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ORIGINAL ARTICLE

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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.[6] 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

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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.[18] In addition, the type of candidemia (catheter-related or non-catheter-related) 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.[19] 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).[20] 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 with Pearson's χ^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-*

Table 1. Clinical backgrounds of patients with candidemia treated with micafungin

Clinical backgrounds	Group I	Group II	*P* value
Age	65.4 ± 16.9	62.5 ± 19.5	0.678
Sex (male:female)	6:7	6:9	0.521
Cancer	5/13 (38.5%)	8/15 (53.3%)	0.343
Diabetes	4/13 (30.8%)	4/15 (26.7%)	0.569
Immunosuppressive agent and/or steroid use	2/13 (15.4%)	3/15 (20%)	0.571
Neutropenia	1/13 (7.7%)	2/15 (13.3%)	0.556
CR: non-CR	7:6	7:8	0.705
Severity of illness (APACHE II >20)	5/13 (38.5%)	8/15 (53.3%)	0.343
Days of micafungin treatment	31.6 ± 3.4	27.6 ± 2.0	0.043

CR, catheter-related candidemia; non-CR, non-catheter-related candidemia; APACHE, acute physiology and chronic health evaluation

Table 2. Species distribution and antifungal susceptibility

(A) *Candida* species

Candida species	Group I (n = 13)	Group II (n = 15)
C. albicans	5	5
C. parapsilosis	3	5
C. glabrata	2	2
C. tropicalis	2	3
Others	1	0

(B) Minimum inhibitory concentration (MIC)

MIC (mg/l)	Group I	Group II
≤0.03	10	9
0.06	0	0
0.12	0	0
0.25	0	0
0.5	1	4
1	1	2
2	1	0
4≤	0	0

(C) Microbiological background

Microbiological background	Group I	Group II	*P* value
Candida species			
A, P, nonAnonP	5:3:5	5:5:5	0.836
Micafungin MIC (≥2 mg/l)	1/13 (7.7%)	0/15 (0%)	0.464

A, *C. albicans*; P, *C. parapsilosis*; nonAnonP, *Candida* spp. other than *C. albicans* or *C. parapsilosis*

silosis was 3/13 (23%) in group I and 5/15 (33%) in group II. The *Candida* isolates showed excellent susceptibility to micafungin (Table 2 parts B and C). No significant differences were observed in susceptibility to micafungin between the two groups. The micafungin MIC was ≥2 g/ml for one *Candida* isolate (*C. parapsilosis*).

Efficacy of micafungin in patients with candidemia

Mortality which was attributable to the fungal infection within 30 days was 15% (2/13) in patients treated with lower doses of micafungin and 7% (1/15) in those treated with higher doses. No significant differences were observed between the two groups (Table 3). Micafungin treatment resulted in an excellent 30-day clinical response: 85.7% (24/28) in total, 76.9% (10/13) in group I, and 93.3% (14/15) in group II. Although there were no significant differences between the two groups, treatment with a higher dose of micafungin led to a greater proportion of patients exhibiting a 30-day clinical response. Furthermore, we compared the duration until clinical response in patients who improved within 30 days. The duration until clinical response was 21.0 ± 4.6 days in group I and 16.9 ± 3.6 days in group II, indicating that treatment with higher doses of micafungin led to a significantly more rapid clinical improvement (P = 0.021).

Table 3. Clinical outcomes in patients with candidemia treated with micafungin

Clinical outcomes	Group I	Group II	*P* value
30-day mortality	2/13 (15%)	1/15 (7%)	0.583
30-day clinical response	10/13 (77%)	14/15 (93%)	0.244
Days until clinical response	21.0 ± 4.6	16.9 ± 3.6	0.021

Table 4. Clinical outcomes in patients with *C. parapsilosis* candidemia treated with micafungin

Clinical outcomes	Total	Group I	Group II
30-day mortality	0/8	0/3	0/5
30-day clinical response	7/8	2/3	5/5

Efficacy of micafungin in patients with *C. parapsilosis* candidemia

We also analyzed the efficacy of micafungin in patients with candidemia involving *C. parapsilosis*. Micafungin was administered to eight patients with *C. parapsilosis* candidemia, and showed excellent activity against this organism. Overall, the 30-day mortality was 0/8 (0%) and the 30-day clinical response was 7/8 (87.5%) (2/3 (66.7%) in group I, and 5/5 (100%) in group II) (Table 4).

Discussion

Appropriate initial treatment is important for treatment success in fungal infections. The administration of an

appropriate dose of antifungal agents is also pivotal. It was recently reported that the dose-dependent properties of fluconazole, and under-dosing fluconazole against less-susceptible *Candida* isolates, have the potential to increase the risk of mortality associated with candidemia.[21] However, at present it remains to be determined what dose of micafungin we should administer for the initial treatment of patients with candidemia. In the present study, micafungin showed a high treatment success rate (87.5%) across all organisms, including *C. parapsilosis*. The overall success rates exceeded 85% in total, and reached 90% in patients with candidemia who were treated with at least 2.25 mg/kg/day of micafungin (Table 3). The response rate seen in this study is in the same range as that previously reported for micafungin.[6] Although no significant differences were observed in the 30-day mortality between the two groups, an initial treatment with the higher dose of micafungin led to a significantly earlier clinical response (Table 3). In a previous report, lower response rates were seen with doses over 150 mg/day.[6] However, this might have been related to dose escalation in the sickest patients, or to the small number of patients in that dosage range. In contrast, the severity of illness and the number of patients did not differ significantly between the two groups in our study. Furthermore, the mean duration of micafungin administration was significantly shorter in patients treated with higher doses. This reflected the earlier clinical responses in these patients. It is our current practice to use antifungal agents for an additional 1 or 2 weeks after a clinical response is obtained. However, on the basis of our results, the duration of micafungin treatment might be shortened. In addition, our study might also imply the possibility of "de-escalation" therapy of micafungin.

This study has several limitations. It was a retrospective analysis with relatively few patients. Moreover, the selection of patients who were treated with micafungin might have been biased. However, about half of the patients with candidemia were treated with micafungin during the study period, and the species distribution seen in this study is very similar to that seen in contemporary epidemiological studies.[4,22–25] Furthermore, the majority of the patients in this study were those with cancer in surgical wards. The fact that the proportion of patients with neutropenia or other forms of immunosuppression was relatively low might have contributed to a higher treatment success. It is particularly notable that all except one patient in group I were treated with micafungin alone in this study, and these cohorts are therefore suitable for analyzing the efficacy of micafungin in candidemia. In addition, we present good evidence that an initial treatment with higher doses of micafungin is better than treatment with lower doses, because there were no significant differences in clinical background, including severity of illness, between the two groups. Nonetheless, a prospective study will naturally be needed to determine at which dose of micafungin we should start to treat patients with candidemia.

Micafungin was well tolerated, as previously reported,[15] and during treatment we observed no episodes of Southwest Oncology Group (SWOG) grade 3 or higher adverse effects causing treatment interruption. In conclusion, micafungin produced an excellent clinical response, and the administration of doses of ≥2.25 mg/kg/day were most useful for patients with candidemia. This corresponds to ≥150 mg of micafungin in Japanese patients with standard constitutions.

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References

1. Denning DW. Echinocandin antifungal drugs. Lancet 2003; 362(9390):1142–51.
2. Graybill JR. Hitting a new target with echinocandins. Why chase something else? Curr Opin Investig Drugs 2001;2:468–71.
3. Odds FC, Brown AJ, Gow NA. Antifungal agents: mechanisms of action. Trends Microbiol 2003;11:272–9.
4. Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002; 347:2020–9.
5. Kartsonis NA, Nielsen J, Douglas CM. Caspofungin: the first in a new class of antifungal agents. Drug Resist Update 2003;6: 197–218.
6. Ostrosky-Zeichner L, Kontoyiannis D, Raffalli J, Mullane KM, Vazquez J, Anaissie EJ, et al. International, open-label, noncomparative, clinical trial of micafungin alone and in combination for treatment of newly diagnosed and refractory candidemia. Eur J Clin Microbiol Infect Dis 2005;24:654–61.
7. van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004;39:1407–16.
8. Kohno S, Masaoka T, Yamaguchi H, Mori T, Urabe A, Ito A, et al. A multicenter, open-label clinical study of micafungin (FK463) in the treatment of deep-seated mycosis in Japan. Scand J Infect Dis 2004;36:372–9.
9. Pettengell K, Mynhardt J, Kluyts T, Lau W, Facklam D, Buell D. Successful treatment of oesophageal candidiasis by micafungin: a novel systemic antifungal agent. Aliment Pharmacol Ther 2004;20: 475–81.
10. Jarvis B, Figgitt DP, Scott LJ. Micafungin. Drugs 2004;64:969–82; discussion p. 983–4.
11. Wiederhold NP, Lewis RE. The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy. Expert Opin Investig Drugs 2003;12:1313–33.
12. Tawara S, Ikeda F, Maki K, Morishita Y, Otomo K, Teratani N, et al. In vitro activities of a new lipopeptide antifungal agent, FK463, against a variety of clinically important fungi. Antimicrob Agents Chemother 2000;44:57–62.
13. Ostrosky-Zeichner L, Rex JH, Pappas PG, Hamill RJ, Larsen RA, Horowitz HW, et al. Antifungal susceptibility survey of 2000 bloodstream *Candida* isolates in the United States. Antimicrob Agents Chemother 2003;47:3149–54.
14. Groll AH, Mickiene D, Petraitis V, Petraitiene R, Ibrahim KH, Piscitelli SC, et al. Compartmental pharmacokinetics and tissue distribution of the antifungal echinocandin lipopeptide micafungin (FK463) in rabbits. Antimicrob Agents Chemother 2001;45: 3322–7.
15. Warn PA, Sharp A, Morrissey G, Denning DW. In vivo activity of micafungin in a persistently neutropenic murine model of disseminated infection caused by *Candida* tropicalis. J Antimicrob Chemother 2002;50:1071–4.
16. de Wet N, Llanos-Cuentas A, Suleiman J, Baraldi E, Krantz EF, Della Negra M, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. Clin Infect Dis 2004;39:842–9.
17. Hiemenz J, Cagnoni P, Simpson D, Devine S, Chao N, Keirns J, et al. Pharmacokinetic and maximum tolerated dose study of mica-

fungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Antimicrob Agents Chemother 2005;49:1331–6.
18. Chang RW, Jacobs S, Lee B. Predicting outcome among intensive care unit patients using computerised trend analysis of daily Apache II scores corrected for organ system failure. Intensive Care Med 1988;14:558–66.
19. Mermel LA, Farr BM, Sherertz RJ, Raad II, O'Grady N, Harris JS, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001;32:1249–72.
20. National Committee for Clinical Laboratory Standards (2002). Reference method for broth dilution antifungal susceptibility testing of yeast. Approved Standard M27-A2. NCCLS W, PA, USA.
21. Pai MP, Turpin RS, Garev KW. Association of fluconazole area under the concentration-time curve/MIC and dose/MIC ratios with mortality in nonneutropenic patients with candidemia. Antimicrob Agents Chemother 2007;51:35–9.
22. Garbino J, Kolarova L, Rohner P, Lew D, Pichna P, Pittet D. Secular trends of candidemia over 12 years in adult patients at a tertiary care hospital. Medicine (Baltimore) 2002;81:425–33.
23. Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 2003;3:685–702.
24. Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis 2003;37:634–43.
25. Rex JH, Pappas PG, Karchmer AW, Sobel J, Edwards JE, Hadley S, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Clin Infect Dis 2003;36:1221–8.