



Original Article

Evaluation of the effectiveness of caspofungin against febrile neutropenia and the factors related to the alteration in its plasma concentration[☆]



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ABSTRACT

Caspofungin (CPFG) is an echinocandin antifungal agent that inhibits the synthesis of β -1, 3-D-glucan, a critical component of the cell wall of target fungi. Several clinical studies have confirmed the efficacy and safety of CPFG in patients with febrile neutropenia (FN); however, there are no reports available in Japanese patients with FN. Therefore, we investigated the therapeutic efficacy and pharmacokinetics of CPFG as an empirical therapy in a Japanese hospital. Twenty-four Japanese patients, who were diagnosed with FN at Gifu University Hospital from February 2014 to August 2017, were enrolled. Blood samples were collected at the end of CPFG dosing (0.5 h after the infusion) on day 1 and immediately prior to the next infusion on days 2, 3, and 4. The concentration of CPFG in plasma was measured by high-performance liquid chromatography. The efficacy was assessed by five of the component endpoints, and safety was monitored according to the Common Terminology Criteria for Adverse Events. CPFG showed an excellent effect against FN (75%, 18/24), without any serious hepatic or renal toxicity. Regarding the pharmacokinetics, the plasma concentration of CPFG was significantly correlated with body weight; although, no correlation was observed between the plasma concentration of CPFG and the other factors investigated, such as gender or laboratory results. These results suggest the high efficacy, safety, and tolerability of CPFG as an empirical antifungal therapy for Japanese patients with FN.

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1. Introduction

Chemotherapy against hematological malignancies frequently causes neutropenia with fever due to the contraction of infections, which is named febrile neutropenia (FN) [1]. In this case, without the identification of the pathogen, an empirical therapy using

antimicrobial agents is applied to improve prognosis. Initially, one of the broad-spectrum antibiotics is selected; if the selected antibiotic is not effective, an antifungal agent is subsequently selected.

In Japan, two antifungal agents, CPFG and liposomal amphotericin B (LAmB), have been approved for suspected fungal infections in FN; however, it has been reported that LAmB shows renal toxicity [2,3].

CPFG is the only echinocandin approved for suspected fungal infections in FN in Japan. Although there are several reports showing the efficacy and tolerability of CPFG against FN [2,4,5], evidence in Japanese patients has not yet been sufficiently established. In other countries, such as those in Europe, dose adjustment

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in patients with a body weight over 80 kg is recommended. However, in Japan, such dose adjustment is not recommended, likely due to the limited data available related to CPFG pharmacokinetic parameters in Japanese patients. To obtain a better therapeutic effect, it is important to elucidate the factors related to the alteration in plasma concentration of CPFG in Japanese patients. Accordingly, in the present study, we evaluated the efficacy of CPFG in Japanese patients with FN. Furthermore, we determined the CPFG concentration in the plasma of patients to investigate the factors causing the variation in CPFG concentration.

2. Patients and methods

2.1. Study design and treatment

The present study was an open-label, non-comparative, single center phase II clinical study of CPFG in adult Japanese FN patients from February 2014 through August 2017, which was approved by the Ethics Committee of Gifu University Hospital (No. 28–172). FN was defined as an absolute neutrophil count $<500/\mu\text{L}$ or $<1000/\mu\text{L}$ and expected to decline to $<500/\mu\text{L}$, accompanied by a fever $>38.0^\circ\text{C}$ or $\leq 37.5^\circ\text{C}$ continuing for 1 h.

2.2. Inclusion and exclusion criteria

Following written consent, patients who were 18 years or older with hematological malignancy and fever (axillary temperature 37.5°C or more) that was refractory to the antibacterial agent and with suspected deep mycosis according to other clinical symptoms and findings were enrolled in the present study.

The exclusion criteria were as follows:

- 1) Patients with a history of allergy to CPFG or other echinocandins;
- 2) Severe liver dysfunction (\geq Child–Pugh score 10);
- 3) Gravida or lactating woman;
- 4) Administration aimed at antifungal prophylaxis in the hematopoietic stem cell transplantation phase;
- 5) Patients diagnosed with a bacterial infection or proven mycosis caused by *Cryptococcus* or pathogenic fungi (zygomycete) of mucormycosis that are out of the application spectrum of CPFG;
- 6) The patient's attending physician determined them an inappropriate subject for the present study.

CPFG was given intravenously at a loading dose of 70 mg on day 1 over approximately 1 h, followed by 50 mg daily thereafter. For patients with moderate hepatic dysfunction, the dose was reduced accordingly. Moreover, in patients taking other drugs expected to decrease the CPFG plasma concentration, a daily dose of 70 mg was considered.

2.3. Assessment of efficacy

An overall favorable response was required to satisfy all five of the component endpoints indicated below:

- (1) Successful treatment of any baseline invasive fungal infection;
- (2) The absence of breakthrough invasive fungal infections up to 7 days post-therapy;
- (3) Survival for 7 days post-therapy;
- (4) No discontinuations due to lack of efficacy or drug toxicity studies;
- (5) Fever resolution 7 days after discontinuation of study therapy irrespective of the presence of neutropenia.

Fever resolution was defined as an armpit temperature $<37.5^\circ\text{C}$ for at least 72 consecutive hours. The European Organization for Research and Treatment of Cancer/Mycoses Study Group guidelines were used for the diagnosis of an invasive fungal infection.

2.4. Assessment of safety

With respect to hepatic and renal function tests, pre- and post-dose values were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.

2.5. Pharmacokinetic study

Blood samples for the assessment of caspofungin concentration were collected at the end of dosing (0.5 h after the infusion) on day 1, and immediately prior to the next infusion on days 2, 3, and 4. CPFG plasma concentration was measured by high-performance liquid chromatography as described previously [6], with slight modifications. Briefly, the prepared samples were separated using a 5C18-MS-II COSMOSIL column (4.6 mm \times 250 mm, 5 μm particulate size) with a mobile phase composed of 20 mM phosphate buffer (pH 2.5) and acetonitrile (65/35, v/v) at a flow rate of 1.2 mL/min. Detection of CPFG was performed by a fluorescence detector, using an excitation wavelength of 224 nm and an emission wavelength of 304 nm.

2.6. Statistical analysis

Pearson's correlation coefficient test was performed to ascertain whether the CPFG concentration in plasma correlated with body weight. When the data were not normally distributed, as ascertained by a test of normality, Spearman's correlation test was performed. $P < 0.05$ was considered statistically significant.

Comparisons of laboratory data, such as AST, ALT, and ALP, between groups were performed using Student's *t*-test. When the data were not equally dispersible, Mann-Whitney *U* test was used. In order to determine the effect of laboratory data on CPFG peak and trough values/the dosage based on weight (peak/D and trough/D), subjects were divided into two groups of high ($n = 12$) and low ($n = 12$) based on each laboratory data. In addition, the relevance of two direction factors was examined using the chi-square test. Moreover, univariate and multivariate regression analyses were performed in order to identify the factors related to peak/D and trough/D.

Furthermore, the cases were classified as effective or ineffective and tested for a difference in the examination value at the start of CPFG administration. Fisher's exact test was used for involvement of gender. The significance level was set to $p < 0.05$.

3. Results

3.1. Patient characteristics

Twenty-four patients, diagnosed with FN that was unresponsive to treatment with antibacterial agents, who had hematological malignancy and were undergoing chemotherapy at Gifu University Hospital, were enrolled in the present study. The baseline demographic characteristics of these Japanese patients are presented in Table 1. All patients received prophylactic azole antifungal perorally.

In the present study, no patients had a dosage adjustment, and the mean duration of therapy (range) was 10.5 (5–18) days.

Table 1
Baseline characteristics and laboratory results at the start of caspofungin administration.

Parameters	
Gender (Male/Female)	17/7
Age (years)	59 (22–76)
Body weight (kg)	55.7 (40.1–72.8)
Fever (°C)	38.2 (37.5–40.8)
AST (IU/L)	12.0 (6.0–19)
ALT (IU/L)	14.5 (4.0–29)
ALP (IU/L)	191 (103–651)
γ-GTP (U/L)	41.5 (14–219)
Alb (g/dL)	3.5 (2.2–4.2)
T-Bil (mg/dL)	0.7 (0.3–3.8)
CRP (mg/dL)	6.6 (0.6–33.4)
Absolute neutrophil count (/μL)	0 (0–296)
<i>Underlying disease</i>	
Acute myeloid leukemia	11 (45.8)
Acute lymphoblastic leukemia	1 (4.2)
Adult T cell leukemia lymphoma	1 (4.2)
Malignant lymphoma	8 (33.3)
Myelodysplastic syndrome	2 (8.3)
Multiple myeloma	1 (4.2)
<i>Azole prophylaxis</i>	
Fluconazole	16 (66.7)
Voriconazole	4 (16.7)
Itraconazole	4 (16.7)

The values are presented as number (%) or median (range).

3.2. Efficacy evaluation

Baseline fungal infection was not observed in the present study. Therapy was determined to be effective in 18 of the 24 studied patients (75%). Of the remaining six patients, one had administration stopped due to defervescence, but thereafter was determined to be ineffective since breakthrough fungal infection occurred. Five patients (21%) discontinued the treatment of CPFG. Among five patients, one patient developed rash probably due to the adverse event of CPFG and another four patients did not show the effect of CPFG against fever during the treatment.

3.3. Safety evaluation

We identified five laboratory values: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP), and serum creatinine (Cre) that were related to hepatic and renal function in pre- and post-dose CTCAE grading. We defined deterioration in hepatic and renal function as an observed exacerbation from Grade (G) 0 and 1 to G 2 and above.

In terms of AST, ALT, ALP, and Cre, all patients were graded as G 0 or 1 pre-dose, which was similar post-dose. Moreover, with respect to γ-GTP, the number of patients graded as G 0 or 1 was 15 and did not change. Although it is known that the major side effect of CPFG is hepatic toxicity, as evaluated by AST, ALT, and γ-GTP [7,8], in the present study, a modest increase in the laboratory results for hepatic function (AST, ALT, and ALP) was observed in some patients, but it was not severe. There were no patients with exacerbated laboratory results for renal function.

No significant difference was observed in patients' baseline characteristics between the effective and ineffective groups (Table 2).

3.4. Pharmacokinetics

The mean plasma concentration at the peak level on day 1 was 8.86 ± 2.84 μg/mL, and at the trough levels on days 2, 3, and 4 was 2.87 ± 0.97 , 2.61 ± 0.76 , and 2.54 ± 0.77 μg/mL, respectively (Fig. 1).

3.5. The analysis of factors affecting plasma concentrations of CPFG

Since there were no relevant differences between the effective and ineffective groups, we analyzed the correlation between factors and plasma concentrations of CPFG by using all patients.

Fig. 2 shows the correlation between dose per kg body weight and peak levels on day 1 and all trough levels on day 2 through day 4. As each *p* value shows, both peak and trough levels were significantly correlated with body weight.

Fig. 3 shows gender difference. Interestingly, in females, the peak levels were significantly correlated with body weight but the trough levels were not, while in males, the trough levels were significantly correlated with body weight but the peak levels were not. From these results, it can be suggested that the transition of CPFG concentration in plasma may be different between genders.

Analysis of the factors related to trough/D and peak/D revealed that being elderly (≥ 59) and having low ALB levels (≤ 3.4 mg/dL) were significantly associated with high trough/D. These two factors were also shown to have a significant effect on trough/D in univariate regression analysis; however, neither factor was regarded as a predictable variable of CPFG concentration in multivariate regression analysis (age; $p = 0.472$, ALB level; $p = 0.166$). Furthermore, by the chi-square test, there was a significant association between being elderly and having low plasma ALB values ($p = 0.022$). Since the ALB level at the start of CPFG administration was not examined in one patient, this patient was not incorporated in the statistical analysis.

4. Discussion

In the present study, we investigated the therapeutic efficacy and pharmacokinetics of CPFG in Japanese patients with FN. Our results show the factors that were correlated with the plasma concentration of CPFG, suggesting the high efficacy, safety, and tolerability of CPFG as an empirical antifungal therapy.

The overall favorable response of CPFG against FN was excellent (75%) and consistent with previous reports [3,9–11]. Moreover, no serious adverse events were observed; thus, these results suggest that CPFG would be effective and tolerable in Japanese patients with FN.

A previous study in healthy subjects demonstrated that the trough levels of CPFG gradually increase, reaching 2 μg/mL approximately two weeks after administration [12]. However, in the present study, it is important to note that the average plasma concentration of CPFG at trough levels exceeded 2 μg/mL from day 1 to day 4 in patients with FN. A concentration of 1 μg/mL CPFG at the trough level exceeded the minimum inhibitory concentration of 90% of clinically isolated fungi [13]. Thus, it is likely that quick achievement of a trough CPFG over 2 μg/mL may contribute to the excellent efficacy in Japanese FN patients. These results are in accordance with previous reports demonstrating that infectious diseases may be one of the factors that elevate trough levels of CPFG [14–16]. Further studies would be needed to evaluate the reason why the CPFG level was elevated.

In general, the good tolerability of CPFG documented in the present study supports previous literature stating the safety and tolerability profiles of CPFG use in FN patients [2–4,17]. In the present study, no patients developed severe deterioration of either renal or hepatic function during the period of treatment; however, one patient discontinued CPFG use due to skin rash. There appeared to be no cause-and-effect relationship between the incidence of adverse events and higher CPFG concentrations.

In the present study, both the peak and trough levels were significantly correlated with body weight. These results are consistent with previous reports [16,18,19]; however, several other

Table 2
Comparison of patient baseline characteristics at the start of caspofungin administration between the effective and ineffective groups.

Parameters	Effective group (n = 18)		Ineffective group (n = 6)		P value
	Average (SD)	Median (range)	Average (SD)	Median (range)	
Male/Female	5/13		2/4		0.59 ^a
Age (years)	55 (15.6)	59 (22–76)	56 (11.5)	57.5 (39–68)	0.85 ^b
Body weight (kg)	56.8 (8.49)	56.3 (40.1–72.3)	54.3 (4.96)	54 (47.1–61.7)	0.49 ^b
Fever (°C)	38.4 (0.72)	38.2 (37.6–40.1)	38.5 (1.21)	38.3 (37.2–40.8)	0.80 ^b
AST (IU/L)	11.9 (3.78)	11.5 (6–19)	13.8 (3.54)	13 (10–19)	0.29 ^b
ALT (IU/L)	16.9 (7.33)	15 (8–29)	12.8 (7.7)	13.5 (4–22)	0.26 ^b
ALP (IU/L)	214.9 (70.6)	194 (103–354)	239.5 (204.5)	173 (104–651)	0.40 ^c
γ-GTP (U/L)	48.7 (26.2)	43.5 (14–118)	66.2 (77.7)	36.5 (14–219)	0.79 ^c
Alb (g/dL)	3.4 (0.51)	3.5 (2.2–4.2)	3.6 (0.43)	3.8 (3–3.9)	0.42 ^b
T-Bil (mg/dL)	1.1 (0.84)	0.9 (0.3–33.4)	0.47 (0.16)	0.45 (0.3–0.7)	0.053 ^c
CRP (mg/dL)	9.6 (7.23)	6.9 (0.83–33.4)	5.3 (4.08)	4.3 (0.62–10.8)	0.18 ^b
Neut (/ μ L)	30.9 (79.2)	0.056 (0–296)	0.43 (0.82)	0 (0–2)	0.12 ^c

^a Fischer's exact test.

^b Student *t*-test.

^c Mann–Whitney *U* test.

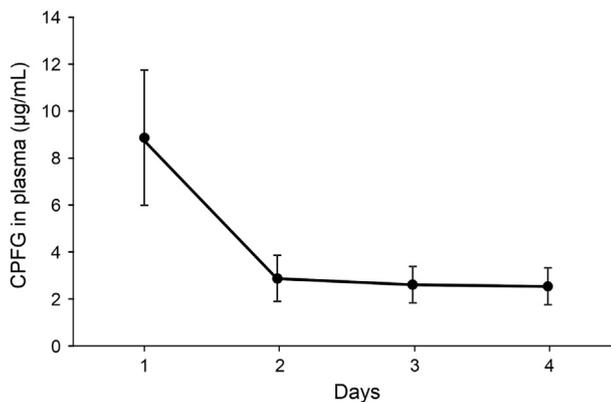


Fig. 1. Mean plasma concentration-time profile in patients treated with caspofungin. All patients received 50 mg caspofungin as a daily maintenance dose following a 70-mg loading dose. Plasma concentrations of caspofungin were trough levels with the exception of peak levels on day 1.

reports are inconsistent [15,20]. The reasons for this inconsistency may be the fixed, non-adjusted dose of CPFG (day 1, 70 mg; day 2, 50 mg) and the difference in hepatic blood flow, relative hepatic size, physiochemical change, and rate of protein binding accompanying increased weight.

We also found that the variance of CPFG concentration in plasma was different between genders. One possible reason is the difference in average body weight between genders (males, 58.4 ± 6.86 kg; females, 50.7 ± 7.36 kg, $p = 0.022$). Moreover, Organic Anion Transporter Polypeptide (OATP) 1B1 assumes a central role in the uptake transport of CPFG from the plasma to hepatocytes [16,21]. There is no report regarding the difference in expression level or activity of OATP1B1 between males and females; however, the difference in OATP1B1 function may be related to gender differences in plasma CPFG concentration.

Considering that trough levels in males exhibit a correlation with body weight, dose (50 mg) escalation may need to be maintained in male patients with a high body weight to benefit from CPFG as an empirical therapy.

Regarding factors associated with trough/D, elder and low Alb levels were found to be related to the high trough/D, and the two factors were correlations with each other. These results suggested that age-related hypoactive physiological function, including that of the liver, is involved in high trough/D. At this stage, other factors such as laboratory results were not significantly correlated with either peak/D or trough/D of CPFG in multivariate regression analysis; however, the number of patients was limited, so studies with a larger population is required.

In conclusion, the results of the present study demonstrate that CPFG is an effective and safe drug for empirical therapy in Japanese

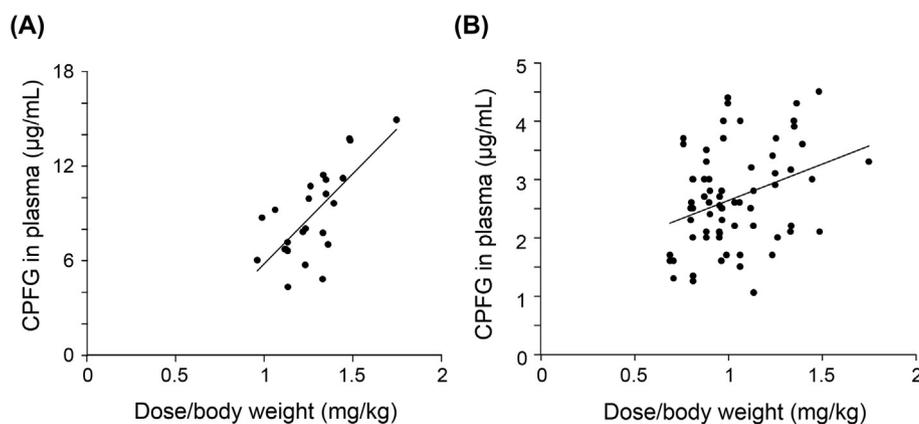


Fig. 2. Relationships between the concentration of caspofungin and the body weight adjusted dosage of caspofungin. Plots show the concentrations at peak levels on day 1 (A) and trough levels on days 2–4 (B). A significant correlation was found between peak levels and dose per kg body weight ($p < 0.01$, Pearson's correlation coefficient test) and between trough levels and dose per kg body weight ($p < 0.01$, Spearman's correlation by rank test).

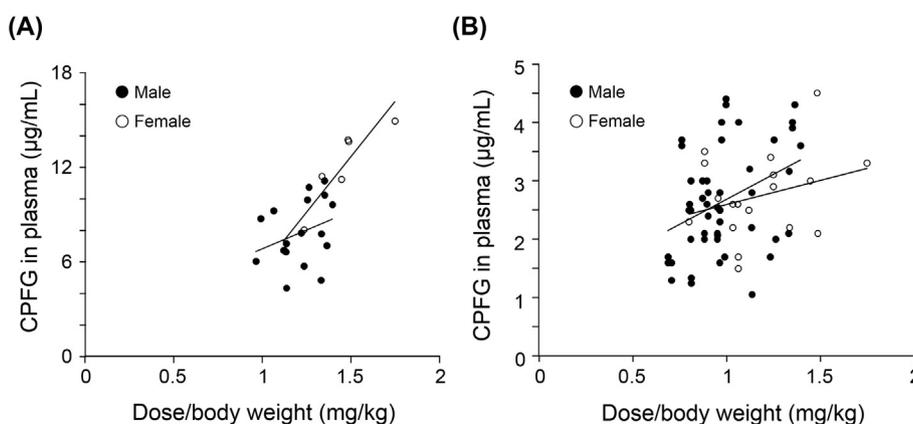


Fig. 3. Impacts of gender on the relationships between the concentration of caspofungin and the body weight adjusted dosage of caspofungin. Plots shows the concentrations at peak levels on day 1 (A) and trough levels on days 2–4 (B). Closed-circle indicates males and open-circle indicates females. A relationship was shown between peak levels and dose per kg body weight ($p = 0.228$ in males, Pearson's correlation coefficient test and $p < 0.01$ in females, Pearson's correlation coefficient test). A relationship was shown between trough levels and dose per kg body weight ($p < 0.01$ in males, Spearman's correlation by rank test and $p = 0.196$ in females, Pearson's correlation coefficient test).

patients with FN. CPFG plasma concentration appears to correlate with body weight and shows a gender difference with respect to the transition of its plasma concentration. Furthermore, it is suggested that aging and low albumin levels are involved in the increase in CPFG troughs; however, these are not powerful enough factors to predict plasma CPFG concentration. Of note, the limitation of the present study is its small sample size; in the future, further studies with an increased number of cases are warranted.

Conflicts of interest

There are no conflicts of interest related to the content of this article.

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