MAJOR ARTICLE

Continuous Infusion of Escalated Doses of Amphotericin B Deoxycholate: An Open-Label Observational Study

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(See the editorial commentary by Hiemenz on pages 952–3)

Amphotericin B deoxycholate (AmB-d) remains a mainstay of antifungal therapy for immunocompromised patients, despite being associated with significant therapy-related toxicity. Because continuous infusion of AmB-d is better tolerated than traditional administration over 2–6 hours, we evaluated escalation of the AmB-d dose in 33 patients (31 of whom were neutropenic), for whom the initial dosage of AmB-d (1 mg/kg/day) was gradually increased to 2.0 mg/kg/day when renal function remained stable and the drug was tolerated. Dose escalation was possible without delay in 28 patients. Median duration of AmB-d therapy was 16 days (range, 7–72 days). Infusion-related reactions accompanied <18% of AmB-d infusions. Twenty-seven patients had a decrease in creatinine clearance while receiving AmB-d therapy. A >2-fold decrease in creatine clearance was observed in 5 patients, and the decrease was dose-limiting in only 1 patient; no dialysis was required. In conclusion, continuous infusion of AmB-d escalated to 2.0 mg/kg/day seems not to cause additional impairment of vital organ functions and to be well tolerated by most patients.

The incidence of systemic opportunistic fungal infections has dramatically increased during the past 20 years, and, presently, opportunistic fungal infections constitute a leading cause of morbidity and mortality in neutropenic patients [1]. Despite advances in the development of new agents, amphotericin B (AmB) remains a cornerstone of antifungal therapy for patients with opportunistic fungal infections. However, clinical use is hindered by the intrinsic toxicity of the molecule, which causes dose-limiting organ dysfunction in some cases, as well as the drug's insolubility in water, which requires addition of the detergent deoxycholate or lipids for administration to humans. Although lipid formulations are associated with fewer side effects, they are expensive and are probably not more effective than AmB deoxycholate (AmB-d) [2, 3].

Traditionally, AmB-d is given in 2–6 h infusions on the basis of the assumption that the severity and frequency of related side effects increases during more-rapid administration. Nevertheless, daily doses of >1.0 mg/kg are usually not recommended, for reasons of toxicity [4, 5]. Recently, continuous infusion of AmB-d has been shown to reduce the incidence of nephrotoxicity and infusion-related side effects, compared with traditional administration of the same amount of drug over 2–6 h [6, 7]. This finding suggests the possibility of further dose escalation, which might offer therapeutic benefit, because clinical data from both

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Table 1. Basic demographic characteristics of and laboratory parameters for patients in a study of amphotericin B deoxycholate (AmB-d) dose escalation.

Characteristic	All patients (n = 33)	AmB-d target dosage group		
		1.5 mg/kg/day (n = 14)	1.75 mg/kg/day (n = 9)	2 mg/kg/day (n = 10)
Age, median years (range)	54.4 (15.8–70.3)	55.0 (23.4–70.3)	42.7 (32.2–67.1)	40.9 (15.8–58.7)
Female sex, no. (%) of patients	15 (45)	7 (50)	4 (44)	4 (40)
Underlying condition, no. of patients				
Acute myeloid leukemia	25	13	7	5
Hairy cell leukemia	1	1	—	—
Acute lymphatic leukemia	2	—	1	1
Non-Hodgkin lymphoma	1	—	—	1
Myelodysplastic syndrome	1	—	1	—
Solid tumor	1	—	—	1
HIV infection	2	—	—	2
Type of fungal infection				
Proven	9	3	2	4
Probable	9	4	2	3
Possible	15	7	5	3
Baseline laboratory parameters, median value (range)[a]				
ANC, neutrophils/μL	30 (10–7250)	20 (10–470)	40 (10–110)	60 (10–7250)
Creatinine, μM	63 (44–95)	62 (53–94)	67 (44–95)	67 (54–92)
AST, U/L	20 (6–105)	20.5 (6–105)	26 (7–92)	18 (7–69)
ALT, U/L	31 (8–158)	26.5 (8–158)	22 (9–118)	44 (10–83)
Total bilirubin, μM	15 (3–40)	14 (9–22)	15 (6–28)	16.5 (3–40)
AP, U/L	74 (16–322)	92 (33–211)	81 (29–299)	69.5 (16–322)
Potassium, mM	3.7 (3.1–5.0)	3.6 (3.1–4.2)	3.8 (3.5–4.2)	3.9 (3.3–5.0)
Magnesium, mM	0.77 (0.65–0.95)	0.76 (0.65–0.95)	0.78 (0.56–0.85)	0.78 (0.68–0.87)
CRP, mg/L	111 (15–348)	106 (15–290)	220 (67–348)	74 (18–215)
Bicarbonate, mM	22.1 (19–28)	22 (20–27)	23 (19–28)	20 (19–27)

NOTE. ALT, alanine aminotransferase; ANC, absolute neutrophil count; AP, alkaline phosphatase; AST, aspartate aminotransferase; CRP, C-reactive protein.

[a] Normal levels and ranges for laboratory values are as follows: creatinine, 70–105 μM; AST, <35 U/L; ALT, <35 U/L; total bilirubin, <25 μM; AP, 30–115 U/L; potassium, 3.5–4.5 mM; magnesium, 0.65–1.0 mM; and CRP, <5 mg/L.

studies of humans and experiments with neutropenic animals have indicated dose-dependent efficacy of AmB-d [8–11].

There is only scant knowledge, however, about the safety and tolerance of dose-escalated AmB-d. These issues were addressed in the present open-label, observational study, which involved a cohort of adult immunocompromised patients, most of whom had chemotherapy-induced neutropenia, to whom AmB-d was given by continuous infusion for treatment of proven, probable, or possible systemic fungal infection.

PATIENTS AND METHODS

Study population. All patients (age, >16 years) at our tertiary care referral center for adult internal medicine (University Hospital of Zurich, Switzerland), including those in the intensive care unit, were eligible for the study if the treating physicians considered treatment with AmB to be necessary. Exclusion criteria were a calculated creatinine clearance of <30 mL/min [12], an estimated duration of antifungal therapy of <7–10 days, pregnancy or lactation, known AmB intolerance, or receipt of systemic AmB treatment within the 12 months before enrollment. The local ethics committee approved the study, and written informed consent was obtained from all participants or legally authorized representatives before study entry. The level of probability of fungal infection was classified according to definitions recently proposed by an international consensus committee (table 1) [13].

Antifungal therapy. On day 1 of the study, 1 mg/kg of AmB-d (Fungizone; Bristol-Myers Squibb) was administered in 500 mL of 5% dextrose, without additives, through a separate

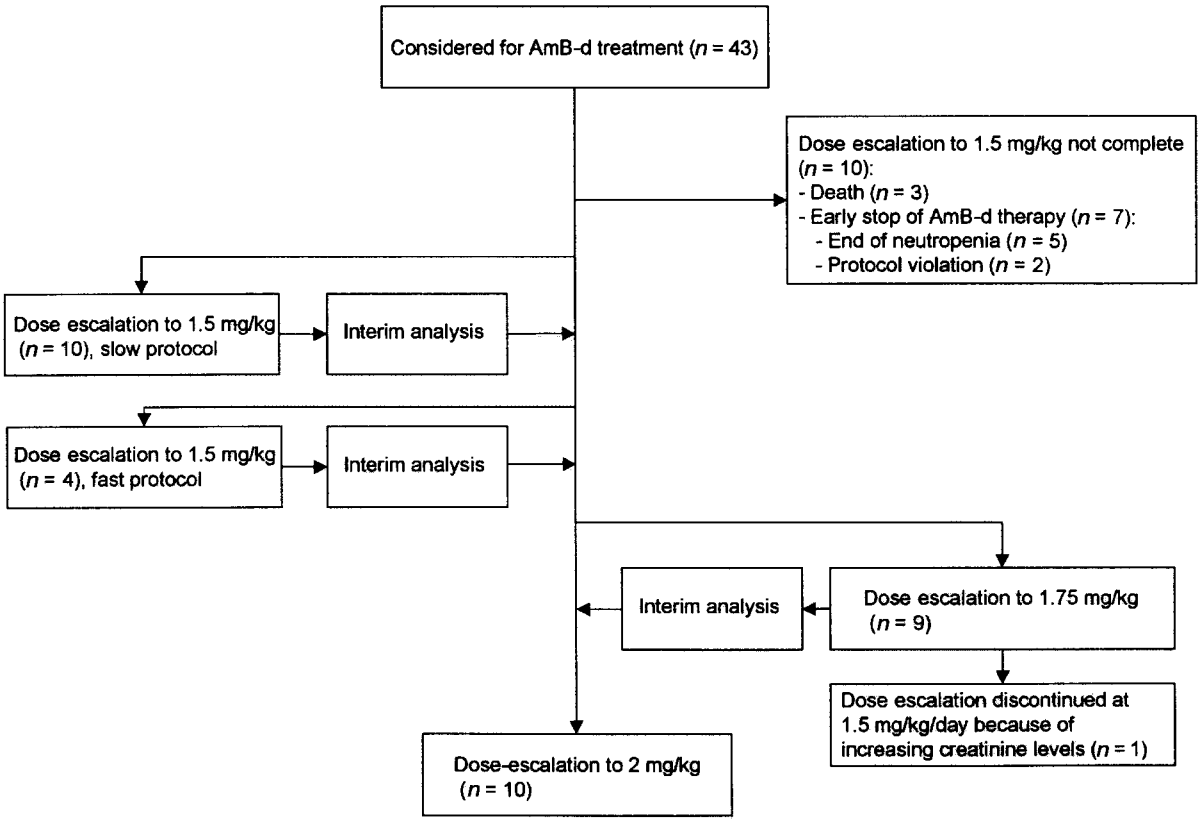

Figure 1. Trial profile. Chart shows flow of patients once entered on study. AmB-d, amphotericin B deoxycholate.

intravenous line by continuous infusion. Administration of drugs to prevent chills or fever was discouraged on this day; otherwise, there were no restrictions on the use of any concomitant treatment. To reduce nephrotoxicity, all patients received an additional 1000 mL of saline every 24 h as standard care, whenever possible [14–17]. The initial protocol allowed dose escalation to start on day 3, when renal function remained stable (i.e., an increase in the serum creatinine level of $\leq$10 μM in 48 h was observed) and when infusion-related side effects were tolerated by the patient. The daily dose was increased by 10 mg every other day, as long as the renal function remained stable (i.e., an increase in the serum creatinine level of $\leq$10 μM in 48 h was observed) and the drug was still tolerated. For practical reasons, the dose was increased by the same amount of drug, regardless of the weight of the patient; thus, the time required to achieve the target dosage varied among patients. After the inclusion of 10 patients with a target dosage of 1.5 mg/kg/day, an interim analysis showed that dose escalation was unproblematic in each patient. As a result, the protocol was modified to allow a target dosage of 1.75 mg/kg/day and dose escalation (again, starting on day 3) by 10 mg per day every day, provided that the serum creatinine level did not increase more than 10 μM per day. After 9 patients were treated with 1.75 mg/kg, another interim analysis again confirmed that dose escalation was unproblematic, and a maximum dosage of 2.0 mg/kg/day was targeted. Potassium was supplemented by continuous infusion to maintain a plasma level of $\geq$3.6 mM. Sodium bicarbonate was administered to keep the plasma level $\geq$16 mM either by bolus or continuous administration. All but 2 patients were treated with antifungal monotherapy. Of these 2 patients, one was treated with a combination of AmB-d and flucytosine because of cryptococcal meningitis, and the other received AmB-d in combination with caspofungin and flucytosine because of life-threatening aspergillosis of the maxilar sinus, with orbital and cerebral invasion; both patients were included in the 2 mg/kg dose group.

Adverse drug-related effects and outcome measures. The occurrence of chills, rigors, vomiting, and feverish reactions was monitored prospectively, and patients were interviewed regularly to find which side effects were experienced. We also evaluated nursing charts for any other adverse reactions. Body temperature was measured with tympanic membrane thermometers at least twice daily; fever was defined as a core temperature of >39.3°C [7]. Sodium, potassium, and creatinine levels were measured daily; magnesium and bicarbonate levels were measured every other day; and hematologic parameters and levels of C-reactive protein, liver transaminases, alkaline phosphatase, bilirubin, calcium, albumin, total cholesterol, and

Table 2. Dosage data for patients who received amphotericin B deoxycholate (AmB-d) therapy and concomitant nephrotoxic drugs.

Regimen, dosage data or drug	All patients (n = 33)	AmB-d target dosage group		
		1.5 mg/kg/day (n = 14)	1.75 mg/kg/day (n = 9)	2 mg/kg/day (n = 10)
AmB-d therapy, median value (range)				
Maximum daily dose, mg/kg	1.72 (1.41–2.28)	1.49 (1.41–1.56)	1.74 (1.64–1.85)	2.08 (1.96–2.28)
Cumulative dose, mg	2245 (370–7995)	1245 (370–3530)	3234 (1290–7185)	2871 (1250–7995)
Cumulative dose, mg/kg	34.93 (6.2–123.24)	19.84 (6.2–55.16)	49.68 (17.43–123.24)	44.29 (21.2–120.23)
Duration of therapy, days	22 (7–72)	14 (7–42)	32 (14–72)	25 (8–67)
Concomitant nephrotoxic drugs, no. of patients				
Aminoglycosides	7	3	2	2
Glycopeptides	15	7	4	4
Diuretics	4	2	1	1
Cyclosporine	2	1	1	—

triglycerides were measured at least on a weekly schedule. All measurements were done in accordance with standard laboratory procedures. Experienced toxicities were rated according to the National Cancer Institute Common Toxicity Criteria (available at: http://ctep.cancer.gov/reporting/ctc.html). Efficacy was monitored for overall mortality and mortality due to invasive fungal infections.

Statistical analysis. All patients who completed dose escalation to ⩾1.5 mg/kg/day were included in the final analysis. Results are presented as median values and ranges. Nonparametric statistical tests were used throughout. Continuous variables were compared using the Kruskal-Wallis 1-way analysis of variance test or the Friedman test with Dunn's multiple comparisons post test, as appropriate, whereas discontinuous variables were compared with the χ^2 test for trend. Statistical calculations were done using InStat software, version 3.05 (GraphPad). $P < .05$ was considered to be statistically significant.

RESULTS

Study population. A total of 43 patients were enrolled in the study (figure 1). Ten patients did not complete dose escalation from 1 mg/kg/day to ⩾1.5 mg/kg/day: 3 patients died during AmB-d dose escalation of progression of underlying disease (acute myeloid leukemia in all patients); 5 patients discontinued use of the drug because the WBC count recovered, rendering AmB-d therapy unnecessary; and dose escalation was erroneously stopped prematurely in 2 patients (because of protocol violation), although no organ dysfunction developed and the drug was well tolerated. Thus, 33 patients, of whom 31 were neutropenic at study entry, were assessable for analysis; their demographic characteristics and baseline laboratory parameters are shown in table 1. Invasive fungal infections were verified by culture for 9 patients (4 patients had pulmonary infections due to *Aspergillus* species, 3 had aspergillosis of the maxillary sinus and the lung, 1 had disseminated histoplasmosis, and 1 had disseminated *Cryptococcus neoformans* infection).

Duration of therapy. As shown in table 2, the duration of antifungal therapy varied considerably, ranging from 7 to 72 days. For the initial 10 patients, dose escalation to 1.5 mg/kg/day necessitated a median of 8.5 days (range, 6–13 days). Dose escalation was possible without delay in 8 patients. In 2 patients who were concomitantly receiving aminoglycosides, an increasing serum creatinine level resulted in delays of 2 and 3 days until the target dose was reached. With the modified protocol, dose escalation was more rapid: a median of 5 days (range, 4–8 days) was required for the remaining patients to achieve a daily dose of 1.5 mg/kg, and dose escalation was possible without any delay for all of these patients. Dose-escalation required 9 days (range, 7–20 days) in the 1.75 mg/kg/day group. In 1 patient, there was a 10-day delay because of increasing liver enzyme values, and, in another patient, intended dose escalation to 1.75 mg/kg/day was discontinued at 1.5 mg/kg/day because of increasing creatinine levels (see "Laboratory parameters" section below). Dose escalation was completed in 8 days (range, 7–14 days) in the 2 mg/kg/day group, and it was delayed in only 2 patients because of nephrotoxicity during concomitant use of flucytosine and aminoglycosides.

After dose escalation was completed, antifungal therapy was maintained for 1–34 days in the 1.5 mg/kg/day group, 1–65 days in the 1.75 mg/kg/day group, and 1–59 days in the 2.0 mg/kg/day group. The daily AmB-d dose had to be reduced after completion of dose escalation in 4 patients: in 3 patients, aminoglycosides were used concomitantly, whereas, in 1 patient, vancomycin was additionally administered.

Infusion-related reactions. The use of drugs to prevent chills or fever was discouraged on day 1 of antifungal therapy to assess infusion-related toxicities. Of the 727 infusions ad-

Table 3. Summary of data on nephrotoxicity for recipients of amphotericin B deoxycholate (AmB-d).

Variable	All patients (n = 33)	AmB-d target dosage group		
		1.5 mg/kg/day (n = 14)	1.75 mg/kg/day (n = 9)	2 mg/kg/day (n = 10)
Creatinine clearance, mL/min				
At baseline	102.2 (61.6–195.8)	107.6 (61.6–195.8)	106.7 (70.0–156.6)	103.2 (79.4–115.9)
At end of dose escalation	86.4 (31.2–119.3)[b]	86.6 (54.4–119.3)	83.0 (31.2–97.2)	87.2 (62.6–116.3)
At end of AmB-d therapy	72.5 (24.0–116.8)[c]	79.4 (44.3–116.8)	72.5 (26.8–83.8)[a]	66.1 (24.0–116.4)[b]
Potassium supplementation, mmol per day				
At baseline	80 (0–330)	70 (0–200)	80 (0–200)	60 (40–330)
At 1.5 mg/kg/day dosing	200 (80–380)	210 (120–360)[c]	240 (100–380)[b]	190 (80–360)[a]
At 1.75 mg/kg/day dosing	250 (80–420)[c]	—	250 (100–420)[c]	225 (80–360)[c]
At 2.0 mg/kg/day dosing	225 (80–360)[c]	—	—	225 (80–360)[c]
Intravenous fluid administration, mL per day				
At baseline	3800 (1500–7520)	3150 (1500–4900)	4400 (2600–6400)	3800 (1500–7520)
At 1.5 mg/kg/day dosing	4200 (2200–6000)	4100 (2800–4700)[a]	4450 (2850–5150)	4050 (2200–6000)
At 1.75 mg/kg/day dosing	4200 (3200–6100)	—	4350 (3250–5300)	4200 (3200–6100)
At 2.0 mg/kg/day dosing	4425 (3800–6150)[a]	—	—	4425 (3800–6150)[a]

NOTE. Data are median (range).

[a] $P < .05$.

[b] $P < .01$.

[c] $P < .001$, compared with the corresponding baseline value.

ministered, 129 (18%) were associated with infusion-related reactions. Seventeen patients (52%) had chills and/or rigor on day 1 or 2. Nausea was noted in 7 patients (21%). Itching was reported by 3 patients (9%). A febrile reaction was noted during treatment in 1 patient. In 1 patient, respiratory decompensation occurred after 10 days of antifungal therapy and was most likely due to the large quantity of infusion that was administered.

Laboratory parameters. The course of renal function during dose escalation and follow-up is shown in table 3. Twenty-seven patients (82%) had a decrease in creatinine clearance while receiving AmB-d therapy. Sixteen patients (48%) had values that were 1.5 times less than the baseline value, 7 (44%) of whom were in the 1.5 mg/kg/day group, 4 (25%) of whom were in the 1.75 mg/kg/day group, and 5 (31%) of whom were in the 2.0 mg/kg/day group ($P = .36$). Five patients (15%) had a value 2 times less than the baseline value: 1 in the 1.5 mg/kg/day group, 3 in the 1.75 mg/kg/day group, and 1 in the 2.0 mg/kg/day group ($P = .42$). In 1 patient, the serum creatinine level increased abruptly (from 79 to 175 μM), necessitating discontinuation of dose escalation. Afterwards, the creatinine level persisted at 166–199 μM until AmB-d therapy was discontinued. In the remaining patients, the range of peak serum creatinine levels was 52–196 μM during the study. After completion of dose escalation, creatinine clearance levels decreased only slightly further, but the deceases were clinically insignificant in most patients (table 3), with only 1 patient (in the 2.0 mg/kg/day group) experiencing a significant increase in the serum creatinine level while developing septic shock due to *Enterococcus faecalis*. No patient required hemodialysis. A dose-dependent increase in the daily required potassium supplementation was found, and, similarly, the daily amount of intravenous fluid administration increased with increasing daily AmB-d doses (table 3). In addition, supplementation with sodium bicarbonate was necessary for 21 patients (64%) because of the development of tubular acidosis (7 [33%] of these 21 patients were in the 1.5 mg/kg/day group, 6 [29%] were in the 1.75 mg/kg/day group, and 8 [38%] were in the 2.0 mg/kg/day group [$P < .0001$]). Hypomagnesemia requiring magnesium substitution occurred in 24 patients (73%), 10 (42%) of whom were in the 1.5 mg/kg/day group, 6 (25%) of whom were in the 1.75 mg/kg/day group, and 8 (33%) of whom were in the 2.0 mg/kg/day group ($P = .42$).

Changes in liver enzyme levels are presented in table 4. Generally, these changes were mild and considered to be clinically insignificant. There was, however, a significant increase in the serum alkaline phosphatase level in the overall population (table 4).

Only 1 patient (who was in the 1.75 mg/kg/day group) had grade 3 hepatotoxicity. This patient, who had acute myeloid leukemia, had normal liver function before antifungal treatment was started. While he was receiving the drug at a dose of 1.2 mg/kg, asymptomatic elevation of the liver enzyme level was noted. However, dose escalation was continued, because the patient's liver function stabilized and remained at in-

Table 4. Summary of data on hepatotoxicity among recipients of amphotericin B deoxycholate (AmB-d).

Laboratory value[a]	All patients (n = 33)	AmB-d target dosage group		
		1.5 mg/kg/day (n = 14)	1.75 mg/kg/day (n = 9)	2 mg/kg/day (n = 10)
AST, U/L				
At baseline	20 (6–105)	20.5 (6–105)	26 (7–92)	18 (7–69)
At end of dose escalation	19 (7–368)	19 (7–46)	16 (9–368)	25 (9–63)
At end of AmB-d therapy	24 (7–298)	23.6 (7–42)	13 (8–298)	32 (14–118)
ALT, U/L				
At baseline	31 (8–158)	26.5 (8–158)	22 (9–118)	44 (10–83)
At end of dose escalation	22 (6–220)	28 (6–167)	17 (13–220)	29 (13–83)
At end of AmB-d therapy	38 (8–284)	40 (11–138)	18 (8–284)	62 (19–197)
AP, U/L				
At baseline	74 (16–322)	92 (33–211)	81 (29–299)	69.5 (16–322)
At end of dose escalation	135 (36–731)[b]	86 (42–385)	115 (36–731)	178 (23–339)
At end of AmB-d therapy	140 (36–1457)[c,d]	119 (43–371)	121 (36–300)	205 (60–1457)[b]
Total bilirubin, μM				
At baseline	15 (3–40)	14 (9–22)	15 (6–28)	16.5 (3–40)
At end of dose escalation	15 (3–23)	14 (6–17)	20 (9–25)	12 (3–23)
At end of AmB-d therapy	13 (7–49)	10 (7–18)	15 (10–34)	27 (9–49)

NOTE. Data are median (range). ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase.

[a] Normal levels and ranges for laboratory values are as follows: AST, <35 IU/L; ALT, <35 IU/L; AP, 30–115 U/L; and total bilirubin, <25 mM.

[b] $P < .05$.

[c] $P < .001$, compared with the corresponding baseline value.

[d] $P < .05$, compared with the value at end of dose escalation.

creased levels during the whole course of treatment. The alanine aminotransferase levels were 111–368 U/L (baseline, 53 UL), the aspartate aminotransferase levels were 83–284 U/L (baseline, 27 U/L), and the alkaline phosphatase levels were 300–731 U/L (baseline, 299 U/L). All levels returned to normal after drug discontinuation. Reexposure to a low dose of AmB-d prompted a rapid increase in the levels with a subsequent return to normal levels when the medication was definitely discontinued.

Outcome. Twenty-four patients (73%) were alive at the end of treatment. Four patients in the 1.5 mg/kg/day group, 2 patients in the 1.75 mg/kg/day group, and 3 patients in the 2.0 mg/kg/day group died during the treatment period ($P = .50$). Death was considered to be unrelated to fungal infection in all of these patients. However, invasive fungi were found at autopsy in 3 patients (2 from the 1.5 mg/kg/day group and 1 from the 1.75 mg/kg/day group). Two months after the termination of antifungal therapy, 22 patients (67%) were still alive. Two patients died of progression of disease unrelated to fungal infection (acute leukemia in both).

DISCUSSION

Animal studies and limited results from clinical trials have demonstrated the dose-dependent efficacy of AmB [8–11], providing the rationale for the administration of the maximum tolerated doses of the drug to severely ill patients [18]. Two different strategies are currently used to reduce dose-limiting, infusion-related side effects and organ dysfunction. In the first, lipid formulations of AmB are used, and results of dose-escalation trials involving liposomal AmB have recently been published [19, 20]. However, these formulations' enormous costs may limit widespread use, and it remains unclear whether they are more effective than conventional AmB-d. Liposomes profoundly alter the pharmacokinetics of AmB [21], and in vitro studies and experimental animal models indicate that lipid formulations of AmB have significantly lower activity than does AmB-d [22, 23]. Accordingly, a mean daily dose of 3 mg/kg of liposomal AmB was found to have a therapeutic efficacy comparable to that of a mean daily dose of 0.6 mg/kg of conventional AmB-d in a large study of 687 patients with persistent fever and neutropenia [10].

Table 5. Frequency of infusion-related side effects and nephrotoxicity during receipt of treatment with liposomal amphotericin B (AmB), conventionally administered AmB deoxycholate (AmB-d), and continuously infused AmB-d (CI AmB-d).

Study, treatment arm	No. of subjects	Chills or rigors on day 1 of treatment	Nausea	Creatinine concentration, multiple of baseline value		
				1.5	2.0	3.0
Walsh et al. [10]						
Liposomal AmB	343	63 (18.4)	42 (12.2)	99 (29)	65 (19)	27 (8)
AmB-d	344	187 (54.4)	35 (10.2)	168 (49)	117 (34)	58 (17)
Eriksson et al. [7]						
CI AmB-d	40	5 (13)	NA	13 (33)	6 (15)	0
Rapid infusion of AmB-d	40	21 (53)	NA	23 (58)	11 (28)	4 (10)
Present report: dose escalation of CI AmB-d[a]						
1.5 mg/kg/day	14	6 (43)[b]	3 (21)	4 (29)	1 (7)	0
1.75 mg/kg/day	9	6 (67)[b]	1 (11)	1 (11)	2 (22)	0
2.0 mg/kg/day	10	1 (10)[b]	3 (30)	1 (10)	1 (10)	1 (10)
Walsh et al. [19]: dose escalation of liposomal AmB[a]						
7.5 mg/kg/day	8	3 (38)	0	3 (38)	2 (25)	NA
10 mg/kg/day	10	0	1 (10)	5 (50)	3 (30)	NA
12.5 mg/kg/day	7	1 (14)	0	4 (57)	3 (43)	NA
15 mg/kg/day	19	1 (5)	0	10 (53)	6 (32)	NA

NOTE. Data are no. (%) of patients. NA, data not available.

[a] Treatment arms are defined according to target dosages.

[b] Data comprise events experienced on day 1 and 2.

In the second approach, AmB-d is administered by continuous infusion. Compared with traditional administration over 2–6 h, continuous drug infusion prevents a majority of infusion-related side effects [6, 7]. Here, we have shown that continuous infusion of AmB-d in doses that were gradually escalated up to 2.0 mg/kg/day is feasible, safe, and well tolerated in most patients. Although a significant number of patients had either an infusion-related side effect and/or laboratory evidence of organ dysfunction, in most cases, these adverse events were generally mild and could be controlled by supportive measures.

Table 5 shows the frequency of infusion-related side effects and the degree of nephrotoxicity observed in the present study, compared with those observed in studies of treatment with standard dose and dose-escalated liposomal AmB, conventionally administered AmB-d, and continuously infused AmB-d at a dose of 1 mg/kg [7, 10, 19]. Overall, the degree of nephrotoxicity and the incidence of infusion-related side effects (chills, rigor, or nausea) appear comparable to those obtained with liposomal AmB [10, 19, 20] and lower doses of continuously infused AmB-d [6, 7]. Infusion-related side effects occurred early (mostly within the first few hours of therapy) and did not recur later in the course of dose escalation. Infusion-related toxicities may be mediated by cytokines [24], and continuous infusion may be better tolerated because of a delayed induction/release of such mediators, as has been suggested elsewhere [6, 7].

AmB affects both glomerular and tubular structures. Acute AmB-induced vasoconstriction of the intrarenal arterioles decreases renal blood flow and the glomerular filtration rate, and this effect can be promoted by concurrent hyponatremia. Accordingly, saline infusion improves renal function and increases AmB tolerance [25]. Therefore, our patients received an additional 1000 mL of saline per day whenever this was tolerated, and in only 1 patient were there respiratory problems caused by significant hyperhydration. Although most of the drug's adverse effects involved renal function, a >2-fold decrease in creatinine clearance was observed in only 5 patients (15%). This is remarkable, because many patients concomitantly received nephrotoxic agents, and 2 of the patients developed a sepsis syndrome with multi-organ failure, which, itself, may have contributed to renal dysfunction. In a recent study, cyclosporine use significantly decreased the level of serum creatinine clearance in patients treated with a continuous infusion of AmB-d [26]. However, impairment of renal function was reversible and clinically tolerated in all cases. In the present study, both patients who received concomitant cyclosporine

therapy completed AmB-d dose escalation without delay. Nevertheless, close monitoring of patients who are concomitantly receiving nephrotoxic medications is warranted.

A second nephrotoxic mechanism is a directly toxic effect on renal tubular cells, resulting in enhanced membrane permeability with subsequent intracellular and tubular loss of electrolytes, mainly potassium and magnesium. Previous studies have shown that the risk of renal insufficiency associated with AmB-d increases with preexisting renal dysfunction, hypovolemia, high cumulative doses of AmB, duration of therapy, and concomitant use of diuretics or other nephrotoxic drugs [7, 27]. However, there was little additional glomerular nephrotoxicity in patients who received daily doses of AmB-d up to 1.5–2.0 mg/kg, compared with those who received daily doses of 1.0 mg/kg (table 5). Although there was no clear evidence of a dose-dependent glomerular dysfunction in this study, there was a dose-dependent effect on tubular dysfunction, which was evidenced by a step-wise increase in the daily requirement for supplemented potassium and in the percentage of patients who required sodium bicarbonate for compensation of tubular acidosis. These findings suggest that the renal tubular epithelium may be more sensitive to high dosages of AmB-d than are cells that regulate renal blood flow and glomerular filtration. Thus, high-dose AmB-d therapy warrants a meticulous approach that involves monitoring of pH and serum electrolyte levels, especially levels of potassium, bicarbonate, and magnesium; such therapy may require extensive supplementation and daily adjustments to treatment.

In contrast to liposomal AmB, AmB-d therapy is infrequently associated with the side effect hepatotoxicity [10, 28, 29]. Increases in bilirubin and liver transaminase levels were mild, asymptomatic, and clinically insignificant in all but 1 patient, whereas an elevation of serum alkaline phosphatase levels was noted in the overall study group. However, some of these changes may have been related to effects of chemotherapy, preparative regimens for bone marrow transplantation, and intercurrent septic events, rather than receipt of AmB-d.

Several novel antifungal agents have emerged in recent years that offer useful alternatives to AmB [18]. For example, itraconazole has a efficacy similar to that of AmB-d at a mean daily dose of 0.71 mg/kg in patients with persistent fever and neutropenia [30], and voriconazole was even more effective than AmB-d in patients with invasive aspergillosis; however, in the latter study, the mean daily dose of AmB-d was 0.97 mg/kg, and there was a wide range of doses administered (0.27–1.5 mg/kg/day) [31]. Assuming a dose-dependent efficacy of AmB, it is conceivable that higher doses of AmB-d could result in better clinical outcome, but this needs to be tested further. It is important to note that the present study was not sufficiently powered to assess clinical efficacy, and no conclusions regarding therapeutic results should therefore be drawn from this trial. However, our experience with gradually increased daily doses of AmB-d given by continuous infusion, as reported herein, may offer a base for future, carefully designed comparative trials aimed at defining the optimal daily dose of AmB-d and elucidating whether dose-escalated AmB-d has an improved efficacy. Given the low additional toxicity of stepwise-escalated AmB-d therapy administered by continuous infusion, it seems justified to use this regimen for comparison with lipid formulations of AmB or one of the newer antifungal agents in larger comparative trials.

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