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Original Article

Caspofungin versus micafungin in the incidence of hepatotoxicity in patients with normal to moderate liver failure

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ABSTRACT

Background: One of the major adverse events of caspofungin and micafungin is hepatotoxicity, however, there are few reports compared the incidence of hepatotoxicity between caspofungin and micafungin. Herein, the primary objective of this study was to compare the incidence of hepatotoxicity between caspofungin and micafungin treatments for patients with fungal or suspected fungal infection.
Methods: In total, 201 patients [caspofungin group: 66 patients; micafungin group: 135 patients] treated with echinocandins from April 2014 to November 2015 at Aichi Medical University Hospital. Investigation item were as follows; sex, age, weight, height, duration of treatment, total dose, disease type, clinical isolates, liver enzyme levels, concomitant medications. Liver function was assessed in accordance with Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. We divided into two groups depend on their liver enzyme levels before treated with echinocandins; normal group (liver enzyme levels $\leq$ CTCAE Grade 1), abnormal group (liver enzyme levels $\geq$ CTCAE Grade 2).
Results: The overall incidence of serious hepatotoxicity (Grade 3 or higher) was 6.1% (4/66) in the caspofungin group and 7.4% (10/135) in the micafungin group. The proportion of patients used caspofungin and micafungin showed serious hepatotoxicity were 0% (0/47) and 6.5% (7/108) in normal group ($p = 0.17$), and 21.1% (4/19) and 10.7% (3/28) in abnormal group ($p = 0.42$).
Conclusion: There was no notable difference in serious hepatotoxicity between the caspofungin group and the micafungin group, even though in patients with abnormal liver enzyme levels (CTCAE grade 2 or higher).

1. Introduction

The importance of deep-seated fungal infections of *Candida* spp. and *Aspergillus* spp. in Japan is considered to be increasing due to the rise in the number of immunocompromised patients associated with the introduction of advanced medical treatment and the aging of the Japanese population as a whole [1,2].

Caspofungin and micafungin are semisynthetic, lipopeptide antifungal agent of the echinocandin class of compounds. Echinocandins inhibit the biosynthesis of (1,3)-β-D-glucan, the structural component of fungal cell wall: they have been shown to be effective as the primary therapy for esophageal candidiasis and invasive candidiasis, as salvage therapy for invasive aspergillosis, and as empirical therapy in patients with persistent fever and neutropenia [3–6]. Moreover, some clinical studies revealed that caspofungin and micafungin showed to be similar clinical effectiveness when they were used as empirical therapy and the treatment for candidemia [7,8].

In general, as echinocandins have revealed that the incidence of drug-related adverse events was relatively low, they are considered as safe antifungals, compared as the other antifungals [9–12]. On the other hands, *in vitro* studies reported that

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micafungin was more uptaken into human hepatocytes than caspofungin because of structure activity relationship [13,14]. Hence, micafungin is expect to be occurred more frequently hepatotoxicity than caspofungin. However, there are few reports was compared the incidence of hepatotoxicity between caspofungin and micafungin, while their main side effect is liver dysfunction. Additionally, although most antifungals were classified as hepatic metabolite group, we usually encounter an opportunity to treat for fungal infection patients with moderate to severe liver failure with antifungals. However, there were few clinical reports to be evaluated the tolerability of echinocandins for patients with moderate to severe liver failure.

Therefore, the primary objective of this study was to compare the incidence of hepatotoxicity between caspofungin and micafungin treatments for patients with fungal or suspected fungal infection. The secondary objective was to compare the tolerability between caspofungin and micafungin treatment in patients with normal liver function and abnormal liver function.

2. Patients and methods

All patients were admitted to the Aichi Medical University Hospital (995 beds) and treated with caspofungin or micafungin from April 2014 to November 2015. Inclusion criteria were as follows: age of >18 years; patients whose liver enzyme levels were measured before initiation and after the completion of echinocandin treatment. Patients who fall under any of the criteria listed below were to be excluded: patients who received echinocandin treatment period was less than 48 h; patients with moderate or severe hepatic insufficiency due to acute hepatitis, hepatic cirrhosis.

Liver function was assessed in accordance with Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [15]. Patients received echinocandin treatment were divided into two groups depend on their liver enzyme levels (≤CTCAE Grade 1; normal group, and ≥CTCAE Grade 2; abnormal group) before the treatment of echinocandin started. Additionally, multiple types of drugs were concomitantly used with antifungals and coexist with various diseases in our population. Hence, any concomitant medications were reported that the incidence of hepatotoxicity was more than 3% in Japanese clinical study, were also assessed.

The study was reviewed and approved by the ethics committee of the Aichi Medical University.

2.1. Assessment of hepatotoxicity

Liver functions were assessed with total bilirubin (T-bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), respectively, before initiation and after completion of caspofungin or micafungin therapy. Hepatotoxicity was defined to admit the elevation more than 1 CTCAE grade in more than one of all liver enzyme levels elevation. Serious hepatotoxicity was defined as Grade 3 or higher liver enzyme levels elevations.

2.2. Statistical analysis

The data were expressed as the median values [minimam–maximam]. Statistical significance of the difference was evaluated with Chi-squared test for categorical data and Mann–Whitney's *U* test for continuous data respectively. Statistical analysis was performed using JMP software, version 10.0 (SAS Institute Inc, Tokyo, Japan). A p value of <0.05 was required to achieve statistical significant.

3. Result

3.1. Patients

Two hundred and one patients were received echinocandins treatment during this study period. Among them, 135 patients (67.2%) were treated with micafungin. The median age of the patients was 73 years [minimum–maximum: 21–92] and the proportion of male patients (66.2%) was greater than that of female patients (33.8%). The median weight was 50.0 kg [28.4–94] and median height was 161.3 cm [138–185]. The median duration of echinocandins treatment was 8 days [2–97]. The median total dose of caspofungin group was 1200 mg [120–3690] and micafungin group was 420 mg [225–14,550]. Major regimen of caspofungin was 70 mg on first day followed by 50 mg once daily dose (95.4%: 63/66) and that of micafungin was 150 mg once daily (81.5%: 110/135).

There was no statistical difference in clinical characteristics between the caspofungin group and the micafungin group except for ALP (Table 1). The proportion of disease type is presented in Table 2. Major underlying disease in caspofungin group was hematologic malignancy (34.8%), following by chronic lung disease (25.8%) and solid tumor (22.7%). Major underlying disease in micafungin group was hematologic malignancy (53.3%), following by chronic lung disease (17.8%). Major infection type in caspofungin group was febrile neutropenia (27.3%), candidemia (25.8%) and pneumonia (19.7%). Major infection type in micafungin group was febrile neutropenia (27.3%) and pneumonia (31.9%). The highest proportion of clinical isolates was *Candida albicans* (19.7%) in both groups (Table 3).

The proportion of patients received concomitant medications is presented in Table 1.

Most of patients were received concomitant medications in the both groups. Maximum number of concomitant medications was 4 drugs in caspofungin group and 5 drugs in micafungin group.

3.2. Hepatotoxicity

The number of patients who reported hepatotoxicity is shown in Table 3. Hepatotoxicity were reported in 48.5% (32/66) and 43.0% (58/135) of patients in the caspofungin and micafungin groups, respectively. There was no statistical difference between the both groups in all liver enzyme levels (Table 4).

On the other hands, the number of patients who was in liver abnormal group (more than grade 2 on CTCAE; abnormal group) before caspofungin and micafungin treatment started was reported in 28.8% (19/66) and 20.7% (28/135). Additionally, the number of patients who admitted serious hepatotoxicity (grade 3 or 4 on CTCAE) after echinocandin treatment started was reported in 0% (0/47) and 6.5% (7/108) in normal group ($p = 0.17$), and 21.1% (4/19) and 10.7% (3/28) in abnormal group ($p = 0.42$). There was no statistical difference between the both groups in all liver enzyme levels. Additionally, we evaluated the incidence of hepatotoxicity with the same population after classification with Child–Pugh scoring (Table 5). There was no statistical difference in the incidence of hepatotoxicity between the both groups in every Child–Pugh scoring classes (A–C) (Table 5). The patients treated with caspofungin, have scored more than 7 in Child–Pugh classification (class B and C), showed numerically higher incidence of serious hepatotoxicity than micafungin, while they were not significantly difference (Table 5).

4. Discussion

Invasive *Candida* and *Aspergillus* infections are an important cause of morbidity and mortality among patients with health care-