Renin-angiotensin system inhibitors may have an advantage over calcium channel blockers in reducing proteinuria in gastric cancer patients receiving ramucirumab

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Received May 11, 2022; Accepted June 7, 2022

DOI: 10.3892/br.2022.1559

Abstract. This study aimed to investigate whether renin-angiotensin system inhibitors (RAS-I) have an advantage over calcium channel blockers (CCB) for suppression of proteinuria in hypertensive patients with gastric cancer receiving ramucirumab (RAM) treatment. Adult Japanese patients with gastric cancer who were outpatients at Asahikawa Medical University Hospital, National Hospital Organization Hokkaido Cancer Center, and Iwate Medical University Hospital between July 1, 2015, and March 31, 2021, were included in this study. Of these patients, those who had received first-time RAM treatment, and those treated with antihypertensive agents including RAS-I or a CCB at initial RAM administration were included. A total of 36 patients were analyzed in this study. Of these patients, 17 patients were classified into the RAS-I group and the remaining 19 into the CCB group. After 12 weeks of RAM administration, the prevalence of proteinuria in the RAS-I group was significantly lower than that in the CCB group. Additionally, Kaplan-Meier analysis showed that the cumulative occurrence of proteinuria in the RAS-I group over 12 weeks following RAM administration was significantly lower than that in the CCB group. Furthermore, simulation of the time course of RAM blood concentrations based on the O'Brien model showed that there may not be differences in the RAM blood concentration profiles over 12 weeks between the two groups. RAS-I may have an advantage over CCB for suppressing proteinuria in hypertensive patients with gastric cancer treated with blood pressure antihypertensive agents. Our results provide useful information to healthcare professionals involved in the administration of RAM treatment.

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Abbreviations: RAS-I, renin-angiotensin system inhibitors; CCB, calcium channel blocker; RAM, ramucirumab; VEGF, vascular endothelial growth factor; VEGFR-2, VEGF receptor 2; PTX, paclitaxel; AII, angiotensin II; ALT, alanine aminotransferase; AST, aspartate amino transferase; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; BMI, body mass index; eNOS, nitric oxidase synthase; TGF-β, transforming growth factor-β

Key words: gastric cancer, ramucirumab, hypertensive patients, renin-angiotensin system inhibitors, calcium channel blocker, proteinuria

Introduction

The molecular-targeted drug ramucirumab (RAM) is a recombinant humanized monoclonal antibody against human vascular endothelial growth factor (VEGF) receptor 2 (VEGFR-2) (1,2). VEGF is a cytokine that promotes angiogenesis by increasing the proliferation rate of endothelial cells and functions as a survival factor (3). RAM binds specifically to VEGFR-2 and interferes with its downstream intracellular signal cascades, inhibiting angiogenesis in tumor tissues and exerting an antitumor effect (1,2). RAM is effective when used in combination with standard chemotherapy for patients with advanced or recurrent gastric cancer in which curative

resection is not possible, those with unresectable advanced or recurrent colorectal cancer, and those with inoperable or recurrent non-small-cell lung cancer (4,5). In particular, amongst the VEGF inhibitors used in Japan including bevacizumab, aflibercept, and RAM, only RAM has the therapeutic indication for unresectable advanced or recurrent gastric cancer, and it is typically combined with paclitaxel (PTX). The typical adverse effects of VEGF inhibitors include hypertension, proteinuria, and bleeding (6,7). In particular, the development of proteinuria causes renal failure and requires discontinuation of VEGF inhibitors (8-10). A previous clinical study conducted on cancer patients receiving the VEGF inhibitor bevacizumab showed that there was a close association between elevated blood pressure and the occurrence of proteinuria (11), indicating that appropriate management of blood pressure during treatment with VEGF inhibitors is important for the reduction of proteinuria. Additionally, we previously reported that management of blood pressure using renin-angiotensin system inhibitors (RAS-I), such as angiotensin-converting enzyme inhibitors and angiotensin II (AII) receptor blockers, may reduce bevacizumab-induced proteinuria occurrence (12). However, this study did not investigate whether RAS-I had an advantage over calcium channel blockers (CCB), which are potent vasodilators, in terms of proteinuria reduction. Furthermore, to the best of our knowledge, there are no studies on RAS-I vs. CCB for gastric cancer patients treated with RAM. This retrospective study aimed to compare the effectiveness of RAS-I and CCB in the reduction of proteinuria in patients with gastric cancer treated with combination therapy with RAM and PTX.

Materials and methods

Patients. Adult Japanese patients with gastric cancer who were outpatients at Asahikawa Medical University Hospital, National Hospital Organization Hokkaido Cancer Center, and Iwate Medical University Hospital between July 1, 2015, and March 31, 2021, were selected for inclusion in this study. Of these patients, those who had received first-time RAM treatment (as concomitant therapy with RAM and PTX), and those treated with hypertension therapy with antihypertensive agents including RAS-I or CCB at initial RAM administration were included. Patients with metastatic pancreatic cancer, diabetes, prior proteinuria, liver and kidney dysfunction, or inadequate laboratory data at the start of RAM administration were excluded from the analysis. In addition, patients who had changed their chemotherapeutic regimen, those with changes in types or dosage of antihypertensive agents, those who had taken any additional antihypertensive agents, those who had taken both RAS-I and CCB, and those who had discontinued RAS-I and CCB administration within 12 weeks of the start of RAM treatment were also excluded. This study was reviewed and approved by the ethics committee of each participating institution. The requirement for informed consent was waived due to the retrospective nature of the study. However, the study was described on the websites of all participating medical institutes, and the patients orally confirmed their agreement or refusal to participate in the study.

Retrospective survey. Data on sex, age, height, weight, doses of RAM and PTX, type of concomitant drugs, the occurrence of proteinuria, laboratory test results [including the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), and blood pressure (systolic and diastolic)] at initial RAM administration, and at 12 weeks following initial RAM administration were retrieved from the medical records. The estimated glomerular filtration rate (eGFR) was calculated using the sex, Scr, and age of each patient using the estimation equation proposed by the Japanese Society of Nephrology (13). Additionally, proteinuria was considered present if the urinary albumin dipstick test results were positive (1+). The progression of proteinuria was evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

Analysis of the association between the occurrence of proteinuria and the type of antihypertensive drug. Patients were classified into a RAS-I or a CCB group based on their use of antihypertensive agents over 12 weeks following initial RAM administration. The prevalence of proteinuria, cumulative doses of RAM and PTX, and laboratory data at 12 weeks following initial RAM administration between the two groups were compared. Additionally, changes in blood pressure and cumulative occurrence of proteinuria over 12 weeks after initial RAM administration between the two groups were compared.

Blood concentration simulation of ramucirumab. RAM concentrations were simulated based on the estimates of O'Brien's model and well-characterized by a two-compartment model (14). The analyses were performed using Phoenix NLME version 8.3 (Certara) and R version 4.1.2 (15,16).

Statistical analysis. The two groups were compared using a χ^2 test, Fisher's exact test, or Student's t-test. The change in blood pressure between groups over the 12 weeks following initial RAM administration was assessed using a two-way ANOVA followed by the Tukey-Kramer post-hoc test. The incidence of proteinuria over 12 weeks after initial RAM administration was analyzed using Kaplan-Meier curves and compared using a log-rank test. Data were analyzed using SPSS version 25.0 (IBM Corp). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients. A total of 78 patients were reviewed in this study; excluded patients were 2 patients who experienced an onset of proteinuria at the onset of RAM administration, 20 who had a change in type or dosage of antihypertensive agents, 16 who had additional hypertensive agents, and 4 who had inadequate liver and renal function from the analysis. Finally, data from 36 patients were analyzed.

Comparison of the occurrence of proteinuria and the changes in blood pressure between RAS-I and CCB groups. Of the 31 patients, 15 were classified into the RAS-I group and the remaining 16 into the CCB group. At the time of commencing RAM administration, age, body mass index (BMI), ALT, AST, Scr, blood pressure (systolic and diastolic), and initial doses of RAM and PTX did not differ significantly between the two groups (Table I).

Table I. Comparison of patient characteristics between the RAS-I and CCB groups at the onset of ramucirumab treatment.

Parameter	RAS-I group, n=17	CCB group, n=19	P-value
Sex, male/female	10/7	10/9	0.709[a]
Age	64.2±2.1	65.6±1.5	0.589[b]
BMI	20.5±0.6	20.2±0.5	0.758[b]
ALT, IU/l	24.5±1.7	21.8±1.7	0.300[b]
AST, IU/l	26.7±1.9	27.0±1.7	0.911[b]
Scr, mg/dl	0.69±0.03	0.72±0.02	0.387[b]
eGFR, ml/min/1.73 m^2	80.0±3.1	73.5±2.4	0.114[b]
Blood pressure, mmHg			
Systolic	125.1±1.6	128.0±2.4	0.347[b]
Diastolic	74.8±1.3	72.6±1.9	0.390[b]
RAM dose, mg/body	435.6±14.0	415.8±15.0	0.358[b]
PTX dose, mg/body	126.2±2.4	121.9±2.6	0.258[b]
RAS-I			-
Azilsartane	4		
Candesartan cilexetil	4		
Enalapril	2		
Olmesartan	5		
Telmisartan	2		
CCB			-
Amlodipine		13	
Azelnidipine		3	
Cilnidipine		1	
Nifedipine		2	
Diuretics	2	3	-
Concomitant drugs			0.973[a]
Antilipidemic	2	3	
Antipodagric	3	3	
Peptic ulcer	11	10	
Diabetes	2	3	
Antithyroid	2	4	
Bone-building	2	5	
Antithrombogenic and anticoagulant	2	2	
Antipyretic and analgesic	2	8	
Hypnotics	2	5	
Anti-anxiety	2	4	
Laxative	3	5	
Stomach and intestinal	4	7	
Others	5	7	

[a]χ^2 test; [b]Student's t-test. Data are presented as the mean ± SEM. AST, aspartate transferase; ALT, alanine aminotransferase; BMI, body mass index; Scr, serum creatinine; eGFR, estimated glomerular filtration rate calculated based on age, sex, and Scr; RAS-I, renin-angiotensin system inhibitors; CCB, calcium channel blockers; RAM, ramucirumab; PTX, paclitaxel.

At 12 weeks after RAM administration, ALT, AST, Scr, blood pressure (systolic and diastolic), and cumulative doses of RAM and PTX were not significantly different between the two groups (Table II). In addition, the changes in systolic and diastolic blood pressure were not significantly different between the two groups (Fig. 1). However, the prevalence of proteinuria in the RAS-I group was significantly lower than that in the CCB group (Table II). Additionally, Kaplan-Meier analysis showed that the cumulative occurrence of proteinuria in the RAS-I group over 12 weeks after RAM administration was significantly lower than that in the CCB group (P=0.01, Fig. 2).

Comparison of the patients' characteristics classified into proteinuria and non-proteinuria groups. Of the 26 patients,

Table II. Comparison of patient characteristics between the RAS-I and CCB groups at 12 weeks following initial ramucirumab treatment.

Parameter	RAS-I group, n=17	CCB group, n=19	P-value
ALT, IU/l	23.9±2.0	23.5±2.2	0.896[b]
AST, IU/l	30.3±1.7	28.1±1.7	0.362[b]
Scr, mg/dl	0.76±0.02	0.80±0.03	0.322[b]
eGFR, ml/min/1.73 m^2	71.7±2.3	65.9±2.5	0.111[b]
Blood pressure, mmHg			
Systolic	133.4±2.3	135.0±2.8	0.676[b]
Diastolic	72.5±1.6	76.2±2.6	0.260[b]
Cumulative RAM dose, mg/body	1,298.1±45.1	1,245.9±44.6	0.432[b]
Cumulative PTX dose, mg/body	371.0±10.3	354.2±10.7	0.279[b]
Proteinuria			0.008[a,c]
Yes	1 (Grade 1)	9 (Grade 1, 6; Grade 2, 3)	
No	16	10	

[a]P<0.05. [b]Student's t-test, [c]Fisher's exact test. Data are presented as the mean ± SEM. AST, aspartate transferase; ALT, alanine aminotransferase; BMI, body mass index; Scr, serum creatinine; eGFR, estimated glomerular filtration rate calculated based on age, sex, and Scr; RAS-I, renin-angiotensin system inhibitors; CCB, calcium channel blockers; RAM, ramucirumab; PTX, paclitaxel.

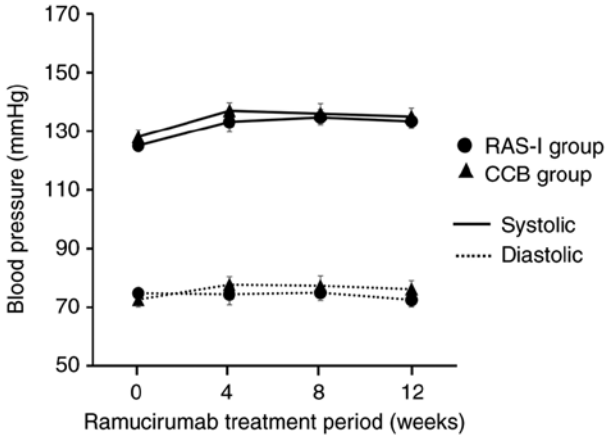

Figure 1. Kaplan-Meier analysis of the cumulative incidence of proteinuria between the RAS-I group and the CCB group. The cumulative incidence of proteinuria in the RAS-I group was significantly lower than that in the CCB group (log rank, P=0.010). CCB, calcium channel blockers; RAS-I, renin-angiotensin system-inhibitors.

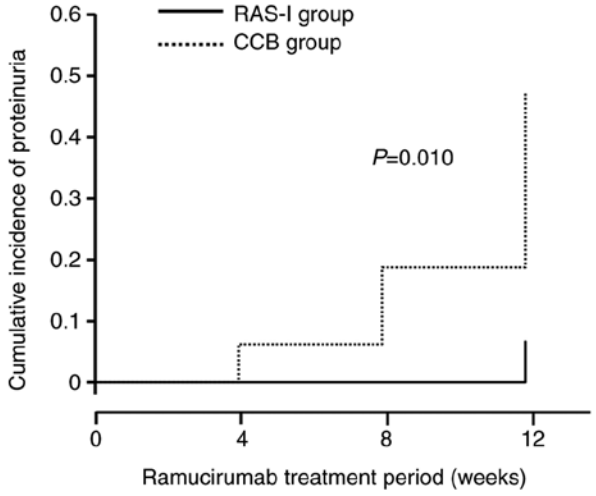

Figure 2. Comparison of the change in blood pressure between the RAS-I group and the CCB group over 12 weeks after initial RAM administration. Data are presented as the mean ± standard error of the mean. There were no significant differences in systolic and diastolic blood pressure profiles at the indicated RAM treatment periods between the two groups, according to two-way ANOVA followed by the Tukey-Kramer test. CCB, calcium channel blockers; RAM, ramucirumab; RAS-I, renin-angiotensin system inhibitors; RAM, ramucirumab.

9 were classified into the proteinuria group and the remaining 17 patients were classified into the non-proteinuria group. At the time of commencing RAM administration, the sex ratio, BMI, ALT, AST, Scr, eGFR, blood pressure, RAM dose, PTX dose, and use of concomitant drugs were not significantly different between the two groups (Table III). At 12 weeks after RAM administration, there remained no significant difference in AST, ALT, Scr, eGFR, blood pressure, and cumulative dose of RAM and PTX between the two groups (Table IV).

Comparison of simulated RAM blood concentrations between the CCB and RAS-I groups. Blood concentration profiles of RAM simulated based on the O'Brien model were compared between CCB and RAS-I groups. There was little difference in the predicted concentration curve of the 5th, 50th and 95th percentile over 12 weeks (2,016 h) after RAM administration between the two groups (Fig. 3A and B). Additionally, there was no significant difference in the predicted minimum steady-state RAM concentrations (trough concentration) at 12 weeks (2,016 h) after RAM administration between CCB (62.9±1.2 μg/ml) and RAS-I (64.2±1.8 μg/ml) groups (Fig. 3C).

Discussion

The objective of this study was to investigate whether RAS-I has an advantage over CCB in proteinuria suppression in

Table III. Comparison of patient characteristics in the proteinuria and non-proteinuria groups at the onset of ramucirumab treatment.

Parameter	Proteinuria, n=10	Non-proteinuria, n=26	P-value
Sex, male/female	7/3	13/13	0.456[a]
Age	64.2±2.1	65.8±1.7	0.602[b]
BMI	20.8±0.7	20.6±0.5	0.836[b]
ALT, IU/l	25.0±2.1	23.9±1.6	0.720[b]
AST, IU/l	26.8±3.2	27.6±1.4	0.803[b]
Scr, mg/dl	0.74±0.03	0.75±0.03	0.871[b]
eGFR, ml/min/1.73 m^2	76.3±3.7	71.3±2.3	0.265[b]
Blood pressure, mmHg			
Systolic	127.3±2.1	125.9±2.8	0.776[b]
Diastolic	72.8±1.8	74.3±1.7	0.625[b]
RAM dose, mg/body	443.5±19.6	427.7±12.4	0.358[b]
PTX dose, mg/body	127.1±3.2	123.9±2.3	0.459[b]
RAS-I			-
Azilsartane	0	4	
Candesartan cilexetil	0	4	
Enalapril	0	2	
Olmesartan	1	4	
Telmisartan	1	1	
CCB			-
Amlodipine	7	6	
Azelnidipine	0	3	
Cilnidipine	0	1	
Nifedipine	1	1	
Diuretics	1	4	-
Concomitant drugs			0.970[c]
Antilipidemic	2	3	
Antipodagric	2	4	
Peptic ulcer	4	17	
Diabetes	1	4	
Antithyroid	2	4	
Bone-building	3	4	
Antithrombogenic and anticoagulant	2	2	
Antipyretic and analgesic	3	7	
Hypnotics	1	6	
Anti-anxiety	2	4	
Laxative	3	5	
Stomachic and intestinal	4	7	
Others	4	8	

[a]Fischer's exact test, [b]Student's t-test, [c]χ^2 test. Data are presented as the mean ± SEM. AST, aspartate transferase; ALT, alanine aminotransferase; BMI, body mass index; Scr, serum creatinine; eGFR, estimated glomerular filtration rate calculated based on age, sex, and Scr; RAS-I, renin-angiotensin system inhibitors; CCB, calcium channel blockers; RAM, ramucirumab; PTX, paclitaxel.

hypertensive patients with gastric cancer receiving RAM treatment. To evaluate this advantage properly, we excluded patients with possible risk factors that may have influenced the evaluation of proteinuria occurrence between the two groups, including a history of VEGF inhibitor use, diabetes, metastatic pancreatic cancer, elevated blood pressure (>160 mmHg), type of cancer, and duration of RAM administration.

Management of blood pressure in cancer patients receiving VEGF inhibitors is closely associated with the prevalence of proteinuria (11). According to The Japanese Society of Hypertension guidelines for the management of hypertension 2019, monotherapy with RAS-I, CCB, or a diuretic is recommended as the first-line therapy for hypertensive patients without complications such as renal or cardiac disease (17).

Table IV. Comparison of patient characteristics in the proteinuria and non-proteinuria groups at 12 weeks following initial ramucirumab treatment.

Parameter	Proteinuria, n=10	Non-proteinuria, n=26	P-value
ALT, IU/l	19.5±1.9	23.2±1.9	0.296[a]
AST, IU/l	25.6±2.7	29.8±1.3	0.131[a]
Scr, mg/dl	0.85±0.06	0.77±0.02	0.256[a]
eGFR, ml/min/1.73 m^2	67.8±3.8	68.3±2.2	0.911[a]
Blood pressure, mmHg			
Systolic	132.4±2.7	135.0±2.3	0.549[a]
Diastolic	72.1±1.6	75.4±2.1	0.368[a]
Cumulative RAM dose, mg/body	1327.1±57.9	1274.0±40.0	0.489[a]
Cumulative PTX dose, mg/body	358.5±29.0	349.4±14.1	0.762[a]

[a]Student's t-test. Data are presented as the mean ± SEM. AST, aspartate transferase; ALT, alanine aminotransferase; BMI, body mass index; Scr, serum creatinine; eGFR, estimated glomerular filtration rate calculated based on age, sex, and Scr; RAS-I, renin-angiotensin system inhibition; CCB, calcium channel blocker; RAM, ramucirumab; PTX, paclitaxel.

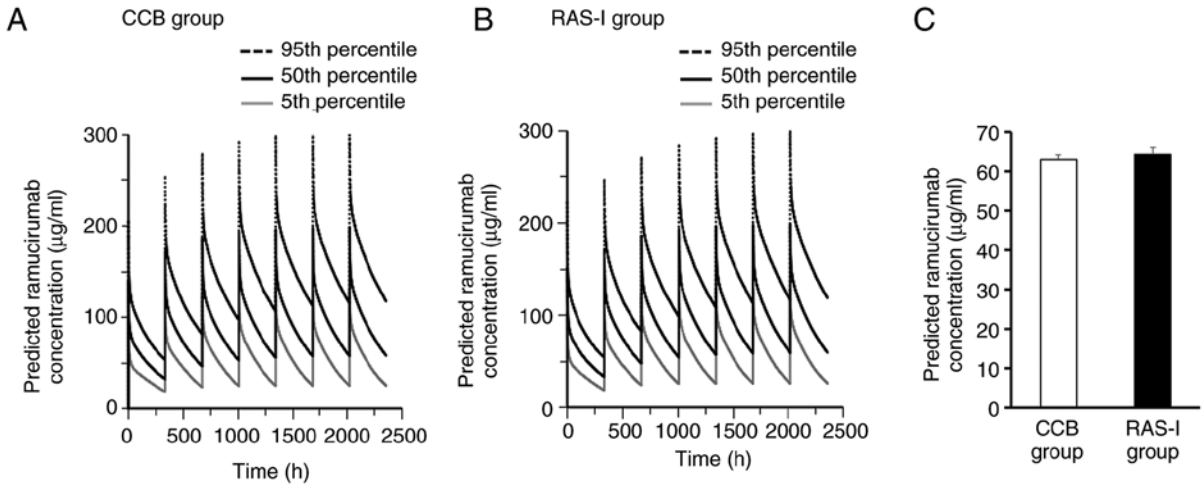

Figure 3. Comparison of the simulated RAM blood concentrations between the CCB and RAS-I groups. Predicted RAM concentration (μg/ml) time profiles following administration of 8 mg/kg every 2 weeks. The gray line and dotted line represent the 5th and 95th percentile RAM concentration calculated from 1,000 simulation iterations. Simulations were performed for patients in the (A) CCB and (B) RAS-I groups. (C) There were no significant differences in the simulated minimum steady-state RAM concentrations (trough concentration) at 12 weeks (2,016 h) after RAM administration between the CCB and RAS-I groups. CCB, calcium channel blockers; RAM, ramucirumab; RAS-I, renin-angiotensin system inhibitors; RAM, ramucirumab.

If the effect of monotherapy is insufficient, concomitant use of two of the aforementioned three agents (RAS-I + CCB, RAS-I + diuretic, or CCB + diuretic) is recommended as a second-line therapy (17). In this study, participants used only diuretics as a concomitant drug with CCB or RAS-I, and there was no significant difference in the use of diuretics between the two groups (Table I, RAS-I group, 2; CCB group, 3). Additionally, we confirmed that the changes in systolic and diastolic blood pressures were not significantly different between the two groups (Fig. 1). These factors suggest that there might not have been a significant difference in the severity of hypertension between the two groups. Moreover, in this study, although the changes in blood pressure over 12 weeks after initial RAM administration were not significantly different between the two groups (Fig. 2), there was a significant difference in both proteinuria occurrence at 12 weeks after RAM administration and cumulative occurrence of proteinuria over 12 weeks after RAM administration between the two groups (Table II, Fig. 1). Additionally, in this study, the mean blood pressure in patients with proteinuria and without proteinuria did not differ (Table IV), indicating that proteinuria in RAM-treated patients was not related to blood pressure. Furthermore, simulation of the time course of RAM blood concentrations based on the O'Brien model showed that there may not be a difference in RAM blood concentration profiles over 12 weeks between the two groups (Fig. 3A-C). These results show that RAS-I may be preferable to CCB when selecting hypertensive agents in hypertensive patients with gastric cancer receiving RAM treatment. Additionally, the difference in proteinuria prevalence between the two groups may be due to the difference in pharmacological action between RAS-I and CCB.

VEGF accelerates endothelial nitric oxidase (NO) synthase (eNOS) phosphorylation and NO production, leading to vasodilatation and vascularization in glomerular endothelial

cells (18,19). VEGF inhibitors, including RAM, cause vasoconstriction by suppressing VEGF/VEGFR-2 signaling (20). Proteinuria is closely associated with glomerular disintegration due to podocyte and glomerular endothelial cells (21). A meta-analysis of patients with hypertension showed that CCB resulted in a significant decrease in albuminuria and proteinuria (22). Additionally, Batova *et al* (23) reported that CCB treatment potentiated VEGF-induced activation of eNOS downstream of VEGFR-2 in bovine aortic endothelial cells. Furthermore, Yuen *et al* (24) showed that acute podocytopathy and heavy proteinuria occurred in eNOS-deficient mice as early as 2 weeks after induction of diabetes with streptozotocin, compared with that in non-eNOS-deficient mice. These results show that the decrease in eNOS activation leads to an increase in proteinuria prevalence and suggest that suppression of proteinuria by CCB may be involved in eNOS activation.

Nakamura *et al* (25) reported that the prevalence of proteinuria in hypertensive patients with chronic kidney disease receiving telmisartan, a RAS-I, was significantly lower than that in patients receiving amlodipine, a CCB, which was consistent with our results. It is well established that AII is a mediator of proteinuria (26). AII increases blood pressure via a decrease in eNOS levels in vascular endothelial cells in various tissues (26,27). Additionally, AII decreases nephrin expression, which is a molecule that constitutes the slit diaphragm in podocytes and suppresses the ultrafiltration barrier in the renal glomerulus (26). These results show that RAS-I may suppress proteinuria via inhibition of eNOS reduction by suppressing the action of AII. Furthermore, AII also induces transforming growth factor-β (TGF-β) expression in tubular endothelial cells (26,28). TGF-β is related to apoptosis in cultured mouse podocytes via upregulation of mitochondrial NADPH oxidase 4, a major inducer of oxidative stress in podocytes (29). This suggests that RAS-I may suppress proteinuria and inhibit eNOS reduction via another mechanism. These multiple mechanisms of RAS-I in suppressing proteinuria may have resulted in the advantage of RAS-I over CCB observed in this study.

In this study, patients in the CCB group had taken amlodipine, azelnidipine, cilnidipine, or nifedipine, and patients in the RAS-I group had taken azilsartan, candesartan cilexetil, enalapril, Olmesartan, or telmisartan (Table I). For the CCB group, an animal study by Nagasu *et al* (30) reported that azelnidipine improved proteinuria compared with amlodipine. For RAS-I, Suehiro *et al* (31) showed that azilsartane had potent antiproteinuric effects compared with candesartan cilexetil. These results imply that RAS-I and CCB have different anti-proteinuria effects. Further studies, including investigating the differences in the anti-proteinuria effect between RAS-I or CCB, should be performed to provide more useful information for medical settings.

In this study, we aimed to investigate which mechanism (inhibition of the renin-angiotensin system or a CCB mechanism) had the superior anti-proteinuria effect in gastric cancer patients with hypertension receiving RAM. To compare the anti-proteinuria effects between RAS-I and CCB groups accurately, we included patients with gastric cancer receiving RAM treatment only to equalize the background characteristics of participants in the two groups as much as possible. We consider that this study bears significant value in the prevalence of proteinuria in the RAS-I group was lower than that in the CCB group, and there was no significant difference in blood pressure control between the two groups during RAM treatment. However, since our study had a small sample size, further studies including more patients should be conducted to verify our results.

This study had several limitations. Firstly, it was a small retrospective investigation conducted in several institutions in a single country. Secondly, the cohort size was small, which constitutes a major limitation of the study. Thirdly, patients with a single type of cancer were selected. Yen *et al* (32) showed that Asian and non-Asian patients with advanced hepatocellular carcinoma showed slightly different incidence rates of hypertension (Asian, 18.5%; non-Asian, 14.9%) and proteinuria (Asian, 20.2%; non-Asian, 23.6%) as adverse effects of RAM. This suggests that race may affect the anti-hypertensive and anti-proteinuria effects of CCB and RAS-I. However, since race is not selected as a significant covariate of RAM pharmacokinetics parameters in population pharmacokinetics analysis, it is possible that race may have little effect on RAM disposition (14). Further studies are required to investigate the racial differences in the anti-proteinuria effects of CCB and RAS-I. Finally, the prevalence of proteinuria was evaluated using a simple urine dipstick method. Evaluating the spot urine albumin-to-creatinine ratio may provide a better assessment of proteinuria than simple urine dipstick measurements. Therefore, our findings require validation in a prospective study using patients with different types of cancer, in which proteinuria and renal function are evaluated with greater reliability and precision.

In conclusion, RAS-I may have an advantage over CCB for suppressing proteinuria in hypertensive patients with gastric cancer who are treated with anti-hypertensive agents for blood pressure management. Our results provide useful information to healthcare professionals involved in the administration of RAM treatment.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

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

Author contributions

TC, HU, YY, KU, ST, KO, KK, and YT collected the patients' data. KS, YN, and TM conducted simulations of ramucirumab blood concentrations. TC performed all data analyses and wrote the manuscript. TM and HS confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This research was conducted according to the Declaration of Helsinki and was reviewed and approved by the Ethics

Committee of each participating institution (Hokkaido University of Science, Approval No. 19-06-022; Iwate Medical University Hospital, Approval No. MH2020-153; Asahikawa university hospital, Approval No. 20119; National Hospital Organization Hokkaido Cancer Center, Approval No. 02-24). Patient consent was obtained though the opt-out method.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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