LIPOSOMAL AMPHOTERICIN B FOR EMPIRICAL THERAPY IN PATIENTS WITH PERSISTENT FEVER AND NEUTROPENIA

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ABSTRACT

Background In patients with persistent fever and neutropenia, amphotericin B is administered empirically for the early treatment and prevention of clinically occult invasive fungal infections. However, breakthrough fungal infections can develop despite treatment, and amphotericin B has substantial toxicity.

Methods We conducted a randomized, double-blind, multicenter trial comparing liposomal amphotericin B with conventional amphotericin B as empirical antifungal therapy.

Results The mean duration of therapy was 10.8 days for liposomal amphotericin B (343 patients) and 10.3 days for conventional amphotericin B (344 patients). The composite rates of successful treatment were similar (50 percent for liposomal amphotericin B and 49 percent for conventional amphotericin B) and were independent of the use of antifungal prophylaxis or colony-stimulating factors. The outcomes were similar with liposomal amphotericin B and conventional amphotericin B with respect to survival (93 percent and 90 percent, respectively), resolution of fever (58 percent and 58 percent), and discontinuation of the study drug because of toxic effects or lack of efficacy (14 percent and 19 percent). There were fewer proved breakthrough fungal infections among patients treated with liposomal amphotericin B (11 patients [3.2 percent]) than among those treated with conventional amphotericin B (27 patients [7.8 percent], P=0.009). With the liposomal preparation significantly fewer patients had infusion-related fever (17 percent vs. 44 percent), chills or rigors (18 percent vs. 54 percent), and other reactions, including hypotension, hypertension, and hypoxia. Nephrotoxic effects (defined by a serum creatinine level two times the upper limit of normal) were significantly less frequent among patients treated with liposomal amphotericin B (19 percent) than among those treated with conventional amphotericin B (34 percent, P<0.001).

Conclusions Liposomal amphotericin B is as effective as conventional amphotericin B for empirical antifungal therapy in patients with fever and neutropenia, and it is associated with fewer breakthrough fungal infections, less infusion-related toxicity, and less nephrotoxicity. (N Engl J Med 1999;340:764-71.)
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INVASIVE fungal infections are an important cause of morbidity and mortality in patients with neutropenia who are receiving chemotherapy for cancer.[1-3] Early diagnosis of these infections is difficult, and persistent fever may be the only sign. A delay in treatment while a diagnosis is pursued may lead to increased morbidity and mortality.

As a standard of care, patients with persistent fever and neutropenia receive empirical antifungal therapy for the early treatment of clinically occult fungal infection or for the prevention of new fungal infections during neutropenia.[4,5] In two randomized, placebo-controlled trials, the frequency of proved invasive fungal infections was reduced in patients treated empirically with conventional amphotericin B desoxycholate.[6,7] Unfortunately, empirical treatment with conventional amphotericin B is limited by breakthrough fungal infections, acute toxic effects related to the infusion, and dose-limiting nephrotoxic reactions.[6-9]

The recent development of lipid formulations of amphotericin B allows empirical antifungal therapy to be administered with potentially improved efficacy and reduced toxicity.[10] Preclinical studies demonstrated that a small unilamellar liposomal formulation of amphotericin B (AmBisome, NeXstar, Boulder, Colo., and Fujisawa USA, Deerfield, Ill.) was more effective in the treatment of invasive aspergillosis and less nephrotoxic than conventional amphotericin B.[11] Open-label phase 1–2 studies in patients with neutropenia indicated that liposomal amphotericin B had minimal nephrotoxicity and was well tolerated.[12,13]

Additional studies demonstrated that this compound was effective in the treatment of invasive fungal infections, including disseminated candidiasis and invasive pulmonary aspergillosis.[14-16] We compared liposomal amphotericin B and conventional amphotericin B as empirical treatment for patients with persistent fever and neutropenia in a randomized, double-blind, multicenter trial.

METHODS

Study Design

The study (National Institute of Allergy and Infectious Diseases Mycoses Study Group study 32) was reviewed by the institutional review boards of all 32 participating centers. Written informed consent was obtained from each patient or his or her legal guardian. The data and safety monitoring board of the Mycoses Study Group was convened to review the data in order to ensure patients' safety.

Enrollment, Stratification, and Randomization

Eligible patients were between 2 and 80 years of age; were receiving chemotherapy for leukemia, lymphoma, or other cancers or had undergone bone marrow or peripheral-blood stem-cell transplantation; and had received empirical antibacterial therapy for at least five days while continuing to have fever and neutropenia (absolute neutrophil count, <500 per cubic millimeter). Patients were not eligible if they had known uncontrolled bacteremia or invasive fungal infection at the time of randomization; had received any form of parenteral amphotericin B within 10 days before administration of the study drug; had serum levels of aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase more than 10 times the upper limit of normal; had total serum bilirubin levels above 3 mg per deciliter (51.3 μmol per liter) if aminotransferase levels were 2 or more times the upper limit of normal or above 5 mg per deciliter (85.5 μmol per liter) if aminotransferase levels were less than 2 times the upper limit of normal; had serum creatinine levels more than 2 times the upper limit of normal; or had a history of anaphylactic reaction to conventional amphotericin B.

All patients, investigators, industrial sponsors, and study coordinators were blinded to the treatment administered. On enrollment, each patient was assigned to a high-risk or a low-risk stratum. Patients at high risk were those undergoing allogeneic bone marrow transplantation, those receiving chemotherapy for a relapse of acute nonlymphocytic leukemia, and those who had received systemic amphotericin B therapy for an episode of fever and neutropenia within the previous three months.[3,17,18] All others were considered to be at low risk. The pharmacist at the patient's institution telephoned a central randomization center to obtain a drug assignment. A computerized system randomly assigned treatment according to center and risk stratum. To maintain the blinded conditions, the study drug concentrations were adjusted so that the volume of solution in the intravenous bag was the same for both study drugs.

Administration of Study Drugs

Patients were randomly assigned in a 1:1 ratio according to center to be treated initially with liposomal amphotericin B (3.0 mg per kilogram of body weight per day) or conventional amphotericin B (0.6 mg per kilogram per day). The starting dose of liposomal amphotericin B was selected by consensus of the participating centers and was based on preclinical and clinical data. A starting dose of conventional amphotericin B was also selected by consensus of the investigators as reflecting the standard of care in their institutions. Blinding with respect to the study drug was considered critical for the objective evaluation of infusion-related toxicity and the determination of antifungal efficacy. Therefore, since liposomal amphotericin B and conventional amphotericin B may be distinguished by their appearance, infusion bottles were concealed by opaque bags and infusion tubing was either opaque or covered with opaque wrapping.

In order to take into account clinical practice patterns, adjustment of the dose of the study drug was permitted when there was evidence of infection or toxicity. Following protocol-defined guidelines, investigators were permitted to increase the dose of liposomal amphotericin B or conventional amphotericin B to intermediate doses of 4.5 or 0.9 mg per kilogram, respectively, or to high doses of 6.0 or 1.2 mg per kilogram, respectively. When toxic effects occurred, reduction of the dose to 1.5 mg of liposomal amphotericin B per kilogram or 0.3 mg of conventional amphotericin B per kilogram was permitted. The patients continued to receive antifungal therapy until recovery from neutropenia.

Monitoring of Infusion-Related Toxicity

All infusion-related reactions were monitored prospectively. Before the first infusion, no premedications for the prevention of infusion-related reactions were permitted. If a patient had an infusion-related toxic reaction during the first infusion, it was treated. For subsequent infusions, appropriate premedications were administered at the discretion of the blinded investigator or primary physician.

Definitions

Fungal infections were defined according to a modification of the criteria of the Mycoses Study Group. Proved pneumonia due to aspergillus species, *Pseudallescheria boydii,* fusarium species, agents of zygomycosis, and other pathogenic dematiaceous or hyaline molds in a patient with persistent or progressive pulmonary infiltrates was established by biopsy or by recovery of one of these organisms from bronchoalveolar-lavage fluid or induced sputum. Probable fungal pneumonia (e.g., aspergillosis) was defined on the basis of characteristic segmental, nodular, cavitary, or halo lesions on radiographic imaging without verification by culture. Possible fungal pneumonia was defined as clinically suspected fungal infection that did not fulfill the criteria for proved or probable fungal infection and that was associated with an increase in the dose of the study drug. Fungal sinusitis was diagnosed if there was clinical and radiographic evidence of acute sinusitis and a sinus needle-aspiration or biopsy sample positive for fungus according to the results of culture or histologic findings. A diagnosis of fungemia required at least one positive blood culture yielding fungus during a febrile episode.

Statistical Analysis

The primary efficacy variable, the success of treatment, was defined as a composite of five criteria: survival for seven days after initiation of the study drug; resolution of fever during the period of neutropenia; successful treatment of any base-line fungal infection, if present; the absence of breakthrough fungal infections during administration of the study drug or within seven days after the completion of treatment; and the absence of premature discontinuation of the study drug because of toxicity or lack of efficacy.

In order to determine with a high level of certainty whether liposomal amphotericin B and conventional amphotericin B were equivalent in terms of efficacy, a difference (delta) of 10 percent was used in the computation of the sample size. A sample of 330 patients who could be evaluated in each treatment group permitted the detection of a 10 percent difference in the rate of resolution of fever between the two treatment groups, with an alpha value of 0.05 and a power of 80 percent in a two-sided test of significance.

Outcome measures were analyzed with the Cochran–Mantel–Haenszel chi-square test, with adjustment for study center. Effects of the study center and other interactions were evaluated by means of the Breslow–Day test. The incidence of adverse events

and other safety variables was tabulated according to treatment group, and selected variables were analyzed by the chi-square test or Fisher's exact test, as appropriate. Kaplan–Meier curves were plotted for survival and time to a nephrotoxic reaction. A two-sided 95 percent confidence interval was constructed for the difference in success rates between the two treatment groups. The results were analyzed on a modified intention-to-treat basis, with all patients who had received at least one dose of study drug included. Liposomal amphotericin B was considered to be equivalent to conventional amphotericin B in efficacy if the confidence interval for the difference in rates of success between the two treatments fell within the range from −0.10 to 0.10. A panel of experts in fungal infections who did not know the patients' treatment assignments reviewed and classified all cases with clinical or microbiologic evidence of fungal infection according to criteria defined in the protocol.

RESULTS

Patients

A total of 702 patients were enrolled in the study between January 1995 and May 1996. Of the 687 patients whose data were included in the modified intention-to-treat analysis, 343 received liposomal amphotericin B and 344 received conventional amphotericin B. Groups were balanced with respect to age, sex, race, and risk category (Table 1). The rates of antibacterial therapy, including the use of aminoglycosides, the use of antiviral agents, and modifications of initial antibiotic therapy, were similar for both treatment groups. Use of antibiotics in different centers had no effect on the success of treatment (P=0.45 by the Breslow–Day test).

Eleven patients in each group were found to have occult candidemia according to base-line cultures. No enrolled patients had base-line chest radiographs that demonstrated proved or probable pulmonary fungal infection, as defined by the protocol. The frequency of base-line chest radiographs showing pulmonary infiltrates consistent with the presence of nonspecific pneumonia was similar in both treatment groups and all centers (Table 1).

Dosage

The mean daily doses throughout the study were 3.0±0.9 mg per kilogram for liposomal amphotericin B and 0.6±0.2 mg per kilogram for conventional amphotericin B. The mean duration of therapy was similar for liposomal amphotericin B (10.8±8.9 days) and conventional amphotericin B (10.3±8.9 days). During the final three days of therapy, 51 percent of patients receiving liposomal amphotericin B and 56 percent of those receiving conventional amphotericin B were still receiving the initial dose, 15 percent of those receiving liposomal amphotericin B and 27 percent of those receiving conventional amphotericin B were receiving a reduced dose (1.5 and 0.3 mg per kilogram, respectively), 23 percent and 11 percent, respectively, were receiving an intermediate dose (4.5 and 0.9 mg per kilogram), and 10 percent and 7 percent were receiving a high dose (6.0 and 1.2 mg per

kilogram). Thus, during the last three days of therapy, 117 patients receiving liposomal amphotericin B (34 percent) and 58 receiving conventional amphotericin B (17 percent) were receiving a higher-than-standard dose (P<0.001). There were also more dose reductions due to toxicity (both infusion-related and non–infusion-related adverse events) among patients

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS RECEIVING LIPOSOMAL AMPHOTERICIN B OR CONVENTIONAL AMPHOTERICIN B.*

CHARACTERISTIC	LIPOSOMAL AMPHOTERICIN B (N=343)	CONVENTIONAL AMPHOTERICIN B (N=344)
Age — yr		
Mean	41	42
Range	2–79	2–80
Age group — no. (%)		
2–12 yr	38 (11)	37 (11)
13–64 yr	268 (78)	258 (75)
≥65 yr	37 (11)	49 (14)
Sex — no. (%)		
Male	184 (54)	190 (55)
Female	159 (46)	154 (45)
Race — no. (%)		
White	301 (88)	292 (85)
Black	19 (6)	35 (10)
Other	23 (7)	17 (5)
Risk category — no. (%)		
High	117 (34)	119 (35)
Low	226 (66)	225 (65)
Bone marrow transplantation — no. (%)	154 (45)	161 (47)
Primary diagnosis — no. (%)		
Acute leukemia	168 (49)	165 (48)
Chronic leukemia	23 (7)	15 (4)
Lymphoma	64 (19)	65 (19)
Myeloma	10 (3)	13 (4)
Myelodysplasia	5 (1)	8 (2)
Solid tumor	59 (17)	56 (16)
Other	14 (4)	22 (6)
Antibiotic treatment — no. (%)		
Aminoglycosides†	69 (20)	65 (19)
Antiviral agents‡	62 (18)	58 (17)
Modification of initial therapy after enrollment	41 (12)	41 (12)
Base-line candidemia — no. (%)§	11 (3)	11 (3)
Base-line chest radiograph demonstrating infiltrates compatible with nonspecific pneumonia — no. (%)¶	35 (10)	34 (10)

*Among 702 patients enrolled, 15 were excluded from the study during screening before receiving either study drug for the following reasons: resolution of neutropenia, receipt of amphotericin B within the previous 10 days, resolution of fever, refusal by the patient, laboratory profiles not fulfilling entry criteria, presence of confirmed mycosis at base line, and absence of a central venous catheter. Because of rounding, percentages may not total 100.

†Aminoglycosides were gentamicin, tobramycin, and amikacin.

‡Antiviral agents were acyclovir, ganciclovir, and foscarnet.

§Base-line cultures of blood drawn before the initiation of the study drugs were reported to be positive after the patient had received one or more doses.

¶The infiltrates were not characteristic of fungal pneumonia (i.e., there were no characteristic segmental, nodular, cavitary, or halo lesions).

TABLE 2. MEASURES OF SUCCESS OF EMPIRICAL ANTIFUNGAL THERAPY WITH LIPOSOMAL AMPHOTERICIN B OR CONVENTIONAL AMPHOTERICIN B.*

MEASURE	LIPOSOMAL AMPHOTERICIN B (N=343)		CONVENTIONAL AMPHOTERICIN B (N=344)	
	NO. OF PATIENTS	SUCCESS RATE (95% CI)	NO. OF PATIENTS	SUCCESS RATE (95% CI)
		%		%
Overall success	172	50.1 (45–56)	170	49.4 (44–55)
Fever resolved during neutropenic period	199	58.0 (53–63)	200	58.1 (53–63)
No breakthrough fungal infection†	309	90.1 (86–93)	307	89.2 (85–92)
Base-line fungal infection cured‡	9	81.8 (48–98)	8	72.7 (39–94)
Survived 7 days after initiation of study drug	318	92.7 (89–95)	308	89.5 (86–93)
Study drug not prematurely discontinued because of toxicity or lack of efficacy	294	85.7 (82–89)	280	81.4 (77–85)

*CI denotes confidence interval.

†Patients receiving liposomal amphotericin B with proved (11 patients), probable (6 patients), or possible (17 patients) breakthrough fungal infections were not included. Patients receiving conventional amphotericin B with proved (27 patients), probable (3 patients), or possible (7 patients) breakthrough fungal infections were not included.

‡Eleven patients in each group had fungal infections at base line.

treated with conventional amphotericin B (101 patients [29 percent]) than among those treated with liposomal amphotericin B (36 patients [10 percent], P<0.001).

Efficacy

The overall success rate according to the composite score was 50.1 percent for patients receiving liposomal amphotericin B and 49.4 percent for those receiving conventional amphotericin B (Table 2). Within the composite score for success, the two treatment groups had similar rates of survival, resolution of fever, successful treatment of any base-line fungal infection, absence of breakthrough fungal infections, and absence of discontinuation of study drug because of toxicity or lack of efficacy. When the differences between those receiving liposomal amphotericin B and those receiving conventional amphotericin B were analyzed for subgroups — adults and children, high-risk and low-risk patients, and those receiving antifungal prophylaxis or recombinant colony-stimulating factor and those not receiving such agents — the results were consistent with the overall results of the study.

There were significantly fewer proved invasive breakthrough fungal infections in patients receiving liposomal amphotericin B (11 patients [3.2 percent]) than in those receiving conventional amphotericin B (27 patients [7.8 percent], P=0.009) (Table 3). This difference was independent of risk category, age group, other antifungal prophylaxis, or previous therapy with cytokines. There also was a significantly lower frequency of breakthrough candidemia in patients receiving liposomal amphotericin B than in those receiving conventional amphotericin B (3 vs. 12, P=0.03). All

TABLE 3. PROVED BREAKTHROUGH FUNGAL INFECTIONS DURING EMPIRICAL ANTIFUNGAL THERAPY WITH LIPOSOMAL AMPHOTERICIN B OR CONVENTIONAL AMPHOTERICIN B.

ORGANISM AND SITE	LIPOSOMAL AMPHOTERICIN B (N=343)	CONVENTIONAL AMPHOTERICIN B (N=344)
	no. (%)	
Aspergillus		
Lungs	5	9
Sinuses	0	2
Wound	1	1
Candida*		
Blood	3	12†
Fusarium		
Blood	1	0
Wound	0	1
Cryptococcus albidus		
Blood	0	1
Zygomycete		
Lung	1	0
Ulocladium		
Lung	0	1
Total	11 (3.2)	27 (7.8)‡

*Breakthrough fungemia in the patients receiving liposomal amphotericin B were due to *Candida parapsilosis* (two cases) or *C. krusei* (one case). In the patients receiving conventional amphotericin B, they were due to *C. parapsilosis* (one case), *C. glabrata* (three cases), *C. albicans* (three cases), *C. tropicalis* (one case), and candida species other than *C. albicans* (two cases). The remaining two isolates were not identified to species level.

†P=0.03 for the comparison with the patients receiving liposomal amphotericin B.

‡P=0.009 for the comparison with the patients receiving liposomal amphotericin B.

but 3 of these 15 patients had fungemia due to candida species other than *Candida albicans.* Six patients receiving liposomal amphotericin B and three patients receiving conventional amphotericin B had probable pulmonary aspergillosis (P=0.5). The radiologic findings in these cases were considered to be consistent with aspergillosis but they were not microbiologically or histologically proved.

There was a trend toward improved survival among patients receiving liposomal amphotericin B; 25 patients receiving liposomal amphotericin B died, as compared with 36 receiving conventional amphotericin B (P=0.18). The investigators blinded to treatment reported fungal infections as a primary or contributing cause of death in 4 patients receiving liposomal amphotericin B and 11 receiving conventional amphotericin B (P=0.11).

Safety and Tolerance

Infusion-Related Toxicity

A total of 7025 infusions were prospectively monitored: 3622 infusions in patients receiving liposomal amphotericin B and 3403 in those receiving conventional amphotericin B. Patients receiving liposomal amphotericin B had fewer infusion-related reactions than did those receiving conventional amphotericin B. This result was found for all infusions and also for the first infusion, when no premedication was permitted for prevention of infusion-related toxicity (Table 4).

When all infusions were analyzed for infusion-related reactions, infusion-related increases in temperature of more than 1°C occurred after 267 infusions of liposomal amphotericin B (7.4 percent) and 544 infusions of conventional amphotericin B (16.0 percent, P<0.001); infusion-related reactions without fever occurred after 746 infusions of liposomal amphotericin B (20.6 percent) and 1776 infusions of conventional amphotericin B (52.2 percent, P<0.001). The latter reactions are presented in greater detail in Table 4. Among the documented cardiorespiratory events, there was a significantly lower incidence of hypertension, tachycardia, hypotension, and hypoxia in recipients of liposomal amphotericin B than in recipients of conventional amphotericin B. Only 1 patient receiving liposomal amphotericin B but 22 patients receiving conventional amphotericin B had documented hypoxia (measured predominantly by pulse oximetry) (P<0.001). Flushing reactions occurred almost exclusively in patients treated with liposomal amphotericin B (P<0.001).

Reflecting the reduced frequency of infusion-related reactions in patients receiving liposomal amphotericin B, these patients were significantly less likely to receive acetaminophen, diphenhydramine, meperidine, hydrocortisone, or lorazepam to prevent such reactions (Table 4).

TABLE 4. INFUSION-RELATED REACTIONS TO LIPOSOMAL AMPHOTERICIN B AND CONVENTIONAL AMPHOTERICIN B.

CATEGORY AND REACTION	LIPOSOMAL AMPHOTERICIN B (N=343)	CONVENTIONAL AMPHOTERICIN B (N=344)
	no. (%)	
Reactions on day 1*		
Fever following infusion (increase of ≥1.0°C)	58 (16.9)	150 (43.6)†
Chills or rigors	63 (18.4)	187 (54.4)†
Nausea	42 (12.2)	35 (10.2)
Vomiting	21 (6.1)	28 (8.1)
Other‡	57 (16.6)	82 (23.8)§
All reactions¶		
Chills	129 (37.6)	253 (73.5)†
Nausea	90 (26.2)	89 (25.9)
Vomiting	52 (15.2)	81 (23.5)‖
Headache	28 (8.2)	29 (8.4)
Flushing	18 (5.2)	2 (0.6)‖
Dyspnea	16 (4.7)	25 (7.3)
Hypotension	12 (3.5)	28 (8.1)‖
Sweating	9 (2.6)	21 (6.1)§
Tachycardia	8 (2.3)	43 (12.5)§
Hypertension	8 (2.3)	39 (11.3)§
Hypoxia	1 (0.3)	22 (6.4)†
Use of premedications after day 1		
Acetaminophen	141 (41.1)	208 (60.5)†
Diphenhydramine	130 (37.9)	203 (59.0)†
Meperidine	36 (10.5)	118 (34.3)†
Hydrocortisone	37 (10.8)	108 (31.4)†
Lorazepam	7 (2.0)	18 (5.2)§

*No premedications were permitted on day 1 of infusion of the study drug.

†P≤0.001 for the comparison with the patients receiving liposomal amphotericin B.

‡Other reactions included dyspnea, hypotension, hypertension, tachycardia, diaphoresis, and flushing.

§P≤0.05 for the comparison with the patients receiving liposomal amphotericin B.

¶Each infusion and its associated reactions were prospectively monitored. There were a total of 7025 infusions: 3622 of liposomal amphotericin B and 3403 of conventional amphotericin B. Listed here are infusion-related reactions observed in at least 5 percent of patients in either treatment group.

‖P≤0.01 for the comparison with the patients receiving liposomal amphotericin B.

Nephrotoxicity and Hepatotoxicity

Significantly fewer patients receiving liposomal amphotericin B had nephrotoxic effects, as indicated by the doubling or tripling of the serum creatinine level (P<0.001) (Table 5) or by peak serum creatinine values above 3.0 mg per deciliter (265 μmol per liter); such levels occurred in 12 percent of those receiving liposomal amphotericin B, as compared with 26 percent of those receiving conventional amphotericin B (P<0.001). This significant reduction in azotemia was also consistent among subgroups of patients receiving concomitant therapy with nephrotoxic agents (P≤0.05). Moreover, there was a reduction in hypokalemia (P=0.02), as well as a trend toward a reduction in hypomagnesemia (P=0.12), in

TABLE 5. EFFECT OF LIPOSOMAL AMPHOTERICIN B AND CONVENTIONAL AMPHOTERICIN B IN TERMS OF NEPHROTOXICITY, HEPATOTOXICITY, AND SEVERE (GRADE 3) OR LIFE-THREATENING (GRADE 4) TOXIC REACTIONS.

EFFECT	LIPOSOMAL AMPHOTERICIN B (N=343)	CONVENTIONAL AMPHOTERICIN B (N=344)
	no. (%)	
Serum creatinine during therapy		
>1.5 times base-line value	101 (29.4)	170 (49.4)*
>2.0 times base-line value	64 (18.7)	116 (33.7)*
>3.0 times base-line value	28 (8.2)	57 (16.6)*
Nephrotoxicity with concomitant nephrotoxic drugs†		
0 or 1 drug	5 (6.3)	14 (15.2)‡
≥2 drugs	59 (22.3)	102 (40.5)*
≥3 drugs	36 (30.0)	54 (45.4)‡
Hypokalemia§	23 (6.7)	40 (11.6)‡
Hypomagnesemia¶	69 (20.1)	89 (25.9)
Hepatotoxicity‖	61 (17.8)	70 (20.3)
Grade 3 or 4 toxicity**		
Fever	24 (7.0)	70 (20.3)*
Chills	35 (10.2)	147 (42.7)*
Hyperbilirubinemia	25 (7.3)	29 (8.4)
Dyspnea	20 (5.8)	37 (10.8)††
Nausea	12 (3.5)	25 (7.3)††
Vomiting	4 (1.2)	19 (5.5)‡‡

*P<0.001 for the comparison with the patients receiving liposomal amphotericin B.

†Nephrotoxicity was defined by a serum creatinine level that was two or more times the base-line value. Concomitant nephrotoxic drugs were aminoglycosides, cyclosporine, and foscarnet. The following numbers of patients took various numbers of drugs: 0 or 1, 79 patients receiving liposomal amphotericin B and 92 receiving conventional amphotericin B; 2 or more, 264 and 252, respectively; and 3 or more, 120 and 119, respectively.

‡P≤0.05 for the comparison with the patients receiving liposomal amphotericin B.

§Hypokalemia was defined as a serum potassium level of ≤2.5 mmol per liter.

¶Hypomagnesemia was defined as a serum magnesium level of ≤0.6 mmol per liter.

‖Hepatotoxicity was defined as a serum aspartate aminotransferase or alanine aminotransferase level more than 5 times the base-line value if the base-line value was less than 2 times the upper limit of normal, more than 3 times the base-line value if the base-line value was 2 to 5 times the upper limit of normal, and more than 2 times the base-line value if the base-line value was 5 to 10 times the upper limit of normal.

**Toxicity was measured on the Southwestern Oncology Group scale.

††P<0.05 for the comparison with the patients receiving liposomal amphotericin B.

‡‡P<0.01 for the comparison with the patients receiving liposomal amphotericin B.

patients receiving liposomal amphotericin B, as compared with those receiving conventional amphotericin B. There was no significant difference in the frequency of hepatotoxicity in the two treatment groups.

Severe Adverse Events

The frequency of all severe adverse events (Southwestern Oncology Group grade 3 or 4) and of several specific severe events (fever, chills, dyspnea, nausea, and vomiting) was significantly lower in the recipients of liposomal amphotericin B (Table 5). There was no significant difference between the groups in the frequency of hyperbilirubinemia.

DISCUSSION

This randomized, double-blind, multicenter trial comparing liposomal amphotericin B with conventional amphotericin B as empirical antifungal therapy in patients with persistent fever and neutropenia demonstrated that the treatments had similar overall success rates according to our composite score. However, liposomal amphotericin B was more effective in reducing the frequency of proved breakthrough fungal infections, infusion-related toxic reactions, and nephrotoxic effects. Although the composite score represents our attempt to address the key variables that influence the outcome of empirical antifungal therapy, the overall rate of success primarily reflects resolution of fever. Hence, the evaluation of the individual variables, including the frequency of breakthrough invasive fungal infections and the development of toxic effects, is important.

The greater efficacy of liposomal amphotericin B in preventing proved breakthrough fungal infections may be related to the fact that this formulation can be given at a dose of 3 mg or more per kilogram with minimal dose-dependent toxicity. Conversely, patients treated with conventional amphotericin B had significantly more dose reductions because of toxicity and fewer dose increases than did those treated with liposomal amphotericin B. The possibility of delivering the desired antifungal therapy with liposomal amphotericin B may afford more sustained protection against breakthrough fungal infections. Centers participating in this clinical trial used an aggressive approach to identify invasive fungal infections by means of blood cultures, bronchoalveolar lavage, percutaneous needle aspiration, and biopsy. There were few cases of probable fungal pneumonia. There were more cases of possible fungal pneumonia in recipients of liposomal amphotericin B than in recipients of conventional amphotericin B (17 vs. 7). However, possible fungal pneumonia was defined in this study as any case with pulmonary infiltrates and fever that led to a dose increase. Since the dose of liposomal amphotericin B was more frequently increased than the dose of conventional amphotericin B, patients receiving liposomal amphotericin B were more frequently classified as having possible infections.

The reduction in the frequency of proved fungal infections was particularly notable for candidemia: 3 patients receiving liposomal amphotericin B and 12 receiving conventional amphotericin B had candidemia. Among the 15 breakthrough episodes of candidemia, all but 3 were caused by species other than C. albicans, signifying an important trend to-

ward the emergence of candida species potentially resistant to conventional antifungal therapy. The minimal inhibitory concentrations and minimal lethal concentrations of conventional amphotericin B are typically higher for other candida species than for *C. albicans*.[19,20] The degree to which these infecting organisms were resistant in vitro to conventional amphotericin B or antifungal azoles has not been assessed.

This study established that liposomal amphotericin B has significantly less infusion-related toxicity than conventional amphotericin B. The statistical strength of these observations is supported by the prospective and blinded bedside monitoring of more than 7000 infusions. The significant reduction in cardiorespiratory events in the group assigned to liposomal amphotericin B was especially encouraging. These benefits may be important in seriously ill patients who have poor tolerance of adverse cardiorespiratory events. Moreover, the reduction in infusion-related toxicity may improve the quality of life for patients with cancer at a time in their care when they are very vulnerable. Although lipid formulations of amphotericin B may cause respiratory distress, such events were less common among patients receiving liposomal amphotericin B than among those receiving conventional amphotericin B.[21,22]

Patients receiving liposomal amphotericin B had better sustained glomerular and tubular function than those receiving conventional amphotericin B, as evidenced by the lower rates of azotemia and hypokalemia. Nearly half the patients had undergone bone marrow or stem-cell transplantation and more than 70 percent had hematologic cancers. Thus, the reductions in nephrotoxic effects were documented in patients at high risk who tolerate serious renal impairment poorly.

Several mechanisms may contribute to the reduced nephrotoxicity of lipid formulations of amphotericin B. Among them are liposome-mediated selective transfer of amphotericin B to fungal cell membranes as compared with mammalian cell membranes; reduced levels of amphotericin B in the kidney in relation to the high levels achieved in the reticuloendothelial system; preferential binding of liposomal amphotericin B to high-density lipoproteins, as compared with conventional amphotericin B, which is bound to low-density lipoproteins; and selective local release of amphotericin B directly onto the fungal cells.[23-28] The toxicity of infusions of conventional amphotericin B is related to the release of tumor necrosis factor α, interleukin-1, and interleukin-6 from monocytes and macrophages. Encapsulation of amphotericin B by the liposomal structure attenuates the release of these proinflammatory cytokines.[29,30]

As patients at higher risk undergo intensive chemotherapy and bone marrow or stem-cell transplan-tation, invasive fungal infections will continue to pose a threat to their successful treatment. This study demonstrates that liposomal amphotericin B is an appropriate alternative to conventional amphotericin B for empirical antifungal therapy and that its use may reduce the frequency of breakthrough fungal infections, preserve renal function, and reduce the frequency of acute infusion-related toxic effects.

APPENDIX

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