Pharmacokinetics and safety of micafungin in pediatric patients with febrile neutropenia: a report from the Japan Association of Childhood Leukemia Study (JACLS)

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Abstract
There is limited information on the pharmacokinetics of micafungin (MCFG) in pediatric patients with febrile neutropenia (FN). Therefore, the pharmacokinetics and safety of MCFG were investigated in pediatric patients with FN. Plasma samples were obtained 1, 1.5, 4, 6, and 24 h after the first administration of MCFG and immediately before and 1 h after the fourth to seventh doses. Plasma MCFG concentration was measured by high-performance liquid chromatography. Plasma concentrations after intravenous infusion of MCFG at 3.8–10 mg/kg/day over 1 h were determined in 7 patients aged 3–9 years old.

The mean total clearance (CL) and distribution volume at steady state after the initial administration of MCFG were 0.351 mL/min/kg and 0.354 L/kg, respectively. Plasma MCFG concentrations decreased with a half-life of 13.4 h. These pharmacokinetic parameters were comparable to reported values in healthy adult volunteers, although CL in pediatric patients was slightly higher. The laboratory parameters of hepatic and renal functions remained unchanged from the baseline to the end of MCFG therapy. No adverse events related to MCFG were observed. The pharmacokinetics of MCFG in pediatric patients with FN is similar to that in adults. MCFG can be safely administered to pediatric patients with FN.

Key words: micafungin, fungal infection, febrile neutropenia, pharmacokinetics, pediatrics

Introduction
Advances in cancer chemotherapy, transplantation procedures, and supportive care have increased survival in children with leu-
kemia and other neoplasms\textsuperscript{17}. However, invasive fungal infections remain an important cause of infection-related mortality and morbidity in pediatric patients\textsuperscript{22}. Therefore, it is important to treat not only bacterial but also invasive fungal infections in addition to the underlying disorder. Echinocandins have become indispensable agents for the treatment of invasive fungal infections in adults\textsuperscript{23}. Although clinical experience with echinocandins in children is limited, therapeutic opportunities for high-risk children (e.g., premature neonates and children with malignancies) are increasing\textsuperscript{24}.

Micafungin (MCFG) is an echinocandin antifungal agent that inhibits the synthesis of (1,3)-β-D-glucan, a critical component of fungal cell walls\textsuperscript{4,5}, and is commonly administered to prevent and treat deep mycoses\textsuperscript{6–8}. Although MCFG has been demonstrated to be as effective as liposomal amphotericin B, there were fewer adverse events when used as the first-line treatment of candidemia and invasive candidiasis in a double-blind, randomized, multinational non-inferiority study\textsuperscript{9}. In addition, MCFG, as an empirical antifungal therapy for persistent febrile neutropenia, does not appear to differ significantly from caspofungin in terms of its safety profile or efficacy in adult patients\textsuperscript{10}. MCFG (25–50 mg) exhibits a dose-proportional increase in the area under the concentration-time curve (AUC) and the maximum plasma concentration (C\textsubscript{max}) in healthy adult volunteers\textsuperscript{11,12}. Furthermore, MCFG is frequently used for the treatment of invasive fungal infections in children and for the prophylaxis of antifungal infections in pediatric patients undergoing hematopoietic stem cell transplantation, and several clinical trials in children have been conducted\textsuperscript{13–15}. However, there are limited data on the pharmacokinetics of MCFG in pediatric patients with febrile neutropenia, and it is unclear whether it is comparable to those in healthy adult volunteers. In this study, we investigated the pharmacokinetics and safety of MCFG in 7 pediatric patients with febrile neutropenia.

Patients and Methods

Patients

Neutropenic patients (absolute neutrophil count, <500 cells/mm\textsuperscript{3}) who met the following criteria were entered into this trial: (1) below the age of 19 years and (2) unexplained persistent fever defined as axillary temperature higher than 37.5°C despite the administration of broad-spectrum antimicrobial agents. The Japan Association of Childhood Leukemia Study Group (JACLS) conducted this study. The study protocol was approved by the institutional review board of each participating institution, and written informed consent was obtained from patients’ parents before the initiation of any study-related procedures.

Administration of MCFG, sample collection, assay, and data analysis

MCFG (Funguard for infusion; Astellas Pharma Inc., Tokyo, Japan) was administered at 1–10 mg/kg body weight (maximum dose, 300 mg) once a day by intravenous infusion over a 1-h period. Blood samples were collected 1, 1.5, 4, 6, and 24 h after the initial dose of MCFG and immediately before and 1 h after the fourth to seventh doses. The samples were centrifuged immediately and the plasma was frozen at each hospital. After that, frozen plasmas were sent to a laboratory. Plasma MCFG concentration was measured by high-performance liquid chromatography using a fluorescence detection system in accordance with previously reported methods\textsuperscript{16}.

The peak and trough plasma concentrations of MCFG were obtained directly from high-performance liquid chromatography measurements. AUC was calculated using the linear trapezoidal rule. The terminal elimination rate constant (k\textsubscript{e}) was calculated as ln(2/k\textsubscript{e}) using plasma concentrations at 4, 6, and 24 h in the elimination phase by log-linear regression, and the half-life (t\textsubscript{1/2}) was estimated as ln(2/k\textsubscript{e}). AUC was extrapolated to infinity (AUC\textsubscript{0–inf}) from the last measurable MCFG concentration (C\textsubscript{last}) as C\textsubscript{last}/k\textsubscript{e}. The total clearance of MCFG (CL) was estimated as dose/AUC\textsubscript{0–inf}. The volume of distribution at steady state (V\textsubscript{dss}) was calculated by multiplying the mean residence time (MRT = [Area under the moment curve (AUMC\textsubscript{0–inf})/AUC\textsubscript{0–inf}] – [Infusion duration/2]) by CL. The analysis of correlations was carried out with Pearson correlation coefficients.

Results

Patient characteristics

Between January 2007 and July 2008, 7 pediatric patients with febrile neutropenia were enrolled in the study. Patient demographics are summarized in Table 1. There were 3 males and 4 females, aged 3 to 9 years old, with a mean body weight of 21.9 kg (range, 13.3–38.3 kg). There were 2 patients with acute lymphoblastic leukemia, 1 with acute myeloid leukemia, 3 with neuroblastoma, and 1 with rhabdomyosarcoma. There was no proven fungus infection in all the patients. The patients were treated with 50–300 mg (3.8–10 mg/kg body weight) of MCFG once daily.

Pharmacokinetic profile of micafungin

The plasma MCFG concentration profile after the initial dose is shown in Fig. 1, and the pharmacokinetic parameters are summarized in Table 1. Peak concentrations after the initial administration were observed at 1 h (i.e., at the end of infusion) in all
<table>
<thead>
<tr>
<th>Subject</th>
<th>Patient No. (Underlying Disease)</th>
<th>Age/Sex</th>
<th>Weight (kg)</th>
<th>MCFG dose (mg/kg)</th>
<th>Study day</th>
<th>Peak concentration (μg/mL)</th>
<th>Trough concentration (μg/mL)</th>
<th>AUC₀⁻∞ (μg・h/mL)</th>
<th>CL (mL/min/kg)</th>
<th>t₁/₂ (h)</th>
<th>Vdss (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (ALL)</td>
<td>8y 11m/M</td>
<td>38.3</td>
<td>3.9</td>
<td>1</td>
<td>31.5</td>
<td>4.5</td>
<td>273.36</td>
<td>0.238</td>
<td>13.3</td>
<td>0.243</td>
<td></td>
</tr>
<tr>
<td>2 (NB)</td>
<td>3y 10m/M</td>
<td>13.9</td>
<td>5.0</td>
<td>1</td>
<td>56.6</td>
<td>3.6</td>
<td>282.32</td>
<td>0.295</td>
<td>11.5</td>
<td>0.203</td>
<td></td>
</tr>
<tr>
<td>3 (NB)</td>
<td>4y 4m/F</td>
<td>15.2</td>
<td>5.3</td>
<td>1</td>
<td>11.1</td>
<td>2.5</td>
<td>169.07</td>
<td>0.522</td>
<td>16.4</td>
<td>0.689</td>
<td></td>
</tr>
<tr>
<td>4 (ALL)</td>
<td>9y 10m/F</td>
<td>21.3</td>
<td>4.7</td>
<td>1</td>
<td>36.1</td>
<td>2.0</td>
<td>146.94</td>
<td>0.533</td>
<td>11.2</td>
<td>0.399</td>
<td></td>
</tr>
<tr>
<td>5 (RMS)</td>
<td>8y 10m/M</td>
<td>21.2</td>
<td>4.7</td>
<td>1</td>
<td>15.3</td>
<td>4.3</td>
<td>285.37</td>
<td>0.275</td>
<td>15.4</td>
<td>0.341</td>
<td></td>
</tr>
<tr>
<td>6 (NB)</td>
<td>4y 1m/F</td>
<td>13.3</td>
<td>3.8</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>7 (AML)</td>
<td>5y 4m/F</td>
<td>30.0</td>
<td>10.0</td>
<td>1</td>
<td>48.3</td>
<td>13.8</td>
<td>680.54</td>
<td>0.245</td>
<td>12.4</td>
<td>0.246</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>3–9y</td>
<td>21.9±9.3</td>
<td>5.3±2.1</td>
<td>1.0–6.0</td>
<td>0–4.0</td>
<td>1.0–6.0</td>
<td>21.9±9.3</td>
<td>5.3±2.1</td>
<td>13.4±2.1</td>
<td>0.354±0.180</td>
<td></td>
</tr>
</tbody>
</table>

Healthy adult volunteers in Japan

| n=24 | 20–50y | 60.7±6.8 | 0.4–2.4 | 1 | – | – | – | 0.19–0.20 | 13.3–14.0 | 0.225–0.232 |
| n=6  | 20–31y | 64.7±0.3 | 1.2     | 4 | – | – | – | 0.18      | 15.2     | 0.24–0.04   |

Pediatric patients in Japan

| n=19 | 8m–15y | 7.4–8.1 | 1.0–6.0 | 4–10 | – | – | – | – | 11.3–14.4 |

Pediatric patients with FN in the USA

| n=77 | 2–17y | 36.5±21.6 | 0.5–4.0 | 1 | – | – | 0.27–0.38 | 11.6–13.2 | 0.24–0.39 |
| n=4  | 2–17y | 36.5±21.6 | 0.5–4.0 | 4 | – | – | 0.24–0.41 | 12.2–17.3 | 0.26–0.42 |

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FN, febrile neutropenia; NB, neuroblastoma; RMS, rhabdomyosarcoma
patients, and the mean (range) CL and Vdss after the initial administration of MCFG were 0.351 (0.245–0.533) mL/min/kg and 0.354 (0.203–0.689) L/kg, respectively. T1/2 was 13.4 h (range, 11.2–16.4 h).

Peak and trough concentrations after repeated administrations over 4–7 days correlated with MCFG dose normalized with body weight, and correlation profiles from the present study were consistent with a previous report involving Japanese pediatric patients with deep mycosis17 (Fig. 2a, b). In addition, the AUC0–inf after the initial administration and trough concentrations after repeated administrations correlated with trough concentrations after the initial administration (Fig. 2c, d). Trough concentrations after repeated administrations were 1.3 (range, 1.1–1.5) times higher than those after the initial administration (Table 1).

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, serum creatinine, and blood urea nitrogen (BUN) levels remained unchanged from baseline (prior to the first dose of MCFG) to the end of MCFG therapy (Table 2). In addition, there was no evidence of adverse events related to MCFG in all patients including Patient 7 who was given a higher dosage (10 mg/kg) by the physician attempting to achieve an immediately high concentration.

**Discussion**

MCFG (25–150 mg) exhibits a dose-proportional increase in AUC and Cmax in healthy Japanese adult volunteers with CL, Vdss, and t1/2 of 0.19–0.21 mL/min/kg, 0.225–0.232 L/kg, and 13.3–14.0 h, respectively (Table 1)12. In febrile neutropenic pediatric patients aged 2 to 17 years, Seibel et al.16 reported that the CL, Vdss, and t1/2 after the initial administration of MCFG (0.5–4.0 mg/kg/day) were 15.9–22.7 mL/h/kg (0.27–0.38 mL/min/kg), 0.24–0.39 L/kg, and 11.6–13.2 h, respectively, suggesting that the overall pharmacokinetic profile in children was similar to that observed in adults. Tabata et al.17 investigated the pharmacokinetics of 19 Japanese pediatric patients (3 infants, 7 toddlers, and 9 school aged children, aged 0.67–15 years) with deep mycosis caused by either Aspergillus or Candida species after repeated administrations of MCFG (1–6 mg/kg) for 4–10 days, and found that Cmax values were comparable to those seen in adults when they were normalized with respect to body weight, and that t1/2 over the dose range was apparently constant at 13.1 h. On the other hand, CL and Vdss values in premature neonates, infants, and younger children (<5 years) were reported to be greater than those in older children (≥5 years) and adults, suggesting that higher weight-based dosages are required for successful therapy in premature neonates, infants, and younger children19–25. In the present study, the mean CL, Vdss, and t1/2 after the first dose in pediatric patients aged 3–9 years old with febrile neutropenia were 0.351 mL/min/kg, 0.354 L/kg, and 13.4 h, respectively. These values were similar to those observed in healthy adult volunteers12,17,18, except that CL in pediatric patients was slightly greater than that in healthy adult volunteers.

The AUC0–inf after the initial administration correlated with trough concentrations after the initial administration (Fig. 2c). This indicates that monitoring of trough concentrations provides a good estimate of AUC0–inf. The trough concentration after repeated administrations was 1.3 times higher than after the initial administration (Table 2), which is consistent with reported values in healthy volunteers (1.6 times)12, suggesting that the pharmacokinetic profile of MCFG in pediatric patients with febrile neutropenia after repeated administrations may be comparable to that of healthy volunteers. Nevertheless, the plasma concentration of MCFG remained well above the reported minimal inhibitory concentration for 90% of isolates (MIC90) including clinically important Candida species such as C. albicans (MIC90, 0.0156–0.5 μg/ml), C. glabrata (0.016–0.25 μg/ml), and C. tropicalis (0.0313–0.5 μg/ml), and Aspergillus species, including A. fumigatus (<0.0156 μg/ml)26,27. Clinical improvement, including defervescence, was observed in all the 7 patients in the present study.

Laboratory parameters of hepatic and renal functions remained unchanged from baseline to the end of MCFG therapy, and no evidence of adverse events related to MCFG was noted. These results indicate that MCFG is safe for pediatric patients with
In conclusion, these results suggest that the pharmacokinetics of MCFG in pediatric patients with febrile neutropenia and adults are similar and that MCFG can be administered safely to pediatric patients with febrile neutropenia. Because CL in pediatric patients seemed slightly greater than that in healthy adult volunteers, a dose increase of MCFG may be taken into consideration when MCFG is not effective against fungal infection in a pediatric patient.

Conflicts of interest: We declare that we have no conflicts of interest.
Essentials of this paper were presented at the 53rd Annual Meeting of the Japanese Society of Pediatric Hematology and Oncology (Gunma).

References