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Evaluation of the safety of ramucirumab in Japanese patients with advanced gastric cancer

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Received December 29, 2017, accepted January 31, 2018

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Pharmazie 73: 309–312 (2018) *doi: 10.1691/ph.2018.7355*

As a result of the RAINBOW trial, ramucirumab plus paclitaxel was established as a second-line treatment of advanced gastric cancer. Regarding the safety of ramucirumab plus paclitaxel in the Japanese, a subgroup analysis of the RAINBOW trial was conducted. The incidence of neutropenia was higher in Japanese patients. However, information is lacking concerning the safety of ramucirumab after marketing in Japanese patients. Therefore, the aim of this study was to evaluate the safety of ramucirumab in Japanese patients with advanced gastric cancer. The inclusion criteria were patients diagnosed with advanced gastric cancer who had commenced treatment with ramucirumab plus paclitaxel or paclitaxel only at Ogaki Municipal Hospital (Gifu, Japan) between January 2015 and December 2016. There were 26 patients in the ramucirumab plus paclitaxel group and 22 patients in the paclitaxel only group. Treatment-related adverse events were documented in 100.0% of the patients in the ramucirumab plus paclitaxel group (Grade 3–4, 73.1%) and 90.9 % of the patients in the paclitaxel only group (Grade 3–4, 45.5 %). The most frequently observed adverse event in both treatment groups was anemia. The second common adverse event was neutropenia. The incidence of neutropenia of Grade ≥3 was significantly higher in the ramucirumab plus paclitaxel group than in the paclitaxel only group. In conclusion, the incidence of neutropenia is high. However, we believe that ramucirumab plus paclitaxel can be safely administered.

1. Introduction

Gastric cancer is the third leading cause of cancer-related deaths in both men and women worldwide (Ferlay et al. 2012). In Japan, gastric cancer was the second common malignancy. However, in 2013, gastric cancer became the most common malignancy in Japan (National Cancer Center Japan). In 2015, the mortality rate of gastric cancer was the third highest in Japan (National Cancer Center Japan). Platinum- and fluoropyrimidine-based combinations are currently accepted worldwide as established first-line therapeutic regimens. Platinum- and fluoropyrimidine-based combinations have also been established in Japan as first-line treatments for advanced-stage disease based on the results of the SPIRITS trial (Koizumi et al. 2008). However, treatment options after failure of first-line therapy are limited, resulting in poor survival (Ford et al. 2014; Kang et al. 2012; Thuss-Patience et al. 2011).

Ramucirumab is a recombinant human immunoglobulin G1-neutralizing monoclonal antibody specific for vascular endothelial growth factor receptor 2 that prevents ligand binding and receptor-mediated pathway activation in endothelial cells (Spratin et al. 2010). In the second-line treatment of advanced gastric cancer, 2 phase III trials, REGARD (Fuchs et al. 2014) and RAINBOW (Wilke et al. 2014), have been conducted. The RAINBOW trial (Wilke et al. 2014) was performed to compare the safety and efficacy of ramucirumab plus paclitaxel *versus* placebo plus paclitaxel in 665 randomly assigned (intent-to-treat) patients with metastatic or unresectable, locally advanced gastric or gastroesophageal junction adenocarcinoma whose disease had progressed during or following first-line treatment with platinum- or fluoropyrimidine-based regimens. The median overall survival was significantly longer in the ramucirumab plus paclitaxel group (9.6 [95.0 % confidence interval: 8.5–10.8] months) than in the placebo plus paclitaxel group (7.4 [95.0% confidence interval: 6.3–8.4] months) (hazard ratio: 0.81 [95.0% confidence interval: 0.678–0.962]; $P < 0.05$). The RAINBOW trial (Wilke et al. 2014) demonstrated that ramucirumab in combination with paclitaxel significantly improved survival. As a result, ramucirumab plus paclitaxel was established as a second-line treatment for advanced gastric cancer. Regarding safety in the Japanese, a subgroup analysis of the RAINBOW trial was conducted by Shitara et al. (2016). The incidence of neutropenia was higher in Japanese patients. However, information is lacking concerning the safety of ramucirumab after marketing in Japanese patients. Therefore, the aim of this study was to evaluate the safety of ramucirumab in Japanese patients with advanced gastric cancer.

2. Investigations and results

2.1. Patient characteristics

There were 26 patients in the ramucirumab plus paclitaxel group and 22 patients in the paclitaxel only group. The baseline characteristics were comparable between the 2 treatment groups (Table 1). The relative dose intensities were >80.0%. The median relative dose intensity of paclitaxel was lower in the ramucirumab plus paclitaxel group than in the paclitaxel only group (83.9 % *vs.* 89.5 %). In contrast, the median cumulative dose of paclitaxel was higher in the ramucirumab plus paclitaxel group than in the paclitaxel only group (584.5 *vs.* 524.3 mg/m^2).

The median number of treatment courses in the ramucirumab plus paclitaxel group and the paclitaxel only group was 3.0 (range, 1.0–10.0) and 2.5 (range, 1.0–12.0), respectively.

Twenty patients in the ramucirumab plus paclitaxel group had received previous treatment with platinum- and fluoropyrimidine-based combinations. Ten patients in the paclitaxel only group

had received previous treatment with platinum- and fluoropyrimidine-based combinations and 7 patients had received previous treatment with a fluoropyrimidine-based regimen.

Table 1: Patient characteristics

Characteristic	Ramucirumab + paclitaxel (*n* = 26)	Paclitaxel (*n* = 22)
Age (years), median (range)	67 (40–77)	66 (37–80)
Sex (M/F)	18/8	13/9
BSA (m^2), median (range)	1.5 (1.1–1.8)	1.5 (1.2–1.9)
RDI (%), median (range)	Ramucirumab 81.3 (13.3–100.0) Paclitaxel 83.9 (34.1–100.0)	Paclitaxel 89.5 (50.3–100.0)
Cumulative dose of paclitaxel (mg/m^2), median (range)	584.5 (79.8-2,317.4)	524.3 (80.0-2,715.4)
Previous treatment		
Platinum- and fluoropyrimidine-based	20	10
Other	6	8
None	0	4
Treatment courses (*n*), median (range)	3.0 (1.0–10.0)	2.5 (1.0–12.0)

Abbreviations: BSA, body surface area; F, female; M, male; RDI, relative dose intensity.

2.2. Treatment discontinuation

Progressive disease was the most common reason for discontinuing treatment in both treatment groups (ramucirumab plus paclitaxel group [*n* = 14]; paclitaxel only group [*n* = 8]) (Table 2). The second common reason for discontinuing treatment was due to adverse events (AEs), which occurred in 5 patients in the ramucirumab plus paclitaxel group and 6 patients in the paclitaxel only group. The third common reason was symptom exacerbation, which occurred in 4 patients in the ramucirumab plus paclitaxel group and 3 patients in the paclitaxel only group. One patient was switched from the paclitaxel only group to the ramucirumab plus paclitaxel group.

Table 2: Reasons for discontinuing treatment

	Ramucirumab + paclitaxel (*n* = 26)	Paclitaxel (*n* = 22)
Progressive disease	14	8
Adverse events	5	6
Symptom exacerbation	4	3
Other	3	5

After discontinuation of treatment, best supportive care was most often used. The proportion of patients receiving postdiscontinuation systemic anticancer therapy was comparable between to the 2 treatment groups. Irinotecan was the most commonly used therapeutic agent for postdiscontinuation therapy in both treatment groups. Other therapeutic agents included taxanes, fluoropyrimidines, and platinum-based compounds.

2.3. Adverse events

Treatment-related AEs were documented in 100.0 % of the patients in the ramucirumab plus paclitaxel group (Grade 3–4, 73.1%) and 90.9% of the patients in the paclitaxel only group (Grade 3–4, 45.5 %) (Table 3). The most frequently observed AE in both treatment groups was anemia. The second common AE was neutropenia. There was no significant difference in the incidence of neutropenia of any grade between the ramucirumab plus paclitaxel group and the paclitaxel only group. However, the incidence of neutropenia of grade ≥3 was significantly higher in the ramucirumab plus paclitaxel group than in the paclitaxel only group. A significant difference in the incidence of edema of any grade was also detected between the 2 treatment groups. However, AEs were more frequently reported in the paclitaxel group than in the ramucirumab plus paclitaxel group; they included nausea, hyponatremia, vomiting, and malaise. The incidence of leukopenia and liver dysfunction of grade ≥3 was higher in the paclitaxel only group than in the ramucirumab plus paclitaxel group.

Table 3: Common treatment-related adverse events

Adverse event	Ramucirumab + paclitaxel (*n* = 26)		Paclitaxel (*n* = 22)		*P*-value	
	All	Grade 3–4	All	Grade 3–4	All	Grade 3–4
Hematological adverse events						
Leukopenia	73.1	11.5	59.1	22.7	0.47	0.52
Neutropenia	76.9	46.2	63.6	13.6	0.49	0.03*
Anemia	96.2	34.6	81.8	27.3	0.25	0.81
Thrombocytopenia	11.5	0.0	0.0	0.0	0.30	–
Elevated ALT	26.9	3.9	22.7	9.1	1.00	0.88
Elevated AST	46.2	3.9	31.8	9.1	0.47	0.88
Elevated blood bilirubin	15.4	3.8	4.6	4.6	0.45	0.55
Elevated creatine	42.3	0.0	27.3	0.0	0.43	–
Hypoalbuminemia	53.8	11.5	45.5	0.0	0.77	0.30
Hyponatremia	42.3	15.4	54.5	4.6	0.58	0.45
Hyperkalemia	42.3	19.2	18.2	0.0	0.14	0.09
Non-hematological adverse events						
Nausea	11.5	0.0	22.7	0.0	0.52	–
Vomiting	3.9	0.0	13.6	0.0	0.48	–
Anorexia	26.9	0.0	13.6	0.0	0.43	–
Stomatitis	19.2	0.0	9.1	0.0	0.56	–
Dysgeusia	19.2	0.0	9.1	0.0	0.56	–
Constipation	53.8	0.0	40.9	0.0	0.55	–
Edema	30.8	0.0	0.0	0.0	0.01*	–
Hypertension	15.4	0.0	0.0	0.0	–	–
Malaise	15.4	0.0	27.3	0.0	0.51	–
Peripheral neuropathy	57.7	3.8	45.5	0.0	0.58	0.93
Any adverse event (%)	100.0	73.1	90.9	45.5	0.40	0.10

*$P < 0.05$.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

3. Discussion

The pivotal phase III RAINBOW trial (Wilke et al. 2014) demonstrated significant overall survival, progression-free survival, and objective response rate benefits of ramucirumab plus paclitaxel *versus* placebo plus paclitaxel in patients with advanced gastric or gastroesophageal junction adenocarcinoma who had previously been treated with platinum and fluoropyrimidine. Progression-free survival and objective response rate benefits were also reported in the Japanese population of the phase III RAINBOW trial (Wilke et al. 2014). As a result, ramucirumab plus paclitaxel was established as a second-line treatment for advanced-stage disease.

All Japanese patients in the phase III RAINBOW trial (Wilke et al. 2014) received ramucirumab as second-line treatment after platinum and fluoropyrimidine, whereas our study included patients who received treatment for recurrence with S-1 (tegafur/gimeracil/oteracil) as adjuvant chemotherapy and third-line treatment after second-line treatment with single-agent chemotherapy.

The median duration of therapy was shorter in this study than in the phase III RAINBOW trial (Wilke et al. 2014). The median duration of therapy was longer in the ramucirumab plus paclitaxel group than in the paclitaxel only group. These results are consistent with those of the phase III RAINBOW trial (Wilke et al. 2014). The median relative dose intensity of paclitaxel in the ramucirumab plus paclitaxel group was higher in this study than in the phase III RAINBOW trial (Wilke et al. 2014). The median relative dose

intensity of paclitaxel in this study was comparable between the two treatment groups. The median cumulative dose of paclitaxel in the ramucirumab plus paclitaxel group was approximately 50.0% lower in this study than in the phase III RAINBOW trial (Wilke et al. 2014). We believe that this may be due to the shorter duration of therapy in this study than in the phase III RAINBOW trial (Wilke et al. 2014). In this study, adjuvant chemotherapy with S-1 was administered for a longer duration in patients with recurrence than in patients receiving third-line treatment. The sample size of our study is relatively small. Therefore, further studies are warranted.

The main reason for discontinuing chemotherapy was progression. Compared with the phase III RAINBOW trial (Wilke et al. 2014), many patients discontinued chemotherapy due to AEs. The common reasons for discontinuation of chemotherapy due to AEs were harmful AEs (e.g., drug-induced lung injury and liver dysfunction). In our hospital, pharmacists are actively involved in the management of AEs. On the day of chemotherapy administration, pharmacists should check for AEs, and explain the supportive therapy proposal and how to take the medicines. For example, we aim to improve the nutritional intake of patients by alleviating nausea with an antiemetic and promoting defecation with a laxative. Moreover, we suggest hand washing, gargling, and explaining the points of caution in daily life, to reduce the chance of infection. Thus, we believe that pharmacists should be actively involved in dealing with AEs, thereby reducing cessation of chemotherapy due to AEs. Furthermore, the use of postdiscontinuation chemotherapy was balanced between the two treatment groups. The proportion of patients who received chemotherapy after discontinuation was lower in this study than in the phase III RAINBOW trial (Wilke et al. 2014). This may be due to the inclusion of patients who received third-line treatment.

The incidence of AEs was consistent with that reported in a subgroup analysis of the phase III RAINBOW trial (Shitara et al. 2016). The majority of AEs were grade 1 or 2. Grade ≥3 AEs of special interest included neutropenia and anemia, which were more common in the ramucirumab plus paclitaxel group than in the paclitaxel only group. There were no reports of anemia-related AEs in the subgroup analysis of the phase III RAINBOW trial (Shitara et al. 2016). However, in this study, since grade ≥3 anemia was reported, we believe that appropriate follow-up is necessary. Current observations are consistent with previous studies reporting higher incidences of grade ≥3 neutropenia associated with weekly paclitaxel treatment (Del Mastro et al. 2005; Hironaka et al. 2006; Kodera et al. 2007; Shitara et al. 2010; Seidman et al. 2008). Notably, the relative increase in the incidence of grade ≥3 neutropenia with the addition of ramucirumab was comparable to the subgroup analysis of the phase III RAINBOW trial (Shitara et al. 2016). In contrast, febrile neutropenia was not reported in this study. Neutropenia was more common. However, we believe that pharmacists may have explained the symptoms of neutropenia, and patients may have prevented febrile neutropenia by preventing infection. Therefore, we believe that neutropenia can be managed safely. However, the incidence of grade ≥3 neutropenia was significantly higher in patients aged ≥70 years ($P = 0.026$). Age (>65 years) is a risk factor for febrile neutropenia. Although febrile neutropenia was not reported in this study, it was suggested that age may become a risk factor for neutropenia. We believe that patients aged >70 years should be careful as the incidence of neutropenia is high. In contrast, the incidence of edema was not very high. It was mild and manageable. However, the incidence of edema was significantly higher in the ramucirumab plus paclitaxel group than in the paclitaxel only group. In the subgroup analysis of the phase III RAINBOW trial (Shitara et al. 2016), edema was not considered a particular problem. However, edema can lead to a reduction in quality of life. Therefore, we believe that it is necessary to take measures to prevent edema.The main limitation of these analyses is the relatively small number of patients in the Japanese population. Therefore, these results should be interpreted with caution.

In conclusion, the incidence of neutropenia is high. However, we believe that ramucirumab plus paclitaxel can be safely administered.

4. Experimental

4.1. Ethical considerations

This study was approved by the Institutional Review Board of Ogaki Municipal Hospital (Gifu, Japan) and was conducted in accordance with the Declaration of Helsinki. Written, informed consent for participation in this study was not obtained from the patients, because this study was not a clinical trial and the data were retrospective and analyzed anonymously.

4.2. Patients

Patients were identified from medical records. The inclusion criteria were as follows: patients diagnosed with advanced gastric cancer who began therapy with ramucirumab plus paclitaxel or paclitaxel only at Ogaki Municipal Hospital (Gifu, Japan) between January 2015 and December 2016. Treatment regimens, body surface area, dosage, and the number of treatment courses were evaluated.

4.3. Treatment regimens

The ramucirumab plus paclitaxel regimen consisted of a 28-day cycle of ramucirumab (8.0 mg/kg on days 1 and 15) and paclitaxel (80.0 mg/m^2 on days 1, 8, and 15). The paclitaxel regimen consisted of a 28-day cycle of paclitaxel (80.0 mg/m^2 on days 1, 8, and 15).

4.4. Adverse events

AEs were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.0 (Cancer Therapy Evaluation Program).

4.5. Statistical analyses

The dose intensity was calculated as the total dose divided by the duration of dosing, while the planned dose intensity was calculated as the planned dose divided by the planned duration of dosing. The relative dose intensity was calculated as the dose intensity divided by the planned dose intensity, multiplied by 100.

Sex was analyzed using the Chi-square test. Intergroup comparisons of age, body surface area, relative dose intensity, and treatment regimens were performed using the Student's *t*-test. The incidence of AEs was assessed using the Fisher's exact test. All statistical analyses were conducted using Easy R version 1.30 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (Kanda 2013). A $P < 0.05$ was considered statistically significant.

Acknowledgements: The authors would like to thank Editage (www.editage.jp) for English language editing.

Conflicts of interest: The authors disclose no conflicts of interest.

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