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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

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Although primary antifungal prophylaxis (PAP) is routinely administered in patients with acute myeloid leukemia (AML) during remission-induction and consolidation chemotherapy, the impact of PAP on the incidence of invasive fungal infections (IFIs) is not well described. We retrospectively analyzed the incidence of IFIs in 152 patients with AML who had been admitted to a tertiary cancer center between August 2009 and March 2011 and received PAP within 120 days after first remission-induction chemotherapy. We excluded patients who had undergone stem cell transplantation. Patients received a PAP drug with anti-*Aspergillus* activity during 72% (7,660/10,572) of prophylaxis-days. The incidence of documented IFIs (definite or probable according to revised European Organization for Research and Treatment of Cancer [EORTC] criteria) was 2.0/1,000 prophylaxis-days (95% confidence interval [CI], 1.23 to 3.04). IFIs due to molds were more common than IFIs due to yeasts (1.5/1,000 prophylaxis-days versus 0.4/1,000 prophylaxis-days; $P = 0.01$). Echinocandin-based PAP (8.6 and 7.1/1,000 prophylaxis-days, respectively) was associated with higher rates of documented IFIs than anti-*Aspergillus* azoles (voriconazole or posaconazole) (2.4 and 1.1/1,000 prophylaxis-days, respectively) at both 42 days ($P = 0.03$) and 120 days ($P < 0.0001$) after first remission-induction chemotherapy. The incidence of overall (documented and presumed) IFIs ($P < 0.001$), documented IFIs ($P < 0.01$), and empirical antifungal therapies ($P < 0.0001$) was higher during the first 42 days than after day 42. Despite the broad use of PAP with anti-*Aspergillus* activity, IFIs, especially molds, remain a significant cause of morbidity and mortality in AML patients, predominantly during the remission-induction phase. Patients receiving echinocandin-based PAP experienced higher rates of IFIs than did those receiving anti-*Aspergillus* azoles.

Despite improvements in diagnosis, prophylaxis, and treatment, invasive fungal infections (IFIs) remain a significant cause of morbidity and mortality in patients with acute myeloid leukemia (AML) (1–3). The incidence of documented IFIs (definite or probable, according to revised European Organization for Research and Treatment of Cancer [EORTC] criteria) has been reported to range from 12 to 34% in patients with AML (4–10). In contrast, lower rates of 2 to 6% have been reported for selected patients with AML/myelodysplastic syndrome (MDS) who were enrolled in clinical trials of antifungal prophylaxis (11–13).

Although there is broad agreement that primary antifungal prophylaxis (PAP) is the standard of care for patients with AML, decisions about which prophylaxis agent to choose and the optimal length of prophylaxis remain controversial (1, 14, 15). Perceived risk for IFIs, institution-specific fungal epidemiology, and diagnostic algorithms make general consensus recommendations difficult (3, 14). To that end, we sought to evaluate the utilization patterns and performances of different classes of modern antifungals used as PAP in a contemporary cohort of patients being treated for newly diagnosed AML in a tertiary cancer center.

MATERIALS AND METHODS

Study design and patients. We performed a retrospective cohort study to quantify both the incidence of IFIs and PAP usage in adult (≥18 years old) patients with newly diagnosed AML registered at the MD Anderson Cancer Center (MDACC) between August 2009 and March 2011. This study was approved by the MDACC institutional review board committee. We reviewed patient records from the time of hospital registration until 120 days after first remission-induction chemotherapy (study period).

The primary endpoints were the incidence and time to documented IFIs in the 120-day period after first remission-induction chemotherapy. Secondary endpoints were the incidence and timing of presumed IFIs, the use of empirical antifungal therapy (EAT), causes associated with PAP change or discontinuation, overall (documented and presumed) IFIs, and death from any cause. We compared the incidences of documented IFIs, presumed IFIs, and EAT per 1,000 prophylaxis-days during anti-*Aspergillus* azole (voriconazole or posaconazole)- and echinocandin (caspofungin, anidulafungin, or micafungin)-based PAP and per 1,000 patient-days during the first 42 days versus 42 to 120 days after first remission-induction chemotherapy.

Definitions. PAP was defined as any systemic antifungal therapy given as prophylaxis for more than two consecutive days to a patient without current or previous clinical, microbiological, and/or radiological evidence of either documented or presumed IFI. Documented and possible IFIs were determined in accordance with EORTC revised definitions (16). Patients with possible IFIs or those with clinical and microbiological evidence of IFI and noncharacteristic computed tomography (CT) scan ab-

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normalities, according to EORTC definitions, were categorized as having presumed IFIs. Overall IFIs included patients with documented and presumed IFIs. EAT was defined as the administration of an antifungal drug(s) in a patient with persistent febrile neutropenia and/or clinical findings possibly related to an IFI in which microbiologic and radiologic findings were negative for IFI. Galactomannan results for diagnosis of "probable aspergillosis" included one or more positive serum samples with an index of ≥0.5 within a 2-week time frame of clinical and radiological evidence of IFI. The date of IFI onset was considered the date of the first clinical manifestations attributable to IFI or the date of the clinical/radiologic/microbiologic diagnosis.

Diagnostic workup of IFIs. The diagnostic workup of IFIs in the hospital during the study period was standardized, patients were closely monitored, and examinations and procedures were performed when indicated. The diagnostic workup did not change during the study period, including procedures in the clinical microbiology laboratory. Serum galactomannan tests were the only biomarker for IFI routinely used as part of the diagnostic workup during the years of study.

Study population. Patients with AML who were treated in the hospital were identified from hospital medical databases. The medical record numbers were sequentially listed in order to identify newly registered AML patients during the period of August 2009 to March 2011. Only patients with newly diagnosed AML had their records reviewed. We investigated retrospectively 198 unselected consecutive patients with newly diagnosed AML, which corresponded to over 75% of patients registered at the MDACC with newly diagnosed AML during the years of study. Forty-six patients (23%) were excluded for the following reasons: 15 patients were not monitored at our institution, 13 patients had prior or subsequent stem cell transplantation during the study period, and 18 patients did not receive any PAP at baseline (14 patients) or during the study (4 patients). Among the 18 patients who did not receive PAP, 8 patients had a diagnosis of probable or presumed IFI at baseline, and 6 received EAT initially and subsequently either died (5 patients) or were lost to follow-up; only 4 patients did not receive any PAP drug during the 120 days after first remission-induction chemotherapy (1 of them developed probable IFI). Consequently, our study population consisted of 152 patients who had received >2 days of PAP and were evaluable for the type and duration of PAP drug use as well as for a diagnosis of IFI.

Data collection. We performed a pilot study to make the data collection uniform. Demographic, clinical, and laboratory data were collected for the period until diagnosis of an IFI, loss of the patient to follow-up, death, or completion of 120 days of therapy after first remission-induction chemotherapy, whichever came first. Data concerning antifungal use were collected from the institution's pharmacy database and were matched with the information in patients' electronic medical records. We collected data about the type, dosage, and duration of antifungal drugs used as PAP as well as about factors associated with PAP drug change or discontinuation at the end of each prophylaxis period in each patient during the study period. The diagnosis of IFI was reviewed by three infectious disease specialists.

Statistical analysis. Categorical and continuous variables were compared by using chi-square or Fisher's exact tests and Wilcoxon rank sum tests, respectively. Poisson distribution and Fisher's exact tests were used to compare incidence rates. Incidence rates per 1,000 prophylaxis-days were calculated by dividing the number of cases with overall IFI, documented IFI, or episodes of EAT, occurring during the use of a particular PAP drug (or antifungal class), by the number of prophylaxis-days with this particular drug (or class) during the study period. The denominator for the rate calculation included the total duration of prophylaxis with a particular PAP drug or class until patients were censored. Incidence rates per 1,000 patient-days were defined as the number of IFIs divided by the sum of patient-days during the study period. Daily prophylaxis per 100 patient-days represents the number of a specific PAP drug or class (or all antifungal drugs) administered daily normalized to 100 patient-days. All tests were two sided, with a significance

TABLE 1 Demographic and clinical characteristics of a cohort of 152 patients with newly diagnosed acute myeloid leukemia

Parameter[k]	Value for AML patients
Demographics	
No. (%) of males	85 (56)
Median age (yr) (range)	65 (19–96)
Median total duration of hospitalization (days) (range)[a]	29 (0–98)
No. of patients admitted to a HEPA filter room/total no. of patients (%)[b]	95/146 (65)
No. (%) of patients with underlying conditions[c]	
Lung disease[d]	34 (22)
Diabetes mellitus or induced hyperglycemia[e]	29 (19)
Renal failure[f]	21 (14)
Abnormal liver tests result[g]	17 (11)
AML characteristics	
No. (%) of patients with WHO AML classification of[h]:	
Therapy-related AML	8 (5)
MDS-related changes	50 (33)
Recurrent genetic abnormalities	32 (21)
Myeloid sarcoma	4 (3)
Acute leukemias of ambiguous lineage	2 (1)
Not otherwise specified	56 (37)
No. (%) of patients in cytogenetic risk group[i]	
Favorable	33 (22)
Intermediate I	10 (7)
Intermediate II	44 (29)
Adverse	65 (43)
Immunosuppressive chemotherapy	
No. (%) of patients with first remission-induction chemotherapy protocol	
Cytarabine-containing regimen	104 (68)
Decitabine-containing regimen	29 (19)
Other regimen	19 (13)
Median no. of chemotherapy cycles (range)	3 (1–5)
No. (%) of patients with complete remission in response to chemotherapy	80 (53)
Neutropenia (ANC of ≤500 cells/mm^3)	
No. (%) of patients with neutropenia at start of PAP administration	85 (56)
No. (%) of patients with no. of episodes of neutropenia	
0	4 (3)
1	55 (36)
≥2	93 (61)
Median duration of neutropenia (days) (range)	40 (0–129)
PAP drugs	
Median no. of PAP drugs used (range)	2 (1–4)
Median no. of PAP drug periods (range)[j]	2 (1–8)
Median duration of total PAP drugs used (days) (range)	75 (4–138)
No. (%) of patients given anti-*Aspergillus* azole (voriconazole or posaconazole)	100 (66)
Median duration of anti-*Aspergillus* azole administration (days) (range)	51 (1–119)
No. (%) of patients given echinocandins	88 (58)
Median duration of echinocandin administration (days) (range)	16 (2–118)
No. (%) of patients given fluconazole	63 (41)
Median duration of fluconazole administration (days) (range)	34 (1–129)

[a] During the 120-day study period.
[b] Without other features described in the total protective environment, during any hospitalization over the 120-day study period.
[c] At hospital admission or history.
[d] Lung infection at hospital admission or concomitant with AML history.
[e] Diagnosis of diabetes mellitus or induced hyperglycemia (glucose level of ≥200 mg/dl).
[f] Diagnosis of renal failure or a 50% increase in the serum creatinine level.
[g] Diagnosis of liver disease or abnormal liver blood tests (serum alanine aminotransferase and/or aspartate aminotransferase levels of >3.0× the upper limit of normal and/or total bilirubin level of >1.5× the upper limit of normal).
[h] According to Vardiman et al. (42).
[i] According to Estey (43).
[j] Prophylaxis period is the period of PAP drug use without discontinuation or change.
[k] AML, acute myeloid leukemia; ANC, absolute neutrophil count; IFI, invasive fungal infection; MDS, myelodysplastic syndrome; PAP, primary antifungal prophylaxis; WHO, World Health Organization.

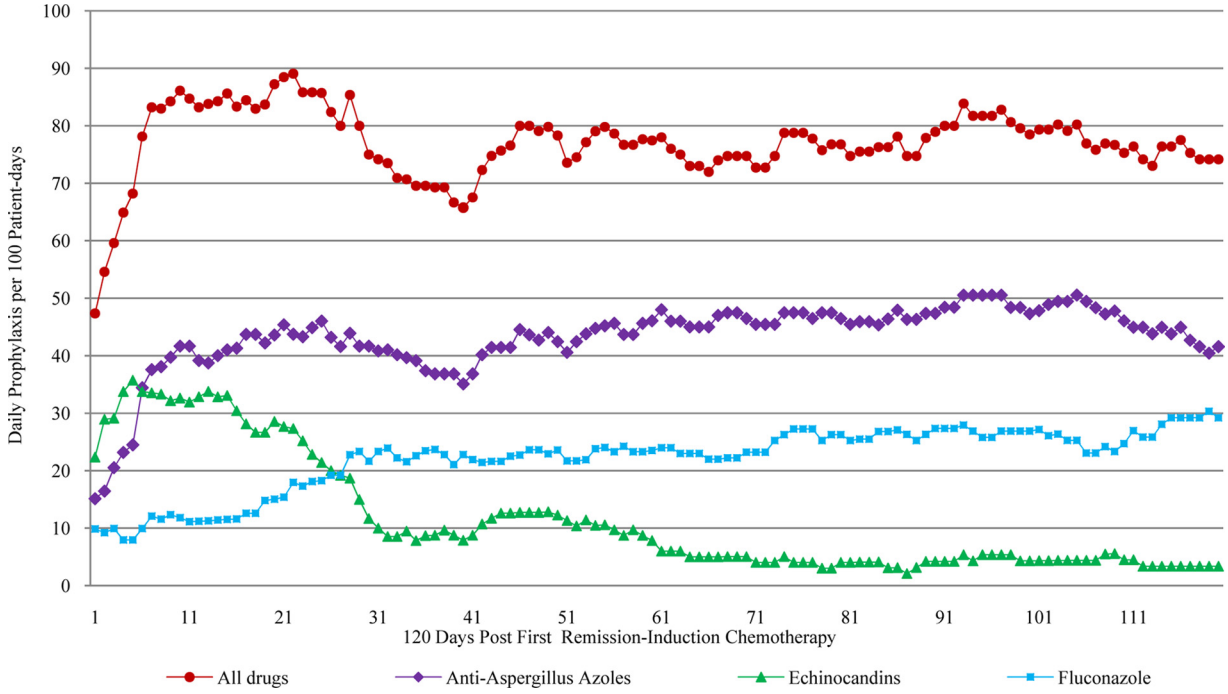

FIG 1 Daily primary antifungal prophylaxis per 100 patient-days over the 120-day study period.

level of 0.05. Analyses were performed by using EPI info 7 (CDC, Atlanta, GA) and SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics. As shown in Table 1, the median age of patients was 65 years (range, 19 to 96 years), and 56% were male. The majority of patients were chemotherapy naive (132/151; 87%). During first remission-induction chemotherapy, 68% of patients (104/152) received a cytarabine-containing regimen, whereas 39% (60/152) received an investigational-drug-containing regimen with or without cytarabine. Patients with AML were hospitalized 82% (4,537 hospitalization-days/5,511 patient-days) of the time during the 42-day initial period. Among patients admitted to the hospital, 65% (95/146) were admitted to rooms with HEPA filters.

Patterns of PAP use. Patients received a median of 2 different antifungal drugs (range, 1 to 4) as PAP, for a median of 2 prophylaxis periods (range, 1 to 8), during a median of 75 days (range, 4 to 138 days) during hospitalizations or as outpatients. The majority of patients (147/152; 97%) received one antifungal drug during each prophylaxis period (PAP drug used without discontinuation or change). A total of 81 daily PAPs/100 patient-days were used during the study period (Fig. 1). Anti-*Aspergillus* PAP was used 72% (7,660/10,572 prophylaxis-days) of the time (Table 2). The number of daily prophylaxes with anti-*Aspergillus* azoles (38 and 48 daily prophylaxes/100 patient-days) was higher ($P < 0.001$) than that with echinocandins (23 and 6 daily prophylaxes/100 patient-days) during the 42- and 120-day study periods, respectively (Fig. 1). The use of fluconazole prophylaxis was significantly lower ($P < 0.0001$) before day 42.

PAP drug discontinuation. Table 3 shows the main factors associated with PAP change or discontinuation per class of antifungals. Anti-*Aspergillus* azoles (33/137 [24%]; 95% confidence interval [CI], 17.66 to 31.93%; $P = 0.002$) and oral (24/101 [24%]; 95% CI, 16.47 to 32.98%; $P = 0.004$) and intravenous (4/11 [36%]; 95% CI, 14.98 to 64.81%; $P = 0.05$) voriconazole were discontinued at significantly higher rates because of adverse events than were echinocandins (11/117 [9%]; 95% CI, 5.18 to 16.2%). Diarrhea ($P = 0.004$) and visual and/or auditory hallucinations ($P = 0.02$) were adverse events significantly leading to anti-*Aspergillus* azole discontinuation, whereas these side effects were not associated to echinocandin discontinuation. Therapeutic-drug monitoring (TDM) was rarely performed (7/152 patients; 5%) during PAP. EAT did not differ between anti-*Aspergillus* antifungal classes but was more frequently associated with fluconazole discontinuation (12/71; 17%) than echinocandins (8/117; 7%) ($P = 0.03$).

IFIs during PAP. Among the 152 patients, 21 (14%) were diagnosed with documented IFIs, and 13 (9%) were diagnosed with presumed IFIs. Severe neutropenia (≤500 cells/mm^3) was present at the onset of infection in the majority of patients with documented (18/20; 90%) and presumed (12/13; 92%) IFIs. Documented and presumed IFIs developed at medians of 21 days (range, 7 to 111 days) and 17 days (range, 4 to 86 days) after first remission-induction chemotherapy, respectively. Documented IFIs developed at a median of 13 days (range, 1 to 82 days) after the initiation of the course of PAP drug associated with IFI; 8 infections (38%) developed when patients were receiving the first PAP drug. Seventeen (81%) documented IFIs developed during hospitalization or within 9 days of hospital discharge (3 patients).

Table 2 also shows the etiology of documented IFIs and the MICs of caspofungin for the echinocandin breakthrough *Candida* species. Twelve patients with probable "invasive aspergillosis" had 26 positive *Aspergillus* galactomannan levels with a median index of 0.64 (range, 0.52 to 1.41).

TABLE 2 Pattern of PAP use and incidence density of documented IFIs in 152 AML patients over 120 days after first remission-induction chemotherapy

PAP drug[a]	No. (%) of patients	No. of prophylaxis-days	No. of cases of documented IFI[b]	Incidence rate per 1,000 prophylaxis-days (95% CI)	Etiological agent(s) of documented IFI
Anti-*Aspergillus* azoles	100 (66)	5,691	6[i]	1.1 (0.38–2.29)	
Voriconazole (p.o./i.v.)[c]	84 (55)	4,266	2	0.5 (0.05–1.70)	
Voriconazole (p.o.)	80 (53)	4,193	2	0.5 (0.05–1.73)	2 IA
Voriconazole (i.v.)	10 (7)	73	0	0	None
Posaconazole[d]	29 (19)	1,425	4[i]	2.8 (0.76–7.27)	*Fusarium* sp. (sputum), sterile hyphae (culture from skin biopsy), 2 IA[i]
Fluconazole (p.o./i.v.)[e]	63 (41)	2,912	2	0.7 (0.07–2.48)	2 IA
Echinocandins	88 (58)	1,969	14[i]	7.1 (3.88–11.93)	
Caspofungin[f]	70 (46)	1,361	6	4.4 (1.61–9.60)	*Fusarium* sp. (lymph node), *Paecilomyces* sp. (lung tissue), 4 IA
Anidulafungin[g]	18 (12)	416	4	9.6 (2.6–24.74)	*Candida glabrata* ($n = 2$; blood samples and bone marrow in 1 patient),[j] *Geotrichum capitatum* (formerly *Blastoschizomyces capitatus*) (blood), 1 IA
Micafungin[h]	11 (7)	192	4[i]	20.8 (5.6–53.3)	*Candida krusei* (blood) and *Candida parapsilosis* (blood and urine),[k] *Coccidioides* sp. (serum-positive IgM immunodiffusion test), hyphae invading tissue (surgical biopsy of nasal lesion), 1 IA[i]

[a] Only 1 patient received itraconazole and another received liposomal amphotericin B as PAP for 17 and 21 days, respectively. AML, acute myeloid leukemia; i.v., intravenous; IA, invasive aspergillosis; IFI, invasive fungal infection; PAP, primary antifungal prophylaxis; p.o., *per os*.
[b] Revised EORTC criteria (16) for definite and probable IFIs.
[c] Ninety-two percent (123/134) of the voriconazole prophylaxis period with a daily dose of 200 mg twice a day.
[d] Ninety-four percent (30/32) of the posaconazole prophylaxis period with a daily dose of 200 mg three times a day (23/32; 72%) or four times a day (7/32; 22%).
[e] Ninety-five percent (90/95) of the fluconazole prophylaxis period with a daily dose of 200 mg once a day.
[f] Ninety-five percent (77/81) of the caspofungin prophylaxis period with a daily dose of 50 mg once a day.
[g] One hundred percent (22/22) of the anidulafungin prophylaxis period with a daily dose of 100 mg once a day.
[h] Ninety-one percent (10/11) of the micafungin prophylaxis period with a daily maintenance dose of 100 mg once a day.
[i] One patient previously colonized with *Aspergillus fumigatus* under PAP with both posaconazole and micafungin.
[j] The MIC of caspofungin was 0.12 mg/liter for *C. glabrata* (susceptible) in one case and 8 mg/liter in another case (nonsusceptible).
[k] The MIC of caspofungin was 0.5 mg/liter for both *C. krusei* (intermediate) and *C. parapsilosis* (susceptible), according to Pfaller et al. (44). Micafungin and anidulafungin were not tested.

IFI incidence. In the 13,114 patient-days analyzed, PAP was administered for a total of 10,572 patient-days, and 6,916 days of neutropenia below ≤500 cells/mm^3 were detected. While PAP was used in 81% of patient-days, periods of severe neutropenia represented only 53% of patient-days. The incidence density of documented IFIs was 2.0 (95% CI, 1.23 to 3.04) per 1,000 prophylaxis-days. We found significantly more overall IFIs, documented IFIs, and EATs in the first 42 days (4.5, 2.9, and 7.3/1,000 patient-days, respectively) than after day 42 (1.2, 0.7, and 2.5/1,000, respectively) ($P < 0.001$, $P < 0.01$, and $P < 0.0001$, respectively). Molds accounted for 76% (16/21) of documented IFIs (Table 2). The incidence of documented IFIs due to mold was 1.5 per 1,000 prophylaxis-days (95% CI, 0.87 to 2.49), whereas the incidence of yeast IFIs was 0.4 per 1,000 prophylaxis-days during the study (95% CI, 0.10 to 0.98; $P = 0.01$). Documented IFIs due to both yeast and mold occurred most often earlier after first remission-induction chemotherapy (Fig. 2).

We detected significant differences in the incidences of overall IFIs, documented IFIs, documented mold IFIs, yeast IFIs, definite IFIs, and probable invasive aspergillosis per 1,000 prophylaxis-days with echinocandin- versus anti-*Aspergillus* azole-based PAP during 120 days (Tables 2 and 4) and of documented IFIs in the first 42 days (Table 4). The proportions of documented IFIs were numerically higher ($P = 0.08$) in patients who received PAP with echinocandins only (7/20 [35%]; 95% CI, 17.95 to 56.84%) than in those receiving only anti-*Aspergillus* azole prophylaxis (4/35 [11%]; 95% CI, 3.94 to 26.55%) for a significantly shorter ($P > 0.01$) duration of echinocandin therapy (median of 12, range of 5 to 94, mean of 19.9, and standard deviation [SD] of 21.61 echinocandin-days versus median of 88, range of 4 to 119, mean of 72.3, and SD of 39.23 anti-*Aspergillus* azole-days). The peak of documented IFI incidence during echinocandin PAP occurred earlier than during PAP with all azoles used (Fig. 3). All breakthrough yeast IFIs occurred during echinocandin-based PAP, and none occurred during azole-based PAP (Table 2). The incidence of presumed IFIs and EATs per 1,000 prophylaxis-days did not differ among antifungal classes (Table 4) or among drugs of the same class. The incidence of documented IFIs was marginally higher ($P = 0.052$) in prophylaxis-days of micafungin than in days of caspofungin (Table 2).

Outcomes. In the 120 days after first remission-induction che-

TABLE 3 Factors associated with PAP drug change or discontinuation per class of antifungal drug in 152 AML patients over 120 days after first remission-induction chemotherapy

Factor associated with PAP drug discontinuation[a]	Value for treatment group		
	Anti-*Aspergillus* azoles ($n = 137$)	Echinocandins ($n = 117$)	*P* value[b]
No. of PAP drug changes/patient	1.3/1	1.2/1	
No. (%) of drug discontinuations due to documented or presumed IFI	13 (10)	16 (14)	0.30
No. (%) of drug discontinuations due to given empirical antifungal treatment	17 (12)	8 (7)	0.14
No. (%) of drug discontinuations due to adverse events	33 (24)	11 (9)	**0.002**
Abnormal LFTs[c]	12 (9)	5 (4)	0.15
Diarrhea	9 (7)	0	**0.004**
Visual or/and auditory hallucinations	6 (4)	0	**0.02**
Rash	4 (3)	3 (3)	>0.99
Altered mental status and/or neurotoxicity[d]	2 (2)	0	**0.31**
Renal failure[e]	1 (1)	2 (2)	0.88
QTc prolongation	1 (1)	1 (1)	>0.99
Arrhythmia and chest pain	0	1 (1)	>0.99
Death[f]	1 (1)	0	0.58
No. (%) of drug discontinuations due to lack of oral tolerability or GI disease	13 (10)	0	**<0.01**
No. (%) of drug discontinuations due to improved oral tolerability, GI disease, or change to oral drug	1 (0.7)	13 (11)	**<0.001**
No. (%) of drug discontinuations due to neutropenia recovery	35 (26)	9 (8)	**<0.001**
No. (%) of drug discontinuations due to hospital discharge	7 (5)	38 (33)	**<0.001**

[a] Other factors, drug discontinuations without information and due to patients lost to follow-up, were found in 7 (5%), 13 (9%), and 6 (4%) anti-*Aspergillus* azole discontinuations, versus 9 (8%), 7 (6%), and 6 (5%) echinocandin discontinuations, respectively. A drug interaction was described only once in the clinical records; we did not look for possible drug interactions associated with PAP drug change or discontinuation in the pharmacy formularies. IFI, invasive fungal infection; GI, gastrointestinal; LFTs, liver function tests; PAP, primary antifungal prophylaxis; QTc, corrected QT interval.

[b] Determined by a chi-squared or Fisher exact test when appropriate. Boldface type indicates statistical significance.

[c] Abnormal liver blood tests with serum alanine aminotransferase and/or aspartate aminotransferase levels >3.0× the upper limit of normal and/or total bilirubin level >1.5× the upper limit of normal.

[d] Excluding visual and/or auditory hallucinations.

[e] A 50% increase in the serum creatinine level.

[f] Death associated with bacterial infection during posaconazole prophylaxis.

motherapy, the crude mortality rate was 14% (21/152). Of the 21 patients who died, 9 (43%; 95% CI, 25 to 67%) had either documented (4 patients) or presumed IFIs. The mortality rate was higher among patients with documented or presumed IFIs (9/34; 26%) than among patients without an IFI (12/118 [10%]; $P = 0.03$). No autopsies were performed. Overall mortality did not differ significantly among patients treated with echinocandin PAP only (4/20; 20%) compared to that among patients treated with an anti-*Aspergillus* azole only (5/35 [14%]; $P = 0.85$).

DISCUSSION

Regardless of the widespread use of broad-spectrum antifungals for PAP, IFIs remain a significant cause of morbidity and mortality in AML patients. In this contemporary single-center study, we

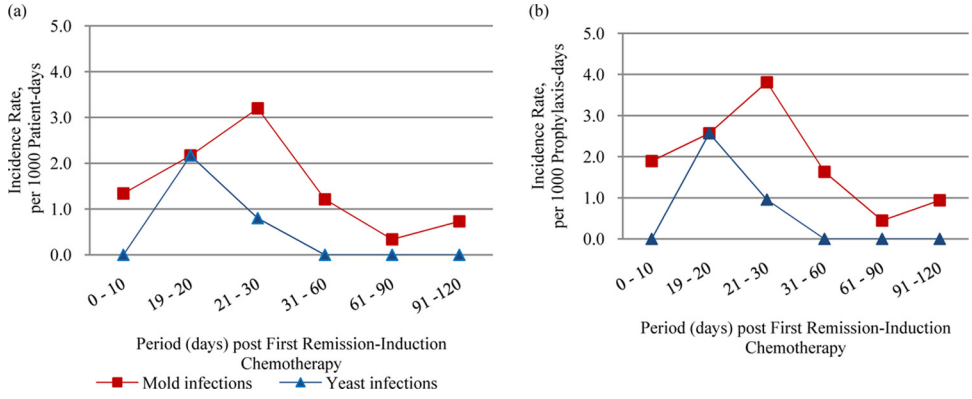

FIG 2 Incidence rates of documented mold and yeast IFIs per 1,000 patient-days (a) and per 1,000 prophylactic-days (b) over the 120-day period after first remission-induction chemotherapy among patients with newly diagnosed AML.

TABLE 4 Incidence of IFIs and EATs during echinocandin- and anti-*Aspergillus* azole-based PAP[a]

Outcome	Incidence during PAP (per 1,000 prophylaxis-days) (95% CI)		*P* value[b]
	Echinocandin	Anti-*Aspergillus* azole	
During the 120-day study period			
Overall IFIs	8.1 (4.64–13.20)	2.3 (1.21–3.90)	**<0.001**
Documented IFIs	7.1 (3.88–11.93)	1.1 (0.3–2.29)	**<0.0001**
Documented mold IFIs	4.6 (2.08–8.67)	1.1 (0.38–2.29)	**<0.01**
Yeast IFIs	2.0 (0.54–5.20)	0	**<0.01**
Definite IFIs	4.1 (1.75–8.01)	0.18 (0.02–9.78)	**<0.001**
Probable invasive aspergillosis	3.0 (1.11–6.63)	0.7 (0.19–1.80)	**0.045**
Presumed IFIs	1.0 (0.11–3.67)	1.2 (0.49–2.53)	0.61
EATs	4.1 (1.75–8.0)	2.8 (1.60–4.56)	0.39
During the 42-day study period			
Documented IFIs	8.6 (4.28–15.37)	2.4 (0.77–5.60)	**0.03**

[a] IFIs, invasive fungal infections; EATs, empirical antifungal therapies; PAP, primary antifungal prophylaxis.
[b] Boldface type indicates statistical significance.

found differences in the incidences of IFIs between different classes of anti-*Aspergillus* drugs used as PAP. Our study is the first to describe the incidence density of IFIs per 1,000 prophylaxis-days and to compare the consumption of antifungals in PAP among patients with newly diagnosed AML.

Despite a pivotal, multi-institutional study (12) and several guidelines (15, 17, 18), the intensity (i.e., broad- versus narrow-spectrum antifungals) and duration of PAP in patients with AML are still a matter of debate (3, 13, 14). The balance between overtreating patients who might never develop IFI and unfavorable treatment outcomes for patients who develop IFIs because of delays in treatment initiation has tipped in favor of PAP, specifically involving anti-*Aspergillus* drugs (7, 9, 10, 12, 14, 15, 19). The ideal antifungal for prophylaxis should have potent extended-spectrum activity for both oral and parenteral use and be well tolerated (1, 14), with reasonable cost, characteristics not found in a single antifungal drug. The use of more than one PAP drug was therefore a common approach for our patients. Another contentious issue is the optimal duration of PAP for AML patients. It is generally accepted that PAP should be used during periods of severe neutropenia (absolute neutrophil count of ≤500 cells/mm^3) (11–13, 15, 19, 20). However, in our real-life experience, PAP was repeatedly used in the absence of this condition.

Azoles were the most commonly used drugs as PAP per AML patient and prophylaxis-days. Although there are insufficient data to recommend PAP with echinocandins in leukemia patients receiving chemotherapy (15, 17), echinocandin-based PAP has been increasingly used (19) and proportionally more during high-risk periods in AML patients. Multiple reasons probably have contributed to this fact. Specifically, intravenous antifungal prophylaxis has the advantage of ensuring adequate drug concentrations during the initial period of profound neutropenia (13, 14). Additionally, the risk of azole-drug interactions specially posed by the frequent use of investigational chemotherapy at our institution, the unpredictable pharmacokinetics of azoles, concerns regarding higher risk for adverse events with azoles, or even patients' comorbidities (e.g., preexisting liver dysfunction) might account for the frequent frontline use of echinocandins as PAP (21). Posaconazole is the only systemic antifungal drug recommended for PAP with an A1 recommendation ranking for AML/MDS (12, 14, 15, 17). To our knowledge, our study is the first to compare the incidences of IFIs during posaconazole- or voriconazole- versus echinocandin-based PAP. We did not detect differences between voriconazole and posaconazole in terms of overall IFI, documented IFI, or EAT incidence rates. We found higher rates of posaconazole discontinuation owing to adverse events (5/25; 20%) than those reported by other studies (0 to 3%) (6, 7, 10) but not when we compared posaconazole with voriconazole ($P = 0.75$).

The proportion of documented IFIs identified in our study was consistent with the results of other recent studies examining PAP (4–10), but it was higher than results documented in clinical trials (11–13). Such differences probably reflect the inclusion of selected patients in randomized studies. Nevertheless, both mold and yeast IFIs remain as a significant problem in this patient population (20, 22). Our results are in agreement with observations that IFI incidence has been increasing over time owing to several factors, including longer survival of immunosuppressed patients and advances in diagnosis of fungal infections (23, 24). The finding that 75% of deaths in AML patients with documented or presumed IFI occurred within 6 weeks of IFI diagnosis is consistent with previous observations that most of the *Aspergillus*-attributable mortality occurs within 6 weeks after the start of IFI therapy (25).

Prophylaxis has been considered to have the most significant

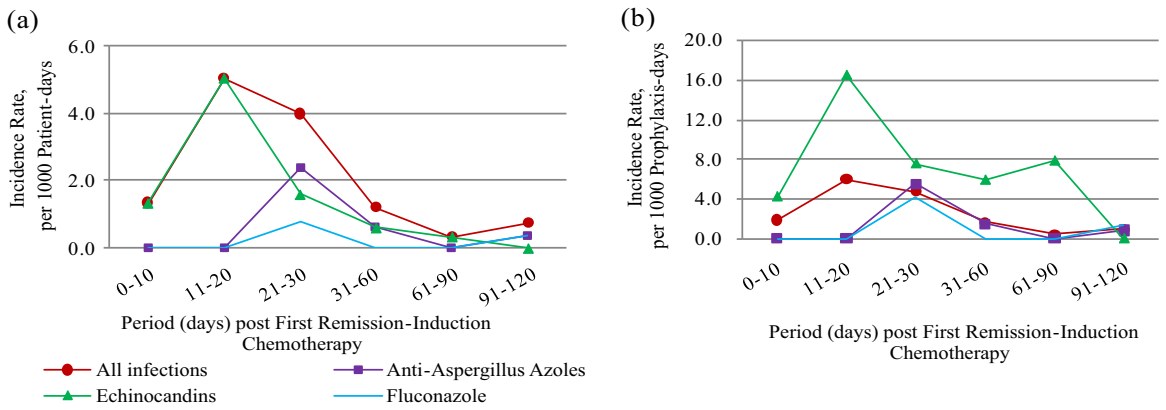

FIG 3 Incidence rates of documented IFIs per 1,000 patient-days (a) and per 1,000 prophylactic-days (b) over the 120-day period after first remission-induction chemotherapy among patients with newly diagnosed AML.

benefit during periods when IFI incidence is ≥15% and minimal benefit when IFI incidence is <5% (14, 26). Overall IFI, documented IFI, and EAT incidence densities were higher during the first 42 days and significantly lower after day 42, suggesting that mold-active PAP should be preserved for the period of higher rates, whereas a preemptive antifungal therapy approach (27, 28) or a less intensive (narrower antifungal spectrum) prophylactic regimen may be more reasonable for the period of lower rates (42 to 120 days).

The epidemiology of IFIs in cancer centers over the last 2 decades has been characterized by increasing rates of infections caused by *Aspergillus* and non-*Aspergillus* molds and azole-resistant yeasts (2, 3, 9, 10, 29, 30). Descriptions of echinocandin-resistant yeast infections in patients previously exposed to echinocandins are increasingly being reported (9, 22, 30–33). Half of our isolated *Candida* species were nonsusceptible to caspofungin, but all isolates were susceptible *in vitro* to anti-*Aspergillus* azoles. Despite the low fungal recovery and the absence of susceptibility tests for molds, the detection during echinocandin prophylaxis of 86% (6/7) of culture-positive documented IFIs caused by fungi innately resistant or sporadically nonsusceptible to echinocandins (*Candida glabrata*, *Candida krusei*, *Fusarium* sp., *Paecilomyces* sp., *Geotrichum capitatum*, and *Coccidiodes* sp.) suggests that resistance was likely an important issue associated with "breakthrough" IFIs during echinocandin prophylaxis. In contrast, among anti-*Aspergillus* azoles, we were able to identify only *Fusarium* sp. as a cause of a breakthrough IFI during posaconazole prophylaxis. However, the exact incidence of various molds in our study is uncertain, as evidence of *Aspergillus* in documented IFIs was based only on galactomannan tests. As several other hyalohyphomycoses could be positive for galactomannan, we cannot exclude other non-*Aspergillus* molds among probable IFIs (34–36). Although azole-resistant *Aspergillus* molds are infrequently reported in the United States (37), we cannot exclude the possibility of breakthrough infection with azole-resistant mold in galactomannan diagnosis-based cases.

In addition to resistance issues, the effectiveness of a particular antifungal agent depends on its pharmacokinetic and pharmacodynamic properties (2, 38, 39). Because new triazoles frequently have unpredictable pharmacokinetics and often interact with other drugs (2), and because TDM has been rarely performed during PAP (3, 9), we cannot rule out that some breakthrough IFIs with azoles were due to suboptimal drug exposure. Additionally, a short washout period between PAP drugs of different antifungal classes may hamper the establishment of an association of a PAP drug to IFI in at least one of our cases. However, we found anti-*Aspergillus* azoles, which have a broader spectrum of activity but more pharmacokinetic problems (2), to be associated with lower IFI incidence rates than echinocandins.

Overall, our findings support the hypothesis that echinocandin-resistant fungi, otherwise susceptible to anti-*Aspergillus* azoles, were selected during the years of study. The relatively restricted antifungal coverage and penetration into some sites of infection by echinocandins (2, 40) may account for the differences in IFI incidence among classes of anti-*Aspergillus* drugs and the likely limitation of the use of echinocandins in PAP in high-risk settings. However, several factors related to baseline characteristics of AML patients, including comorbidities, the chemotherapy regimen used, the degree of immunosuppression, previous fungal colonization, or even environmental exposures, could influence the overall risk for IFI development in AML patients (23, 26) and interfere with IFI incidences among classes of antifungal drugs. These features will be the subject of a future multivariate analysis and comparison of patients using either antifungal class only.

Our study had several limitations, including its retrospective nature, its small sample size, and the fact that it was conducted in a single center. Decisions about PAP initiation, type, switch, and discontinuation were left at the discretion of the treating hematologists. In addition, documented IFI rates were probably underestimated, mainly because the diagnosis of documented mold IFIs relied heavily on galactomannan tests, and the autopsy rate was negligible. Although differences among PAP classes in terms of the incidences of definite (fungi recovered from sterile sites and/or histology showing fungal forms) and documented yeast IFIs were independent of galactomannan results, prophylaxis based on *Aspergillus*-active agents influences the performance of galactomannan tests (41). Moreover, caution should be taken in extrapolating our findings to other cancer centers, because the epidemiology of IFIs and antifungal use may vary among institutions.

In summary, IFIs, especially molds, remain a significant cause of morbidity and mortality in AML patients, despite the widespread use of broad-spectrum PAP during chemotherapy for AML. The results were unfavorable for echinocandins as PAP in AML patients but were quite favorable for anti-*Aspergillus* azoles; however, prospective studies are necessary to confirm our findings. A key message of this study is that the overuse of PAP may hamper their benefit, allowing the selection of more resistant fungi. Our study suggested that (i) mold-active PAP should be preserved for the period of higher rates of infection, typically during the initial acute phase of chemotherapy treatment in AML patients; (ii) preemptive antifungal therapy or a less intensive prophylactic regimen may be more reasonable for the periods of lower rates; and (iii) surveillance for resistant fungi (44) and antifungal stewardship programs should be implemented in high-risk settings. These approaches may contribute to increasing the useful life of antifungal drugs.

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