Efficacy and safety of Micafungin in febrile neutropenic patients treated for hematological malignancies.

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Abstract

Objective: The purpose of this study was to prospectively evaluate the efficacy and safety of micafungin (MCFG) in empirical therapy for febrile neutropenic patients for whom antibiotic therapy was not effective for hematological malignancies.

Patients and Methods: Twenty-three hematological patients aged 27-82 years with febrile neutropenia for whom antibiotic therapy was not effective were enrolled in this study and responses to treatment were evaluated.

Results: Treatment success rate was 73.9%. Treatment success rates by primary diagnosis were 77.8% in patients with AML, 50.0% in patients with NHL and 87.5% in patients with other diseases. Moreover, MCFG at a dose of 100 mg or more have a tendency to be effective. One or more adverse events occurred in five (27.7%) of the patients during the study. All of these adverse events were below grade 2 toxicity.

Conclusions: Although the number of patients studied was limited, MCFG as a monotherapy seems to be effective and safe as an empirical therapy in patients with febrile neutropenia. However, further investigation using large-scale studies is needed. This study demonstrated the clinical efficacy and safety of MCFG in patients with febrile neutropenia and with hematological malignancies.

Key words: Febrile neutropenia, Fungal infection, Empirical antifungal therapy, Hematological malignancies, Micafungin.

Introduction

Invasive fungal infections (IFI) by *Candida* and *Aspergillus* species have become an increasing cause of morbidity and mortality in neutropenic patients treated for hematological malignancies. The risk of infection is associated with the degree and duration of neutropenia, disruption of protective skin and mucosal surface barriers, use of corticosteroids, underlying disease, treatment given and prophylaxis used, and age. Persistent fever in patients with neutropenia who are receiving broad-spectrum antibiotics may be the only clinical indication for administration of empiric antifungal drugs. Studies in patients undergoing either chemotherapy or bone marrow transplantation have shown that the resulting neutropenia carries a risk for IFI of 2-40% (1). Rates of mortality from invasive aspergillosis are 50% in patients with neutropenia alone and 86.0% in patients who have had undergone a stem-cell transplantation (2). Amphotericin B (AMPH-B) and its lipid formulations, as well as triazoles [fluconazole (FLCZ), itraconazole (ICZ) and voriconazole], have been tested as empirical antifungal agents in patients with persistent fever and neutropenia (3-8). However, AMPH-B is associated with significant toxicity, including dose-limiting nephrotoxicity (9, 10). ICZ has a broad spectrum of activity against both *Aspergillus* and *Candida* species, but its gastrointestinal absorption is often poor in severely ill patients (11) and an intravenous formulation of ICZ is not currently available in Japan. Voriconazole has been approved recently in the USA for treatment of invasive aspergillosis, but it has been reported to sometimes cause reversible visual

disturbance (12).

Micafungin (MCFG, FK463, Astellas), a member of the new echinocandin class, is a parenteral antifungal agent that inhibits the synthesis of (1, 3)-β-D-glucan, an essential component of fungal cell walls (13). Non-clinical studies using of MCFG have indicated that it has broad-spectrum fungistatic activity against *Aspergillus* species and fungicidal activity against *Candida* species (13). Antifungal efficacy in an animal model is considered to be the combined result of the action of the host defense system and the direct antifungal effect of the drug itself (14). There has also been a report on the combined action of MCFG and human phagocytes for antifungal activity against *Aspergillus fumigatus* (15). MCFG is currently licensed in Japan for the treatment of invasive fungal infections and is expected to soon become more widely available. Advantages of MCFG include low toxicity, fungicidal activity against most *Candida* isolates, and a pharmacokinetic profile that allows reliable once-daily dosing (13, 16, 17).

Studies have recently been conducted to assess the efficacy and safety of MCFG for clinical treatment (18-22). A study carried out to determine the minimum effective dose and safety of MCFG in the treatment of human immunodeficiency virus (HIV) -related esophageal candidiasis revealed that MCFG at doses ranging from 12.5 mg to 100 mg administered for up to 21 days was effective, well-tolerated and safe (18). Moreover, a randomized, double-blind, parallel-group, dose-response study on the efficacy of MCFG compared with that of FLCZ for the treatment of esophageal

candidasis in HIV-positive patients showed a greater efficacy of MCFG at 100 mg and 150 mg per day than that of MCFG at 50 mg per day and a greater efficacy of MCFG than that of FLCZ (19). The clinical responses in trials in Japan studying the safety and efficacy of MCFG monotherapy (MCFG dosage: 12.5 mg-150 mg) were 60.0% in patients with invasive pulmonary aspergillosis, 67.0% in patients with chronic necrotizing pulmonary aspergillosis, 55.0% in patients with pulmonary aspergilloma, 100% in patients with candidemia, and 71.0% in patients with esophageal candidiasis (20). A randomized, double-blind, multicenter trial of MCFG versus FLCZ for prophylaxis against IFI during neutropenia in patients undergoing hematopoietic stem cell transplantation (HSCT) demonstrated that MCFG was at least as effective as FLCZ (21). Yanada et al reported that the efficacy of MCFG was 78 % in the acute leukemia patients with febrile neutropenia (22). However, there has been no report on the efficacy and safety of MCFG in the empirical therapy for febrile neutropenic patients treated for all hematological malignancies.

The purpose of this study was therefore to prospectively evaluate the efficacy and safety of MCFG in empirical therapy for febrile neutropenic patients for which antibiotic therapy was not effective treated for hematological malignancies.

Patients and methods

Patients

A total of 16 male and 7 female patients (aged 27-82 years) with febrile neutropenia for which antibiotic therapy was not effective who were treated for hematological malignancies during the period from January 2003 to May 2004 at Hokkaido University Hospital and associated hospitals were enrolled in this prospective non-randomized study. The eligible patients were enrolled in this study by the primary physicians after explaining the purpose of the study, study design, and possible beneficial and adverse effects of treatment. Informed consent was obtained before the start of treatment from the patients who were willing to participate in the study. The protocol was reviewed and approved by the institutional review board. Patients were eligible if they had neutrophil counts of <1000 / μ l with a predicted decline to <500 / μ l and fever with a single axillary temperature of ≥ 37.5℃ that was not associated with the administration of pyrogenic substances (blood transfusions, immunotherapeutic agents, etc…) and that persisted after the initial antibiotic therapy. Patients were included irrespective of whether or not they received antifungal agents for prophylaxis or granulocyte colony-stimulating factor (G-CSF). However, they could not be administered systemic antifungal therapy at the same time. Patients who developed febrile neutropenia received antibacterial treatment immediately after enrollment. The selection of the initial antibacterial drugs was based on the guidelines of the Infectious Disease Society of America (23). MCFG was added for

those remaining neutropenic and having persistent or recurrent fever after at least 3-5 days of antibacterial therapy. The patients underwent a thorough history and physical examination, complete blood count, urinalysis, blood chemistry profiles, c-reactive protein (CRP), chest radiograph, one or two sets of blood cultures, and other appropriate cultures in cases of a possible focus of infection. Serological tests for the detection of β-D-glucan [the plasma 1,3-beta-D-glucan levels were measured by Beta-Glucan test WAKO (Wako Pure Chemical Industries, Ltd., Tokyo, Japan), normal range <11pg/ml] were used as subsidiary tests because their sensitivity and specificity are still insufficient. Patients received a once-daily intravenous infusion of MCFG at dosages between 50 and 300 mg/day according to the attending physicians' discretion for a minimum of 5 days. These initial administration doses were determined on the basis of the results of the study testing MCFG for the treatment of documented fungal infection (20). Therapy was continued until both defervescence (<37.0 ℃) and absolute neutrophil count above 500 / μ l for more than 2 successive days were achieved. Patients were excluded if they met any of the following criteria: allergy to the study drug; HIV seropositivity; pregnancy or lactating woman; or receiving systemic antifungal therapy within 72 hours before registration.

Assessments

The primary efficacy endpoint was treatment success, defined as treatment success response based

on the investigator's assessment of clinical and mycological response at the end of therapy. We used a modified version of the published criteria for efficacy assessment (7). Treatment success was defined as defervescence during the neutropenic period, and cure for proven baseline fungal infection, if present. Treatment failure was defined as the presence of any of the following conditions: development of breakthrough fungal infections; discontinued of MCFG due to serious adverse events or lack of efficacy; addition of other antifungal drugs; and death from any cause during study period. Patients underwent evaluations before administration of the study drug, on days 3, 7 and 14 after the start of administration of the study drug, at the end of treatment, and at 2 weeks after the end of treatment. Evaluations included measurements of vital signs and laboratory values as well as clinical assessments.

Safety assessment

All adverse events, including abnormal laboratory profiles that occurred during treatment were recorded. Ongoing adverse events at the end of therapy were followed up until they were resolved. For safety analysis, the incidence of drug-related adverse events, including abnormal laboratory profiles, was assessed for all patients who received at least 1 dose of MCFG. Adverse events were graded based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

Statistical analysis

The rates of successful clinical response at the lowest and highest dose levels were compared by Fisher's test. CRP and neutrophil counts before and after administration were compared by Wilcoxon's rank sum test.

Results

Patients

A total of 32 patients were initially enrolled in this study between January 2003 and May 2004. Two of the patients were excluded because they had no hematological malignancies. Of the remaining 30 patients, a further 7 were later excluded because they did not show febrile neutropenia. The remaining 23 patients that fulfilled the protocol-defined criteria were used for evaluation of the efficacy and safety of MCFG. The following analyses were restricted to the 23 patients. Patient demographics and baseline characteristics of the 23 patients are shown in Table 1. The most common diagnosis was acute myelogenous leukemia (AML) (in 39.1% of the patients). Most patients (95.6%) had received previous antifungal prophylaxis. The agents used for antifungal prophylaxis were oral FLCZ (39.1%), FLCZ intravenous injection (21.7%), oral ICZ (26.0%), FLCZ injection + ICZ + AMPH-B (4.4%), and FLCZ injection + AMPH-B (4.4%). The combination of two or three antifungal drugs for prophylaxis was administered to stem cell transplantation patients and there was no probable fungal infection. The mean number of drugs administered to each patient for antibacterial therapy was 1.6 drugs. The median neutrophil count at the start of MCFG treatment was 0 / μ l (0-864/ μ l) and the median duration of neutropenia was 14 days (range:5-43 days). The mean duration of treatment was 17.8±9.9 (5-43) days. The highest daily dose of MCFG (in 43.5% of the patients) was 150 mg/day. There were 4 β-D-glucan-positive patients (19.1%) before the start of

treatment, but fungus was not detected by blood culture in any of those patients. Baseline chest radiographs demonstrated infiltrates compatible with nonspecific pneumonia in 8 of the patients (38.1%).

Clinical responses

Clinical results are summarized in Table 2. Treatment success rate was 73.9% (17/23). None of these patients developed documented breakthrough fungal infections, discontinued the drug due to lack of efficacy, or died during the study period. The treatment success rates by primary diagnosis were 77.8% in patients with AML, 50.0% in patients with NHL, and 87.5% in patients with other diseases. On the other hand, treatment failure was observed in 6 patients. Although these patients did not develop breakthrough fungal infection, clinical symptoms were not improved and therefore the administration of MCFG was discontinued. Five of 6 patients were not in remission status of primary disease and one patient died from primary disease (AML). Moreover, treatment was changed in 4 of 6 patients from MCFG to ICZ (2 patients), FLCZ (1 patient), and cessation of MCFG (1 patient). The initial doses of MCFG and of the persistent neutropenic periods were not associated with treatment failure. The treatment success rate in patients who had previously received antifungal prophylaxis was not significantly different from those who had not received prophylaxis. The response to empirical antifungal therapy was also evaluated in relation to neutorophil counts before

administration. The treatment success rate for patients with mild neutropenia (501 -1000 cells/μl) was 100% (5 of 5 patients). In the same way, treatment success rate for patients with moderate neutropenia (101 - 500 cells/μl) and severe neutropenia (100 or less cells/μl) were both 66.7% (2 of 3 patients with moderate neutropenia and 10 /15 patients with severe neutropenia). The treatment success rate in the severe neutropenia group and mild neutropenia group were not significantly different (P=0.266). The treatment success rate by maximum doses of MCFG were 0% in patients administered 50 mg and 75 mg (0 /2 and 0 /1, respectively), 100% in patients administered 100 mg (8 /8), 70.0% in patients administered 150 mg (7 /10) and 100% in patients administered 300 mg (2 /2). Thus, MCFG at a dose of 100 mg or more had a tendency to be effective.

Mycological response was assessed in patients in whom mycological examination could be performed both before and after treatment using β-D-glucan. All β-D –glucan -positive patients prior to administration were not detected after administration of MCFG. Moreover, the overall response rate in patients in whom baseline chest radiographs showed infiltrates compatible with nonspecific pneumonia was 75.0% (Table 2).

Safety and toxicity

Safety and toxicity analyses were done for 23 patients in this study. Treatment was not discontinued because of an adverse event in any of the patients. One or more adverse events occurred in 5 (21.7%)

of the patients during the study. No dose dependency was demonstrated for any individual adverse event (Table 3). All of the adverse events were liver function abnormalities (Grade 2 toxicity). Mild or moderate elevations in alanin aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (γ-GTP), and bilirubin levels were observed. These adverse events were not shown after finishing administration of MCFG. However, apparent nephrotoxicty, infusion-related reaction or histamine-like reaction was not observed. One patient of the treatment failure group died from progression of primary disease during the period of treatment with MCFG.

Discussion

Diagnosis of fungal infection in patients with febrile neutropenia is difficult, and delays in initiating effective antifungal therapy may be associated with increased mortality. Therefore, empirical antifungal therapy has become accepted in clinical practice.

This study demonstrated the high efficacy of MCFG as an empirical antifungal therapy in persistently febrile neutropenic patients with hematological malignancies. Although the number of patients was limited, the treatment success rate was 73.9%, and higher doses of MCFG (100 mg/day or more) have a tendency to be effective in these patients. These findings suggest that persistently febrile neutropenic patients with hematological malignancies should be administered MCFG at an initially high dose. All of the patients who were β-D –glucan -positive prior to administration of MCFG turned out to be negative for β-D -glucan after MCFG administration (Table 2). Moreover, the treatment success rate in patients in whom baseline chest radiographs showed infiltrates compatible with nonspecific pneumonia was 75.0% (6/8). MCFG treatment was effective in patients who had received prior antifungal prophylaxis treatment that was considered to be ineffective.

Some previous studies in empirical therapy in febrile neutoropenic patients have been carried out as an open randomized, controlled, multicenter trial (3-8). Walsh *et al* reported that the over-all success rates according to the composite score between conventional AMPH-B and liposomal AMPH-B were similar (50.0% for liposomal AMPH-B and 49.0% for conventional AMPH-B) (3). Winston *et*

al reported that intravenous FLCZ is an effective (67.0% for intravenous FLCZ and 67.0% for conventional AMPH-B) and safe alternative to AMPH-B for empiric antifungal therapy in many neutropenic patients with persistent fever who did not respond to antibacterial therapy (5). Boogaerts *et al* demonstrated that the efficacy of ICZ is similar to that of AMPH-B (response rates of 47.0% and 38.0% for ICZ and AMPH-B, respectively) as empirical antifungal therapy in neutropenic patients with cancer (6). Walsh *et al* showed that voriconazole is a suitable alternative to liposomal AMPH-B preparations (overall success rates of 26.0% and 30.6% for voriconazole and liposomal AMPH-B, respectively) for empirical antifungal therapy in patients with neutropenia and persistent fever (7). In the same way, more recently, Walsh *et al* showed that caspofungin is as effective as liposomal AMPH-B (overall success rates of 33.9% and 33.7% for caspofungin and liposomal AMPH-B, respectively) as empirical antifungal therapy in patients with neutropenia and persistent fever (8). Although the present results cannot be simply compared with the results of those randomized, double-blind, multinational trials because only a small number of patients were enrolled in our non-randomized study, the overall treatment success rate in our study was encouraging.

MCFG has broad-spectrum activity against *Aspergillus* species and *Candida* species. Because its mechanism of action inhibiting fungal cell wall synthesis differs from the mechanisms of actions other antifungal agents, it is also active against fungi resistant to other drugs. Therefore, MCFG is expected to provide a new type of antifungal treatment. In a persistently neutropenic rabbit model

involving pulmonary aspergillosis due to *A. fumigatus*, MCFG –treated animals demonstrated decreased blood vessel invasion, prevention of organism-mediated pulmonary injury, and improved survival compared with untreated controls (24). Recently, Yanada et al reported that efficacy of MCFG were 78 % in the acute leukemia patients with febrile neutropenia (22). However, there has been no report on the efficacy and safety of MCFG in empirical therapy for febrile neutropenic patients treated for all hematological malignancies.

Recently, it is possible that use of MCFG may exert selective pressure for growth of resistant fungi, such as *Tricosporon* species. Indeed, breakthrough trichosporonosis in a patient receiving caspofungin acetate, a similar antifungal agent of the echinocandin class, has been reported (25). Moreover, 4 patients reportedly developed disseminated tricosporonosis during the use of MCFG (26). However, van Burik et al reported that no trichosporonosis was observed in the prophylactic use of micafungin during the neutropenic period among 425 patients undergoing hematopoietic stem cell transplantation (21). We have not encountered breakthrough tricosporonosis. Therefore, there was no distinct association between MCFG and tricospronosis.

Voriconazole has a broad spectrum in *in vitro*, potent activity in *in vivo*, favorable safety profile, and excellent bioavailability (27, 28). Voricobazole was licensed in 2005 in Japan for the treatment of invasive fungal infections. Voriconazole is a suitable alternative to amphotericin B preparation for empiric antifungal therapy in patients with neutropenia and persistent fever (7). Therefore,

randomized, double-blind, multinational trials between voriconazole and MCFG are needed.

MCFG was tolerated well. The incidence of most adverse events was low; mild liver dysfunction occurred in only 21.7% of the patients. Moreover, no dose dependency was demonstrated for any individual adverse event. In contrast to AMPH-B, the use of MCFG was not associated with nephrotoxicity or infusion-related reaction. FLCZ interacts with other drugs that are hepatically metabolized through the cytochrome P450 3A4 pathway, whereas MCFG appears to be metabolized through the O-methyl transferase pathway, thus minimizing the probability of drug interactions in complicated patients with neutropenia. Thus, the outcome associated with MCFG may be related both to its antifungal efficacy and to its safety profile.

In conclusion, although the number of patients studied was limited, MCFG as a monotherapy seems to be effective and safe as empirical therapy in patients with febrile neutropenia. We suggested that MCFG may play an important role in the treatment of this field. However, we need further investigation in large-scale studies. This is the study to demonstrate the clinical efficacy and safety of MCFG in patients with febrile neutropenia and with hematological malignancy.

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Table 1. Demographic baseline characteristics of the patients.

Characteristic		
Gender		
Male		16 (69.6)
Female		7 (30.4)
Age (years)		
Mean ± S.D		57 ± 14.3
Range		27-82
Weight (kg)		
Mean ± S.D		59.2 ± 9.6
Range		40.5-70.0
Primary Diagnosis		
Acute myelogenous leukemia (AML)		9 (39.1)
Non-Hodgkin lymphoma (NHL)		6 (26.2)
Multiple myeloma (MM)		2 (8.7)
Acute lymphocytic leukemia (ALL)		2 (8.7)
Adult T-cell leukemia (ATL)		2 (8.7)
Chronic myelogenous leukemia (CML)		1 (4.3)
Myelodysplastic syndrome (MDS)		1 (4.3)
Previous antifungal prophylaxis		
Fluconazole	oral	9 (39.1)
	intravenous injection	5 (21.7)
Itraconazole	oral	6 (26.0)
Fluconazole injection+itraconazole + Amphotericin B		1 (4.4)
Fluconazole injection+ Amphotericin B		1 (4.4)
None		1 (4.4)
Neutrophil count at time of administration of MCFG, cells/ μ l		
median		0 (0-864)
≦ 100		15 (65.2)
101-500		3 (13.1)
501- 1000		5 (21.7)
Median duration of neutropenia, days		14 (5-43)
Receiving granulocyte colony stimulating factor		13 (56.5)
Measurement of β-D-glucan value of at the time of administration		21

Positive	4 (19.1)
Negative	17 (80.9)
Detect of fungus by blood culture at the time of administration	
	0 /16
Base-line chest radiograph demonstrating infiltrates compatible with nonspecific pneumonia	
	8 /21 (38.1)
The mean duration of treatment, days	17.8±9.9 (5-43)
The mean duration of defervescence, days	13.2±5.4 (4-25)
Max doses of administration of MCFG	
50mg	2 (8.7)
75mg	1 (4.3)
100mg	8 (34.8)
150mg	10 (43.5)
300mg	2 (8.7)

Table 2. Overall clinical response.

Characteristic		
Overall		
	Treatment success	17 /23 (73.9)
	Treatment failure	6 / 23 (26.1)
By primary diagnosis		
	Acute myelogenous leukemia (AML)	7 / 9 (77.8)
	Non-Hodgkin lymphoma (NHL)	3 / 6 (50.0))
	Multiple myeloma (MM)	1 /2 (50.0))
	Acute lymphocytic leukemia (ALL)	2 /2 (100.0)
	Adult T-cell leukemia (ATL)	2 /2 (100.0)
	Chronic myelogenous leukemia (CML)	1 / 1 (100.0)
	Myelodysplastic syndrome (MDS)	1 / 1 (100.0)
By previous antifungal prophylaxis		
	Fluconazole oral	9 / 9 (100.0)
	intravenous injection	2 / 5 (40.0)
	Itraconazole oral	5 / 6 (83.3)
	Fluconazole injection+itraconazole +Amphotericin B	0 / 1 (0.0)
	Fluconazole injection+ Amphotericin B	1 / 1 (100.0)
	None	0 /1 (0.0)
By neutrophil count at time of administration of MCFG, cells/ μ l		
	≦100	10 / 15 (66.7)
	101-500	2 / 3 (66.7)
	501- 1000	5 / 5 (100.0)
By max doses of administration of MCFG		
	50mg	0/2 (0)
	75mg	0/1 (0)
	100mg	8/8 (100)
	150mg	7/10 (70)
	300mg	2/2 (100)
	Total	17/23 (73.9)
By base-line chest radiograph demonstrating infiltrates compatible with nonspecific pneumonia		
	Positive	6 / 8 (75.0)
	Negative	11 /15 (73.3)

Table 3. Incidence of the liver dysfunction in different MCFG dose groups.

	Max MCFG dose level (mg /day)					
	50	75	100	150	300	Total
Case number	2	1	8	10	2	23
Liver dysfunction	1	0	1	3	0	5