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Retrospective analysis of risk factors for liposomal amphotericin B-associated nephrotoxicity

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In this study, we examined patients who received liposomal amphotericin B (L-AMB) to determine the risk factors associated with nephrotoxicity before and during L-AMB treatment. In this retrospective, single-center, observational cohort study, we examined 37 patients who received L-AMB treatment between April 2018 and December 2019. Nephrotoxicity was observed in 11 (29.7%) patients. We focused on the baseline albumin level and body surface area (BSA) before L-AMB treatment. Univariate analysis showed that the BSA and baseline albumin levels in patients with nephrotoxicity were significantly higher than those in patients without nephrotoxicity. Moreover, univariate analysis showed that albumin supplementation was significantly associated with the frequency of nephrotoxicity during L-AMB treatment. Multiple logistic regression analysis revealed the following independent risk factors for nephrotoxicity before or during L-AMB treatment: baseline albumin level (odds ratio [OR] = 16.000; 95% CI 1.480–172.000; $P = 0.022$) and albumin supplementation (OR = 40.800; 95% CI 2.210–753.000; $P = 0.013$). In conclusion, we identified baseline albumin level and albumin supplementation as novel risk factors for L-AMB-induced nephrotoxicity.

1. Introduction

Liposomal amphotericin B (L-AMB) is a broad-spectrum antifungal drug that interferes directly with the cell membrane of fungi (Miceli and Chandrasekar 2012). It is used to treat infections caused by several fungal species, including *Candida*, *Aspergillus*, and *Cryptococcus* spp. It is also used to empirically treat patients with febrile neutropenia in which fungal infection is suspected and the causative agent is unknown (Wingard et al. 2000). Although amphotericin B (AMPH-B), the active ingredient in L-AMB, is highly efficient against fungal infections, it frequently induces adverse effects such as renal dysfunction and hypokalemia (Falagas et al. 2007; Laniado and Cabrales 2009).

L-AMB is a drug delivery system that was developed to reduce the nephrotoxicity and sustain the therapeutic utility of AMPH-B using a liposomal formulation. Although a previous multicenter, randomized, double-blind study has shown that L-AMB causes fewer adverse effects than conventional AMPH-B (Walsh et al. 1999), the frequency of L-AMB-induced nephrotoxicity is still high (Safdar et al. 2010; Saliba and Dupont 2008). Several studies have also shown that more than 30% of patients treated with L-AMB develop nephrotoxicity (Saito et al. 2014; Malani et al. 2005). Although it is not necessary to reduce the dosage of L-AMB following a decrease in renal function, nephrotoxicity may lead to restrictions on concomitant medications or affect the quality of life of patients. Therefore, by identifying patients with a high probability of developing nephrotoxicity, we may continue to treat fungal infections without interrupting L-AMB treatment regimens and negatively affecting the prognosis/quality of life of patients. Previous reports demonstrated that factors such as concomitant nephrotoxic drugs and renal function of baseline are a risk for L-AMB-induced nephrotoxicity (Saito et al. 2014; Kato et al. 2018; Yamazaki et al. 2018). However, there are very few reports that investigate the risk factors for nephrotoxicity both before and during L-AMB treatment. Therefore, the identification of novel risk factors for nephrotoxicity is necessary to safely prescribe L-AMB for fungal infections. In this study, we aimed to identify risk factors for nephrotoxicity before or during L-AMB treatment.

2. Investigations and results

2.1. Patients' characteristics

Although 42 patients received L-AMB, five patients were excluded from the study: two patients aged <18 years and three patients lacking the necessary laboratory data. Therefore, the final enrolled patient number in this study is 37 patients. The baseline characteristics of the 37 patients are shown in Table 1. Among the 37 patients who received L-AMB treatment, nephrotoxicity occurred in 11 (29.7%) patients (Table 1).

Table 1: Characteristics of the 37 patients enrolled in this study

Characteristics	Numbers (%) or median (range)
Sex (male/female)	24/13
Age (years)	63 (24–86)
Body weight (kg)	53.8 (31.0–76.2)
BMI (kg/m^2)	21.9 (12.0–30.6)
BSA (m^2)	1.55 (1.19–1.91)
eGFR (mL/min/1.73 m^2)	76.4 (16.0–165.7)
Potassium (mEq/L)	3.8 (2.4–6.5)
AST (U/L)	18 (7–466)
ALT (U/L)	21 (6–224)
γ-GTP (U/L)	56 (14–411)
Albumin (g/dL)	2.80 (0.88–4.21)

Characteristics	Numbers (%) or median (range)
Clinical department	
Hematology	24 (64.9%)
Rheumatology and Infectious Diseases	4 (10.8%)
Gastroenterology	2 (5.4%)
Emergency	2 (5.4%)
Gastrointestinal, Endocrine and Pediatric surgery	2 (5.4%)
Neurology	1 (2.7%)
Hepatology	1 (2.7%)
Dermatology	1 (2.7%)
Frequency of nephrotoxicity	
Nephrotoxicity (+)	11 (29.7%)
Nephrotoxicity (-)	26 (70.3%)
Concomitant nephrotoxic drugs	
Furosemide	12 (32.4%)
Vancomycin	10 (27.0%)
Tacrolimus	8 (21.6%)
Foscarnet	1 (2.7%)

Data are expressed as number of patients (percent) or median (range).
BMI: body mass index, BSA: body surface area, eGFR: estimated glomerular filtration rate, AST: aspartate transaminase, ALT: alanine transaminase, γ-GTP: γ-glutamyl transpeptidase.

2.2. Univariate and multivariate analyses

To analyse the differences between patients with and without nephrotoxicity, we compared the baseline data of patients recorded before L-AMB treatment. As shown in Table 2, the body surface area (BSA) and baseline albumin level in patients who experienced nephrotoxicity were significantly higher than those in patients without nephrotoxicity ($P = 0.041$ and $P = 0.018$, respectively).

Table 2: Comparison of the baseline measurements between patients with and without nephrotoxicity

Factor	Nephrotoxicity (+) (n = 11)	Nephrotoxicity (-) (n = 26)	*P* value
Sex (male/female)	8/3	16/10	0.711[a]
Body weight (kg)	61.3 ± 12.6	53.4 ± 11.4	0.069[b]
BMI (kg/m^2)	22.3 ± 3.4	21.1 ± 4.3	0.409[b]
BSA (m^2)	1.67 ± 0.20	1.53 ± 0.17	0.041[b]
Dose (mg/kg)	3.84 ± 1.01	3.56 ± 0.99	0.431[b]
Baseline eGFR (mL/min/1.73 m^2)	87.3 ± 26.8	72.8 ± 39.4	0.272[b]
Baseline BUN (mg/dL)	18.1 ± 7.7	24.5 ± 18.0	0.271[b]
Baseline potassium (mEq/L)	3.5 ± 0.5	4.0 ± 0.8	0.086[b]
Baseline AST (U/L)	34.9 ± 55.0	46.9 ± 89.5	0.683[b]
Baseline ALT (U/L)	41.6 ± 56.4	38.8 ± 45.8	0.875[b]
Baseline γ-GTP (U/L)	131.6 ± 98.5	77.4 ± 91.4	0.167[b]
Baseline albumin (g/dL)	3.09 ± 0.70	2.48 ± 0.69	0.018[b]

Data are expressed as number of patients or mean ± standard deviation.
[a] Fisher's Exact test [b] Student's *t*-test
BMI: body mass index, BSA: body surface area, eGFR: estimated glomerular filtration rate, BUN: blood urea nitrogen, AST: aspartate transaminase, ALT: alanine transaminase, γ-GTP: γ-glutamyl transpeptidase.

To identify risk factors that affected the incidence of nephrotoxicity during treatment, we focused on the use of concomitant nephrotoxic drugs and albumin supplementation history. As shown in Table 3, albumin supplementation was significantly associated with a higher incidence of nephrotoxicity ($P = 0.028$).
We used multiple logistic regression analysis to determine whether BSA, baseline albumin levels, and albumin supplementation were independent risk factors for nephrotoxicity. As shown in Table 4, we identified two independent risk factors for nephrotoxicity before or during L-AMB treatment: baseline albumin level (odds ratio [OR] = 16.000; 95% CI 1.480–172.000; $P = 0.022$) and albumin supplementation (OR = 40.800; 95% CI 2.210–753.000; $P = 0.013$).

Table 3: Comparison of the clinical characteristics between patients with and without nephrotoxicity during L-AMB treatment

Factor	Nephrotoxicity (+) (n = 11)	Nephrotoxicity (-) (n = 26)	*P* value
Concomitant nephrotoxic drugs (+/-)	9/2	12/14	0.071[a]
Albumin supplementation (+/-)	7/4	6/20	0.028[a]

Data are expressed as the number of patients.
[a] Fisher's Exact test

Table 4: Multiple logistic regression analysis for identifying risk factors for L-AMB-induced nephrotoxicity

Factor	Odds ratio	95% CI	*P* value
BSA	5.610	0.041–777.000	0.493
Baseline albumin	16.000	1.480–172.000	0.022
Albumin supplementation (+)	40.800	2.210–753.000	0.013

BSA: body surface area, CI: confidence interval.

3. Discussion

L-AMB is used against various types of fungal infections, owing to its high therapeutic efficacy and broad-spectrum activity. However, nephrotoxicity is frequently observed in patients who receive L-AMB despite it being less nephrotoxic than AMPH-B. Studies have shown that the incidence of nephrotoxicity in patients treated with L-AMB is over 30% (Malani et al. 2005; Kato et al. 2018). In the present study, the frequency of nephrotoxicity (29.7%) was consistent with that reported previously, using the same definition of nephrotoxicity. Therefore, the population in this study and the incidence of nephrotoxicity are considered generally reasonable.
We also revealed that the baseline serum albumin level before L-AMB treatment was an independent risk factor for nephrotoxicity (Table 4). Moreover, we showed that albumin supplementation is a risk factor for nephrotoxicity during L-AMB treatment (Table 4). These results suggest that albumin may increase the risk of nephrotoxicity in patients receiving L-AMB. We considered that the interaction between L-AMB and serum albumin induced the leakage of AMPH-B from liposomes, and the free AMPH-B might have caused renal damage. The U.S. Food and Drug Administration has provided guidance for industries producing liposomal drug products, such as L-AMB, and has suggested that interactions between the liposome surface and plasma proteins may alter the rate of drug release from the liposomes. A previous study showed that plasma proteins, such as albumin, enhance the release of mitomycin from liposomes (Hosokawa et al. 2003). Another study reported that among all plasma proteins, albumin binds to L-AMB most frequently (Amici et al. 2017). In the present study, we revealed that the baseline albumin level and albumin supplementation are risk factors for L-AMB-induced nephrotoxicity. The obtained results suggest that albumin may induce the release of AMPH-B from L-AMB and subsequently induce renal damage.
Hypokalemia is another typical adverse effect associated with L-AMB treatment (Okada et al. 2018; Walsh et al. 2002). Matsuoka et al. showed that the level of serum albumin before L-AMB treatment in patients with hypokalemia was significantly higher than that in patients without hypokalemia (Matsuoka et al. 2011). This study suggested that the baseline albumin level is a predictor of hypokalemia induced by L-AMB. Similarly, in the present study, we showed that the baseline albumin level in patients with nephrotoxicity was significantly higher than that in patients without nephrotoxicity (Table 2). The baseline albumin levels were higher in patients with both nephrotoxicity and hypokalemia during L-AMB treatment in the present study and previous study (Matsuoka et al. 2011), respectively. Moreover, we identified baseline albumin level and albumin supplementation as risk factors for nephrotoxicity. Thus, our findings, in addition to those of others, indicate that albumin is involved in L-AMB-induced nephrotoxicity. Although the mechanism through which albumin induces nephrotoxicity and hypokalemia is still unknown, nephrotoxicity and hypokalemia may occur *via* a common mechanism among patients who receive L-AMB.

Studies have shown that the use of concomitant nephrotoxic drugs is a risk factor for nephrotoxicity associated with L-AMB treatment (Yamazaki et al. 2018; Stanzani et al. 2017). However, we revealed that there was no significant association between the concomitant use of nephrotoxic drugs and the incidence of nephrotoxicity (Table 3). In the present study, the nephrotoxicity of a drug was determined from its package insert, but the relationship between the dosage of the nephrotoxic drug and the incidence of L-AMB-induced nephrotoxicity was not examined. Therefore, to address this limitation, it is necessary to investigate the dosage of nephrotoxic drugs and increase the subject of drugs, including other nephrotoxic drugs such as non-steroidal anti-inflammatory agents, angiotensin-receptor blockers and angiotensin converting enzyme inhibitors in the future.

Our study has some limitations, being a retrospective analysis of a single-center study with a small sample size. Several considerations should be noted when interpreting our results. First, we needed the number of patients with nephrotoxicity induced by L-AMB. Nevertheless, the frequency of nephrotoxicity (29.7%) was consistent with that observed in a previous report (Kato et al. 2018), using the same definition of nephrotoxicity. Second, this study could not determine values such as the cut-off value of the baseline albumin level and the number of albumin supplementation that induces nephrotoxicity by L-AMB. Hence, further investigation with an increased patient population would be needed to support our clinical data.

In conclusion, the present study showed that baseline albumin level and albumin supplementation are risk factors for L-AMB-induced nephrotoxicity. We suggest that patients with these risk factors should be closely monitored during L-AMB treatment to avoid nephrotoxicity. The mechanism by which the interaction between L-AMB and albumin induces nephrotoxicity should be identified, although we believe that the interaction with albumin alters the liposomal stability of L-AMB. Further studies regarding the relationship between L-AMB-induced nephrotoxicity and albumin are needed to obtain more drug information.

4. Experimental

4.1. Study design

This study was approved by the ethics review committee of the Faculty of Medicine at the University of Miyazaki, Japan (O-0699). We retrospectively assessed the data of patients who received L-AMB (AmBisome®; Dainippon Sumitomo Pharma, Osaka, Japan) from April 2018 to December 2019 at our institution. Patients aged < 18 years and those who lacked sufficient laboratory data were excluded from the study. Finally, we enrolled 37 patients. Nephrotoxicity was defined as a ≥0.5 mg/dL increase in serum creatinine level compared with that before L-AMB treatment.

4.2. Data collection

The data of patients were obtained from the electronic medical record system. The following clinical data of patients before L-AMB treatment were extracted: age, height, body weight, sex, body mass index, and BSA. The following recorded laboratory data were also collected: serum creatinine, blood urea nitrogen, serum potassium, and serum albumin levels, and aspartate transaminase, alanine transaminase, and γ-glutamyl transpeptidase activities. These data were monitored until the termination of L-AMB therapy. We also investigated weight-normalized daily dose, albumin supplementation history, and concomitant use of nephrotoxic drugs (furosemide, ciclosporin, tacrolimus, aminoglycosides, glycopeptides, and foscarnet). Concomitant nephrotoxic drugs were extracted from the drugs listed in the package insert of L-AMB.

4.3. Statistical analysis

All data were analyzed using R version 3.6.3 (www.r-project.org). Statistical differences between the nephrotoxicity and no-nephrotoxicity groups were analyzed using Student's *t*-test or Fisher's exact test. The OR of factors related to nephrotoxicity was determined using a multiple logistic regression analysis. Results with P value < 0.05 were considered statistically significant.

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Conflicts of interest: None declared.

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