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Original Article

Relationship between renal dysfunction and change in serum electrolyte levels in patients administered with liposomal amphotericin B

Kaito Yamashiro[1,2], Atsushi Hirata[2], Ryosuke Ota[2], Fumihiko Ogata[1], Takehiro Nakamura[1] and Naohito Kawasaki[1]

[1]Faculty of Pharmacy, Kindai University, 3-4-1, Kowakae, Higashi-Osaka, Osaka 577-8502, Japan
[2]Department of Pharmacy, Kindai University Nara Hospital, 1248-1, Otodacho, Ikoma, Nara 630-0293, Japan

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ABSTRACT — Liposomal amphotericin B (L-AMB) causes renal dysfunction and hypokalemia, but little is known about the relationship between serum electrolyte levels before or after administration and renal dysfunction. The changes in serum electrolyte levels before and after administration in patients with L-AMB-induced renal dysfunction were examined. This study included 87 patients administered L-AMB at Kindai University Nara Hospital. The number of patients with G1 (serum creatinine (Scr) levels (mg/dL) > 1.07–1.605 in male and > 0.79–1.185 in female) and G2 (Scr level > 1.605–3.21 in male and > 1.185–2.37 in female) was 25 (28.7%) and 14 (16.1%), respectively. Multivariable logistic regression analysis revealed the onset of G2 was significantly associated with baseline estimated glomerular filtration rate (eGFR), odds ratio (OR): 0.99, 95% confidential interval (95% CI): 0.95–1.02 and, baseline serum potassium levels, OR: 3.50, 95% CI: 1.16–12.06. Serum potassium levels were significantly higher in the G2 group than in the G0 group (Scr levels < 1.07 in male and < 0.79 in female) during the study period. These results indicated the changes in serum potassium levels are associated with renal dysfunction. Monitoring of serum potassium levels before and after administration may contribute to the evaluation of renal dysfunction in patients receiving L-AMB.

Key words: Liposomal amphotericin B, Renal dysfunction, Time-dependent changes, Serum electrolyte level

INTRODUCTION

Liposomal amphotericin B (L-AMB) is a lipid formulation of amphotericin B and is a broad-spectrum antifungal drug used for the treatment of aspergillosis, cryptococcal meningitis, and invasive candidiasis and L-AMB acts by binding ergosterol in fungal cell membranes, leading to ion leakage and cell death (Stone *et al*., 2016). The adverse effects of L-AMB include renal dysfunction (Patel *et al*., 2011), hepatoxicity (Fischer *et al*., 2005; Patel *et al*., 2011), and electrolyte abnormalities such as hypokalemia (Walsh *et al*., 2002). Although liposomalization reduces renal dysfunction and hypokalemia, L-AMB-induced renal dysfunction is one of the most common side effects. Safdar *et al*. (2010) reported that the incidence of L-AMB-induced renal dysfunction is 2.8%–32.0%, which is lower than that of amphotericin B-induced renal dysfunction. The risk factors for renal dysfunction include prior treatment with angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and concomi-

Correspondence: Naohito Kawasaki (E-mail: kawasaki@phar.kindai.ac.jp)

tant administration of catecholamines or immunosuppressants (Takazono *et al*., 2020). The increased rate of L-AMB-induced renal dysfunction has been associated with the combination of cyclosporine, cyclosporine plus furosemide, and cyclosporine plus foscarnet (Stanzani *et al*., 2017). Additionally, Yokota *et al*. (2020) have reported that renal dysfunction is associated with baseline albumin levels and albumin supplementation. These previous studies have focused on the association between L-AMB-induced renal dysfunction and concomitant medications. L-AMB-induced renal dysfunction may be related to patients' initial renal function and electrolyte levels. However, little is known about the relationship between renal dysfunction and patient background, such as serum electrolyte levels, in patients receiving L-AMB.

In a study by Personett *et al*. (2019), serum creatine (Scr) levels in 48.0% of patients with L-AMB-induced renal dysfunction did not return to within 25% of the pretreatment levels within the first 30 days after renal dysfunction. It is also important to monitor patients after L-AMB treatment for the prevention of renal dysfunction. In these patients, notable parameters are renal function and serum electrolyte levels. However, little is known about the evaluation of serum electrolyte levels over time after administration. It is assumed that L-AMB-induced renal dysfunction is associated with serum electrolyte levels before administration, and prediction of this dysfunction is needed to continue the treatment.

This study aimed to provide new evidence regarding L-AMB-induced renal dysfunction and examine how the onset of renal dysfunction is associated with patient background and how it affects time-dependent changes in serum electrolyte levels.

MATERIALS AND METHODS

Study design and objectives

This retrospective study aimed to investigate L-AMB-induced renal dysfunction in patients who received L-AMB from July 2006 to April 2020 at Kindai University Nara Hospital. Of the 176 patients enrolled, 87 patients were eligible to participate in the present study. The main eligibility criteria included measurement of laboratory parameters before and after administration, > 1 L-AMB administration, and normal range of baseline renal function. Scr (mg/dL), albumin (Alb, g/dL), sodium (mmol/L), potassium (mmol/L), and calcium (mg/dL) levels were measured before and after L-AMB administration. Serum calcium levels were corrected using Payne's equation (Payne *et al*., 1973). The adjusted estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated using the following formula for Japanese individuals (Matsuo *et al*., 2009). The Scr was set to 0.6 mg/dL when the Scr was < 0.6 mg/dL.

Adjusted eGFR (mL/min/1.73 m^2) = (194 × Scr [mg/dL] –1.094 × age [years]–0.287) (× 0.739, for females).

Concomitant drugs included precautions for co-administration drugs listed in the package insert to L-AMB as follows: steroid; cyclosporine; tacrolimus; aminoglycoside; vancomycin; teicoplanin; cisplatin; pentamidine; ganciclovir; foscarnet; arsenic trioxide; flucytosine; diuretic. These drugs may affect renal function or serum electrolyte levels. Additionally, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin-receptor blockers (ARB) were investigated because these drugs may affect serum potassium levels. The study period for concomitant drugs was defined as one week before the start of L-AMB administration.

Definition of renal dysfunction and electrolyte abnormalities

Renal dysfunction and electrolyte abnormalities were graded according to the Common Terminology Criteria for Adverse Events version 5.0, translated by the Japanese Clinical Oncology Group (CTCAE ver. 5.0 JCOG version) (Japanese Clinical Oncology Group, 2019). Renal dysfunction was defined by CTCAE because the same criteria were used in Safdar's meta-analysis (Safdar *et al*., 2010). Renal dysfunction during L-AMB administration was defined as follows: G0, Scr level < 1.07 in males and < 0.79 in females; G1, Scr level > 1.07–1.605 in males and > 0.79–1.185 in females; G2, Scr level > 1.605–3.21 in males and > 1.185–2.37 in females; G3, Scr level > 3.21–6.42 in males and > 2.37–4.74 in females; and G4, Scr level > 6.42 in males and > 4.74 in females. Patients with Scr levels of grade ≥ 1 before L-AMB administration were excluded from the study.

Statistical analysis

Statistical analyses were performed using JMP Pro (version 15.0.0; SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant when the p-value was < 0.05. Relationships between the onset of renal dysfunction and patient characteristics or treatment details were evaluated using Fisher's exact test, Dunnett's test (between G0 and G1 or G2), or Steel's multiple comparison test (between G0 and G1 or G2). Univariate logistic regression analysis was performed to identify the relationship between renal dysfunction and patient characteristics. Multivariate logistic regression analysis was performed with variables with a p-value of < 0.05 in univariate logistic regression analysis. The

time to the incidence of G1 in the two groups (G1 and G2) was described using the Kaplan–Meier curve. Finally, repeated-measures analysis of variance was used to evaluate the differences in serum sodium and potassium levels between the three groups (G0, G1, and G2). The following patient characteristics were evaluated: sex; age; body height and weight; body mass index (BMI); history of hematopoietic stem cell transplantation (HSCT); baseline eGFR; serum Alb, aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), sodium, potassium, and calcium levels; and disease type. The following treatment details were evaluated: treatment period (days), initial dose (mg/kg), and cumulative dose (g), concomitant drugs.

Ethical consideration

This study was approved by the ethics committee of Kindai University Nara Hospital (approval ID: 20–12) on September 28, 2020. All procedures in this study were conducted according to the ethical standards of the institutional research committee and the Declaration of Helsinki. Patients were not required to provide informed consent for study participation because this was a retrospective study. We used an opt-out method to obtain consent for this study. The opt-out method was approved by the ethics committee of Kindai University Nara Hospital.

RESULTS

Patient characteristics, treatment details and, assessment of risk factors for renal dysfunction

Figure 1 shows a flowchart of patient selection. A total of 176 patients received L-AMB during the study period. Thirty-one patients were excluded because their serum Ca and Alb levels were not measured during the study period. Further, 22 patients with poor general conditions and 21 patients with Scr levels of grade ≥ 1 before L-AMB administration were excluded. Additionally, eight patients with a history of artificial dialysis, three patients who received L-AMB only once, two patients who had undergone L-AMB therapy, and two patients aged < 18 years were excluded. Therefore, the remaining 87 patients (62 men and 25 women) were included. The proportion of patients with G0, G1, and G2 was 55.2, 28.7, and 16.1%, respectively. There were no patients with G3 or G4. Table 1 shows a comparison of patient characteristics between the grades of Scr levels. The mean age of the patients was 61.7 ± 16.7 years. Significant differences were observed in laboratory data between G1 and eGFR (p = 0.024) and between G2 and serum potassium levels (p = 0.017). Most patients who received L-AMB had

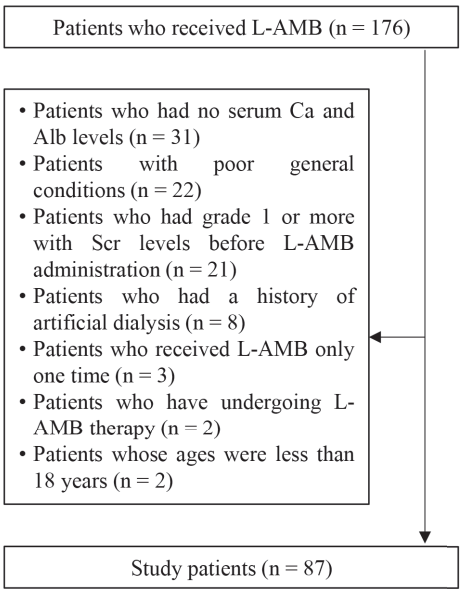

Fig. 1. Flowchart of patient selection.

hematological cancers such as leukemia, lymphoma, and multiple myeloma. Table 2 shows a comparison of patient characteristics between the grade of Scr levels. The mean values of the treatment period, initial dose, and cumulative dose were 15.3 ± 11.9 days, 2.4 ± 0.8 mg/kg, and 2.3 ± 2.6 g, respectively. The most common concomitant drugs were in the order of vancomycin (14.9%), teicoplanin (18.4%), followed by diuretic (42.5%), and steroids (69.0%). The number of patients who received cisplatin and flucytosine was one. There were no patients who received concomitant use of pentamidine, foscarnet, or arsenic trioxide. Furthermore, no significant associations were observed between renal dysfunction and the use of concomitant drugs.

Table 3a and 3b show the relationships between the Scr grade and patient characteristics or treatment details according to univariate and multivariate logistic regression analysis. The onset of G2 was significantly associated with baseline eGFR (OR: 0.96, 95% CI: 0.93–0.996, p = 0.044) and baseline serum potassium levels (OR: 5.30, 95% CI: 1.57–22.89, p = 0.013). The onset of renal dysfunction (G1+G2) was significantly associated with BMI (OR: 1.17, 95% CI: 1.02–1.36, p = 0.021) and baseline eGFR (OR: 0.96, 95% CI: 0.94–0.99, p = 0.002). However, no significant associations were observed between renal dysfunction and treatment details or concomitant drugs. Multivariable logistic regression analysis revealed the following independent risk factors for

Table 1. Comparison of the patient characteristics between different serum creatinine grade.

	All patients	Grade of Scr			*p*-value	
		No change (%)	G0 to G1 (%)	G0 to G2 (%)	G1	G2
Total number	87	48 (55.2)	25 (28.7)	14 (16.1)	-	
Male/Female[a)]	62 / 25	37 / 11	17 / 8	8 / 6	0.283	
Age (year)	61.7 ± 16.7	62.1 ± 18.2	63.1 ± 14.2	57.8 ± 15.7	0.939	0.299
Body Height (m)[b)]	1.64 ± 0.08	1.65 ± 0.08	1.62 ± 0.08	1.64 ± 0.09	0.385	0.895
Body Weight (kg)[b)]	56.9 ± 10.4	55.5 ± 9.0	58.5 ± 12.4	59.3 ± 10.6	0.404	0.396
BMI (kg/m^2)[b)]	21.1 ± 3.3	20.4 ± 3.0	22.1 ± 4.2	21.9 ± 2.3	0.073	0.244
HSCT[a)]	25	10 (20.8)	10 (40.0)	5 (35.7)	0.211	
Before administration						
Alb (g/dL)	3.0 ± 0.6	2.9 ± 0.5	3.2 ± 0.5	3.1 ± 0.8	0.144	1.000
Scr (mg/dL)	0.61 ± 0.17	0.57 ± 0.15	0.67 ± 0.16	0.67 ± 0.21	0.020*	0.241
eGFR (mL/min/1.73m^2)	87.6 ± 19.4	93.2 ± 19.8	80.7 ± 16.5	80.8 ± 17.8	0.024*	0.140
AST (U/L)	28.6 ± 20.9	26.8 ± 15.5	33.3 ± 31.6	26.4 ± 10.9	0.099	0.902
ALT (U/L)	39.1 ± 33.2	41.6 ± 38.3	36.1 ± 25.5	35.9 ± 26.9	0.996	0.881
Na (mmol/L)	137.9 ± 4.7	137.3 ± 4.6	139.7 ± 4.8	137.0 ± 4.1	0.102	0.839
K (mmol/L)[b)]	3.9 ± 0.5	3.8 ± 0.4	3.9 ± 0.6	4.3 ± 0.7	0.837	0.017*
Ca (mg/dL)[b)]	9.3 ± 0.4	9.2 ± 0.4	9.3 ± 0.4	9.2 ± 0.5	0.850	0.903
Type of diseases[a)]						
Leukemia	42	23 (47.9)	12 (48.0)	7 (50.0)	1.000	
Malignant lymphoma	21	9 (18.8)	7 (28.0)	5 (35.7)	0.350	
Myelodysplastic syndrome	7	5 (10.4)	2 (8.0)	0 (0.0)	0.662	
Aplastic anemia	4	3 (6.3)	1 (4.0)	0 (0.0)	1.000	
Multiple myeloma	3	2 (4.2)	0 (0.0)	1 (7.1)	0.412	
Other	10	6 (12.5)	3 (12.0)	1 (7.1)	1.000	

Mean ± standard deviation. BMI: body mass index, HSCT: hematopoietic stem cell transplant, Alb: albumin, Scr: serum creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Na: sodium, K: potassium, Ca: calcium. *$p < 0.05$, *p*: statistical significance obtained using Steel's multiple comparison test between No change and G0 to G1 or G0 to G2, a): Fisher's exact test, b): Dunnett's test between No change and G0 to G1 or G0 to G2.

Table 2. Comparison of the treatment details between different serum creatinine grade.

	All patients	Grade of Scr			*p*-value	
		No change (%)	G0 to G1 (%)	G0 to G2 (%)	G1	G2
Total number	87	48 (55.2)	25 (28.7)	14 (16.1)	-	
Treatment details						
Treatment period (day)	15.3 ± 11.9	13.6 ± 9.3	17.6 ± 15.8	16.9 ± 11.9	0.261	0.517
Initial dose (mg/kg)	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.5	2.5 ± 0.9	0.591	0.976
Cumulative dose (g)	2.3 ± 2.6	1.9 ± 1.7	2.6 ± 3.2	3 ± 3.7	0.086	0.326
Concomitant drugs[a)]						
Steroid	60 (69.0)	32 (66.7)	21 (84.0)	7 (50.0)	0.078	
Cyclosporine	7 (8.0)	3 (6.3)	2 (8.0)	2 (14.3)	0.574	
Tacrolimus	7 (8.0)	2 (4.2)	4 (16.0)	1 (7.1)	0.211	
Aminoglycoside	4 (4.6)	3 (6.3)	0 (0.0)	1 (7.1)	0.476	
Vancomycin	13 (14.9)	5 (10.4)	6 (24.0)	2 (14.3)	0.320	
Teicoplanin	16 (18.4)	7 (14.6)	6 (24.0)	3 (21.4)	0.562	
Cisplatin	1 (1.1)	1 (2.1)	0 (0.0)	0 (0.0)	1.000	
Pentamidine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	
Ganciclovir	8 (9.2)	3 (6.3)	2 (8.0)	3 (21.4)	0.252	
Foscarnet	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	
Arsenic trioxide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	
Flucytosine	1 (1.1)	1 (2.1)	0 (0.0)	0 (0.0)	1.000	
Diuretic	37 (42.5)	17 (35.4)	13 (52.0)	7 (50.0)	0.345	
ACE-I/ARB	8 (9.2)	5 (10.4)	3 (12.0)	0 (0.0)	0.223	

Mean ± standard deviation. The study period for concomitant drugs was defined as one week before the start of L-AMB administration. ACE-I/ARB: angiotensin-converting enzyme inhibitor/Angiotensin II Receptor Blocker. *p*: statistical significance obtained using Steel's multiple comparison test between No change and G0 to G1 or G0 to G2, a): Fisher's exact test.

Table 3a. Relationships between serum creatinine grade and patient characteristics or treatment details.

Variable	G2 (n = 14) vs. G0 + G1 (n = 73)					
	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Sex (Male/Female)[a)]	0.40	0.11–1.39	0.178			
Age (year)	0.99	0.95–1.02	0.418			
BMI (kg/m^2)	1.20	0.98–1.52	0.093			
HSCT (Yes/No)[a)]	2.11	0.58–7.72	0.296			
Before administration						
Alb (g/dL)	1.48	0.51–4.23	0.459			
eGFR (mL/min/1.73 m^2)	0.96	0.93–1.00[b)]	0.044*	0.99	0.95–1.02	0.405
AST (U/L)	1.00	0.95–1.04	0.913			
ALT (U/L)	0.99	0.97–1.01	0.596			
Na (mmol/L)	0.99	0.86–1.13	0.842			
K (mmol/L)	5.30	1.57–22.89	0.013*	3.50	1.16–12.06	0.034*
Ca (mg/dL)	0.75	0.18–3.11	0.694			
Treatment details						
Treatment period (day)	1.03	0.97–1.09	0.277			
Initial dose (mg/kg)	1.11	0.52–2.18	0.766			
Cumulative dose (g)	1.19	0.94–1.53	0.146			
Concomitant drugs[a)]						
Steroid	0.45	0.14–1.53	0.219			
Cyclosporine	2.50	0.37–16.70	0.314			
Tacrolimus	1.77	0.15–21.09	0.543			
Aminoglycoside	1.15	0.11–12.05	1.000			
Vancomycin	1.43	0.25–8.33	0.651			
Teicoplanin	1.60	0.35–7.21	0.681			
Ganciclovir	4.09	0.72–23.09	0.122			
Diuretic	1.82	0.55–6.07	0.363			

OR: odds ratio, CI: confidence interval, HSCT: hematopoietic stem cell transplant, BMI: body mass index, Alb: albumin, Scr: serum creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Na: sodium, K: potassium, Ca: calcium. *$p < 0.05$, *$p < 0.01$, p: statistical significance obtained using logistic regression analysis, a): Fisher's exact test. b) 0.996.

L-AMB-induced renal dysfunction: G1 and G2 model, baseline eGFR (OR: 0.96, 95% CI: 0.93–0.99, $p = 0.005$), baseline serum Na levels (OR: 1.07, 95% CI: 0.97–1.19, $p = 0.196$), and BMI (OR: 1.14, 95% CI: 0.98–1.33, $p = 0.090$), while G2 model, baseline eGFR (OR: 0.99, 95% CI: 0.95–1.02, $p = 0.405$) and baseline serum K levels (OR: 3.50, 95% CI: 1.16–12.06, $p = 0.034$).

Changes in the Scr grade and serum electrolyte levels over time

Figure 2 shows the Kaplan–Meier curves for the renal dysfunction (G1) rate between Scr grades (G1 and G2). The log-rank test revealed no significant difference in the G1 rate between the G1 and G2 groups. Additionally, the mean period of the change in G1 to G2 was 3.7 ± 3.0 days. In two patients, G2 was caused without a change in G1, and the period until the onset was 2 days. These results indicate that it is important to predict the onset of G2 because it develops promptly after the change in G1. In two patients, G2 was caused without a change in G1, and the period until the onset was 2 days. Additionally, the mean period of the change in G1 to G2 was 3.7 ± 3.0 days.

Figure 3 shows the changes in serum potassium and sodium levels in patients with Scr grades G0, G1, and G2. Serum potassium levels were significantly higher in the G2 group (least-square mean (LS mean): 4.2 mmol/L, 95% CI: 3.9–4.5) than in the G0 group (LS mean: 3.5 mmol/L, 95% CI: 3.3–3.7, $p < 0.001$). Serum potassium levels were not significantly different between the G0 and G1 (LS mean: 3.8 mmol/L, 95% CI: 3.6–4.1, $p = 0.079$) during the study period. Moreover, serum potassium levels were significantly higher in the G2 group than in the G0 group at 1 ($p = 0.019$) and > 4 weeks ($p = 0.020$) after administration and higher in the G1 group than in the G0 group at > 4 weeks ($p = 0.034$) after administration. In the patient who developed G0, the LS mean serum potassium level was < 3.6 mmol/L (hypokalemia) 1 week after administration. In contrast, serum sodium levels were not significantly different between the G0 (LS mean: 138.4 mmol/L, 95% CI: 137.0–139.9)

Table 3b. Relationships between serum creatinine grade and patient characteristics or treatment details.

Variable	G1 + G2 (n = 39) vs. G0 (n = 49)					
	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Sex (Male/Female)[a)]	0.53	0.21–1.36	0.235			
Age (year)	1.00	0.97–1.02	0.791			
BMI (kg/m^2)	1.17	1.02–1.36	0.021*	1.14	0.98–1.33	0.090
HSCT (Yes/No)[a)]	2.38	0.92–6.14	0.096			
Before administration						
Alb (g/dL)	1.85	0.86–4.16	0.118			
eGFR (mL/min/1.73 m^2)	0.96	0.94–0.99	0.002**	0.96	0.93–0.99	0.005**
AST (U/L)	1.01	0.99–1.03	0.377			
ALT (U/L)	0.99	0.98–1.01	0.422			
Na (mmol/L)	1.07	0.98–1.18	0.147	1.07	0.97–1.19	0.196
K (mmol/L)	2.00	0.90–4.66	0.088			
Ca (mg/dL)	1.09	0.40–3.03	0.867			
Treatment details						
Treatment period (day)	1.03	0.99–1.08	0.131			
Initial dose (mg/kg)	1.02	0.58–1.81	0.934			
Cumulative dose (g)	1.16	0.97–1.47	0.100			
Concomitant drugs[a)]						
Steroid	0.81	0.33–1.99	0.656			
Cyclosporine	1.71	0.36–8.16	0.696			
Tacrolimus	3.38	0.62–18.49	0.235			
Aminoglycoside	0.39	0.04–3.95	0.625			
Vancomycin	2.22	0.66–7.44	0.234			
Teicoplanin	1.76	0.59–5.25	0.406			
Ganciclovir	2.21	0.49–9.88	0.458			
Diuretic	1.92	0.81–4.55	0.191			

OR: odds ratio, CI: confidence interval, HSCT: hematopoietic stem cell transplant, BMI: body mass index, Alb: albumin, Scr: serum creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Na: sodium, K: potassium, Ca: calcium. *$p < 0.05$, *$p < 0.01$, p: statistical significance obtained using logistic regression analysis, a): Fisher's exact test. b) 0.996.

and G1 (LS mean: 138.0 mmol/L, 95%CI: 136.1–139.8, $p = 0.919$) or G2 groups (LS mean: 135.3mmol/L, 95% CI: 132.9–137.8, $p = 0.078$) during the study period. After > 4 weeks of administration, serum sodium levels were significantly lower in the G1 ($p < 0.001$) and G2 ($p < 0.001$) groups than in the G0 group.

DISCUSSION

L-AMB causes renal dysfunction and hypokalemia; however, little is known about the relationship between renal dysfunction and patient background. In this study, we have shown that moderate renal dysfunction is associated with serum potassium levels before L-AMB administration, and the serum potassium levels during the treatment period remained high in the G2 group and remained in the hypokalemia range in the G0 group. This is the first study to assess the relationship between renal dysfunction and serum potassium levels before and after administration in patients receiving L-AMB.

Multivariate logistic regression analysis revealed that baseline potassium levels in the G2 group were risk factors for renal dysfunction. L-AMB is known to disrupt cellular membranes and decrease the reabsorption of electrolytes, resulting in increased excretion of electrolytes such as potassium and magnesium (Perazella, 2009). As a result, the glomerular filtration rate may decrease because of the vasoconstriction of the afferent arteriolar due to tubuloglomerular feedback (TGF) (Branch, 1988; Laniado-Laborín and Cabrales-Vargas, 2009; Perazella, 2009; Sabra *et al*., 2001). Patients with high baseline serum potassium levels may be influenced stronger on TGF than low levels, and may more onset to renal dysfunction. L-AMB is known to cause hypokalemia (Moen *et al*., 2009), and serum potassium levels may contribute to the degree of TGF in patients receiving L-AMB than in other patients. However, potassium depletion occasionally induces further renal damage (Bernardo *et al*., 1995; Cremer and Bock, 1977; Kobayashi *et al*., 2018). Patients with chronic hypokalemia should also be monitored for hypokalemia because tubular toxicity may be enhanced in these patients. These results suggest that serum potassium level in patients receiving L-AMB is a risk factor for severe

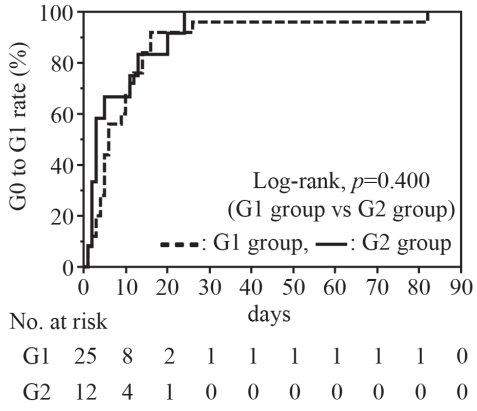

Fig. 2. Kaplan–Meier curves for the renal dysfunction (G0 to G1) rate between the serum creatinine grades.

renal dysfunction. The other independent risk factor for renal dysfunction was the baseline eGFR. Yamazaki *et al*. (2018) reported that the risk factors for renal dysfunction are pre-existing renal dysfunction and HSCT, but not sex and weight-normalized doses. In the present study, the risk factors were similar to those reported by Yamasaki *et al*., except HSCT. The relationship between renal dysfunction and HSCT was not observed because our study criteria excluded pre-existing renal dysfunction. The incidence of renal dysfunction was not significantly different to the degree of baseline eGFR, but the Scr level after administration was significantly increased in patients with eGFR > 60 mL/min (Kato *et al*., 2018). These results suggest that baseline eGFR is a useful risk factor for L-AMB-induced renal dysfunction in patients with normal renal function. In contrast, a positive association was reported between the risk of chronic kidney disease (CKD) and BMI (Fox *et al*., 2004). Although this previous study investigated CKD, our current findings were similar to their results.

The monitoring of L-AMB after administration as well as the evaluation of patient characteristics is essential for the prevention of L-AMB-induced renal dysfunction. On the day of renal dysfunction onset, the Kaplan–Meier curves for the renal dysfunction (G1) rate between the Scr grade (G1 and G2) revealed that a significant difference was not observed between the groups and that it is important to predict the onset of G2. Yamazaki *et al*. (2018) reported that the time from medication to renal dysfunction occurrence was 11.9 ± 10.1 days, and our results agree with this. Serum potassium levels were significantly higher in the G2 group than in the G0 group during the study period, whereas serum sodium levels were not significantly different among the three groups. Moreover, serum potassium levels were significantly higher in the G2 group than in the G0 group at 1 and 4 weeks after administration. The median day of hypokalemia onset was 4–10 days (Kobayashi *et al*., 2018; Yamazaki *et al*., 2018), and it was shorter than that of renal dysfunction. Until the first week after administration, the serum potassium levels in the G2 group did not vary due to strong adjustment by TGF, whereas that of the G0 group was

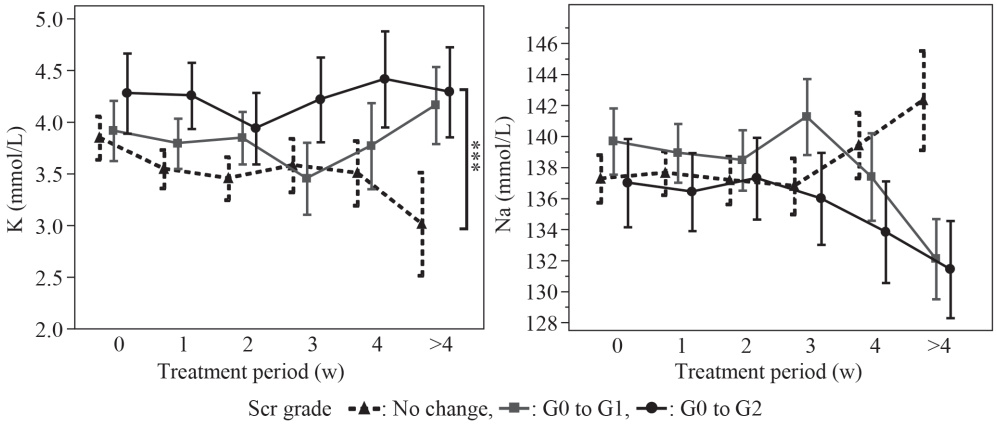

Fig. 3. Changes in serum potassium and sodium levels in patients with different serum creatinine grades. The data are presented as least square (LS) mean ± 95% confidence interval (CI). The potassium levels of each grade were as follows: G0, 3.5 ± 3.3–3.7; G1, 3.8 ± 3.6–4.1; G2, 4.2 ± 3.9–4.5. The sodium levels of each grade were as follows: G0, 138.4 ± 137.0–139.9; G1, 138.0 ± 136.1–139.8; G2, 135.3 ± 132.9–137.8. ***$p < 0.001$, p: statistical significance obtained using the repeated-measures ANOVA with Tukey's test compared with G0 group.

reduced. Thereafter, the serum potassium levels in the G0 group were reduced in a time-dependent manner due to weak adjustment by TGF. Two weeks after administration, serum potassium levels in the G2 group increased in a time-dependent manner. It is assumed that this is due to the inhibition of excretion by renal dysfunction and adjustment by TGF. These results indicate that the onset of hypokalemia should be monitored in patients with normal renal function, while serum potassium levels should be monitored in patients with renal dysfunction.

This study had several limitations. First, this study had a retrospective design, and the number of patients with renal dysfunction of G2 was small. Second, we limited the patients to the normal range of Scr levels before L-AMB administration. This is because the change in renal function grade was accurately assessed by setting the renal function before administration as G0. Third, there were no patients with G3 or G4, and we could not classify each grade separately. In the future, a prospective study is needed to evaluate the management of serum sodium or potassium levels using our findings. To our knowledge, this is the first study to clarify the relationship between L-AMB-induced renal dysfunction and serum electrolyte levels before and after administration. Here, we provide new evidence that serum potassium levels before and after administration are useful factors for evaluating L-AMB-induced renal dysfunction.

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Conflict of interest---- The authors declare that there is no conflict of interest.

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