

Effectiveness of Primary Anti-*Aspergillus* Prophylaxis during Remission Induction Chemotherapy of Acute Myeloid Leukemia

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Although antifungal prophylaxis is frequently administered to patients with acute myeloid leukemia (AML) during remission-induction chemotherapy (RIC), its impact on reducing invasive fungal infections (IFIs) outside clinical trials is rarely reported. We performed a retrospective observational study to identify risk factors for development of IFIs (definite or probable, using revised European Organization for Research and Treatment of Cancer [EORTC] criteria) and all-cause mortality in a cohort of 152 AML patients receiving RIC (2009 to 2011). We also compared rates of IFI and mortality in patients who received echinocandin versus anti-*Aspergillus* azole (voriconazole or posaconazole) prophylaxis during the first 120 days of RIC. In multivariate analysis, clofarabine-based RIC (hazard ratio [HR], 3.5; 95% confidence interval [CI], 1.5 to 8.3; $P = 0.004$) and echinocandin prophylaxis (HR, 4.6; 95% CI, 1.8 to 11.9; $P = 0.002$) were independently associated with higher rates of IFI rates during RIC. Subsequent analysis failed to identify any malignancy- or chemotherapy-related covariates linked to echinocandin prophylaxis that accounted for the higher rates of breakthrough IFI. Although the possibility of other confounding variables cannot be excluded, our findings suggest that echinocandin-based prophylaxis during RIC for AML may be associated with a higher risk of breakthrough IFI.

Patients with acute myeloid leukemia (AML) undergoing remission-induction chemotherapy (RIC) are among those in the highest risk group for developing invasive fungal infections (IFIs), especially mold infections (1–3). However, the optimal strategy for using antifungal prophylaxis in this population (i.e., which drug should be administered and whether it should be a broad- or narrow-spectrum drug) continues to be debated and often differs from one treatment center to the next (4–7).

Recently we reported on the incidence density of documented IFIs (definite or probable; revised European Organization for Research and Treatment of Cancer [EORTC] and Mycoses Study Group [MSG] criteria) (8) in a contemporary cohort of patients with newly diagnosed AML who received primary antifungal prophylaxis (PAP) during RIC (3). Despite the frequent use of voriconazole or posaconazole prophylaxis (72% of evaluated cases), the incidence density of documented IFIs was 2.0 infections per 1,000 prophylaxis days, and the majority of breakthrough infections were caused by invasive molds (3). Importantly, in this epidemiological study we also observed a higher incidence density of breakthrough IFI among patients receiving an echinocandin as primary antifungal prophylaxis. As several confounding variables may influence the risk for breakthrough IFI independently of the type of prophylaxis selected, we examined whether specific patient risk factors that are independent of echinocandin use may explain the higher rates of breakthrough IFI documented among AML patients undergoing RIC.

MATERIALS AND METHODS

Study designs and patients. We performed a retrospective, observational study to investigate predictive factors for documented IFIs and death within 120 days of starting remission induction chemotherapy (RIC) in a cohort of 152 adult (18 years of age and older) patients with newly diagnosed AML. The study population was drawn from consecutive unselected patients at the University of Texas MD Anderson Cancer Center who were admitted during 2009 to 2011 for RIC. All patients were prescribed antifungal prophylaxis during their treatment (3). We excluded

patients with a history of prior stem cell transplantation (SCT) or patients who received transplantation within 120 days of the first admission. Details concerning the study population and variable definitions have been previously reported (3) and are summarized as supplemental information (see File S1 in the supplemental material). This observational study was approved by the MD Anderson Institutional Review Board Committee.

Two analyses were performed to evaluate risk factors associated with the development of IFI and, as a secondary endpoint, all-cause mortality following initiation of RIC. First, we compared malignancy-, chemotherapy-, and infection-related risk factors in patients who developed IFIs versus patients who were IFI free at 120 days following the initiation of RIC. We then compared risk factors for mortality at 120 days. Patients were excluded from the analysis if they did not complete RIC in the hospital ($n = 6$) or received only fluconazole prophylaxis ($n = 12$). The drug, dose, and duration of primary antifungal prophylaxis were determined by the treating hematologist and were not standardized per an institutional prophylaxis protocol for AML patients.

After screening disease- and chemotherapy-related covariates associated with breakthrough IFI and all-cause mortality, we then compared risk factors for IFI in patients who received anti-*Aspergillus* triazoles (voriconazole or posaconazole) versus echinocandin prophylaxis. For the purposes of this analysis, patients must have received the anti-*Aspergillus* triazole or echinocandin for more than two consecutive days before

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switching to another antifungal agent. Patients were not included in the analysis if they had received multiple *Aspergillus*-active therapies or fluconazole-only prophylaxis or had not been hospitalized during the first 42 days of RIC. We did not exclude patients if they had a period of overlapping fluconazole prophylaxis with either a mold-active triazole or an echinocandin.

Data collection. Data were extracted from patients' electronic medical records and collected until diagnosis of an IFI, loss to follow-up, death, or completion of 120 days post-RIC, whichever came first.

Information regarding antifungal use, including the type and duration of antifungal drugs used for prophylaxis, from the institutional pharmacy database was confirmed and matched with the electronic patient medical record. Candidate predictive variables were screened for their association with documented IFI and their frequency among patients receiving echinocandin versus voriconazole or posaconazole prophylaxis. These variables included the following: baseline disease characteristics, admission to the high-efficiency particulate air (HEPA) filter room, the type of immunosuppressive chemotherapy regimen received during first remission-induction chemotherapy, episodes and duration of hospitalization and neutropenia, time to overall remission (9), and the use of primary antifungal prophylaxis during the study period.

Statistical analysis. Categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using Wilcoxon rank sum tests. Cox proportional hazard models were used to identify predictive factors for documented IFI and mortality. First, univariate analyses were performed to evaluate the predictive effect of each factor alone. Then, any factor with a P value < 0.20 from its univariate test was selected to construct a full multivariate Cox regression model. Finally, the full model was reduced to a final model using the stepwise selection method so that all the factors remaining in the model were statistically significant. The proportional hazard assumptions were tested for the final Cox models by including the interactions of all the predictors with log of survival time. Hospitalization, neutropenia, overall remission, and anti-*Aspergillus* triazole, echinocandin, and fluconazole use were treated as time-dependent variables in the analysis. In addition, Kaplan-Meier curves were constructed to estimate the probability of being IFI free stratified by antifungal prophylaxis strategy. All tests were two-sided with a significance level of 0.05. The analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Study cohort. Demographic and clinical characteristic comparisons between 21 subjects with documented IFI and 104 patients who were IFI free 120 days after beginning RIC are shown in Table 1. A majority (82%) of the AML study population remained in the hospital for the first 42 days after initiating RIC. After the inclusion criteria described above were applied, data from 21 patients with episodes of IFI and 104 controls were available for analysis.

Antifungal prophylaxis in documented IFI cases. Table S1 in the supplemental material describes the epidemiology, clinical features, and outcome determined for 21 AML patients with documented IFIs during the 120-day study period. Documented IFIs developed a median of 20 days (interquartile range [IQR], 15 to 32 days) after RIC (see Table S1). During periods of echinocandin prophylaxis, breakthrough infections included culture- or histology-proven *Paecilomyces* pulmonary and rib osteomyelitis infections ($n = 1$), fusariosis ($n = 1$), and sinopulmonary mold infection ($n = 1$); probable aspergillosis ($n = 6$); coccidiomycosis ($n = 1$); candidemia ($n = 3$); and *Saprochaete capitata* (*Blastoschizomyces capitatus*) bloodstream infection ($n = 1$). Breakthrough infections during posaconazole/voriconazole prophylaxis included proven mold infection (sterile hyphae) ($n = 1$); probable aspergillosis ($n = 4$); and probable fusariosis ($n = 1$).

Predictive factors for IFI and mortality. Univariate analysis revealed that patients with documented IFIs were more likely to be female ($P = 0.05$), have had prior chemotherapy-related AML ($P = 0.03$), have a history of prior chemotherapy ($P = 0.04$), and have received clofarabine-based RIC ($P = 0.006$) or echinocandin prophylaxis ($P = 0.002$). Patients who died during the first 120 days after beginning RIC were more likely to have had lung disease or infection ($P = 0.04$) or cardiovascular disease ($P = 0.05$) as an underlying condition and less likely to have achieved remission during chemotherapy ($P = 0.02$) and to have received posaconazole/voriconazole primary antifungal prophylaxis ($P = 0.026$).

In the final multivariate Cox regression model for IFI, risk-only echinocandin prophylaxis ($P = 0.002$) and receipt of clofarabine-based chemotherapy ($P = 0.004$) were retained as independent factors associated with breakthrough IFI. Independent predictors for increased mortality were hospitalization ($P = 0.017$) and having lung disease or infection as an underlying condition ($P = 0.031$). In our study cohort, receipt of echinocandin ($P = 0.47$) or posaconazole/voriconazole prophylaxis ($P = 0.09$) did not independently influence the patient mortality rate.

Comparison of anti-*Aspergillus* prophylaxis data. In univariate analysis, patients who initially received primary antifungal prophylaxis with an echinocandin versus a mold-active triazole were older (median age of 69 versus 66, $P = 0.027$) and less likely to be treated with standard cytarabine-based RIC protocols (61% versus 86%, $P = 0.01$) and achieved lower overall remission rates during RIC (42% versus 69%, $P = 0.015$) (Table 2). Patients who received only echinocandin prophylaxis generally experienced a shorter duration of neutropenia (median of 28 versus 46 days, $P = 0.04$) and received prophylaxis for a shorter period (19 versus 86 days, $P < 0.001$) (Fig. 1) before switching to another agent or drug discontinuation. The total number of prophylaxis days (with or without receiving fluconazole during any prophylaxis period) was 1,650 days in the echinocandin group (ratio of 43 days per patient) versus 3,164 days in the anti-*Aspergillus* azole group (ratio of 75 days per patient). The majority (84/152, 55%) of patients who received voriconazole prophylaxis in our study received the oral formulation, representing 98% of voriconazole prophylaxis days (4,193/4,266 days). The frequencies of overlapping periods of fluconazole were comparable in patients receiving echinocandin versus voriconazole/posaconazole prophylaxis (50% versus 31%, respectively, $P = 0.11$), and the durations of fluconazole prophylaxis for the two groups were similar. The median time to initiate anti-*Aspergillus* drug class after first remission-induction chemotherapy was 2 days less in the echinocandin group than in the voriconazole/posaconazole group (medians of 1 and 3 days; $P = 0.04$).

The frequency of documented IFI, in particular, invasive candidiasis, was higher among patients who received only echinocandin versus anti-*Aspergillus* azole-based prophylaxis (8% versus 0%, $P = 0.09$). To compare rates of IFI among patients, including those who switched antifungal prophylaxis during the study period ($n = 45$ patients), we constructed Kaplan-Meier curves for the probability of being free of IFI stratified by antifungal prophylaxis as a time-dependent covariate (Fig. 2). Marked differences in the probability of being IFI free were evident between patients who received primary antifungal prophylaxis with voriconazole or posaconazole and patients who received an echinocandin, even though the rates of empirical antifungal therapy use by the two prophylaxis groups were similar (32% versus 40%, $P = 0.41$). All-cause mortality rates did not differ between the echinocandin

TABLE 1 Candidate risk factors for documented IFI in patients with AML during first 120 days after first remission-induction chemotherapy

Demographic ^p	Documented IFI (n = 21)	No IFI (n = 104)	P value ^a
Male, n (%)	7 (33)	62 (60)	0.05
Median age (IQR), yrs	63 (57–70)	65 (51–73)	0.7
Hospitalization ^b			0.11
Median no. of hospitalizations (IQR)	1 (1–1)	2 (1–3)	
Median duration (IQR), days	21 (14–29)	31 (22–39)	
Admission to the HEPA filter room, n (%)	8 (38)	35 (34)	0.7
Underlying conditions, ^c n (%)			
Lung disease or infection ^d	5 (24)	26 (25)	0.95
Concomitant bacterial infection ^e	5 (24)	15 (14)	0.3
Cardiovascular disease or condition	8 (38)	32 (31)	0.46
Diabetes mellitus or hyperglycemia ^f	5 (24)	18 (17)	0.57
History of renal failure or renal dysfunction ^g	1 (5)	15 (14)	0.23
Abnormal liver tests ^h	2 (10)	13 (13)	0.76
No. (%) with other malignancy ⁱ	7 (33)	19 (18)	0.13
No. (%) chemotherapy naive	16/21 (80)	94/103 (91)	0.04
WHO AML classification, ^j n (%)			
Therapy-related AML	4/21 (19)	4/102 (4)	0.03
MDS-related changes	8/21 (38)	29/102 (28)	0.46
Recurrent genetic abnormalities	5/21 (24)	20/102 (20)	0.71
Myeloid sarcoma	0/21 (0)	3/102 (3)	0.31
Acute leukemia of ambiguous lineage	0/21 (0)	2/102 (2)	0.37
Not specified	4/21 (19)	44/102 (43)	0.07
Cytogenetic risk group, ^k n (%)			
Favorable	5 (24)	19 (18)	0.58
Intermediate I	1 (5)	9 (9)	0.65
Intermediate II	7 (33)	30 (29)	0.32
Adverse	8 (38)	46 (44)	0.41
Remission-induction chemotherapy, n (%)			
Cytarabine-based regimen	16 (76)	77 (74)	0.82
Other regimen	5 (24)	27 (26)	0.99
Investigational chemotherapy ^l	14 (67)	37 (36)	0.10
Clofarabine-based regimen ^m	10 (48)	19 (18)	0.006
Overall remission			0.3
Overall remission, n (%) ⁿ	4 (19)	71 (68)	
Neutropenia			0.12
Neutropenia at start of prophylaxis, n (%)	12 (57)	54 (52)	
Median no. of episodes of neutropenia (IQR)	1 (1–2)	3 (1–4)	
Median duration of neutropenia (IQR), days ^o	23 (16–31)	47 (28–70)	
Primary antifungal prophylaxis			0.009
Anti- <i>Aspergillus</i> azole (voriconazole or posaconazole)			

TABLE 1 (Continued)

Demographic ^p	Documented IFI (n = 21)	No IFI (n = 104)	P value ^a
Anti- <i>Aspergillus</i> azole use, n (%)	10 (48)	77 (74)	
Median duration of anti- <i>Aspergillus</i> azoles (days), IQR	19 (13–25)	75 (29–101)	
Fluconazole			0.4
Fluconazole use, n (%)	7 (33)	40 (38)	
Median duration of fluconazole (days), IQR	5 (2–35)	31 (7–80)	
Echinocandin			0.002
Echinocandin use, n (%)	17 (81)	66 (63)	
Median duration of echinocandins (days), IQR	11 (7–21)	17 (9–28)	

^a Univariate Cox regression analysis.

^b Time-dependent variable.

^c At-hospital admission or history.

^d Lung infection at hospital admission or concomitant to AML history.

^e At-hospital admission or concomitant to AML history according to the patient's treating physician based on clinical, microbiology, and antibiotic prescription data.

^f Diagnosis of diabetes mellitus or induced hyperglycemia (glucose \geq 200 mg/dl).

^g Diagnosis of renal failure or a 50% increase in serum creatinine level.

^h Diagnosis of liver disease or abnormal liver blood tests (serum alanine aminotransferase and/or aspartate aminotransferase levels $>$ 3.0 \times upper limit of normality [ULN] and/or total bilirubin $>$ 1.5 \times ULN).

ⁱ Solid cancers in breast (9 patients), skin (7), prostate (4), parotid (2), thyroid (1), vocal cord (1), and cervix uteri (1); chronic myelomonocytic leukemia (2); acute lymphoblastic leukemia (1); Hodgkin's lymphoma (1); not specified (3).

^j Data are from Vardiman et al. (20).

^k Data are from Estey (21).

^l Eleven investigational chemotherapy protocols.

^m Three investigational clofarabine-containing protocols in FRIC: (i) clofarabine plus low-dose cytarabine followed by consolidation of clofarabine plus low-dose cytarabine alternating with decitabine in frontline AML and high-risk MDS (n = 20 patients); (ii) clofarabine, idarubicin, and cytarabine combination as induction therapy for younger patients with AML (n = 7 patients); (iii) phase I/II study of plerixafor and clofarabine in previously untreated older (\geq 60 years of age) adult patients with AML with two or more unfavorable prognostic factors for whom standard induction chemotherapy is unlikely to be of benefit (n = 2 patients).

ⁿ Overall remission as described by Faderl et al. (9).

^o Considering all episodes of neutropenia.

^p HEPA, high-efficiency particulate air; MDS, myelodysplastic syndrome.

and anti-*Aspergillus* triazole prophylaxis patients (13% and 10% $P = 0.73$).

DISCUSSION

In a previous epidemiological analysis of IFIs in the AML population, we found significantly higher IFI rates during remission-induction chemotherapy (RIC) among patients who received prophylaxis with an echinocandin than among those who received prophylaxis with an anti-*Aspergillus* triazole (voriconazole or posaconazole) (7.1 versus 1.1 per 1,000 prophylaxis days, $P < 0.0001$) (3). Given the relatively limited evidence supporting front-line use of echinocandins for primary prophylaxis in AML, we suspected that echinocandin prophylaxis might have been used predominantly in older or higher-risk AML patients (i.e., those with chemotherapy-associated AML) who had multiple comorbidities that prevented use of a triazole. Alternatively, echinocandin prophylaxis may have been used more frequently for patients whose drug interactions or risk for increased hepatic toxicity with investigational chemotherapy was a concern (3), which precluded the use of voriconazole or

TABLE 2 Clinical and treatment-associated risk factors for IFI and mortality among AML patients who received voriconazole/posaconazole versus echinocandin primary antifungal prophylaxis

Demographic or clinical characteristic ^p	Voriconazole/ posaconazole (n = 42)	Echinocandin (n = 38)	P
Male, n (%)	26 (62)	23 (61)	0.9
Median age (IQR), yrs	66 (38–71)	69 (61–77)	0.03
Race, white, n (%)	33 (79)	30 (79)	0.97
Admission to the HEPA filter room during FRIC, n (%)	10 (24)	16 (42)	0.10
Underlying conditions, ^a n (%)			
Lung disease or infection ^b	11 (26)	7 (18)	0.41
Bacterial infection ^c	9 (21)	3 (8)	0.12
Cardiovascular disease or condition	15 (36)	11 (29)	0.52
Diabetes mellitus or induced hyperglycemia ^d	6 (14)	7 (18)	0.62
Renal failure ^e	7 (17)	7 (18)	0.84
Abnormal liver test ^f	5 (12)	4 (11)	>0.99
Other malignancy ^g	6 (14)	8 (21)	0.43
Chemotherapy naïve	38 (90)	35 (92)	>0.99
WHO AML classifications, ^h n (%)			
Therapy-related AML	1/41 (2)	3/38 (5)	0.61
MDS-related changes	15/41 (37)	13/38 (34)	0.83
Recurrent genetic abnormalities	12/41 (29)	8/38 (21)	0.4
Myeloid sarcoma	1/41 (2)	1/38 (3)	>0.99
Acute leukemia of ambiguous lineage	0/41 (0)	1/38 (3)	0.48
Not otherwise specified	13/41 (32)	14/38 (37)	0.63
Cytogenetic risk group, ⁱ n (%)			
Favorable	12 (29)	6 (16)	0.17
Intermediate I	4 (10)	2 (5)	0.68
Intermediate II	16 (38)	16 (42)	0.71
Adverse	10 (24)	14 (37)	0.20
FRIC protocol, n (%)			
Cytarabine-containing regimen	36 (86)	23 (61)	0.01
Other regimen	6 (14)	15 (39)	
Investigational chemotherapy ^j	14 (33)	21 (55)	0.07
Clofarabine-containing protocol ^k	10 (24)	10 (26)	0.80
Overall remission, ^l n (%)	29 (69)	16 (42)	0.02
Neutropenia (ANC ≤ 500 cells/mm ³)			
At start of PAP drug, n (%)	21 (50)	16 (42)	0.48
Median no. of episodes (IQR)	3 (1–4)	2 (1–3)	0.33
Median duration (IQR), ^m days	46 (26–61)	28 (16–45)	0.04
Primary antifungal prophylaxis			
Median no. of days to start PAP after FRIC, (IQR)	3 (0–5)	1 (0–4)	0.04
Median duration of prophylaxis (IQR), ⁿ days	86 (45–106)	19 (10–88)	<0.001
Prophylaxis periods ≥ 5 days, ⁿ n (%)	42 (100)	35 (92)	0.10
Concomitant fluconazole use, n (%)	13 (31)	19 (50)	0.11

TABLE 2 (Continued)

Demographic or clinical characteristic ^p	Voriconazole/ posaconazole (n = 42)	Echinocandin (n = 38)	P
Median duration of fluconazole use (days), ^o IQR	11 (5–31)	21 (3–89)	0.59

^a At-hospital admission or history.

^b Lung infection at hospital admission or concomitant to AML history.

^c At-hospital admission or concomitant to AML history according to patient's treating physician based on clinical, microbiology, and antibiotic prescription data.

^d Diagnosis of diabetes mellitus or induced hyperglycemia (glucose ≥ 200 mg/dl).

^e Diagnosis of renal failure or a 50% increase in serum creatinine level.

^f Diagnosis of liver disease or abnormal liver blood tests (serum alanine aminotransferase and/or aspartate aminotransferase levels > 3.0 × upper limit of normality [ULN] and/or total bilirubin > 1.5 × ULN).

^g Solid cancers in breast (9 patients), skin (7), prostate (4), parotid (2), thyroid (1), vocal cord (1) and cervix uteri (1); chronic myelomonocytic leukemia (2); acute lymphoblastic leukemia (1); Hodgkin's lymphoma (1); not specified (3 patients).

^h Data are from Vardiman et al. (20).

ⁱ Data are from Estey (21).

^j Eleven investigational chemotherapy protocols.

^k Three investigational clofarabine-containing protocols in FRIC (see footnote to Table 1).

^l Overall remission as described by Faderl et al. (9).

^m Considering all episodes of neutropenia.

ⁿ Prophylaxis period, prophylaxis with same drug and formulation without discontinuation.

^o Duration per prophylaxis period.

^p AML, acute myeloid leukemia; ANC, absolute neutrophil count; FRIC, first remission-induction chemotherapy; HEPA, high-efficiency particulate air; MDS, myelodysplastic syndrome; PAP, primary antifungal prophylaxis; WHO, World Health Organization.

posaconazole. Because many of these variables could be associated with increased IFI risk, it is important to ascertain whether echinocandin prophylaxis is an independent risk factor, *per se*, for breakthrough IFI in AML patients undergoing RIC.

Our analysis revealed clofarabine-containing chemotherapy regimen and echinocandin prophylaxis to be two independent risk factors for developing documented IFI during the first 120 days of RIC. Clofarabine is a broad-spectrum purine nucleoside analog considered to be an effective agent for older patients with AML who are unsuitable for anthracycline-based regimens or who have unfavorable risk factors/cytogenetics, which are common in therapy-associated AML (9–11). Clofarabine is associated with significant myelosuppression and gastrointestinal toxicity compared to lower-dose cytarabine regimens used in older AML patients, which may account for the higher rate of breakthrough IFI (9, 11–14). Therefore, it is not surprising that clofarabine RIC was retained as an independent risk factor for breakthrough IFI. Nevertheless, clofarabine-based RIC was used in similar proportions of AML patients who received echinocandin versus voriconazole or posaconazole prophylaxis (26% versus 24%, *P* = 0.80). Similarly, other IFI risk factors identified in univariate analysis associated with IFI (AML classification, cytogenetics, prior chemotherapy exposure, failed response to RIC) and neutropenia frequency, depth, and duration did not favor patients who received voriconazole or posaconazole prophylaxis (Table 2). Hence, we believe that our analysis points to the hypothesis that echinocandin antifungals are less effective prophylactic agents than triazole antifungals for preventing IFI in AML patients receiving RIC.

Although the number of infections available for analysis was limited, differences in the pattern of breakthrough IFIs also sug-

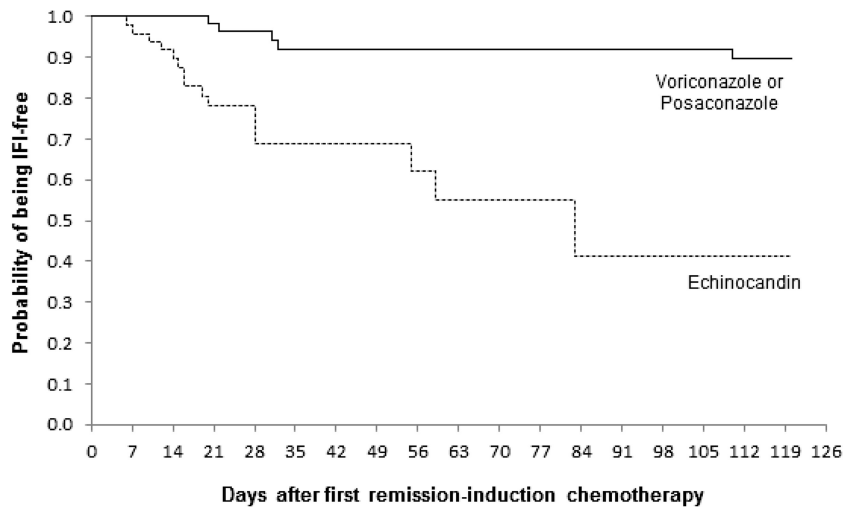


FIG 1 Kaplan-Meier estimates of being documented IFI-free during the 120 days after first remission-induction chemotherapy. Patients were stratified on the basis of the current prophylaxis agent, which was analyzed as a time-dependent covariate. No *P* value was calculated because 45 patients had changes in their antifungal prophylaxis during the analysis period.

gest that the echinocandins may be less effective as PAP, in agreement with our previous findings where the incidence density rates of both mold and yeast IFIs per prophylaxis day were significantly in favor of azoles (3). Compared to patients receiving posaconazole/voriconazole prophylaxis, patients receiving echinocandins had slightly higher numbers of proven (culture-based) cases of mold infections. Yet the largest difference appeared to be in the rates of breakthrough yeast infections, specifically, yeasts that have intrinsic resistance or a propensity for breakthrough infections during echinocandin therapy (i.e., *Candida glabrata*, *C. parapsilosis*, *Saprochaete capitata* [*Blastoschizomyces capitatus*]), which may have been prevented with triazole prophylaxis. Besides the differences in spectra of activity, pharmacokinetic limitations of echinocandins versus broad-spectrum triazoles may also play a role in the higher IFI rate (15–18).

Our data set has several limitations, including its retrospective nature and relatively small sample size that was composed of primarily higher-risk, older AML patients from a single large cancer

treatment center. Moreover, we were not able to capture data concerning why particular primary antifungal prophylaxis regimens were selected, discontinued, or changed by the treating hematologists. As such, we had to retrospectively designate a duration of therapy that could be considered prophylaxis (at least 3 days before switching) in our analysis. To overcome problems with switching therapies, we also analyzed rates of breakthrough IFI modeling prophylaxis as a time-dependent variable (Fig. 2). As highlighted in our previous study (3), IFI rates are probably underestimated because diagnosis relies heavily on positive results in galactomannan tests, which have reduced sensitivity in patients receiving antifungal prophylaxis (19). Finally, we analyzed all breakthrough IFIs as a single outcome, even though the pathogenesis and risk factors for invasive molds versus yeast bloodstream infections differ.

In conclusion, we found that antifungal prophylaxis is not uniformly effective in preventing IFI during RIC of AML, especially among members of a cohort of older, higher-risk patients. We also

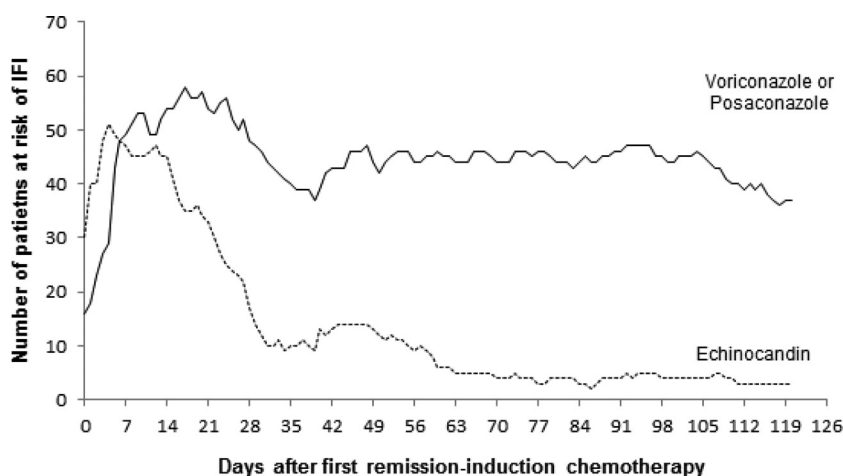


FIG 2 Numbers of patients at risk of IFI during the 120 days after first remission-induction chemotherapy. Patients were stratified on the basis of the current prophylaxis agent, which was treated as a time-dependent covariate.

found that the class of prophylactic agent received significantly influences the patient's risk and the type of breakthrough IFI. Overall, use of echinocandin prophylaxis during RIC was associated with a significantly higher risk of breakthrough IFI compared to use of mold-active triazoles, especially with yeast. This excess risk could not be easily explained by underlying hematological disease status, severity of immunosuppression, or chemotherapy-associated risk factors. Nevertheless, larger multicentric prospective studies or well-designed AML patient registry databases of antifungal prophylaxis would be required to confirm our findings of reduced efficacy of echinocandins as primary antifungal prophylaxis during RIC for AML.

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