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Original article

Pharmacokinetics, efficacy, and safety of caspofungin in Japanese pediatric patients with invasive candidiasis and invasive aspergillosis

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ABSTRACT

The antifungal agents approved in Japan for pediatric use are limited and many unapproved drugs are actually used without clear instruction for dosage. We investigated the pharmacokinetics of caspofungin for the treatment of invasive candidiasis and invasive aspergillosis in 20 Japanese pediatric patients using a pediatric-specific dosage based on body surface area. Caspofungin was administered intravenously over 60 min as 70 mg/m^2 on Day 1, followed by 50 mg/m^2 per day. Five or 4 point blood sampling were done in 15 patients on Day 4–5 to calculate $AUC_{0-24\ h}$. The geometric means (95% confidence interval) of $C_{24\ h}$ and $AUC_{0-24\ h}$ in the pediatric patients were 3.3(2.5, 4.4) μg/mL and 175.1 (139.3, 220.1) μg hr/mL, respectively, which were comparable to those in Japanese adult patients [3.2 (2.8, 3.5) μg/mL and 144.9 (131.7, 159.3) μg hr/mL, respectively]. Among the 20 patients, 10 (50%) had at least 1 drug-related adverse event which was considered related to caspofungin therapy. No drug-related serious adverse event and no death occurred. The most common drug-related adverse events were events relating to hepatic function (mainly increases in ALT and AST). The overall success in efficacy was observed in 13 of 20 patients. In conclusion, once daily administration of caspofungin (70 mg/m^2 on Day 1, followed by 50 mg/m^2 [maximum daily dose not to exceed 70 mg]), which is the same dosage being used in overseas, achieved sufficient drug exposure and a favorable efficacy and acceptable safety profile in Japanese pediatric patients with invasive fungal infections.

1. Introduction

With increasingly potent chemotherapies, radiation, and the use of steroids for hematopoietic stem cell transplantation and anti-cancer therapy in pediatric patients, the frequency of invasive

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fungal infection (IFI) in children is increasing. Although epidemiologic data in the field of pediatric mycology is very limited in Japan [1], *Candida* and *Aspergillus* spp. are the most common and important pathogens in pediatric patients, as also reported in adults patients [2].

The drugs currently approved for the parenteral treatment of IFI in the pediatric population in Japan are limited to fluconazole, micafungin, voriconazole and liposomal amphotericin B. However, other antifungal agents not approved for pediatric use and not recommended by any treatment guidelines have been frequently used in clinical practice in Japan [3].

Caspofungin has been approved for use in adult patients in over 80 countries. In Japan, a study of caspofungin versus micafungin in the treatment of candidiasis and aspergillosis was conducted by Kohno et al. [4], and, based on the results of this study, caspofungin was approved for the use in Japanese adult population in 2012.

The pharmacokinetics of caspofungin have been investigated in various non-Japanese pediatric age groups [5,6], and the optimal clinical dosage for these pediatric patients was determined as 70 mg/m^2 on Day 1 as a loading dose, followed thereafter by 50 mg/m^2 (maximum 70 mg daily). Using this body surface area (BSA) dosing regimen, empiric antifungal efficacy in non-Japanese pediatric patients with febrile neutropenia [7] and the treatment efficacy in non-Japanese pediatric patients with invasive aspergillosis and candidiasis [8] were confirmed. The population pharmacokinetic analysis from the various pediatric studies was also reported in a total of 125 non-Japanese pediatric patients [9], ultimately confirming the pharmacokinetic profile in pediatrics. Based on the data including these studies, the use in pediatric patients (3 month–17 years old of age) has been approved for the same indication as in adults in approximately 60 countries outside of Japan.

All these reports were based on the data in studies outside of Japan, and no study has reported pharmacokinetics of caspofungin in Japanese pediatric patients. In this paper, we report the first study of caspofungin in Japanese pediatric patients with invasive candidiasis or invasive aspergillosis; this trial helped the application of caspofungin for pediatric use in Japan. The efficacy and safety of caspofungin in Japanese pediatric patients are also described.

2. Patients and methods

This study was a multicenter, prospective, open-label, non-comparative study of caspofungin in Japanese children and adolescents 1–17 years of age with invasive candidiasis or invasive aspergillosis. The study was conducted in 12 sites in Japan from Sep 2010 through Sep 2013. The protocol was approved by the institutional review boards of all the participating sites. Written informed consent was obtained from parent or guardian of all the enrolled pediatric patients and written assent was obtained from the patient if possible. The protocol was registered on clinicaltrial.gov (NCT01165320).

2.1. Inclusion and exclusion criteria

Patients who meet the following definitions at screening (within 7 days of study entry) were enrolled in this study;

2.1.1. Candidemia

Fungal infection was strongly suspected based on fever (either >38 °C or >37.5 °C continuing for more than one hour) despite antibiotic therapy and the patient's clinical course, AND at least one of the following 3 conditions: (a) Positive serological fungal test (β-1,3-D-glucan or Candida antigen ELISA), OR (b) Yeast observed by direct microscopy of the blood, OR (c) *Candida* spp. observed by culture testing of the blood.

2.1.2. Invasive candidiasis other than candidemia

Fungal infection was strongly suspected based on the presence of refractory fever (not responding to antibiotic agent) or other clinical symptoms at the site of disease, or the patient's clinical course (such as perforation of the gastrointestinal tract), AND at least one of the following 3 conditions: (a) both radiographic imaging findings to suspect fungal infection and positive serological fungal test (β-1,3-D-glucan or Candida antigen ELISA), OR (b) Positive finding of Yeast (direct microscopy or histopathological test), OR (c) Positive culture from an invasive, normally sterile body site for *Candida* spp.

2.1.3. Invasive aspergillosis

Fungal infection was strongly suspected based on the clinical symptoms and the patient's clinical course, AND characteristic radiographic imaging findings were observed, AND at least one of the following 4 conditions: (a) Patient with risk factors predisposing to a fungal infection, OR (b) Positive serological test for fungus (on β-1,3-D-glucan or ELISA for Aspergillus galactomannan antigen), OR (c) Positive finding of mold (acute-branching mold with septated hyphae) in specimens including the sputum OR (d) Positive culture of *Aspergillus* spp. in an invasive, normally sterile specimen, including the sputum.

In this study, patients with positive culture were categorized in definitive diagnosis, patients with positive serological test results (β-D-glucan and/or *Aspergillus* galactomannan antigen) were categorized in presumed diagnosis, and the cases with clinical symptom/radiological findings and/or host factors were categorized in possible diagnosis.

Major exclusion criteria included a history of serious drug-related allergy or sensitivity; the use of newly started systemic antifungal agents in the screening period; the use of micafungin over the dosage of 1 mg/kg for more than 3 days in the week prior to initiation of study therapy; evidence of moderate or severe hepatic insufficiency; or any of the following laboratory abnormalities: total bilirubin >5 x upper limit of normal (ULN), aspartate aminotransferase (AST) > 5 x ULN, or alanine aminotransferase (ALT) > 5 x ULN. For invasive candidiasis, the following excluding criteria also applied: (1) no clinical evidence of invasive infection and/or a positive culture for *Candida* species is limited to sputum; (2) evidence of *Candida* endocarditis, meningitis, osteomyelitis; (3) presence of a prosthetic device (except for an indwelling vascular catheter). For aspergillosis, patients with disease limited to allergic sinus aspergillosis, allergic bronchopulmonary aspergillosis, or ocular disease were also excluded. Concomitant use of other systemic antifungal drugs, rifampin and cyclosporine A was prohibited.

2.2. Treatment regimen

Caspofungin was administered intravenously over 60 min to all the patients at a dose of 70 mg/m^2 on Day 1, followed thereafter by 50 mg/m^2 per day (maximum daily dose not to exceed 70 mg). The daily dosage was determined based on the body surface (BSA) which was calculated using Mosteller's equation as shown below.

$$\mathrm{BSA}\left(\mathrm{m}^2\right) = \sqrt{\mathrm{Height\ (cm)} \times \mathrm{Weight\ (kg)}/3600}$$

A dose escalation to a 70 mg/m^2 maintenance dose was allowed in patients who have not responded adequately after 4 days provided caspofungin has been well tolerated at the initially prescribed dose. In all patients (including dose-escalated patients), the

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