0		0	
Fatigue	8 (72.7%)	(3 : 5)	0	
Alopecia	6 (54.5%)	(3 : 3)	0	
Urticaria	2 (18.2%)	(2 : 0)	0	
Watering eyes	1 (9.1%)	(1 : 0)	0	
Oral pain	1 (9.1%)	(1 : 0)	0	

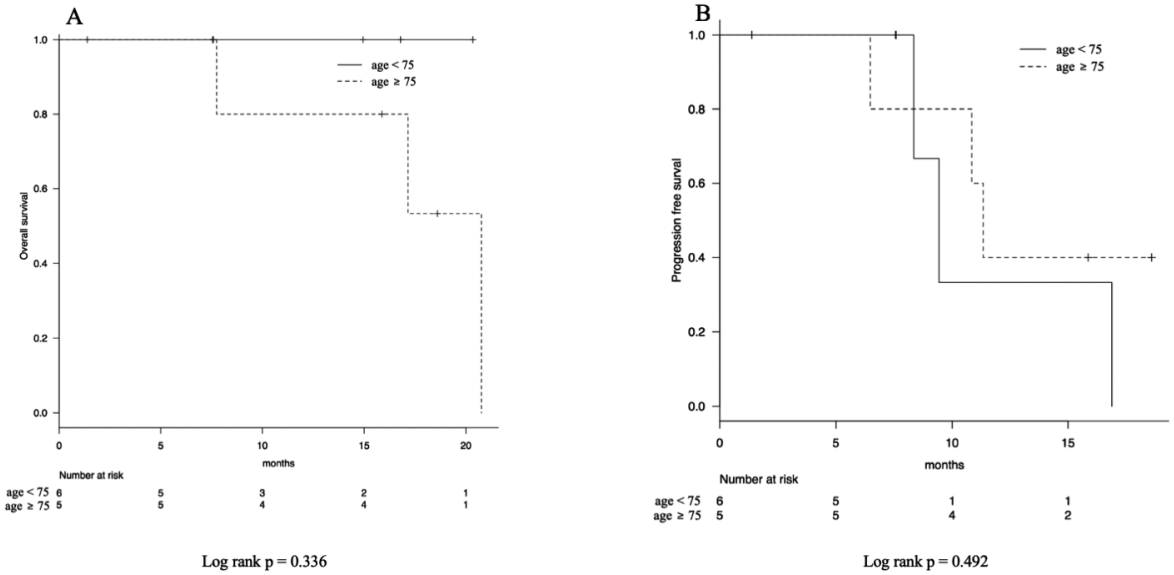

Fig. 3. Progression-free survival (PFS) analysis of the patients receiving RAM plus PTX according to age.
Kaplan-Meier curves for PFS according to the age of patients receiving RAM plus PTX. Solid line, patients aged <75 years ; dashed line, patients aged ≥75 years.

After a successful treatment with trastuzumab for HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA trial)[9], several molecular target agents have been developed for advanced gastric cancer, including lapatinib and bevacizumab[10,11], with a number of combination or line settings, although unfortunately there has been no success. Under these circumstances, RAM plus PTX as a second-line treatment has been shown to significantly increase the OS and PFS of patients with unresectable and recurrent gastric cancer[6], which indicates that this is a novel strategy to treat gastric cancer.

Since RAM plus PTX therapy is recommended for unresectable and recurrent gastric cancer as a second-line treatment in the Japanese Gastric Can-

cer Treatment Guidelines 2015, the RAM plus PTX regimen is widely used in Japan currently, and the regimen is a part of the standard protocol in our department. In the present study, the result from RAM plus PTX treatment in our department (median OS=20.8 month and median PFS=11.3 months) was found to be even better in terms of OS and PFS in comparison to the results of the RAINBOW trial[6], which is the largest trial in a second-line gastric cancer treatment, and was the first report of the survival benefits of a VEGFR-2 targeted antibody in combination with chemotherapy (median OS= 9.6 months and median PFS=4.4 months). Although our results are based on a small number of patients and this study is retrospective analysis with patient selection bias, our survival data of patients treated with RAM plus PTX therapy indicate that it is significantly effective. One of the reasons for our positive results might be the continuation of RAM plus PTX for as long as possible in each patient. In the present study, the median number of courses of RAM plus PTX was 10.0 (range : 2-21), which is superior to that of the RAINBOW trial (5.0 range : 1-22). A possible explanation for this better continuation rate may be based on the dose reduction and adjustment in dosing interval, in which seven patients had their doses reduced and five patients received RAM plus PTX every other week. It is likely that the current study's longer continuation of the RAM plus PTX regimen may have contributed to a higher disease control rate in our series.

It has also been reported that the addition of RAM to PTX did not worsen, but rather maintained patient quality of life compared to the addition of a placebo to PTX[12]. In the current study, RAM plus PTX was generally well tolerated with few adverse events including febrile neutropenia, anemia, and proteinuria. Although the neutropenia and hypertension that occurred in our patients were grade 3 or 4 adverse events, all of them were manageable by supportive treatment. As a result, the management for adverse events may have contributed to a continuation of RAM plus PTX.

To date, a standard chemotherapy for elderly cancer patients has not yet been defined. It has been reported that the number of deaths from gastric cancer aged 70 or over was about 35,000 per year, which accounted for about 75% of all deaths from gastric cancer in Japan[13]. As such, elucidating the effects of chemotherapy in elderly people is of critical importance. In the present study, about half of the patients were aged 75 years or older, and these patients exhibited the efficacy of RAM plus PTX with manageable adverse events, indicating that the tolerability and feasibility of RAM plus PTX for elderly patients is acceptable and promising.

As described above, our study has limitations. First, the study population was small with a short follow up period. Second, it was a single-center study. Third, the retrospective nature of the study has a selection bias. Further study is required to examine the effectiveness of RAM plus PTX with a large number of patients and a longer follow-up period.

In conclusion, the results of the present study suggest that the combination chemotherapy of RAM plus PTX was effective in unresectable and recurrent gastric cancer patients as a second- or later-line therapy and that it is safe and feasible for treating elderly patients.

Conflict of interest

The authors declare that they have no conflicts of interest relevant to this article.

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