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ORIGINAL ARTICLE

Renin–angiotensin system inhibitors for countering proteinuria induced by angiogenesis inhibitors: a retrospective observational analysis

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Abstract

Purpose Occurrence of proteinuria could result in cessation of bevacizumab and ramucirumab treatments. Renin–angiotensin system (RAS) inhibitors exert a renoprotective effect by countering proteinuria. However, the association between renoprotective effect of RAS inhibitors and blood pressure control is unclear. This study assessed the risk factors for proteinuria induced by bevacizumab or ramucirumab and the relationship between renoprotective effect of RAS inhibitors and blood pressure control.

Methods A retrospective observational analysis was conducted at Tokyo Women's Medical University, Medical Center East from June 2015 to May 2018. Multivariate logistic regression analysis was used to identify risk factors for proteinuria induced by treatment with bevacizumab and ramucirumab. Renoprotective effect was assessed by analyzing blood pressure data in association with the use of RAS inhibitors.

Results Out of 208 patients included in this study, proteinuria was observed in 50 (24%) patients. Body mass index ≥ 24 kg/m^2 (OR = 2.45, 95% CI 1.21–4.96, $p = 0.01$), colorectal cancer (OR = 1.95, 95% CI 1.00–3.80, $p < 0.05$), and use of RAS inhibitors (OR = 0.25 95% CI 0.07–0.92, $p = 0.04$) were associated with proteinuria induced by treatment with bevacizumab and ramucirumab. A change in systolic blood pressure at second visit was higher in patients with RAS inhibitors compared with those in patients without RAS inhibitors (25 mmHg vs − 5 mmHg, $p = 0.04$).

Conclusion Although RAS inhibitors protected patients from proteinuria induced by bevacizumab or ramucirumab, RAS inhibitors could not adequately control their blood pressures in patients with proteinuria.

Keywords Bevacizumab · Ramucirumab · Proteinuria · Renin–angiotensin system inhibitors · Blood pressure

Introduction

Angiogenesis inhibitors, such as bevacizumab and ramucirumab, significantly prolong overall survival and progression-free survival in various cancers, such as lung, gastric, colorectal, and ovarian cancers [1–4]. Angiogenesis inhibitors exert antitumor effects by inhibiting the binding of vascular endothelial growth factor to its receptor [5].

The toxicity profile of angiogenesis inhibitors differs from those of cytotoxic chemotherapy agents; use of angiogenesis inhibitors is commonly associated with hypertension and proteinuria [1–4]. The occurrence of proteinuria limits the use of angiogenesis inhibitors [6, 7]. In addition, development of proteinuria is not associated with better prognosis [8]. Therefore, it is important to prevent the onset of severe proteinuria induced by angiogenesis inhibitors. Several studies have reported that the use of renin–angiotensin system (RAS) inhibitors to counter proteinuria, because they are known to exert a renoprotective effect [9]. RAS inhibitors have been reported to improve prognosis of cancer patients and prevent development of proteinuria by angiogenesis inhibitors [10–12].

However, it remains unclear how RAS inhibitors protect cancer patients from developing proteinuria. Therefore, we hypothesize that even RAS inhibitors could not control

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blood pressure (BP) in patients with proteinuria induced by angiogenesis inhibitor treatment.

The purpose of this study was to identify the risk factors for bevacizumab- and ramucirumab-induced proteinuria and to elucidate the relationship between renoprotective effect of RAS inhibitors and blood pressure control.

Methods

Study patients and design

A retrospective observational analysis was conducted at Tokyo Women's Medical University, Medical Center East. Patients were included if they were received bevacizumab or ramucirumab between June 2015 and May 2018. Patients were excluded if they were less than 20 years. The study design was approved by the Institutional Review Board of Tokyo Women's Medical University (#4815).

Data collection

Using electronic medical records, demographic data [sex, age, height, body weight, body mass index (BMI), and body surface area], indications for cancer (type of cancer and presence of any metastasis), presence of comorbidity (hypertension), laboratory data [serum creatinine and estimated glomerular filtration rate (eGFR)], administration of angiogenesis inhibitors (doses of bevacizumab and ramucirumab), chemotherapy regimen (fluorouracil-based and platinum-based), medications that influence BP (RAS inhibitors, calcium channel blockers, loop or thiazide diuretics, non-steroidal anti-inflammatory drugs, and Japanese Kampo medicines including licorice), and vital signs [systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR)] were collected. eGFR was calculated using prediction equation as previously described [13]. The presence of hypertension was assessed by prescriptions of antihypertensive drugs. Clinical information was collected from the initial administration of bevacizumab or ramucirumab to the end of the treatment.

Assessment of vital signs

SBP, DBP, and HR were recorded at the time of visits to our institution. In addition to SBP and DBP, pulse pressure (PP) and mean arterial pressure (MAP) were used in subsequent analysis, because the previous reports demonstrated their association with the development of proteinuria [14, 15]. PP and MAP were calculated as follows: PP = SBP – DBP, and MAP = DBP +1/3 PP.

Changes in vital signs during bevacizumab or ramucirumab treatment were calculated following the equation: changes in vital signs = vital signs at a certain visit—those before the first administration of bevacizumab or ramucirumab. Changes in vital signs were calculated and compared stratified by the presence of proteinuria if SBP, DBP, and HR were recorded for more than 50% of the study population.

Outcome

Primary outcome was defined as an occurrence of grade ≥ 2 proteinuria according to the CTCAE [16]. We used this definition, because Izzedine reported that ≥ 1 g per day proteinuria was recommended to consult nephrologist [17]. Proteinuria was assessed by urinary protein-to-creatinine ratio. We checked the presence of causes for proteinuria other than bevacizumab or ramucirumab from electronic medical records. If patients experienced multiple primary outcomes, data of the first event were adopted.

Statistical analysis

Continuous variables are expressed as mean and standard deviation or median and interquartile range (IQR) as needed. Student's *t* test or Mann–Whitney's *U* test was used to compare continuous variables. Categorical variables are expressed as number and percentage. Chi-square test or Fisher's exact test was used to examine heterogeneity.

To investigate risk factors for grade ≥ 2 proteinuria, we performed multivariate logistic regression analysis. Dependent variable was an occurrence of grade ≥ 2 proteinuria. Independent variables were demographic data, indications for cancer, presence of comorbidity, laboratory data, chemotherapy regimen, medications, and changes in vital signs between first and second visits. BMI was categorized into two groups using the cut-off value determined by receiver operating characteristic curve. Type of cancer was categorized into binary variables, because colorectal cancers have a high prevalence of proteinuria compared to lung cancers [18]. eGFR was categorized into two groups (< 60 mL/min/1.73 m^2 and ≥ 60 mL/min/1.73 m^2) according to the definition of chronic kidney disease. Univariate logistic regression analysis was performed to identify potential independent variables for grade ≥ 2 proteinuria. Potential independent variables were considered if *p* value was less than 0.20. We checked if there was a multicollinearity between independent variables, we selected one of them based on clinical relevance. Using the stepwise forward selection method, the final logistic regression model was determined according to Akaike's Information Criterion. Multivariate logistic regression analysis was performed to determine odds ratio (OR) and 95% confidence interval (95% CI). Interactions between independent variables and angiogenesis inhibitors were assessed in the final model.

Changes in vital signs during bevacizumab or ramucirumab treatment were stratified by the presence of proteinuria and the use of RAS inhibitors to investigate whether RAS inhibitors exerted antiproteinuric effect by lowering BP values.

Statistical analyses were performed using JMP Pro 14 (SAS Institute, Cary, NC, USA). A p value less than 0.05 was considered statistically significant unless otherwise noted.

Results

Among the 208 patients included in this study, 171 (82%) received bevacizumab and 37 (18%) patients received ramucirumab during study period. All patients were > 20 years. Figure 1 shows the flow chart of patient selection. Table 1 shows in the clinical characteristics of patients before the first administration of bevacizumab or ramucirumab. Vital signs during bevacizumab or ramucirumab treatment stratified by the presence of proteinuria are shown in Table 2. Vital signs were measured for more than 50% of study population from the initiation of bevacizumab or ramucirumab treatment to fifth visit at our institution. There were two patients who were required to intensify hypertensive treatment over this time period. Changes in vital signs were comparable between the two groups irrespective of the presence of proteinuria (Table 2).

Out of 208, 50 (24%) patients had grade ≥ 2 proteinuria. There were no patients having any causes for proteinuria other than bevacizumab or ramucirumab. Median [IQR] treatment duration was 149 [62–274] days for patients with proteinuria and 322 [156–517] days for patients without proteinuria. Among proteinuric patients, 30 (60%) patients continued the treatment of bevacizumab or ramucirumab, 4 (8%) patients discontinued the treatment of bevacizumab or ramucirumab due to proteinuria, and 11 (22%) patients discontinued the treatment of bevacizumab or ramucirumab because of other side effects such as hypertension and thrombosis. The remaining 5 (10%) patients discontinued bevacizumab or ramucirumab by a reason irrelevant to angiogenesis inhibitors treatment.

The receiver operating characteristic curve determined that BMI cut-off value was set at 24 kg/m^2. Univariate logistic regression analysis revealed that male sex, height, BMI ≥ 24 kg/m^2, colorectal cancer, presence of metastasis, eGFR < 60 mL/min/1.73 m^2, fluorouracil-based regimen, use of RAS inhibitors, use of non-steroidal anti-inflammatory drugs, and changes in SBP and PP between first and second visit were associated with an occurrence of grade ≥ 2 proteinuria. There was no multicollinearity between independent variables. Using a stepwise forward selection method, BMI ≥ 24 kg/m^2, colorectal cancer, and the use of RAS inhibitors were risk factors for the development of grade ≥ 2 proteinuria. Multivariate logistic regression analysis revealed that body mass index ≥ 24 kg/m^2 (OR = 2.45, 95% CI 1.21–4.96, $p = 0.01$), colorectal cancer (OR = 1.95, 95% CI 1.00–3.80, $p < 0.05$), and the use of RAS inhibitors (OR = 0.25, 95% CI 0.07–0.92, $p = 0.04$) were associated with the development of grade ≥ 2 proteinuria (Table 3). The final model had no interactions between independent variables and bevacizumab or ramucirumab treatment.

All changes in vital signs were comparable in patients without proteinuria, regardless of the use of RAS inhibitors (Table 4). On the other hand, changes in SBP between first and second visit were significantly higher in patients with proteinuria and treated with RAS inhibitors than in those with proteinuria but not treated with RAS inhibitors ($p = 0.04$, Table 5).

Discussion

This study identified BMI ≥ 24 kg/m^2 and colorectal cancer as risk factors for proteinuria when the patient is under treatment with bevacizumab and ramucirumab. On the contrary, although the use of RAS inhibitors had a renoprotective effect and allow patients to complete the treatment, RAS inhibitors could not control BP in patients with proteinuria.

The previous studies indicated that diabetes was associated with the occurrence of proteinuria during bevacizumab treatment [19]. However, we could not collect data regarding diabetes in our study; therefore, we could not perform multivariate logistic regression analysis. Furthermore, SBP before administration of bevacizumab or ramucirumab was not a risk factor for proteinuria in our study (data not shown), even when cut-off value was set at SBP ≥ 130 mmHg which is a risk factor for proteinuria induced by bevacizumab [20]. The reason for this remains unclear, and other patient characteristics may have a greater role in causing proteinuria. Although

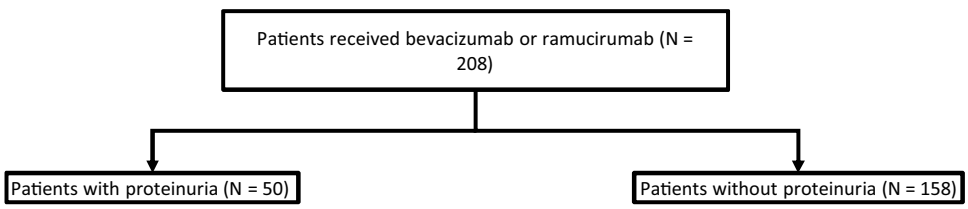

Fig. 1 Flow chart of patient's selection

Table 1 Clinical characteristics of patients before the first administration of bevacizumab or ramucirumab

	No proteinuria ($N=158$)	Proteinuria ($N=50$)	p value
Demographical data			
Male, *n* (%)	91 (58)	23 (46)	0.15
Age, years	67 ± 12	69 ± 12	0.44
Height, cm	160.7 ± 9.6	158.0 ± 9.7	0.08
Body weight, kg	55.5 ± 11.2	56.1 ± 11.5	0.74
Body mass index, kg/m^2	21.4 ± 3.6	22.4 ± 3.8	0.10
Body mass index ≥ 24 kg/m^2, *n* (%)	35 (22)	20 (40)	0.01
Body surface area, m^2	1.57 ± 0.18	1.56 ± 0.19	0.68
Type of cancer			
Lung cancer, *n* (%)	42 (27)	12 (24)	0.72
Gastric cancer, *n* (%)	35 (22)	2 (4)	< 0.01
Colorectal cancer, *n* (%)	60 (38)	27 (54)	0.05
Others, *n* (%)	21 (13)	9 (18)	0.41
Presence of metastasis, *n* (%)	90 (57)	22 (44)	0.11
Comorbidity			
Hypertension, *n* (%)	39 (25)	11 (22)	0.91
Laboratory data			
Serum creatinine, mg/dL	0.69 [0.58–0.87][a]	0.81 [0.64–0.93][a]	0.07
eGFR, mL/min/1.73 m^2	74.3 ± 22.8	65.7 ± 19.8	0.02
eGFR < 60 mL/min/1.73 m^2, n (%)	36 (23)	19 (38)	0.03
Angiogenesis inhibitors			
Bevacizumab/Ramucirumab, *n* (%)/*n* (%)	123 (78)/35 (22)	48 (96)/2 (4)	< 0.01
Bevacizumab dose, mg	500 [360–700][a]	490 [311–688][a]	0.41
Ramucirumab dose, mg	400 [352–456][a]	400 [300–500][a]	0.92
Chemotherapy regimen			
Fluorouracil-based, *n* (%)	61 (39)	25 (50)	0.15
Platinum-based, *n* (%)	63 (40)	16 (32)	0.32
Medications			
RAS inhibitors, *n* (%)	24 (15)	3 (6)	0.09
Calcium channel inhibitors, *n* (%)	25 (16)	10 (20)	0.49
Loop or thiazide diuretics, *n* (%)	18 (11)	4 (8)	0.50
NSAIDs, *n* (%)	29 (18)	4 (8)	0.08
Japanese Kampo medicine including licorice, *n* (%)	11 (7)	3 (6)	0.82
Vital signs before administration			
SBP, mmHg	131.3 ± 21.4	132.5 ± 18.6	0.73
DBP, mmHg	77.2 ± 14.4	77.6 ± 13.5	0.86
HR, bpm	82.8 ± 15.3	79.4 ± 11.7	0.16
PP[b], mmHg	54.1 ± 13.8	54.8 ± 11.9	0.73
MAP[c], mmHg	95.2 ± 15.8	95.9 ± 14.3	0.80

Continuous variables are expressed as mean ± standard deviation or median [interquartile range] as needed. Categorical variables are expressed as the number and percentage

bpm beats per minute, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *HR* heart rate, *MAP* mean arterial pressure, *NSAIDs* non-steroidal anti-inflammatory drugs, *PP* pulse pressure, *RAS inhibitors* renin–angiotensin system inhibitors, *SBP* systolic blood pressure

[a]Data are expressed as median [interquartile range]

[b]Pulse pressure was calculated by the equation: systolic blood pressure minus diastolic blood pressure

[c]Mean arterial pressure was calculated by the equation: diastolic blood pressure plus a third of pulse pressure

Table 2 Changes in vital signs during angiogenesis inhibitor treatment stratified by the presence of proteinuria

Timing	Proteinuria	ΔSBP (mmHg)	ΔDBP (mmHg)	ΔHR (bpm)	ΔPP (mmHg)	ΔMAP (mmHg)
First visit	No proteinuria ($N=153$)	0	0	0	0	0
	Proteinuria ($N=50$)	0	0	0	0	0
Second visit	No proteinuria ($N=153$)	2 [– 7 to 16]	2 [– 7 to 10]	1 [– 5 to 9] [a]	1 [– 7 to 9]	2 [– 5 to 10]
	Proteinuria ($N=50$)	– 4 [– 11 to 13]	0 [– 7 to 6]	2 [– 5 to 8]	– 2 [– 10 to 5]	– 2 [– 6 to 7]
Third visit	No proteinuria ($N=142$)	2 [– 11 to 14]	2 [– 6 to 9]	3 [– 5 to 11][b]	1 [– 9 to 9]	2 [– 7 to 11]
	Proteinuria ($N=50$)	5 [– 6 to 21]	4 [– 2 to 11]	0 [– 6 to 11][b]	2 [– 7 to 12]	3 [– 3 to 14]
Fourth visit	No proteinuria ($N=129$)	3 [– 12 to 18]	2 [– 5 to 12]	3 [– 5 to 13][b]	1 [– 6 to 9]	2 [– 8 to 14]
	Proteinuria ($N=45$)	5 [– 9 to 22]	3 [– 6 to 14]	1 [– 8 to 10]	6 [– 5 to 15]	4 [– 4 to 15]
Fifth visit	No proteinuria ($N=115$)	3 [– 10 to 11]	1 [– 7 to 10]	1 [– 6 to 8][b]	0 [– 8 to 8]	1 [– 8 to 9]
	Proteinuria ($N=42$)	3 [– 14 to 18]	2 [– 8 to 8]	0 [– 10 to 8]	2 [– 7 to 11]	3 [– 8 to 13]

Data are expressed as median [interquartile range]. We could not obtain vital signs in five patients without proteinuria at the initiation of treatment. All patients with proteinuria were recorded vital signs at the initiation of treatment. Changes in vital signs during bevacizumab or ramucirumab treatment were calculated following the equation: vital signs at each administration minus those at first administration of bevacizumab or ramucirumab

bpm beats per minute, *DBP* diastolic blood pressure, *HR* heart rate, *MAP* mean arterial pressure, *PP* pulse pressure, *SBP* systolic blood pressure

[a]There are two missing values

[b]There is one missing value

Table 3 Multivariate logistic regression analysis for proteinuria

	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Male	0.63	0.33–1.19	0.15			
Body mass index ≥ 24 kg/m^2	2.34	1.19–4.62	0.02	2.45	1.21–4.96	0.01
Colorectal cancer	1.92	1.01–3.64	0.05	1.95	1.00–3.80	< 0.05
Presence of metastasis	0.59	0.31–1.13	0.11			
eGFR < 60 mL/min/1.73 m^2	2.09	1.05–4.17	0.04			
Fluorouracil-based	1.59	0.84–3.02	0.15			
Use of RAS inhibitors	0.36	0.10–1.24	0.09	0.25	0.07–0.92	0.04
Use of NSAIDs	0.39	0.13–1.16	0.08			
Change in SBP between first and second visit	1.02	1.00–1.04	0.09			
Change in PP[a] between first and second visit	1.02	0.99–1.05	0.16			

95% CI 95% confidence interval, *NSAIDs* non-steroidal anti-inflammatory drugs, *OR* odds ratio, *PP* pulse pressure, *RAS inhibitors* renin–angiotensin system inhibitors, *SBP* systolic blood pressure

[a]Pulse pressure was calculated by the equation: systolic blood pressure minus diastolic blood pressure

a clinical trial demonstrated that ramucirumab was associated with the development of proteinuria [2], few reports investigated the risk factors for developing ramucirumab-induced proteinuria. A meta-analysis revealed a higher incidence of adverse events in East Asian patients treated with ramucirumab [21]. However, there were not enough patients to investigate sensitivity analysis focusing on angiogenesis inhibitors in this study.

BMI ≥ 24 kg/m^2 is associated with occurrence of proteinuria by bevacizumab or ramucirumab. The previous reports demonstrated that obesity was recognized as a risk factor for the development of proteinuria [22–24] and these supports our results. Obesity activates the RAS system, resulting in the augmentation of intraglomerular pressure and promoting the activity of sympathetic nervous system, leading to kidney injury [25, 26]. Although we could not measure serum aldosterone levels and sympathetic nervous system activity, or collect renal biopsy data, clinicians should pay close attention to obese patients receiving bevacizumab or ramucirumab treatment.

The incidence of proteinuria in colorectal cancer patients was higher than that in non-small-cell lung cancer patients [18]. In addition, high incidence of hypertension was also observed in colorectal cancer patients [18] and this may contribute to an occurrence of proteinuria. Proteinuria was associated with increased mortality in digestive organ cancer

Table 4 Changes in vital signs during angiogenesis inhibitor treatment in patients without proteinuria stratified by the use of renin–angiotensin system inhibitors

Timing	Treatment	ΔSBP (mmHg)	ΔDBP (mmHg)	ΔHR (bpm)	ΔPP (mmHg)	ΔMAP (mmHg)
First visit	No RAS inhibitors ($N=130$)	0	0	0	0	0
	RAS inhibitors ($N=23$)	0	0	0	0	0
Second visit	No RAS inhibitors ($N=130$)	2 [– 6 to 16]	2 [– 4 to 9]	3 [– 6 to 10]	1 [– 7 to 9]	2 [– 4 to 11]
	RAS inhibitors ($N=23$)	– 2 [– 15 to 22]	– 3 [– 7 to 9]	– 1 [– 7 to 7][a]	– 1 [– 4 to 10]	0 [– 9 to 10]
Third visit	No RAS inhibitors ($N=119$)	4 [– 11 to 15]	2 [– 6 to 8]	2 [– 5 to 11][b]	1 [– 8 to 10]	3 [– 7 to 10]
	RAS inhibitors ($N=23$)	3 [– 12 to 18]	3 [– 6 to 12]	2 [– 5 to 11]	1 [– 6 to 8]	2 [– 8 to 14]
Fourth visit	No RAS inhibitors ($N=108$)	3 [– 12 to 18]	3 [– 6 to 12]	2 [– 5 to 11][b]	1 [– 6 to 8]	2 [– 8 to 14]
	RAS inhibitors ($N=21$)	5 [– 13 to 15]	0 [– 4 to 11]	6 [– 2 to 18]	1 [– 11 to 11]	2 [– 7 to 12]
Fifth visit	No RAS inhibitors ($N=96$)	3 [– 9 to 11]	2 [– 7 to 10]	1 [– 6 to 8][b]	0 [– 8 to 7]	1 [– 8 to 9]
	RAS inhibitors ($N=19$)	2 [– 13 to 13]	– 1 [– 6 to 10]	2 [– 10 to 13]	0 [– 9 to 9]	1 [– 8 to 10]

Data are expressed as median [interquartile range]. We could not obtain vital signs in four patients without RAS inhibitors and 1 patient with RAS inhibitors at the initiation of treatment. Changes in vital signs during bevacizumab or ramucirumab treatment were calculated following the equation: vital signs at each administration minus those at first administration of bevacizumab or ramucirumab

bpm beats per minute, *DBP* diastolic blood pressure, *HR* heart rate, *MAP* mean arterial, pressure, *PP* pulse pressure, *RAS inhibitors* renin–angiotensin system inhibitors, *SBP* systolic blood pressure

[a]There are 2 missing values

[b]There is 1 missing value

Table 5 Changes in vital signs during angiogenesis inhibitor treatment in patients with proteinuria stratified by the use of renin–angiotensin system inhibitors

Timing	Treatment	ΔSBP (mmHg)	ΔDBP (mmHg)	ΔHR (bpm)	ΔPP (mmHg)	ΔMAP (mmHg)
First visit	No RAS inhibitors ($N=47$)	0	0	0	0	0
	RAS inhibitors ($N=3$)	0	0	0	0	0
Second visit	No RAS inhibitors ($N=47$)	– 5 [– 11 to 12]	2 [– 5 to 8]	0 [– 7 to 4]	– 2 [– 10 to 4]	– 4 [– 7 to 16]
	RAS inhibitors ($N=3$)	25 [2 to 35][*]	0 [– 15 to 14]	14 [0 to 26]	2 [– 1 to 21]	21 [1 to 26]
Third visit	No RAS inhibitors ($N=47$)	4 [– 7 to 19]	3 [– 2 to 9]	0 [– 5 to 10][a]	1 [– 8 to 11]	2 [– 3 to 14]
	RAS inhibitors ($N=3$)	30 [– 1 to 35]	13 [– 2 to 16]	2 [– 8 to 35]	14 [1 to 22]	20 [– 2 to 21]
Fourth visit	No RAS inhibitors ($N=42$)	5 [– 9 to 21]	2 [– 8 to 11]	0 [– 8 to 10]	6 [– 5 to 14]	2 [– 5 to 11]
	RAS inhibitors ($N=3$)	26 [4 to 52]	18 [6 to 20]	2 [– 12 to 25]	8 [– 2 to 32]	21 [5 to 31]
Fifth visit	No RAS inhibitors ($N=39$)	2 [– 14 to 17]	2 [– 9 to 8]	0 [– 10 to 8]	2 [– 7 to 10]	3 [– 7 to 10]
	RAS inhibitors ($N=3$)	21 [– 14 to 45]	9 [– 6 to 21]	1 [– 14 to 16]	12 [– 8 to 24]	13 [– 9 to 29]

Data are expressed as median [interquartile range]. All patients were recorded vital signs at the initiation of treatment irrespective of the use of RAS inhibitors. Changes in vital signs during bevacizumab or ramucirumab treatment were calculated following the equation: vital signs at each administration minus those at first administration of bevacizumab or ramucirumab

bpm beats per minute, *DBP* diastolic blood pressure, *HR* heart rate, *MAP* mean arterial, pressure, *PP* pulse pressure, *RAS inhibitors* renin–angiotensin system inhibitors, *SBP* systolic blood pressure

*$p=0.04$ versus no RAS inhibitors using Mann–Whitney's U test

[a]There is 1 missing value

patients [27]. Notably, colorectal cancer patients with proteinuria have a poor prognosis [28]. We should follow up proteinuria during treatment of angiogenesis inhibitor in colorectal cancer. Further studies are required to clarify this reason.

RAS inhibitors reduce not only BP, but also proteinuria and intraglomerular pressure by dilating efferent arterioles [29, 30]. RAS inhibitors prevent cardiovascular events [29] and are effective treatment options for certain cancers, such as renal cell and hepatocellular carcinomas [10, 11]. Our results demonstrate that RAS inhibitors have an antiproteinuric effect. Therefore, RAS inhibitors could be suitable for patients undergoing angiogenesis inhibitor treatment in the point of antiproteinuric effect as well as prognosis for cancer.

It is believed that RAS inhibitors lower BP; however, our results revealed that patients with proteinuria have elevated SBP despite the use of RAS inhibitors. These findings implied that aggressive treatment of hypertension targeting

SBP may be required for proteinuric patients who did not respond to RAS inhibitors. Although all BP parameters were correlated with the development of proteinuria, SBP was the best predictor for the development of proteinuria [31]. RAS inhibitors improved urinary vascular endothelial growth factor levels, BP, and albumin excretion rates in diabetic nephropathy patients [32]. Compared to our results, these findings were controversial in terms of BP control. This difference may be attributed to the sensitivity of RAS inhibitors. For instance, calcium channel blockers increased the development of proteinuria induced by angiogenesis inhibitors [12]. Additional studies using a large sample size are required to validate these results.

This study has several limitations. First, this was a single-center retrospective observational study, and we could not collect data on genetic factors related to angiogenesis inhibitors affecting sensitivity of antiangiogenetic medications [33], patient compliance, or performance status. In addition, none of the patients received aflibercept or other antihypertensive medication (α_1 blockers and β blockers). Second, owing to the small sample size, we could not perform further analysis to identify how to use RAS inhibitors to prevent proteinuria induced by bevacizumab or ramucirumab. Third, the frequency of measuring proteinuria differed among study patients, potentially leading to a bias. Fourth, we used urine protein-to-creatinine ratio to assess proteinuria, which may be inaccurate compared to diagnosing proteinuria based on 24-h urine samples [34]. Finally, it remains unclear whether intensification of hypertensive treatment was performed at another institution.

Conclusion

In summary, clinicians should take particular care to monitor the occurrence of proteinuria induced by treatment with bevacizumab or ramucirumab in obese and colorectal cancer patients. RAS inhibitors have a renoprotective effect and high SBP may represent no renoprotective effect of RAS inhibitors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. For this type of study, formal consent is not required.

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