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Successful Treatment with Micafungin for a Hepatic Fungal Infection in a Patient with Acute Myeloid Leukemia who had Undergone Allogenic Stem Cell Transplantation

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Abstract：A history of deep-seated fungal infections prior to hematopoietic stem cell transplantation (SCT) is a known risk for invasive fungal infection in the early post-SCT period. We herein report a 21-year-old female patient who demonstrated acute myeloid leukemia (AML) inv (16) (p13q22). She was complicated with a hepatic fungal infection during re-induction therapy for AML. Fluconazole was not effective and liposomal amphotericin B was not tolerated by the patient because of an anaphylactic reaction. Her hepatic fungal infection was a breakthrough infection on fluconazole, and it was successfully treated with a novel candin antifungal agent, micafungin (MCFG). Thereafter, she underwent allogeneic peripheral blood SCT and a complete remission was achieved. There was no recurrence of the fungal infection under the prophylactic administration of MCFG. Our findings indicate that MCFG is a useful therapeutic alternative when azoles or amphotericin B cannot be used. It could also be used prophylactically to prevent a recurrence of a systemic fungal infection when SCT is performed for patients with a history of significant fungal infection.

Key words：**Micafungin, Hepatic fungal infection, Acute myeloid leukemia, Allogeneic PBSCT**

Introduction

Patients with a history of documented fungal infections prior to hematopoietic stem cell transplantation (SCT) are at high risk for invasive fungal infection in the early post-SCT period.[1)] Although, amphotericin B (AMPH-B) is used as a first line therapy for fungal infections in immunocompromized hosts, it may cause significant adverse reactions in virtually all patients. In contrast, fluconazole (FLCZ) is less toxic and easy to use, but the development of resistance to Candida species due to the extensive use of this agent has been reported.[2)]

Micafungin (MCFG), a candin antifungal agent, has a broad therapeutic potential against major causatives of deep-seated mycoses such as Candida and Aspergillus species.[3)] We herein report a patient with acute myelogenous leukemia (AML) who was complicated with a hepatic fungal infection was successfully treated with MCFG, and eventually underwent SCT.

Case report

A 21-year-old Japanese woman was diagnosed to have acute myeloid leukaemia with inv (16) (p13q22). However, after she achieved a complete remission and then received intensive consolidation chemotherapy, her leukemia recurred after eight months. She therefore received re-induction thera-

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py with a standard dose of cytarabine (Ara－C) and daunorubicin(Figure 1). The absolute neutrophil count of $<0.5\times10^9$/L was 21 days. She became febrile on day 11 of the chemotherapy. Cefepime (CFPM) was empirically started soon after she became febrile, but it was switched to panipenem (PAPM/BP) on day 19 due to persistent fever. FLCZ was also started at a dose of 400 mg/day from day 23 as an empiric therapy.

She began to complain of right upper quadrant pain on day 28. The serum alkaline phosphatase level elevated to 437 IU/L, whereas the serum bilirubin and transaminase levels remained normal. An abdominal computed tomographic (CT) scan showed multiple nodular lesions in the liver(Figure 2A) suggesting a liver abscess. The aspiration of the hepatic lesions revealed fungal dark-walled hyphae (Figure 3). A culture of the aspirated specimen was negative. (1→3)－β－D－glucan was 23.0 pg/mL (normal≦20), Candida enzyme－linked immunosorbent assay (UNITIKA), and antigens to Aspergillus and Candida were negative in a serological examination. Since the hepatic abscess developed during FLCZ-treatment, FLCZ was considered to be ineffective and it was switched to liposomal AMPH-B. However, it was discontinued because of an anaphylaxic reaction. Next, MCFG at a dose of 150 mg/day was started intravenously from day 46. A significant improvement of right hypochondralgia was observed within 8 days, and a CT scan obtained at 37 days after the start of MCFG treatment demonstrated the complete disappearance of the hepatic lesions(Figure 2B).

Fortunately, she thereafter entered into a second remission of AML, and an allogeneic peripheral blood SCT (PBSCT) from a human leukocyte antigen-matched brother was performed. Oral busulfan 4 mg/kg/day divided into 4 doses for 4 days and intravenous cyclophosphamide 60 mg/kg once daily on pre-transplantation day 3 and 2 were given as a conditioning regimen. Cyclosporin (CYA) and short-term methotrexate were used as a prophylaxis for graft versus host disease (GVHD).

She received granulocyte colony-stimulating factor (G-CSF；nartograstim 8 μg/kg once daily, intravenously) from post-transplantation day (PTD) 5 to 11. Her neutrophil and platelet counts recovered to 0.5×10^9/L and 20×10^9/L by PTD 11, respectively. Skin GVHD (stage 1) and acute gut GVHD (stage 1) were observed at PTD 11, respectively. A twelve percent body weight gain and

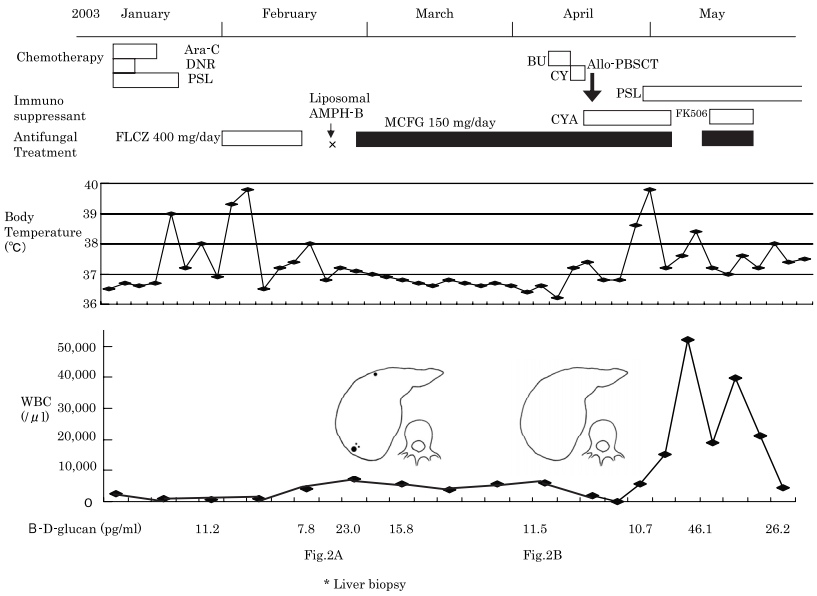

Figure. 1. Clinical course
A patient with acute myelogenous leukemia who was complicated with a hepatic fungal infection was successfully treated with MCFG, and eventually underwent stem cell transplantation.

an elevation of serum bilirubin to 9.6 mg/dL, thus indicating hepatic veno-occulusive disease (VOD), developed on PTD 17. However, these symptoms resolved after the start of predonisolone (PSL) and a discontinuation of CYA while withholding MCFG for 6 days. Next, tacrolimus (FK506) was started from PTD 26 and MCFG was restarted, but hepatic VOD reappeared on PTD 32. Again both FK506 and MCFG had to be discontinued. Hepatic VOD also improved. A repeated abdominal CT scan showed no new lesions in the liver or spleen and the cumulative dose of MCFG was already 11,700 mg at this point.

As of November 2006, or 43 months after undergoing allo-PBSCT, the patient continued to show a complete remission for AML with mild persistent chronic GVHD, but no recurrence of a fungal infection while being managed by immunosuppressive PSL treatment.

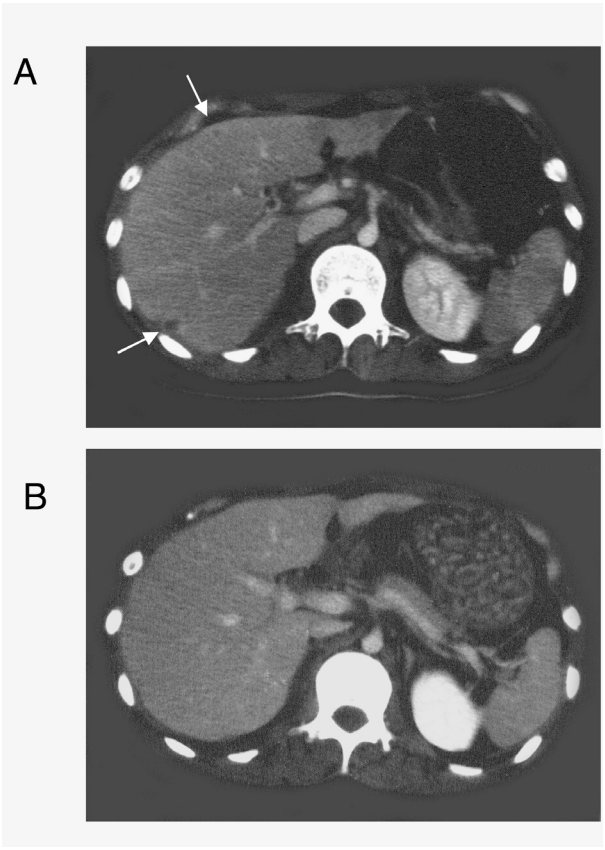

Figure. 2. A An abdominal CT scan before micafungin treatment shows multiple small hypodense areas in Segments 5 and 7(arrows).
B An abdominal CT scan during micafungin treatment shows the disappearance of hypodense areas.

Discussion

The present patient was able to tolerate allo-PBSCT despite a hepatic fungal infection treated with MCFG followed by the prophylactic use of MCFG. AMPH-B has been a recommended agent for chronic hepatosplenic fungal infection in Japan because of its potency and the wide spectrum of its antifungal activity. Liposomal AMPH-B was offered to the patient, but it had to be discontinued due to an anaphylaxic reaction in this case.

MCFG acts against Candida by inhibiting the biosynthesis of 1,3-β-D-glucan, a major and specific component of the fungal cell wall,[4] and it thus exhibits fungicidal activity.[5] Regarding the protective effect against Candida species as evalu-

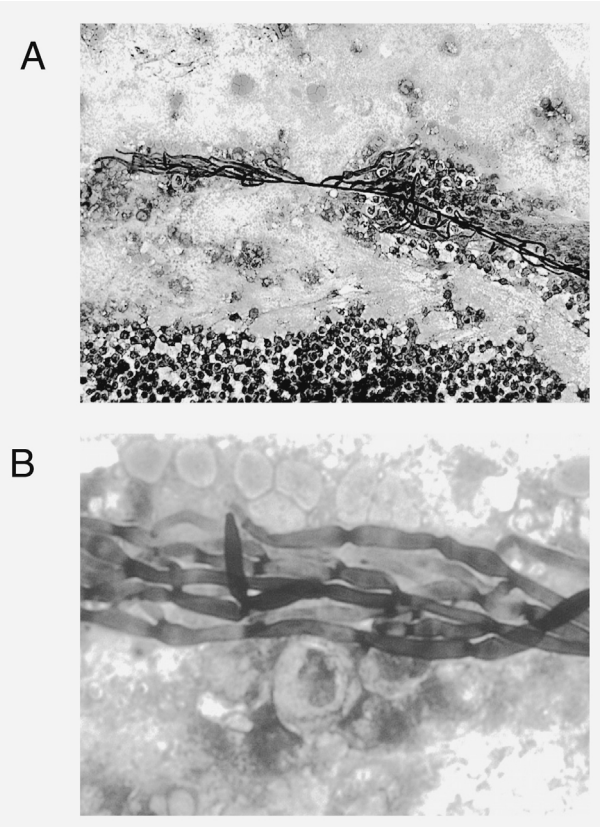

Figure. 3. A Low magnification of an aspiration specimen of the liver abscess (Grocott stain, original magnification ×200).
Both longated branching structures with constriction at the septae and neutrophil infiltration are observed.
B High magnification of the specimen (Grocott stain, original magnification ×1,000).
Dark-walled hyphae are seen.

ated in various mouse models, MCFG has been reported to be comparable with AMPH-B.[6]

Tawara *et al*[5] demonstrated that MCFG possesses the lowest minimum inhibitory concentrations (MICs) in comparison to AMPH-B and FLCZ against Candida (C.) species, including FLCZ-resistant strains of C. tropicalis, C. glabrata and C. krusei. Liver abscesses which develop during the period of long-term neutropenia, such as seen in this case, are usually caused by candida species. The improvement of the abscess by MCFG indicated that the microorganisms were susceptible to MCFG, ie, some of the Candida species. This fungus has dark-walled hyphae based on H-E staining. Such dark-walled hypae are also seen in dematiaceous fungus. MCFG exhibited an in vitro antifungal activity against dematiaceous fungi which include Cladosporium trichoides, Exophiala spinifera, Fonsecaea pedrosoi, and Exophiala dermatitidis.[7] A culture of the aspirated specimen didnot grow. In addition, a biopsy specimen was also too small to perform immunostaining against specific pathogens.

In the present patient MCFG was found to cure a breakthrough fungal infection which had occurred during FLCZ administration. MCFG was also used as an antifungal prophylaxis during her SCT. Van Burik *et al*[8] reported a double-blind trial investigating the prophylactic effect of 50 mg MCFG in comparison to 400 mg of FLCZ in neutropenic patients undergoing SCT. In their study, the drug was initiated within 48 h after a transplant-related conditioning regimen was begun. The median duration of therapy was 18 days. MCFG was thus found to be able to prevent both suspected and proven invasive infections and it was also superior to FLCZ regarding the overall treatment success.

An increased area under the curve (AUC) of busulfan is a known risk factor of VOD.[9] The major cause of VOD in this case is considered to be busulfan, because a retrospective pharmacokinetic study revealed a low busulfan clearance to 60% of the clearance in the general population. The effects of MCFG on p450(CYP) 3 A is reported to be modest.[10] Therefore, the decreased busulfan clearance and VOD are thought to be independent of the coadministration of MCFG.

This report indicates that MCFG is an effective antifungal agent not only as a therapeutic modality but also as a prophylactic treatment for systemic fungal infections when high-dose chemotherapy is used. Importantly, MCFG is also safe and well tolerated despite the presence of the Grade Ⅱ acute GVHD and VOD.

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