AAC Journals.ASM.org

Risk for Invasive Fungal Infections during Acute Myeloid Leukemia Induction Therapy: a True Association with Echinocandins?

Bernard L. Marini,[a] Anthony J. Perissinotti,[a] Angela M. Huang,[b] David G. Frame,[a] Daniel R. Kaul[c]

Department of Pharmacy, University of Michigan Health System, Ann Arbor, Michigan, USA[a]; Department of Pharmacy, Froedtert & Medical College of Wisconsin, Milwaukee, Wisconsin, USA[b]; Department of Internal Medicine, Division of Infectious Diseases, University of Michigan Health System and Medical School, Ann Arbor, Michigan, USA[c]

We read the report by Gomes and colleagues characterizing the incidence of invasive fungal infections (IFIs) in patients with acute myeloid leukemia (AML) during remission induction chemotherapy (1). Given the high density of IFIs in the first 42 days after induction chemotherapy, as well as a randomized prospective trial showing the benefit of posaconazole prophylaxis in patients with AML, we agree that mold-active prophylaxis is most useful during this period (1, 2). However, this conclusion is not supported by the Gomes et al. article, as the rate of IFIs was no different in the fluconazole group. It is interesting that receipt of echinocandins (ECs) was associated with an increase in IFIs; however, there are many other potential explanations for this association that must be given due attention.

In the aforementioned study, rates of IFIs were reported as the incidence per 1,000 prophylaxis days (1). From Fig. 1 in reference 1, it is clear that anti-*Aspergillus* azole antifungals were evenly distributed throughout the 120 days postchemotherapy. In contrast, EC use was concentrated in the first 30 days postchemotherapy (1). It is well accepted that prolonged and profound neutropenia, typically seen in the first 30 days after induction chemotherapy, is associated with IFIs (3). The use of anti-*Aspergillus* azole antifungals during the nonneutropenic, low-risk period may have diluted the rate of IFIs associated with these agents and skewed the results against EC-based prophylaxis.

The authors acknowledge that the choice of primary antifungal prophylaxis (PAP) was left to the discretion of the treating hematologist (1). This inherent selection bias must be emphasized. EC-based prophylaxis is often utilized in patients who cannot tolerate oral therapy, typically due to severe mucositis related to intensive induction chemotherapy. Disruption of the intestinal tract, whether due to intensive chemotherapy or other comorbidities, is a major risk factor for the development of IFIs due to *Candida* spp. (3–6). ECs also often replace azoles in patients with liver dysfunction or in those receiving chemotherapy that may also cause hepatic injury. Patients with liver disease are at high risk for IFIs, including *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., and *Coccidioides* spp. (7, 8). In addition, compared to ECs, more patients discontinued anti-*Aspergillus* azoles due to adverse events (1). It is likely that these patients were then started on ECs, potentially enriching the EC prophylaxis group with patients with baseline toxicities and greater comorbidities. Inability to tolerate oral medications, switching to EC prophylaxis due to toxicity, and liver disease are also likely surrogate markers for severity of illness, another predictor of IFIs (9, 10). The lowest rate of IFI in this study was actually seen in the fluconazole group (Fig. 3), further reinforcing the importance of selection bias.

Although Gomes and colleagues found that 6/7 culture-positive IFIs were caused by fungi innately resistant or sporadically nonsusceptible to ECs, no MICs were reported, and overall, only 2/14 IFIs represent documented infections by organisms innately resistant *in vitro* to ECs (*Geotrichum capitatum* and *Paecilomyces* spp.) (1). Additionally, ECs have been shown to be not inferior to itraconazole, an anti-*Aspergillus* azole, for prophylaxis in patients with AML (11).

Baseline characteristics, specific chemotherapy regimens received, treatment response, and the aforementioned covariates should be reported and accounted for in the future multivariate analysis; however, the inherent limitations of a retrospective analysis in this population may still limit the applicability of these results to clinical practice. Without randomized controlled trials demonstrating a clear difference in rates of IFIs with ECs and anti-*Aspergillus* azole antifungals, it is difficult to support the conclusion that ECs may be inferior to anti-*Aspergillus* azole antifungals as PAP in patients receiving induction chemotherapy for AML.

REFERENCES

1. **Gomes MZR, Mulanovich VE, Jiang Y, Lewis RE, Kontoyiannis DP.** 2014. Incidence density of invasive fungal infections during primary antifungal prophylaxis in newly diagnosed acute myeloid leukemia patients in a tertiary cancer center, 2009 to 2011. Antimicrob. Agents Chemother. **58:**865–873. http://dx.doi.org/10.1128/AAC.01525-13.
2. **Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D.** 2007. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N. Engl. J. Med. **356:**348–359. http://dx.doi.org/10.1056/NEJMoa061094.
3. **Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR, Infectious Diseases Society of America.** 2011. 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. **52:**e56–e93. http://dx.doi.org/10.1093/cid/cir073.
4. **Bow EJ, Loewen R, Cheang MS, Shore TB, Rubinger M, Schacter B.** 1997. Cytotoxic therapy-induced D-xylose malabsorption and invasive infection during remission-induction therapy for acute myeloid leukemia in adults. J. Clin. Oncol. **15:**2254–2261.
5. **Blijlevens NM, Donnelly JP, de Pauw BE.** 2002. Impaired gut function as risk factor for invasive candidiasis in neutropenic patients. Br. J. Haematol. **117:**259–264. http://dx.doi.org/10.1046/j.1365-2141.2002.03394.x.
6. **Nucci M, Anaissie E.** 2001. Revisiting the source of candidemia: skin or gut? Clin. Infect. Dis. **33:**1959–1967. http://dx.doi.org/10.1086/323759.
7. **Cheruvattath R, Balan V.** 2007. Infections in patients with end-stage liver

Address correspondence to Bernard L. Marini, bernmari@med.umich.edu.

For the author reply, see doi:10.1128/AAC.03224-14.

doi:10.1128/AAC.03044-14

disease. J. Clin. Gastroenterol. **41:**403–411. http://dx.doi.org/10.1097/01.mcg.0000248018.08515.f9.

8. **Rolando N, Harvey F, Brahm J, Philpott-Howard J, Alexander G, Casewell M, Fagan E, Williams R.** 1991. Fungal infection: a common, unrecognised complication of acute liver failure. J. Hepatol. **12:**1–9. http://dx.doi.org/10.1016/0168-8278(91)90900-V.
9. **Ostrosky-Zeichner L, Pappas PG.** 2006. Invasive candidiasis in the intensive care unit. Crit. Care Med. **34:**857–863. http://dx.doi.org/10.1097/01.CCM.0000201897.78123.44.
10. **Muskett H, Shahin J, Eyres G, Harvey S, Rowan K, Harrison D.** 2011. Risk factors for invasive fungal disease in critically ill adult patients: a systematic review. Crit. Care **15:**R287. http://dx.doi.org/10.1186/cc10574.
11. **Mattiuzzi GN, Alvarado G, Giles FJ, Ostrosky-Zeichner L, Cortes J, O'brien S, Verstovsek S, Faderl S, Zhou X, Raad II, Bekele BN, Leitz GJ, Lopez-Roman I, Estey EH.** 2006. Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies. Antimicrob. Agents Chemother. **50:**143–147. http://dx.doi.org/10.1128/AAC.50.1.143-147.2006.