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ORIGINAL ARTICLE

Efficacy of micafungin in empirical therapy of deep mycosis in surgically ill patients

Kohji Okamoto · Takefumi Katsuki · Toshihisa Tamura · Shuichi Kanemitsu · Noritaka Minagawa · Takayuki Torigoe · Kazunori Shibao · Aiichirou Higure · Koji Yamaguchi

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Abstract Micafungin (MCFG), an echinocandin antifungal agent, exhibits antifungal activity against *Candida albicans* and non-*albicans Candida*. The fungicidal activity of MCFG against clinical isolates of C*andida* species was investigated, and the clinical efficacy of MCFG in therapy of deep mycosis in surgery was studied using the AKOTT algorithm. The minimum inhibitory concentration and minimum fungicidal concentration values of fluconazole were ≤0.06–4 and >64 μg/ml, respectively, for each strain, whereas these values of MCFG were 0.008–0.5 and 0.016–1 μg/ml, suggesting that MCFG provided superior fungicidal ability against *Candida albicans* and non-*albicans Candida*. The subjects were separated into two groups: group A consisted of 20 subjects with both persisting fever refractory to broad-spectrum antibiotics and positive reaction to β-D-glucan test, and group B consisted of 20 subjects with either of those conditions. The overall response was evaluated as "effective" in 17 patients (85%) and 20 patients (100%) in groups A and B, respectively. In total, response was evaluated as "effective" in 37 patients (92.5%) and "ineffective" in 3 patients (7.5%). These findings suggest that MCFG administration should be used as empirical therapy for deep mycosis in surgically ill patients as it was shown to be an effective antifungal drug lacking serious adverse effects.

K. Okamoto (✉) · T. Katsuki · T. Tamura · S. Kanemitsu · N. Minagawa · T. Torigoe · K. Shibao · A. Higure · K. Yamaguchi
The Department of Surgery I, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan
e-mail: k-okamot@med.uoeh-u.ac.jp

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Introduction

Deep mycosis is a lethal opportunistic infection that often causes serious complications in critically ill patients with depressed immune function. Ideally, treatment for deep mycosis should be administered at the early stage of disease onset [1]. However, because treatment is often delayed until diagnosis is confirmed, this disease is associated with low treatment success [2]. To date, an effective early diagnostic method for deep mycosis has not yet been established; instead, empirical therapy is often applied based on information obtained from the immune status of patients [3], persisting fever refractory to broad-spectrum antibiotics [3], blood β-D-glucan test [4], or mycotic colonization by surveillance culture [5]. *Candida albicans*, which confers susceptibility to fluconazole (FLCZ), has been identified as a major pathogen responsible for deep mycosis in surgery [6, 7]. Therefore, FLCZ has been widely used as a first-line therapy drug. However, in recent years non-*albicans Candida*, which confers low or no susceptibility to FLCZ, has been increasingly isolated [8, 9], indicating a need to review application of this first-line therapy drug.

Recently, a novel algorithm, AKOTT (an acronym created from the first letter of the surname of each of the five members of the evaluation committee), was formulated as an evaluation method of the possible influence of bacterial infection combined with fungal infection and antibacterial therapy [10]. The AKOTT algorithm has been demonstrated to provide an objective method for evaluating clinical efficacy of antifungal agents [10].

It is well known that micafungin (MCFG), an echinocandin antifungal agent, exhibits antifungal activity against *Candida albicans* and non-*albicans Candida* [9], but to date no clinical trial with a large number of cases has been reported. Therefore, we investigated the fungicidal activity of MCFG against clinical isolates of *Candida* species and performed an efficacy study for MCFG in therapy of deep mycosis in surgically ill patients using the AKOTT algorithm.

Patients and methods

Susceptibility [minimum inhibitory concentration (MIC); minimum fungicidal concentration (MFC)] to various antifungal agents was measured using 27 *Candida* strains (19 *C. albicans*, 4 *C. tropicalis*, 3 *C. glabrata*, 1 *C. guilliermondii*) isolated from inpatients at the Department of Surgery I at the University of Occupational and Environmental Health, Japan, in 2004 and 2005. The broth microdilution technique used for antifungal susceptibility testing was performed based on the Clinical Laboratory Standard Institute M27-A broth microdilution methods [11].

Subjects were selected from surgically ill patients with high-risk factors for deep mycosis admitted to the surgical center of our hospital from 2005 to 2008. The following were considered high-risk factors: intensive care unit (ICU) stay for 7 days or more; respirator applied for 48 h or more; renal insufficiency and dialysis patients; severe acute pancreatitis; diabetes mellitus; upper gastrointestinal tract perforation; intravenous hyperalimentation (IVH) custody; hyperalimentation; steroid usage for 3 weeks or more; administration of immunosuppressant within the last 30 days; other serious complications; and with persisting fever refractory to broad-spectrum antibiotics for 3 days or more and/or positive to β-D-glucan test (cutoff value, 11 pg/ml: β-D-glucan test kit; Wako Pure Chemical). Patients were excluded for the following reasons: infected with fungi (*Cryptococcus*, *Trichosporon*) that do not confer susceptibility to MCFG; symptom disappeared with removal of intravenous catheter; inadequate for drug evaluation; and family doctors decided patient not suitable for the study. The subjects were separated into two groups because it is generally accepted that the possibility of deep mycosis in patients with both persisting fever refractory to broad-spectrum antibiotics and positivity to β-D-glucan test (group A) is greater than that in patients with only one of these conditions (group B).

As a general rule, subjects were intravenously administered 100 mg (valence) MCFG once a day for 7 days after surveillance culture for fungi. Primary evaluation was performed on the seventh day after the initial administration, and administration was terminated if infectious symptoms disappeared, body temperature became normal, and β-D-glucan and surveillance culture were negative. If fever persisted or β-D-glucan or surveillance culture was positive, the administration was continued. MCFG was increased to 150–300 mg in patients with exacerbated infectious symptoms. The use of concomitant drugs, including antibacterial drugs, was not restricted, but additional antifungal drugs were prohibited (Fig. 1). The efficacy of MCFG was evaluated based on clinical response, mycological response, diagnostic imaging response, and serological response using the AKOTT algorithm [10] (Fig. 2). The overall response was rated as either effective and ineffective. A data review board reviewed the clinical investigator's assessment. Cases with a breakthrough of deep mycosis or any change in antifungal drugs used were excluded. In the safety evaluation, any undesired effect on patients observed after starting the administration of drugs, including anomalous fluctuations in clinical examinations, was defined as an adverse event. The seriousness of adverse events was graded according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE)–December 12, 2003.

This study was approved by the ethics committee of the University of Occupational and Environmental Health, and informed consent was obtained from all patients or their families.

Results

The MIC value of FLCZ was $\leq$0.06–4 μg/ml, and the MFC value, which is the indicator of disinfectant activity, was >64 μg/ml for each strain. In contrast, the MIC value of MCFG was 0.008–0.5 μg/ml and its MFC value was 0.016–1 μg/ml, and it was confirmed that MCFG provided superior disinfectant ability against *Candida albicans* and non-*albicans Candida* (Table 1). In the strains isolated from inpatients in our department, although *Candida albicans* and non-*albicans Candida* were susceptible to FLCZ treatment, FLCZ was not a good disinfectant. On the other hand, MCFG provided superior disinfectant ability against both *Candida albicans* and non-*albicans Candida.*

Of 40 subjects treated with MCFG who underwent surgical therapy for gastrointestinal disease as a preexisting disease, 31 were male and 9 were female, with median age of 68 years (range, 16–88 years). The subjects were separated into two groups: group A consisted of 20 subjects with both persisting fever refractory to broad-spectrum antibiotics and positive reaction to β-D-glucan test, and group B consisted of 20 subjects with either condition. The mean (±SD) duration of MCFG administration was 16.6 ± 8.8 days. Treatment doses and schedules are listed