Initial Treatment of Cancer Patients with Fluconazole-Susceptible Dose-Dependent *Candida glabrata* Fungemia: Better Outcome with an Echinocandin or Polyene Compared to an Azole?

Audrey Le,^a Dimitrios Farmakiotis,^b Jeffrey J. Tarrand,^c Dimitrios P. Kontoyiannis^d

Department of Internal Medicine^a and Division of Infectious Diseases,^b Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA; Departments of Laboratory Medicine^c and Infectious Diseases, Infection Control and Employee Health,^d the University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

ABSTRACT The 28-day crude mortality rate in 68 cancer patients with fluconazole-susceptible dose-dependent *Candida glabrata* fungemia started on treatment (within 48 h after blood culture collection) with an echinocandin or liposomal amphotericin-B was better (30%) than those treated with azole monotherapy (52%) ($P = 0.07$). After adjusting for confounders, azole monotherapy also was associated with worse 28-day survival (hazard ratio, 3.8; $P = 0.003$).

KEYWORDS *Candida glabrata*, azole monotherapy, echinocandin, candidemia, polyenes

Candida glabrata is one of the most common *Candida* species causing invasive disease and the main species exhibiting antifungal resistance, including multidrug resistance (resistance to ≥ 2 classes of antifungals) (1, 2). Cancer patients are particularly vulnerable to systemic infection caused by *C. glabrata* (2, 3). *C. glabrata* clinical isolates often exhibit intrinsically decreased susceptibility to azoles or, if they are initially susceptible, development of inducible multiazole resistance (4, 5). Yet, there are limited data comparing clinical outcomes of cancer patients with *C. glabrata* fungemia treated initially with an azole as opposed to an echinocandin or polyene. Current recommendations favor echinocandins as first-line empirical therapy for candidemia (6, 7). However, a recent study showed that initial treatment of patients with *C. glabrata* fungemia with fluconazole was not associated with worse clinical outcomes than those associated with an echinocandin or polyene (8). We compared all-cause mortality between cancer patients with *C. glabrata* fungemia treated initially (within 48 h after blood culture collection) with an azole to those treated with an echinocandin or polyene, after exclusion of patients with azole-resistant *C. glabrata* strains.

We performed a retrospective review of clinical and laboratory data for patients with *C. glabrata* fungemia caused by strains with dose-dependent *in vitro* susceptibility to fluconazole (MIC by broth microdilution, ≤ 32 mg/liter) treated at the M.D. Anderson Cancer Center in Houston, TX, between March 2005 and September 2013, as previously described (2, 9). We excluded patients with a fluconazole-resistant strain (MIC, > 32 mg/liter) (10) and those who did not receive antifungal treatment within the first 48 h after the collection of blood for culture.

Continuous variables were compared using Student's *t* test or the Mann-Whitney U criterion for variables that were not normally distributed. Categorical variables were compared using the χ^2 or Fisher exact test (expected frequency, < 5). Twenty-eight-day

Received 29 March 2017 Returned for modification 16 May 2017 Accepted 29 May 2017

Accepted manuscript posted online 5 June 2017

Citation Le A, Farmakiotis D, Tarrand JJ, Kontoyiannis DP. 2017. Initial treatment of cancer patients with fluconazole-susceptible dose-dependent *Candida glabrata* fungemia: better outcome with an echinocandin or polyene compared to an azole? Antimicrob Agents Chemother 61:e00631-17. <https://doi.org/10.1128/AAC.00631-17>.

Copyright © 2017 American Society for Microbiology. All Rights Reserved.

Address correspondence to Dimitrios Farmakiotis, dimitrios.farmakiotis@lifespan.org, or Dimitrios P. Kontoyiannis, dkontoyi@mdanderson.org.

FIG 1 Kaplan-Meier curves comparing 28-day all-cause mortality between cancer patients with fluconazole-susceptible dose-dependent *C. glabrata* fungemia treated within the first 48 h with azole monotherapy after the collection of blood for culture and those treated with an echinocandin or polyene.

survival was analyzed using the log-rank test and Cox regression. The proportional hazards assumption was tested graphically and by building time-dependent variables. Clinically relevant parameters (univariate $P \leq 0.2$) were included at model entry and retained in the final model if the P value was <0.05 ; we retained the Acute Physiology and Chronic Health Evaluation II (APACHE II) score in the final model, given the trend for significance ($P = 0.08$) (Fig. 1).

We studied 68 patients. Twenty-five patients initially received azole monotherapy (20 received fluconazole [200 to 400 mg daily, 2.2 to 9 mg/kg, dose (mg)-to-MIC (mg/liter) ratio, ≥ 12.5], 4 received voriconazole, and 1 received posaconazole), and 43 patients received an echinocandin ($n = 39$), liposomal amphotericin-B ($n = 1$), or both ($n = 3$). Clinical and basic laboratory characteristics are summarized in Table 1. Most patients had a solid tumor and were not neutropenic at the time of the collection of blood for culture. More patients who received initial treatment with an echinocandin or polyene were in the intensive care unit than were those initially treated with an azole. The 28-day all-cause mortality rate was 52% (13/25) for initial azole monotherapy and 30% (13/43) for treatment with an echinocandin or polyene ($P = 0.07$). The 14-day all-cause mortality rate was 32% (8/25) for initial azole monotherapy and 19% (8/43) for treatment with an echinocandin or polyene ($P = 0.2$). After adjusting for confounders, azole monotherapy was associated with worse 28-day survival (adjusted hazard ratio [HR], 3.8; 95% confidence interval [CI], 1.6 to 8.9; $P = 0.003$) (Table 2, Fig. 1) than treatment with an echinocandin or polyene. Among the 20 patients initially treated with fluconazole, we did not find any association between mortality and dose.

To our knowledge, this is the first study of cancer patients with *C. glabrata* fungemia, all of whom received an antifungal agent within 48 h after the collection of blood for culture, after the exclusion of patients with a fluconazole-resistant strain. We found higher survival rates after initial treatment with an echinocandin or polyene than after initial treatment with azole monotherapy (Table 2, Fig. 1).

Our findings are in contrast with those reported in another study of 69 patients with *C. glabrata* fungemia, where clinical outcomes at day 14 were comparable between patients initially treated with fluconazole and those treated with an echinocandin or polyene, after multivariate adjustments, including propensity score (8). However, in that study, more than half of the patients initially treated with fluconazole were changed to

TABLE 1 Baseline parameters

Parameter ^a	Azole monotherapy (N = 25) ^b	Echinocandin or polyene (N = 43) ^b	P
Gender (F)	11 (44)	22 (51)	0.6
Age (yrs)	57 ± 14	54 ± 15	0.4
Acute leukemia	3 (12)	7 (16)	0.6
HSCT	4 (16)	2 (5)	0.1
ANC < 500/μl	4 (16)	10 (23)	0.5
ALC < 100/μl	4 (16)	13 (30)	0.2
AMC < 100/μl	7 (28)	14 (33)	0.7
ICU	7 (28)	23 (54)	0.04
APACHE II score	14 ± 7	15 ± 6	0.4
Fever (temp > 100.4°F)	12 (48)	21 (49)	0.9
Mixed bloodstream infection	3 (12)	8 (19)	0.5
Central line-related candidemia ^c	12 (48)	23 (54)	0.7
Early ^d central line removal	6 (24)	10 (23)	0.7
Diabetes	4 (16)	6 (14)	0.8
CKD	6 (24)	7 (16)	0.4
AKI	6 (24)	21 (49)	0.04
28-Day all-cause mortality	13 (52)	13 (30)	0.07

^aAbbreviations: HSCT, hematopoietic stem cell transplantation; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; CKD, chronic kidney disease; AKI, acute kidney injury.

^bValues are number (percentage) or mean ± SD.

^cColony count in a blood culture obtained via a central venous catheter (CVC) at least 5-fold greater than the colony count in a peripheral blood culture or a positive catheter tip culture.

^dWithin 48 h after collection of blood for culture.

a different antifungal within a median of 3 days. In two other studies, choice of antifungal was not associated with all-cause mortality differences among patients with *C. glabrata*, but the use of echinocandins led to higher rates of treatment success (clinical improvement and resolution of candidemia) compared to azoles or polyenes (11) and compared to fluconazole (12). It should be noted, though, that none of those studies focused exclusively on cancer patients, and mortality rates were significantly higher in our cohort than in the others, reflecting the severely immunocompromised patient population included in our study.

Our report has limitations that should be taken into consideration in the design of future studies. First, it was a small single-center retrospective case series. Second, we did not provide information on use of azole prophylaxis. Third, we did not capture microbiologic outcomes, recurrent or persistent candidemia, or development of resistance while on treatment. Last, none of the patients received high-dose fluconazole (800 mg daily for normal renal function), as recommended for *C. glabrata* infection (6), contrary to the study by Puig-Asensio et al., where 85% of patients received a high fluconazole dose, and no difference was observed between initial treatment with fluconazole and initial treatment with an echinocandin or polyene (8).

In conclusion, we observed increased all-cause mortality with initial azole mono-

TABLE 2 Factors associated with 28-day (from the day of candidemia, i.e., of positive blood culture collection) all-cause mortality in cancer patients with fluconazole-susceptible dose-dependent *C. glabrata* fungemia^a

Parameters	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
AMC < 100/μl	2.65	1.22–5.74	0.014	3.94	1.69–9.19	0.001
ICU	1.97	0.9–4.29	0.088	2.95	1.15–7.6	0.025
APACHE II score (per unit)	1.06	1–1.13	0.04	1.06	0.99–1.13	0.08
Fever (temp > 100.4°F)	0.48	0.21–1.08	0.074			
Mixed bloodstream infection	2.7	1.13–6.47	0.03			
Azole monotherapy	2.08	0.98–2.12	0.06	3.77	1.59–8.9	0.003

^aAbbreviations: HR, hazard ratio; CI, confidence interval; AMC, absolute monocyte count; ICU, intensive care unit; APACHE, Acute Physiology And Chronic Health Evaluation; T, temperature.

therapy compared to that with early treatment with an echinocandin or polyene in cancer patients with *C. glabrata* fungemia caused by a strain with dose-dependent *in vitro* susceptibility to fluconazole and after adjustment for confounders. Our findings provide evidence against the initial use of azole monotherapy in cancer patients with *C. glabrata* fungemia, further supporting recent guidelines (6, 7).

REFERENCES

- Alexander BD, Johnson MD, Pfeiffer CD, Jimenez-Ortigosa C, Catania J, Booker R, Castanheira M, Messer SA, Perlin DS, Pfaller MA. 2013. Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. *Clin Infect Dis* 56:1724–1732. <https://doi.org/10.1093/cid/cit136>.
- Farmakiotis D, Tarrand JJ, Kontoyiannis DP. 2014. Drug-resistant *Candida glabrata* infection in cancer patients. *Emerg Infect Dis* 20:1833–1840. <https://doi.org/10.3201/eid2011.140685>.
- Hachem R, Hanna H, Kontoyiannis D, Jiang Y, Raad I. 2008. The changing epidemiology of invasive candidiasis: *Candida glabrata* and *Candida krusei* as the leading causes of candidemia in hematologic malignancy. *Cancer* 112:2493–2499. <https://doi.org/10.1002/cncr.23466>.
- Rodrigues CF, Silva S, Henriques H. 2013. *Candida glabrata*: a review of its features and resistance. *Eur J Clin Microbiol Infect Dis* 33:673–688.
- Thakur JK, Arthanari H, Yang F, Pan SJ, Fan X, Breger J, Frueh DP, Gulshan K, Li DK, Mylonakis E, Struhl K, Moye-Rowley WS, Cormack BP, Wagner G, Naar AM. 2008. A nuclear receptor-like pathway regulating multidrug resistance in fungi. *Nature* 452:604–609. <https://doi.org/10.1038/nature06836>.
- Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. 2016. Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 62:409–417. <https://doi.org/10.1093/cid/civ1194>.
- Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, Meersseman W, Akova M, Arendrup MC, Arikan-Akdagli S, Bille J, Castagnola E, Cuenca-Estrella M, Donnelly JP, Groll AH, Herbrecht R, Hope WW, Jensen HE, Lass-Flörl C, Petrikos G, Richardson MD, Roilides E, Verweij PE, Viscoli C, Ullmann AJ; ESCMID Fungal Infection Study Group. 2012. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: nonneutropenic adult patients. *Clin Microbiol Infect* 18: 19–37. <https://doi.org/10.1111/1469-0691.12039>.
- Puig-Asensio M, Fernandez-Ruiz M, Aguado JM, Lora-Pablos D, Guinea J, Martin-Davila P, Cuenca-Estrella M, Almirante B. 2016. Propensity score analysis of the role of initial antifungal therapy in the outcome of *Candida glabrata* bloodstream infection. *Antimicrob Agents Chemother* 60:3291–3300. <https://doi.org/10.1128/AAC.00195-16>.
- Farmakiotis D, Kyvernitakis A, Tarrand JJ, Kontoyiannis DP. 2015. Early initiation of appropriate treatment is associated with increased survival in cancer patients with *Candida glabrata* fungemia: a potential benefit from infectious disease consultation. *Clin Microbiol Infect* 21:79–86. <https://doi.org/10.1016/j.cmi.2014.07.006>.
- CLSI. 2012. Reference method for broth dilution antifungal susceptibility testing of yeasts. Fourth Informational Supplement, M27-S4. CLSI, Wayne, Philadelphia.
- Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, Sobel JD, Pappas PG, Kullberg BJ; Mycoses Study Group. 2012. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clin Infect Dis* 54:1110–1122. <https://doi.org/10.1093/cid/cis021>.
- Eschenauer GA, Carver PL, Lin SW, Klinker KP, Chen YC, Potoski BA, Shields RK, Clancy CJ, Nguyen MH, Lam SW. 2013. Fluconazole versus an echinocandin for *Candida glabrata* fungemia: a retrospective cohort study. *J Antimicrob Chemother* 68:922–926. <https://doi.org/10.1093/jac/dks482>.