Mnuscript number: 07-133

Main category: D. Transplantation & Cell Therapy

Subcategory: D.-2) Allogeneic Transplantation

Type of Manuscript: Full-length papers

Type of Computer: MAC

Application: WORD

Administration of micafungin as prophylactic antifungal therapy in patients undergoing allogeneic stem cell transplantation

Satoshi Hashino, Lena Morita, Mutsumi Takahata, Masahiro Onozawa, Masao Nakagawa, Takahito Kawamura, Fumie Fujisawa, Kaoru Kahata, Koh Izumiyama, Masakatsu Yonezumi, Koji Chiba, Takeshi Kondo, Masahiro Asaka

Department of Gastroenterology and Hematology, Hokkaido University Graduate School of Medicine

Short running title: Micafungin as antifungal prophylaxis in allogeneic SCT

Correspondeng author's name: Satoshi Hashino, MD and PhD

Department of Gastroenterology and Hematology, Hokkaido University Graduate School

of Medicine, Kita-15 Nishi-7, Kita-ku, Sapporo 060-8638, JAPAN

TEL:+81-11-716-1161(ext.5920)

FAX:+81-11-706-7867

e-mail:shashino@med.hokudai.ac.jp

Abstract

Objective: Invasive fungal infection is one of the major causes of death in neutropenic patients undergoing allogeneic stem cell transplantation (SCT). Although prophylactic antifungal therapy with fluconazole (FLCZ) has become the standard care for these patients, there remains a need for more effective and cost-beneficial alternative drugs.

Patients and Methods: We conducted a prospective study to evaluate the usefulness of the administration of micafungin (MCFG) as a prophylactic antifungal therapy for patients undergoing allogeneic SCT. The results were compared with previous data for patients who had received FLCZ.

Results: A total of 44 patients who underwent allogeneic SCT were enrolled in the study. Data from 29 patients who received allogeneic SCT using prophylactic FLCZ before this study were used as historical control data. Underlying diseases included acute leukemia (n=16), non-Hodgkin's lymphoma (n=11), myelodysplastic syndrome (n=6), and others (n=11) in the MCFG group and acute leukemia (n=18), chronic myelogenous leukemia (n=6), and others (n=5) in the FLCZ group. The median durations of administration of MCFG and FLCZ were 36 and 34 days, respectively. Prophylactic success, defined as the absence of proven, probable, and possible invasive fungal infection (IFI) until the end of prophylactic therapy was achieved in 36 (87.8%) of the 41 evaluated patients in the MCFG group and in 65.5% of the patients in the FLCZ group (p=0.038). No patients in the MCFG group showed proven or probable IFI, whereas proven or probable IFI was observed in 3 patients in the FLCZ group. Four patients in the MCFG group required dose

escalation due to febrile neutropenia. Although one patient in the MCFG group required the discontinuation of MCFG due to allergic skin eruption (grade 2), none of the other patients in either group required dose reduction due to adverse effects.

Conclusions: Although the study design was not a prospective randomized trial, our results indicate that the administration of MCFG at a daily dose of 100 mg is promising for prophylactic antifungal therapy in patients undergoing allogeneic SCT.

Key words: invasive fungal infection, micafungin, fluconazole, allogeneic stem cell transplantation

Introduction

Although the mortality rate in patients with infection occurring early after allogeneic stem cell transplantation (SCT) has been markedly decreased due to the administration of G-CSF and prophylactic use of anti-viral drugs against VZV/HSV and CMV, invasive fungal infection (IFI) still remains a major cause of death. Once IFI has occurred in patients who have received immunosuppressants for prophylaxis or treatment of acute graft-versus-host disease (GVHD), the prognosis is very poor. The incidence of IFI in patients who have undergone allogeneic SCT is higher than that in those who have undergone autologous SCT [1]. For this indication, fluconazole (FLCZ) has been routinely used in many institutions and has shown excellent antifungal effects in both patients who have undergone autologous SCT and allogeneic SCT [2, 3]. However, its use is associated with breakthrough fungal infection in some patients and expensive costs in cases with intravenous administration. Moreover, FLCZ does not protect patients from invasive aspergillosis. In this regard, there is a need for more effective and less expensive alternative drugs in allogeneic SCT.

Micafungin (MCFG) is a novel antifungal agent of the echinocandin class that inhibits the synthesis of 1, 3-β-D-glucan, an essential component of the fungal cell wall [4]. This drug has been demonstrated to exhibit an excellent *in vitro* activity against both *Candida* and *Aspergillus* [4], and clinical studies have also shown good activity in patients with febrile neutropenia and invasive candidiasis [5, 6]. Moreover, MCFG is also effective against FLCZ-resistant *Candida albicans*. Azoles other than FLCZ have serious

drug-to-drug interaction effects through the cytochrome P450 3A4 pathway, and so the use of other azoles in allogeneic SCT is therefore difficult. Moreover, although FLCZ has few side effects, itraconazole (ITCZ) and voriocnazole (VRCZ) usually have gastrointestinal or visual side effects. For these reasons, we considered MCFG to be a potential alternative to FLCZ, and we performed a prospective study to evaluate the usefulness of MCFG in prophylactic therapy for neutropenic patients undergoing allogeneic SCT.

Patients and Methods

Study design

This was a prospective study conducted in a single institution. The major objective of this study was to evaluate the efficacy, feasibility, and cost-benefit of prophylactic therapy with MCFG for patients undergoing allogeneic SCT. The primary end point was treatment success, which was defined as the absence of proven, probable, or possible IFI until day 21 after the SCT. The secondary end point was the absence of proven or probable IFI until day 49 after the SCT [7]. Types of IFI were defined by the European Organization for Research and Treatment of Cancer/Mycology Study Group (EORTC/MSG) criteria [8]. After obtaining written informed consent, patients were treated according to the protocol. The protocol was reviewed and approved by the Institutional Review Board. The data obtained from this study were compared with historical data from patients who received prophylactic FLCZ at 400 mg/day before the start of this study.

Patients

Adult patients with hematological and non-hematological malignancy undergoing allogeneic SCT were eligible for the study if they did not have significant hepatic or renal dysfunctions (defined as a level of bilirubin, ALT, AST, or creatinine that was less than two times the upper limit of the normal range). Patients were excluded if they had a previous history of allergy to MCFG or active IFI at the time of enrollment. Patients

receiving antifungal prophylaxis with other drugs were allowed to participate; however, administration of any other antifungal drug used had to be discontinued at the time when treatment with MCFG was started. All patients were isolated in a room equipped with a laminar airflow system and had a central venous catheter. All patients were given oral levofloxacin at a daily dose of 300 mg for bacterial prophylaxis, which was also begun 14 days before the transplantation.

Treatment protocol

After enrollment, prophylactic MCFG was started at a daily dose of 100 mg (14,014 Japanese yen) once a day intravenously over 1 hour from 14 days before allogeneic SCT. The dose of MCFG was increased to 150~300 mg as the treatment dose or MCFG was changed to another antifungal drug when patients were suspected of having febrile neutropenia or IFI. Therapy was continued until the patient had achieved hematological engraftment (defined as an absolute neutrophil count of over 500/μl after the nadir) and was able to take medicine. After the discontinuation of MCFG, FLCZ was administered orally at 200 mg/day until the cessation of immunosuppressants.

Historical control patients were administered FLCZ at 400 mg/day orally or intravenously (19,908 Japanese yen) starting 14 days before allogeneic SCT, and the dose was decreased to 200 mg orally when the patient had achieved hematological engraftment and was able to take medicine. In cases with possible, probable, or proven IFI, FLCZ was changed to another antifungal drug.

Clinical and laboratory evaluations

Patients were monitored daily for clinical signs and symptoms. Analysis of complete blood counts and chemistry parameters was performed at least 3 times a week. Surveillance cultures were obtained from the throat, urine, and stools once a week throughout the study period. Blood cultures and chest X-rays were performed when the patients suffered from fever up to 37.5□. Serum β–D-glucan and *Aspergillus*-antigen (galactomannan) were checked once a week during the study. CT scanning was performed in patients with suspected pulmonary infections. Adverse events were graded on the basis of the National Cancer Institute Common Toxicity Criteria version 2.0.

Statistical analysis

Fisher's exact test and Student's *t*-test were used for analysis. All comparisons were 2-sided, with a significance level of 5%.

Results

Patients

Between January 2004 and March 2007, a total of 44 patients were enrolled in the MCFG group. Data for 29 historical cases treated with FLCZ were also analyzed. Clinical characteristics of the patients are listed in Table 1. Underlying diseases included acute leukemia (n=16), non-Hodgkin's lymphoma (n=11), myelodysplastic syndrome (n=6), and others (n=11) in the MCFG group and acute leukemia (n=18), chronic myelogenous leukemia (n=6), and others (n=5) in the FLCZ group. Two patients in the MCFG group had a past history of IFI. Baseline fungal infections defined by EORTC/MSG criteria were absent in all patients before starting MCFG or FLCZ treatment. The median age of patients in the MCFG group was more advanced than that of patients in the FLCZ group (p=0.006). Rates of non-myeloablative conditioning and tacrolimus for acute GVHD prophylaxis were higher in the MCFG group (p=0.00006 and p=0.044, respectively). The median day of engraftment was day 15 in both groups (data not shown). Therefore, durations of neutropenia (until day 15 after the SCT) in the two groups were similar. The numbers of cases with grade II to IV acute GVHD that needed prednisolone (PSL) administration were 10 in the MCFG group and 4 in the FLCZ group (p=0.3680) (Table 1).

Treatment and efficacy

MCFG was given to 44 patients for prophylaxis. The initial dose for 42 patients was 100

mg. Treatment was started at a dose of 150 mg in two patients because of a previous history of IFI. The dose was increased to 150 mg in four patients because of febrile neutropenia, but there was no case requiring dose reduction due to adverse effects. FLCZ was given to 29 patients. In one patient, the dose was increased from 200 to 400 mg, but treatment with FLCZ was started at a dose of 400 mg in the other 28 patients. The median duration of administration of MCFG was 36 days (range: 11 to 80 days) and that of FCLZ was 34 days (range: 14 to 114 days) (Table 2).

Treatment success was achieved in 36 patients (87.8% of the 41 evaluable patients) in the MCFG group and in 19 patients (65.5% of the 29 evaluable patients) in the FLCZ group (p=0.038). None of the patients in the MCFG group fulfilled the EORTC/ NIAID criteria for proven and probable IFI. In the patients treated with FLCZ, there was one with disseminated candidiasis (caused by *Candida krusei*) and one with invasive pulmonary aspergillosis (IPA) (proven by autopsy). Since positive results for β-D-glucan and pneumonia of unknown etiology were obtained in two and three MCFG patients, respectively, these 5 patients were diagnosed as having possible IFI. Seven patients in the FLCZ group were diagnosed as having possible IFI: two cases with positive results for β-D-glucan and five cases with pneumonia of unknown etiology. MCFG was switched to VRCZ in one patient because of possible toxicity-induced hepatic dysfunction. In two patients in the MCFG group, *Candida glabrata* had colonized multiple sites before the start of MCFG treatment. *Candida albicans* and *Candida krusei* had infected two patients and one patient, respectively, in the FLCZ group. However, clinical *Candida* infection was not observed in any of those patients. Treatment success was analyzed by clinical

characteristics (Table 3). In this study, there was no significant risk factor in the patient characteristics other than the administration of MCFG or FLCZ.

Toxicity

Skin rash of grade 2 developed soon after administration in one patient in the MCFG group. Hepatic dysfunction of grade 2 and elevation of creatinine of grade 1 were observed in the FCLZ group.

Discussion

The beneficial role of FLCZ in patients undergoing allogeneic SCT was documented in a previous report [9]. However, its use was costly because most patients suffered from severe stomatitis and required the intravenous administration of FLCZ instead of oral capsules. Moreover, the rates of treatment success of FLCZ in allogeneic SCT settings are 68 to 81% [7, 10, 11]. One of the major concerns about the use of FLCZ is its lack of activity against *Aspergillus* species and some non-*albicans Candida* species. An increasing prevalence of such resistant strains has been reported, primarily due to the widespread use of prophylactic FLCZ [12, 13, 14]. Moreover, the incidence of aspergillosis in patients undergoing allogeneic SCT has been reported to be increasing, even in a bio-clean room equipped with laminar airflow [15]. Recently, several studies have shown that the incidence of invasive aspergillosis was higher in patients treated with non-myeloablative conditioning, who are administered stronger immunosuppressants than those in patients receiving myeloablative conditioning [16, 17]. Moreover, FLCZ inhibits the activity of hepatic cytochrome P450 3A4, as do other azoles, resulting in increased serum concentrations of cyclosporine A and tacrolimus. Therefore, less expensive, more effective, and safer alternative drugs are needed.

Recently, lipid formulations of AMPH-B have been shown to be equivalent to conventional AMPH-B in terms of efficacy, with less nephrotoxicity and infusion-related reactions. However, its routine use is limited due to its high cost. The use of oral ITCZ is also limited because of the wide ranging bioavailability of the capsule form and the

adverse gastrointestinal effects of the oral solution.

MCFG, similar to caspofungin, is an echinoicandin agent that targets fungal cell walls. *In vitro* and *in vivo* studies have shown that it has a broad spectrum and strong activity with fewer adverse effects in patients with candidaemia and invasive candidiasis [4, 6]. There is only one report of MCFG being used as prophylaxis in allogeneic SCT [7]. Although the number of patients in the present study was limited and the protocol design was not a randomized prospective study, this is the first study showing that administration of MCFG at a daily dose of 100 mg as prophylactic antifungal therapy in patients undergoing allogeneic SCT resulted in the prevention of proven and probable IFI. Compared with the results of previous studies, ours are encouraging.

It is also notable that none of the patients except one required discontinuation or dose reduction of the drug due to adverse events. Both MCFG and FLCZ were generally well tolerated.

The major problem lies in the diagnostic uncertainty of fungal infections. It is difficult to obtain a proven diagnosis of IFI before autopsy because of the difficulty in tissue biopsy due to neutropenia and severe thrombocytopenia. Since Hofmeister et al. reported that analysis of bronchoalveolar lavage or transbronchial biopsy did not lead to any survival benefit from an addition to the treatment regimen after a positive result, such invasive diagnostic procedures may be replaced by serological and radiological examinations [18]. In order to solve this problem, the EORTC/MSG criteria have recently been proposed [8]. However, since these criteria have not been used in most previous studies, we could not make a strict comparison with historical data. Frequent serological

examinations for IFI using different methods, including 1-3β–D-glucan and galactomannan antigenemia, are important for early diagnosis. Marr et al. reported that the use of a cutoff index of galactomannan reduced to 0.5 facilitated a more specific diagnosis of aspergillosis [19].

An optimal treatment design of MCFG in patients undergoing allogeneic SCT is also a problem to be solved. When we started this study, there was little information on optimal treatment, and we therefore used a slightly higher dose than that employed in a previous study [7]. A lower dose of MCFG (50 mg) is now allowed by the Health Insurance System in Japan for IFI prophylaxis; however, further investigation is needed to determine the optimal dose. Although the feasibility of persistent protection by FLCZ has been described in one report, the optimal duration of prophylaxis also remains uncertain for patients who are administered immunosuppressants for a long time, especially in cases with non-myeloablative cord blood transplantation [9]. Although several authors have reported that acute GVHD and the administration of PSL were risk factors for invasive aspergillosis, our study did not show such a relationship because of the small number of patients, as Winston et al. reported previously [11, 14, 20]. Although a long neutropenic period is also a risk factor for IFI, the difference between neutropenic periods in the two groups in this study was not significant. Moreover, two breakthrough definitive fungal infections in the patients receiving FLCZ occurred early after HSCT. Therefore, the difference in prophylactic efficacy was not due to a difference in the neutropenic period.

In summary, although this study was not a prospective randomized study and the

number of enrolled patients was small, the results of our clinical trial demonstrated that MCFG administered to allogeneic SCT patients at a daily dose of 100 mg was able to completely prevent both probable and proven IFI and was superior to FLCZ in overall efficacy. Marr et al. reported that not short-term but prolonged FLCZ prophylaxis was associated with persistent protection against candidiasis-related death in patients undergoing allogeneic SCT, and that the median day of onset of IFI after engraftment in cord blood transplantation is day 100 [9, 21]. Therefore, the effects and safety of the prolonged administration of antifungal drugs may be the next area of investigation.

References

1. Strasfeld L, Weinstock DM. Antifungal prophylaxis among allogeneic hematopoietic stem cell transplant recipients: current issues and new agents. *Exper Rev Anti Infect Ther* 2007; 4: 457-468.

2. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992; 32: 845-851.

3. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation: a prospective, randomized, double-blind study. *J Infect Dis* 1995; 171: 1545-1552, 1995.

4. Denning DW. Echinocandin antifungal drugs. *Lancet* 2003; 362: 1142-1151.

5. Yanada M, Kiyoi H, Murata M, et al. Micafungin, a novel antifungal agent, as empirical therapy in acute leukemia patients with febrile neutropenia. *Int Med* 2006; 45: 259-264.

6. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidiasis: a phase III randomized double-blind trial. *Lancet* 2007; 369: 1519-1527.

7. van Burik JH, Ratanatharathorn V, Stephan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis* 2004; 39: 1407-1416.

8. De Pauw B, Walsh T, Donnely JP, et al. EORCT/MSG Consensus revised definitions

draft VI (http://www.doctorfungus.org/lecture/EORTC_MSG_rev06.htm)

9. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood* 2000; 96: 2055-2061.

10. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infection in patients receiving allogeneic stem cell transplants. *Blood* 2004; 103: 1527-1533.

11. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematpoietic stem-cell transplant recipients. A multicenter, randomized trial. *Ann Intern Med* 2003; 138: 705-713.

12. Wingard JR, Merz WG, Rinaldi MG, Miller CB, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N End J Med* 1991; 325: 1274-1277.

13. Wingard JR, Merz WG, Rinaldi MG, Miller CB, Karp JE, Saral R. Association of *Torulopsis glabrata* infections with fluconazole prophylaxis in neutropenic bone marrow transplant patients. *Antimicrob Agents Chemother* 1993; 37: 1847-1849.

14. Marr KA, Carter RA, Boeckh M, Martin P, Corey U. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. *Blood* 2002; 100: 4359-4366.

15. Kami M, Machida U, Okuzumi K, et al. Effect of fluconazole prophylaxis on fungal blood cultures: an autopsy-based study involving 720 patients with haematological malignancy. *Br J Haematol* 2002; 117: 40-46.

16. Kojima R, Kami M, Nannya Y, et al. Incidence of invasive aspergillosis after allogeneic hematopoietic stem cell transplantation with a reduced-intensity regimen compared with transplantation with a conventional regimen. *Biol Blood Marrow Transplant* 2004; 10: 645-652.

17. Miyakoshi S, Kusumi E, Matsumura T, et al. Invasive fungal infection following reduced-intensity cord blood transplantation for adults patients with hematological diseases. *Bio Blood Marrow Transplant* 2007; 13: 771-777.

18. Hofmeister CC, Czerlanis C, Forsythe S, Stiff PJ. Retrospective utility of bronchoscopy after hematopoietic stem cell transplant. *Bone Marrow Transplant* 2006; 38:693-698.

19. Marr KA Balajee SA, McLaughlin L, Tabouret M, Bentsen C, Walsh TJ. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. *J Infect Dis* 2004; 190: 641-649.

20. Fukuda T, Boeckh M, Carter RA, et al. Risks and outocomes of invasive fungal infections of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood* 2003; 102: 3979-3986.

21. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Bio Blood Marrow Transplant* 2000; 6: 659-713.

Table 1. Clinical characteristics of the study patients.

Characteristics	MCFG group (n=44)	FLCZ group (n=29)	
Male/female	25/19	20/9	NS (p=0.334)
Age, median (range)	47 (16-69)	31 (16-66)	p=0.006
Weight, mean kg (range)	60.6 (36.5-99.5)	61.0 (41.2-86.0)	NS (p=0.460)
Underlying disease			
Acute myelogenous leukemia	10	10	
Acute lymphoblastic leukemia	6	8	
Non-Hodgkin’s lymphoma	11	1	
Myelodysplastic syndrome	6	2	
Chronic myelogenous leukemia	3	6	
Multiple myeloma	3	0	
Rhabdomyosarcoma	2	0	
Essental thrombocytemia	1	0	
Chronic active EBV infection	1	0	
Dysmoplastic small round cell tumor	1	0	
Colon cancer	0	1	
Aplastic anemia	0	1	
Transplant conditioning			p=0.00006

Myeloablative	19	26	
CY+VP+TBI	13	16	
MCNU+CY+TBI+SI	3	4	
CY+Ara-C+TBI	0	3	
BU+CY	2	1	
BU+Ara-C+CY	0	1	
BU+CY+SI	0	1	
CY+TBI	1	0	
Non-myeloablative	25	3	
FLU+BU	0	1	
FLU+L-PAM	0	1	
FLU+BU+TBI	23	0	
FLU+L-PAM+TBI	1	0	
FLU+L-PAM+TLI	1	0	
ALG+CY+TLI	0	1	
Stem cell source			NS (p=0.170)
Bone marrow	33	26	
Peripheral blood	1	1	
Cord blood	10	2	
GVHD prophylaxis			p=0.044
CsA+short-term MTX	35	28	

FK+short term MTX	9	1	
Acute GVHD with PSL (grade II to IV)	10/41	4/29	NS (p=0.3680)

Abbreviations: MCFG, micafungin; FLCZ, fluconazole; EBV, Epstein-Barr virus; CY, cyclophosphamide; VP, etoposide; TBI, total body irradiation; MCNU, ranimustine; SI, splenic irradiation; Ara-C, cytarabine; FLU, fludarabine phosphate; BU, busulfan; L-PAM, melphalan; TLI, total lymphoid irradiation; GVHD, graft-versus-host disease; CsA, cyclosporine A; MTX, methotrexate; FK, tacrolimus; NS, not significant.

Table 2. Treatment failure and outcome.

	MCFG group (n=44)	FLCZ group (n=29)	
Administration days: mean (range)	36.0 (11~80)	34.1 (14~114)	
Removed from the first efficacy analysis	3	0	
Drug allergy to MCFG	1		
Early death before evaluation of the study	2		
MRSA pneumonia	1		
Capillary leak syndrome	1		
Primary end point (day 21 after SCT)	5/41	10/29	p=0.038
Proven IFI	0	2	
Aspergillosis (IPA)		1	
Candidiasis (candidemia)		1	
Probable IFI	0	1	
Candidiasis (pneumonia)		1	
Possible IFI	5	7	

Removed from the second analysis	2	3	
Early death before the second end point	2	3	
Multi-organ failure	1	0	
MRSA pneumonia	1	0	
IPA	0	1	
Disseminated candidiasis	0	1	
GPC septic shock	0	1	
Secondary end point (day 49 after SCT)	1/39	1/26	NS (p=1.000)
Possible IFI	1	1	
Colonization during treatment period	2/41	3/29	
Candida albicans	0	2	
Candida glabrata	2	0	
Candida krusei	0	1	
Adverse effects related to treatment			
Rash (grade 2)	1	0	
Hepatic-related (ALT: grade 2)	0	1	
Urogenital-related (Cr: grade 1)	0	1	

Death at secondary end point	4/44	3/29	NS (p=1)

Abbreviations: MCFG, micafungin; FLCZ, fluconazole; MRSA, methycillin-resistant *Staphylococcus aureus*; IFI, invasive fungal infection; SCT, stem cell transplantation; IPA, invasive pulmonary aspergillosis; GPC, Gram-positive coccus; GVHD, graft-versus-host disease; PSL, prednisolone.

Table 3. Treatment success at the primary end point by prespecified clinical characteristics.

Characteristics	MCFG group (n=41)	FLCZ group (n=29)
Conditioning		
Myeloablative	16/18	18/27
Non-myeloablative	20/23	1/2
	NS	NS
Sex		
Male	20/23	14/20
Female	16/18	5/9
	NS	NS
Age, years		
16-60	32/37	19/28
60<	4/4	0/1
	NS	NS
Acute GVHD		
0 to I	28/31	18/25
II to IV	8/10	1/4
	NS	NS (p=0.635)

Abbreviations: MCFG, micafungin; FLCZ, fluconazole; GVHD, graft-versus-host disease.