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Short communication

Micafungin alone or in combination with other systemic antifungal therapies in hematopoietic stem cell transplant recipients with invasive aspergillosis

D.P. Kontoyiannis, V. Ratanatharathorn, J.-A. Young, J. Raymond, M. Laverdière, D.W. Denning, T.F. Patterson, D. Facklam, L. Kovanda, L. Arnold, W. Lau, D. Buell, K.A. Marr. Micafungin alone or in combination with other systemic antifungal therapies in hematopoietic stem cell transplant recipients with invasive aspergillosis. Transpl Infect Dis 2009: **11**: 89–93. All rights reserved

Abstract: We describe herein 98 hematopoietic stem cell transplant (HSCT) recipients with invasive aspergillosis (IA) (refractory in 83) who received micafungin either alone (8 patients) or in combination with other licensed antifungal therapies (OLAT) (90 patients). Of the 8 monotherapy patients, 4 were failing OLAT, received *de novo* micafungin, or were intolerant to prior OLAT (2 patients each). Of the 90 patients treated with combination, 7 had *de novo* IA and 83 had refractory infection. Most patients (81) had pulmonary IA, 42 (43%) had graft-versus-host disease (GVHD), and 26 (27%) were neutropenic (absolute neutrophil count <500 cells/mm^3) at onset of treatment. Successful response was seen in 25/98 (26%); an additional 12 patients achieved stable disease. Response was seen in 2/9 (22%) in *de novo* treatment, 21/87 (24%) in refractory patients, and 2/2 (100%) in toxicity failure patients. Additionally, response was seen in 22 of the 90 (24%) patients treated with combination therapy, and in 3 of 8 (38%) patients who were treated with micafungin alone. No significant differences in responses were found based on type of HSCT, GVHD status, site of IA, or *Aspergillus* species, and no significant toxicity was seen. Micafungin was well tolerated, even at high doses, and is a reasonable option for treatment of IA in this high-risk patient population.

D.P. Kontoyiannis[1], V. Ratanatharathorn[2], J.-A. Young[3], J. Raymond[4], M. Laverdière[5], D.W. Denning[6], T.F. Patterson[7], D. Facklam[8], L. Kovanda[8], L. Arnold[8], W. Lau[8], D. Buell[8], K.A. Marr[9]

[1]The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA, [2]Wayne State University, Detroit, Michigan, USA, [3]University of Minnesota, Minneapolis, Minnesota, USA, [4]Western Pennsylvania Cancer Institute, Pittsburgh, Pennsylvania, USA, [5]Hospital Maisonneuve Rosemont, Montreal, Quebec, Canada, [6]Wythenshawe Hospital and University of Manchester, Manchester, UK, [7]University of Texas HSC, San Antonio, Texas, USA, [8]Astellas Pharma US Inc., Deerfield, Illinois, USA, [9]Oregon Health and Science University, Portland, Oregon, USA

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Correspondence to:
Dimitrios P. Kontoyiannis, Department of Infectious Diseases, Infection Control and Employee Health, Unit 402, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 USA
Tel: 713 792 6237
Fax: 713 745 6839
E-mail: dkontoyi@mdanderson.org

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Invasive aspergillosis (IA) is the most common opportunistic mold infection in patients undergoing hematopoietic stem cell transplantation (HSCT) and carries a high rate of treatment failure and poor prognosis (1). Further, IA is more common and has a more severe natural history in allogeneic compared with autologous stem cell recipients, and the poorer prognosis in the former group reflects more sustained and complex immune dysfunction, especially in the setting of graft-versus-host disease (GVHD) (2). The introduction of the echinocandins, a novel class of cell-wall-active antifungals (3), has stimulated further interest in their use in combination with other agents for IA. Experience is limited with combinations of echinocandins and cell-membrane-active antifungal agents, such as azoles and polyenes, for the treatment of IA (4, 5). Therefore, we conducted an open-label, non-comparative international trial that enrolled 331 patients with IA, treated with micafungin alone or in combination with other licensed antifungal therapy from January 1999 to December 2002. The composite results of all subjects in this trial have been previously described (5). Herein we describe the experience of the subset of HSCT recipients only.

Methods

Adult and pediatric patients with proven or probable IA according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria (6) were included. Only patients with pulmonary IA could be enrolled as probable cases. Galactomannan was not a required diagnostic criterion; therefore, data on its use for defining probable IA were not obtained in this study. Exclusion criteria included the following: aspartate transaminase or alanine transaminase level >10 times the upper limit of normal, or bilirubin or alkaline phosphatase level >5 times the upper limit of normal; estimated life expectancy <5 days; a history of allergy, sensitivity, or any serious reaction to an echinocandin; or allergic bronchopulmonary aspergillosis, aspergilloma, sinus aspergillosis, or external otitis without histological evidence of invasion. Patients could have had either newly diagnosed (<48 h of systemic antifungal therapy) *de novo* IA or IA refractory to prior therapy. Refractoriness was defined as no improvement or progression of attributable signs and symptoms of IA after at least 72 h of systemic antifungal therapy. Treatment-toxicity failure was defined as intolerance to alternative antifungal therapy because of adverse events associated with the therapy.

We administered micafungin (Astellas Pharma US Inc., Deerfield, Illinois, USA) at 75 mg/day (1.5 mg/kg/day for patients weighing <40 kg) as a 1-h infusion in either an inpatient or outpatient setting, alone or in addition to the patient's current systemic antifungal regimen. The other antifungal regimen was to have remained constant for at least 72 h before the addition of micafungin, and for the duration of the treatment period. The micafungin dose could be increased in 75-mg increments after at least 5 days of treatment at the initial dose, in patients without evidence of improvement. Patients could receive micafungin for up to 90 days; extensions could be approved by the medical monitor. The primary endpoint was the global response to treatment, based on clinical, radiological, and mycological assessment at the end of therapy. We used standardized definitions for complete (i.e., resolution of all attributable signs, symptoms, and radiographic or bronchoscopic abnormalities) and partial response (i.e., major improvement of all attributable signs and symptoms, including radiographic or bronchoscopic abnormalities), and stabilization and progression of IA (5). Patients included in this efficacy analysis received at least 1 dose of micafungin and had confirmed IA, as determined by an independent expert panel (authors D.W.D., K.A.M., and T.F.P.). This panel also reviewed and confirmed all outcomes at the end of therapy. Adverse events were monitored throughout the course of therapy. Laboratory evaluations were conducted weekly during therapy and at the end of therapy.

Results

We enrolled (from 62 sites) a total of 98 HSCT patients (88 allogeneic and 10 autologous) with confirmed IA who received at least 1 dose of micafungin. Twenty-seven of these 98 were pediatric patients (<16 years). Of these patients, 9 were enrolled as having *de novo* IA, and 87 were enrolled as having refractory IA; 2 patients (1 patient each, liposomal amphotericin B [AMB] and AMB lipid complex) were enrolled as toxicity failures (defined as serum creatinine >2 times upper limit of normal) because of prior AMB-related nephrotoxicity. Eight of the 98 patients received micafungin as monotherapy: 4 experienced failure of other systemic antifungal therapy, 2 had newly diagnosed IA, and 2 did not tolerate prior AMB-based therapy. Of the remaining 90 patients who received combination therapy with micafungin, 7 had newly diagnosed IA and 83 had refractory IA. This patient population reflects the classification by the independent review. Of the 7 patients considered to have newly diagnosed IA who received combination therapy, 5 patients were considered by the investigator to be 'efficacy failures' and micafungin was added to their current treatment; 2 patients, considered by both the investigator and independent review to have newly diagnosed IA, were noted to have protocol deviations reported because of concomitant use of another antifungal during therapy with micafungin.

The majority of the patients (81) had pulmonary IA. Forty-two patients (43%) had GVHD, and 26 patients (26%) were neutropenic (absolute neutrophil count <500 cells/mm^3) at the onset of micafungin-based treatment. The most common underlying diseases were acute leukemia (54 patients), lymphoma (18 patients), and chronic leukemia (8 patients). Of the 87 patients with refractory IA, 73 (84%) had progression of IA at the time of enrollment, and 12 (14%) had stable IA; the status of the infection at baseline was indeterminate in 2 patients. The mean ± standard deviation (SD) length of infection at entry in patients with refractory IA was 36.8 ± 62.7 days.

The majority of the patients with refractory IA (73) received prior lipid formulations of AMB (L-AMB; mean ± SD duration, 27 ± 38 days; mean ± SD daily dose, 6.0 ± 2.6 mg/kg). An additional 30 patients had received conventional AMB, and 29 had received itraconazole. Only 4 patients had received voriconazole and 3 patients had received posaconazole before entry, because these agents were investigational at the time of this trial. Of note, patients may have been on more than one antifungal before starting the study. The mean ± SD dose of micafungin was 105 ± 60 mg/day (range, 11–292 mg/day), and 57 patients (58%) underwent micafungin dose escalation during the study. The mean ± SD duration of treatment with mica-

fungin was 51 ± 60 days (range, 2–425 days). Fourteen patients switched to intermittent dosing after an average of 78 days (range, 8–296 days) of daily dosing. The average duration of intermittent dosing was 66 days (range, 12–383).

The overall (complete plus partial) response rate was 26% (25/98 patients). An additional 12 patients had stable infections. A response to treatment was seen in 22% (2/9) of the patients in the *de novo* treatment group, 24% (21/87) in the refractory IA group, 100% (2/2) in the toxicity failure group, 24% (22/90) in the combination therapy group, and 38% (3/8) in the micafungin-alone group. We observed no significant differences in response according to the type of transplant, site of infection, or infecting *Aspergillus* species (Table 1). Isolates were not systematically collected for this study; therefore, minimum inhibitory concentration (MIC) data are limited, available for only 35 patients of 331 overall. Further, the role of MIC testing in determining outcome in IA is a matter of debate, with no consensus to date.

Drug-related adverse events were rare, occurring in no more than 6% of patients. Related adverse events that occurred in >2% of patients included nausea, increased alanine aminotransferase, vomiting, hyperbilirubinemia, and arthralgia. We found no evidence of any significant toxic effects when we administered micafungin in combination with primarily an AMB product.

Treatment success rates at end of therapy

Patient group	Response rate No./total no. (%)	*P*-value[1]
Overall	25/98 (26)	
Complete	5/25 (5)	
Partial	20/25 (20)	
De novo	2/9 (22)	
Monotherapy	1/2 (50)	
Combination therapy	1/7 (14)	
Refractory	21/87 (24)	
Monotherapy	0/4 (0)	
Combination	21/83 (25)	
Toxicity failure (monotherapy)	2/2 (100)	
All monotherapy (*de novo*, refractory, toxicity failure)	3/8 (38)	
All combination therapy (*de novo*, refractory)	22/90 (24)	
Refractory IA/combination therapy with micafungin		
L-AMB	15/63 (24)	
Conventional AMB	3/10 (30)	
L-AMB + itraconazole	1/8 (13)	
Conventional AMB + itraconazole	1/2 (50)	
L-AMB + fluconazole	0/2 (0)	
Itraconazole	1/1 (100)	
Fluconazole + itraconazole	0/1 (0)	
L-AMB + voriconazole	0/1 (0)	
Subgroups		
Pediatric	5/27 (19)	
Adult	20/71 (28)	
Allogeneic transplant	22/88 (25)	0.71
Autologous/syngeneic transplant	3/10 (30)	
GVHD absent[2]	12/49 (24)	1.0
GVHD present	10/42 (24)	
Grade I	2/8 (25)	
Grade II	3/15 (20)	
Grade III	4/13 (31)	
Grade IV	1/6 (17)	
Not neutropenic at baseline	19/72 (26)	0.8
Neutropenic at baseline	6/26 (23)	
Pulmonary infection	20/81 (25)	
Disseminated infection	3/12 (25)	
Proven infection	17/66 (26)	
Probable infection (lung)	8/32 (25)	
Infection stable at baseline[3]	3/12 (25)	

Discussion

Combination antifungal therapy for IA has become a subject of debate because of the poor responses to single agents, especially in the HSCT setting (7), and high cost of treatment. Studies of combination antifungal therapy are challenging to perform because of the complexity and heterogeneity of patients with IA, relative infrequency of IA, and lack of reliable laboratory surrogate markers for monitoring the clinical outcome of antifungal combinations (7). However, emerging uncontrolled data about antifungal combinations for IA indicate that some (4, 7–12) but not all (13, 14) combinations are helpful for IA. Specifically, prospective (8) and retrospective (9) studies examining the efficacy of combination therapy for IA with caspofungin and voriconazole given as primary or salvage therapy suggested that this combination may be clinically beneficial. However, because voriconazole has become the preferred antifungal in primary therapy for IA (15), one cannot assume that the combination of an echinocandin and a triazole is of value in patients who experience failure of voriconazole-based monotherapy or in breakthrough to mold-active triazole-based prophylaxis (e.g., voriconazole, itraconazole, posaconazole) for IA. These scenarios invite

Table 1 Continued

Patient group	Response rate No./total no. (%)	*P*-value[1]
Infection progressing at baseline	18/73 (25)	
Infecting species[4]		
Aspergillus fumigatus	17/53 (32)	0.16
Aspergillus non-*fumigatus*	9/45 (20)	
Aspergillus species NOS	5/25 (20)	
Aspergillus flavus	2/13 (15)	
Aspergillus nidulans	1/1 (100)	
Aspergillus versicolor	1/1 (100)	

No., number; IA, invasive aspergillosis; GVHD, graft-versus-host disease; NOS, non-specified; AMB, amphotericin B; L-AMB, lipid formulations of amphotericin B.
Overall response = complete and partial response rates combined.
[1]*P*-value calculated by χ^2 test.
[2]GVHD status was recorded for all patients; 49 patients had no GVHD; 42 patients had GVHD, and in 7 patients the GVHD assessment was missing.
[3]Assessments on 11 patients were not applicable (9 *de novo* and 2 toxicity failure) and 2 patients were indeterminate, as assessed by the independent review.
[4]Patients may have been diagnosed with infections of more than 1 *Aspergillus* species.

Table 1

examination of the strategy of combining an echinocandin with L-AMB for refractory IA. The potential value of this strategy is suggested by both a recent open-label small prospective study (10) and single-institution retrospective studies (11, 12).

To our knowledge this is the largest reported prospective, non-comparative experience with the use of an echinocandin, micafungin, given either alone or in combination with other systemic antifungal therapies for documented IA in a relatively homogeneous patient population: adult and pediatric HSCT recipients. Patients received micafungin in a variety of clinical scenarios: primary therapy, salvage therapy, monotherapy, and combination therapy. The relatively low overall response rate (26%) suggests that our trial included truly salvage cases. In fact, the majority of the patients were experiencing failure of prolonged maximal systemic therapy, primarily with L-AMB, at the time of study entry. Because this trial took place before the availability of voriconazole, the combination therapy generally consisted of micafungin and L-AMB; nevertheless, we observed treatment successes in high-risk patients, i.e., those with GVHD, neutropenia, or disseminated IA. Although the results are not directly comparable, a previous retrospective study of patients undergoing HSCT who received caspofungin plus L-AMB for IA that was refractory to L-AMB alone showed similarly low response rates (12). Finally, micafungin was well tolerated in the present study, with minimal evidence of treatment-emergent adverse events, even in very ill patients. This lack of adverse events is not surprising and is consistent with the remarkable safety of the echinocandins and their fungus-specific mechanism of action (3).

Our study had several limitations because of its small size and lack of a comparative group. Thus, bias caused by the selection of survivors of the less acute forms of IA and the fact that the choice of treatment combination and decisions about duration of therapy were not controlled, but made according to each physician's discretion, are significant confounding factors. Furthermore, we did not stratify responses according to the number of previous antifungal therapy failures because of the small number of subjects. Finally, our study did not include a long follow-up period that would have allowed estimation of the risk of relapse of IA in the setting of subsequent intensification of immunosuppression.

In conclusion, our experience supports the need for randomized trials of echinocandins, such as micafungin plus either L-AMB or triazoles in patients undergoing HSCT, a setting in which outcomes of patients receiving monotherapy have been historically poor. Until these results become available, our experience suggests that micafungin, given either alone or in combination with other agents, is a reasonable option for IA in this high-risk patient population.

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Astellas Canada, Merck Frosst Canada; and is in the speaker's bureau for Pfizer Canada, Astellas Canada, and Merck Frosst Canada; T.F.P. has had grant support from Astellas Pharma US Inc., Enzon, Nektar Therapeutics, Merck & Co., Pfizer Inc., and Schering-Plough Corporation, and has been a consultant for Astellas Pharma US Inc., Basilea, Merck & Co., Nektar Therapeutics, Pfizer Inc., Schering-Plough Corporation, and Stiefel Laboratories Inc., and has been on the speaker's bureau for Merck & Co. and Pfizer Inc.; J.-A.Y. has received research support and honoraria from Schering-Plough, Pfizer, Astellas Pharma Inc., Enzon Pharmaceuticals, and Merck and Co. Inc.; K.A.M. has been a consultant and member of advisory boards for: Astellas, Basilea, Enzon, Merck, Pfizer, and Schering Plough; D.F., L.K., L.A., W.L., and D.B. are Astellas employees; V.R. and J.R. report no potential conflicts.

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