A Randomized, Double-Blind Comparative Trial Evaluating the Safety of Liposomal Amphotericin B versus Amphotericin B Lipid Complex in the Empirical Treatment of Febrile Neutropenia

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In this double-blind study to compare safety of 2 lipid formulations of amphotericin B, neutropenic patients with unresolved fever after 3 days of antibacterial therapy were randomized (1:1:1) to receive amphotericin B lipid complex (ABLC) at a dose of 5 mg/kg/d (n = 78), liposomal amphotericin B (L Amph) at a dose of 3 mg/kg/d (n = 85), or L Amph at a dose of 5 mg/kg/d (n = 81). L Amph (3 mg/kg/d and 5 mg/kg/d) had lower rates of fever (23.5% and 19.8% vs. 57.7% on day 1; $P < .001$), chills/rigors (18.8% and 23.5% vs. 79.5% on day 1; $P < .001$), nephrotoxicity (14.1% and 14.8% vs. 42.3%; $P < .01$), and toxicity-related discontinuations of therapy (12.9% and 12.3% vs. 32.1%; $P = .004$). After day 1, infusional reactions were less frequent with ABLC, but chills/rigors were still higher (21.0% and 24.3% vs. 50.7%; $P < .001$). Therapeutic success was similar in all 3 groups.

The 2 most common invasive fungal infections in neutropenic patients are candidiasis and aspergillosis [1]. Both are difficult to diagnose in immunocompromised individuals, especially in the early stages of infection, since their manifestations are often indistinguishable from other types of infection, radiation pneumonitis, or graft-versus-host disease. The mortality associated with untreated invasive fungal infection is high [1–3]; hence, empirical systemic antifungal therapy is commonly administered after ⩾3 days of febrile neutropenia [4–7] unresponsive to antibiotics.

Although amphotericin B has demonstrated efficacy against both *Candida* and *Aspergillus* and its administration has been the standard of care for febrile neutropenic patients unresponsive to broad-spectrum antibacterial therapy, its traditional formulation has a less-than-optimal safety profile, and its therapeutic efficacy can be limited by toxicity-associated dose constraints [8, 9]. For that reason, lipid formulations of amphotericin B were developed to improve the therapeutic ratio [10–13]. Three lipid formulations of amphotericin B are now licensed for the treatment of invasive fungal infection: amphotericin B in lipid complex (ABLC; Abelcet, The Liposome Company, Princeton, NJ), amphotericin B colloidal dispersion (ABCD; Amphotec, Alza Corporation, Palo Alto, CA), and amphotericin B liposome (L Amph; AmBisome, Fujisawa Healthcare, Deerfield, IL). All 3 agents have demonstrated significantly lower nephrotoxicity in controlled trials than amphotericin B [14–19]. In one study, fewer infusional toxic effects occurred in patients treated by liposomal amphotericin B than in those treated with amphotericin B [15].

See the editorial response by Bennett on pages 1164–5.

It is difficult to analyze the comparative rates of toxicity across studies because of different patient populations, different methods of ascertainment of infusional toxic effects, and different dose schedules. The present double-blind, randomized study directly compared the frequency of chills/rigors and other infusion-related reactions (IRRs), the frequency of nephrotoxicity, and other safety parameters of ABLC and L Amph administered empirically to febrile neutropenic patients at risk for fungal infections.

Patients and Methods

Patient population. This study was conducted at 18 centers in the United States between October 1997 and August 1998 in accordance with the Declaration of Helsinki and good clinical practices [20]. The protocol and all amendments to the protocol were approved by an institutional review board at each center.

Neutropenic patients (absolute neutrophil count, <500 cells/mm^3)

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Informed consent was obtained from patients or their parents/guardians, and the guidelines for human experimentation of the US Department of Health and Human Services and those of the participating institutions were followed in the conduct of this clinical research.

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who were aged ⩾2 years were enrolled in this study if they had a suspected fungal infection, as demonstrated by fever after at least 72 h of broad-spectrum antibacterial therapy. Fever, for the purposes of study enrollment, was defined as 2 oral-equivalent temperatures >38°C measured at least 4 h apart or a single oral-equivalent temperature >38.5°C. In addition, patients were required to have a central venous catheter or sufficient venous access to permit administration of study drug and monitoring of safety variables.

Patients were excluded from this study if they had moderate or severe liver disease, as defined by transaminase levels >10 times the upper limits of normal or a total bilirubin or alkaline phosphatase level >5 times the upper limit of normal; however, an exception for these criteria could be granted after a physician–medical monitor consultation. Inclusion deviations were granted for 25 patients (10 in the lower-dose L Amph treatment group, 8 in the higher-dose L Amph group, and 7 in the ABLC group) for the following reasons: pregnancy test not done (4 patients) or done out of date range (5 patients); chest radiography not done (2 patients) or done out of date range (10 patients); occurrence of only 1 temperature ⩾38.0°C (2 patients) or temperatures measured only 2 h apart (1 patient); and participation in a blinded cancer-treatment study (1 patient). None of these differed between the 3 treatment groups.

Patients were also ineligible for this study if they had a serum creatinine level >3 mg/dL, had uncontrolled bacteremia, had received >2 doses of systemic amphotericin B or preparations containing amphotericin B within the previous 10 days, or had an anticipated survival of ⩽2 weeks. Clinical or other evidence indicating a deep or disseminated fungal infection prior to enrollment was also grounds for exclusion; however, patients who were found to have had a fungal infection at baseline but who had already been randomized and received the study drug when the culture results were available were eligible to continue in the study.

Patients were stratified at each investigative center on the basis of the use ("high risk") or nonuse ("low risk") of nephrotoxic immunosuppressants (cyclosporine or tacrolimus) before being randomized (1:1:1 by study center) to a treatment group. Although there was no reason to believe that infusional reactions would differ in these strata, it was known that nephrotoxicity rates were likely to be substantially higher among patients receiving cyclosporine or tacrolimus, resulting in different dropout rates and durations of remaining in the study. Stratification was used to ensure similar assignments in each cohort. A patient was to be withdrawn from the study if unacceptable toxicity developed, if an alternative systemic antifungal agent was required because of clinical or mycologic evidence of worsening fungal infection, if the investigator decided it was in the patient's best interest to discontinue, or if the patient declined further study participation.

Study drug administration. ABLC (Abelcet; The Liposome Company) was administered in the study at its approved dosage for secondary treatment of fungal infections (5 mg/kg/d of amphotericin B as ABLC). L Amph (AmBisome; Fujisawa Healthcare) was administered at a dose equivalent to that of ABLC (5 mg/kg/d of amphotericin B as L Amph) or at a dose of 3 mg/kg/d, previously demonstrated to be effective for the empirical treatment of febrile neutropenic patients [15].

Study drug was administered once daily through a central venous catheter over 120 min. The investigator, patient, and study coordinator(s) were blinded to the treatment administered. Although both agents are yellow, differences in color and opacity of each agent in the bag existed; therefore, each infusion dose was covered by an opaque bag. A member of the pharmacy staff prepared the study drug and provided blind-labeled infusion bags/bottles for administration. There were no visible differences between the agents in the iv tubing, and the tubing was not masked.

Administration of premedications prior to the first administration of medication was prohibited. The use of hydrocortisone, antiinflammatory agents and acetaminophen was not permitted. After day 1, however, the clinician was allowed the option of premedications if a reaction to the first dose occurred. Saline loading was not standardized; it was permitted to be used according to standard practices at each center. Because of the blinded design of this study, it was assumed that saline loading did not differ between the 3 cohorts. According to the protocol guidelines, therapy was continued until the patient recovered from neutropenia (absolute neutrophil count, ⩾500 cells/mm^3) or for up to 3 days after neutrophil recovery, to a maximum of 42 days.

Assessments. Temperatures, pulse rate, and blood pressure were recorded at baseline, as well as before (0 min) and 60 and 120 min after the start of each administration of study drug, for the first 5 days of therapy. Throughout the period of study drug therapy and up to 24 h after its discontinuation, temperature was determined every 4–6 h while the patient was awake. Daily minimum and maximum temperatures were recorded (excluding temperatures taken during or within 1 h of study drug or blood product transfusions). Through the 7-day posttreatment follow-up visit, adverse events, the clinical laboratory profile (at baseline and as clinically appropriate), and fungal infection status (weekly) were evaluated. In addition, serum creatinine was measured thrice weekly and the absolute neutrophil count was determined daily during the study.

The frequency of infusion-related chills/rigors during infusion or for up to 1 h after infusion on the day of the first dose (day 1) was the primary end point in this study. Elevated temperatures between the start of the study drug infusion and up to 1 h after infusion were considered attributable to the study drug. All other elevated temperatures were considered in the response end points. In order to more accurately assess chills/rigors and other IRRs, premedication to prevent IRRs on day 1 was not permitted. Nephrotoxicity (recorded from day 1 through the 7-day follow-up evaluation) was defined as an increase in serum creatinine value >100% above baseline value (>2 times baseline value); for patients aged ⩾16 years, the postbaseline peak serum creatinine value also had to be >1.2 mg/dL to meet the criterion for nephrotoxicity. Increases in serum creatinine by >50% above baseline value (> 1.5 times baseline value) were also evaluated, as were hypokalemia (serum potassium level, <3 mEq/L or ⩽2.5 mEq/L), anemia (hemoglobin level, ⩽8 g/dL), and hepatotoxicity (increases in transaminase serum concentrations of >5 times to >2 times baseline, where baseline is <2 times to >5 times the upper limit of normal, respectively).

Efficacy. Successful response was defined as fever resolution during the neutropenic period; improvement/cure for patients with a proven baseline fungal infection; absence of treatment-emergent probable or proven fungal infections; nonoccurrence of death with fungal infection as a primary or contributing factor, either during the study or within 7 days of the last administration of study drug; no discontinuation of study drug due to toxicity; and no admin-

Table 1. Demographic and other baseline characteristics of patients with febrile neutropenia enrolled in a comparative trial of empirical treatments.

Characteristic	L Amph 3 mg/kg/d (n = 85)	L Amph 5 mg/kg/d (n = 81)	ABLC 5 mg/kg/d (n = 78)	Total (n = 244)
Sex				
Female	34 (40.0)	43 (53.1)	37 (47.4)	114 (46.7)
Male	51 (60.0)	38 (46.9)	41 (52.6)	130 (53.3)
Race				
White	71 (83.5)	71 (87.7)	70 (89.7)	212 (86.9)
Black	6 (7.1)	7 (8.6)	6 (7.7)	19 (7.8)
Other	8 (9.4)	3 (3.7)	2 (2.6)	13 (5.3)
Age (y)				
Mean ± SD	41.4 ± 20.8	42.0 ± 21.2	42.8 ± 19.4	42.0 ± 20.4
Median (range)	45.0 (3–74)	44.0 (2–84)	47.0 (2–76)	45.0 (2–84)
<16	15 (17.6)	14 (17.3)	13 (16.7)	42 (17.2)
⩾16	70 (82.4)	67 (82.7)	65 (83.3)	202 (82.8)
BMT patients	39 (45.9)	40 (49.4)	40 (51.3)	119 (48.8)
Autologous	25 (29.4)	26 (32.1)	28 (35.9)	79 (32.4)
Allogeneic	13 (15.3)	13 (16.0)	12 (15.4)	38 (15.6)
Syngeneic	1 (1.2)	1 (1.2)	0	2 (0.8)
Non-BMT patients				
Solid tumor	5 (5.9)	7 (8.6)	1 (1.3)	13 (5.3)
Acute leukemia	31 (36.5)	24 (29.6)	26 (33.3)	81 (33.2)
Lymphoma	4 (4.7)	6 (7.4)	6 (7.7)	16 (6.6)
Myelodysplasia			1 (1.5)	1 (0.4)
Multiple myeloma	1 (1.2)	1 (1.2)	2 (2.6)	4 (1.6)
Other	5 (5.9)	3 (3.7)	2 (2.6)	10 (4.1)
Use of tacrolimus or cyclosporine	13 (15.3)	11 (13.6)	11 (14.1)	35 (14.3)

NOTE. Data are no. (%) of patients except as indicated. ABLC, amphotericin B lipid complex; BMT, bone marrow transplantation; L Amph, liposomal amphotericin B.

istration of an alternative systemic antifungal agent for a probable or proven fungal infection. Modified Mycosis Study Group definitions were used for proven or probable infection [21].

Sample size determination. Sample sizes per treatment group were calculated on the basis of the ability to detect a treatment difference of 25% in the frequency of day 1 chill/rigors with 80% power at $\alpha = .05$ in a 2-tailed test. Using an estimated rate of day 1 chills/rigors of 50% in the ABLC group, a sample size of 80 patients per group (240 total patients) would allow detection of this difference. This sample size also allowed detection of a difference of 20% in the rate of day 1 chills/rigors in the combined L Amph groups versus the ABLC group.

Data analysis. For this double-blind study, all randomized patients who received ⩾1 dose of study drug were included in the safety and efficacy analyses, with the exception of 1 patient enrolled a second time who did receive 1 dose of study drug and was withdrawn because of protocol violation.

Statistical analyses were performed with use of χ^2 or Fisher's (2-tailed) exact test for ordinal measurements. Analysis of variance was used on continuous data. Unless otherwise specified, all comparisons between and among treatment groups were 2-tailed.

There were no adjustments made for multiple comparisons. However, to avoid chance differences due to multiple comparisons, only P values of ⩽.01 were considered significant.

The primary end point in this study was the incidence of chills/rigors on day 1. Comparisons between each L Amph group and the ABLC group were performed with a 2-tailed Fisher's exact test with an α value of .05. χ^2 test statistics were used to compare nephrotoxicity rates among the treatment groups.

Results

Patient population. A total of 342 patients underwent screening evaluation; of these, 250 patients were enrolled in the study. For administrative reasons, 6 of the enrolled patients did not receive study drug. Patients who were randomized and received ⩾1 dose of study drug totaled 244.

There were no statistically significant differences between the L Amph and ABLC treatment groups with respect to demographic and other baseline characteristics (table 1). All patients were neutropenic at baseline. The majority of patients presented with nonhematologic laboratory parameters within normal limits. The median serum creatinine value at baseline was 0.7 mg/dL in each of the 3 groups. An elevation in serum creatinine level at baseline was noted in 9% of patients, without any difference between any of the 3 groups. The median bilirubin value was 0.8 mg/dL. An elevation in serum bilirubin level was noted at baseline in 27% of the population at large, with no difference between any of the 3 groups. The majority of patients in the L Amph groups (81.3%) and ABLC group (88.5%) received prior antifungal therapy, predominantly with fluconazole.

Study drug exposure. Table 2 shows the number of days and infusions of study drug in each of the 3 groups and the cumulative doses. There were no significant differences in drug exposure among the 3 groups. Many patients received ⩾1 nephrotoxic agent. There were no significant differences between groups as to the number of nephrotoxic agents given.

Infusion-related reactions. There was a lower frequency of infusion-related chills/rigors on day 1 among patients administered L Amph than among those administered ABLC ($P <$ .001; table 3). This lower frequency was evident regardless of age, sex, receipt of a bone marrow transplant, transplant type,

Table 2. Study drug exposure in the 3 treatment groups.

Variable	L Amph 3 mg/kg/d (n = 85)	L Amph 5 mg/kg/d (n = 81)	ABLC 5 mg/kg/d (n = 78)
Days study drug received, mean no. ± SD	8.6 ± 5.5	8.3 ± 7.4	7.5 ± 6.6
Infusions per patient, no.			
Mean ± SD	8.5 ± 5.4	8.2 ± 7.2	7.2 ± 6.4
Median (range)	7 (1–28)	6 (1–40)	5 (1–33)
Cumulative dose, mg/kg			
Mean ± SD	25 ± 15.9	40.6 ± 36.7	35.3 ± 31.9
Median (range)	21 (3–84)	30 (0.1–203.2)	25 (1.1–165)
No. of nephrotoxic medications[a] received, no. (%) of patients			
0	32 (37.6)	25 (30.9)	27 (34.6)
1	31 (36.5)	33 (40.7)	36 (46.2)
2	16 (18.8)	18 (22.2)	13 (16.7)
⩾3	6 (7.1)	5 (6.2)	2 (2.6)

[a] Amikacin, cisplatin, cyclosporine, furosemide, gentamicin, pentamidine, tacrolimus, tobramycin, or foscarnet sodium.

Table 3. Incidence of infusion-related reactions among the patients in the 3 treatment groups.

	Day 1			Days 2–5		
	L Amph		ABLC	L Amph		ABLC
Infusion-related reaction[a]	3 mg/kg/d (n = 85)	5 mg/kg/d (n = 81)	5 mg/kg/d (n = 78)	3 mg/kg/d (n = 81)	5 mg/kg/d (n = 74)	5 mg/kg/d (n = 71)
Chills/rigors	16 (18.8)[d]	19 (23.5)[d]	62 (79.5)	17 (21.0)[b]	18 (24.3)[b]	36 (50.7)
Fever: ⩾1.0°C increase in temperature	20 (23.5)[b]	16 (19.8)[b]	45 (57.7)	16 (19.8)[b]	21 (28.4)	32 (45.1)
Nausea	9 (10.6)	7 (8.6)	9 (11.5)	8 (9.9)	11 (14.9)	8 (11.3)
Vomiting	5 (5.9)	5 (6.2)	11 (14.1)	5 (6.2)	6 (8.1)	7 (9.9)
Other reactions[e]	16 (18.8)[c]	21 (25.9)	32 (41.0)	21 (25.9)	13 (17.6)	21 (29.6)
Total[f]	44 (51.8)[b]	39 (48.1)[b]	69 (88.5)	40 (49.4)	33 (44.6)[c]	47 (66.2)

NOTE. Data are no. (%) of patients. Patients were not administered premedications to prevent infusion-related reactions prior to the day-1 study drug infusion; such medications were permitted after day 1, however.

[a] Patients could be included in >1 category.

[b] $P \leqslant .001$, L Amph versus ABLC group on the indicated day; χ^2 test.

[c] $P \leqslant .01$, L Amph versus ABLC group on the indicated day; χ^2 test.

[d] $P \leqslant .001$, L Amph versus ABLC group on the indicated day; Fisher's exact test.

[e] These included pain, hypertension, tachycardia, chest pain, vasodilatation and hypotension.

[f] The most conservative definition of fever was used for reporting the total number of IRRs (i.e., a ⩾1.0°C increase in temperature).

or the use of immunosuppressants (data not shown). Similarly, on day 1, L Amph was associated with a significantly lower overall frequency of IRRs such as fever, vomiting, pain, hypertension, tachycardia, chest pain, vasodilatation, and hypotension (table 3). Medications such as acetaminophen, meperidine, diphenhydramine, and hydrocortisone were used to treat IRRs in 43.5% of the 3-mg/kg L Amph group, 37.0% of the 5-mg/kg L Amph group, and 73.1% of the ABLC group ($P <$ .001 for each of the L Amph comparisons with ABLC).

After day 1, when premedication to prevent IRRs was permitted, the overall frequency of IRRs (with use of a ⩾1.0°C increase in temperature for the fever criterion) was lower in the ABLC group but unchanged for the 2 L Amph groups (table 3). There were lower overall trends of IRR rates in the L Amph groups than in the ABLC group; the difference in trends was significant for the 5-mg/kg L Amph group (P = .009) but nonsignificant for the 3-mg/kg L Amph group (P = .037 when compared to ABLC). The incidence of infusion-related chills was significantly lower in both L Amph groups than in the ABLC group, but that of fever was significantly lower only in the 3-mg/kg L Amph group. The use of premedication to prevent IRRs after day 1 was lower in both L Amph groups (38.8% and 44.4%) than in the ABLC group (73.1%) ($P <$ .001; Fisher's exact test). In the 3 treatment groups, the proportions of patients needing medication for IRRs that occurred after day 1 were 42.4%, 44.4%, and 53.8% (P = NS).

Nephrotoxicity. Significantly less nephrotoxicity was observed among patients given L Amph than among those given ABLC (table 4). As with infusion-related chills/rigors, this lower frequency of nephrotoxicity by all protocol-specified measures with L Amph than with ABLC was also evident regardless of age, receipt of a bone marrow transplant, transplant type, or use of immunosuppressants (data not shown). A peak creatinine value >3 mg/dL occurred in 7.1% of the 3-mg/kg L Amph group, 1.2% of the 5-mg/kg L Amph group, and 12.8% of the ABLC group ($P <$ .01 for 5-mg/kg L Amph group and P = NS for 3-mg/kg L Amph group when compared with the ABLC group). Although there was a nonsignificant trend toward higher proportions of patients with elevated peak creatinine values in the 3-mg/kg L Amph group than in the 5-mg/kg L Amph group, there were no statistically significant differences in any of the nephrotoxicity measures in table 4 between the 2 L Amph regimens.

Rates of nephrotoxicity were evaluated by patient-risk strata. In the high-risk stratum there were no statistical differences between the 3 treatment groups, but the number of patients in each group was small (<15 in each group). There was a nonsignificant trend toward higher nephrotoxicity in the high-risk stratum than in the low-risk stratum for the 5-mg/kg L Amph group (36.4% vs. 11.4%; P = .053). However, there were no statistical differences between high- and low-risk patients in the other L Amph group (15.4% vs. 13.9%) or the ABLC group (45.5% vs. 41.8%).

Patients were divided into 3 age groups: <16 years, 16–40 years, and >40 years. For the 2 L Amph cohorts, there was no association between age and any of these nephrotoxicity end points. For the ABLC cohort there were no differences by age with regard to doubling of creatinine value, but there was a nonsignificant trend toward higher peak creatinine values at the 2.0, 2.5, and 3.0 mg/dL end points for older individuals in this group (data not shown). For example, only 2 (15.3%) of 13 ABLC patients aged <16 years, 3 (18.8%) of 16 patients aged 16–40 years, and 14 (28.6%) of 49 patients aged >40 years had a peak serum creatinine value >2.0 mg/dL (P = .52). Twenty-nine patients had received prior amphotericin B. There were no differences in the number included in each of the 3 study cohorts. The nephrotoxicity end points were recalculated after

exclusion of those individuals from the analyses, and all of the differences remained statistically significant (data not shown).

Hepatotoxicity, hypokalemia, and anemia. There were no statistically significant differences between the L Amph and ABLC treatment groups with respect to hepatotoxicity, which occurred in 11.5% of all patients. Rates of hepatotoxicity did not differ by patient-risk strata for the 3 treatment groups. In addition, although there was no difference in frequency of hypokalemia with between patients who received the study drugs at a dose of 5 mg/kg/d, a nonsignificant trend toward a higher frequency of hypokalemia (defined as a serum potassium level <3 mEq/L) was observed among patients receiving ABLC (37.2%) than among those receiving the 3-mg/kg dose of L Amph (22.4%; $P = .041$ by χ^2 test).

There was a nonsignificant trend toward a higher frequency of anemia (hemoglobin, ≤8 g/dL) among patients receiving ABLC (59.0%) than among those receiving either the 3-mg/kg dose of L Amph (36.5%; $P = .004$ by χ^2 test) or the 5-mg/kg dose of L Amph (40.7%; $P = .022$ by χ^2 test). We checked for site interaction since different centers may have had different RBC transfusion thresholds. We pooled together sites with <20 patients. The Breslow-Day test was not significant for 2-site interaction; the aforementioned nonsignificant trend remained for the cohorts who received a dose of a given size.

Adverse events. In addition to IRRs and nephrotoxicity, adverse events of any type were recorded for all patients in the study, whether or not they were related to the study medication, underlying disease, or an anticancer treatment regimen. Adverse events of some type were noted in practically all patients, with no difference among cohorts. With respect to the 2 5-mg/kg dosage groups (L Amph and ABLC), the only statistically significant difference noted was a higher rate of hypoxia in the latter (20.5% vs. 6.2%; $P = .009$). On day 1, there were trends of both chills and fever with hypoxia ($P = .32$ for chills and $P = .04$ for fever), but most episodes of hypoxia occurred later, after the peak times when fever was notable. Approximately 11% of the episodes of hypoxia due to any drug occurred on the first study day, whereas 20% occurred on the second day, and 70% after the second day. Of those deemed life-threatening by the investigator, none occurred on the first study day. There were also nonsignificant trends of higher rates of hypotension (19.2% vs. 7.4%; $P = .035$) and hyperventilation (9% vs. 1.2%; $P = .032$) in ABLC patients.

When L Amph (3 mg/kg) was compared with ABLC (5 mg/kg), lower rates of hypertension (10.6% vs. 23.1%; $P = .037$), tachycardia (9.4% vs. 23.1%; $P = .02$), hypoxia (7.1% vs. 20.5%; $P = .02$), and asthma (0 vs. 5.1%; $P = .05$) were noted in the L Amph group, as well as a higher rate of confusion (12.9% vs. 3.8%; $P = .05$). None of these differences was statistically significant. None of the incidents of confusion occurred during the first several days of the study. They were all regarded as mild to moderate in nature and did not appear to be temporally associated with any psychoactive medications, such as meperidine, given for infusional reactions.

Deaths. A total of 18 patients (7.3%) died during the course of the study. Fourteen of the 18 patients died during the 1-week follow-up period (within 1 week after discontinuation of the study drug administration). Seven patients (4.2%) given L Amph and 11 (14.1%) given ABLC died during the study. Mortality was higher for patients treated with ABLC (14.1%) than for those treated with the 5-mg/kg dose of L Amph (2.5%; $P = .009$ by Fisher's exact test), but the rate was not different from that for patients treated with the 3-mg/kg dose of L Amph ($P = .11$).

The causes of death in all treatment groups were consistent with the underlying diseases of this patient population. Fungal infection was a primary or contributing cause of death for only 4 of these 18 patients: 1 in the 3-mg/kg L Amph group (*Candida krusei* fungemia) and 3 in the ABLC group (disseminated candidiasis, hepatic candidiasis, aspergillosis). Other causes of death included veno-occlusive disease (1 patient), retroperitoneal hemorrhage (1 patient), acute lymphoblastic leukemia (1 patient), adult respiratory distress syndrome (1 patient), acute myelogenous leukemia (2 patients), and bacteremia (1 patient) in the L Amph groups and viral pneumonia (1 patient), septicemia (2 patients), adult respiratory distress syndrome (1 patient), cyclophosphamide-induced myocarditis (1 patient), refractory acute lymphoblastic leukemia (1 patient), and lymphoma (1 patient) for ABLC-treated patients.

Response. No statistically significant treatment differences were observed with respect to successful response for the 3 groups (table 5). Treatment failed for 150 patients (61.4%) (no difference between the 3 groups). The reasons for treatment failure are given in table 5.

One-hundred and sixty-one patients completed treatment, including 72.3% of those administered L Amph and 52.6% of those administered ABLC. A lower percentage of patients completed treatment in the ABLC group primarily because a significantly higher percentage of prematurely discontinued treatments as a result of adverse events (32.1%) in comparison with the L Amph groups (12.7%; $P = .001$ by Fisher's exact test). The adverse events primarily responsible for the increased frequency of ABLC discontinuations were fever, increased creatinine level, and hypoxia.

At baseline, there were a total of 5 fungal infections (2 proven and 3 probable). Both of the patients with proven baseline fungal infections died; fungal infection was the primary cause of death. An L Amph recipient had *C. krusei* sepsis, received the study drug for 8 days, and died on day 11. An ABLC patient with *Candida parapsilosis* disseminated infection received only 1 dose of study drug and died on day 8.

Of the 3 patients with baseline probable infections, 2 were in the 5-mg/kg L Amph group and discontinued receiving the study drug (after 3 doses and 5 doses) because of lack of efficacy, and the third patient, who was receiving the 3-mg/kg

Table 4. Incidence of nephrotoxicity in the 3 treatment groups.

Variable	L Amph		ABLC
	3 mg/kg/d (n = 85)	5 mg/kg/d (n = 81)	5 mg/kg/d (n = 78)
Nephrotoxicity			
1.5 × Baseline creatinine value	25 (29.4)[a]	21 (25.9)[a]	49 (62.8)
2 × Baseline creatinine value	12 (14.1)[a]	12 (14.8)[a]	33 (42.3)
3 × Baseline creatinine value	5 (5.9)[b]	5 (6.2)[b]	21 (26.9)
Change, baseline-to-peak serum creatinine value (mg/dL)			
Mean ± SD	0.5 ± 0.8[c]	0.4 ± 0.4[c]	1.0 ± 1.0
Median (range)	0.3 (0–4.7)	0.2 (−0.1 to 2.1)	0.7 (0–5.3)
Peak creatinine value (mg/dL)			
Mean ± SD	1.3 ± 1.0[c]	1.2 ± 0.6[c]	1.8 ± 1.2
Median (range)	1.1 (0.3–6.3)	0.9 (0.3–3.3)	1.5 (0.5–6.0)
>1.5	22 (25.9)[d]	19 (23.5)[b]	38 (48.7)
>2.0	14 (16.5)	5 (6.2)[d]	19 (24.4)
>2.5	6 (7.1)	3 (3.7)[d]	14 (17.9)
>3.0	6 (7.1)	1 (1.2)[d]	10 (12.8)

NOTE. Data are no. (%) of patients unless otherwise indicated.
[a] $P \leq .001$, L Amph versus ABLC group; χ^2 test.
[b] $P \leq .001$, L Amph versus ABLC group; Fisher's exact test.
[c] $P \leq .001$, L Amph versus ABLC group; analysis of variance.
[d] $P \leq .01$, L Amph versus ABLC group; Fisher's exact test.

dose of L Amph, completed treatment (5 doses), with neutrophil recovery. However, that treatment was considered to have failed because of persistent fever and the addition of another antifungal agent to the regimen.

During the course of the study, there were 9 emergent fungal infections (4 proven, 5 probable) in 8 patients (table 5). Five infections (2 proven, 3 probable) were due to *Aspergillus* species, 1 (proven) was due to *Acremonium* species, and one (proven) was due to *Candida albicans.* Two (probable) were histologically documented but no organism was cultured. Of these patients with emergent infections, amphotericin B was used to treat 4, ABLC was used to treat 3 (for 2, in combination with either itraconazole or fluconazole), and L Amph was used to treat 1. The conditions of 3 patients improved with treatment and those of 2 were unchanged; the remaining 3 died.

Discussion

This study is the first randomized, blinded trial to directly compare the frequency of IRRs with 2 commercially available lipid-based amphotericin B formulations, L Amph and ABLC. We compared empirical therapy for 244 neutropenic patients, and found that L Amph was associated with a significantly lower frequency of IRRs, including chills/rigors and fever, than was ABLC. A significantly lower frequency of the treatment failure criterion "discontinuation for drug toxicity" was also observed with L Amph than with ABLC.

L Amph is licensed to be administered initially as a 2-h infusion, with the option to reduce infusion to 1 h if it can be tolerated. For purposes of blinding, all doses of both drugs were administered as 2-h infusions, the licensed infusion duration for ABLC. Whether or not higher infusional reaction rates after day 1 would have been encountered with L Amph if it were administered over 1 h was not addressed.

It is noted that infusional toxicity decreased in frequency after day 1 for ABLC. Furthermore, with premedications, the differences between L Amph and ABLC after day 1 were substantially lower. This attenuation of infusional reactions over time with amphotericin B has been noted in the past. Whether the attenuation of infusional reactions beyond day 1 was due to the premedications or whether it was due to tachyphylaxis is beyond the scope of this study. In addition, whether or not differences between the 2 agents would have been attenuated by premedication prior to the first doses, as has been seen with amphotericin B [22], cannot be answered by these data.

The adverse event associated with amphotericin B that is of most concern is nephrotoxicity. Several lipid formulations of amphotericin B have been reported to decrease the nephrotoxic potential associated with deoxycholate amphotericin B. L Amph is a liposomal formulation, whereas ABLC is a lipid-complexed formulation [10, 23, 24]. Laboratory-based research suggests that the amphotericin B in these products has differing membrane-damaging potential on the order of ABLC > L Amph [24]. However, the relative nephrotoxic potential among these lipid amphotericin B formulations has not been previously explored. In the present study, significantly less nephrotoxicity (determined on the basis of increases from baseline serum creatinine levels) was associated with L Amph than with ABLC. Although on average the rise in creatinine level was modest for all 3 arms of the study (median increase of 0.2–0.7 mg/dL), the proportion of patients with substantial elevations (>3 mg/dL) was higher in the ABLC group than in the 5-mg/kg L Amph group (12.8% vs. 1.2%; $P = .0042$).

The findings that the rate of nephrotoxicity was higher for

Table 5. Parameters of response to treatment in the 3 study groups.

Variable	L Amph		ABLC
	3 mg/kg/d (n = 85)	5 mg/kg/d (n = 81)	5 mg/kg/d (n = 78)
Successful response	34 (40.0)	34 (42.0)	26 (33.3)
Treatment failure[a]	51	47	52
Reason for failure			
Fungal infection			
Baseline, persistent or progressive[b]	1 (1.2)	0	1 (1.3)
Emergent[c]	3 (3.6)	2 (2.5)	3 (3.8)
Persistent fever	34 (40)	24 (29.6)	21 (26.9)
Required other systemic antifungal agent(s)	5 (5.9)	4 (4.9)	4 (5.1)
Drug withdrawn because of toxicity	11 (12.9)[d]	10 (12.3)[d]	25 (32.1)
Infusion-related reaction	2 (2.4)	5 (6.2)	9 (11.5)
Non–infusion-related reaction	9 (10.6)	5 (6.2)[d]	16 (20.5)
Death related to fungal infection	1 (1.2)	0	3 (3.8)

NOTE. Data are no. (%) of patients.

[a] Some patients qualified under >1 component of failure. For Patients with an unknown response for any failure component, treatment was considered to have failed.

[b] Proven infections only.

[c] Of the 9 emergent infections in these 8 patients, 4 were proven and 5 were probable.

[d] For indicated L Amph treatment group versus ABLC, $P \leq .01$ by Fisher's exact test.

ABLC-treated patients than for L Amph–treated patients and that there was a higher rate of ABLC discontinuation (32% vs. 13% for L Amph) in this study are initially surprising from what we know about this agent. However, the nephrotoxicity data for ABLC illustrate the fact that all previous studies with this agent have been performed with an open-label design. Specifically, ABLC was usually given to patients with refractory fungal infections or, more commonly, to those with amphotericin B–induced or preexisting renal dysfunction; such clinical features might make discontinuation of a salvage study drug unlikely. In addition, the results of those previous published studies demonstrated that the ameliorating renal effect of ABLC was most apparent when compared with the potential or already realized risk of nephrotoxicity with amphotericin B; namely, in many cases, the serum creatinine level actually declined from its amphotericin B–associated peak while patients continued to receive ABLC.

Although differences in rates of nephrotoxicity were statistically significant, one could argue that the differences in creatinine changes in the 3 groups were only modestly different. This raises the question as to the clinical meaning of these changes and whether the differences between the agents are meaningful. In a previous study [25], we attempted to ascertain the clinical significance of nephrotoxicity with amphotericin B. We found that increases in the serum creatinine level to ⩾2.5 mg/dL with use of amphotericin B led to a substantial risk for hemodialysis and were associated with greater mortality. In another study [26], a doubling of the creatinine level in patients receiving amphotericin B as empirical therapy for persistent neutropenic fever was associated with a significant prolongation of hospitalization and increase in hospital costs. Clearly, nephrotoxicity led to an increase in the use of resources.

Saline loading was not controlled for in this trial. One could also speculate as to whether saline loading, an intervention found to reduce nephrotoxicity associated with amphotericin B, could have attenuated the difference between the 2 compounds [27]. Again, this is a matter for future study.

With regard to discontinuation rates, the only randomized trial comparing ABLC with amphotericin B was an open-label treatment of invasive candidiasis [16]. In that study, knowledge of treatment assignment may have affected discontinuation rates in favor of the approved agent, amphotericin B, so that (1) ABLC, the unfamiliar investigational agent, could have been discontinued owing to a moderately severe infusion reaction before the development of renal toxicity or (2) minor elevations in creatinine values led to discontinuation, dose reduction, or administration delays before a study end point for nephrotoxicity was reached, whereas the not-unexpected creatinine levels induced by amphotericin B were tolerated until that end point was reached. For whatever reason, the true nephrotoxic potential of ABLC, on a comparative basis, may have been missed. The details of that trial have not yet been published.

Discontinuation rates for a similarly designed, randomized, double-blind trial of empirical antifungal therapy in neutropenic patients were high as well [17]. In that trial, the discontinuation rate for amphotericin B was 50%; for the comparison lipid agent, ABCD, it was 45%; and for the study overall, it was 47%. In fact, these rates should not be surprising in light of the extraordinarily high incidence of any adverse event in study participants and the marginally optional nature of empirical antifungal treatment (compared with directed therapy for a proven fungal infection).

In this study, unlike all other comparative trials evaluating the lipid formulations of amphotericin B, there was no provision for dose reduction or dose interruption. Any patient in this trial to whom the full dose could not be delivered had to be removed from the study. In contrast, in previous trials, clinicians had the opportunity to reduce the dose or to interrupt the schedule. Therefore, the lack of such a provision in this study may well have contributed substantially to the high withdrawal rates.

In this study, the pivotal comparison was between the 2 lipid formulations at a dose of 5 mg/kg/d. Are the drugs equipotent? Previous studies that have compared either of the 2 lipid formulations with amphotericin B as treatment for established invasive fungal infections have evaluated doses of 3–6 mg/kg/d [14, 16, 28]. In those studies, response and survival rates at such doses were similar to those with conventional amphotericin B at doses of 0.7–1.0 mg/kg/d. Since these agents were used to treat different invasive fungal infections and in different pa-

tient populations, it is not certain that the agents, given in equal doses, provide similar efficacy. These limited data formed the rationale behind an equidose comparison in this trial.

It is possible that the differences in infusional reactions and nephrotoxicity between the 2 drugs would be less if one were to compare each at a dose of 3 mg/kg/d. There were no statistically significant differences between either infusional toxic effects (table 3) or nephrotoxicity (table 4) at either of the 2 dose schedules for L Amph. It is certainly possible that lower doses of ABLC, in contrast, may have shown such a difference. There are several study reports describing ABLC doses of 2.5–3 mg/kg/d [29–31]. In only one [31] were there data permitting a comparison of nephrotoxicity rates at different doses. In this study by Sharkey et al. [31], cohorts of patients (8–21 in number) were given ABLC at doses of 1.2 mg/kg/d, 2.5 mg/kg/d, and 5 mg/kg/d for 2 weeks and then changed to a different schedule. In that study, there did appear to be a lower rate of nephrotoxicity between the 2.5 mg/kg/d dose and the 5 mg/kg/d dose at 2 weeks, but no statistical comparison was made.

With respect to infusional toxicity, in one small study [30] the rate of infusional toxicity was very low (4%). In another study report, the authors commented that there was no difference in infusional toxicity rates at the various doses evaluated [31]. Thus, the data are insufficient to indicate whether or not a different dose or dose schedule would have yielded different results.

The infusion-related toxicity of deoxycholate amphotericin B is related to the release of TNF, IL-1, and IL-6 from monocytes and macrophages. Encapsulation of amphotericin B by the liposomal structure of L Amph attenuates the release of TNF, IL-6, and IL-1 receptor antagonist [32]. In contrast, the rapid removal of ABLC from circulation by the reticuloendothelial tissues, particularly in the liver [33, 34], may result in the release of proinflammatory cytokines from the engulfing macrophages and account for the IRRs associated with ABLC administration.

Confusion was reported more frequently (a nonsignificant trend) for patients given L Amph (3 mg/kg/d) than for those given ABLC (12.9% vs. 3.8%; $P = .05$). The rate of confusion in patients receiving 5-mg/kg L Amph was lower (8.6%). These rates are comparable to the rate of confusion in patients in an earlier study [15] who were given L Amph at a dose of 3 mg/kg/d (11.4%). In that study, the rate of confusion with conventional amphotericin B was 13.4%. The explanation for the confusion is uncertain. It did not occur with the initial doses, was not temporally associated with other psychoactive medications, and was not associated with the cumulative dose. In all cases it was short-lived, and in this and the earlier study there were no discontinuations or dose reductions due to confusion.

Efficacy data were collected and reported to ensure that lower rates of toxicity were not achieved at a cost of diminished efficacy. No statistically significant difference between L Amph and ABLC treatment groups was observed with respect to overall response rate. However, this trial was not adequately powered to enable a conclusion to be drawn about the efficacy equivalence of L Amph and ABLC. It should be noted that this study was designed to detect differences in toxicity, not efficacy, and the power to detect a difference in success based on success rates of 41% vs. 33% is only 16%.

In this study, empirical antifungal therapy was begun after 3 days of unexplained fever in accordance with a previous study [6] and consensus guidelines of the Infectious Diseases Society of America [35, 36]. Different trials have used various start dates between 3 and 7 days after onset of persistent fever. No trial to date has compared early versus late initiation of empirical antifungal therapy to ascertain the optimal starting time for minimizing morbidity and mortality associated with fungal disease as well as to minimize the toxicity and cost of the antifungal therapy. This should be the subject of subsequent trials. One could suppose that initiation of empirical antifungal therapy for patients receiving fluconazole prophylaxis should be later than for patients not receiving prophylaxis, for 2 reasons: first, fluconazole would suppress many *Candida* pathogens, and second, aspergillus infections often occur later during neutropenia. This also warrants further scrutiny in subsequent trials.

In conclusion, L Amph at a dose of 5 mg/kg/d or 3 mg/kg/d presented a superior safety profile in comparison with ABLC at a dose of 5 mg/kg/d, along with better tolerance, significantly fewer infusion-associated reactions, and significantly lower nephrotoxicity.

L Amph/ABLC Collaborative Study Group

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