

# Amphotericin B Lipid Complex as Prophylaxis of Invasive Fungal Infections in Patients with Acute Myelogenous Leukemia and Myelodysplastic Syndrome Undergoing Induction Chemotherapy

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**BACKGROUND.** The optimal antifungal prophylactic regimen for patients with acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (MDS) undergoing induction chemotherapy has yet to be identified. A prospective historical control study evaluated the efficacy and safety of amphotericin B lipid complex (ABLC) in this patient population.

**METHODS.** Newly diagnosed patients with AML or high-risk MDS who were undergoing induction chemotherapy received prophylactic ABLC 2.5 mg/kg intravenously 3 times weekly. This treatment group was compared with a historical control group that had similar baseline characteristics and received prophylactic liposomal amphotericin B (L-AmB) 3 mg/kg 3 times weekly. The primary endpoint was the incidence of documented or suspected fungal infections during and up to 4 weeks after cessation of prophylaxis. Reported adverse events were used to assess tolerability.

**RESULTS.** The overall efficacy of antifungal prophylaxis was similar in patients who received ABLC and patients who received L-AmB ( $P = 0.95$ ). Among 131 ABLC-treated patients and 70 L-AmB-treated patients who were assessed for efficacy and safety, 49% of patients in each group completed therapy without developing a documented or suspected fungal infection. Documented fungal infections occurred in 5% of ABLC-treated patients and in 4% of L-AmB-treated patients. Alternative antifungal strategies were required because of persistent fever or pneumonia of unknown pathogen in 28% and 32% of ABLC-treated and L-AmB-treated patients, respectively. Grade 3 and 4 adverse events, therapy discontinuations due to adverse events, and survival rates also were similar between treatment groups.

**CONCLUSIONS.** ABLC and L-AmB appeared to have similar efficacy and were tolerated well as antifungal prophylaxis in patients with AML and high-risk MDS who were undergoing induction chemotherapy. *Cancer* 2004;100:581-9.

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**KEYWORDS:** acute leukemia, amphotericin B, fungal infection, myelodysplastic syndrome, antifungal prophylaxis, amphotericin B lipid complex, liposomal amphotericin B.

The intensive chemotherapy used to induce remission in patients with acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (MDS) causes prolonged periods of neutropenia and impairment of mucosal and dermatologic barriers, increasing a patient's susceptibility to infectious complications.<sup>1,2</sup> Bacterial infections often are prevented successfully or are treated with the use of broad-spectrum antibiotics. Invasive fungal infections (IFIs), how-

ever, remain a major cause of morbidity and mortality in patients with hematologic malignancies: approximately 20–50% of patients have evidence of an IFI at autopsy.<sup>1</sup> Because the early diagnosis and treatment of fungal infections often are difficult and are associated with a high mortality rate in neutropenic patients, prevention of these infections has become an important strategy to reduce overall morbidity and mortality rates in patients with hematologic malignancies.<sup>2,3</sup>

Many antifungal agents have been evaluated as antifungal prophylaxis in patients with hematologic malignancies, including orally and intravenously (i.v.) administered polyenes, imidazoles, or triazoles, and i.v. administered caspofungin; however, the results of clinical trials evaluating these agents have been inconsistent.<sup>2,4–18</sup> Differences in study design, patient characteristics, cytotoxic regimens, antifungal dosage regimens, durations of neutropenia, and fungal resistance patterns may have contributed to these mixed results.<sup>2</sup> A recent metaanalysis by Bow and colleagues evaluated the results of randomized, controlled trials comparing azoles or i.v. amphotericin B formulations with placebo or polyene-based controls in severely neutropenic chemotherapy patients; the metaanalysis results showed that azole or amphotericin B antifungal prophylaxis reduced both the need for parenteral antifungal therapy and the incidence of superficial fungal infection, IFI, and IFI-related mortality.<sup>2</sup> These effects were most pronounced in patients with prolonged neutropenia, such as patients with AML who were undergoing induction chemotherapy, and in patients undergoing hematopoietic stem cell transplantation (HSCT). A reduction in the overall mortality rate, however, was observed in the HSCT population only, and a reduction in the incidence of invasive aspergillosis was not observed in either group.

The benefit of antifungal prophylaxis with either azoles or polyenes (primarily fluconazole or amphotericin B) in patients with AML who are undergoing induction chemotherapy was confirmed recently in a retrospective review of 322 assessable patients who experienced 833 episodes of neutropenia.<sup>19</sup> The results showed that antifungal prophylaxis was associated with fewer IFIs ( $P < 0.001$ ) and less frequent use of empiric amphotericin B ( $P = 0.006$ ). In addition, death within 30 days of the first episode of neutropenia was reduced with the use of antifungal prophylaxis compared with no antifungal prophylaxis (23% vs. 35%;  $P = 0.026$ ). These results suggest that patients with AML who are undergoing induction chemotherapy are likely to benefit from antifungal prophylaxis,

but the optimal antifungal regimen has yet to be identified.

For many years, amphotericin B has been the gold standard for treatment of IFIs, including those caused by *Candida* and *Aspergillus* species, the most common fungal pathogens in leukemic patients; however, antifungal prophylaxis with amphotericin B often produces nephrotoxicity and infusion-related adverse effects, limiting administration of adequate doses.<sup>1,5</sup> Reduced nephrotoxicity has been observed with lipid formulations of amphotericin B, such as amphotericin B colloidal dispersion (ABCD) (Amphotec®; InterMune; Brisbane, CA), amphotericin B lipid complex (ABLC) (ABELCET®; Enzon [formerly The Liposome Company], Piscataway, NJ), and liposomal amphotericin B (L-AmB) (AmBisome®; Fujisawa USA Inc., Deerfield, IL).<sup>1</sup> In addition, it has been shown that ABLC and L-AmB are equally effective in the treatment of suspected or documented fungal infections in patients with acute leukemia, but only L-AmB has been evaluated as a prophylactic agent in patients with AML or MDS.<sup>11,20</sup>

It has been shown that L-AmB is effective as antifungal prophylaxis during induction chemotherapy for patients with AML and high-risk MDS, with 49% of patients completing prophylaxis and only 4% of patients developing proven fungal infections during L-AmB prophylaxis.<sup>11</sup> The prospective historical control study reported herein compared ABLC with L-AmB as antifungal prophylaxis in patients with AML and high-risk MDS who were undergoing induction chemotherapy.

## **MATERIALS AND METHODS**

### **Patients**

#### *Eligibility criteria*

Patients were eligible for this study if they 1) were age  $\geq 15$  years; 2) were undergoing initial induction chemotherapy for AML, acute undifferentiated leukemia (AUL), or high-risk MDS at The University of Texas M. D. Anderson Cancer Center; and 3) had a serum creatinine (SCr) level  $< 3.0$  mg/dL. Excluded from the study were pregnant or lactating women; women of childbearing potential who were unwilling to use effective contraception throughout the study; patients with a previously documented, serious, idiosyncratic reaction to amphotericin B or any amphotericin B-containing product; and patients with baseline clinical or radiographic evidence of suspected or documented fungal infection.

#### *Historical control group*

The control group included patients who underwent initial induction chemotherapy for treatment of AML

or high-risk MDS between April 1998 and May 1999; they were enrolled in a prospective, randomized study comparing the prophylactic administration of L-AmB with a fluconazole-itraconazole combination and were randomized to receive L-AmB.<sup>11</sup> This group was chosen as the control group because of the similar study design. All patients in the control group received L-AmB 3 mg/kg 3 times weekly during induction chemotherapy and during the subsequent neutropenic period.<sup>11</sup>

### Study Design

The current open-label, historical control, single-institution study was approved by The University of Texas M. D. Anderson Cancer Center Investigational Review Board. Informed consent was obtained from each patient or from a legally authorized representative before the initiation of ABLC prophylaxis.

### Drug administration

ABLC (ABELCET®; Enzon) was supplied as a sterile suspension in isotonic saline containing 5 mg/mL of amphotericin B and was prepared according to the manufacturer's instructions.<sup>21</sup> All patients received ABLC 2.5 mg/kg i.v. through a peripheral i.v. line or a central venous catheter over 1–2 hours 3 times each week (i.e., Monday, Wednesday, and Friday) beginning on the first day of induction chemotherapy. Because ABLC has a prolonged half-life (173 hours), it was expected that the intermittent administration of ABLC in this protocol would be effective.<sup>21</sup>

Patients were premedicated with acetaminophen 650 mg orally, meperidine 25–50 mg i.v., and hydrocortisone 25–50 mg i.v.. The use of i.v. meperidine and acetaminophen every 1–2 hours after the ABLC infusion was permitted as treatment of infusion-related adverse events.

ABLC prophylaxis was continued until 1) the absolute neutrophil count was  $\geq 500$  cells/mm<sup>3</sup> for 2 consecutive days in the absence of fungal infection signs and symptoms; 2) a patient developed a proven or probable fungal infection, as defined by Asciglu and colleagues<sup>22</sup>; 3) a patient had neutropenia lasting  $\geq 6$  weeks; 4) a patient had intolerable Grade 3–4 adverse events; or 5) a patient was declared resistant to treatment, achieved a complete response, or died. At the discretion of the investigator, treatment discontinuation was permitted if a patient's SCr level increased to  $> 3$  mg/dL for more than 3 consecutive days or serum transaminase levels increased to  $\geq 8$  times the normal level. Resumption of ABLC administration at 1.25 mg/kg per day 3 times weekly was permitted once nephrotoxicity or hepatotoxicity de-

creased to Grade 1 or 2 according to the National Cancer Institute (NCI) Common Toxicity Criteria.<sup>23</sup>

Antibacterial prophylaxis with trimethoprim/sulfamethoxazole 80/400 mg i.v. twice daily or ciprofloxacin 200 mg i.v. twice daily and antiviral prophylaxis with oral valacyclovir 500 mg daily was administered to all patients during the neutropenic period. No other concomitant antifungal agents were allowed.

### Efficacy assessment

Each patient who received at least four doses of ABLC was assessed for efficacy. The primary efficacy endpoint was the incidence of fungal infections or pneumonia of unknown pathogen (PUP) that did not respond to broad-spectrum antibiotics and that required additional amphotericin B therapy during the 4-week follow-up. The secondary endpoint was the absence of signs and symptoms of a suspected or documented fungal infection that required amphotericin B therapy at the time of neutrophil recovery (i.e.,  $\geq 500$  cells/mm<sup>3</sup>).

At the onset of fever, blood samples were obtained for culture, and additional blood samples were obtained for culture as needed if fever persisted. Chest radiographs were performed at the time of hospital admission and at the onset of fever or of signs and symptoms of pulmonary compromise. If fever persisted, then chest radiographs were performed every 3–4 days. Bronchoalveolar lavage (BAL) specimens were obtained for culture in patients with extensive pulmonary infiltrates or in patients who developed new pulmonary infiltrates while they were receiving antibacterial agents; computed tomography scans were performed at the physician's discretion.

Documented fungal infections were diagnosed by the presence of morphologic, pathologic, or culture evidence of a fungus in the 1) blood, 2) skin, 3) subcutaneous tissues, 4) other infected tissues, 5) bronchoscopic material, or 6) other tissues that were obtained from other procedures. Suspected fungal infections were defined as a persistent or worsening fever and signs and symptoms of fungal infection after 72 hours of antibacterial therapy without microbiologic confirmation of a bacterial infection. Suspected fungal infections were categorized further as either PUP or fever of unknown origin (FUO). Patients with radiographic and clinical findings consistent with pneumonia were classified with PUP; otherwise, patients were classified with FUO.

### Safety assessment

All patients who received at least one dose of ABLC were assessed for safety. Safety was assessed during prophylactic antifungal administration, at the comple-

tion of the study, and 2 weeks and 4 weeks after the study was completed. All adverse events were graded and recorded using the NCI Common Toxicity Criteria.

### Statistical Analysis

A Bayesian sequential monitoring design for a single-arm clinical trial with multiple outcomes was used to determine the sample size and rules for prematurely stopping the study.<sup>24</sup> Prior probability distributions were derived from institutional data on patients with newly diagnosed AML or high-risk MDS who were treated from 1995 through 1996. Given the objective of this study—to decrease the 1995–1996 rate of fungal infections and PUPs of 19% to an estimated rate of 10% while simultaneously not increasing the rate of FUO by 10% (i.e., from the 1995–1996 rate of 41% to > 51%)—a sample size of 50 patients was required. An additional 100 patients, for a total sample size of 150 patients, were required to estimate more precisely the effects of risk factors on overall survival.

Univariate analyses, including the use of the *t* test for continuous variables and the chi-square test for categoric variables, evaluated a potential imbalance among patient characteristics and risk factors. The Fisher exact test was performed to evaluate Zubrod grade because of the small sample size. Clinical outcomes were analyzed using a variety of methods. The efficacy of antifungal prophylaxis and chemotherapy response rates were compared using frequency tests. Univariate and multivariate logistic regression models were developed to evaluate the effects of other covariates on fungal infection rates. The time to treatment failure was defined as the time from ABLC initiation to the time when ABLC therapy was discontinued because of a documented fungal infection, FUO, or PUP. Time-to-treatment-failure curves were estimated using the Kaplan–Meier method and were compared using the log-rank test. Survival was defined as the time from the initiation of chemotherapy until the date of either death due to any cause or the last follow-up. Survival curves were estimated using the Kaplan–Meier method. The univariate and multivariate Cox proportional hazards regression models were used to assess the relation between prognostic factors and overall survival. Predictive variables in the Cox model were identified by performing a forward, stepwise selection of variables with a *P* value < 0.05. The final Cox model allowed reentry of any previously deleted variables with a *P* value < 0.05. All tests measuring statistical significance were performed using a two-sided, 5%, type-I error rate. Statistical analysis was performed using SAS software (version 8.0; SAS

Inc., Cary, NC) and S-plus 2000 software (Cambridge, MA) on a Compaq W4000 computer.

## RESULTS

### Patient Characteristics

Between September 1997 and February 2000, 148 patients were enrolled in the study, including 131 patients who could be assessed fully and had received ABLC prophylaxis. Nine patients were excluded from the efficacy and safety analyses because they did not complete the first ABLC dose; the remaining eight patients were excluded because of protocol violations. The patient characteristics and risk factors of the ABLC group and the historical control group were similar, except for underlying diagnoses, baseline total bilirubin levels, baseline albumin levels, and length of antifungal prophylaxis therapy (Table 1). More L-AmB-treated patients had AML compared with ABLC-treated patients (76% vs. 51%; *P* = 0.0007). ABLC-treated patients had a significantly higher baseline total bilirubin level compared with L-AmB-treated patients (0.7 ng/dL vs. 0.6 mg/dL; *P* = 0.002); L-AmB-treated patients, however, had higher baseline albumin levels (3.6 g/dL vs. 3.4 g/dL; *P* = 0.015). Patients in the ABLC group received antifungal prophylaxis for a longer duration compared with patients in the L-AmB group (17 days vs. 13.5 days; *P* < 0.0001).

Most L-AmB-treated patients (93%) received topotecan as the primary induction chemotherapy agent; whereas ABLC-treated patients most commonly received topotecan, fludarabine, or an anthracycline as the primary induction chemotherapy agent (65%, 16%, and 18%, respectively). The rate of complete response to induction chemotherapy was similar between the ABLC-treated group and the historical control group (Table 2).

### Clinical Outcomes

The efficacy of antifungal prophylaxis therapy was similar between treatment groups (*P* = 0.95) (see Table 2). Of 131 ABLC-treated patients and 70 L-AmB-treated patients who were assessable for efficacy (i.e., patients who received at least 4 days of antifungal prophylaxis), 64 patients (49%) and 34 patients (49%), respectively, completed antifungal prophylaxis without developing a documented or suspected fungal infection. The time to treatment failure of antifungal prophylaxis also was similar between treatment groups (*P* = 0.102) (Fig. 1).

### Documented fungal infections

Documented IFIs were diagnosed in 6 ABLC-treated patients (5%) and in 3 L-AmB-treated patients (4%) between Day 4 and Day 24 of antifungal prophylaxis.

**TABLE 1**  
Patient Characteristics and Risk Factors

Characteristic	ABLC <sup>a</sup>	L-AmB <sup>a</sup>	P value
No. of patients	131	70	
Age (yrs)			
Median	65	63	0.98
Range	21–87	36–83	
Gender			
Male	85 (65)	42 (60)	0.49
Female	46 (35)	28 (40)	
Underlying disease			
AML	67 (51)	53 (76)	0.0007
MDS	64 (49)	17 (24)	
Zubrod performance status			
0–2	127 (97)	70 (100)	0.83
≥ 3	4 (3)	0 (0)	
Protected environment	107 (82)	54 (77)	0.44
Nonfungal infection at start of study	27 (21)	13 (19)	0.73
Baseline serum creatinine level (mg/dL)			
Median	0.9	1.0	0.11
Range	0.4–1.6	0.5–2.1	
Baseline total bilirubin level (mg/dL)			
Median	0.7	0.6	0.002
Range	0.3–3.5	0.2–1.6	
Baseline albumin level (g/dL)			
Median	3.4	3.6	0.015
Range	2.1–4.7	2.6–4.3	
Baseline absolute neutrophil count (μL)			
Median	1134	613	0.55
Range	0–56,392	0–46,748	
Duration of prophylaxis (days)			
Median	17	13.5	< 0.0001
Range	3–32	0–28	

ABLC: amphotericin B lipid complex; AML: acute myelogenous leukemia; L-AmB: liposomal amphotericin B; MDS: myelodysplastic syndrome.

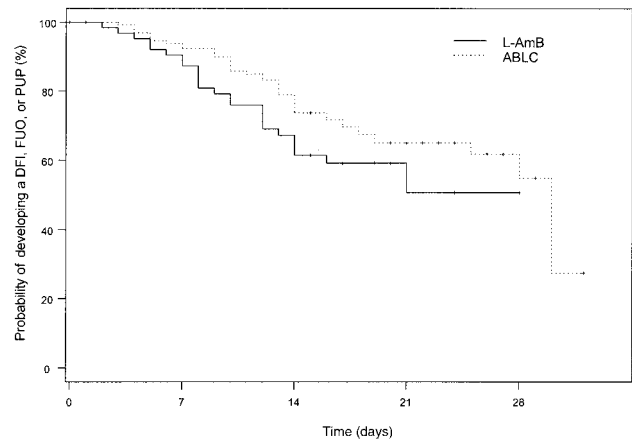
<sup>a</sup>No. of patients (%), unless otherwise indicated.

Table 3 shows the types of documented fungal infections in both groups. Both yeast and mold infections occurred in patients who received ABLC, whereas only yeast infections occurred in the historical control group. Of four patients with yeast infections, three had fungemia (one patient in the ABLC group and two patients in the L-AmB group), and one L-AmB-treated patient had cellulitis. In the ABLC-treated group, all patients with aspergillosis had pulmonary involvement, including sinopulmonary disease in one patient and pneumonia in two patients. Two patients who received ABLC prophylaxis developed disseminated *Fusarium* infections. The results of a multivariate analysis showed that a longer duration of prophylaxis significantly increased the risk of a documented fungal

**TABLE 2**  
Clinical Outcomes

Response	No. of patients (%)		P value
	ABLC	L-AmB	
No. of assessable patients	131	70	
Response to antifungal prophylaxis			0.95
Completion of prophylaxis	64 (49)	34 (49)	
Withdrawal from prophylaxis because of toxicity	24 (18)	10 (15)	
Documented fungal infection	6 (5)	3 (4)	
FUO	28 (21)	16 (23)	
PUP	9 (7)	6 (9)	
Response to induction chemotherapy			0.28
Complete response	89 (68)	42 (60)	
Resistance	32 (24)	18 (26)	
Death	10 (8)	10 (14)	

ABLC: amphotericin B lipid complex; L-AmB: liposomal amphotericin B; FUO: fever of unknown origin; PUP: pneumonia of unknown pathogen.



**FIGURE 1.** Kaplan–Meier time-to-treatment-failure curves indicating the proportion of patients who did not complete antifungal prophylaxis successfully because of the development of a documented fungal infection (DFI), fever of unknown origin (FUO), or pneumonia of unknown pathogen (PUP). The 2 curves did not differ according to the results of a log-rank test ( $P = 0.102$ ). The 3-week infection-free rate was 78.9% (95% confidence interval, 72.0–86.5%) for patients who received amphotericin B lipid complex (ABLC) and 67.2% (95% confidence interval, 56.3–80.2%) for patients who received liposomal amphotericin B (L-AmB).

infection, regardless of the antifungal agent administered ( $P = 0.011$ ).

**Suspected fungal infections**

The incidence of suspected fungal infections was comparable between the two treatment groups. Twenty-eight patients (21%) in the ABLC group and 16 patients

**TABLE 3**  
Types of Documented Fungal Infections

Infection	No. of patients (%)	
	ABLC (n = 131)	L-AmB (n = 70)
Yeast infections		
<i>Candida glabrata</i>	0	2 (3.0)
<i>Candida parapsilosis</i>	0	1 (1.0)
<i>Candida pseudotropicalis</i>	1 (< 1.0)	0
Mold infections		
<i>Aspergillus fumigatus</i> and <i>Aspergillus terreus</i>	1 (< 1.0)	0
<i>Aspergillus terreus</i>	2 (1.5)	0
<i>Fusarium spp</i>	2 (1.5)	0
Total	6 (5.0)	3 (4.0)

ABLC: amphotericin B lipid complex; L-AmB: liposomal amphotericin B.

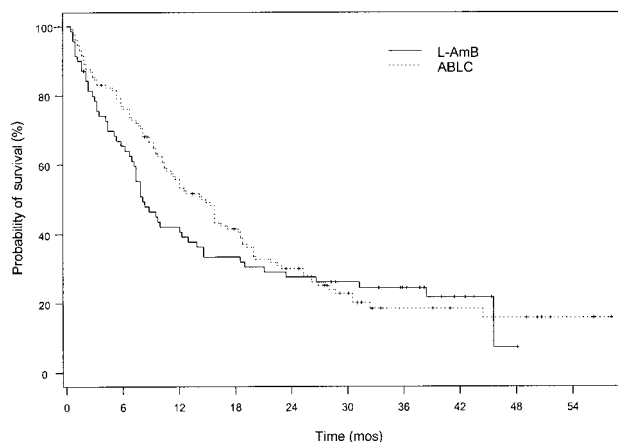
(23%) in the historical control group developed an FUO during antifungal prophylaxis (see Table 2). PUP developed in 9 ABLC-treated patients (7%) and in 6 L-AmB-treated patients (9%).

The ABLC dosage was increased to 5 mg/kg per day in 19 of 28 ABLC-treated patients who developed FUO. Of the 9 remaining patients, 7 patients were treated empirically with L-AmB 5 mg/kg per day rather than ABLC, because these patients experienced an increased SCr level (Grade 1–2) at the time of fever onset; and alternative, broad-spectrum, i.v. antifungal agents were not available commercially during the study period: one patient who was not experiencing neutropenia received oral itraconazole, and the other patient received a combination of itraconazole and fluconazole. Appropriate antimicrobial therapy was initiated in 7 of 28 patients with FUO who had subsequent positive blood culture results (vancomycin-resistant *Enterococcus* in 2 patients, methacillin-resistant *Staphylococcus aureus* in 2 patients, and  $\alpha$ -hemolytic *Streptococcus* in 3 patients).

All 9 patients who developed a PUP during antifungal prophylaxis received empiric therapy with higher dosages of ABLC (5 mg/kg per day). Two patients had BAL specimen results that were positive for *Pseudomonas*, and one other patient had a positive blood culture result for *Enterococcus*. None of the patients developed documented IFI.

### Mortality

Ten patients each in the ABLC group and the historical control group died during the study. Fungal infections were the cause of death in 3 of 10 ABLC-treated patients. Two patients, both of whom failed to recover from neutropenia, died with aspergillosis; one patient died of disseminated aspergillosis after receiving



**FIGURE 2.** Kaplan–Meier survival curves indicating the proportion of patients who survived over time. The 2 curves did not differ according to the results of a log-rank test ( $P = 0.37$ ). The median survival was 8.1 weeks (95% confidence interval, 7.2–13.9 weeks) for patients who received amphotericin B lipid complex (ABLC) and 14.8 weeks (95% confidence interval, 11.1–18.5 weeks) for patients who received liposomal amphotericin B (L-AmB).

ABLC, aerosolized amphotericin B, and itraconazole, and the other patient died of *Aspergillus* pneumonia before antifungal therapy was initiated. The third patient died of multiorgan failure after receiving L-AmB for a disseminated *Fusarium* infection. In the historical control group, one patient with *Candida glabrata* fungemia was treated with L-AmB but failed to recover from neutropenia and died. The causes of nonfungal-related deaths included sepsis (in two ABLC-treated patients and seven L-AmB-treated patients) and leukemia-related or chemotherapy-related complications (in five ABLC-treated patients and two L-AmB-treated patients). No death was related to study drug administration.

Kaplan–Meier estimated survival was similar between treatment groups (Fig. 2). Results of a covariate-adjusted univariate analysis showed that both older age and lower baseline albumin levels were associated with a significant increase in the risk of death ( $P = 0.006$  and  $P = 0.030$ , respectively). The results of a covariate-adjusted multivariate analysis also showed that older age was associated with a significantly increased risk of death ( $P = 0.003$ ) (Table 4).

### Adverse events

One hundred thirty-one ABLC-treated patients and 70 L-AmB-treated patients were assessable for safety. More ABLC-treated patients than L-AmB-treated patients withdrew from the study because of probable drug-related adverse effects (18% vs. 15%); however, Grade 3 and 4 toxicity rates were similar between the

**TABLE 4**  
**Risk Factors for Death<sup>a</sup>**

Factor	Estimate	SD	P value	RR
Age (older vs. younger)	0.03	0.008	0.003	1.02
Nonfungal infection at start of study (yes vs. no)	0.40	0.2	0.047	1.48
Prophylaxis (ABLC vs. L-AmB)	-0.20	0.17	0.25	0.82

SD: standard deviation; RR: relative risk; ABLC: amphotericin B lipid complex; L-AmB: liposomal amphotericin B.

<sup>a</sup>Determined using the multivariate Cox proportional hazards model.

2 groups. Moderately severe to severe hyperbilirubinemia occurred in 4 ABLC-treated patients (3%) and in 4 L-AmB-treated patients (6%). The incidence of Grade 3 and 4 infusion-related symptoms also was similar (ABLC, 4%; L-AmB, 7%). Grade 3 or 4 nephrotoxicity did not occur in either treatment group

**DISCUSSION**

The current study is the second to document the efficacy of a lipid-based amphotericin B product as antifungal prophylaxis in patients with AML or high-risk MDS who were undergoing induction chemotherapy.<sup>11</sup> The results of the current study show that ABLC and L-AmB have comparable efficacy and safety in the prevention of fungal infections in patients with AML and high-risk MDS, with 49% of patients in each treatment group completing antifungal prophylaxis without developing a documented or suspected fungal infection. Only 5% and 4% of patients who received ABLC and L-AmB, respectively, developed documented fungal infections. These rates of proven IFIs are comparable to the rates observed in other published clinical trials evaluating fluconazole and itraconazole as antifungal prophylaxis in patients with hematologic malignancies (fluconazole, 4.3–9%; itraconazole, 1.7–10.9%).<sup>6,8–10,12,15–17</sup>

Although amphotericin B prophylaxis has not been critically evaluated in patients with hematologic malignancies, its efficacy as a prophylactic antifungal agent has been well documented in patients undergoing HSCT—another patient population at high risk for developing fungal infections.<sup>2,18,25–27</sup> The results of 4 randomized, double-blind, placebo-controlled clinical trials comparing low-dose amphotericin B (0.1 mg/kg per day) with L-AmB (1 mg/kg per day or 2 mg/kg 3 times weekly) as antifungal prophylaxis in patients undergoing HSCT showed that both drugs are effective in preventing documented or suspected fungal infections (low-dose amphotericin B, 21–53%; L-AmB, 36–83%)<sup>18,25–27</sup>; these infection rates are comparable to the infection rates observed in our

study. The rates of documented fungal infections in our historical control study are slightly higher than the rates observed in prospective, controlled clinical trials evaluating low-dose amphotericin B and L-AmB in patients undergoing HSCT (0–2% vs. 0–3%, respectively). Differences in the patient populations studied and study designs may account for this difference.<sup>18,25–27</sup>

The incidence of documented fungal infections observed in the current study appears to be related to the duration of antifungal prophylaxis, regardless of the lipid-based amphotericin B product administered. Because prolonged duration of neutropenia is a known risk factor for the development of fungal infections, it is not surprising that the incidence of documented fungal infections increases with a prolonged duration of antifungal prophylaxis (i.e., a prolonged duration of neutropenia).<sup>3</sup> Although ABLC-treated patients received antifungal prophylaxis longer than patients who received L-AmB, the time to treatment failure of the antifungal prophylactic regimen was similar between treatment groups, suggesting that the duration of antifungal prophylaxis may be related to other factors, such as duration of neutropenia. In addition, the prolonged use of antifungal agents has been associated with the development of resistant fungal species; however, microbiologic data were unavailable in the current study.<sup>1,3</sup>

More mold infections developed in patients who received ABLC than in patients who received L-AmB, although the difference was not statistically significant. All of the mold infections that developed in ABLC-treated patients were caused by *Aspergillus terreus* or *Fusarium*, molds that generally are resistant to conventional or lipid-based amphotericin B in vitro, and, in many instances, in vivo.<sup>28–30</sup> Because the results of microbiologic tests were unavailable, resistance of these specific molds to ABLC is unknown. Until recently, the only drug available for treating infections caused by these molds was amphotericin B.<sup>31</sup> However, the results of preclinical studies evaluating voriconazole (Vefend®; Pfizer) have shown excellent fungicidal activity against *Aspergillus* species, including *A. terreus*, and variable fungicidal activity against *Fusarium* species, suggesting that voriconazole may be an effective therapy for amphotericin B-resistant molds.<sup>31,32</sup> Further randomized controlled studies are warranted to determine whether the incidence of mold infections varies among lipid-based amphotericin B agents and newer antifungal agents when administered as prophylaxis to patients with hematologic malignancies.

The incidence of suspected IFIs, including FUO and PUP, also was similar in patients who received

ABLC and patients who received L-AmB (28% and 32%, respectively). These results are within the range of those reported in published clinical trials evaluating triazoles as antifungal prophylaxis in patients with hematologic malignancies (11–64%); however, suspected fungal infections were defined differently in each of these clinical trials, making direct comparisons of the study results difficult.<sup>6,8–10,12,15,17</sup>

Because ABLC is a larger lipid-based molecule than L-AmB, it is removed rapidly from systemic circulation by the reticuloendothelial system.<sup>33</sup> This more rapid removal of ABLC compared with L-AmB may result in the release of proinflammatory cytokines from the engulfing macrophages and an increased incidence of infusion-related toxicities.<sup>34,35</sup> The study results show, however, that no statistically significant difference in the incidence of Grade 3 and 4 infusion-related toxicities was observed in patients who received ABLC or L-AmB (4% and 7%, respectively). This incidence of infusion-related toxicities is similar to the incidence reported in a randomized study comparing ABLC and L-AmB as treatment of suspected or documented fungal infections in adult patients with leukemia (2% and 5%, respectively).<sup>20</sup>

Lipid-based amphotericin B products have been associated with a decreased incidence of nephrotoxicity compared with amphotericin B.<sup>33,35</sup> The results of the current study support this finding, with no ABLC-treated or L-AmB-treated patients developing Grade 3 or 4 nephrotoxicity. Moderately severe-to-severe hyperbilirubinemia, which also has been reported with ABLC and L-AmB, was rare and occurred in both treatment groups.<sup>35</sup>

Another noteworthy finding of the current study was the similar overall mortality rates in patients who received ABLC and patients who received L-AmB (8% and 10%, respectively). Fungal infection-related deaths were uncommon, occurring in only 2.3% and 1.4% of ABLC-treated and L-AmB-treated patients, respectively. Although more fungal-related deaths occurred in patients who received ABLC, the difference was not statistically significant. Autopsies were not performed; thus, the causes of death could not be confirmed. In addition, two of three ABLC-treated patients were neutropenic at the time of death, a factor known to increase the risk of death due to a fungal infection.<sup>3</sup> A third ABLC-treated patient died of multiorgan failure; whether the death was due to multiorgan failure as result of the fungal infection, leukemia treatment, or disease-related complications is unknown (an autopsy was not performed). Nonetheless, these fungal infection-related mortality rates are comparable to those reported from other clinical studies evaluating fluconazole and itraconazole (fluconazole,

1.2–3.0%; itraconazole, < 1.0–15.2%).<sup>8,9,12,15–17</sup> In addition, no prophylaxis-related deaths occurred with either lipid-based amphotericin B product.

The limitations of the current study include the nonrandomized design, the limited number of autopsies to confirm the causes of death, and the relatively small sample size of the treatment groups. The results of the study, however, suggest that ABLC and L-AmB have comparable efficacy and toxicity as antifungal prophylaxis in patients with AML or high-risk MDS who are undergoing induction chemotherapy. In addition, these results are similar to results from other studies evaluating triazoles in this patient population. Thus, these agents may be useful in patients who experience hypersensitivity reactions with triazoles or patients with elevated serum creatinine or total bilirubin levels, in whom the use of triazoles is contraindicated. Further studies are warranted to confirm the results of this study.

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