Potential Usefulness of Early Potassium Supplementation for Preventing Severe Hypokalemia Induced by Liposomal Amphotericin B in Hematologic Patients: A Retrospective Study

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ABSTRACT

Purpose: Liposomal amphotericin B (L-AMB) is an essential antifungal agent for patients with hematologic diseases; however, the drug causes severe hypokalemia at a high frequency. Meanwhile, there is little evidence regarding the risk factors for L-AMB–induced severe hypokalemia, and the prevention protocol has not been established. The goal of this study was to identify the risk factors related to severe hypokalemia induced by L-AMB in hematologic patients.

Methods: Seventy-eight hematologic patients with a first administration of L-AMB were enrolled in the study. Eleven patients who had serum potassium levels <3.0 mmol/L before L-AMB administration and 12 patients who received L-AMB administration within 3 days were excluded. Patients who had a serum potassium level <3.0 mmol/L during L-AMB administration were classified into a hypokalemia group (n = 26), and those who had a serum potassium level ≥3.0 mmol/L were classified into a non-hypokalemia group (n = 29). The patient characteristics were analyzed retrospectively. In addition, the usefulness of potassium supplementation was analyzed for those patients who received potassium formulations (non-hypokalemia group, n = 15; hypokalemia group, n = 24).

Findings: Twenty-six patients had hypolalemia after L-AMB administration. Hypokalemia with serum potassium levels <3.0 mmol/L was observed ~7 days after starting L-AMB administration. The patient characteristics, L-AMB dose, and L-AMB administration period did not differ between the 2 groups. In the patients who received potassium formulations, the period between starting L-AMB administration and starting potassium supplementation was significantly shorter in the non-hypokalemia group than in the hypokalemia group (median, 0 vs 4 days, respectively; $P < 0.01$); the potassium dose was not different between the 2 groups. A receiver-operating characteristic curve revealed that the cutoff time for the start of potassium supplementation to reduce the incidence of L-AMB–induced hypokalemia was 3 days. Multivariate logistic regression analysis revealed that beginning potassium supplementation within 2 days from the start of L-AMB administration was an independent factor reducing the risk of L-AMB–induced hypokalemia (odds ratio, 0.094 [95% CI, 0.019–0.47]).

Implications: This study showed that starting administration of a potassium formulation within 2 days from the start of L-AMB administration was a risk reduction factor for L-AMB–induced hypokalemia. This finding indicates that early potassium supplementation should be incorporated into the regimen of hypokalemia management when L-AMB is used. (*Clin Ther.* 2017;▮:▮▮▮–▮▮▮)

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Key words: hypokalemia, liposomal amphotericin B, potassium supplementation, risk factor.

INTRODUCTION

In the treatment of hematologic malignancies, high-intensity therapy, such as high-dose chemotherapy and hematopoietic stem cell transplantation, is performed to achieve a maximum therapeutic outcome.[1] These treatments cause various adverse effects, however.[2] In particular, severe neutropenia occurs at a high frequency. It is therefore important to prevent and treat infectious diseases during the treatment of hematologic malignancies.[3] Among the infectious diseases experienced by hematologic patients, fungal infections occur more frequently than others, and thus their prevention and treatment are important for successful chemotherapy.[4] It has been reported that fluconazole is effective for the prevention of *Candida* infections during chemotherapy or after hematopoietic stem cell transplantation.[5] However, *Candida albicans* is susceptible to fluconazole, whereas non-albicans *Candida* species such as *Candida glabrata* and *Aspergillus* species are resistant to the drug. These fluconazole-resistant fungal infections are treated with echinocandins or amphotericin B.[6]

Amphotericin B is recommended for the treatment of severe fungal infections caused by non-albicans *Candida* species or *Aspergillus* species[7] and thus is an indispensable antifungal agent for hematologic patients who frequently experience such infections owing to immunodeficiency.[8,9] The liposomal amphotericin B (L-AMB) preparation reportedly has a lower risk of nephrotoxicity than that of amphotericin B and is commonly used in clinical practice worldwide instead of regular amphotericin B.[10] However, L-AMB increases the membrane permeability owing to the disturbance of distal renal tubular epithelial cells, causing potassium leakage into the urine.[11] This adverse effect causes hypokalemia in clinical practice. The incidence of severe hypokalemia induced by L-AMB has been reported to be 12% to 51%.[12–14] The management of hypokalemia is therefore important for the proper use of L-AMB. However, no protocols have been developed to prevent L-AMB–induced hypokalemia, despite its high frequency. It is thus important to establish such a protocol to use L-AMB safely.

The goal of the present study was to identify the risk factors related to severe hypokalemia induced by L-AMB in hematologic patients to establish a protocol for proper use of L-AMB.

PATIENTS AND METHODS

Study Design

We analyzed 78 case records of hematologic patients who received a first administration of L-AMB between April 2011 and March 2017 at the Tokushima University Hospital. Hypokalemia was defined as a serum potassium level <3.0 mmol/L during the administration of L-AMB. Patients were excluded if they had a serum potassium level <3.0 mmol/L before L-AMB administration (n = 11) or received L-AMB within 3 days (n = 12), which left 55 patients who were eligible for this study. These 55 patients were divided into a non-hypokalemia group (n = 29), in which patients had serum potassium levels ≥ 3.0 mmol/L during the L-AMB administration, and a hypokalemia group (n = 26), in which patients had serum potassium levels <3.0 mmol/L during the L-AMB administration. Of the enrolled patients, those who received potassium supplementation by a potassium formulation (non-hypokalemia group, n = 15; hypokalemia group, n = 24) were evaluated for the usefulness of potassium supplementation. Figure 1 presents the details of patient selection.

The survey content and methods to protect personal information were approved by the Tokushima

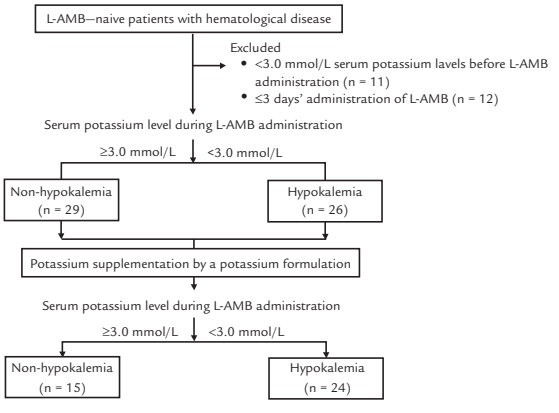

Figure 1. Study design. Hypokalemia was defined as a serum potassium level <3.0 mmol/L during the administration of liposomal amphotericin B (L-AMB).