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Original Article

The evaluation of frequency of nephrotoxicity caused by liposomal amphotericin B☆

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ABSTRACT

Background: Liposomal amphotericin B (L-AmB) was developed to reduce nephrotoxicity and maximize the therapeutic utility of amphotericin B in the treatment of invasive fungal infections. However, there is little investigation into the safety of L-AmB in patients with several renal functions. Therefore, we retrospectively evaluated the clinical safety of L-AmB among patients with several renal functions.
Methods: We divided patients treated with L-AmB from April 2014 to September 2016 into 4 groups (estimated glomerular filtration rate (eGFR)≥60, 60 > eGFR≥30, eGFR<30 and hemodialysis). The main endpoint was the incidence of nephrotoxicity and the difference in the serum creatinine values at the end of L-AmB treatment as compared with baseline.
Results: The incidence of nephrotoxicity was not significantly different among four groups (eGFR≥60; 27.0%, 60 > eGFR≥30; 30.8%, eGFR<30; 50.0%, hemodialysis; 40.0%, $p = 0.56$).Only one group of patients with eGFR≥60 admitted the significant increase of serum creatinine value after L-AmB treatment started ($p < 0.01$). Patients admitted 0.5 mg/dL or more of increase in serum creatinine values until 9 days from the L-AmB therapy started (eGFR≥60; 5.0 days [3.0–8.0 days], 60 > eGFR≥30; 5.0 days [4.0–9.0 days], eGFR<30; 4.5 days [3.0–5.0 days], hemodialysis; 5.5 days [4.0–7.0 days], $p = 0.46$).
Conclusion: Take previous clinical study results together, our data suggested that L-AmB is safer agent than amphotericin B for the treatment of fungal infections in patients with eGFR<60 and hemodialysis patients at the start of treatment. Also, especially, we should use L-AmB more carefully until 9 days from the treatment started.

1. Introduction

Invasive fungal infections are important causes of morbidity and mortality among hospitalized patients. These infections included disseminated candidiasis, pulmonary aspergillosis, zygomycosis, and fusariosis. In recent years, the addition of new antifungal agents to the therapeutic armamentarium of the critically ill patient, the proposal of clinical guidelines for treatment of invasive fungal infections [1], and the development of prediction roles to identify patients at risk of invasive candidiasis have contributed to more individualized treatment strategies. Then, liposomal amphotericin B (L-AmB) is considered the treatment of choice for most of these infections [2–4].

L-AmB is a lipid formulation of amphotericin B. It was developed to reduce nephrotoxicity and maximize the therapeutic utility of amphotericin B in the treatment of invasive fungal infections [5]. Because, nephrotoxicity is the main treatment-limiting adverse effect of amphotericin B, and the risk varies depending on the patient population, daily administered dose, duration of therapy, and receipt of concurrent nephrotoxic agents [6,7].

Of note, clinical guidelines recommend to use other antifungals, such as fluconazole or echinocandins for critically ill patients with moderate to severe renal failure [8]. L-AmB has been recommended to alert its prescription in patients with decreased renal function or in those with a higher risk of renal function, such as elderly patients, concomitant use of other nephrotoxic agents or patients

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with hemodynamic instability. However, Francisco et al. showed that the impact of L-AmB on renal function was minimal in critically ill patients with impaired renal function [9].

Therefore, this study was designed to evaluate if the incidence of L-AmB-associated nephrotoxicity among patients would be difference, depend on their renal function at the initiation of antifungal treatment. And, second goal of this study was to reveal the risk factor of L-AmB-associated nephrotoxicity.

2. Patients and methods

2.1. Patients

This study was conducted at the Aichi Medical University Hospital (995 beds). The study was reviewed and approved by the ethics committee of the Aichi Medical University.

In total, 82 patients treated with L-AmB from April 2014 to September 2016. We divided patients into 4 groups according to their renal function with estimate glomerular filtration rate (eGFR) [10]. Because, overestimation by older serum creatinine methods resulted in an underestimation of creatinine clearance [11]. eGFR provided a less biased estimate of patient's renal function [12]. The four groups comprised patients who showed (i) eGFR $\geq$ 60, (ii) 60 > eGFR $\geq$ 30, (iii) eGFR < 30 and (iv) hemodialysis patients at the beginning of treatment with L-AmB.

We excluded the patients treated with L-AmB less than 2 days, < 18 years old and patients who lacked the laboratory data necessary for this study. Study patients were monitored up to discharge from the hospital. Because the purpose of the study was to determine the use of L-AmB in daily practice, the decision to treat patients with L-AmB monotherapy or in combination with other fungal agents was taken by the physician in charge.

2.2. Data collection

The medical records of the study population were analyzed, retrospectively. Clinical and laboratory data were extracted from patient medical records. Data was extracted by trained reviewers and included demographics, hospitalization history, concomitant medications, source of infection and laboratory data. Baseline demographics were collected including age, gender, baseline serum creatinine, immunosuppressant regimen, intravenous contrast exposure, and the length of L-AmB treatment.

To assess the impact of L-AmB on renal function, the concomitant use of nephrotoxic agents (aminoglycosides, glycopeptides, foscarnet, cyclosporine, and tacrolimus) and the presence of severe hemodynamic instability (duration of hypotension, use of inotropic agents) were recorded.

2.3. Study endpoints

We focused on the change of serum creatinine value for safety evaluation. The primary endpoint was the incidence of nephrotoxicity. We assessed the difference in the serum creatinine values at the end of L-AmB treatment as compared with baseline (pre-treatment). Then, nephrotoxicity was defined as an increase in serum creatinine values of $\geq$0.5 mg/dL. Secondary endpoints were the time from the start of L-AmB therapy to the occurrence of nephrotoxicity.

2.4. Statistical analysis

The data for parametric data and nonparametric data were expressed as the mean ± S.D. (standard deviation) and the median values [minimum-maximum], respectively. Statistical significance of the difference was evaluated by Kruskal-Wallis test or paired *t*-test for categorical data and Scheffe test for continuous data, respectively. Statistical analysis was performed with JMP, version 10.0 (SAS Institute Inc, Tokyo, Japan). A p value of <0.05 was required to achieve statistical significance.

3. Result

3.1. Patient characteristics and infections

During the study period, 76 patients of 82 patients were received L-AmB therapy for $\geq$48 h. Eleven patients did not have the measures of eGFR at the start or end of L-AmB treatments. Hence, 65 patients took part in this study. Among them, 37 patients who showed eGFR $\geq$60 (group 1), 13 patients who showed 60 > eGFR $\geq$ 30 (group 2), 10 patients who showed eGFR < 30 (group 3) and 5 hemodialysis patients (group 4) were included in this study. Demographics and clinical characteristics of this study population are displayed in Table 1. The duration (day), dosage (mg/kg) and total dose (mg) of L-AmB therapy did not show significant difference among 4 groups. There was no patient changed L-AmB dosage. The median eGFR [range] was 91 mL/min/1.73 m^2 [61–167 mL/min/1.73 m^2] in group 1, 49 mL/min/1.73 m^2 [33–59 mL/min/1.73 m^2] in group 2, 14 mL/min/1.73 m^2 [8–25 mL/min/1.73 m^2] in group 3 and 13 mL/min/1.73 m^2 [9–18 mL/min/1.73 m^2] in group 4 ($p < 0.01$) (Table 1).

The most frequent type of infection in this study population was bacteremia (29.2%: group 1; n = 7, group 2; n = 7, group 3; n = 4, group 4; n = 1) and second frequent type of infection was pneumoniae (26.2%: group 1; n = 15, group 2; n = 0, group 3; n = 1, group 4; n = 1) (Table 2.1). Isolated fungus were 39 strains (13 *Candida albicans*, 8 *Candida parapsillosis*, 5 *Candida glabrata* and 7 *Aspergilus fumigatus*., et al.). Of 65 patients, 8 patients had negative culture (group 1; n = 5, group 2; n = 2, group 3; n = 0, group 4; n = 1) and 18 patients did not obtain any specimen for culture during their treatments (Table 2.2).

3.2. Tolerability

The number of patients who was admitted as nephrotoxicity was 10 (27.0%) in group 1, 4 (30.8%) in group 2, 5 (50.0%) in group 3 and 2 (40.0%) in group 4 ($p = 0.56$). And, the changes of serum creatinine in pre-treatment and post-treatment of L-AmB were shown in Table 3. The only group 1 showed significant increase of serum creatinine value after L-AmB treatment (pre-treatment of L-AmB; 0.63 ± 0.28 mg/dL, post-treatment of L-AmB; 1.12 ± 1.28 mg/dL, $p < 0.01$). Comparing the patients data, nephrotoxicity patients did not showed significantly difference on demographic data and L-AmB dosage regimens in group 1, compared with non-nephrotoxicity patients (positive vs negative: age; 73.5 years [46.0–85.0 years] vs 73.0 years [31.0–84.0 years] $p = 0.22$, body weight; 54.4 kg [40–65.2 kg] vs 51.4 kg [30.6–82.7 kg] $p = 0.87$, duration of L-AmB therapy; 12.5 days [3.0–94.0 days] vs 10.0 days [3.0–55.0 days] $p = 0.41$, dosage; 2.7 mg/kg [2.1–4.8 mg/kg] vs 2.6 mg/kg [1.4–4.5 mg/kg] $p = 0.14$, total dose; 1625 mg [600–10600 mg] vs 1600 mg [300–6700 mg] $p = 0.15$).

In addition, only 6 patients in group 1 were administered nephrotoxic agents (vancomycin or foscarnet). Of 6 patients, 5 patients were admitted as nephrotoxicity at post-treatment of L-AmB (83.3% (5/6)). The Patients received nephrotoxic agents showed significant higher incidence of nephrotoxicity than that of patients who did not receive nephrotoxic agents (16.1% (5/31)) in group 1 ($p < 0.01$). But, the incidence of nephrotoxicity in patients who did not receive any nephrotoxic agents did not show significant difference among 4 groups, while numerically less incidence of nephrotoxicity were admitted in group 1, compared with the other