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# A comparative analysis of micafungin and caspofungin for empirical antifungal therapy in antibiotic-unresponsive febrile patients with hematologic malignancies

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This study was retrospectively carried out to compare the efficacy of echinocandins such as micafungin (MCFG) and caspofungin (CPFG) in the treatment of antibiotic-unresponsive febrile patients with hematologic malignancies. A total of 163 patients received either MCFG or CPFG. We evaluated the efficacy of echinocandin against fever decline in all patients. Fever decline, defined as a body temperature of less than 37.5 °C sustained for more than 48 h without scheduled antipyretic medication. Efficacy assessments showed that the incidence of fever decline was not significantly different between the MCFG and CPFG groups (P=0.599). The median number of days from the start of echinocandin administration to fever decline was 5 in both the MCFG and CPFG groups. Multivariate analysis showed that the use of anti-MRSA drugs (HR, 0.64; 95%CI, 0.45-0.90; P=0.011) and a change from echinocandins to voriconazole or liposomal-amphotericin B (HR, 0.50; 95%CI, 0.30-0.74; P<0.001) are significant risk factors for sustained fever. A significant difference (P=0.002) in incidence of fever decline was however associated with differences in the timing of anti-MRSA drug administration. The median number of days from the start of echinocandin administration to fever decline was 5 when administration of the anti-MRSA drug occurred "simultaneously or prior to echinocandin start" and 11 in the "next day or later of echinocandin start" group. In other words, starting anti-MRSA drug treatment after echinocandin treatment is a risk factor. In conclusion, MCFG and CPFG have similar efficacy as empirical antifungal agents in the treatment of antibiotic-unresponsive febrile patients with hematopoietic malignancies.

## 1. Introduction

The prevalence of invasive fungal infections tends to increase, year by year, owing to medical advancements (Kume et al. 2011). This is a serious problem for patients who have been immunosuppressed by treatments with powerful chemotherapy and have clinical symptoms associated with hematopoietic malignancies.

Broad-spectrum antibiotics are commonly prescribed for the treatment of fever in immunosuppressed patients. However, fever can often persist in these patients (Tamura et al. 2002). According to the Japanese Guidelines for Management of Febrile Neutropenia (Masaoka 2000), empiric antifungal therapy should be considered for high-risk patients who continue to have fever after 4-7 days of treatment. This is the case even when broad-spectrum antibiotics are being administered and when the fever source has not been identified.

Antifungal agents currently available for the treatment of existing mycoses include polyene macrolides, pyrimidine fluoride, azole, and echinocandins. The echinocandins inhibit the synthesis of (1,3)-β-d-glucan, an essential component of fungal cell walls (Tawara et al. 2000). Micafungin (MCFG) and caspofungin (CPFG) are members of the echinocandin class. The efficacy and safety of CPFG have been demonstrated in a controlled trial with liposomal-amphotericin B (L-AMB)-treated patients with febrile neutropenia (FN) (Walsh et al. 2004), and CPFG has indications against FN. Conversely, MCFG does not have such indications, but some utility in empiric therapy has been reported (Yoshida et al. 2012; Tomomi et al. 2007).

A controlled trial of MCFG and CPFG treatments in cases of deep-seated mycoses proved that these two treatments are not different from each other in terms of efficacy or safety (Kohno et al. 2013). However, few cases can confirm deep-seated mycoses at the beginning of treatment with antifungal agents in clinical practice.

The goal of this study was to compare the efficacy of empiric treatments with CPFG and MCFG for fever in antibiotic-unresponsive patients with hematopoietic malignancies.

## 2. Investigations and results

### *2.1. Patients*

For enrolment in the study, we retrospectively analyzed the medical records of patients with hematopoietic malignancies (n=188) who received MCFG or CPFG as empiric therapy for the treatment of antibiotic-unresponsive fever and who were hospitalized at the Ogaki Municipal Hospital Blood Department of Internal Medicine from January 2012 to December 2013. We excluded 25 patients including those who stopped receiving echinocandins within 2 days (n=3), those at the beginning of echinocandin administration without a fever (n=9), those that died during echinocandin administration (n=8), and those where bacteria were detected in the bloodstream (n=5).

The study was conducted in accordance with the Helsinki Declaration and was approved by the Ethics Committee of the Ogaki Municipal Hospital (2015-1119-2).

Fever was defined, based on guidelines for management of FN, as a body temperature higher than 37.5 °C. Fever decline was defined as a body temperature of less than 37.5 °C sustained for more than 48 h without scheduled antipyretic medication. Antibiotic-unresponsive fever was defined as fever that persisted for more than 4 days even when antibiotics were being administered.
The CPFG dose regimen was once a day (50 mg daily) following a 70 mg loading dose on Day 1. The MCFG dose regimen was once a day (150 mg daily).

### 2.2. Efficacy assessments

We evaluated the efficacy of echinocandin administration on fever decline in all patients and that of empiric therapy in a subgroup of patients associated with infection with unknown pathogenic bacteria. These patients were β-d-glucan-negative prior to the start of echinocandin administration. Serological tests for the detection of β-d-glucan used the Fungitec G test MK (Seikagaku Corp., Tokyo, Japan) kit using alkaline-pretreatment, normal range, < 20 pg/ml.

### 2.3. Investigation of risk factors for fever decline

We conducted factor analysis to evaluate the time taken for fever decline in patients with antibiotic-unresponsive fever and treated with MCFG or CPFG. We assessed 14 parameters: age, gender, type of echinocandin, primary diagnosis, pretherapy, combination antibiotics, previous antifungal prophylaxis, administration chemotherapy, administration of anti-MRSA (methicillin-resistant *Staphylococcus aureus*) drugs, switching to voriconazole (VRCZ) or L-AMB, > Grade 4 neutropenia, β-d-glucan, administration of ST (sulfamethoxazole/trimethoprime), and administration of NSAIDs. Neutrophil counts and β-d-glucan level measurements were taken at the start of antifungal drug administration. The severity classifications of neutropenia were conducted according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. We defined "pretherapy" as antibiotics used just prior to echinocandin administration.

### 2.4. Initiation times of anti-MRSA drug treatment

Two groups were classified based on the time of initiation of anti-MRSA treatment; these were "simultaneously or prior to echinocandin" and "the next day or later after echinocandin." Time to fever decline was assessed. Patients administered with anti-MRSA drugs were classified further within the MCFG and CPFG groups.

### 2.5. Efficacy assessments

Efficacy assessments of the incidence of fever decline were not significantly different between the MCFG and CPFG groups (P=0.599). The median number of days from the start of echinocandin administration to fever was also 5 in the MCFG and CPFG groups. The rates of fever decline within 7 days were 74.4% for the MCFG group and 68.2% in the CPFG group. In the sub-group of β-d-glucan-negative patients, there was no difference between the MCFG and CPFG groups; the median number of days from the start of echinocandin administration to fever was 5 (n=139; P=0.976) (Fig. 1).

### 2.6. Impacts of various parameters on the fever decline

Univariate analysis of the rate of fever decline showed that administration of anti-MRSA drugs (P<0.001) and switching to VRCZ or L-AMB (P<0.001) correlated with a low rate of pyretolysis. Differences in echinocandin treatment (i.e. administration of either MCFG or CPFG) were not revealed to be a risk factor (Table 1).
Factors with P-values < 0.05 in the univariate analyses, "administration of anti-MRSA drug" and "switching to VRCZ or L-AMB" were included in the multivariate analysis.
This revealed that administration of anti-MRSA drug (HR, 0.64; 95% CI, 0.45-0.90; P=0.011) and the switching to VRCZ or L-AMB (HR, 0.50; 95%CI, 0.30-0.74; P<0.001) were statistically significant risk factors. The multivariate analysis confirmed that the type of echinocandin had no significant impact on outcomes (P=0.206).

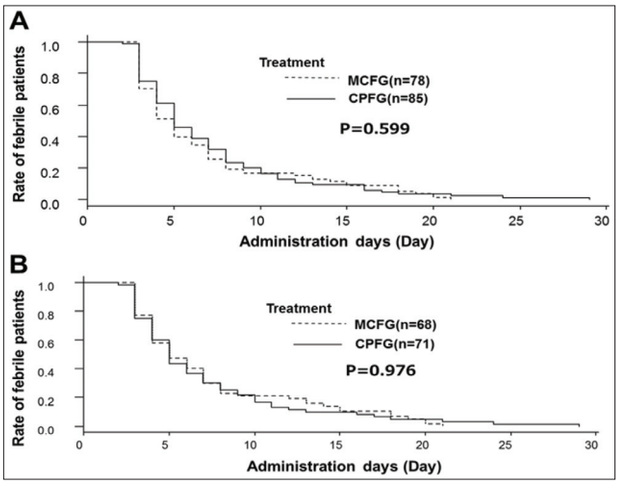


Fig. 1: Fever decline in febrile patients
Kaplan-Meier estimation for the rate of fever decline in (A) all patients (n=163) and (B) patients who were β-D-glucan negative (n=139).

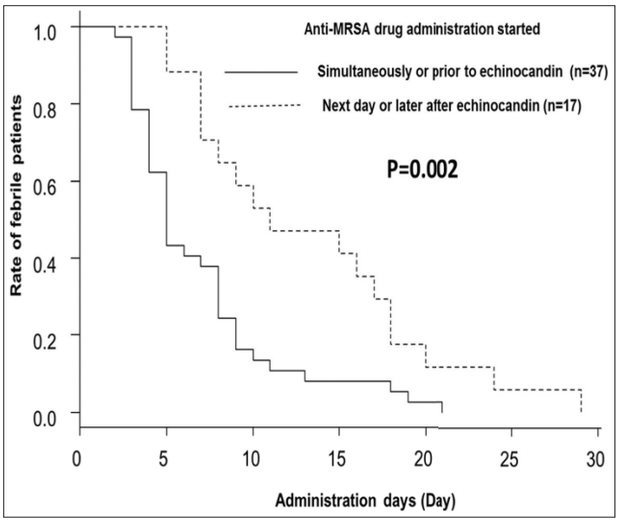


Fig. 2: Fever decline in febrile patients
Kaplan-Meier estimation for the rate of decline of fever about administration with anti-MRSA drug.

### 2.7. Initiation time of anti-MRSA drug treatment

The number of patients where anti-MRSA drug administration started "simultaneously or prior to echinocandin" was 37. The number of patients starting "next day or later after echinocandin" was 17. No significant difference in fever decline between the MCFG (n=23) and CPFG group (n=31: P=0.769; Table 2) sharing the same time of ant-MRSA drug administration was observed. A significant difference in incidence of fever decline was associated with differences in the timing of anti-MRSA drug administration (P=0.002; Fig. 2). The median number of days from the start of echinocandin administration to fever decline was 5 when administration of the anti-MRSA drug occurred "simultaneously or prior to echinocandin start" and 11 in the "next day or later of echinocandin start" group.

## 3. Discussion

Early intervention is necessary for the treatment of deep-seated mycosis, as any delay worsens prognosis (Kollef et al. 2012). It has been reported that the incidence and mortality of deep-seated mycosis in FN patients is reduced by empiric antifungal therapy (EORTC

**Table 1: Univariate and multivariate analysis of the factors associated with days to decline of fever**

| | Univariate analysis | Multivariate analysis | |
|---|---|---|---|
| | P-value | HR(95%CI) | P-value |
| Age | | | |
| <65/>65 | 0.167 | | |
| Gender | | | |
| Male/Female | 0.162 | | |
| Type of echinocandin | | | |
| MCFG/CPFG | 0.599 | 1.23(0.89-1.68) | 0.206 |
| Primary diagnosis | | | |
| ALL | 0.575 | | |
| AML | | | |
| CML | | | |
| MDS | | | |
| MM | | | |
| ML | | | |
| Pretherapy | | | |
| CFPM | 0.616 | | |
| CZOP | | | |
| DRPM | | | |
| MEPM | | | |
| PAPM/BP | | | |
| TAZ/PIPC | | | |
| LVFX | | | |
| Combination antibiotics | | | |
| CAZ | 0.153 | | |
| CFPM | | | |
| CZOP | | | |
| DRPM | | | |
| MEPM | | | |
| PAPM/BP | | | |
| TAZ/PIPC | | | |
| LVFX | | | |
| Previous antifungal prophylaxis | | | |
| Yes/No | 0.146 | | |
| Administration chemotherapy | | | |
| Yes/No | 0.232 | | |
| Administration of anti-MRSA drug | | | |
| Yes/No | <0.001 | 0.64(0.45-0.90) | 0.011 |
| Switching to VRCZ or L-AMB | | | |
| Yes/No | <0.001 | 0.50(0.30-0.74) | <0.001 |
| >Grade 4 neutropenia | | | |
| Yes/No | 0.864 | | |
| β-D-glucan-positive | | | |
| Yes/No | 0.293 | | |
| Administration of ST | | | |
| Yes/No | 0.064 | | |
| Administration of NSAIDs | | | |
| Yes/No | 0.832 | | |

HR, hazard ratio; CI, confidence interval

**Table2: Initiation time of anti-MRSA drug treatment**

| Anti-MRSA drug administration started | Type of echinocandin | | P-value |
|---|---|---|---|
| | MCFG(n=23) | CPFG(n=31) | |
| Simultaneously or prior to echinocandin | 15 | 22 | 0.769 |
| Next day or later after echinocandin | 8 | 9 | |

International Antimicrobial Therapy Cooperative Group 1989) Therefore, empiric therapy with antifungal agents is commonly prescribed.
In a comparative analysis of empiric treatment with antifungal agents, VRCZ did not prove superior to L-AMB, although breakthrough infection significantly decreased (Walsh et al. 2002). Meanwhile, CPFG and L-AMB have been shown to have comparable efficacy, but with CPFG proving to improve adverse events more so than L-AMB (Walsh et al. 2004). Therefore, the use of CPFG in empiric therapy has been strongly recommended by the Japanese Guidelines for the Diagnosis and Treatment of Deep-Seated Mycosis 2014.
Trials comparing MCFG and CPFG in targeted therapy have been implemented. No differences in efficacy and safety were shown in treatments of candidiasis or of aspergillosis (Kohno et al. 2013). Here we show that there is no difference in the time to fever decline associated with empiric therapy of MCFG and CPFG in the treatment of antibiotic-unresponsive fever. Therefore, we consider that MCFG and CPFG, not only as targeted therapy, but also in empiric treatments, have identical utility.
In antibiotic-unresponsive febrile patients with hematologic malignancies, not only are antifungal agents used but also antibiotics. The neutrophil count also greatly varies among patients. Therefore we performed multivariate analysis in order to investigate those factors, which extended the time to fever decline in antibiotic-unresponsive fever patients. As a result, "using an anti-MRSA drug" was identified as a risk factor. However, a meta-analysis that examined the effect of glycopeptide antibiotics on fever period has been reported (Vardakas et al. 2005). This reported no difference in the time to fever decline with or without the use of glycopeptide antibiotics.
Here, a significant difference in incidence of fever decline was associated with differences in the timing of anti-MRSA drug administration. The median number of days from the start of echinocandin administration to fever decline was 5 when administration of the anti-MRSA drug occurred "simultaneously or prior to echinocandin start" and eleven in the "next day or later of echinocandin start" group. In other words, starting anti-MRSA drug treatment after echinocandin treatment" is a risk factor.
In summary, antibiotic-unresponsive fever in patients with hematopoietic malignancies is best alleviated when both the anti-MRSA and antifungal agents are administered at the start on empirical therapy. However, further study in terms of safety and economy is required, as many patients have shown fever decline on treatment with antifungal agents only.
Switching to VRCZ or L-AMB was also identified as a factor for sustained fever. For patients with sustained fever after echinocandin administration, switching of antifungal agents is often considered. This is because many fungal infections are insensitive to echinocandin treatment. However, no echinocandin-hyposensitive fungi were detected in this study. We consider that fever cases that respond to switching to VRCZ or L-AMB, are associated with non-infectious diseases.
The guidelines for management of deep-seated mycoses states that "it cannot be said that there are many patients receiving a benefit of the empiric treatment, because it is only 5% of whole that can confirm fungal infection among the patients receiving empirical treatment with antifungal agent". For that reason, it is necessary to examine the medical economy of empiric treatments with antifungal agents. From the viewpoint of toxicity and drug interactions, we consider the empiric treatment with echinocandins to be useful.
In a package insert in Japan, a wide dose range for MCFG of 50-300 mg a day is typically prescribed. The 150 mg dose is lower than that prescribed here; so, full efficacy may not have been attained. However, the recommended dose in empiric therapy is 100-150 mg based on the guidelines for management of deep-seated mycoses. Accordingly, we should exclude the possibility of "Effects insufficient with dose deficiency" which is an important consideration when assessing empirical therapy. In addition, it should be noted that the CPFG (50 mg) and MCFG (150 mg) are comparably low in terms of pharmaceutical pricing (at current 2015 prices in Japan). In our study, we had no limitations of pharmaceutical pricing.
In conclusion, MCFG and CPFG have similar efficacy as empiric antifungal agents in the treatment of antibiotic-unresponsive febrile patients with hematopoietic malignancies. In terms of economy and convenience, CPFG may be the better option. An implication of our study is that the echinocandins may continue to be essential therapies as the prevalence of fungal infections increases. The timing of their co-administration with anti-MRSA drugs will be important in ensuring efficacy.

## 4. Experimental

### *4.1. Patients*

A total of 78 patients were administered MCFG. A total of 85 patients received CPFG. Clinical characteristics of the treated patients are shown in Table 3. No difference in characteristics was observed between the two treatment groups.

**Table 3: Characteristics of patients**

| | | Type of echinocandin | | P-value |
|---|---|---|---|---|
| | | MCFG (n=78) | CPFG (n=85) | |
| Administration Dose/Day | | 150mg | 50mg* | |
| Median administration days | | 11.5(3-32) | 11(3-33) | 0.698 |
| Median age | | 62.3(22-95) | 64(37-94) | 0.995 |
| Gender | Male/Female | 38/40 | 48/37 | 0.349 |
| Primary diagnosis | | | | |
| ALL | | 1 | 0 | 0.528 |
| AML | | 16 | 24 | |
| CML | | 0 | 1 | |
| MDS | | 11 | 15 | |
| MM | | 8 | 6 | |
| ML | | 42 | 39 | |
| Prior to the administration of antibiotics | | | | |
| CFPM | | 37 | 39 | 0.938 |
| CZOP | | 1 | 1 | |
| DRPM | | 7 | 11 | |
| MEPM | | 24 | 28 | |
| PAPM/BP | | 3 | 2 | |
| TAZ/PIPC | | 2 | 2 | |
| LVFX | | 4 | 2 | |

| | | Type of echinocandin | | P-value |
|---|---|---|---|---|
| | | MCFG (n=78) | CPFG (n=85) | |
| Combination antibiotics | | | | |
| CAZ | | 1 | 0 | 0.059 |
| CFPM | | 12 | 18 | |
| CZOP | | 2 | 1 | |
| DRPM | | 16 | 29 | |
| MEPM | | 39 | 29 | |
| PAPM/BP | | 3 | 1 | |
| TAZ/PIPC | | 2 | 7 | |
| LVFX | | 1 | 0 | |
| Previous antifungal prophylaxis | Yes/No | 10/68 | 11/74 | 1 |
| Administration chemotherapy | Yes/No | 62/16 | 64/21 | 0.577 |
| Administration of anti-MRSA drug | Yes/No | 23/55 | 31/54 | 0.406 |
| Switching to VRCZ or L-AMB | Yes/No | 25/53 | 18/67 | 0.154 |
| >Grade 4 neutropenia | Yes/No | 25/53 | 35/50 | 0.257 |
| β-D-glucan-positive | Yes/No | 10/57 | 14/60 | 0.655 |
| Administration of ST | Yes/No | 26/52 | 22/63 | 0.308 |
| Administration of NSAIDs | Yes/No | 12/66 | 9/76 | 0.483 |

*The CPFG dose regimen was once a day (50 mg daily) following a 70 mg loading dose on Day 1
ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndromes; MM, myelodysplastic syndromes; ML, malignant lymphoma
CFPM, Cefepime; CZOP, Cefozopran; DRPM, Doripenem; MEPM, Meropenem; PAPM/BP, Panipenem/Betamipron; TAZ/PIPC, Tazobactam/Piperacillin; LVFX, Levofloxacin; CAZ, Ceftazidime

### *4.2. Statistical analysis*

Comparison of categorical variables was conducted between the different treatment groups. Analysis of categorical variables utilized Fisher's exact test. Numerical variables were assessed by a Mann-Whitney U test. The incidence of fever decline was calculated using the Kaplan-Meier method, and the log-rank test was applied to evaluate whether the difference was significant. The effects of various parameters on fever decline were evaluated in univariate analyses with log-rank tests, and in multivariate analyses using the Cox proportional hazards regression model. All P-values are two-sided, with the type I error rate fixed at 0.05.
Statistical analyses were performed with EZR version 1.29 (Kanda 2013).

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