J Infect Chemother (2013) 19:691–697
DOI 10.1007/s10156-012-0545-x

ORIGINAL ARTICLE

Efficacy and safety of liposomal amphotericin B for deep mycosis in patients with connective tissue disease

Takuya Kotani · Tohru Takeuchi · Shigeki Makino · Kenichiro Hata · Shuzo Yoshida · Koji Nagai · Daisuke Wakura · Kentaro Isoda · Toshiaki Hanafusa

Received: 27 July 2012 / Accepted: 20 December 2012 / Published online: 17 January 2013

Abstract The efficacy and safety of liposomal amphotericin B (L-AMB) in the treatment of invasive fungal infections (IFIs) were retrospectively evaluated for patients with connective tissue diseases (CTDs) during treatment with immunosuppressive therapy. Subjects were 13 patients with CTDs complicated by IFI, on the basis of clinical symptoms, imaging findings, and microbiological and histological examinations. All patients were treated with L-AMB. Efficacy and safety were evaluated before and after administration of L-AMB. Underlying diseases were systemic lupus erythematosus for 4 patients, rheumatoid arthritis for 3, microscopic polyangiitis for 2, adult-onset Still disease for 1, dermatomyositis for 1, and mixed connective tissue disease for 1. Eight patients were resistant to other antifungal drugs. Prednisolone was given to 11 patients and the median dose was 10 mg/day. Immunosuppressants were used for 8 patients. The median duration of administration of L-AMB was 8.5 days (range 4–38 days). In proven and probable diagnosis patients ($n = 5$), the treatment was effective for 3 patients and ineffective for 2 (efficacy rate 60 %). Serum 1,3-β-D-glucan antigenemia (BG) levels decreased after treatment in the 2 patients who were positive for BG. Serum *Aspergillus* galactomannan antigen levels decreased in 3 of 4 patients with *Aspergillus* infection. No patient died of IFI. Regarding potential adverse reactions, there were no significant changes in serum creatinine and potassium levels. L-AMB is effective and well-tolerated for treatment of IFI in patients with CTDs.

T. Kotani · T. Takeuchi (✉) · S. Makino · K. Hata · S. Yoshida · K. Nagai · D. Wakura · K. Isoda · T. Hanafusa
Department of Internal Medicine (I), Osaka Medical College, 2-7 Daigaku-Machi, Takatsuki, Osaka 569-8686, Japan
e-mail: t-takeuchi@poh.osaka-med.ac.jp

Keywords Liposomal amphotericin B · Invasive fungal infection · Connective tissue disease · Preemptive treatment

Introduction

Connective tissue diseases (CTDs) are likely to be complicated by opportunistic infections during immunosuppressive therapy. Invasive fungal infection (IFI) is a particularly serious complication and is a prognostic factor of CTDs. The mortality of patients with systemic lupus erythematosus (SLE) and IFI is 46.7 % [1]. Mycosis is a strong risk factor for infectious death in patients with ANCA-associated vasculitis [2], and IFI has been detected in 10–20 % of patients with CTDs at autopsy [3]. Therefore, more effective and safer therapy for IFI is required.

Amphotericin B (AMPH-B) has potent antifungal action and broad antifungal activity against almost all yeasts, including *Candida*, and molds, for example *Aspergillus* and *Zygomycetes* [4, 5]. However, many patients cannot be given therapeutic doses because of severe adverse reactions including nephrotoxicity, infusion-related reactions, fever, and vomiting [6]. Liposomal amphotericin B (L-AMB) is a lipid formulation of AMPH-B produced by use of drug-delivery techniques developed to reduce adverse reactions while maintaining the potent antifungal activity of AMPH-B [7]. L-AMB and voriconazole are the most recommended products (evidence level: A–I) in the Practice Guidelines for Diseases caused by *Aspergillus* and Clinical Practice Guidelines for the Management of *Candidiasis* published by The Infectious Diseases Society of America [8, 9]. Azole antifungal drugs, for example voriconazole, are a substrate for cytochrome P450 (CYP) metabolism whereas L-AMB is

not. Thus, L-AMB does not interact with drugs that undergo CYP metabolism.

In this study, the efficacy and safety of L-AMB were retrospectively evaluated for patients with CTDs in whom IFI developed during immunosuppressive therapy.

Patients and methods

Patients

Subjects were 13 patients with CTDs and complications because of IFI confirmed or suspected on the basis of clinical symptoms, imaging findings, microbiological and histological examinations, serum 1,3-β-D-glucan antigenemia (BG) levels, and serum-specific antigen tests for *Aspergillus* and *Candida*. All patients were treated with L-AMB at Osaka Medical College Hospital between October 2006 and October 2009.

Diagnosis of IFI

IFI was diagnosed on the basis of criteria established by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group (EORTC/MSG) [10]. These criteria include:

1. host factors: long-term use of steroids (prednisolone (PSL) >0.3 mg/kg/day for ≥3 weeks) and use of immunosuppressants for >90 days;
2. clinical criteria: refractory to broad-spectrum antibiotics, and fungal infection suspected on the basis of symptoms and imaging findings;
3. mycological criteria: findings suggesting fungi in auxiliary (serum) diagnosis or fungi detected by a direct test (microscopical examination of smear and culture); and
4. proved diagnosis: fungi found in aseptic sites (including biopsy specimens, blood, and spinal fluid).

Patients who met criteria 1, 2, and 3 were regarded as probable diagnosis; those who met 1 and 2 were regarded as possible diagnosis. In addition to the EORTC/MSG criteria, patients who met 1 and 3 were classified as suspected diagnosis. The host factors in the EORTC/MSG criteria (protracted neutropenia, hematopoietic stem cell transplantation, and hereditary severe immunodeficiency) were excluded from the criteria.

Investigation items

Data collected for CTDs included underlying diseases, sex, age, immunosuppressive therapy, pathogenic fungi, premedication with antifungal agents, and prognosis after L-AMB therapy. White blood cell (WBC) count, lymphocyte count, and serum albumin (Alb), serum immunoglobulin G (IgG), serum creatinine (Cr), serum potassium (K), and serum C-reactive protein (CRP) levels were measured before administration, at the end of administration, and 4 weeks after the end of administration. Serum *Aspergillus* galactomannan antigen (GM) levels were examined by use of enzyme-linked immunosorbent assays (Platelia; BioRad; cut-off ≥0.5). BG levels were examined using a dilution and heating-turbidimetric method—kinetic-turbidimetric technique (Wako Pure Industries, Osaka, Japan; cut-off ≥11 pg/mL). Regarding BG, a level lower than the detection limit was regarded as negative. Imaging and fungal culture tests were also performed.

Treatment

All patients were treated with preemptive L-AMB therapy at a dose of 2.0–2.5 mg/kg. Preemptive therapy is a strategy in which antifungal agents are started when a positive result is obtained in an auxiliary diagnosis test for fungal infection (BG, various fungal antigens), in addition to the presence of symptoms and imaging findings indicating possible fungal infection [11, 12]. Premedication to prevent fever, nausea, and vomiting was not administered.

Efficacy evaluation

The efficacy of L-AMB was evaluated by use of the AKOTT algorithm as follows [13]. Treatment was classified as effective for a patient with at least one improved finding by imaging or mycologically, and improved clinical symptoms that were believed to involve fungi. Treatment was defined as ineffective for a patient with no improved findings. Patients who died from causes other than IFI during administration of L-AMB and those who discontinued L-AMB because of adverse reactions were not evaluated. Serological effects were evaluated from GM and BG values before administration of L-AMB and at the completion of administration. Imaging therapeutic effects of L-AMB were assessed by X-ray, CT, and endoscopy.

Safety evaluation

Safety was evaluated on the basis of serum ALT, Cr, and K levels before administration of L-AMB, at the completion of administration, and 4 weeks later. Changes in serum Cr and K levels were evaluated for all subjects except two hemodialysis patients. The presence of a hypersensitivity reaction to L-AMB was also examined.