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ORIGINAL ARTICLE

Efficacy and safety of micafungin in unrelated cord blood transplant recipients

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Abstract

Micafungin (MCFG) is an echinocandin antifungal drug used for prophylaxis and treatment of fungal infections after allogeneic hematopoietic cell transplantation (HCT). However, its efficacy and safety in patients undergoing cord blood transplantation (CBT) has not been clarified. We retrospectively analyzed the efficacy and safety of MCFG in 92 adult patients undergoing CBT in our institute. Of the entire cohort, 83 patients (90%) received MCFG for empirical or preemptive therapy. Documented breakthrough fungal infection occurred in 2 patients during MCFG treatment. Among the 49 patients who received MCFG as empirical therapy for febrile neutropenia, 41 (84%) patients had resolution of fever during neutropenia. Elevation of serum levels of hepatobiliary parameters during MCFG treatment was commonly observed, but grade 3 or higher elevation was rare. We also compared the efficacy and safety of 2 different initial daily doses of MCFG (150 mg vs. 300 mg). There were no significant differences of efficacy and safety between the two groups. These data suggest that MCFG was effective and safe for adult patients undergoing CBT. The optimal daily dose of MCFG treatment is a matter of future investigation for adult patients undergoing CBT.

Keywords Micafungin · Cord blood transplantation · Efficacy · Adverse events · Daily dose · Echinocandin

Introduction

Invasive fungal infections (IFIs), mainly due to *Candida* and *Aspergillus* species, cause significant mortality and morbidity in allogeneic hematopoietic cell transplantation (HCT) recipients [1]. Micafungin (MCFG) is an echinocandin antifungal drug that inhibits the synthesis of the fungal cell wall by binding to the (1,3)-β-D-glucan synthase enzyme complex [2, 3]. MCFG does not have affect mammalian cells, because of the lack of a cell wall in mammalian cells. Moreover, MCFG has little to no effect on CYP450 isoenzymes and P-glycoprotein transport systems. Therefore, MCFG has a favorable profile of safety and drug interaction compared with other antifungal agents such as amphotericin B and triazoles [2, 3].

Cord blood transplantation (CBT) has been a valuable alternative for adult patients who lack a matched related or unrelated donor [4–8]. However, delayed hematopoietic recovery and immune reconstitution compared with HCT from other graft sources are the main disadvantages of CBT, which result in higher risk of fungal infections in the early phase of CBT [9, 10]. Although several studies have demonstrated that MCFG is effective in prophylaxis and treatment of IFIs for patients undergoing allogeneic HCT [11–18], the efficacy and safety of MCFG in patients undergoing CBT has not been clarified. Therefore, we retrospectively analyzed the efficacy and safety of MCFG in adult patients undergoing CBT in our institute.

Takeo Yasu and Takaaki Konuma contributed equally to this work.

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Patients and methods

Study patients and data collection

We performed a retrospective study involving 92 adult patients who received MCFG for at least 4 days during admission for single-unit unrelated CBT for hematological diseases at the Institute of Medical Science, The University of Tokyo, between March 2004 and April 2018. The indication of MCFG and a daily initial dose of MCFG were determined by the physicians. If patients received two or more cycles of MCFG treatment during admission for CBT, only the first cycle of MCFG treatment was included in this study.

All patients fed a neutropenic diet and were isolated in single rooms with high-efficiency particulate air-filtration from the beginning of the conditioning until neutrophil engraftment. Oral quinolones and triazoles were used for bacterial and fungal prophylaxis from 14 days before CBT in patients without infectious and febrile episodes before CBT. At first, neutropenic episode was usually treated with empirically with intravenous piperacillin–tazobactam, cefepime, or meropenem. When persistent or recurrent fever was present despite for broad-spectrum antibacterial treatment, vancomycin or other glycopeptides were added, and/or prophylactic antifungal drug was also changed to intravenous antifungal drugs, such as MCFG, voriconazole, or liposomal amphotericin B by the treating physicians.

During MCFG treatment, the clinical data, which included the characteristics of patients and transplantations, MCFG treatment, and laboratory hepatobiliary and renal parameters, were collected from the medical records. The institutional review board of the Institute of Medical Science, The University of Tokyo, has approved this retrospective study (30-84-B0304).

Endpoints and definitions

The primary endpoints of this retrospective study were the efficacy and safety of MCFG treatment during CBT. The secondary endpoints were the efficacy and safety of two different initial daily doses of MCFG (150 mg vs. 300 mg). Efficacy was assessed according to the five endpoints that were used in a previous report [19]: (1) absence of any breakthrough fungal infection during therapy or within 7 days after the end of therapy; (2) successful MCFG treatment of any baseline fungal infection; (3) survival for 7 days after the end of therapy; (4) no premature discontinuation of MCFG treatment because of drug-related toxicity or lack of efficacy; (5) resolution of fever, which was defined as a body temperature below 38 °C for at least 48 h, during neutropenia. Fungal infection was classified as proven or probable according to the criteria of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group (EORTC/MSG) [20].

Safety was assessed according to adverse events (AEs), which were evaluated according to the Common Terminology Criteria for AEs (CTCAE) version 4.0. For the evaluation of hepatobiliary and renal AEs, 11 patients who developed elevations of hepatobiliary and renal parameters, probably due to multiple organ failure within 7 days before death ($n = 7$) or graft-versus-host disease (GVHD) (n = 4), were excluded. Finally, we assessed the hepatobiliary and renal AEs of 81 patients.

Statistical analyses

Categorical variables were compared with Fisher's exact test. Continuous variables were compared with the Mann–Whitney U test. Statistical analyses were performed in EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) [21]. All P values were two-sided, and P values < 0.05 were considered significant.

Results

Characteristics of patients and transplantations

The characteristics of patients and CBTs are summarized in Table 1. The median age was 44 years (range, 16–68 years), 58 (63%) of the patients were male, and the median body weight was 55.6 kg (range, 38.4–90.6 kg). The most common disease type was acute myeloid leukemia in 41 (45%) patients. The myeloablative conditioning (MAC) regimen (84%) and methotrexate-based GVHD prophylaxis (79%) were more commonly performed in this study group.

Treatment of MCFG

The characteristics of MCFG treatment are summarized in Table 2. Of the entire cohort, 83 patients (90%) received MCFG for empirical or preemptive therapy, and 9 patients (10%) received MCFG for prophylaxis. The median daily dose of MCFG based on actual body weight was 2.8 mg/kg/day (range, 1.1–7.0 mg/kg/day). The median duration of MCFG administration was 44 days (range, 4–186 days). The median cumulative dose of MCFG based on actual body weight was 116.9 mg/kg (range, 8.6–920.9 mg/kg). The initial daily dose of MCFG was 75 mg for 5 patients, 150 mg for 72 patients, and 300 mg for 15 patients. Before switching to MCFG, all patients had received prophylactic antifungal drugs with either fluconazole ($n = 67$), itraconazole ($n = 7$), voriconazole ($n = 15$), amphotericin B oral suspension ($n =$

Table 1 Characteristics of the patients and cord blood transplantations

Characteristic	Value
Number of patients	92
Age at CBT, median (range), years	44 (16–68)
Body weight, median (range), kg	55.6 (38.4–90.6)
Sex	
Male	58 (63%)
Female	34 (37%)
Disease type	
Acute myeloid leukemia	41 (45%)
Acute lymphoblastic leukemia	12 (13%)
Myelodysplastic syndrome/chronic myelomonocytic leukemia	25 (27%)
Chronic myelogenous leukemia/myeloproliferative neoplasm	4 (4%)
Non-Hodgkin's lymphoma/adult T cell leukemia–lymphoma	8 (9%)
Chronic active Epstein–Barr virus infection	1 (1%)
Severe aplastic anemia	1 (1%)
Conditioning regimen	
Myeloablative conditioning	77 (84%)
Reduced-intensity conditioning	15 (16%)
GVHD prophylaxis	
Cyclosporine + methotrexate	73 (79%)
Cyclosporine + mycophenolate mofetil	13 (14%)
Cyclosporine	6 (7%)

CBT, cord blood transplantation; *GVHD*, graft-versus-host disease

2), or liposomal amphotericin B ($n = 1$). In contrast, after switching from MCFG, 83 patients received antifungal drugs with either fluconazole ($n = 43$), itraconazole ($n = 11$), voriconazole ($n = 23$), or liposomal amphotericin B ($n = 6$) due to de-escalation of MCFG treatment ($n = 55$), lack of efficacy ($n = 21$), or drug-related toxicity ($n = 7$). During MCFG treatment, calcineurin inhibitors and corticosteroids were concomitantly used in 81 (88%) and 30 (33%) patients, respectively.

The median white blood cell count and absolute neutrophil count (ANC) at the time of starting MCFG treatment were 20/μL (range, 0–9960/μL) and 3/μL (range, 0–7889/μL), respectively. Seventy-four (80%) patients started to receive MCFG during neutropenia, which was defined as an ANC of less than 500/μL. Among 74 patients with neutropenia at the time of starting MCFG treatment, the median duration from starting MCFG treatment until neutrophil recovery was 13 days (range, 4–39 days). Among 74 patients with neutropenia, 49 patients received MCFG as empirical therapy for febrile neutropenia, which was defined as a temperature of 38 °C or higher and an ANC of less than 500/μL.

Among 83 patients who received MCFG for empirical or preemptive therapy, serum β-D-glucan and galactomannan were elevated in 2 (2%) patients and 1 (1%) patient, respectively. Multiple pulmonary nodules detected by computed tomography were observed in 1 (1%) patient.

Efficacy of MCFG treatment

The efficacy of MCFG treatment after CBT is summarized in Supplementary Table 1. Documented breakthrough fungal infection occurred in 2 patients during MCFG treatment (proven fungemia due to *Candida fermentati*, $n = 1$; probable invasive pulmonary aspergillosis, $n = 1$) indicating that the absence of breakthrough fungal infection was observed in 90 (98%) of the 92 patients. Within 7 days after the end of MCFG treatment, 7 patients died of GVHD ($n = 3$), sepsis ($n = 2$), relapse ($n = 1$), or graft failure ($n = 1$). Therefore, 85 (92.4%) patients survived for at least 7 days after the end of MCFG treatment. Among the 85 patients who survived for at least 7 days after the end of MCFG treatment, 25 (29%) patients prematurely discontinued MCFG treatment because of drug-related toxicity ($n = 7$) or lack of efficacy ($n = 18$). Among the 49 patients who received MCFG as empirical therapy for febrile neutropenia, 41 (84%) patients had resolution of fever during neutropenia. Because no patients had basal fungal infection at the time of starting MCFG treatment,

Table 2 Characteristics of MCFG treatment

Characteristic	Value
Indication of MCFG treatment	
Prophylaxis	9 (10%)
Empirical or preemptive therapy	83 (90%)
Daily dose of MCFG, mg/kg/day, median (range)	2.8 (1.1–7.0)
Duration of MCFG treatment, days, median (range)	44 (4–186)
Cumulative dose of MCFG, mg/kg, median (range)	116.9 (8.6–920.9)
Initial daily dose of MCFG	
75 mg	5 (5%)
150 mg	72 (78%)
300 mg	15 (16%)
Before switching to MCFG	
Fluconazole	67 (73%)
Itraconazole	7 (8%)
Voriconazole	15 (16%)
Amphotericin B oral suspension	2 (2%)
Liposomal amphotericin B	1 (1%)
After switching from MCFG	
Fluconazole	43 (47%)
Itraconazole	11 (12%)
Voriconazole	23 (25%)
Liposomal amphotericin B	6 (7%)
Concomitant use of other drugs during MCFG treatment	
Calcineurin inhibitors	81 (88%)
Glucocorticoids	30 (33%)

successful MCFG treatment of any baseline fungal infection could not be evaluated in our study.

Adverse events of MCFG treatment

AEs of MCFG treatment after CBT are summarized in Supplementary Table 2. No patients experienced infusion-related hypersensitivity associated anaphylactic shock. Regarding hepatobiliary AEs, elevations of serum levels of aspartate amino transaminase (AST), alanine amino transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP), and total-bilirubin during MCFG treatment were commonly observed, but grade 3 or higher elevations of ALT or GGTP were observed in 3 (4%) and 6 (7%) patients, respectively. Regarding renal AEs, elevation of the serum level of creatinine during MCFG treatment was commonly observed, but no patients developed grade 3 or higher elevation of serum creatinine.

Mortality after MCFG treatment

At 30 days after starting of MCFG treatment, 10 (11%) patients had died. The primary causes of death were GVHD with or without infection in 5 patients, sepsis due to bacteria ($n = 2$), or *Fusarium* ($n = 1$) in 3 patients, graft failure in one patient, and underlying hematologic disease in one patient.

Comparison of efficacy and safety of two different initial daily doses of MCFG

We also compared the efficacy and safety of two different initial daily doses of MCFG. In the entire cohort, 72 patients were administered a dose of 150 mg, whereas 15 patients were administered a dose of 300 mg. However, the dose of MCFG was increased from 150 to 300 mg in 1 patient, or decreased from 150–300 mg to 75–150 mg in 7 patients. Finally, 69 patients who were administered a fixed dose of 150 mg and 10 patients who were administered a fixed dose of 300 mg were included for further analysis.

There were significant differences in duration of MCFG treatment ($P = 0.002$), daily dose of MCFG based on body weight ($P < 0.001$), and cumulative dose of MCFG based on body weight ($P < 0.001$) between the two groups (Table 3). As for efficacy, there were no significant differences between the two groups in view of breakthrough fungal infection, survival for at least 7 days after the end of treatment, discontinuation due to toxicity or lack of efficacy, and resolution of fever during neutropenia (Table 3). As for hepatobiliary and renal AEs, there were also no significant differences between the two groups (Table 3).

Discussion

The purpose of this retrospective study was to evaluate the efficacy and safety of MCFG treatment in adult patients undergoing CBT. The majority of patients (90%) received MCFG as empirical or preemptive therapy. Only 2 (2%) patients developed breakthrough fungal infection. Among 49 patients with febrile neutropenia at the time of starting MCFG treatment, 41 (84%) patients had resolution of fever during neutropenia. Grade 3 hepatobiliary AE was observed for 6 patients. The daily dose of MCFG was not significantly associated with efficacy or hepatobiliary and renal AEs in our study, but the optimal daily dose of MCFG for adult patients undergoing CBT is unclear, because the sample size of patients in each group was small.

Several studies, including randomized control studies and a retrospective cohort study, have demonstrated that micafungin is either similar or superior to fluconazole for prophylaxis of fungal infections among patients undergoing HCT [11, 13, 14, 16]. A meta-analysis by Lee et al. also showed that MCFG was significantly associated with higher treatment success, lower rates of IFIs, and fewer AEs compared with triazoles [22]. Based on these studies, MCFG is currently approved by the FDA for prophylaxis of IFIs among patients undergoing

Table 3 Efficacy and adverse events according to different initial daily doses of MCFG

	150 mg	300 mg	*P* value
Number of patients	69	10	
Daily dose of MCFG, mg/kg/day, median (range)	2.7 (1.7–3.9)	5.3 (4.0–7.0)	*< 0.001*
Duration of MCFG treatment, days, median (range)	42 (4–141)	72 (29–123)	*0.002*
Cumulative dose of MCFG, mg/kg, median (range)	99.6 (8.6–409.9)	358.1 (99.7–920.9)	*< 0.001*
Efficacy			
No breakthrough fungal infection	68/69 (99%)	9/10 (90%)	0.239
Survival for at least 7 days after the end of treatment	66/69 (96%)	9/10 (90%)	0.425
No discontinuation due to toxicity or lack of efficacy	45/66 (68%)	8/9 (89%)	0.254
Resolution of fever during neutropenia	31/39 (79%)	6/6 (100%)	0.624
Adverse events			
Number of assessable patients	63	9	
All grades			
AST elevation	48 (76%)	8 (89%)	0.673
ALT elevation	43 (68%)	8 (89%)	0.268
ALP elevation	48 (76%)	9 (100%)	0.189
GGTP elevation	38 (60%)	6 (67%)	1
Total bilirubin elevation	10 (16%)	0	0.343
Serum creatinine elevation	51 (81%)	8 (89%)	1
Grades 3 to 4			
AST elevation	0	0	
ALT elevation	1 (2%)	0	1
ALP elevation	0	0	
GGTP elevation	4 (6%)	0	1
Total bilirubin elevation	0	0	
Serum creatinine elevation	0	0	

AST, aspartate amino transferase; *ALT*, alanine amino transferase; *ALP*, alkaline phosphatase; *GGTP*, gamma-glutamyl transpeptidase. The *P* values in italic are statistically significant (<0.05)

HCT. In contrast, the majority of patients received MCFG as empirical or preemptive therapy with or without neutropenia in our study. For empirical therapy for neutropenic fever in patients with hematological malignancies, there were two prospective studies that compared MCFG with triazole [17, 23]. Oyake et al. reported that MCFG had a similar efficacy to voriconazole in patients with neutropenic fever [17]. Jeong et al. reported that MCFG had a more favorable efficacy and safety than itraconazole in patients with neutropenic fever [23]. Recently, a meta-analysis by Chen et al. showed that echinocandins, including caspofungin and micafungin, appear to be the most effective for empiric therapy for IFIs in patients with neutropenic fever [24]. However, these studies included none or small number of patients undergoing CBT. In our study, the rate of resolution of neutropenic fever in MCFG treatment was higher than that in previous reports [17, 23]. The resolution of neutropenic fever after CBT might be partly due to the resolution of pre-engraftment syndrome, which is a unique clinical manifestation characterized by non-infectious fever and erythematous skin rash after CBT but before neutrophil engraftment [24–28], with a median time of initiation of MCFG treatment at 8.5 days after CBT. On the other hand, only 2 (2%) patients developed breakthrough fungal infection in our study, which was slightly lower than in previous studies [17, 23]. In our study, the causative breakthrough fungemia was *Candida fermentati* with an fks1p mutation, as previously reported [29]. Recently, Kimura et al. reported that 30 candidemia and 9 fungemia other than candidemia were observed in hematological patients under MCFG treatment [30]. Although the most common cause of fungemia in this report was *C. parapsilosis* [30], breakthrough candidemia caused by *C. parapsilosis* was not observed in our study. Indeed, when colonization of *C. parapsilosis* was identified under MCFG treatment in our cohort, MCFG was switched to the susceptible triazoles before the development of candidemia. Whether active surveillance culture and decolonization intervention for MCFG resistant strains can contribute to prevention of breakthrough fungus infections is a matter of future investigation for patients undergoing allogeneic HCT, particularly for CBT under MCFG treatment.

Our study showed that hepatobiliary AEs during MCFG treatment were commonly observed, but grade 3 or higher AEs were rare. Grade 3 hepatobiliary AEs were not significantly associated with the duration of MCFG treatment (*P* =

0.182, Mann–Whitney *U* test) or cumulative dose of MCFG ($P = 0.308$, Mann–Whitney *U* test). Based on these data, grade 3 hepatobiliary AEs appeared to be dose-independent of the toxicity of MCFG, which is consistent with a previous study [31]. Only 7 (8%) patients discontinued MCFG due to AEs, which was slightly lower than in previous studies [17, 23]. However, development of hepatobiliary toxicity under MCFG treatment often leads to discontinuation of MCFG regardless of causality. Indeed, the cause of hepatobiliary toxicity is likely to be multifactorial in allogeneic HCT. Therefore, it was difficult to determine whether hepatobiliary AEs were due to MCFG or other complications following CBT, such as concomitant use of other potentially hepatotoxic drugs, GVHD, or hepatic sinusoidal obstruction syndrome. Moreover, MCFG did not alter the pharmacokinetic profiles of cyclosporine, tacrolimus, prednisolone, mycofenolate mofetil, fluconazole, and voriconazole [2], which are frequently used for CBT recipients. However, concomitant use of triazoles with other drugs can lead to serious drug interactions, because triazoles are metabolized by cytochrome P450 isozymes. These data suggest that MCFG had a more favorable tolerability profile and fewer drug interactions in patients undergoing CBT.

Several studies have investigated the efficacy and safety of different doses of MCFG [12, 15, 32–34]. Ota et al. reported a better clinical response for administration of an initial dose of ≥ 2.25 mg/kg/day compared with < 2.25 mg/kg/day for patients with candidemia [32]. Yamazaki et al. also showed that treatment of IFIs and febrile neutropenia was significantly better for a daily dose of 300 mg compared with 150 mg [33]. However, the dose of MCFG did not affect the efficacy in our study. Interestingly, almost all of these previous studies demonstrated that the higher daily dose of MCFG did not increase the AEs [12, 15, 33, 34], which is consistent with our study. The optimal daily dose of MCFG might be dependent on the strategy for prophylaxis and treatment and the types of fungal infections. Prospective randomized studies are required to clarify the relationship between the optimal daily dose of MCFG and efficacy or safety in patients undergoing CBT.

The present study had several limitations. First, our study could not divide empirical and preemptive therapy to evaluate the efficacy of MCFG treatment. Cordonnier et al. conducted a randomized trial to compare outcomes with empirical treatment versus preemptive antifungal treatment in patients with neutropenic fever, and found that empirical treatment decreased the incidence of probable or proven IFIs, whereas preemptive treatment decreased the costs of antifungal drugs [35]. Therefore, further studies are warranted to compare an empirical treatment with a preemptive one of MCFG in patients undergoing CBT. Second, previous studies demonstrated that delayed T cell reconstitution was associated with increased incidence of virus infection in patients received CBT [36]. However, 74 (80%) patients received MCFG during neutropenia and only 13 patients received MCFG after neutrophil engraftment in our study. Therefore, association between T cell reconstitution and efficacy of MCFG after CBT should be clarified in the future study.

In summary, our data demonstrated that MCFG was effective and safe for adult patients undergoing CBT. The optimal daily dose of MCFG treatment is a matter of future investigation for adult patients undergoing CBT.

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Compliance with ethical standards

This case study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Girmenia C, Ferretti A, Barberi W (2014) Epidemiology and risk factors for invasive fungal diseases in hematopoietic stem cell transplantation. Curr Opin Hematol 21:459–465
2. Patil A, Majumdar S (2017) Echinocandins in antifungal pharmacotherapy. J Pharm Pharmacol 69:1635–1660
3. Aguilar-Zapata D, Petraitiene R, Petraitis V (2015) Echinocandins: the expanding antifungal armamentarium. Clin Infect Dis 61(Suppl 6):S604–S611
4. Takahashi S, Iseki T, Ooi J, Tomonari A, Takasugi K, Shimohakamada Y, Yamada T, Uchimaru K, Tojo A, Shirafuji N, Kodo H, Tani K, Takahashi T, Yamaguchi T, Asano S (2004) Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematologic malignancies. Blood 104:3813–3820
5. Takahashi S, Ooi J, Tomonari A, Konuma T, Tsukada N, Oiwa-Monna M, Fukuno K, Uchiyama M, Takasugi K, Iseki T, Tojo A, Yamaguchi T, Asano S (2007) Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem-cell transplants from related donors in adult patients with hematologic malignancies after myeloablative conditioning regimen. Blood 109:1322–1330
6. Eapen M, Rocha V, Sanz G, Scaradavou A, Zhang MJ, Arcese W, Sirvent A, Champlin RE, Chao N, Gee AP, Isola L, Laughlin MJ, Marks DI, Nabhan S, Ruggeri A, Soiffer R, Horowitz MM, Gluckman E, Wagner JE, Center for International Blood and Marrow Transplant Research; Acute Leukemia Working Party Eurocord (the European Group for Blood Marrow Transplantation); National Cord Blood Program of the New York Blood Center (2010) Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. Lancet Oncol 11:653–660
7. Terakura S, Atsuta Y, Tsukada N, Kobayashi T, Tanaka M, Kanda J, Najima Y, Fukuda T, Uchida N, Takahashi S, Nagamura-Inoue T, Morishima Y, Miyamura K, Japan Society for Hematopoietic Cell Transplantation (2016) Comparison of outcomes of 8/8 and 7/8 allele-matched unrelated bone marrow transplantation and single-

unit cord blood transplantation in adults with acute leukemia. Biol Blood Marrow Transplant 22:330–338
8. Konuma T, Tsukada N, Kanda J, Uchida N, Ohno Y, Miyakoshi S, Kanamori H, Hidaka M, Sakura T, Onizuka M, Kobayashi N, Sawa M, Eto T, Matsuhashi Y, Kato K, Ichinohe T, Atsuta Y, Miyamura K, Donor/Source Working Group of the Japan Society for Hematopoietic Cell Transplantation (2016) Comparison of transplant outcomes from matched sibling bone marrow or peripheral blood stem cell and unrelated cord blood in patients 50 years or older. Am J Hematol 91:E284–E292
9. Girmenia C, Raiola AM, Piciocchi A, Algarotti A, Stanzani M, Cudillo L, Pecoraro C, Guidi S, Iori AP, Montante B, Chiusolo P, Lanino E, Carella AM, Zucchetti E, Bruno B, Irrera G, Patriarca F, Baronciani D, Musso M, Prete A, Risitano AM, Russo D, Mordini N, Pastore D, Vacca A, Onida F, Falcioni S, Pisapia G, Milone G, Vallisa D, Olivieri A, Bonini A, Castagnola E, Sica S, Majolino I, Bosi A, Busca A, Arcese W, Bandini G, Bacigalupo A, Rambaldi A, Locasciulli A (2014) Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transplant 20:872–880
10. Choi JK, Cho SY, Yoon SS, Moon JH, Kim SH, Lee JH, Kim JS, Cheong JW, Jang JH, Seo BJ, Kim YJ, Lee HJ, Lee J, Lee JW, Lee DG (2017) Epidemiology and risk factors for invasive fungal diseases among allogeneic hematopoietic stem cell transplant recipients in Korea: results of "RISK" study. Biol Blood Marrow Transplant 23:1773–1779
11. van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, Bunin N, Wall DA, Hiemenz JW, Satoi Y, Lee JM, Walsh TJ, National Institute of Allergy and Infectious Diseases Mycoses Study Group (2004) Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 39:1407–1416
12. Sirohi B, Powles RL, Chopra R, Russell N, Byrne JL, Prentice HG, Potter M, Koblinger S (2006) A study to determine the safety profile and maximum tolerated dose of micafungin (FK463) in patients undergoing haematopoietic stem cell transplantation. Bone Marrow Transplant 38:47–51
13. Hashino S, Morita L, Takahata M, Onozawa M, Nakagawa M, Kawamura T, Fujisawa F, Kahata K, Izumiyama K, Yonezumi M, Chiba K, Kondo T, Asaka M (2008) Administration of micafungin as prophylactic antifungal therapy in patients undergoing allogeneic stem cell transplantation. Int J Hematol 87:91–97
14. Hiramatsu Y, Maeda Y, Fujii N, Saito T, Nawa Y, Hara M, Yano T, Asakura S, Sunami K, Tabayashi T, Miyata A, Matsuoka KI, Shinagawa K, Ikeda K, Matsuo K, Tanimoto M, West-Japan Hematology and Oncology Group (West-JHOG) (2008) Use of micafungin versus fluconazole for antifungal prophylaxis in neutropenic patients receiving hematopoietic stem cell transplantation. Int J Hematol 88:588–595
15. Langebrake C, Rohde H, Lellek H, Wolschke C, Kröger NM (2014) Micafungin as antifungal prophylaxis in recipients of allogeneic hematopoietic stem cell transplantation: results of different dosage levels in clinical practice. Clin Transpl 28:286–291
16. Park S, Kim K, Jang JH, Kim SJ, Kim WS, Chung DR, Kang CI, Peck KR, Jung CW (2016) Randomized trial of micafungin versus fluconazole as prophylaxis against invasive fungal infections in hematopoietic stem cell transplant recipients. J Inf Secur 73:496–505
17. Oyake T, Kowata S, Murai K, Ito S, Akagi T, Kubo K, Sawada K, Ishida Y (2016) Comparison of micafungin and voriconazole as empirical antifungal therapies in febrile neutropenic patients with hematological disorders: a randomized controlled trial. Eur J Haematol 96:602–609
18. Epstein DJ, Seo SK, Brown JM, Papanicolaou GA (2018) Echinocandin prophylaxis in patients undergoing haematopoietic cell transplantation and other treatments for haematological malignancies. J Antimicrob Chemother 73:i60–i72
19. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, Cornely OA, Bourque MR, Lupinacci RJ, Sable CA, dePauw BE (2004) Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 351:1391–1402
20. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Muñoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group (2008) Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 46:1813–1821
21. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48:452–458
22. Lee CH, Lin JC, Ho CL, Sun M, Yen WT, Lin C (2017) Efficacy and safety of micafungin versus extensive azoles in the prevention and treatment of invasive fungal infections for neutropenia patients with hematological malignancies: a meta-analysis of randomized controlled trials. PLoS One 12:e0180050
23. Jeong SH, Kim DY, Jang JH, Mun YC, Choi CW, Kim SH, Kim JS, Park JS (2016) Efficacy and safety of micafungin versus intravenous itraconazole as empirical antifungal therapy for febrile neutropenic patients with hematological malignancies: a randomized, controlled, prospective, multicenter study. Ann Hematol 95:337–344
24. Chen K, Wang Q, Pleasants RA, Ge L, Liu W, Peng K, Zhai S (2017) Empiric treatment against invasive fungal diseases in febrile neutropenic patients: a systematic review and network meta-analysis. BMC Infect Dis 17:159
25. Patel KJ, Rice RD, Hawke R, Abboud M, Heller G, Scaradavou A, Young JW, Barker JN (2010) Pre-engraftment syndrome after double-unit cord blood transplantation: a distinct syndrome not associated with acute graft-versus-host disease. Biol Blood Marrow Transplant 16:435–440
26. Frangoul H, Wang L, Harrell FE Jr, Ho R, Domm J (2009) Preengraftment syndrome after unrelated cord blood transplant is a strong predictor of acute and chronic graft-versus-host disease. Biol Blood Marrow Transplant 15:1485–1488
27. Kishi Y, Kami M, Miyakoshi S, Kanda Y, Murashige N, Teshima T, Kusumi E, Hara S, Matsumura T, Yuji K, Masuoka K, Wake A, Morinaga S, Kanemaru M, Hayashi T, Tanaka Y, Taniguchi S, Tokyo Stem Cell Transplant Consortium (2005) Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. Transplantation 80:34–40
28. Konuma T, Kohara C, Watanabe E, Mizukami M, Nagai E, Oiwa-Monna M, Tanoue S, Isobe M, Kato S, Tojo A, Takahashi S (2017) Cytokine profiles of pre-engraftment syndrome after single-unit cord blood transplantation for adult patients. Biol Blood Marrow Transplant 23:1932–1938
29. Konuma T, Takahashi S, Kiyuna T, Miharu Y, Suzuki M, Shibata H, Kato S, Takahashi S, Tojo A (2017) Breakthrough fungemia due to Candida fermentati with fks1p mutation under micafungin treatment in a cord blood transplant recipient. Transpl Infect Dis 19

30. Kimura M, Araoka H, Yamamoto H, Asano-Mori Y, Nakamura S, Yamagoe S, Ohno H, Miyazaki Y, Abe M, Yuasa M, Kaji D, Kageyama K, Nishida A, Ishiwata K, Takagi S, Yamamoto G, Uchida N, Izutsu K, Wake A, Taniguchi S, Yoneyama A (2017) Clinical and microbiological characteristics of breakthrough candidemia in allogeneic hematopoietic stem cell transplant recipients in a Japanese hospital. Antimicrob Agents Chemother 61: e01791–e01716
31. Kohno S, Masaoka T, Yamaguchi H, Mori T, Urabe A, Ito A, Niki Y, Ikemoto H (2004) A multicenter, open-label clinical study of micafungin (FK463) in the treatment of deep-seated mycosis in Japan. Scand J Infect Dis 36:372–379
32. Ota Y, Tatsuno K, Okugawa S, Yanagimoto S, Kitazawa T, Fukushima A, Tsukada K, Koike K (2007) Relationship between the initial dose of micafungin and its efficacy in patients with candidemia. J Infect Chemother 13:208–212
33. Yamazaki S, Nakamura F, Yoshimi A, Ichikawa M, Nannya Y, Kurokawa M (2014) Safety of high-dose micafungin for patients with hematological diseases. Leuk Lymphoma 55:2572–2576
34. Heimann SM, Vehreschild MJ, Meintker L, Heinz W, Schroeder T, von Bergwelt-Baildon M, Cornely OA, Vehreschild JJ (2014) Different doses of micafungin for prophylaxis of invasive fungal diseases in hemato-oncological high-risk patients: a web-based non-interventional trial in four large university hospitals in Germany. Transpl Infect Dis 16:968–974
35. Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, Suarez F, Dhédin N, Isnard F, Ades L, Kuhnowski F, Foulet F, Kuentz M, Maison P, Bretagne S, Schwarzinger M (2009) Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis 48:1042–1051
36. Servais S, Lengline E, Porcher R, Carmagnat M, Peffault de Latour R, Robin M, Sicre de Fontebrune F, Clave E, Maki G, Granier C, Xhaard A, Dhedin N, Molina JM, Toubert A, Moins-Teisserenc H, Socie G (2014) Long-term immune reconstitution and infection burden after mismatched hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 20:507–517