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Bridging antifungal prophylaxis with 50 mg or 100 mg micafungin in allogeneic stem cell transplantation: A retrospective analysis

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Abstract

Objective: Fluconazole or posaconazole is a standard of care in antifungal prophylaxis for patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). However, many patients need to interrupt standard prophylaxis due to intolerability, drug-drug interactions, or toxicity. Micafungin has come to prominence for these patients. However, the optimal biological dose of micafungin stays unclear.

Methods: We retrospectively evaluated the efficacy of micafungin as antifungal prophylaxis in HSCT patients. Micafungin was applied as bridging in patients who were not eligible to receive oral posaconazole. Micafungin was either given at a dose of 100 mg or 50 mg SID.

Results: A total of 173 patients received micafungin prophylaxis, 62 in the 100 mg and 111 in the 50 mg dose group. The incidence of probable or proven breakthrough IFDs during the observation period was one in the 100 mg and one in the 50 mg group. Fungal-free survival after 100 days was 98% and 99% (P = .842), and overall survival after 365 days was 60% and 63% (P = .8) respectively. In both groups, micafungin was well tolerated with no grade 3 or 4 toxicities.

Conclusion: In this retrospective analysis, which was not powered to detect non-inferiority, micafungin is effective and complements posaconazole as fungal prophylaxis in HSCT.

KEYWORDS

immunology and infectious diseases, transplantation

1 | INTRODUCTION

Fluconazole was considered to be gold-standard antifungal prophylaxis for patients undergoing allogeneic HSCT for many years[1] and remains a standard of care. However, many centers have moved onto newer antifungal agents. These are commonly administered from conditioning chemotherapy until cessation of immunosuppressive treatment. Recently, the antifungal armamentarium was

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broadened with the development of extended-spectrum azoles and echinocandins. These antifungal agents were shown to be beneficial as a prophylaxis rather than as a treatment upon clinical signs of infection.[2]

A reduction in IFD during HSCT was achieved using micafungin, voriconazole, and posaconazole for antifungal prophylaxis.[3] Itraconazole, voriconazole, and micafungin showed a trend toward less breakthrough mold infections and less need for empiric or targeted antifungal treatment compared to fluconazole, but did not result in an improved survival.[1,4,5]

Challenges of newer antifungal agents in high-risk individuals like allogeneic HSCT recipients include side effects, drug-drug interactions, and a lack of an oral and intravenous formulation.[6] The evaluation of 86 clinical trials comprising 16.922 patients showed that only a few trials yielded significant differences in efficacy. Fluconazole improved the incidence rates of IFD and attributable mortality in allogeneic stem cell recipients. Posaconazole reduced the incidence of IFD and attributable mortality in allogeneic stem cell recipients with severe graft-versus-host disease and additionally reduced overall mortality.[7] Micafungin has proven its significance in the treatment of candidemia and invasive candidiasis. All echinocandins display concentration-dependent fungicidal (for *Candida* spp.) or fungistatic (for *Aspergillus* spp.) activity.[8] Micafungin was compared to liposomal amphotericin B[9] and caspofungin[10] as treatment for invasive candida infection. Both studies showed non-inferiority for micafungin. There was no statistical difference in safety and efficacy regarding the treatment of candidiasis and of aspergillosis.[11] Micafungin was demonstrated to be effective in more resistant *Candida* spp. (including *C glabrata* and *C krusei*) as well as for fungal biofilms as reviewed by Glöckner.[12]

Micafungin prophylaxis in patients undergoing HSCT was established based on a randomized phase III trial by van Burik et al,[13] which demonstrated 50 mg/d micafungin to be superior to fluconazole 400 mg/d in 882 patients. Treatment success characterized as the absence of proven, probable, or suspected IFD until the end of prophylaxis and 4 weeks post-treatment was significantly better for micafungin (80% vs 73.5%, respectively). Since its approval by EMA and FDA, micafungin is recommended for prophylaxis of fungal infections in HSCT patients by European as well as American expert boards.[14-17]

Yet, the optimal dose for prophylaxis, as well as the applicability in an outpatient setting, remains to be determined.[18] Micafungin 100 mg/d was evaluated in a historical comparison to fluconazole.[19] The absence IFD until the end of prophylactic treatment was achieved in 87.8% of the 41 evaluated patients in the micafungin and in 65.5% of the 29 patients in the fluconazole group. A prospective randomized trial assessed the efficacy and tolerance of 150 mg/d micafungin compared with fluconazole as prophylaxis in 104 patients undergoing HSCT.[20] While the overall efficacy of micafungin was comparable to fluconazole (94% vs 88%), there was no increase in adverse events in the micafungin group.

Thereafter, two dose-escalation studies of patients undergoing HSCT reported effectiveness and an good safety profile of micafungin: Hiemenz et al[21] described that the maximum tolerated dose (MTD) was not reached at doses up to 200 mg/d. Sirohi et al[22] demonstrated that daily doses of 8 mg/kg were well tolerated and effective.[21]

Micafungin was also demonstrated to be as effective as itraconazole in preventing IFD in HSCT patients. However, significant differences in the incidence of drug-related adverse events (8% vs 26.5%) were shown between micafungin and itraconazole.[23]

Here, we want to further assess the optimal dose of micafungin prophylaxis of IFD in HSCT patients. The Department I of Internal Medicine of the University of Cologne is a major German provider of HSCT, serving a population of 2.5 million. Due to frequently occurring drug-drug interactions, side effects (severe mucositis, elevated liver enzymes, long QT syndrome, nausea, low plasma levels, and/or diarrhea), and difficulties with patient compliance in using posaconazole, a bridging antifungal prophylaxis with micafungin in a dose of eather 50 mg/d or 100 mg/d was introduced in these patients. The here presented data were collected and analyzed retrospectively.

Novelty statement

1. The new aspect of our work is the impact of a lower dose of antifungal agent without loosing its effectiveness.
2. The central finding is that micafungin complements posaconazole as fungal prophylaxis in HSCT.
3. Antifungal prophylaxis with micafungin in HSCT could easily be transferred into the clinic and alter the standard of care in this setting.

2 | METHODS

2.1 | Setting

The objective of this retrospective analysis was to assess the safety and effectiveness of micafungin prophylaxis at different doses for bridging during the neutropenic phase of patients undergoing allogeneic HSCT. No changes in diagnostic and therapeutic standards were made during the observation period. In particular, hygiene procedures and the low-germ diet remained the same. Patients stayed on the transplantation ward for the entire time from conditioning treatment until engraftment. Standard procedures demanded antimicrobial and antiviral prophylaxis from the beginning of the conditioning regimen onwards and antifungal prophylaxis from day one after stem cell transplantation. Galactomannan screening was done in all patients before initiation of the chemotherapy. No patient had an increased galactomannan upon start of the antifungal prophylaxis and all were free of IFD.

As standard of care, oral posaconazole prophylaxis in liquid formulation at a dose of 200 mg three times daily was conducted. In case of no history of IFD, posaconazole was administered from day one

after HSCT, and in case of a history of IFD, posaconazole was administered from the day of the admission. In patients who were ineligible to continue posaconazole in the period between the stem cell transplantation and the engraftment phase due to mucositis or nausea, diarrhea, significantly elevated liver enzyme, long QT syndrome, intestinal GvHD, low posaconazole plasma concentrations, or drug-drug interactions, intravenous micafungin was given once a day over 30 minutes at a dose of either 50 mg or 100 mg. The selection of the dosage was not randomized, but based on decision of the treating physician.

In all patients, a neutropenic phase of 10-14 days was expected. Upon fever persisting for more than 72 hours, a chest CT and in case of lung infiltrates, bronchoscopy and bronchoalveolar lavage (BAL) were performed. There was no upper age limit for inclusion in our analysis.

After the engraftment, the patients were switched to the standard oral posaconazole prophylaxis.

2.2 | Documentation

Data for this retrospective analysis were extracted from the Cologne Cohort of Neutropenic Patients (CoCoNut), a non-interventional prospective cohort study assessing risk factors, interventions, and outcome of immunosuppressed patients.[24] The here presented data include patients who underwent allogeneic HSCT between the years 2009 and 2013.

Data capture included underlying disease, type of cytostatic chemotherapy, duration of neutropenia, length of stay, incidence and duration of fever, administration of antifungals, blood culture results, histopathology, galactomannan antigen from blood and BAL, chest CT imaging studies, and survival. A galactomannan test was considered positive if two consecutive blood samples or a single BAL fluid sample with an index ≥0.5 was documented. To avoid false-positive results, galactomannan was not evaluated when sampled on days of concomitant treatment with piperacillin/tazobactam.

2.3 | Ethical statement

Data collection and storage were performed on-site by site personnel using current techniques of privacy assurance. Data were extracted from the non-interventional CoCoNut cohort in which data on risk factors, interventions, and outcome of immunocompromised patients at risk of opportunistic infections are collected (NCT01821456). The CoCoNut has been approved by the local institutional review board and ethics committee (ID 13-108).

2.4 | Data analysis, definitions, and endpoints

The observation period was defined as the beginning of the conditioning regimen until either discharge, death or day 100 after SCT, whichever occured first. Primary endpoints were the incidence of probable or proven breakthrough IFDs, as defined by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG).[25] Secondary endpoints were the incidence of persistent neutropenic fever unresponsive to broad-spectrum antibiotic treatment for ≥72 hours, pneumonia, and possible IFD (eg, lung infiltrates such as circumscribed lesions with or without halo sign, cavity or air-crescent sign) indicative of invasive pulmonal aspergillosis according to EORTC/MSG consensus definitions[26] or positive galactomannan test, the duration of hospitalization as well as IFD-free survival during the observation period and overall survival after 365 days. Pneumonia was defined as fever with positive diagnostic imaging of the lung. Fungal-free survival was defined as survival without probable or proven IFD. All chest CT scans of the department are routinely evaluated by infectious disease specialists while being unaware of current patient treatment. Toxicity, death, and discontinuation of study treatment at the treating physician's decision were monitored. Toxicities were assessed according to National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Statistical analyses were carried out using IBM SPSS Statistics software (version 24, IBM Corporation). Mann-Whitney's non-parametric test was used to assess differences in continuous and Pearson's chi-squared test or Fisher's exact test to assess differences in discrete characteristics between groups. Kaplan-Meier curves were drawn and log-rank tests applied to detect differences in mortality and fungal-free survival as well as mortality at day 365. For all analyses, a P-value <.05 was considered significant.

3 | RESULTS

A total of 374 patients were included in the retrospective analysis. The patient characteristics are described in Table 1. Gender, conditioning regimen, donor type and mismatches, the number of patients who received radiation, the immunosuppressive prophylaxis, and days of neutropenia were similar in both groups, and hospital days as well as the duration of micafungin were similar in the two groups.

Patients in the micafungin 50 mg (Mica50) group were older than in the micafungin 100 mg (Mica100) group (median age 56 vs 49 years). All patients were diagnosed with a hematological malignancy and underwent conditioning chemotherapy regimens. There were more lymphoma and CLL patients in the Mica50 and more ALL and myeloma patients in the Mica100 group. The proportion of AML patients was similar in both groups. The GvHD rate of any grade was slightly higher in the Mica50 group. Posaconalzole prophylaxis had been abrogated and micafungin initiated in 173/374 (46%) patients. Sixty-two patients were switched to micafungin 100 mg an 111 patients to micafungin 50 mg based on the decision of the treating physician. Treatment duration was 4-132 days with

TABLE 1 Patient characteristics

	Micafungin 50 mg bridging (N = 111)	Micafungin 100 mg bridging (N= 62)	*P*-value
Age – years[a]			
Mean (y) and SD	56	49	*.033*
Range	18-74	21-74	
Female – no. (%)[b]	53 (48)	28 (45)	.744
Underlying condition – no. (%)[b]			*.012*
AML/MDS	56 (50)	27 (44)	
ALL	13 (12)	14 (23)	
Lymphoma	15 (14)	5 (8)	
MM	1 (1)	6 (10)	
CLL	8 (7)	0	
CML	7 (6)	5 (8)	
Other	11 (10)	5 (8)	
Conditioning regimen – no. (%)[b]			.128
Myeloablative	18 (16)	16 (25)	
Reduced intensity	93 (84)	46 (75)	
Donor type – no. (%)[b]			.079
Related	21 (19)	19 (31)	
Unrelated	90 (81)	43 (69)	
Mismatches – no. (%)[b]			.637
10/10	79 (71)	49 (79)	
9/10	28 (25)	11 (18)	
≤8/10	4 (4)	2 (3)	
CMV positive donor status – no. (%)[b]	67 (60)	27 (44)	*.033*
Radiation – no. (%)[b]	30 (27)	23 (37)	.168
Immunosuppressive prophylaxis – no. (%)[b]			
Calcineurin inhibitors	108 (97)	57 (92)	.107
ATG	35 (32)	20 (32)	.922
MMF	91 (82)	47 (76)	.332
Steroids	0	0	
GvHD – no. (%)[b]			
Any	88 (79)	38 (62)	*.011*
Grade 1-2	53 (48)	24 (39)	.251
Grade 3-4	35 (31)	14 (23)	.210
Duration of neutropenia – days[a]			
Median (Range)	20 (6-75)	22 (10-83)	*.019*
Length of stay – days[a]			
Median (Range)	44 (14-139)	42.5 (15-153)	.114
Duration of micafungin – days[a]			
Median (Range)	21 (1-105)	17 (4-131)	.117
Duration of prophylaxis – days[a]			
Median (Range)	41 (10-129)	37 n	.092

Abbreviations: 95% CI, confidence interval; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ATG, antithymocyte globulin; CLL, chronic lymphatic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MMF, mycophenolate mofetil; SD, standard deviation.

[a]Mann-Whitney *U* test (two-sided).

[b]Pearson chi-square test (two-sided).

p-values in italic are significant

TABLE 2 The assessment of the efficacy parameters

	Micafungin 50 mg bridging (N = 111)	Micafungin 100 mg bridging (N = 62)	*P*-value
Persistent febrile neutropenia no. (%)[b]	66 (59%)	27 (44%)	*.044*
Positive galactomannan no. (%)[c]	2 (1.8%)	0	.288
Pneumonia no. (%)[b]	39 (35%)	17 (27%)	.298
Possible IFD[a] (%)[b]	11 (12%)	6 (10%)	.961
Probable or proven IFD[a,c] (%)			
Aspergillosis	1 (1%)	0	.454
Candidiasis	0	1 (1.6%)	.358
Other IFD	0	0	1

Note: Incidence of breakthrough infections.

Abbreviations: IFD, Invasive fungal disease; n.a., not applicable.

[a]As per revised EORTC/MSG criteria.[25]

[b]Pearson chi-square test (two-sided).

[c]Fisher's exact test

p-values in italic are significant

a median of 17 days in the Mica100 and 1-105 days with a median of 21 days in the Mica50 group. Before discharge, all patients were switched to oral posaconazole prophylaxis.

The assessed efficacy parameters are summarized in Table 2 and Figure 1. In detail, differences between Mica50 and Mica100 were as follows: In the Mica100 group, there was one proven IFD with the detection of *Candida glabrata* in blood culture and no probable IFD. In the Mica50 group, there was no proven IFD. Two patients in the Mica 50 group were tested positive for galactomannan. One of these patients also presented with typical CT infiltrates and thus was considered as a probable IFD. The second patient tested positive for galactomannan had no clinical sign of IFD. In one patient, candida antigen in the serum was positive, which was not considered as to be of clinical significance. This patient also had mold typical CT infiltrates., but no mycological detection of a systemic mold infection. These patients were considered as possible IFD. In total, 6/62 patients in the Mica100 and 11/111 patients in the Mica50 group were diagnosed with possible IFD, 10 of these due to the detection of typical lung infiltrates. Furthermore, 48/62 patients in the Mica100 group experienced fever, which was persistent in 27 patients. Of these, 17 patients developed pneumonia and 6 fungal typical lung infiltrates. In the Mica50 group, 88/111 patients developed fever, of whom 66 patients suffered from persistent fever. Of these, 39 patients were diagnosed with pneumonia and 11 showed fungal typical lung infiltrates. The rate of persistent febrile neutropenia was higher in the Mica50 group (59% vs 44%, *P* = .044). The fungal-free survival was 111/111 patients (100%) in the Mica50 and 61/62 patients (98%) in the Mica100 group with a *P*-value of .842 (Figure 1A) and the 365-day OS 37/62 patients (60%) and 70/111 patients (63%) with a *P*-value of .752 (Figure 1B) in the Mica100 and Mica50 groups, respectively.

There was no grade III or IV toxicity related to antifungal prophylaxis with micafungin in either group. No patient had to discontinue micafungin prophylaxis due to adverse events or intolerance clearly attributed to micafungin.

4 | DISCUSSION

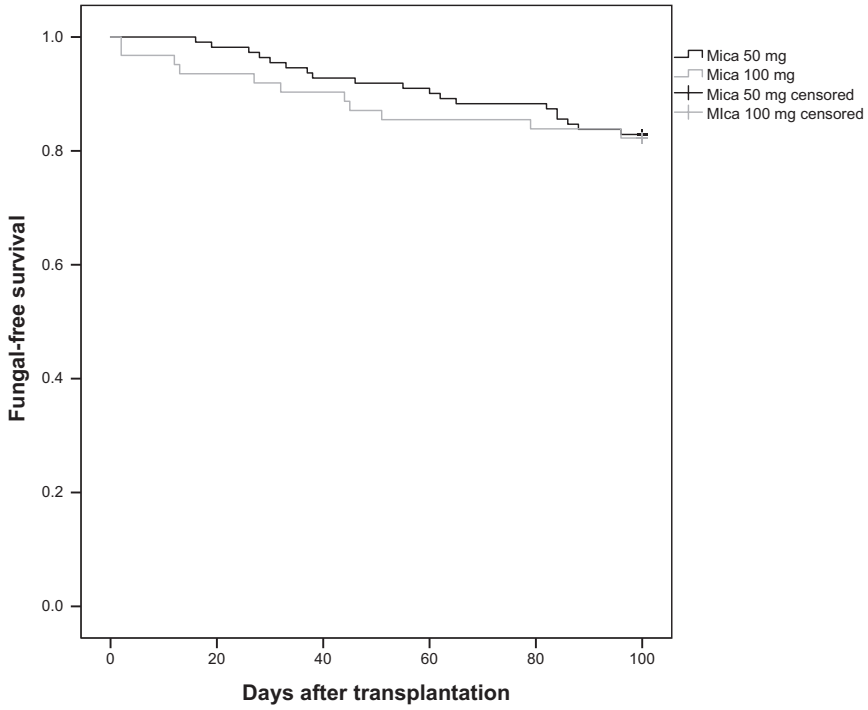
The use of a broad-spectrum and mold-active drug is recommended for antifungal prophylaxis in allogeneic HSCT recipients who develop complications, such as infection and graft-versus-host disease.[27] Resistance against echinocandins is rare.[28] Echinocandins are generally well tolerated with little impact on hepatic function as well as little drug-drug interactions with immunosuppressants. No dose reduction is necessary for kidney dysfunction or mild-to-moderate liver dysfunction.

From October 2009 to June 2013, we retrospectively evaluated the effectiveness of bridging oral posaconazole prophylaxis with intravenous micafungin at doses of 50 or 100 mg in HSCT recipients. These patients were temporarily unable to continue oral posaconazole due to side effects, drug-drug interactions, or other symptoms that might impair posaconazole absorption and thus were at a high risk for contracting IFDs. Micafungin prophylaxis was shown to be effective and safe in this setting.[24,29,30] Only little data are available on the use of micafungin as a bridging agent. However, different doses of micafungin were shown to be effective for prophylaxis of invasive fungal diseases in hemato-oncological high-risk patients in a web-based non-interventional trial.[31]

In our analysis, the incidence of probable or proven IFD was low and in line with expectations due to the short treatment period but remarkable with respect to the high-risk patient group. Considering the clinical challenges to establish a diagnosis of IFD, we included a number of secondary outcome parameters, such as fungal "specific" lung infiltrates, pneumonia, and persistent fever, as well as fungal-free survival and overall survival in the analysis.

(A) Fungal-free Survival (Kaplan-Meier-plot)

Follow-up was complete for all patients in the trial (no cases censored). Table shows patients at risk during different time periods (p = 0.842).



(B) Overall survival

Follow-up was complete for all patients in the trial (no cases censored). Table shows patients at risk during different time periods (p = 0.752).

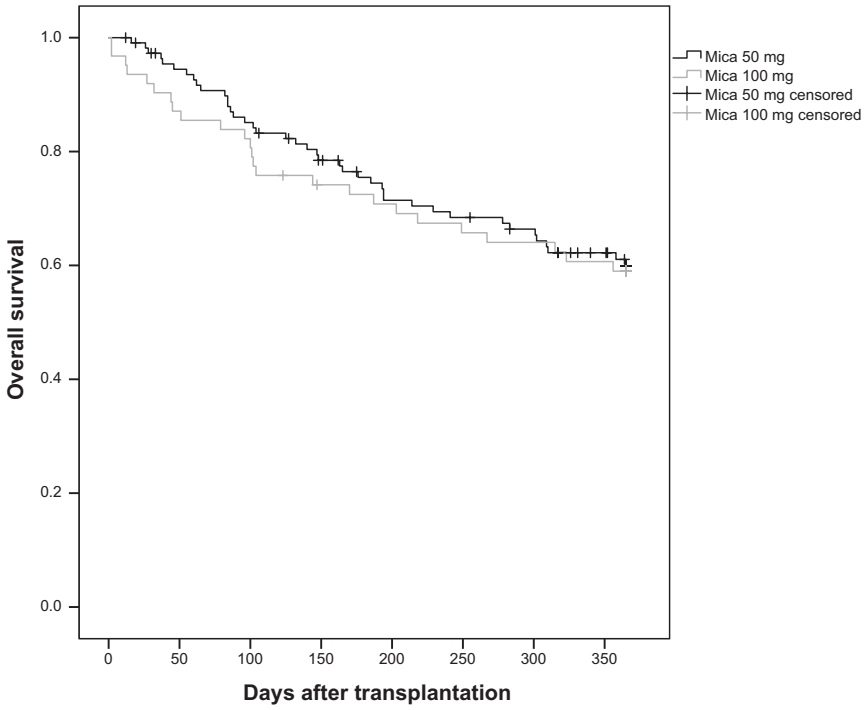


FIGURE 1 A, Fungal-free Survival (Kaplan-Meier-plot). Follow-up was complete for all patients in the trial (no cases censored). Table shows patients at risk during different time periods (*P* = .842). B, Overall survival. Follow-up was complete for all patients in the trial (no cases censored). Table shows patients at risk during different time periods (*P* = .752)

In particular, the overall incidence of lung infiltrates has been discussed as a sensitive marker of prophylactic efficacy in a previous trial.[32]

There was no significant toxicity induced by micafungin. This is in accordance with an evaluation of a pooled clinical trial data set including 3028 patients, which showed no clear association

between higher doses of micafungin or longer treatment durations and increased incidence rates of treatment-related adverse events.[33] It has to be mentioned that hepatocellular tumors were observed after prolonged exposure in preclinical animal experiments, with a threshold for tumor induction in the range of human therapeutic exposure.[34] However, a recently published cohort study showed that micafungin is not associated with higher risk of HCC.[35]

There were significant differences in some baseline characteristics between groups, that is, age, underlying condition, CMV donor status, which we assume do not have an impact on the evidence of the effectiveness of the micafungin prophylaxis. We observed a lower, but not statistically significant rate of radiation therapy in the Mica50 group. Lower radiation dosage may cause a less severe impairment of the immune system and may be considered as a protective factor against the acquisition of IFD. However, the potentially higher chance of GvHD in these patients may require an intensified immune suppression and consequently might cause a higher secondary risk for IFD. There was a slightly higher rate of GvHD of any grade in the micafungin 50 mg group, but no difference in the grade ½ and ¾ subgroups. The difference in duration of neutropenia (20 days in the micafungin 50 mg and 22 days in the micafungin 100 mg group) was significant ($P = .011$), but is probably a consequence to the broad range. We do not assume any impact on the endpoint analysis.

Patients with previously acquired an IFD remain at a high risk of relapse during later chemotherapy cycles or allogeneic stem cell transplantation.[36,37] Frequently, patients contracting an IFD early in their treatment course stay on antifungal treatment for many months.[38,39] For HSCT patients, antifungal prophylaxis requires a low side effect profile and intravenous availability for conditioning phase and the neutropenic phase thereafter as well as an orally available drug for the outpatient phase under immunosuppression.

Micafungin is approved for the prophylaxis of candidiasis in hematopoietic stem cell transplant recipients at a dose of 50 mg/d. Different doses such as 100 mg/d and 150 mg/d have been evaluated and seem to be safe and effective. Micafungin is effective against *Candida* spp. and *Aspergillus* spp., has a favorable pharmacokinetic profile and is very well tolerated with almost no relevant drug-drug interactions.

In summary, our here presented data indicate that bridging antifungal prophylaxis with micafungin facilitates a more stringent continuity of the prophylaxis with a higher overall drug exposure as standard posaconazole prophylaxis. Both micafungin doses were well tolerated, safe, and effective. The difference between the 50 mg and the 100 mg micafungin group for the primary and the secondary outcome parameters was insignificant. We conclude that micafungin could complement posaconazole prophylaxis and that a dose of 50 mg micafungin is sufficient to prevent IFD in this setting. However, we want to emphasize that this study is retrospective in nature and therefore not powered to truly detect non-inferiority of the different dosages assessed.

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REFERENCES

1. 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;326:845-851.
2. Almyroudis NG, Segal BH. Antifungal prophylaxis and therapy in patients with hematological malignancies and hematopoietic stem cell transplant recipients. *Expert Rev Anti Infect Ther*. 2010;8:1451-1466.
3. Xu SX, Shen JL, Tang XF, Feng B. Newer antifungal agents for fungal infection prevention during hematopoietic cell transplantation: a meta-analysis. *Transplant Proc*. 2013;45:407-414.
4. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010;116:5111-5118.
5. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood*. 2004;103:1527-1533.
6. Wilson DT, Drew RH, Perfect JR. Antifungal therapy for invasive fungal diseases in allogeneic stem cell transplant recipients: an update. *Mycopathologia*. 2009;168:313-327.
7. Cornely OA, Bohme A, Buchheidt D, et al. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. *Haematologica*. 2009;94:113-122.
8. Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs*. 2011;71:11-41.
9. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet*. 2007;369:1519-1527.
10. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis*. 2007;45:883-893.
11. Kohno S, Izumikawa K, Yoshida M, et al. A double-blind comparative study of the safety and efficacy of caspofungin versus micafungin in the treatment of candidiasis and aspergillosis. *Eur J Clin Microbiol Infect Dis*. 2012;32:387-397.
12. Glockner A. Treatment and prophylaxis of invasive candidiasis with anidulafungin, caspofungin and micafungin: review of the literature. *Eur J Med Res*. 2011;16:167-179.
13. van Burik JA, Ratanatharathorn V, Stepan 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.
14. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections. V 1/2012. National Comprehensive Cancer Network Web site. http://www.nccn.org. Accessed October 26, 2012.
15. Cornely OA, Aversa F, Cook P, et al. Evaluating the role of prophylaxis in the management of invasive fungal infections in patients with hematologic malignancy. *Eur J Haematol*. 2011;87:289-301.
16. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. *Clin Infect Dis*. 2011;52:e56-93.
17. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15:1143-1238.

18. Salavert M, Jarque I. Is micafungin useful in the prophylaxis of invasive fungal disease in hematological patients? *Enferm Infecc Microbiol Clin*. 2011;29(Suppl 2):43-49.
19. Hashino S, Morita L, Takahata M, et al. Administration of micafungin as prophylactic antifungal therapy in patients undergoing allogeneic stem cell transplantation. *Int J Hematol*. 2008;87:91-97.
20. Hiramatsu Y, Maeda Y, Fujii N, et al. Use of micafungin versus fluconazole for antifungal prophylaxis in neutropenic patients receiving hematopoietic stem cell transplantation. *Int J Hematol*. 2008;88:588-595.
21. Hiemenz J, Cagnoni P, Simpson D, et al. Pharmacokinetic and maximum tolerated dose study of micafungin in combination with fluconazole versus fluconazole alone for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. *Antimicrob Agents Chemother*. 2005;49:1331-1336.
22. Sirohi B, Powles RL, Chopra R, et al. A study to determine the safety profile and maximum tolerated dose of micafungin (FK463) in patients undergoing haematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2006;38(1):47–51.
23. Huang X, Chen H, Han M, et al. Multicenter, randomized, open-label study comparing the efficacy and safety of micafungin versus itraconazole for prophylaxis of invasive fungal infections in patients undergoing hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2012;18:1509-1516.
24. Vehreschild MJ, von Bergwelt-Baildon M, Tran L, et al. Feasibility and effectiveness of posaconazole prophylaxis in combination with micafungin bridging for patients undergoing allogeneic stem cell transplantation: a 6-yr analysis from the cologne cohort for neutropenic patients. *Eur J Haematol*. 2014;93:400-406.
25. De Pauw B, Walsh TJ, Donnelly JP, et al. 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*. 2008;46:1813-1821.
26. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis*. 2002;34:7-14.
27. McCoy D, Depestel DD, Carver PL. Primary antifungal prophylaxis in adult hematopoietic stem cell transplant recipients: current therapeutic concepts. *Pharmacotherapy*. 2009;29:1306-1325.
28. Sun HY, Singh N. Characterisation of breakthrough invasive mycoses in echinocandin recipients: an evidence-based review. *Int J Antimicrob Agents*. 2010;35:211-218.
29. Heimann SM, Vehreschild MJ, Cornely OA, et al. A cost and resource utilization analysis of micafungin bridging for hemato-oncological high-risk patients undergoing allogeneic stem cell transplantation. *Eur J Haematol*. 2015;94:526-531.
30. Xu SX, Shen JL, Tang XF, Feng B, Xu HQ. Newer antifungal agents micafungin and voriconazole for fungal infection prevention during hematopoietic cell transplantation: a meta-analysis. *Eur Rev Med Pharmacol Sci*. 2016;20:381-390.
31. Heimann SM, Vehreschild MJ, Meintker L, et al. 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*. 2014;16:968-974.
32. Farowski F, Vehreschild JJ, Cornely OA. Posaconazole: a next-generation triazole antifungal. *Future Microbiol*. 2007;2:231-243.
33. Cornely OA, Pappas PG, Young JA, Maddison P, Ullmann AJ. Accumulated safety data of micafungin in therapy and prophylaxis in fungal diseases. *Expert Opin Drug Saf*. 2011;10:171-183.
34. European Medicines agency. MycamineR summary of product characteristics. 2010
35. Schneeweiss S, Carver PL, Datta K, et al. Long-term risk of hepatocellular carcinoma mortality in 23220 hospitalized patients treated with micafungin or other parenteral antifungals. *J Antimicrob Chemother*. 2020;75:221-228.
36. Liu F, Wu T, Wang JB, et al. Risk factors for recurrence of invasive fungal infection during secondary antifungal prophylaxis in allogeneic hematopoietic stem cell transplant recipients. *Transpl Infect Dis*. 2013;15:243-250.
37. Sipsas NV, Kontoyiannis DP. Clinical issues regarding relapsing aspergillosis and the efficacy of secondary antifungal prophylaxis in patients with hematological malignancies. *Clin Infect Dis*. 2006;42:1584-1591.
38. Cordonnier C, Maury S, Pautas C, et al. Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. *Bone Marrow Transplant*. 2004;33:943-948.
39. Vehreschild JJ, Sieniawski M, Reuter S, et al. Efficacy of caspofungin and itraconazole as secondary antifungal prophylaxis: analysis of data from a multinational case registry. *Int J Antimicrob Agents*. 2009;34:446-450.

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