Relationship between the initial dose of micafungin and its efficacy in patients with candidemia

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Abstract Micafungin, the first licensed echinocandin in Japan, has shown excellent in vitro and in vivo activity against all Candida species. However, the appropriate dose for the initial treatment of candidemia remains to be determined. In this study, we retrospectively examined the relationship between the clinical outcome of candidemia and the initial dose of micafungin. Patients were divided into two groups according to the initial dose of micafungin administered: group I (<2.25 mg/kg/day) and group II (≥2.25 mg/kg/day). Micafungin produced an excellent 30-day clinical response in patients with candidemia, including Candida parapsilosis; the overall 30-day clinical response was 86%. The administration of higher doses of micafungin accelerated the clinical response and duration until the clinical response in group II was significantly shorter than that in group I (P = 0.021). However, no significant differences were observed in the 30-day mortality attributable to the fungal infection between the two groups. Considering these results, we recommend the administration of 2.25 mg/kg/day or more of micafungin in the initial treatment of patients with candidemia.

Key words Micafungin · Candidemia · Candida · C. parapsilosis · Echinocandin

Introduction

The echinocandins are a new class of antifungal drugs that inhibit β-1,3-D-glucan synthesis.1–3 Experimental and clinical data for caspofungin, the first licensed echinocandin in the USA and Europe, have been excellent for the treatment of candidemia.4,5 Micafungin, the first licensed echinocandin in Japan, has also shown excellent in vitro and in vivo activity against all Candida spp.6 Clinical trials of micafungin as a prophylaxis against candidemia in stem cell transplant patients and for the treatment of esophageal candidiasis have also shown excellent efficacy and safety.7–11 However, two important queries remain regarding micafungin treatment for candidiasis. First, uncertainty exists regarding its effectiveness against C. parapsilosis. Certain studies have demonstrated that, in contrast to their potent activity against most Candida spp., echinocandins, including micafungin, had lower levels of activity against C. parapsilosis.12,13 However, in a recently published report, micafungin produced high treatment response rates across all organisms, including C. parapsilosis (86.4%).6 The second question is: What dose of micafungin is appropriate for the initial treatment of candidemia? At dosages of 0.5–2 mg/kg, micafungin shows a linear disposition and achieves potentially therapeutic drug concentrations in plasma and tissues that are common sites of invasive fungal infections in healthy rabbits.14 When administered at doses of 1 mg/kg or higher, micafungin was highly effective (in a dose-dependent fashion) at reducing the organ burden in disseminated sepsis caused by C. tropicalis in a persistently neutropenic mouse model, and higher doses of micafungin (2–10 mg/kg) were the only treatment regimes able to reduce C. tropicalis cfu to below detectable levels in organs.15 It was also demonstrated in a human study that micafungin shows a greater efficacy at 100 and 150 mg/day than at 50 mg/day in patients with HIV-associated esophageal candidiasis.16 In candidemia, doses of micafungin in the range 75–150 mg/day resulted in higher response rates (>90%) than those of 75 mg/day or less, although the clinical efficacy of micafungin at doses of 150 mg/day or more remains to be determined owing to the small number of patients.8 In addition, the maximum tolerated dose (MTD) of micafungin was not reached even at doses up to 200 mg/day for 4 weeks in adult patients undergoing bone marrow or peripheral stem cell transplantation.17 It is therefore very important to determine the initial appropriate dose of micafungin for the treatment of candidemia. The purpose of this study was to
examine the relationship between the clinical outcome of candidemia and the initial dose of micafungin.

**Material and methods**

**Study population**

All patients with candidemia who were initially treated with micafungin during the period from April 2003 through March 2006 at the University of Tokyo Hospital (a teaching hospital of 1200 beds) were enrolled in this study. Patients were evaluated for the outcome analysis if they received continuous unchanged therapy with micafungin for ≥7 days. Patients were divided into two groups according to their initial dose of micafungin: group I (<2.25 mg/kg/day) and group II (≥2.25 mg/kg/day). The cut-off dose, 2.25 mg/kg/day, was the micafungin dose which made a maximal difference in 30-day clinical response between the two groups. The ethical committee of the University of Tokyo approved this project.

**Evaluation of clinical background**

The clinical courses of the patients were retrospectively reviewed to determine the following demographic characteristics: age, sex, underlying disease (cancer, diabetes mellitus, use of steroids or immunosuppressive agents, or neutropenia), and severity of illness. To measure the severity of their illness, the acute physiology and chronic health evaluation (APACHE) II score was used. In addition, the type of their illness, the acute physiology and chronic health evaluation, proportion of catheter-related candidemia, or severity of illness. However, the duration of micafungin treatment was also determined. The efficacy end-points were 30-day mortality and 30-day clinical response. We also examined the duration until a clinical response in cases that showed a clinical response within 30 days. The clinical response was evaluated on the investigator’s assessment of the clinical and mycological response, including improvements in attributable signs and symptoms, inflammatory markers (WBC and CRP), and radiographic abnormalities, in addition to a negative culture of the infecting Candida spp. from blood and the primary site of infection. The duration of the micafungin treatment was also determined. Hematological investigations and serum chemistry were performed at least twice weekly during therapy.

**Definition**

Candidemia was defined as at least one blood culture which was positive for Candida spp. in the presence of signs and symptoms of infection. Catheter-related blood-stream infection (CR-BSI) for Candida spp. was defined as candidemia in a patient with an intravascular catheter whose culture was positive for the same Candida spp. and who had no other sources of Candida infection. Non-catheter-related blood-stream infection (non-CR-BSI) was defined as candidemia which did not meet the conditions of CR-BSI. The onset of candidemia was defined as the day of the first positive blood culture. Candidemias that occurred >30 days after the initial case were considered to be new cases. Potential risk factors were considered relevant if they were present within 30 days prior to the onset of candidemia. Neutropenia was defined as an absolute neutrophil count of <1000 cells/µl. The death of a patient was considered to be related or attributable to the candidemic episode if it occurred during the phase of active infection. Only attributable or related mortality was used in the analysis.

**Antifungal susceptibility**

Blood specimens were inoculated into BacT/ALERT FA bottles (bioMerieux), and the blood culture was judged to be positive automatically by the BacT/ALERT 3D system. Antifungal susceptibility assays to determine the minimum inhibitory concentrations (MICs) of antifungal agents were performed by the broth microdilution methods according to M27-A2 guidelines recommended by the Clinical Laboratory Standards Institute (CLSI). The MICs of micafungin for Candida spp. were defined as the lowest concentrations at which no visible growth was observed.

**Statistical analysis**

Relationships between categorical variables were analyzed using Pearson’s \( \chi^2 \) test. Continuous variables were compared using Student’s t-test. A \( P \) value of <0.05 was considered significant. All analyses were performed with SPSS software for Windows (Ver.10.1).

**Results**

Clinical backgrounds of patients with candidemia who were treated with micafungin

During the 3-year surveillance period, 30 patients with candidemia were initially treated with micafungin. Two cases were excluded owing to insufficient data. All patients except one in group I were treated with micafungin alone. Of the 28 patients, 13 were initially treated with lower doses (<2.25 mg/kg/day) and 15 with higher doses (≥2.25 mg/kg/day) of micafungin. The clinical backgrounds of the patients in the two groups are summarized in Table 1. No significant intergroup differences were observed in age, sex, underlying disease, proportion of catheter-related candidemia, or severity of illness. However, the duration of micafungin treatment was significantly longer in patients treated with lower doses of micafungin than in those with higher doses (\( P = 0.043 \)).

Species distribution and antifungal susceptibility

The species distribution of candidemia is summarized in Table 2 parts A and C. No significant differences were noted between the two groups. The percentage of C. parap-