INTRODUCTION

Fluconazole was considered to be gold-standard antifungal prophylaxis for patients undergoing allogeneic HSCT for many years 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...
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 aspergillus.\(^11\) 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.

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 either 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 losing 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. 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 occurred 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). 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 pulmonary aspergillosis according to EORTC/MSG consensus definitions 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/ctcae_v3.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. Posaconazole prophylaxis had been abrogated and micafungin initiated in 173/374 (46%) patients. Sixty-two patients were switched to micafungin 100 mg and 111 patients to micafungin 50 mg based on the decision of the treating physician. Treatment duration was 4-132 days with...
|                          | 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. (%)\(^b\) |   |                                   | .033    |
| Radiation – no. (%)\(^b\) |                                   |                                   | .168    |
| any                      | 30 (27)                            | 23 (37)                           |         |
| Grade 1-2                | 53 (48)                            | 24 (39)                           | .251    |
| Grade 3-4                | 35 (31)                            | 14 (23)                           | .210    |
| Duration of neutropenia – days\(^a\) |                   |                                   | .019    |
| Median (Range)           | 20 (6-75)                          | 22 (10-83)                        |         |
| Length of stay – days\(^a\) |                                   |                                   | .114    |
| Median (Range)           | 44 (14-139)                        | 42.5 (15-153)                     |         |
| Duration of micafungin – days\(^a\) |                      |                                   | .117    |
| Median (Range)           | 21 (1-105)                         | 17 (4-131)                        |         |
| Duration of prophylaxis – days\(^a\) |                     |                                   | .092    |
| Median (Range)           | 41 (10-129)                        | 37 n                              |         |

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
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 Mica100 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.

### 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. Resistance against echinocandins is rare. 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. 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 hematological high-risk patients in a web-based non-interventional trial.

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.
In particular, the overall incidence of lung infiltrates has been discussed as a sensitive marker of prophylactic efficacy in a previous trial.\textsuperscript{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.\textsuperscript{23} 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.\textsuperscript{34} However, a recently published cohort study showed that micafungin is not associated with higher risk of HCC.\textsuperscript{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.\textsuperscript{36,37} Frequently, patients contracting an IFD early in their treatment course stay on antifungal treatment for many months.\textsuperscript{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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