JPPT | Single Center Retrospective Study

A Retrospective Analysis of Micafungin Prophylaxis in Children Under 12 Years Undergoing Chemotherapy or Hematopoietic Stem Cell Transplantation

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OBJECTIVES Literature is limited regarding ideal micafungin dosing in pediatric patients with hematologic malignancies receiving chemotherapy or hematopoietic stem cell transplantation. Micafungin is an intravenous echinocandin with activity against *Candida* and *Aspergillus* species and has a favorable safety profile compared with other antifungal classes. Our objective was to evaluate the breakthrough invasive fungal infection (IFI) rate in pediatric patients who received a prophylactic micafungin course at our institution.

METHODS A single-center, retrospective study was conducted between January 1, 2011, and July 31, 2017, to determine the IFI rate in patients receiving micafungin prophylaxis. Patients with suspected IFI were evaluated for probable or proven infection based on 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 Consensus Group invasive fungal disease definitions. Statistical analyses were descriptive.

RESULTS A total of 170 prophylactic micafungin courses from 129 unique patients ages <12 years at a median dose of 3 mg/kg daily were identified. The rate of probable or proven breakthrough IFIs was 2.4% as determined by clinical, radiologic, microbiologic, and histopathologic criteria.

CONCLUSIONS A low rate of breakthrough IFI was seen with micafungin prophylaxis that is consistent with prior published adult hematopoietic stem cell transplantation studies. Micafungin was well tolerated, with liver function test elevations being transient in most cases and thought to be related to alternative factors.

ABBREVIATIONS FDA, US Food and Drug Administration; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; IFI, invasive fungal infection; IV, intravenous; LFT, liver function test; PK, pharmacokinetics

KEYWORDS children; hematology; micafungin; oncology; pediatrics; transplant

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Introduction

Invasive fungal infections (IFIs) have been reported in pediatric patients with hematologic malignancies or pediatric recipients of allogeneic hematopoietic stem cell transplantation (HSCT), with reported rates of IFI ranging between 5% and 22% in retrospective studies.[1–5] Fungal infections can be difficult to diagnose early and can lead to significant morbidity and mortality.[6] *Candida* and *Aspergillus* species (spp) are predominant pathogens causing IFIs.[7–9] Risk factors that are associated with IFIs in pediatric oncology and HSCT patients include the patient's primary malignancy, with highest risk seen with diagnoses of acute myeloid leukemia, high-risk acute lymphoblastic leukemia, or recurrent acute leukemia. Additional factors contributing to IFI risk, similar to those seen in adults, include prolonged duration of neutropenia (absolute neutrophil count ≤500 cells/μL for ≥10 days), a high-intensity chemotherapy regimen (i.e., a regimen containing alkylating agents or antimetabolites), and prolonged use of systemic corticosteroids (≥0.3 mg/kg/day of prednisone or equivalent for >3 weeks), receipt of HSCT, and the presence of graft-versus-host disease (GVHD).[8,10]

Micafungin (Mycamine, Astellas Pharma, Northbrook, IL) is an intravenous (IV) echinocandin that inhibits β-(1,3)-D-glucan synthase and exhibits *in vitro* activity against a range of *Candida spp*, in addition to *Aspergillus spp*.[7–9] This agent is US Food and Drug Administration (FDA) approved for use in pediatric patients 4 months and older for prophylaxis of *Candida* infections in HSCT recipients. It is also approved for treatment of candidemia, acute disseminated candidiasis,

and esophageal candidiasis. The FDA-approved dosing of micafungin in pediatrics for prophylaxis is 1 mg/kg/day and for treatment ranges from 2 to 3 mg/kg/day depending on the specific indication and the patient's weight, with maximum doses consistent with the approved adult dose.[11] However, higher doses, ranging from 4 to 15 mg/kg/day, have been used in small pediatric studies, predominantly in neonatal/infant populations or older pediatric patients where dose escalation occurred during IFI treatment.[12–15]

Currently, the literature is limited regarding ideal micafungin dosing in pediatric patients ages <12 years and more narrowly in those ages <2 years who are receiving chemotherapy or HSCT. An open-label, dose escalation study in pediatric patients with febrile neutropenia who empirically started micafungin found that pharmacokinetics (PK) was linear with doses ranging from 0.5 to 3 mg/kg/day.[16] Pharmacokinetic modeling in pediatric patients has demonstrated trends that patients <10 to 15 kg and patients ages 4 months to 5 years have higher micafungin clearance in comparison with larger or older patients in 2 separate studies.[17,18]

In comparison with other classes of antifungals, echinocandins are well tolerated, with infrequent side effects that are generally limited to gastrointestinal disturbances, fever, pruritus, and rash.[9,19,20] Additionally, this agent may be preferable for patients who take other medications that may interact with azoles, have renal insufficiency limiting use of amphotericin, or are unable to take oral medications.[20]

The efficacy of micafungin prophylaxis in the adult HSCT population has been well explored, with breakthrough infection rates reported between 1.6% and 6%.[21,22] Although pediatric PK studies are reported in certain populations, in pediatric oncology and HSCT patients the efficacy of micafungin prophylaxis appears to be narrow. Two prospective studies have assessed the efficacy and safety of micafungin prophylaxis at a dose of 1 mg/kg/day (maximum 50 mg) in pediatric and adolescent patients who either received autologous HSCT in 1 study, or allogeneic HSCT in the second. Investigators determined the rate of probable IFI to be 0.9% and 1.5% in these respective populations.[23,24] The primary objective of this study was to evaluate the efficacy of micafungin for antifungal prophylaxis in pediatric oncology and HSCT patients ages <12 years. The secondary objective was to assess the hepatic safety profile of micafungin in this age group.

Materials and Methods

This was a single-center retrospective cohort study of patients ages <12 years receiving chemotherapy or HSCT who received micafungin for prophylaxis of IFI between January 1, 2011, and July 31, 2017. We included patients who received micafungin for a minimum of 7 consecutive days for antifungal prophylaxis. Patients with missing data for appropriate evaluation or those receiving micafungin for empiric management of febrile neutropenia or treatment of IFI were excluded. Prophylaxis was initiated at the onset of neutropenia or the beginning of conditioning chemotherapy in preparation for HSCT for patients undergoing HSCT or for high-risk patients. During the study period, prophylactic micafungin was generally dosed at 1 to 3 mg/kg IV in a single daily dose, with a maximum daily dose of 4 mg/kg IV. Patients 40 kg and above received prophylactic micafungin at 100 mg IV once daily, with a maximum dose of 150 mg IV once daily if clinically indicated Micafungin doses were infused during 1 hour as per manufacturer recommendations.

Patients were identified using the electronic medical record. Information collected included demographics, underlying diagnosis, micafungin dose per kg, number of doses, frequency, recorded adverse effects, laboratory data (absolute neutrophil count, platelets, serum creatinine, and liver enzymes: aspartate transaminase, alanine transaminase, total bilirubin), transplantation data (transplantation date, type, donor type), last date of chemotherapy administration, and concomitant corticosteroids. Results from radiologic studies, cultures, pathology, serum and bronchoalveolar lavage galactomannan antigen tests, and serum 1,3-β-D-glucan tests were also collected.

Patients with suspected IFI were evaluated based on 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 Consensus Group invasive fungal disease definitions.[25] Report of the breakthrough IFI rate consisted of probable or proven infection in patients receiving micafungin for prophylaxis. The severity of abnormal liver function test (LFT) results was evaluated based on Common Terminology Criteria for Adverse Events.[26] Patient and micafungin course characteristics were summarized with medians and ranges for continuous covariates, and frequency and percentage for categoric covariates. Prevalence of IFI breakthrough was described along with an exact 95% CI. Analyses were done using software R 3.4.3.

Results

A total of 768 micafungin orders were reviewed and a total of 170 courses from 129 unique patients were ultimately included for analysis (Supplemental Figure). Micafungin was administered inpatient for 159 of these courses, and 11 courses were either administered in part or completely on an outpatient basis. Baseline patient characteristics are shown in Table 1. The median age of the patients included in the study was 4 years (range, 0–11). In 153 courses (90%) the patient was <40 kg, warranting weight-based dosing of micafungin. Most patients had an underlying diagnosis of acute lymphoblastic leukemia or acute myeloid leukemia (28.2%), and additional underlying diagnoses are broken down in Table 2.

Table 1. Patient Demographics

Characteristic (N = 129 Patients)	Value
Male sex, n (%)	76 (58.9)
Diagnosis, n (%) Hematologic malignancy Solid tumor Other (e.g., immunodeficiency, bone marrow failure)	 70 (54.3) 12 (9.3) 47 (36.4)
N = 170 (courses)	
Age, median (range), yr Age <2 yr, n (%)	4 (0–11) 30 (17.6)
Weight, median (range), kg	18.3 (4.7–100.8)
Weight <40 kg, n (%)	153 (90)
HSCT recipient, n (%) Allogeneic Autologous with stem cell rescues	150 (88.2) 133 (88.6) 17 (11.3)
Prolonged steroid use (0.3 mg/kg/day prednisone equivalent for >3 wk), n (%)	22 (12.9)
Neutropenia at start of micafungin course (ANC <0.5 K/μL), n (%)	41 (24.1)

ANC, absolute neutrophil count; HSCT, hematopoietic stem cell transplant

Table 2. Underlying Diagnoses of Study Population

Diagnosis (N = 129)	n (%)
ALL	12 (9.3)
Relapsed/refractory ALL	22 (17.1)
Myeloid neoplasms	34 (26.4)
Non-Hodgkin lymphoma	2 (1.6)
Bone marrow failure	16 (12.4)
Non-malignant hematologic disorders	5 (3.9)
Severe combined immunodeficiency	11 (8.5)
Other immune deficiencies	13 (10)
Solid tumors	13 (10)
Cerebral adrenoleukodystrophy	1 (0.7)

ALL, acute lymphoblastic leukemia

Table 3. Micafungin Course Summary

Characteristic (N = 170)	HSCT Prophylaxis (n = 123)	Other Prophylaxis (n = 47)
Dose, median (range), mg/kg/day IV during 1 hr once daily Patients <40 kg Patients ≥40 kg	 3 (2–5) 150 (110–150)	 3 (1–5) 150 (50–150)
Duration of treatment, median (range), days	33 (8–131)	28 (6–131)
Dosing frequency, n (%) Every 24 hr 3 times weekly Combination	 123 (100) — —	 44 (93.6) 2 (4.3) 1 (2.1)
Reason for discontinuation, n (%) Completed therapy Switch to alternative antifungal (IV) Switch to alternative antifungal (po) Transfer to outside hospital Died	 98 (57.6) 45 (26.5) 23 (13.5) 3 (1.8) 1 (0.6)	

HSCT, hematopoietic stem cell transplant; IV, intravenous; po, oral

Micafungin indication, dosing, duration, and discontinuation information is displayed in Table 3. The median dose of micafungin in this population was 3 mg/kg/day administered once daily. Most micafungin was initiated as institutional standard prophylaxis for HSCT (123 courses; 72.4%), initiated at the start of patients' conditioning regimens. The remaining (47 courses; 27.6%) were for prophylaxis at provider discretion in patients with high-risk factors. These included patients receiving chemotherapy for a hematologic malignancy and at risk for prolonged neutropenia, diagnosis of an immunodeficiency syndrome, prolonged systemic corticosteroid use, or GVHD.

A total of 4 (2.4%; 95% CI, 0.9–6.1) individual patients had a proven breakthrough infection. Three patients developed fungemias (*Candida parapsilosis* [n = 2]; *Rhodotorula mucilaginosa* [n = 1]), and 1 patient developed a lung infection (*Aspergillus fumigatus*). All 4 patients who developed breakthrough IFIs were allogeneic HSCT recipients. Three received HSCT <30 days prior and one >2 years ago but had transplantation-related complications, including GVHD. In a total of 72 courses (42%), patients demonstrated an elevation in liver enzymes (grade 1 or above) during micafungin treatment. Of these, in 21 courses (12%) the patient had any grade 3 LFT elevation, and there was 1 isolated grade 4 aspartate transaminase elevation. All grade 3 elevations improved or resolved during micafungin therapy except in 5 courses and the single grade 4 elevation resolved during therapy. In 4 courses, patients demonstrated grade 3 LFT elevations prior to initiation of micafungin, all of which resolved during micafungin therapy.

Discussion

Studies looking at the efficacy, safety, and dosing of micafungin in children ages <12 years remain limited.

We retrospectively reviewed the use of micafungin during a 6-year period in children ages 0 to <12 years, with approximately one fifth of the patients being <2 years old at their first treatment. The median dose of micafungin was 3 mg/kg administered once daily in our study population, which is concurrent with the recommended standard at our institution for HSCT prophylaxis for most of the study period. We saw a low (2.4%) incidence of IFI with micafungin prophylaxis, which is consistent with prior published pediatric and adult studies in HSCT.[21–24] In those patients who had a breakthrough IFI, all were allogeneic HSCT recipients. This was unsurprising because this group of patients is where we as a pediatric department primarily use micafungin in addition to the known increased risk allogeneic HSCT carries for IFI, most notably due to prolonged periods of neutropenia and the potential for transplant-related complications that may result in prolonged periods of high-dose systemic corticosteroid use, such as GVHD. Higher risk of IFI has been demonstrated in patients with baseline diagnoses, including acute leukemias and inherited severe immunodeficiencies. Underlying diagnoses in the group having breakthrough IFIs in this study consisted of hematologic malignancies and syndromes or conditions resulting in immunodeficiency, which correlates with the potential increased risk for fungal infections these patients are at as well.

In considering the fungal organisms identified in the patients with breakthrough IFI, 2 of the 4 developed *Candida parapsilosis* fungemias, which parallels reports of an increasing proportion of *Candida non-albicans* strains isolated in adult oncology patients; however, this could be considered surprising given the expected activity of echinocandins toward this species.[27] The species identified in the other 2 patients with proven IFI were *Rhodotorula mucilaginosa* and *Aspergillus fumigatus*, organisms that have some level of resistance to the echinocandin class and thus would not have been optimally targeted with micafungin alone.[28,29]

Overall, micafungin was found to be generally safe, with LFT elevations being transient and thought to be related to factors such as chemotherapy conditioning regimen and sinusoidal obstruction syndrome. Grade 3 LFT elevations did not resolve in 5 patients prior to discontinuing micafungin, and further assessment was not explored. In the 2 prospective studies that have evaluated hepatic toxicity in pediatric and adolescent HSCT patients, the rates of any grade LFT elevation were reported at 8% and 45%, the latter being similar to our cohort study.[23,24] The reason for the discontinuation of micafungin was mostly due to no further need for antifungals. Patients were switched to alternative IV antifungals in about one quarter of courses. In the 23 patients switched to an alternative oral antifungal, this was in the setting of transitioning to a more reasonable regimen to administer in the outpatient setting, an element to be considered to limit extended hospital admissions and provide reasonable administration expectations for patients.

As a retrospective study, there is potential for selection bias, and there were several limitations identified within this study. During the period of patient review, patients transferred care to a local pediatric intensive care unit prior to the opening of our institutional pediatric intensive care unit in 2014, so evaluation of these patients upon transfer was not able to be completed unless they were transferred back with appropriate documentation. Also, because of a significant number of referrals at our institution, IFI history was difficult to interpret if the patient had a history of IFI that was treated at an outside hospital or in the setting of patients being transferred and continuing treatment for IFI that was initiated elsewhere. Additionally, in patients who were discharged to receive micafungin following their inpatient stay, assessment of follow-up doses was difficult to evaluate if doses were not received in our outpatient clinic and especially if patients were receiving doses at home through homecare services. Because of the homogeneity of dosing, whereby most patients received 3 mg/kg/day dosing, we were unable to evaluate the optimal dose in this study population. A recent PK/pharmacodynamic study, published following the data collection period of our current study, demonstrated that prophylactic dosing of 2 mg/kg/day should be considered to prevent *Candida spp* infections, and would optimize efficacy against *Candida albicans* when compared to the FDA-approved prophylaxis dosing.[30] Our group of patients was also extremely complex and there was a mixture of patients at higher risk and lower risk for IFI, so the external applicability of this study may be limited to centers that also see a diverse pediatric hematology/oncology population.

Thorough evaluation of concomitant medications that may contribute to hepatotoxicity was not performed and was challenging to assess given the capabilities of the electronic medical record. In the setting of this study population predominantly being HSCT patients it may have been helpful to correlate specific hepatotoxic cytoreduction regimens to elevations in LFTs seen. Based on the observation that LFT increases were often transient, and that micafungin is usually initiated at admission or when the patient becomes neutropenic, it is likely that LFT elevations in most cases were due to other causes, such as conditioning chemotherapy; however, the exact cause could not be confirmed.

Conclusions

We report that micafungin in children receiving chemotherapy or HSCT is effective for antifungal prophylaxis at a median dose of 3 mg/kg administered once daily, and no serious toxicities were identified. When used for prophylaxis, we saw a 2.4% incidence

of breakthrough IFI that is consistent with prior published pediatric and adult studies in HSCT. Micafungin was associated with LFT elevations, but they were transient, and in most cases attributed to factors such as chemotherapy conditioning and sinusoidal obstruction syndrome.

Article Information

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