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MAJOR ARTICLE

When Azoles Cannot Be Used: The Clinical Effectiveness of Intermittent Liposomal Amphotericin Prophylaxis in Hematology Patients

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Background. Patients unable to take azoles are a neglected group lacking a standardized approach to antifungal prophylaxis. We evaluated the effectiveness and safety of intermittent liposomal amphotericin B (L-AMB) prophylaxis in a heterogenous group of hematology patients.

Methods. A retrospective cohort of all hematology patients who received a course of intravenous L-AMB, defined as 1 mg/kg thrice weekly from July 1, 2013 to June 30, 2018, were identified from pharmacy records. Outcomes included breakthrough-invasive fungal disease (BIFD), reasons for premature discontinuation, and acute kidney injury.

Results. There were 198 patients who received 273 courses of L-AMB prophylaxis. Using a conservative definition, the BIFD rate was 9.6% (n = 19 of 198) occurring either during L-AMB prophylaxis or up to 7 days from cessation in patients who received a course. Probable/proven BIFD occurred in 13 patients (6.6%, 13 of 198), including molds in 54% (n = 7) and non-*albicans* Candidemia in 46% (n = 6). Cumulative incidence of BIFD was highest in patients with acute myeloid leukemia (6.8%) followed by acute lymphoblastic leukemia (2.7%) and allogeneic stem cell transplantation (2.5%). The most common indication for L-AMB was chemotherapy, or anticancer drug-azole interactions (75% of courses) dominated by vincristine, or acute myeloid leukemia clinical trials, followed by gut absorption concerns (13%) and liver function abnormalities (8.8%). Acute kidney injury, using a modified international definition, complicated 27% of courses but was not clinically significant, accounting for only 3.3% (9 of 273) of discontinuations.

Conclusions. Our findings demonstrate a high rate of BIFD among patients receiving L-AMB prophylaxis. Pragmatic trials will help researchers find the optimal regimen of L-AMB prophylaxis for the many clinical scenarios in which azoles are unsuitable, especially as targeted anticancer drugs increase in use.

Keywords. antifungal prophylaxis; breakthrough fungal infection; invasive fungal disease; liposomal amphotericin B; malignant hematology.

Azole antifungal drugs are the mainstay of prophylaxis used to prevent invasive fungal diseases (IFDs) in patients with high-risk hematological malignancies or hematopoietic stem cell transplant (HSCT) recipients. However, there are circumstances in which patients may be unable to safely take azoles due to intolerance, toxicity, or drug-drug interactions. The latter is seen in patients undergoing treatment for acute lymphoblastic leukemia (ALL), where azoles can potentiate vincristine-associated toxicity [1], and where tyrosine kinase inhibitors are used in Philadelphia-positive disease [2], but it is increasingly seen in patients with acute myeloid leukemia (AML) on targeted anticancer drugs [3].

The polyene antifungal, liposomal amphotericin B (L-AMB), has been evaluated over the years as an alternative to azoles with mixed results [4–10]. Liposomal amphotericin B has several favorable characteristics that promote intermittent or extended-interval dosing, including a long terminal half-life of 152 hours [11, 12], retention in tissues, along with an absence of interactions with agents such as cyclosporine and tacrolimus [13]. It is unfortunate that the only placebo-controlled, randomized, clinical trial in the modern era, which comprised L-AMB 5 mg/kg twice weekly in patients with ALL undergoing remission-induction chemotherapy, did not demonstrate a statistically significant reduction in short-term IFD rates (7.9% vs 11.7%, P = .24) [6]. Despite this result, an unmet clinical need remains not only for ALL, but for a range of clinical scenarios. These have usually been

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disaggregated in studies of L-AMB prophylactic efficacy into either neutropenia [8, 10], transplant [7, 8], or acute leukemia [4–6, 9] but are likely much wider given the heterogeneity of patients in clinical practice.

When azoles are avoided, several Australian centers including ours, have resorted to using intermittent L-AMB prophylaxis [12]. The aim of this study was to describe the real-world clinical effectiveness and safety of intermittent L-AMB prophylaxis in a heterogeneous but contemporary group of hematology patients. The clinical scenario described here represents the real-world challenges we navigate often without high-quality evidence.

METHODS

Study Design and Setting

This was a single-center retrospective cohort study of hematology patients at The Alfred Hospital who received systemic L-AMB prophylaxis from 1 July 2013 to 30 June 2018. The Alfred Hospital is 638-bed quaternary university-affiliated adult center located in Melbourne, Australia, with trauma, heart/lung transplantation, allogeneic HSCT, cystic fibrosis, burns, hyperbaric medicine, and human immunodeficiency virus state-wide services.

Antifungal prophylaxis is prescribed according to an institutional protocol. Since 2012, patients unable to take azole drugs have been given 1 mg/kg of L-AMB (based on real body weight) intravenously 3 times per week on Monday, Wednesday, and Friday, both as inpatients and outpatients, with 250 mL of either 5% dextrose or saline prehydration. For the majority of patients, this translates to 50 to 120 mg 3 times weekly, but it is usually either 50 or 100 mg thrice weekly depending on patient weight.

Chest computed tomography is performed for suspected IFD with bronchoalveolar lavage or biopsy is performed as tolerated. A surveillance-driven approach using serum galactomannan or *Aspergillus* PCR surveillance is not routine, and, when they are performed, these are send-away tests performed as part of the diagnostic work-up when IFD is suspected. Empiric antifungal therapy is sometimes commenced in the presence of suspicious radiologic changes while awaiting diagnostic investigations. Since April 2005, all patients have been treated in high efficiency particulate air-filtration rooms. An infectious diseases physician and registrar perform regular ward rounds on a referral basis for hematology patients.

Patient Consent Statement

Institutional ethics approval from Alfred Health with a patient waiver of consent was obtained (Project no. 104/17).

Study Criteria and Clinical Variables

Hematology patients who received L-AMB for any indication were identified from pharmacy dispensing records. From these, all patients who received at least 3 consecutive alternate day doses of intravenous L-AMB typically on Monday, Wednesday, and Friday, which define a course, were identified. Patients were excluded if they did not receive a course of L-AMB prophylaxis, received treatment dosing, were administered different L-AMB-dosing regimens (eg, 5 mg/kg twice weekly) as part of a hematology clinical trial, or were on more than 1 antifungal agent. Secondary courses of L-AMB were not excluded because we were interested in determining whether any courses were complicated by additional breakthrough-invasive fungal disease (BIFD). Data collected included the following: patient demographics; IFD details; outcomes including short-term mortality up to 12 weeks from the last L-AMB dose; adverse reactions; reasons for starting or premature discontinuation of L-AMB; and renal function at baseline, weekly, and up to 14 days after L-AMB cessation.

Clinical Definitions

Our primary outcome was BIFD, classified by investigators (R.B., B.J.G., M.A.-R.) according to updated international consensus criteria [14] in which a probable/proven case required fungal isolation, whereas a possible case lacked positive microbiology but satisfied radiographic and host criteria. Date of IFD diagnosis was defined as date of positive microbiology or supportive imaging, whichever came first.

Breakthrough-invasive fungal disease was adjudicated by adapting published definitions to aid comparability with future studies. Breakthrough-invasive fungal disease was defined using conservative, intermediate, and broad criteria as follows. A conservative definition was IFD occurring during L-AMB prophylaxis or up to 7 days from cessation, similar to the definition by Ananda-Rajah et al [15]; however, an intermediate definition was IFD occurring up to 15 days postprophylaxis, similar to the definition by Lerolle et al [16], in patients who received at least 1 L-AMB course. We also included a broad modified intention-to-treat analysis, in which BIFD at any time point after 1 dose of L-AMB was included. Breakthrough-invasive fungal disease using all 3 definitions is reported, but the conservative definition by Ananda-Rajah et al [15] was preferred because a postprophylaxis interval of 7 days approximates the terminal half-life of L-AMB, which is 152 hours [11, 12].

Duration of L-AMB prophylaxis was the number of days from date of commencement to completion inclusive of nonadministered days (rather than days of therapy). Excess days of prophylaxis was calculated as the number of days L-AMB was continued (inclusive of nonadministered days) after resolution of neutropenia (ie, absolute neutrophil count $<0.5 \times 10^9$/L), surmising that this may represent unnecessary L-AMB exposure.

Acute kidney injury (AKI) was recorded if it was documented in the medical record as the reason for discontinuation. Acute kidney injury was also defined by modifying the Kidney Disease Improving Global Outcomes (KDIGO) criteria by retaining changes to serum creatinine up to 14 days postprophylaxis but excluding urine output, which was not available for many patients [17].

Statistical Analysis

The primary objective of this study was to evaluate the clinical effectiveness of L-AMB prophylaxis, defined as the incidence of BIFD. Secondary outcomes were renal toxicity and tolerability. Descriptive analyses were based on percentages and frequencies for categorical variables and for continuous variables, as means with standard deviation or medians with interquartile range (IQR), if the data were skewed. Creatinine values were plotted for each patient over time, by the number of weeks followed-up, and those with levels above the upper limit of normal at baseline were grouped separately. Kaplan-Meier survival plots were used to display time to event data, with groups compared using the log-rank test. When comparing those who had BIFD to those who did not, the start of L-AMB prophylaxis was considered time zero and patients were assessed to date of death or, if still alive, censored at the maximum follow-up time. To quantify the effect of BIFD and other known risk factors on death, Cox regression analysis was used. Other known risk factors included acute disease (AML or ALL vs all other conditions), disease status at the start of the L-AMB course (ie, active defined as partial remission, progressive or refractory disease; new or relapsed disease), HSCT type (allo-, auto- or none), and presence or absence of neutropenia. Cumulative incidence of BIFD from the time of hematological diagnosis (but excluding IFD occurring in the period before the start of L-AMB prophylaxis) was calculated at 3 years for the overall cohort and for AML, ALL, and HSCT subgroups. *P* values were 2-tailed, and a *P* value less than .05 was considered statistically significant. Analyses were completed using Stata 15.1 software (StataCorp, College Station, TX). Data were recorded onto a REDCap database.

RESULTS

Clinical Characteristics

We identified a total of 198 patients who received 273 courses of L-AMB prophylaxis from pharmacy dispensing records (Table 1). There was a male predominance (62%), mean age was 52 years (range, 16–83 years), and 35% were aged 65 years or more. Liposomal amphotericin B was administered during remission induction chemotherapy for newly diagnosed disease or in patients with active (ie, partial remission/progressive or refractory) disease in 45% and 40% of courses, respectively (Table 2). Hematological malignancies accounted for the majority of underlying conditions (97%) dominated by AML in 46% and ALL in 27% of patients. Allogeneic HSCT accounted for the majority of HSCT recipients (27 of 29). Patient acuity and resource ultilization was high with 29% of patients requiring intensive care unit admission. Mortality at 30 days and 12 weeks from the end of prophylaxis was 17% and 22%, respectively (Table 1).

Table 1. Clinical Characteristics of Patients Receiving Intermittent Liposomal Amphotericin B Prophylaxis

Characteristic	Patients, n = 198 (%)
Male sex, no. (%)	123 (62)
Age at diagnosis, mean (range)	52 (16–83)
Weight, mean (range, kg)	74 (31–165)
Ethnic origin, no. (%)	
Caucasian	166 (84)
Asian	12 (6.1)
Indian subcontinent	7 (3.5)
Pacific Islander	3 (1.5)
Middle Eastern	6 (3.0)
African	3 (1.5)
Hispanic	1 (0.5)
Comorbidities, no. (%)	
Diabetes	34 (17)
Chronic kidney disease	12 (6.1)
Chronic liver disease	13 (6.6)
Underlying hematological disease, no. (%)	
Acute myeloid leukemia	92 (46)
Acute lymphoblastic leukemia	53 (27)
Acute promyelocytic leukemia	16 (8.1)
Non-Hodgkin's lymphoma	13 (6.6)
Multiple myeloma	10 (5.1)
Chronic myeloid leukemia	4 (2.0)
Chronic lymphocytic leukemia	1 (0.5)
Myelodysplastic syndrome	4 (2.0)
Hodgkin's lymphoma	2 (1.0)
Myelofibrosis	2 (1.0)
Blastic plasmacytoid dendritic cell neoplasm	1 (0.5)
HSCT recipients	29 (15)
HSCT type, no. (%)	
Allogeneic	27 (93)
Autologous	2 (6.9)
Allograft characteristics, n = 27	
HLA matched	13 (48)
Single antigen mismatch	1 (3.7)
Unrelated donor	13 (48)
Presence of GVHD	21 (78)
Clinical outcomes	
ICU admission	57 (29)
30-day mortality from last dose, n = 196[a]	33 (17)
12-week mortality from last dose, n = 193[a]	42 (22)

Abbreviations: GVHD, graft versus host disease; HLA, human leucocyte antigen; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit.

[a]Two and 5 patients were lost to follow-up before 30 days and 12 weeks, respectively.

Characteristics and Indications for Liposomal Amphotericin B Prophylaxis

The median duration of L-AMB prophylaxis was 16 days (IQR, 10–27 days) with a median of 7 doses (IQR, 5–11) administered. The majority of courses were associated with neutropenia (87%), which was prolonged and lasted 3 weeks or more in 45% of courses associated with neutropenia at L-AMB administration (Table 2). Liposomal amphotericin B prophylaxis was continued beyond neutrophil recovery in 23 (8.4%) courses. The median number of excess days of L-AMB administered was 10 (IQR, 5–19) days, approximating 6 additional doses of L-AMB for these 23 courses.

Table 2. Characteristics of Liposomal Amphotericin B Prophylaxis Courses

Characteristic	Total Courses[a], n = 273 (%)
Status of Hematological Disease at Start of L-AMB Prophylaxis	
New diagnosis, no prior treatment	123 (45)
Active disease[b]	110 (40)
Relapsed disease	40 (15)
Presence of neutropenia (<0.5 × 10^9/L) at start of L-AMB prophylaxis	237 (87)
Neutrophil count, mean ± SD	0.2 ± 0.15
Of Those Neutropenic, Duration of Neutropenia	
>5 weeks	46 (19)
3–5 weeks	62 (26)
7 days–3 weeks	103 (43)
<7 days	26 (11)
L-AMB continued despite neutrophil count recovery	23 (8.4)
Additional days of L-AMB prophylaxis, median (IQR)	10 (5–19)
Indication for L-AMB prophylaxis (may be >1)	
Chemotherapy regimens contraindicating azole use	206 (75)
ALL on vincristine in 93, dasatinib in 1	94 (46)
Enrolled in clinical trial[c]	80 (39)
APML in cycle 1	16 (7.8)
Burkitt's lymphoma on CODOX-M/IVAC	6 (2.9)
NHL on hyperCVAD regimen	6 (2.9)
CML on vincristine (n = 2) or dasatinib (n = 1)	3 (1.5)
Blastic plasmacytoid dendritic cell neoplasm on hyperCVAD	1 (0.5)
Gastrointestinal absorption concerns	35 (13)
Gastrointestinal GVHD	28 (82)
Mucositis	6 (18)
CMV colitis	1 (2.9)
Liver function derangement	24 (8.8)
Allergy or intolerance to azoles[d]	7 (2.6)
Drug interaction outside cytotoxic therapies	3 (1.1)
Secondary prophylaxis for IFD[e]	2 (0.73)
Dose and duration of prophylaxis courses	
Duration in days of L-AMB prophylaxis per course, median (IQR)	16 (10–27)
Number of doses of L-AMB per course, median (IQR)	7 (5–11)
Cumulative L-AMB dose per course adjusted for patient weight (mg/kg), median (IQR)	8.6 (5.4 – 14)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; CML, chronic myeloid leukemia; L-AMB, liposomal amphotericin B; CMV, cytomegalovirus; CODOX-M/IVAC, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate; GVHD, graft versus host disease; hyperCVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine; IFD, invasive fungal disease; IQR, interquartile range; IVAC, ifosfamide, etoposide, high-dose cytarabine; NHL, non-Hodgkin lymphoma; SD, standard deviation.

[a]Course defined as receipt of at least 3 alternate day doses of L-AMB for prophylaxis.

[b]Active disease defined as partial remission, progressive or refractory disease.

[c]Underlying hematological malignancy in trial episodes: AML n = 74, ALL and myelodysplasia n = 2 each, CML and multiple myeloma n = 1 each.

[d]Hallucinations to voriconazole in 4, unspecified allergy in 2, nausea in 1 course.

[e]Two patients had 2 courses of L-AMB as secondary prophylaxis for previous possible and proven IFD, respectively. Neither of these patients developed breakthrough IFD while on L-AMB prophylaxis.

Chemotherapy or anticancer drugs contraindicating azole antifungal prophylaxis was the most common indication for L-AMB prophylaxis and accounted for 75% (n = 206) of courses. This comprised vincristine-based treatment of ALL (93 of 206, 45%) and patients enrolled in clinical trials (80 of 206, 39%). The majority of L-AMB courses for anticancer drugs were for patients with AML (93%, n = 74 of 80) receiving venetoclax (n = 49 courses), sorafenib/placebo (n = 7 courses), or a variety of other agents (Supplementary Figure 1). Other reasons for L-AMB use included impaired gastrointestinal absorption in 13% of courses (mostly due to graft versus host disease [GVHD] and mucositis) and liver function abnormalities in 8.8%. Documented allergy or intolerance to azoles was uncommon and accounted for 2.6% (n = 7) of L-AMB courses.

Breakthrough Invasive Fungal Disease

Using a conservative definition adapted from [15], the BIFD rate was 9.6% (19 of 198), comprising 13 (68%) probable/proven IFD and 6 (32%) possible IFD episodes (Table 3). Breakthrough invasive fungal disease rates using intermediate and broad definitions were 12.1% (24 of 198) and 13.1% (26 of 198), respectively. This translated to 3.3, 4.2, and 4.6 BIFDs per 1000 L-AMB prophylaxis days for the conservative, intermediate, and broad BIFD definitions. The respiratory tract (lung and sinus) accounted for 74% (14 of 19) of BIFDs followed by blood in 32% (6 of 19). Molds were slightly more common than *Candida* species (54% vs 46%) among probable/proven cases comprising *Paecilomyces* in 1 and bronchoalveolar galactomannan in 6 cases. All proven episodes were caused by non-*albicans* candidemia. All mold infections were probable

Table 3. Characteristics of Breakthrough Invasive Fungal Disease

Characteristic	Patients, n = 198 (%)
BIFD[a]	19 (9.6)
Proven/probable	13 (68)
Possible	6 (32)
Localized	12 (63)
Disseminated	7 (37)
Site of BIFD	
Lung	13 (68)
Bloodstream	6 (32)
Sinus	1 (5.3)
Skin	1 (5.3)
Organism in probable/proven BIFD episodes, n = 13	
Candida species	6 (46)
Candida glabrata	3 (50)
Candida krusei	1 (17)
Candida kefyr	1 (17)
Candida guilliermondii	1 (17)
Mold species	7 (54)
Positive BAL galactomannan	6 (86)
Paecilomyces	1 (14)
Aspergillus PCR	3 (23)

Abbreviations: BAL, bronchoalveolar lavage; BIFD, breakthrough invasive fungal disease; PCR, polymerase chain reaction.

[a]A conservative BIFD definition adapted from [15]. Intermediate BIFD definition adapted from [16], n = 24 (12.1%), and a broad definition according to a modified intention-to-treat analysis was n = 26 (13.1%).

and mostly diagnosed by positive galactomannan on bronchoscopy (86%). No BIFD episodes complicated the 2 courses of L-AMB given for secondary prophylaxis. Patient-level data on BIFD are shown in a swimmer plot in Figure 1. Acute leukemia was present in 12 of 19 BIFD patients (AML in 8, ALL in 4) with remission-induction chemotherapy in 9 (AML = 6, ALL = 3). The AML subgroup with BIFD also included 5 patients enrolled in a clinical trial. Using intermediate [16] and broad definitions, the BIFD rate was 12.1% (24 of 198) and 13.1% (26 of 198), respectively.

Cumulative incidence curves showing time to BIFD using an intention-to-treat definition censored at 3 years from date of leukemia diagnosis and date of HSCT, stratified by hematological conditions, are shown in Figure 2. Overall cumulative incidence was 13.8% (95% confidence interval [CI], 9.53% to 19.9%). Corresponding cumulative incidence for AML, ALL, and HSCT was 6.8% (95% CI, 3.9% to 11.7%), 2.7% (95% CI, 1.1% to 6.3%), and 2.5% (95% CI, 0.9% to 6.5%), respectively.

Outcomes

There were 84 deaths among 166 patients (Figure 3). Median survival was significantly lower in patients with BIFD who died earlier (62 days versus 976 days, $P = .0007$). Patients with BIFD had a significantly higher risk of death (unadjusted hazard ratio [HR], 3.0; 95% CI, 1.7–5.1; $P = .001$). Survival at 100 days from start of L-AMB prophylaxis for those with BIFD was 45% (95% CI, 24% to 64%) compared with 85% (95% CI, 78% to 90%) in those patients without BIFD. After adjusting for acute leukemia (AML, ALL vs others), active disease, HSCT, and presence of neutropenia, BIFD remained significantly independently associated with death (adjusted HR, 2.8; 95% CI, 1.6 to 4.9; $P < .001$) in addition to new diagnosis of hematological condition, neutropenia, and allo-HSCT (Table 4).

Safety and Tolerability

Liposomal amphotericin B prophylaxis was well tolerated with few premature discontinuations (12.8%, 35 of 273) (Table 5). These were due to IFD onset (7.7%, n = 21) followed collectively by AKI, lack of perceived efficacy, infusion-related pain, and liver function abnormality in 5.1% (n = 14). Acute kidney injury according to a modified KDIGO criteria, occurring up to 2 weeks postprophylaxis, complicated 27% (n = 75) of courses. A KDIGO grade 3 occurred in 6.2% (n = 17) of courses, denoting an increase in serum creatinine to 3 times baseline, or ≥353.6 mmol/L, or initiation of renal replacement therapy. Median creatinine remained lower than baseline until after week 5 but did not exceed 50% of baseline, as shown in Supplementary Figure 2. Weekly trends in serum creatinine per course indicated that patients who started with high values tended to remain high (Supplementary Figure 3).

DISCUSSION

Intermittent L-AMB prophylaxis emerged historically in response to an unmet need among malignant hematology

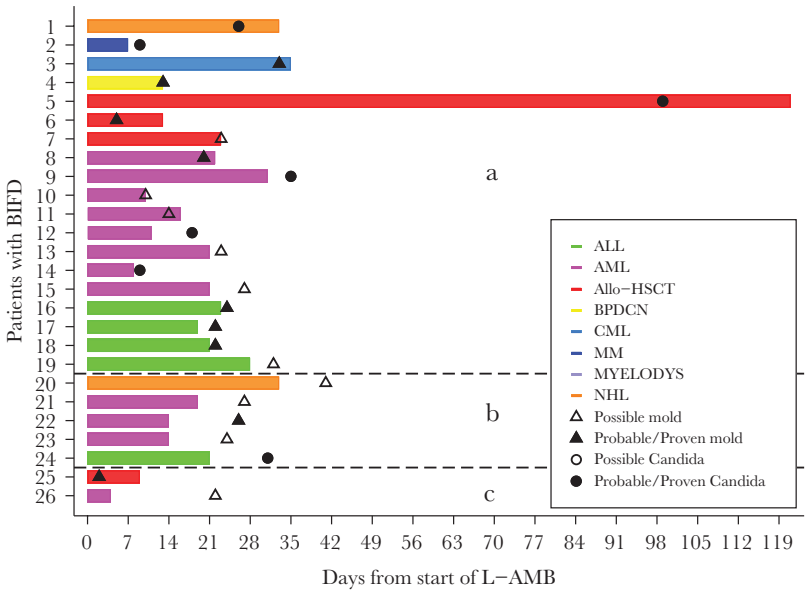

Figure 1. Swimmers plot demonstrating breakthrough invasive fungal disease (BIFD) relative to course of liposomal amphotericin B (L-AMB) prophylaxis shown by lanes, using 3 definitions (a, b, c). The BIFD definitions are adapted from [15] in (a, a conservative definition being up to 7 days from cessation of at least one course of L-AMB); [16] in (a+b, an intermediate definition being up to 15 days from cessation of at least one course of L-AMB), and a modified intention-to-treat analysis in (a+b+c, a broad definition being at any time point after at least one dose of L-AMB). ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic-hematopoietic stem cell transplant; AML, acute myeloid leukemia; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CML, chronic myeloid leukemia; MM, multiple myeloma; Myelodys, myelodysplasia; NHL, Non-Hodgkin's lymphoma.

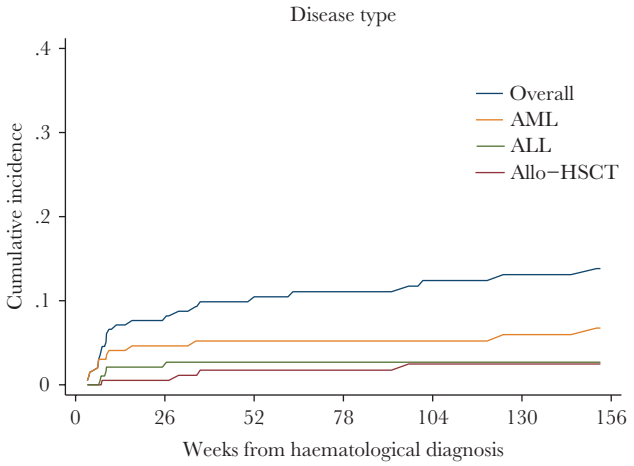

Figure 2. Cumulative incidence curves of time to breakthrough-invasive fungal disease (n = 26) stratified by acute leukemia and allogeneic hematopoietic stem cell transplant (Allo-HSCT) status. This was taken from date of leukemia diagnosis and date of HSCT to 3-year interval. Cumulative incidence in percentages are as follows: overall, 13.8% (95% confidence interval [CI], 9.53 to 19.9); acute myeloid leukemia (AML), 6.75% (95% CI, 3.85 to 11.7); acute lymphoblastic leukemia (ALL), 2.69% (95% CI, 1.13 to 6.34); and Allo-HSCT, 2.48% (95% CI, 0.93 to 6.51).

patients unable to take azole antifungals [12]. This study demonstrates that the current 1 mg/kg 3 times per week dosing strategy is associated with a high incidence of BIFD, which was 9.6% using a conservative [15] definition. This was associated with a 3-fold higher mortality compared with patients without BIFD, being most marked in the first 100 days from the start of prophylaxis. In our cohort, patients with acute leukemia were at highest risk for BIFD (Figure 2). Patients with AML and ALL accounted for 12 of 19 BIFD cases with AML responsible for 8 cases alone. Remission-induction chemotherapy was especially high risk for acute leukemia patients, with BIFD complicating 9 cases (AML = 6, ALL = 3) overall. The most common reason for L-AMB prophylaxis was interactions with anticancer drugs or cytotoxic chemotherapy in 75% of courses. This subgroup was dominated by (1) AML patients on investigational anticancer drugs (who tend to be at high risk for IFD due to chronic immunosuppression) and (2) patients on vincristine-based therapy for ALL, with lesser contributions from Burkitt's lymphoma, non-Hodgkin's lymphoma (NHL), and chronic myeloid leukemia (CML). An evidence-based approach to managing patients unable to take azole prophylaxis is urgently needed, noting that targeted anticancer drugs for AML are exploding [18] and a standardized approach to IFD prevention in ALL remains unresolved.

There remains considerable uncertainty regarding the appropriate regimen of L-AMB in the setting of prophylaxis, particularly for ambulatory patients. Extended interval prophylaxis studies with either 7.5 mg/kg [7], 10 mg/kg [5], or 15 mg/kg [4] once weekly of L-AMB were not powered for efficacy and were associated with dose-limiting toxicity. Intermittent regimens of 2 mg/kg [8] or 3 mg/kg 3 times per week [9] and 5 mg/kg twice a week [6] found no statistical difference in fungal infections compared with placebo [6, 8] or a combination of itraconazole and fluconazole [9]. An exception to this pattern is a placebo-controlled study of alternate day L-AMB 50 mg in neutropenic patients with AML, ALL, and non-NHL, which was associated with a significant reduction in proven/probable IFD but was restricted to inpatients from a single center [10]. There is

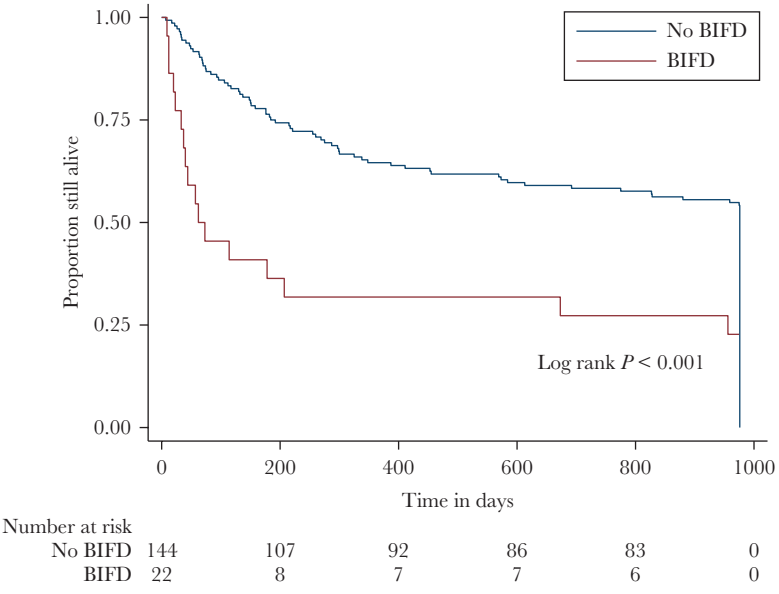

Figure 3. Kaplan-Meier curve showing survival from start of liposomal amphotericin B prophylaxis in patients with breakthrough-invasive fungal disease (BIFD) versus others with known outcome: overall, 84 deaths in 166 patients (17 with BIFD using intention-to-treat definition, 149 without BIFD).

Table 4. Risk Factors for Death (n = 166 Patients With Known Outcome)

Risk Factors	Adjusted Hazard Ratio (95% CI)	*P* Value
Breakthrough IFD	2.83 (1.64–4.87)	<.001
Acute leukemia (AML or ALL) vs all other conditions	1.44 (0.81–2.56)	.220
Disease status[a]		
Active disease	Reference	
New hematological diagnosis	0.52 (0.29–0.91)	.022
Relapsed disease	1.36 (0.72–2.59)	.343
HSCT status[a]		
No HSCT	Reference	
Allo-HSCT	3.66 (1.37–9.73)	.009
Auto-HSCT	1.44 (0.32–6.47)	.636
Presence of neutropenia	3.43 (1.13–10.4)	.029

Abbreviations: ALL, acute lymphoblastic leukemia; Allo, allogeneic; AML, acute myeloid leukemia; Auto, autologous; CI, confidence interval; HSCT, hematopoietic stem cell transplant; IFD, invasive fungal disease.

[a]Risk is assessed against the reference group, eg, the hazard ratio for allo-HSCT was 3.7 when compared with non-HSCT recipients.

Table 5. Safety of Liposomal Amphotericin B Prophylaxis

Characteristic	Total Courses, n = 273 (%)
Reason for cessation of L-AMB prophylaxis	
Neutrophil count recovery	154 (56)
Treatment completed uneventfully	71 (26)
Due to IFD	21 (7.7)
Palliation or death	13 (4.8)
Acute kidney injury	9 (3.3)
Lack of perceived efficacy leading to commencement of other systemic antifungal therapy (excluding IFD)	2 (0.7)
Pain[a]	2 (0.7)
Liver function derangement	1 (0.4)
Acute kidney injury[b]	75 (27)
KDIGO Grade 1	38 (14)
KDIGO Grade 2	20 (7.3)
KDIGO Grade 3	17 (6.2)

Abbreviations: IFD, invasive fungal disease; KDIGO, Kidney Disease Improving Global Outcomes; L-AMB, liposomal amphotericin B.

[a]One each for gastrointestinal or musculoskeletal pain.

[b]Maximal or worst KDIGO criteria during prophylaxis course and up to 2 weeks from L-AMB cessation.

some in-human evidence to support weight-based dosing for L-AMB [19], and one possible explanation for our findings is that our patients simply received insufficient doses. However, plasma concentrations alone are not necessarily reflective of the biological activity of L-AMB in tissue and cellular compartments, and distinguishing liposome-associated, tissue-bound, protein-bound, or free drug [13, 19] under variable immunosuppression conditions (eg, neutropenia and nonneutropenia immunosuppressive states) is complex.

Uncertainties around L-AMB prophylaxis dosing risks undermining the anticipated gains of the anticancer precision drug era due to opportunistic infections such as IFD. Our patients were enrolled in clinical trials for a variety of investigational drugs including inhibitors of BCL2, Pim/tyrosine kinase, and hedgehog signaling pathways predominantly for AML but also for ALL, myelodysplasia, CML, and multiple myeloma. Indeed, 5 of 19 patients who developed BIFD were enrolled in clinical trials, all for AML. Our previous study of invasive mold infections in unselected hematology patients from 2008 to 2018, revealed that 1 in 5 patients were enrolled in clinical trials [20]. It also highlighted the high fraction of BIFD, using a definition by Lerolle et al [16], which accounted for 60% of probable/proven infections (53 of 88) across a variety of antifungal prophylaxis regimens [20]. In that study, it is notable that intermittent L-AMB prophylaxis was associated with the highest incidence of BIFD in AML patients, but direct comparisons between azoles and L-AMB are not possible given heterogeneity between groups.

Real-world approaches to antifungal prophylaxis are variable because no single antifungal regimen can cover all clinical scenarios. Azole prophylaxis was precluded due to organ dysfunction in 22% of courses, including gut absorption concerns and liver function abnormalities. Allergy or intolerance (hallucinations, nausea) to azoles and drug-azole interactions (eg, prolonged QT) were rarely implicated. Our study emphasises that switching from azoles to L-AMB is not a trivial decision, and all steps should be taken to mitigate this change with, for example, therapeutic drug monitoring, intravenous azole formulations, dose adjustment of chemotherapy agents, or use of azoles with less cytochrome P450 inhibition like isavuconazole. In 8.4% of courses, excess doses of L-AMB were administered beyond neutrophil recovery, presenting a potential opportunity for antifungal stewardship, and noting that there may have been other valid reasons to continue such as GVHD on immunosuppression. The issues of emerging groups at risk for IFD on targeted anticancer therapies and optimizing antifungal stewardship in outpatients were corroborated by clinicians in a recent qualitative study on antifungal practice [21].

Liposomal amphotericin B prophylaxis was well tolerated with few premature discontinuations. Although the frequency of AKI was high at 27%, clinically significant nephrotoxicity resulting in premature discontinuation was rare at 3.3%. Severe nephrotoxicity developed in 6.2% of courses, suggesting that a cautious approach to patients with poor renal function at baseline is warranted or if prolonged courses greater than 5 weeks are anticipated (Supplementary Figure 3).

Recent definitions for BIFD are an attempt to standardize reporting, but we found the goodness of fit of these recommendations to be poor for L-AMB [22]. The period of protection conferred by L-AMB after its discontinuation is difficult to quantify because its in vivo behavior is characterized by sequestration in specific organs and variable clearance depending on dose [13, 19], notwithstanding the unknowns regarding its biologically

active component. The preponderance of fluconazole-resistant Candidaemia, which comprised all proven BIFDs is concerning and consistent with the shift to non-*albicans Candida* species in large epidemiological studies [23]. It also underscores the importance of ongoing surveillance, audit, and feedback of IFD to inform institutional policies because local "centre effects" dictate fungal epidemiology to a high degree [20, 24, 25].

The limitations of this study include its single-center focus, observational design, and retrospective analysis of a heterogenous group of hematology patients. We did not capture all toxicities, but we focused on clinically relevant ones resulting in premature discontinuation. We provided a range of BIFD definitions to aid future comparisons, but we acknowledge the difficulties in application when scientific knowledge of the in vivo behavior of L-AMB is incomplete [19]. Comparisons with triazole prophylaxis were difficult when there were legitimate reasons for avoiding them, but a 9.6% BIFD rate does not compare favorably to possible/probable/proven BIFD on posaconazole of 3% [15] and 4.7% [16], respectively, from real-world studies.

CONCLUSIONS

Evidence-based alternatives to azole prophylaxis are urgently required for this increasingly large and complex group of hematology patients. We propose pragmatic trials for antifungal prophylaxis that can accommodate the heterogeneity of clinical practice and span the microevolutionary changes in cancer care that are already upon us. Intermittent L-AMB will continue to have a role to play even when novel nonazole antifungals come online, but it deserves further study to optimize its efficacy.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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