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【 ORIGINAL ARTICLE 】

# Efficacy and Safety of Caspofungin Treatment in Febrile Neutropenic Patients with Hematological Disorders: A Multicenter Consecutive Case Series

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**Abstract:**

**Introduction** Invasive fungal infections have been attracting attention as significant fatal complications in patients with febrile neutropenia (FN) who undergo intensive chemotherapy or hematopoietic stem cell transplantation to treat hematological malignancies. Although clinical trials are already underway in other countries, evidence supporting the use of caspofungin (CAS) in FN patients in Japan is still insufficient.

**Methods** A retrospective study of patients treated with CAS for FN associated with hematological diseases between April 2015 and March 2018 was conducted to determine the treatment efficacy and safety. The study was conducted as a multicenter collaboration, and the data of 52 patients who met all of the inclusion criteria were analyzed. A five-composite-endpoint method was used, and the treatment was judged to be effective when all five endpoints (defervescence during neutropenia; no breakthrough fungal infections; resolution of baseline fungal infections; a survival for seven days or more after the completion of therapy; and no discontinuation of therapy due to side effects or invalidity) were met.

**Results** The efficacy rate was 53.8% (28/52), which is close to the average reported efficacy rate. Adverse events included liver dysfunction and electrolyte abnormalities, but no renal dysfunction or serious events were seen.

**Conclusion** These results suggest that the use of CAS in FN patients with hematological diseases is effective and well-tolerated, and we believe that the use of CAS could become a significant treatment in Japan.

**Key words:** caspofungin, febrile neutropenia, fungal infection, hematological disease

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## Introduction

The occurrence of fungal infections in cancer patients has increased in recent years, mainly due to the increased use of immunosuppressive drugs for hematological disorders and cancer; high-dose chemotherapy, such as for bone marrow transplants; and a reduced host immune status due to the intensity of chemotherapy (1, 2). Neutrophils play a major role in host immunity against bacterial and fungal infections. The risk of infection increases as the depth and duration of neutropenia increase (3).

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The overall in-hospital mortality rate for febrile neutropenia (FN) is 9.5%, and that for FN with ≥2 complications is ≥21.4% (4). Although fungal infections are generally not the main cause of FN, fungi have been reported to be the causative microorganisms of bloodstream infections during acute myeloid leukemia induction therapy in Japan, and *Candida* infection is the most common, occurring in 10% to 16% of cases (5, 6). The high mortality rate of FN with complications suggests that physicians need to be alert for invasive fungal infections in patients with blood disorders (7-10).

A definitive diagnosis of invasive fungal infections requires tests, such as biopsies, needle aspirations, and blood cultures; however, even when such tests are performed, a definitive diagnosis often remains elusive. Although clinical manifestations are important for a diagnosis, a fever is often the only symptom observed during periods of neutropenia (3, 5, 11). For this reason, empirical broad-spectrum antimicrobial therapy has been used. Furthermore, the addition of antifungal agents is recommended for fevers lasting four to seven days after the initiation of empirical broad-spectrum antimicrobial therapy and for neutropenia lasting more than seven days (12).

Amphotericin B has a broad antifungal spectrum but is prone to causing renal dysfunction and electrolyte abnormalities. Caution should be taken when concomitantly using diuretics or nephrotoxic drugs, as there is a high possibility of further deterioration of the renal function (13). Among azoles, fluconazole has a narrow spectrum (14, 15), and oral itraconazole has inconsistent bioavailability; in addition, gastrointestinal side effects often limit their use (16). Voriconazole, a newer azole, has a broader spectrum than fluconazole but is more expensive and may cause visual impairment and liver dysfunction. Intravenous drugs are contraindicated in patients with renal dysfunction due to cyclodextrin (17, 18). Posaconazole has an antifungal spectrum similar to that of other azoles, and it shows excellent antifungal activity against *Mucor* species. In Japan, it is indicated for the prevention of invasive fungal infections in patients with hematopoietic stem cell transplants and hematologic malignancies (19-21).

Echinocandins are expected to be a highly effective treatment with low toxicity (22). In Japan, echinocandins are available as micafungin (MFG) and caspofungin (CAS), and CAS is only indicated for FN. CAS was approved in Mexico in 2000 as the first echinocandin antifungal drug and has since become widely used in other countries. In Japan, it was first approved in 2012 and is now available for use. Based on the above, in recent years, in our institution and related institutions, when a fever persists even after initial antimicrobial therapy for FN, echinocandins (MFG or CAS) are often added because they have a broad spectrum that covers *Candida* and *Aspergillus* species and are less toxic than amphotericin B. Although clinical trials have already been undertaken abroad and evidence for the use of MFG has been accumulated, the accumulation of evidence supporting the use of CAS in FN patients in Japan is still insufficient.

Thus, the present study investigated the efficacy and safety of CAS administration for FN in Japanese patients with hematological disorders.

## Materials and Methods

### Study design

This was an observational, retrospective, multi-institutional consecutive case series study. It was designed to evaluate the efficacy and safety of treatment with CAS in patients with persistent FN who had failed initial broad-spectrum antimicrobial therapy. The study was conducted at six centers (University of Fukui Hospital, Red Cross Fukui Hospital, Fukui Prefectural Hospital, National Hospital Organization Kanazawa Medical Center, Fukui-ken Saiseikai Hospital, and National Hospital Organization Tsuruga Medical Center) between April 2015 and March 2018, and the respective institutional review boards approved the study protocol.

In this study, FN was defined in cases with an axillary temperature of ≥37.5°C (defined as a fever) and an absolute neutrophil count <500/μL or a count <1,000/μL that was expected to further decrease below 500/μL. The neutropenic period was defined as the period when the absolute neutrophil count was <1,000/μL. Invasive fungal disease (IFD) was defined with reference to the revised European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definition (11). Proven IFD was defined as a fungal infection for which the causative microorganism was identified by culture or pathological identification. Probable IFD was defined as a fungal infection that was indicated by host factors and clinical features, including radiographic and mycological evidence, such as serological examinations. Possible IFD was defined as a fungal infection that was clinically considered but did not meet the criteria for proven IFD or probable IFD. The diagnosis of fungemia was defined as the presence of fungal pathogens detected by blood culture during FN.

### Patients

Eligible patients were ≥18 years old and had an underlying hematologic disease. They were diagnosed with FN during the course of chemotherapy, and initial broad-spectrum antimicrobial therapy was started; however, when this treatment was later deemed to be ineffective by the attending physician, CAS was subsequently added. Cases in which MFG or other antifungal agents were added and cases in which no antifungal agents were added were excluded. All patients who met the above criteria were included in the study. In addition, fluconazole and itraconazole were allowed as prophylactic oral medications, but all patients had completed them by the time CAS was started.

### Treatment

CAS was only considered for use at 70 mg (day 1) and 50 mg (from day 2). Initial empiric antimicrobial therapy was continued after the addition of CAS. Granulocyte-colony-stimulating factor administration was also allowed if necessary.

### Therapeutic endpoints

The primary endpoint was assessed using a five-point composite endpoint method according to previous reports on empiric antifungal therapy for FN (23). The treatment was judged to be effective when all 5 of the following endpoints were met: 1) defervescence (<37.5°C) during neutropenia; 2) no breakthrough fungal infections; 3) resolution of baseline fungal infections (fungal infections present at the start of treatment); 4) a survival for ≥7 days after the completion of therapy; and 5) no discontinuation of therapy due to side effects or invalidity. Fungal infections at the start of treatment were evaluated by the method of Tamura et al. (24); according to their report, efficacy was assessed by the clinical symptoms and physical findings, mycological findings from culture and histopathology, and imaging findings as well as improvements in serological tests, such as the detection of β-D-glucan and galactomannan. The final efficacy determination was based on an algorithm that combines the clinical findings, mycological findings, imaging findings, and serological tests at the end of treatment to determine the treatment efficacy or inefficacy, and the patients were thus divided into CAS-effective and CAS-ineffective groups.

### Adverse effects

Adverse effects were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (25). The maximum grade during CAS treatment was defined as the grade of adverse effect.

### Statistical analyses

The required sample size was calculated using a binomial test. The estimation was based on a threshold efficacy rate of 34%, an expected efficacy rate of 54%, a power of 80%, and an alpha value of 0.05 (two-sided). The target sample size was set to at least 43 patients, assuming that 2% of patients would not be eligible. The threshold efficacy rate and expected efficacy rate were based on the reported efficacy of CAS (26, 27). Comparisons of the patient characteristics between the CAS-effective and CAS-ineffective groups were performed using Student's *t*-test or Welch's *t*-test. When the parameters were not normally distributed, the Mann-Whitney *U* test was used. The categorical variables, such as acute leukemia, complete remission, and transplantation, were evaluated using the chi-squared test.

The sample size calculation was performed using EZR version 1.54 (Jichi Medical University, Saitama Medical Center, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (28). All data were examined using the statistical software program GraphPad Prism ver. 9.1.1 for Windows (GraphPad Software, San Diego, USA). A p value <0.05 was considered to be statistically significant.

## Results

### Patient background characteristics

Fifty-two Japanese patients who met all of the above criteria from April 2015 to March 2018 were included in the study. The demographic and clinical characteristics of the patients are summarized in Table 1. Acute leukemia was the most common underlying disease, followed by malignant lymphoma. There were seven transplant patients (three allogeneic and four autologous). The most common prophylactic medications were azoles, especially fluconazole. The most common initial empiric antimicrobial agents were carbapenems, followed by piperacillin/tazobactam. In addition, anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents were added in approximately 35% of cases. No patients in this study underwent dose adjustment, and the median time from the onset of FN to the administration of CAS was four days, while the median duration of treatment was nine days. The method of measuring (1→3)-β-D-glucan differed among facilities, with normal ranges of <11.0 pg/mL or <20.0 pg/mL (Table 1).

In addition, we compared the patient background data of the CAS-effective and CAS-ineffective groups (Table 1), including sex, age, underlying diseases, transplantation status, remission status of acute leukemia, treatment, neutrophil count, duration of neutropenia, β-D-glucan, galactomannan antigen, and C-reactive protein. We also compared the serum total protein and serum albumin concentrations, because among echinocandin antifungals, CAS has been reported to have a lower protein-binding rate and higher free-drug concentration (29). However, we found no significant difference in the protein or albumin concentrations. The parameters that showed a significant difference were as follows: malignant lymphoma in the underlying disease; prophylactic antimicrobials; use of anti-MRSA drugs; duration of neutropenia; and duration of CAS used during neutropenia.

### Treatment effects

The treatment effects evaluated according to the composite endpoints are shown in Table 2. Twenty-eight of the 52 patients (53.8%) were in the CAS-effective group. There were no fungal infections at the start of treatment, no patients met the definition for IFD, and no patients had fungemia. Two breakthrough infections were observed, and both were considered probable invasive pulmonary aspergillosis. Only one patient died within seven days of the end of treatment, and the cause of death was thought to be *Enterococcus faecium* bacteremia. A fever during the neutropenic period was observed in 29 patients. CAS was discontinued in eight patients due to the inefficacy of treatment, and two

**Table 1. Demographic and Clinical Characteristics and Laboratory Data of Patients Treated with Caspofungin.**

| Parameters | All (n=52) | CAS-effective group (n=28) | CAS-ineffective group (n=24) | p value |
|---|---|---|---|---|
| Female sex, n (%) | 28 (53.8) | 14 (50.0) | 10 (41.7) | 0.548[c] |
| Age, years (median, IQR) | 67.5 (52.8-74.0) | 68.0 (50.8-74.0) | 66.5 (54.5-73.5) | 0.900[a] |
| Body weight, kg (median, IQR) | 52.0 (46.1-61.4) | 51.7 (45.6-64.0) | 53.2 (49.3-60.4) | 0.839[a] |
| Underlying disease | | | | |
| Acute leukemia, n (%) | 27 (51.9) | 16 (57.1) | 11 (45.8) | 0.416[c] |
| Malignant lymphoma, n (%) | 14 (26.9) | 5 (17.9) | 9 (37.5) | 0.029[c] |
| Myelodysplastic syndromes, n (%) | 6 (11.5) | 5 (17.9) | 1 (4.2) | 0.123[c] |
| Chronic myelomonocytic leukemia, n (%) | 1 (1.9) | 0 | 1 (4.2) | 0.275[c] |
| Multiple myeloma, n (%) | 2 (3.8) | 0 | 2 (8.3) | 0.119[c] |
| Aplastic anemia, n (%) | 2 (3.8) | 2 (7.1) | 0 | 0.182[c] |
| Transplantation, n (%) | 7 (13.5) (allo 3/auto 4) | 3 (10.7) (allo 2/auto 1) | 4 (16.7) (allo 1/auto 3) | 0.531[c] |
| Complete remission of acute leukemia, n (%) | 8 (29.6) | 5 (31.3) | 3 (27.3) | 0.824[c] |
| Treatment | | | | |
| Prophylactic antibacterial agents, n (%) | 31 (59.6) | 18 (64.3) | 13 (54.2) | 0.459[c] |
| Trimethoprim/sulfamethoxazole p.o., n (%) | 12 (23.1) | 3 (10.7) | 9 (37.5) | 0.022[c] |
| Levofloxacin p.o., n (%) | 20 (38.5) | 16 (57.1) | 4 (16.7) | 0.003[c] |
| Prophylactic antifungal agents, n (%) | 20 (38.5) | 13 (46.4) | 7 (29.2) | 0.202[c] |
| Fluconazole p.o., n (%) | 19 (36.5) | 12 (42.9) | 7 (29.2) | 0.307[c] |
| Itraconazole oral solution, n (%) | 1 (1.9) | 1 (3.6) | 0 | 0.350[c] |
| Initial empiric antibacterial agents | | | | |
| Cefozopran, n (%) | 1 (1.9) | 1 (3.6) | 0 | 0.350[c] |
| Cefepime, n (%) | 9 (17.3) | 5 (17.9) | 4 (16.7) | 0.910[c] |
| Piperacillin/tazobactam, n (%) | 18 (34.6) | 11 (39.3) | 7 (29.2) | 0.445[c] |
| Meropenem, n (%) | 14 (26.9) | 8 (28.6) | 6 (25.0) | 0.772[c] |
| Doripenem, n (%) | 10 (19.2) | 3 (10.7) | 7 (29.2) | 0.092[c] |
| Anti-MRSA agents, n (%) | 18 (34.6) | 6 (21.4) | 12 (50.0) | 0.031[c] |
| Teicoplanin, n (%) | 1 (1.9) | 1 (3.6) | 0 | 0.350[c] |
| Vancomycin, n (%) | 11 (21.2) | 3 (10.7) | 8 (33.3) | 0.047[c] |
| Daptomycin, n (%) | 6 (11.5) | 2 (7.1) | 4 (16.7) | 0.284[c] |
| Granulocyte-colony stimulating factor, n (%) | 24 (46.2) | 10 (35.7) | 14 (58.3) | 0.103[c] |
| Duration from the onset of FN to the start of caspofungin treatment, days (median, IQR) | 4.0 (3.0-6.0) | 5.0 (3.0-6.0) | 4.0 (3.0-5.3) | 0.680[b] |
| Duration of caspofungin treatment, days (median, IQR) | 9.0 (7.8-13.3) | 9.0 (7.8-11.5) | 11.0 (7.8-14.0) | 0.302[a] |
| Duration of caspofungin treatment during neutrophils <500/μL, days (median, IQR) | 7.0 (3.0-11.0) | 8.5 (5.8-11.5) | 4.0 (2.0-8.5) | 0.040[a] |
| Neutrophil count at the onset of FN, /μL (median, IQR) | 42.0 (0.0-228.5) | 41.5 (0.0-213.5) | 54.0 (0.8-228.5) | 0.340[b] |
| Duration of neutropenia, <500/μL, days (median, IQR) | 20.5 (6.0-56.0) | 28.0 (12.5-95.0) | 8.0 (5.0-46.0) | 0.025[d] |
| Duration of neutropenia, <1,000/μL, days (IQR) | 23.0 (9.8-57.3) | 35.0 (20.0-107.0) | 11.0 (6.0-38.0) | 0.008[d] |
| Clinical and laboratory parameters at the start of caspofungin treatment | | | | |
| Fever, °C (median, IQR) | 38.6 (38.0-39.1) | 38.6 (38.0-39.0) | 38.7 (38.1-39.2) | 0.927[a] |
| (1 → 3)-β-D-glucan, pg/mL (median, IQR) [normal: <11.0 pg/mL] | 6.0 (6.0-6.3) | 6.0 (6.0-6.0) | 6.0 (6.0-8.6) | 0.096[b] |
| (1 → 3)-β-D-glucan, pg/mL (median, IQR) [normal: <20.0 pg/mL] | 7.5 (6.7-11.6) | 7.0 (6.7-10.5) | 8.0 (6.5-12.9) | 0.968[a] |
| Galactomannan antigen, cut-off index (median, IQR) [normal: <0.5] | 0.1 (0.0-0.1) | 0.1 (0.1-0.1) | 0.1 (0.0-0.1) | 0.267[b] |
| White blood cell count, /μL (median, IQR) | 400.0 (200.0-800.0) | 400.0 (200.0-800.0) | 350.0 (187.5-750.0) | 0.447[b] |
| Neutrophil count, /μL (median, IQR) | 32.5 (1.0-127.5) | 32.5 (1.0-82.0) | 43.5 (0.0-156.8) | 0.794[a] |
| Total protein, g/dL (IQR) | 5.8 (5.3-6.4) | 5.9 (5.7-6.5) | 5.5 (5.1-6.4) | 0.262[a] |
| Albumin, g/dL (IQR) | 2.8 (2.6-3.1) | 2.9 (2.7-3.3) | 2.7 (2.3-3.0) | 0.068[a] |
| C-reactive protein, mg/dL (median, IQR) | 9.0 (5.7-13.5) | 8.2 (5.0-11.6) | 10.9 (8.2-16.6) | 0.065[d] |

p values were calculated by comparing the CAS-effective and CAS-ineffective groups.

[a] Student's *t*-test.

[b] Welch's *t*-test.

[c] Chi-squared test.

[d] Mann-Whitney *U* test.

CAS: caspofungin, FN: febrile neutropenia, IQR: interquartile range, MRSA: methicillin-resistant *Staphylococcus aureus*, p.o.: *per os*, allo: allogeneic, auto: autologous

**Table 2. Efficacy of Treatment.**

| Endpoints | Number (%) |
|---|---|
| The five composite endpoints: | |
| Defervescence during neutropenia | 29 (55.8) |
| No breakthrough fungal infections | 50 (96.2) |
| Resolution of baseline fungal infections | Not applicable |
| Survival for 7 days or more after the completion of therapy | 51 (98.1) |
| No discontinuation of therapy due to side effects or invalidity | 44 (84.6) |
| Overall favorable response | 28 (53.8) |

**Table 3. Caspofungin-related Adverse Events[a].**

| Adverse events | Number of episodes | | | | | Total |
|---|---|---|---|---|---|---|
| | Grade[b] 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | |
| *Elevated liver enzyme levels* | 20 | 5 | 0 | 0 | 0 | 25 |
| Total bilirubin | 1 | 0 | 0 | 0 | 0 | 1 |
| Aspartate transaminase | 8 | 1 | 0 | 0 | 0 | 9 |
| Alanine transaminase | 9 | 2 | 0 | 0 | 0 | 11 |
| Alkaline phosphatase | 2 | 2 | 0 | 0 | 0 | 4 |
| *Elevated creatinine level* | 0 | 0 | 0 | 0 | 0 | 0 |
| *Electrolyte abnormalities* | 4 | 0 | 0 | 0 | 0 | 4 |
| Decreased blood potassium | 4 | 0 | 0 | 0 | 0 | 4 |
| Total | 24 | 5 | 0 | 0 | 0 | 29 |

Twenty-nine episodes of overall treatment-related adverse events were observed in 52 patients. Twenty-five episodes of grade 1 or 2 elevated liver enzyme levels were observed in 13 patients. Four episodes of grade 1 electrolyte abnormalities were observed in 4 patients.

[a] Determined by the investigator whether it was definitely, probably, or possibly caspofungin-related.

[b] Evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

of these patients were switched to liposomal amphotericin B (L-AMB). There were no discontinuations or changes due to adverse events.

### Safety evaluations

We assessed the total bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, and creatinine levels to evaluate the adverse effects on the hepatic and renal functions and electrolytes (sodium, potassium, and chlorine) to evaluate the adverse effects of electrolyte abnormalities (Table 3). The adverse events observed in this study included hepatic dysfunction (grade 1 to 2) in 13 patients (25.0%), and electrolyte abnormalities (grade 1) in 4 patients (7.7%). Overall, including those who experienced at least 1 adverse event, 15 patients (28.8%) had adverse events. However, no deterioration of the renal function was observed.

## Discussion

In the present study, Japanese patients with FN and hematological disorders who received CAS at a loading dose of 70 mg/day and a maintenance dose of 50 mg/day were examined. The efficacy rate of CAS in this study was 53.8%, as assessed by the 5-composite-endpoint method. There was one death within the first seven days after the completion of treatment, and there were no breakthrough fungal infections.

Several large-scale randomized controlled trials have reported efficacy rates of 33.9% and 33.7% for CAS and L-AMB, respectively (26), and 26.0% and 30.6% for voriconazole and L-AMB, respectively (18). A more recent study in Japan reported an efficacy rate of 75% for CAS using a similar evaluation method, although the number of cases was somewhat smaller (27). Empiric antifungal treatment in FN patients has been examined using a network meta-analysis, and CAS was rated as the highest in the rank probability plot, while MFG was rated as superior in the response rate (7). Interestingly, a considerable difference in the efficacy rate of CAS has been seen between reports from Japan and those from abroad, and in the present study, we re-examined the efficacy rate in Japanese FN patients. Therefore, we compared the background of the patients in this study with those in the studies of Walsh et al. and Shibata et al. (Supplementary material 1) (26, 27). In the study by Walsh et al. the rate of acute leukemia was higher than in other studies, but the rest of the parameters were similar (26). Although the possibility that differences in underlying diseases may have affected the results cannot be denied, the efficacy of CAS in this study was not inferior to that in other studies.

In the sub-analysis, we compared the parameters that might affect the treatment effect between the CAS-effective

**Table 4.** **Characteristics and Courses of 6 Patients with Elevated Levels of β-D-glucan or the Presence of Galactomannan Antigen.**

| Case No. | Age (years) | Sex | Under-lying disease | β-DG (normal range, pg/mL) | GM antigen | CT scan findings[a] | Diagnosis of base-line IFD | Diagnosis of IFD after CAS therapy | Efficacy of CAS | Antibacte-rial agents | Clinical course |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 85 | Female | AML | 39.5 (<11.0) | 4.5 | Unilateral infiltrate and surrounding GGO | Not applicable | IPA, probable | Ineffective | FEP → TZP+VAN | After 17 days of changing CAS to VRC, GM antigen was negative, but high β-DG levels persisted, and CT findings showed improvement. |
| **2** | 70 | Male | MM | 73.8 (<11.0) | >5.0 | Bilateral infiltrates and GGO | Not applicable | IPA, probable | Ineffective | TZP+VAN | Died 6 days after CAS was changed to L-AMB, no GM antigen or β-DG retest. Autopsy showed no *Aspergillus* lesion in the lungs. Blood culture was positive for *Enterococcus faecium*. |
| **3** | 78 | Female | AML | 13.3 (<11.0) | 0.0 | Bilateral multiple nodules | Not applicable | Not applicable | Ineffective | MEM → TZP+DAP | Culture of BAL fluid was negative, and the patient was switched from CAS to L-AMB, then to VRC without deterioration in imaging findings. |
| **4** | 82 | Female | AML | 18.6 (<11.0) | 0.1 | Bilateral infiltrates and multiple nodules | Not applicable | Not applicable | Ineffective | MEM | Although β-DG became negative after CAS administration, a possible liver abscess appeared on a CT scan, and the patient was switched to L-AMB. |
| **5** | 29 | Male | ALL | 24.0 (<11.0) | 0.0 | No findings of infection | Not applicable | Not applicable | Ineffective | MEM+DAP | 27 days after CAS administration, β-DG became negative. MRCNS was detected in blood culture. |
| **6** | 47 | Female | AML | 26.0 (<20.0) | 0.6 | Not tested | Not applicable | Not applicable | Effective | TZP | Negative blood and pharyngeal cultures; no follow-up for β-DG and GM antigen. |

[a] None of the patients had underwent imaging studies prior to the onset of FN, and imaging findings were obtained after the onset of FN.

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, BAL: bronchoalveolar lavage, β-DG: (1 → 3)-β-D-glucan, CAS: caspofungin, CT: computed tomography, DAP: daptomycin, FEP: cefepime, FN: febrile neutropenia, GGO: ground-glass opacity, GM antigen: galactomannan antigen, IFD: invasive fungal disease, IPA: invasive pulmonary aspergillosis, L-AMB: liposomal amphotericin B, MEM: meropenem, MM: multiple myeloma, MRCNS: methicillin-resistant coagulase-negative *Staphylococcus*, TZP: piperacillin/tazobactam, VAN: vancomycin, VRC: voriconazole

and CAS-ineffective groups. In the CAS-ineffective group, anti-MRSA drugs were used more frequently. This may indicate that anti-MRSA drugs are used to cover a spectrum that cannot be covered by the use of broad-spectrum antimicrobials and CAS. In the present study, because the efficacy endpoint included defervescence during the neutropenic period, it cannot be denied that the use of CAS during the neutropenic period may not have been sufficient in the CAS-ineffective group.

Six cases showed an elevated β-D-glucan level or the presence of galactomannan antigen (Table 4). In these cases, β-D-glucan and galactomannan antigen were tested for screening purposes after the onset of FN, and chest computed tomography was performed as needed. Three patients were positive for galactomannan antigen, including two who were suspected of having breakthrough invasive pulmonary aspergillosis based on combined imaging and serologic findings, while the other four patients were not considered to have IFD. Four patients were on concomitant anti-MRSA agents, and two of them had blood cultures that were positive for *E. faecium* or methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS). Five of the 6 patients (83.3%) did not respond to CAS, and 4 were switched to voriconazole or L-AMB. One patient died on day 7 after discontinuation of CAS, and an autopsy showed no evidence of pulmonary aspergillosis.

Besides the antifungal activity of CAS, we also considered other activities of CAS that may be useful for controlling inflammation or modulating cytokine production (30). Increased production of pro-inflammatory cytokines and chemokines has been reported in patients with FN (31). Furthermore, increased pro-inflammatory cytokine production has been reported in fungal sepsis as well as bacteremia (32). This excessive production of inflammatory cytokines and chemokines has been shown to be involved in organ damage, and to affect the patient prognosis (33-35). Although azole and echinocandin antifungal agents have both been shown to inhibit inflammatory cytokine and chemokine production, an effect that is independent of their antimicrobial effects, echinocandin antifungal agents have shown stronger inhibitory effects (30, 36). In addition, CAS has been shown to be involved in the suppression of spleen tyrosine kinase-dependent signaling pathways in host immune cells (30). Thus, it has been suggested that the suppression of inflammatory cytokine and chemokine production by CAS may help reduce the severity of infections. We believe that CAS is useful as an antifungal agent against FN and also has anti-inflammatory effects, but its antifungal efficacy is limited, and discontinuation or switching should be considered when there is a high probability of infection by microorganisms outside of the spectrum.

According to a report comparing hepatic dysfunction due to CAS and MFG (37), overall hepatic dysfunction due to CAS was seen in 48.5% of the patients, CTCAE grade 3 or higher was seen in 6.1% of the patients, and there was no marked difference between CAS and MFG. A more recent systematic review and meta-analysis comparing the empirical treatment of FN patients with echinocandin and other antifungal agents reported that echinocandin antifungal agents were superior with respect to the mortality risk and adverse effects (38). In the present study, hepatic dysfunction was observed in 25.0% of patients, but no grade ≥3 adverse events were observed.

Several limitations associated with the present study warrant mention. First, this study is a retrospective analysis, and the treatment protocol was not standardized. Second, selection bias cannot be ruled out because of the selection of patients who received CAS. Third, comparisons of efficacy cannot be performed, simply because patient backgrounds differ among clinical trials. Fourth, since this study is a multicenter study, we were unable to prevent the diversity of treatment strategies, including initial antimicrobial administration methods, and antibiograms among hospitals.

In the present study, we analyzed the use of CAS in FN patients with hematological disorders at multiple institutions, and the results suggested that the drug was effective and well tolerated in Japanese patients.

This study was performed based on the Declaration of Helsinki and its amendments and the Ethical Guidelines for Clinical Research by the Ministry of Health, Labor and Welfare, Japan. Publication of this study was approved by the University of Fukui Hospital, Red Cross Fukui Hospital, Fukui Prefectural Hospital, National Hospital Organization Kanazawa Medical Center, Fukui-ken Saiseikai Hospital, and National Hospital Organization Tsuruga Medical Center Clinical Research Review Board.

**The authors state that they have no Conflict of Interest (COI).**

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