Original Article

Severe hypertension development significantly improves progression-free survival in regorafenib treatment for metastatic colorectal cancer

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ABSTRACT

Purpose

Regorafenib is the first multikinase inhibitor used for metastatic colorectal cancer (mCRC) treatment. Reports regarding other multikinase inhibitors have suggested that the development of hypertension is associated with improved clinical benefits. We aimed to reveal the relationship between the development of severe hypertension and regorafenib efficacy in an mCRC real-world setting.

Methods

Patients with mCRC (n=100) who received regorafenib were assessed retrospectively. The primary endpoint was a comparison of progression-free survival (PFS) between patients with and without ≥grade 3 hypertension. The secondary endpoints were overall survival (OS), disease control rate (DCR), and adverse effects.

Results

Patients developing ≥grade 3 hypertension accounted for 30%, and obtained significantly longer PFS than control patients (median PFS of 53 and 56 days, 95% confidence interval [CI] of 46–144 and 49–63 days, respectively; *P*=0.04). In contrast, OS and DCR were not statistically different between the groups (*P*=0.13 and *P*=0.46, respectively). The incidence and severity of adverse effects were not significantly different, except for hypertension. Treatment interruption was significantly more

frequent in patients with hypertension (*P*=0.04). Multivariate Cox hazard analysis suggested that the development of ≥grade 3 severe hypertension was an independent factor for improved PFS (adjusted hazard ratio 0.57, 95% CI 0.35–0.93; *P*=0.02). In contrast, baseline hypoalbuminemia was associated with a worse PFS (1.85, 1.14–3.01; *P*=0.01).

Conclusion

We have revealed that patients who develop severe hypertension after regorafenib treatment for mCRC have improved PFS. Management of hypertension is important for effective treatment with less burden; therefore, further evaluation is needed.

Keywords: regorafenib, severe hypertension, metastatic colorectal cancer (mCRC), vascular endothelial growth factor (VEGF), progression-free survival, multikinase inhibitor

Introduction

Regorafenib is the first small-molecule multikinase inhibitor for metastatic colorectal cancer (mCRC) treatment that blocks the pathways of tumor angiogenesis (vascular endothelial growth factor receptor [VEGFR] 1–3, TIE2), oncogenesis (KIT, RET, RAF1, BRAF, and BRAFV600E), and the tumor microenvironment (platelet-derived growth factor receptor and fibroblast growth factor receptor) [1, 2]. In contrast, severe adverse effects such as hand-foot skin reaction (HFSR), hypertension, and liver dysfunction induce treatment interruption (49%), dose reduction (42%), and treatment discontinuation (35%) [3]. These symptoms usually appear within the first 4 weeks after regorafenib initiation [3], therefore, cautious monitoring during the early stages of treatment is required.

We have reported that 55% of patients developed hypertension, including 30% of ≥ grade 3 cases in regorafenib mCRC treatment [4]. The mechanisms underlying multikinase inhibitor-induced hypertension include decreased nitric oxide production, increased endothelin-1, activation of the renin-angiotensin-aldosterone system, and capillary rarefaction, all of which are caused by the anti-VEGF effect [1, 5, 6], suggesting that symptom occurrence can reflect clinical benefits. Several studies suggested the correlation between bevacizumab (the most representative anti-VEGF

monoclonal antibody)-induced hypertension and better disease control [7–10]. In another report regarding initial multikinase inhibitor treatment with a few mCRC patients receiving regorafenib, hypertension development while on multikinase inhibitor treatment, age <60 years, renal cell carcinoma and gastrointestinal stromal tumor, and body mass index (BMI) ≥25 kg/m^2 were associated with improved survival benefits [11]. In contrast, patients with mCRC generally receive anti-VEGF agents such as bevacizumab, ramucirumab, and aflibercept beta in front-line treatment for a certain period of time [12], suggesting that patients receiving regorafenib in a real-world setting are different from those evaluated in the reported studies.

In the present study, we aimed to determine whether patients with severe hypertension developed better regorafenib efficacy in real-world mCRC treatments.

Methods

1. Patients

Patients with mCRC who received regorafenib between May 2013 and March 2022 at the Hokkaido University Hospital were retrospectively evaluated. All enrolled patients met the following inclusion criteria: (1) age ≥20 years, (2) sufficient liver and renal function for regorafenib induction, (3) 0 to 2 Eastern Cooperative Oncology Group

performance status (ECOG-PS), and (4) sufficient information available from medical records. Patients who had uncontrolled baseline hypertension (≥grade 3 symptoms), discontinued the treatment due to severe adverse effects or disease progression within the first week after initiation, and transferred to another hospital during the treatment were excluded. The patient population in the present study was the same as that in our previous evaluation of risk factors for severe hypertension development [4]. The patients were divided into two groups: a control group with ≤grade 2 hypertension during regorafenib treatment from May 2013 to March 2022, and a hypertensive group with ≥grade 3 regorafenib-induced severe hypertension from May 2013 to October 2021. This study was approved by the Ethical Review Board for Life Science and Medical Research of Hokkaido University Hospital (approval number:022-0064), and was performed in accordance with the Declaration of Helsinki and the STROBE statement. Given the retrospective nature of this study, the requirement for informed consent was waived.

2. Treatment methods

Regorafenib at a dose of 80–160 mg/day on days 1–21, every 4 weeks was orally administered [1, 2]. When the patient received a reduced starting dosage, it was increased (40 mg weekly, up to 160 mg) depending on adverse effects, as reported in a

previous report [13]. Treatment interruption and/or dose reduction was conducted according to the criteria stated in the medical package insert [14]. Antihypertensive medications, such as angiotensin II receptor blockers (ARB), calcium channel blockers, and diuretics, were administered to attenuate the symptoms at the physician's discretion.

3. Survey of the incidence and severity of hypertension, and regorafenib treatment efficacy

All the required patient information was obtained from the patients' medical records. Patients basically visited the hospital weekly during the first two months to assess adverse effects. Physicians or pharmacists evaluated adverse effects by referring to the treatment diary, which all patients kept, in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 at every visit. The incidence and severity of adverse effects during the entire treatment period were assessed. Hypertension in this study was defined as the occurrence of any of the following: 1) diagnosis of hypertension in the medical records, 2) at least one antihypertensive medication prescription, and 3) blood pressure (home and visit) ≥CTCAE grade 2, as in our previous study [4]. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were overall survival (OS), disease control rate (DCR), and safety between the two groups. As baseline primary hypertension and prior anti-VEGF

treatment for ≥700 days were suggested as independent risk factors for ≥grade 3 reforafenib-induced hypertension in our previous study [4], we additionally assessed PFS and OS between patients with and without these factors. PFS was calculated from the date of regorafenib initiation until disease progression, death, or last follow-up. OS was defined as the time from the initiation of regorafenib administration until death from any cause or last follow-up. Tumor response was classified as complete response, partial response, stable disease, or progressive disease, according to the Response Evaluation Criteria in Solid Tumors (version 1.1).

4. Statistical analysis

The differences in baseline clinical characteristics between the control and hypertensive groups were assessed using Fisher's exact probability test for categorical outcome variables and the Mann-Whitney *U* test for continuous parameters. PFS and OS were analyzed in an intention-to-treat manner using the Kaplan-Meier method, and the differences were compared using the log-rank test. Univariate and multivariate Cox proportional hazard regression was used to adjust the PFS results from clinical variables including sex, age, ECOG-PS, clinical stage, KRAS status, primary lesion, body surface area, BMI, existence of liver metastasis, hypoalbuminemia, liver dysfunction (grade 2 or higher aspartate aminotransferase, alanine aminotransferase, total bilirubin

elevation), renal dysfunction (creatinine clearance less than 60 mL/min), number of previously administered anti-VEGF agents at baseline, dose reduction from treatment initiation, development of ≥grade 3 HFSR or hypertension, and hypertension development within 7 days from regorafenib initiation by referring previous reports [4, 11]. Variables that showed a potential association in the univariate analysis (P<0.10) were considered when building the multivariable model. All analyses were performed using JMP version 16.2 statistical software (SAS Institute Japan, Tokyo, Japan). Statistical significance was set at P value <0.05.

Results

1. Patient characteristics

A total of 100 patients with mCRC were enrolled in this study (Figure 1). Patients developing ≥grade 3 hypertension accounted for 30% of the patients. Baseline patient characteristics of the control and hypertensive groups are shown in Table 1. Patients with baseline preexisting hypertension, particularly hypertension complications before the first anti-VEGF treatment (primary hypertension), were significantly more likely to be included in the hypertension group. In addition, patients in the hypertensive group received multiple antihypertensive treatments at a higher rate than those in the control

group. The starting dose was not significantly different between the groups. The number of treatments tended to be higher in the hypertensive group than the control group, but the difference was not significant. As described in the previous manuscript, the median appearance time of ≥grade 3 hypertension was 7 days from treatment initiation (range: 1–56 days) [4]. Symptoms developed within 7 days in 70% of the patients, days 8–14 in 16.7%, and days 35–56 in 13.3% [4].

2. Treatment efficacy

Figure 2 shows the Kaplan-Meier plots of PFS and OS after regorafenib treatment. Patients in the hypertensive group had a significantly longer PFS than those in the control group (median PFS of 53 and 56 days, 95% confidence interval [CI] of 46–144 and 49–63 days, respectively; *P*=0.04). In contrast, the median OS in the hypertensive group was 205 days (148–423 days), which was not significantly different from that in the control group (187 days; 145–267 days; *P*=0.13). The DCR in the control and hypertensive groups was not significantly different (24.3% vs. 33.3%, respectively, without complete and partial responses; *P*=0.46).

3. Adverse effects and regorafenib dosage

Table 2 shows major adverse effects during regorafenib treatment. Incidence of all and severe grades of HFSR, diarrhea, fatigue, anorexia, and liver dysfunction were not

statistically different between the groups. Patients in the hypertensive group tended to experience fatigue, which was considered to be derived from severe hypertension, in higher rates, but was not significantly different.

Treatment interruption due to adverse effects was observed in 60.0% of the patients in the control group and 83.3% of the patients in the hypertensive group, which was significantly different (P=0.04). Dose reduction from the starting dosage was observed in 24.5% of the control patients and 36.2% of the hypertensive patients (P=0.27). Only two patients in the control group received dose escalation (80 mg to 120 mg and 120 mg to 160 mg). The final regorafenib dosage in the control and hypertensive groups was 20.0% for 160 mg in both groups, 28.6% and 40.0% for 120 mg, respectively, and 51.4% and 40.0% for 80 mg, respectively, which were not significantly different (P=0.43).

4. Association between patient factors and regorafenib PFS

We also evaluated the association between patient characteristics and PFS (Table 3). Multivariate Cox hazard analysis suggested that the development of ≥grade 3 severe hypertension was an independent factor for improved PFS (adjusted hazard ratio 0.57, 95% CI 0.35–0.93; P=0.02). In contrast, baseline hypoalbuminemia was associated with a worse PFS (1.85, 1.14–3.01; P=0.01). Severe HFSR development and dose reduction

from treatment initiation tended to be, but not statistically, associated with PFS.

Discussion

We have previously reported that 30% of regorafenib-receiving patients develop severe hypertension, which is predominantly caused by the anti-VEGF effect, in a real-world setting [4]. As the anti-VEGF effect is one of the main antitumor mechanisms of regorafenib, we considered that patients developing severe hypertension may obtain better clinical benefits and evaluated its correlation.

As a result, patients developing ≥grade 3 regorafenib-induced hypertension had a longer PFS than those with ≤grade 2 symptoms. This is the first report to reveal that patients developing severe hypertension after regorafenib treatment for mCRC have improved PFS. We further evaluated the relationship between ≥grade 2 symptom development and PFS, which resulted in non-correlation (data not shown). Therefore, we consider that hypertension severity, rather than total incidence, is strongly associated with the antitumor efficacy of regorafenib. In addition, ≥grade 3 hypertension development within 7 days from treatment initiation was not associated with treatment outcomes, although multikinase inhibitor-induced hypertension occurs relatively at the early stage and stabilizes after a certain period [4]. Moreover, most of the hypertensive

patients (93.3%) developed the symptom earlier than the shortest PFS. Consequently, we consider that severe hypertension development regardless of the developing time is associated with better treatment outcomes, and lead-time bias in this study was small. However, OS did not differ between the groups. Therefore, we additionally evaluated the number of later treatments, suggesting that it tended to be higher in control patients than in hypertensive patients, without statistical difference (number of later treatments: 0, 1, 2, 3 or more, 44.3% vs. 63.3%, 31.4% vs. 23.3%, 18.6% vs. 6.7%, and 5.7% vs. 6.6% in the control and hypertensive groups, respectively; P=0.09). Consequently, we considered that later treatments affected the OS results.

Baseline hypoalbuminemia, which is considered to be caused by cachexia, was associated with poor PFS. Cachexia leads to approximately 20% of deaths among patients with cancer and is associated with higher rates of chemotherapeutic toxicities, poor prognosis, and reduced quality of life [17], which might have affected the results.

In our previous study, we revealed that pre-existing primary hypertension and prior anti-VEGF treatment ≥700 days were independent risk factors for regorafenib-induced severe hypertension [4]. Therefore, we additionally assessed whether patients with these factors obtained PFS benefits by replacing these contents with ≥grade 3 hypertension development in the multivariate Cox hazard analysis. As a result, prior anti-VEGF

treatment ≥700 days was significantly associated with longer PFS (adjusted hazard ratio of 0.61, 95% CI of 0.38–0.96; *P*=0.03), although baseline preexisting primary hypertension was not related (0.77, 0.49–1.22; *P*=0.26). In addition, PFS and OS were significantly prolonged in patients receiving previous anti-VEGF treatment for ≥700 days compared to those with <700 days (74 days [49–105 days] vs. 49 days [42–56 days] for median PFS [95% CI]; *P*=0.02; 271 days [173–423 days] vs. 159 days [126–226 days] for median OS; *P*=0.01; Supplemental Figure 1). Long-term inhibition or modification of the VEGF signaling pathway by previous treatment may activate other signaling pathways that regorafenib inhibits. In this study, the median PFS was similar between the two groups; however, more hypertensive patients obtained longer benefits, suggesting the possibility of a specific population existence. Hypertensive patients with a longer anti-VEGF treatment history may be the population; therefore, further studies are needed to elucidate this rationale.

Hypertension is associated with cardiovascular events in patients receiving multikinase inhibitors; in general, it also induces renal events [18–23]. Therefore, it should be strictly managed to ensure the safe administration of regorafenib. However, management guidelines for anti-VEGF treatment-induced hypertension have not been established [4, 23]. It also remains unclear whether antihypertensive treatment decreases

the antitumor efficacy of anti-VEGF treatments. Further studies regarding appropriate antihypertensive strategies focusing on antihypertensive effects and their influence on antitumor efficacy are required.

This study has some limitations. First, this study was retrospectively performed in a relatively small patient population from a single institution. Second, as we did not assess home blood pressure measurement methods, this might have affected the results. Third, as previously mentioned, since this is a real-world retrospective study, later treatment including rechallenged oxaliplatin or investigational new drugs might have affected the OS results. Finally, we did not evaluate the blood concentrations of regorafenib or its metabolites. It has been reported that the trough concentration levels of N-oxide/desmethyl regorafenib metabolites are associated with the severity of hypertension or rash [24]. Although the correlation between the blood levels of regorafenib or its metabolites and treatment efficacy remains unclear, it might have affected the obtained results.

Considering these limitations, our preliminary findings should be confirmed in further studies.

In conclusion, we have revealed that patients who develop severe hypertension after regorafenib treatment for mCRC have improved PFS. Management of symptoms is

important for effective treatment provision with less burden; therefore, further evaluation is needed.

Statements and Declarations

Funding: None.

Conflict of Interest: YS, YT, and MS have no conflicts of interest. YK reports receiving grants and personal fees from Ono, TAIHO, CHUGAI, Eli Lilly, Yakult, Bristol-Myers, Merck, Takeda, Novartis, Bayer, and Daiichi-Sankyo and grants from Iqvia outside the submitted work.

Ethical approval: All procedures performed in this study involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was waived by the Ethical Review Board for Life Science and Medical Research at Hokkaido University Hospital.

Consent to participate: Formal consent was not required for this type of study.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions:

Participated in research design: YS and YK; Conducted experiments: YS; Performed data analysis: YS; Wrote the paper: YS and YT; All authors have read and approved the manuscript.

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Table 1 Patient characteristics

	Control group (n=70)	Hypertensive group (n=30)	*P*-value
Sex (male/female)	40/30	16/14	0.83
Age (median, range)	67 (44–83)	63 (28–80)	0.55
Performance status (ECOG)			
0-1/2	64/6	29/1	0.67
Primary site (n)			
Rectum	27	8	
Sigmoid colon	20	11	
Ascending colon	8	6	
Cecum	8	0	
Descending colon	5	3	
Transverse colon	2	1	
Ileocecal region	0	1	0.13
Right/left	18/52	8/22	1.00
Recurrence (n, %)	32 (45.7%)	17 (56.7%)	0.38
KRAS mutation (n, %)	34 (48.6%)	13 (43.3%)	0.67
Liver metastasis presence (n, %)	45 (64.3%)	21 (70.0%)	0.65
BSA (m^2) (median, range)	1.59 (1.28–2.10)	1.62 (1.34–2.06)	0.55
BMI (kg/m^2) (median, range)	22.82 (14.95–29.80)	22.73 (17.04–30.39)	0.38
Albumin (g/dL) (median, range)	3.8 (2.1–4.7)	3.6 (3.0–4.5)	0.10

Number of less than LLN (n, %)	23 (32.9%)	5 (16.7%)	0.14
[a]Liver dysfunction (n, %)	2 (2.9%)	1 (3.3%)	1.00
CCr (mL/min) (median, range)	89.2 (23.0–156.1)	90.7 (41.3–135.2)	0.93
CCr of less than 60 mL/min (n, %)	9 (12.9%)	6 (20.0%)	0.37
Number of prior treatment regimens (n, %)			
1–2	20 (28.6%)	3 (10.0%)	
3 or more	50 (71.4%)	27 (90.0%)	0.07
Number of prior anti-VEGF agents (n, %)			
1	64 (91.4%)	24 (80.0%)	
2	6 (8.6%)	6 (20.0%)	0.18
Duration from last anti-VEGF administration (days)(median, range)	110 (11–1554)	106 (14–1086)	0.97
Duration of previous anti-VEGF treatment (days)(median, range)	461 (42–1916)	747 (52–1634)	0.06
Baseline preexisting hypertension (n, %)	31 (44.3%)	24 (80.0%)	0.001**
Before anti-VEGF treatment (primary hypertension)	13 (18.6%)	20 (66.7%)	<0.001**
After anti-VEGF treatment	24 (34.3%)	13 (43.3%)	0.50
Baseline antihypertensive treatment (n, %)	30 (42.9%)	18 (60.0%)	0.13
Number of antihypertensive drugs (n, %)			
0–1	56 (80.0%)	17 (56.7%)	
2 or more	14 (20.0%)	13 (43.3%)	0.03*
Type of antihypertensive drugs (n, %)			
RASI	22 (31.4%)	13 (43.3%)	0.26
Calcium channel blockers	21 (30.0%)	13 (43.3%)	0.25
Diuretics or beta-blockers	3 (4.3%)	5 (16.7%)	0.05

Starting dosage of regorafenib (n, %)			
160 mg	33 (47.1%)	16 (53.3%)	
120 mg	19 (27.1%)	10 (33.3%)	
80 mg	18 (25.7%)	4 (13.3%)	0.40
Dose reduction from initiation of the treatment (n, %)	37 (46.7%)	14 (52.9%)	0.66

$^{*}P<0.05$, $^{**}P<0.01$

[a]Liver dysfunction: grade 2 or higher aspartate aminotransferase, alanine aminotransferase, or total bilirubin elevation.

Baseline preexisting hypertension details and type of antihypertensive agents include reduplication.

ECOG, Eastern Cooperative Oncology Group; BSA, body surface area; BMI, body mass index; LLN, lower limit of normal; CCr, creatinine clearance; VEGF, vascular endothelial growth factor; RASI, renin–angiotensin system inhibitors.

Table 2 Adverse effects

	Control group (n=32)	Hypertensive group (n=41)	*P*-value
Hand-foot skin reaction			
All grade	56 (80.0%)	24 (80.0%)	1.00
Grade 3/4	14 (20.0%)	5 (16.7%)	0.79
Diarrhea			
All grade	6 (8.6%)	5 (16.7%)	0.30
Grade 3/4	0 (0%)	0 (0%)	1.00
Fatigue			
All grade	29 (41.4%)	19 (63.3%)	0.05
Grade 3/4	3 (4.3%)	1 (3.3%)	1.00
Anorexia			
All grade	23 (32.9%)	10 (33.3%)	1.00
Grade 3/4	1 (1.4%)	1 (3.3%)	0.51
[a]Liver dysfunction			
All grade	37 (52.9%)	16 (53.3%)	1.00
Grade 3/4	7 (10.0%)	0 (0%)	0.10

[a]Liver dysfunction included that of aspartate aminotransferase, alanine aminotransferase, or total bilirubin elevation.

Table 3 Univariate and multivariate analyses of variable assessing for impact on PFS

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Sex				
Male/Female	0.80 (0.52–1.21)	0.29	Excluded	-
Age (years)				
≥65/<65	0.88 (0.58–1.34)	0.55	Excluded	-
Performance status (ECOG)				
2/0 or 1	1.59 (0.73–3.45)	0.24	Excluded	-
Clinical stage				
IV/Recurrence	1.11 (0.73–1.68)	0.64	Excluded	-
KRAS status				
Wild/Mutant	0.85 (0.56–1.30)	0.46	Excluded	-
Primary lesion				
Left/right	0.73 (0.45–1.16)	0.19	Excluded	-
BSA (m^2)				
≥1.5/<1.5	0.81 (0.51–1.30)	0.39	Excluded	-
BMI (kg/m^2)				
≥25.0/<25.0	1.00 (0.62–1.62)	1.00	Excluded	-
Liver metastasis				
Present/Absent	0.91 (0.59–1.42)	0.69	Excluded	-
Hypoalbuminemia				

Present/Absent	1.63 (1.01–2.64)	0.04*	1.85 (1.14–3.01)	0.01*
[a]Liver dysfunction				
Present/Absent	1.28 (0.40–4.05)	0.68	Excluded	-
[b]Renal dysfunction				
Present/Absent	0.85 (0.47–1.54)	0.60	Excluded	-
Number of previous treatment regimens				
3 or more/1–2	0.69 (0.42–1.13)	0.14	Excluded	-
Number of previous anti-VEGF agents				
2 or more/1	1.59 (0.73–3.45)	0.24	Excluded	-
Dose reduction from treatment initiation				
Present/Absent	1.43 (0.94–2.18)	0.09	1.46 (0.95–2.23)	0.08
≥G3 hand-foot skin reaction development				
Present/Absent	0.60 (0.34–1.05)	0.07	0.60 (0.34–1.06)	0.08
≥G3 hypertension development				
Present/Absent	0.61 (0.37–1.00)	0.048*	0.57 (0.35–0.93)	0.02*
≥G3 hypertension development within 7 days				
Present/Absent	0.67 (0.38–1.17)	0.16	Excluded	-

*$P<0.05$

[a]Liver dysfunction: ≥grade 2 aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels

[b]Renal dysfunction: creatinine clearance of less than 60 mL/min.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; BSA, body surface area; BMI, body mass index; VEGF, vascular endothelial growth factor.

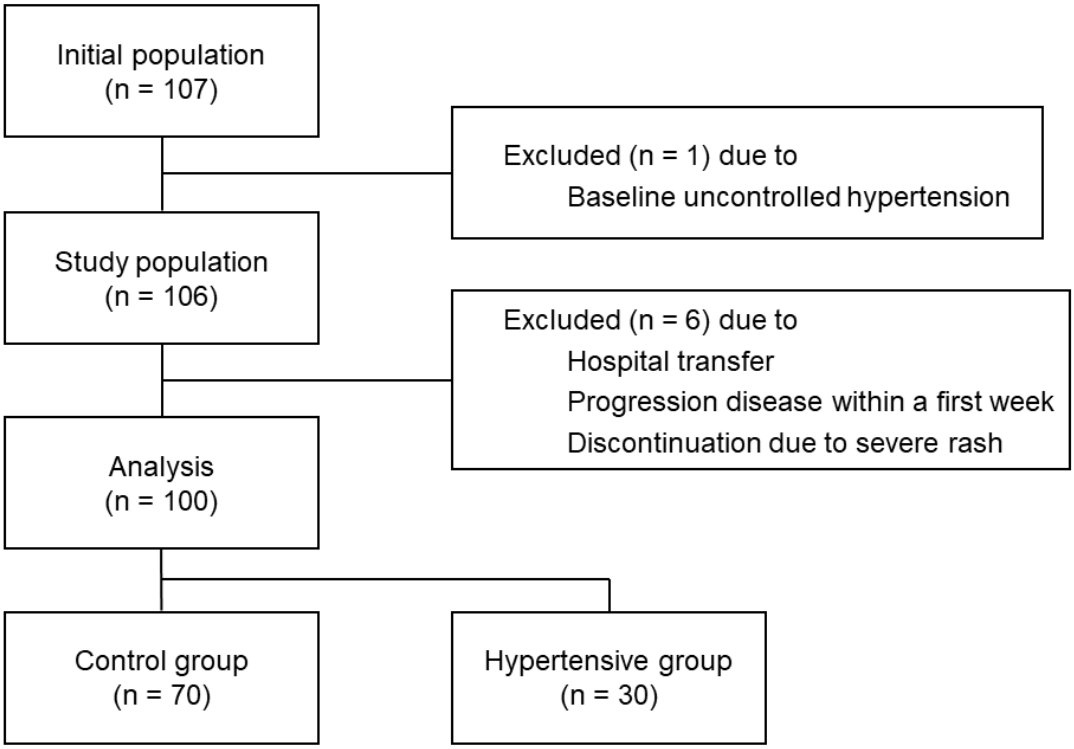

Fig. 1 Study design

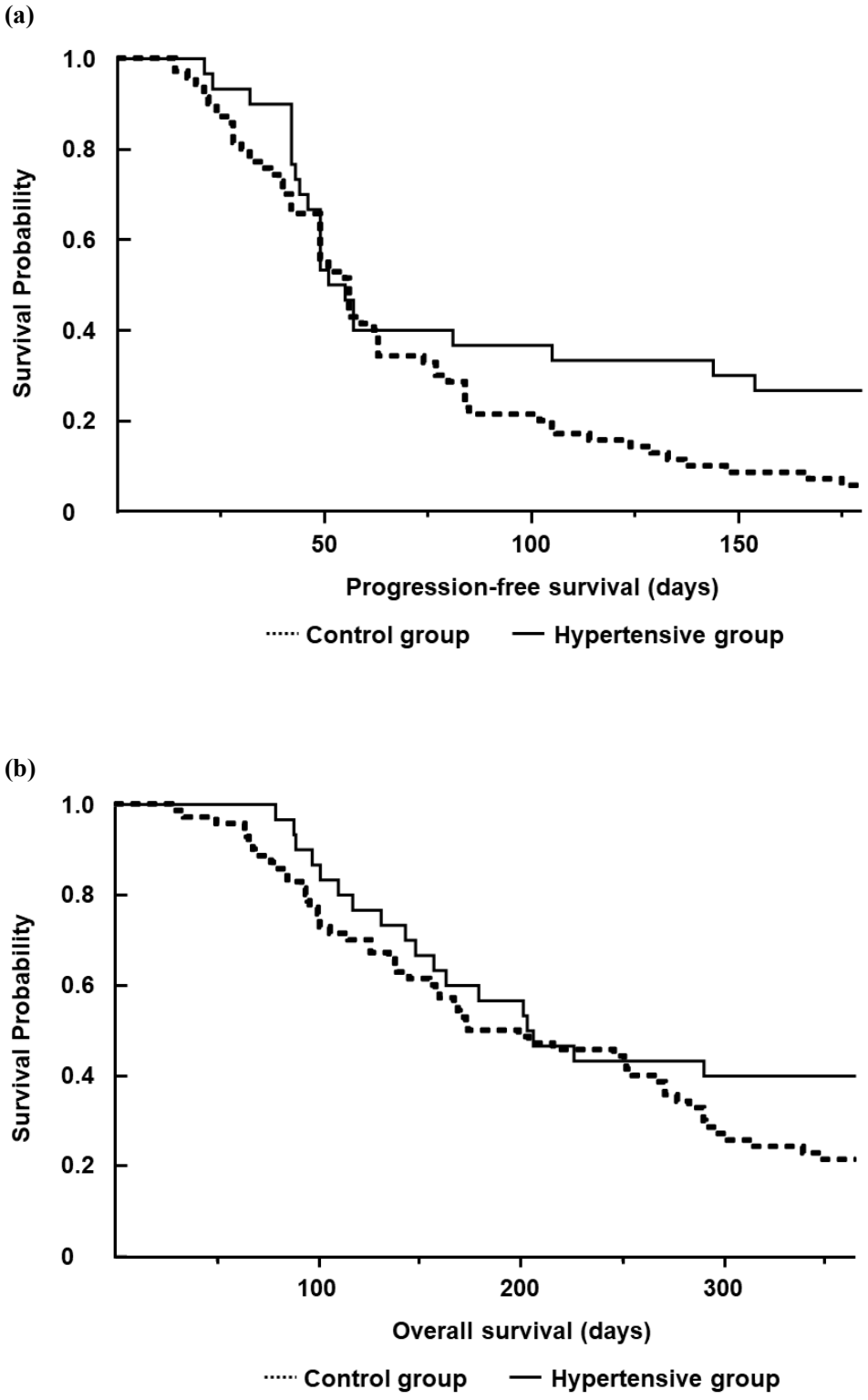

Fig. 2 Kaplan-Meier survival curves of (a) progression-free survival and (b) overall survival between control and hypertensive groups