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ORIGINAL ARTICLE

Efficacy and safety of micafungin as an empirical therapy for invasive fungal infections in patients with hematologic disorders: a multicenter, prospective study

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Abstract This study was conducted as a prospective, multicenter trial to evaluate the efficacy and safety of micafungin as an empirical therapy for suspected invasive fungal infections (IFIs), including febrile neutropenia (FN), and to evaluate the usefulness of β-D-glucan (BG) and *Aspergillus* galactomannan (GM) antigen in patients with hematologic diseases. A total of 121 patients were enrolled and assessed for safety, and 119 were examined for clinical efficacy. The main underlying diseases were acute myeloid leukemia (38.0%), acute lymphoblastic leukemia (18.2%), and malignant lymphoma (18.2%). The median initial daily dose and duration of micafungin treatment were 150 mg/day and 13 days, respectively. The overall response rate for suspected IFIs (n=119), based on four composite endpoints, including baseline IFI, breakthrough IFIs (proven and probable), survival, and premature discontinuation, was 79.0%. In addition, the response rate for FN (n=81), based on these four endpoints as well as defervescence during neutropenia, was 39.5%. Breakthrough IFIs (proven, probable, and possible) occurred in five patients during micafungin treatment. All of these patients were positive for either BG or GM before the breakthrough IFIs. The incidence of adverse events (AEs) associated with micafungin was 10.7% and most were mild. The majority of AEs were liver dysfunction. These results indicate the effectiveness and safety of micafungin as an empirical therapy for suspected IFIs, including FN, and the usefulness of monitoring both BG and GM to detect breakthrough IFIs.

Keywords Micafungin · Empirical therapy · Fungal infection · Febrile neutropenia · β-D-glucan · *Aspergillus* galactomannan antigen

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Introduction

Invasive fungal infections (IFIs), mainly caused by *Candida* and *Aspergillus* species, often occur in patients with

hematologic disorders who are undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT) [1–3]. IFIs can be fatal if the appropriate antifungal treatment is delayed [4, 5]. However, because it is difficult to diagnose early IFIs and the efficacy of targeted antifungal treatments for proven IFIs is unsatisfactory [6, 7], empirical antifungal therapy is usually administered to patients with suspected IFIs, especially febrile neutropenia (FN) that is unresponsive to broad-spectrum antibiotics.

Several antifungal agents, such as caspofungin, voriconazole, liposomal amphotericin B, and itraconazole, have been evaluated in patients with FN in prospective, multicenter, randomized controlled trials (RCTs) [8–11]. These trials have examined the following five composite endpoints to assess efficacy: successful treatment of the baseline fungal infection, absence of breakthrough fungal infections, survival for 7 days after completing the study therapy, resolution of fever during neutropenia, and premature discontinuation because of toxicity or lack of efficacy. Among the examined antifungal agents, caspofungin, an echinocandin antifungal, was comparatively effective and generally well tolerated. Micafungin, another echinocandin antifungal agent, has a novel mechanism of action. Micafungin inhibits 1,3-β-D-glucan synthase, an enzyme responsible for the synthesis of an essential component of fungal cell walls [12]. Micafungin has potent antifungal activities against both *Candida* spp. and *Aspergillus* spp. [13, 14] and has been shown to be a safe and effective treatment for IFIs in some clinical settings and trials [15–20]. However, there are limited data on the efficacy and safety of micafungin for suspected IFIs, especially for FN, in patients with hematologic disorders [21–24]. Furthermore, in these studies on FN, the above-mentioned five composite endpoints have not been used as clinical criteria to evaluate the efficacy of micafungin. *Aspergillus* galactomannan (GM) antigen had been one of the microbiological criteria for probable and possible IFIs in the European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) 2002 definitions [25], and the GM cutoff index was recently changed from 1.5 to 0.5 [26]. Furthermore, in the revised EORTC/MSG 2008 definitions [27], β-D-glucan (BG), as well as GM, is adopted as the mycological criteria for probable invasive fungal diseases. However, although the usefulness of each serological test has been examined for various fungal infections [26, 28–31], there are no data on the usability of the combination of BG and GM to detect breakthrough IFIs in patients with FN. We herein report our study results on the efficacy and safety of micafungin as an empirical antifungal therapy for suspected IFIs, including FN, using clinical criteria based on composite endpoints in patients with hematologic disorders. We also evaluated the usefulness of two serological tests, BG and GM, to detect IFIs.

Patients and methods

Study design

We conducted a prospective multicenter study to evaluate the efficacy and safety of micafungin. This study was performed between April 2007 and June 2009 at Kanazawa University Hospital and five affiliated municipal hospitals in Japan.

The study was approved by the institutional review board at each institute, and written informed consent was obtained from each patient before the initiation of micafungin treatment.

Patients

Male and female inpatients aged 14 years and older who had hematologic disorders and received anticancer chemotherapy, immunosuppressive therapy, or HSCT were eligible for this study. Patients with positive clinical symptoms and physical findings (fever or C-reactive protein), radiological imaging (chest X-ray), or serological testing (BG or GM), which were refractory to broad-spectrum antibacterial treatment for at least 96 h, were enrolled if they met one of the following criteria: (1) had FN, (2) at high risk for IFIs (prolonged neutropenia, allogeneic HSCT/graft-versus-host disease (GVHD), prolonged administration of immunosuppressants or corticosteroids), (3) had symptoms and signs diagnosed as needing antifungal treatment by a physician (afebrile neutropenia). "Febrile" was defined as an axillary temperature ≥37.5°C or an oral temperature ≥38°C with a single measurement [32]. "Neutropenia" was defined as a neutrophil count of <500 or <1,000/μL with a predicted decrease to <500/μL within several days. Efficacy and safety analyses were conducted in the patients who had received a minimum of two consecutive doses and at least one dose of micafungin, respectively.

Empirical treatment with micafungin

In principle, 150 mg of micafungin was intravenously injected once daily [25, 26]. However, the micafungin dosage was flexible according to physicians' decisions. Therapy was continued until the responsible physician decided that the patient no longer required micafungin treatment based on the patient's symptoms and signs. Prophylactic administration of antifungal agents was allowed, but it had to be discontinued at the time micafungin treatment started. Concomitant administration of other antifungal agents and micafungin was not allowed in this study.

Clinical and laboratory procedures

The patients were examined daily for symptoms and signs and a surveillance culture (blood, sputum, urine, and stool) was

performed when necessary during this study. Just before starting micafungin treatment, two serological tests, BG [β-glucan Wako test, cutoff value of 11.0 pg/mL (Wako Pure Chemical Industries, Ltd., Osaka, Japan)] and GM [Platelia *Aspergillus*, cutoff index of 0.5 (Fujirebio, Tokyo, Japan)], a blood culture, and a chest X-ray were performed in addition to a routine complete blood count and biochemical blood test. BG and GM were measured weekly during micafungin administration and once within a week after the micafungin treatment ended. When these tests showed findings suggestive of IFIs, further examinations such as a chest computed tomography were performed as soon as possible. BG and GM were measured at a central laboratory.

Clinical efficacy of micafungin for suspected IFIs

Based on the abovementioned clinical observations and laboratory tests, we evaluated the efficacy of micafungin for suspected IFIs and FN. The clinical efficacy for FN was an overall favorable response, as determined by five composite endpoints according to the previous reports by Walsh et al. [8–10] and Boogaerts et al. [11]. The response was defined as favorable if all five criteria for evaluation were fulfilled, that is, if the patient did not have a breakthrough fungal infection (proven and probable in the EORTC/MSG 2002 definitions) during therapy and within 7 days after the completion of therapy, survived for more than 7 days beyond the cessation of micafungin therapy, did not prematurely discontinue micafungin therapy, resolved fever during the period of neutropenia, and was successfully treated for any baseline fungal infection.

The clinical efficacy for suspected IFIs was an overall favorable response, as determined by four composite endpoints that were established by eliminating defervescence during neutropenia from the five composite endpoints for FN because some patients in this study were afebrile. Furthermore, these four composite endpoints have been recently used as efficacy criteria for FN [24, 33].

Safety assessment

All adverse events (AEs) including abnormal laboratory profiles with any causality during micafungin treatment were recorded. These AEs were classified according to the Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf). All AEs were followed up until they resolved. Drug-related AEs were defined as those with a probable and possible causality.

Statistical analysis

A chi-square test was used to assess efficacy via a stratified analysis with respect to reasons for treatment, underlying disease, treatment of underlying disease, and antifungal prophylaxis. P values <0.05 were considered statistically significant.

Results

Patient backgrounds

The baseline demographic and clinical characteristics of 121 patients enrolled in this study are shown in Table 1. The patients consisted of 69 males (57.0%) and 52 females (43.0%). The median age and body weight were 53 years (range, 15–87 years) and 56 kg (range, 32–117 kg), respectively. The main underlying diseases were acute myeloid leukemia (AML; 38.0%), acute lymphoblastic leukemia (ALL; 18.2%), and malignant lymphoma (ML; 18.2%). Seventy-nine patients (65.3%) had undergone chemotherapy, 30 (24.8%) had undergone HSCT, and the remaining 12 (9.9%) had received immunosuppressive

Table 1 Demographic and clinical characteristics of patients

Characteristics (n=121)	
Gender, n (%)	
Male	69 (57.0)
Female	52 (43.0)
Age, years	
Median	53
Range	15–87
Weight, kg	
Median	56
Range	32–117
Underlying diseases, n (%)	
AML	46 (38.0)
ALL	22 (18.2)
ML	22 (18.2)
Myelodysplastic syndrome	10 (8.3)
Acute promyelocytic leukemia	9 (7.4)
Aplastic anemia	5 (4.1)
Multiple myeloma	3 (2.5)
Other	4 (3.3)
Treatment of hematologic diseases, n (%)	
Chemotherapy	79 (65.3)
HSCT[a]	30 (24.8)
Other	12 (9.9)
Antifungal prophylaxis, n (%)	
Fluconazole	18 (14.9)
Itraconazole	2 (1.6)
None	101 (83.5)

[a] Eight autologous and 22 allogeneic transplantations

therapy or were scheduled to be treated for hematologic disorders. Fluconazole and itraconazole were administered as an antifungal prophylaxis to 18 and 2 patients, respectively.

Empirical treatment with micafungin

Data from two patients were excluded from the clinical efficacy analysis due to noncompliance with drug administration. The treatment characteristics are summarized in Table 2. Of 119 patients that were evaluated for the clinical efficacy of micafungin, 81 (68.1%) fulfilled the criteria for FN at the beginning of micafungin therapy and 38 (31.9%), who met either of inclusion criteria 2 or 3, were diagnosed with other suspected fungal infections. Of 81 patients with FN, the median duration of neutropenia and duration of neutropenia before initiating therapy were 8 days (range, 2–91 days) and 3 days (range, 0–6 days), respectively. The median initial daily dose and duration of micafungin treatment were 150 mg/day (range, 50–300 mg/day) and 13 days (range, 2–91 days), respectively. The therapy dose was increased during the study (four patients, mainly initiated with a low dose due to fear of AEs), decreased (ten patients, mainly after treatment success), and decreased following an increase (three patients). One patient undergoing chemotherapy was treated with micafungin at a dosage of 150 mg/day for 91 days. This patient had drug-resistant AML and showed long-term neutropenia after chemotherapy. Eventually, the patient received cord blood transplantation 72 days after starting micafungin treatment.

Table 2 Micafungin treatment

Variable (n=119)	
Reasons for treatment, n (%)	
FN	81 (68.1)
Other suspected fungal infection	38 (31.9)
Duration of neutropenia, days (n=81)	
Median	8
Range	2–91
Duration of neutropenia before initiation of therapy, days (n=81)	
Median	3
Range	0–6
Initial daily dose, mg	
Median	150
Range	50–300
Dose change, n (%)	
None	102 (85.7)
Increased	4 (3.4)
Decreased	10 (8.4)
Decreased following increase	3 (2.5)
Duration of micafungin treatment, days	
Median	13
Range	2–91

Evaluation of micafungin efficacy for suspected IFI

The outcomes of empirical antifungal treatment with micafungin for suspected IFIs are shown in Table 3. Of 119 patients with suspected IFIs, including FN, 94 (79.0%) had a favorable response. There were no significant differences in the response rates among reasons for treatment (FN, 79.0%; other suspected IFIs, 78.9%), treatment of underlying disease [chemotherapy, 79.5% (AML, 69.2%; ML, 92.9%); HSCT, 75.9%], or antifungal prophylaxis (with, 85.0%; without, 77.8%). For underlying disease, the response rate in lymphoma patients (95.2%) was significantly superior to that in leukemia patients (78.3%) [P=0.0167].

Evaluation of micafungin efficacy for FN

Table 4 summarized the outcomes of empirical antifungal treatment with micafungin for FN. Of 81 evaluable patients with FN, three patients developed breakthrough fungal infections, consisting of proven *C. albicans* candidemia, proven *C. parapsilosis* candidemia, and probable pulmonary aspergillosis. Resolution of fever during neutropenia was achieved in 38 patients (46.9%). Six patients died during or within 7 days after completion of micafungin treatment [two with primary disease (AML), one with primary disease (AML) and bacterial and/or fungal infection (*C. parapsilosis*), one with bacterial infection, one with viral encephalitis, and one with brain hemorrhage]. Premature discontinuation of micafungin treatment occurred in 12 patients because of toxicity (three patients: all skin eruption) or lack of efficacy (nine patients: three with breakthrough IFIs, four with persistent fever, and two with persistent fever and clinical deterioration). There were no baseline fungal infections. As a consequence, 32 of 81 patients (39.5%) had a favorable overall response.

Relationship between BG and/or GM and breakthrough IFIs

For 105 patients, both BG and GM serological tests were measured before, during, and within a week after micafungin therapy (Table 5). All five patients who developed proven, probable, or possible breakthrough IFIs during micafungin therapy became or had been positive for either BG or GM test. On the other hand, no patients who became or had been negative for both BG and GM developed breakthrough IFIs. In two patients who contracted proven breakthrough candidemia, caused by *C. albicans* and *C.*

Table 3 Outcomes of empirical antifungal treatment with micafungin for suspected fungal infections

Variable (n=119)	Response rate (%)	P value
Overall favorable response	94/119 (79.0)	
Reasons for treatment		0.9935
FN	64/81 (79.0)	
Other suspected fungal infection	30/38 (78.9)	
Underlying disease		
Leukemia	59/80 (78.3)	0.0167 (leukemia vs lymphoma)
Lymphoma	20/21 (95.2)	
Other	15/18 (83.3)	
Treatment of underlying disease		
Chemotherapy	62/78 (79.5)	0.6875 (chemotherapy vs HSCT)
HSCT	22/29 (75.9)	
Other	10/12 (83.3)	
Antifungal prophylaxis		0.4551
With	17/20 (85.0)	
Without	77/99 (77.8)	

parapsilosis, the BG values increased and became positive despite empirical therapy with micafungin. In two other patients with probable and possible breakthrough pulmonary aspergillosis, the GM test had been negative before micafungin treatment. However, they became positive for GM after and despite micafungin treatment. One patient who had a simultaneous elevation in both GM and BG levels during micafungin therapy developed a possible fungal infection (presumably aspergillosis) with bilateral pulmonary shadows. Seven patients continued micafungin treatment after BG and/or GM tests became positive. Two of these seven patients died from causes other than fungal infections (one with brain hemorrhage and the other with GVHD/renal disorder in other suspected IFI patients). The remaining five patients successively completed antifungal treatment with continued micafungin therapy. Among six patients who became positive for BG, two patients received immunoglobulin and/or albumin. On the other hand, nine patients, except for the two patients described above, who received immunoglobulin and/or albumin did not become positive for BG.

Table 4 Evaluation of outcomes of empirical micafungin treatment for FN according to Walsh's protocol

Endpoints	Response rate (%)
Overall response	32/81 (39.5)
Successful treatment of baseline fungal infection	–
Absence of breakthrough fungal infections during therapy and within seven days after completion of micafungin treatment	78/81 (96.3)
Resolution of fever during neutropenia	38/81 (46.9)
Survival for more than seven days after completion of micafungin treatment	75/81 (92.6)
Absence of premature discontinuation of micafungin treatment because of toxicity or lack of efficacy	69/81 (85.2)

Evaluation for safety of micafungin

A total of 13 patients (10.7%) out of 121 evaluable patients had 15 drug-related AEs during and after micafungin treatment (Table 6). The most frequent drug-related AE was liver dysfunction, which was observed in eight patients (four with grade 1, two with grade 2, one with grade 3, and one with grade 4). One patient with liver dysfunction discontinued micafungin treatment (increase in alanine aminotransferase/aspartate aminotransferase; grade 3). Seven other patients with liver dysfunction continued micafungin treatment without dose reduction. Three patients with skin eruption also discontinued micafungin treatment.

Discussion

In this study, we evaluated the efficacy and safety of empirical therapy with micafungin in Japanese patients with hematologic malignancies. We evaluated the therapeutic efficacy based on two different criteria: (1) an overall favorable response for suspected IFIs, as determined by four composite endpoints that were established by eliminating defervescence during neutropenia from the five composite endpoints (absence of breakthrough fungal infections, survival for more than 7 days after ending therapy, no discontinuation of micafungin because of toxicity or lack of efficacy, defervescence during neutropenia, and successful treatment of baseline fungal infection) [24,

Table 5 Relationship between the serological BG or GM test and breakthrough fungal infections

BG or GM levels before micafungin treatment			BG or GM levels during or after micafungin treatment			Breakthrough fungal infections[a]
BG	GM	n	BG	GM	n	
−	−	96	−	−	88	
			+	−	2	Proven *C. albicans* candidemia (1)
			−	+	3	Probable pulmonary aspergillosis (1)
						Possible pulmonary aspergillosis (1)
			+	+	3	Proven *C. parapsilosis* candidemia (1)
+	−	3	−	−	2	
			−	+	1	
−	+	6	−	−	3	
			−	+	2	
			+	+	1	Possible fungal infection (1)

[a] Values in parentheses are numbers of patients who developed breakthrough fungal infections

32], and (2) an overall favorable response for FN, as determined by the five composite endpoints [8–11].

Based on the four composite endpoints, the overall response rates of micafungin were 79.0% (94 out of 119) for all suspected IFIs, 79.0% (64 out of 81) for FN, and 78.9% (30 out of 38) for other suspected IFIs. Recently, Kubiak et al. [24] reported the efficacies of micafungin and caspofungin in a retrospective sequential cohort analysis of empirical antifungal therapy in adult patients with persistent FN. In this analysis, the four composite endpoints were adopted as the efficacy criteria [32], and the response rates of micafungin and caspofungin were 81.0% and 81.9%, respectively [24], which were comparable to that of micafungin (79.0%) in our study.

On the other hand, the overall response rate of micafungin for FN in our study using the five composite endpoints was 39.5% (32 out of 81), which was also comparable with those of previous RCTs, including liposomal amphotericin B (50.1%) versus amphotericin B (49.4%) [8], voriconazole (26.0%) versus liposomal amphotericin B (30.6%) [9], caspofungin (33.9%) versus liposomal amphotericin B (33.7%) [10], and itraconazole (47.0%) versus amphotericin B (38.0%) [11]. Although our study population for efficacy analysis was a per-protocol set and not a modified intention-to-treat population like previous RCTs, there were no differences in the inclusion criteria or the five composite endpoints between our study and previous RCTs.

Table 6 Drug-related AEs

AEs (n=121)	Number (percent)
Liver dysfunction	8 (6.6)
Increase in ALT/AST	3 (2.5)
Increase in ALT	1 (0.8)
Increase in total bilirubin	3 (2.5)
Jaundice	1 (0.8)
Skin eruption	3 (2.5)
Elevated serum BUN	2 (1.7)
Consciousness disturbance	1 (0.8)
Diarrhea/hematochezia	1 (0.8)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen

Two breakthrough cases of candidemia, caused by *C. albicans* and *C. parapsilosis*, were observed in our study. *C. albicans* was isolated from a patient with refractory AML who had been treated with 100 mg/day of micafungin for 29 days before the breakthrough infection. *C. parapsilosis* was isolated from another patient with refractory AML who had been treated with 150 mg/day of micafungin for 90 days and undergone unrelated cord blood transplantation before the breakthrough infection. The minimum inhibitory concentrations of micafungin against these *C. albicans* and *C. parapsilosis* isolates were ≤0.015 and 0.5 μg/mL, respectively, as determined by the Clinical and Laboratory Standards Institute M27-A2 method [34]. According to the breakpoint for micafungin proposed by Pfaller et al. [35], both of these isolates were susceptible to micafungin. Although the blood concentrations of micafungin were not measured in both cases, more micafungin doses might have prevented the onset of breakthrough candidemia caused by micafungin-susceptible *Candida* isolates. These cases suggest that we should be alert for symptoms and signs of breakthrough fungal infections in severely immunocompromised patients who have been treated with micafungin for a long time period at the dosages of 150 mg/day or less.

Recently, breakthrough trichosporonosis has been reported in patients with hematologic malignancies who were receiving echinocandin antifungal agents including micafungin [36–39]. However, van Burik et al. [40] did not observe any cases of trichosporonosis when micafungin was used prophylactically during neutropenia for 425 patients who underwent HSCT. In addition, there have been no reports of breakthrough trichosporonosis during micafungin treatment for suspected IFIs, including FN, in patients with hematologic disorders [21–24]. In our present study, we also did not encounter breakthrough trichosporonosis during micafungin therapy in 121 patients. Therefore, it is possible that breakthrough trichosporonosis occurs infrequently during micafungin therapy, and there is not a distinct association between micafungin and trichosporonosis. Nevertheless, we should pay attention to trichosporonosis as a lethal infection in immunocompromised patients.

In the revised EORTC/MSG 2008 definitions [27], BG, as well as GM, is adopted as the mycological criteria for probable invasive fungal diseases. Marr et al. [26] and Maertens et al. [28] reported the usefulness of GM to diagnose invasive aspergillosis. Pazos et al. [29] and Ostrosky-Zeichner et al. [30] described the usability of BG to diagnose invasive aspergillosis and IFIs, respectively. Kawazu et al. [31] evaluated the diagnostic potential of three tests, polymerase chain reaction, GM, and BG, for invasive aspergillosis and recommended using GM at a cutoff of 0.6. However, there are no reports on the usefulness of a combination of BG and GM to detect IFIs in patients with FN. In our present study, all five patients who developed proven, probable, or possible breakthrough IFIs became or had been positive for either BG or GM test during micafungin therapy. On the other hand, no patients who became or had been negative for both BG and GM developed breakthrough IFIs. Furthermore, although the administration of albumin or immunoglobulin products is reported to result in an increase in serum BG [41, 42], our data indicates that these medical sources do not always produce a false-positive result. These data suggest that a combination of two serological tests for BG and GM is a good tool to detect breakthrough IFIs during antifungal therapy.

The patient with breakthrough *C. parapsilosis* candidemia was also positive for GM (Table 5). When GM increased, piperacillin–tazobactam was administered to this patient. Since piperacillin–tazobactam has strong cross-reactivity with the GM test [43, 44], we considered this result a false-positive.

Drug-related AEs were observed in 13 patients (10.7%), but only 4 patients were required to discontinue micafungin therapy (3 patients with skin eruptions and 1 patient with liver dysfunction). Other drug-related AEs were mild and transient, and the most frequent drug-related AE was liver dysfunction. This safety and toxicity profile of micafungin was consistent with previous reports [15–24, 40].

In conclusion, micafungin is an effective empirical therapy for suspected IFIs, including FN, in patients with hematologic disorders. Micafungin could be used as a first-line empirical therapy because it has antifungal activity against the predominant causative fungi, *Candida* spp. and *Aspergillus* spp., and is associated with a low incidence of AEs.

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