

## Safety, Tolerance, and Pharmacokinetics of Amphotericin B Lipid Complex in Children with Hepatosplenic Candidiasis

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Received 13 December 1996/Returned for modification 18 June 1997/Accepted 30 June 1997

The safety, tolerance, and pharmacokinetics of amphotericin B lipid complex (ABLC) were studied in a cohort of pediatric cancer patients. Six children with hepatosplenic candidiasis (HSC) received 2.5 mg of ABLC/kg of body weight/day for 6 weeks for a total dosage of 105 mg/kg. Mean serum creatinine ( $0.85 \pm 0.12$  mg/dl at baseline) was stable at the end of therapy at  $0.85 \pm 0.18$  mg/dl and at 1-month follow-up at  $0.72 \pm 0.12$  mg/dl. There was no increase in hepatic transaminases. Mean plasma concentrations over the dosing interval ( $C_{ave}$ ) and area under the curve from 0 to 24 h ( $AUC_{0-24h}$ ) increased between the first and seventh doses but were similar between doses 7 and 42, suggesting that steady state was achieved by day 7 of therapy. Following the final (42nd) dose of ABLC, mean  $AUC_{0-24h}$  was  $11.9 \pm 2.6$   $\mu\text{g} \cdot \text{h}/\text{ml}$ ,  $C_{ave}$  was  $0.50 \pm 0.11$   $\mu\text{g}/\text{ml}$ , maximum concentration of the drug in whole blood was  $1.69 \pm 0.75$   $\mu\text{g}/\text{ml}$ , and clearance was  $3.64 \pm 0.78$  ml/min/kg. Response of hepatic and splenic lesions was monitored by serial computerized tomographic and magnetic resonance imaging scans. The five evaluable patients responded to ABLC with complete or partial resolution of physical findings and of lesions of HSC. During the course of ABLC infusions and follow-up, there was no progression of HSC, breakthrough fungemia, or posttherapy recurrence. Hepatic lesions continued to resolve after the completion of administration of ABLC. Thus, ABLC administered in multiple doses to children was safe, was characterized by a steady state attainable within 1 week of therapy, and was effective in treatment of HSC.

Amphotericin B lipid complex (ABELCET) (ABLC) was recently approved by the Food and Drug Administration for treatment of invasive fungal infections in children and adults who are refractory to or intolerant of conventional antifungal therapy (8). Little is known, however, about ABLC in children, and to our knowledge there are no reports of the safety, tolerance, and pharmacokinetics of ABLC in a pediatric population.

Invasive candidiasis is an important cause of morbidity and mortality in children with neoplastic diseases (5, 25, 28). Among the different patterns of invasive candidiasis in children receiving cytotoxic chemotherapy, hepatosplenic candidiasis (HSC), or chronic disseminated candidiasis, is an infrequent but serious infection (17, 21–23, 27). As ABLC is highly concentrated in the reticuloendothelial system of the liver and spleen, this compound is a pharmacologically rational choice for treatment of HSC (9). We therefore investigated the safety, tolerance, and pharmacokinetics of ABLC in a phase I to II study in children with HSC.

### MATERIALS AND METHODS

**Patients.** The study was performed at the Pediatric Branch of the National Cancer Institute at the Warren Grant Magnuson Clinical Center under a pro-

ocol approved by the institute's internal review board. Patients with neoplastic disease were eligible for enrollment in the study if they were 2 to 18 years of age and had a history of histopathologically or culture proven *Candida* spp. in the liver or spleen. Hepatosplenic candidiasis was defined as a biopsy-proven chronic *Candida* infection of the liver in patients with a history of chemotherapy-induced neutropenia. If the biopsy was negative, clinical and radiographic findings consistent with HSC must have been present in association with a positive blood culture for *Candida* spp. recovered during a preceding episode of neutropenia. All patients were required to enter the study with an absolute neutrophil count of  $>1,000/\text{ml}$ .

**Drug administration and duration of therapy.** Patients received an initial test dose of 1 mg of ABLC over 15 to 20 min. A daily dose of 2.5 mg of ABLC/kg of body weight for 42 doses was administered over 6 weeks with a total cumulative dose of 105 mg/kg. ABLC was infused initially over 1 h for the first infusion and then over one-half hour, if tolerated, for subsequent infusions.

The dosage of 5 mg/kg/day used in the open-label study of ABLC in patients refractory to or intolerant of conventional amphotericin B was selected to treat invasive aspergillosis (7, 26). Studies of experimental disseminated candidiasis in our laboratory and in other laboratories revealed that disseminated candidiasis could be treated with lower dosages than those required for invasive aspergillosis. Thus, in order to reduce unwarranted drug exposure and prevent possible toxicity, the dosage of 2.5 mg/kg/day was utilized.

**Monitoring of safety and tolerance.** All patients who received at least one dose of the study drug were included in the analysis for safety and tolerance. During therapy, clinical and laboratory parameters were reviewed for safety and the patient was monitored for tolerance of the study drug. Further analyses of safety and tolerance were performed at 1, 2, 3, 6, 9, and 12 months after the completion of therapy.

The infusion-related tolerance of the first 2.5-mg/kg dose of ABLC was assessed without initial empirical premedications. If the patient experienced infusion-related side effects during the first infusion, then appropriate medications were administered to ameliorate the symptoms and premedications were administered on subsequent infusions. Fever, chills, rigor, headache, nausea, and vomiting were evaluated according to the common toxicity criteria of the World Health Organization by using a symptom scale of 1 to 4, with 4 being the worst grade of toxicity (16). Drugs used as premedications and for treatment of infusion-related toxicity were prescribed per protocol and included acetaminophen, diphenhydramine, meperidine, lorazepam, or hydrocortisone, as indicated.

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During antifungal therapy, patients were assessed daily for safety and tolerance of ABLC as well as for signs and symptoms of HSC. The pretherapy clinical evaluation for staging of disseminated candidiasis included physical examination, fundoscopy, chest radiograph, and computerized tomographic (CT) and magnetic resonance imaging (MRI) scans of the abdomen. Baseline laboratory studies included a complete blood count, prothrombin time, partial thromboplastin time, a serum chemistry profile (including electrolytes, blood urea nitrogen, creatinine, magnesium, serum transaminases, alkaline phosphatase, and amylase), a viral hepatitis screen, cultures for fungi and bacteria (blood, urine, and tissue biopsy specimens), and urinalysis.

Any normally sterile body site that was culture positive or histologically positive for *Candida* spp. at baseline was monitored throughout the study. Any laboratory parameter that was abnormal at any evaluation point and whose abnormality was attributed to treatment with ABLC was monitored until resolution of the abnormality.

For ABLC, infusion-related events were defined as fever, chills, headache, nausea, or vomiting occurring during the infusion and for 1 h following the end of infusion. All such events were reported and graded for severity. Any new or worsening signs or symptoms, other than the infusion-related events described above, were reported as adverse events. Serious adverse events included, but were not restricted to, events which were fatal, life threatening, or permanently disabling or which required or prolonged inpatient hospitalization; congenital anomalies; overdoses; and new diagnoses of malignancy.

**Pharmacokinetic sampling.** Patients who had not received amphotericin B during the previous 2 months, or who had received <3 mg of amphotericin B/kg within the past 2 months but had received none for at least 7 days prior to enrollment in this study, were eligible to be studied for ABLC pharmacokinetics. Samples were obtained at the following time points: days 1, 7, and 42 (preinfusion and postinfusion [1, 2, 3, 7, 19, and 23 h]); days 8 through 13 (daily, preinfusion); days 14, 21, 28, and 35 (preinfusion and postinfusion); and 1, 2, 3, 6, 9, and 12 months posttherapy.

**Pharmacokinetic analysis.** Pharmacokinetic parameters for ABLC were determined by using model-independent analysis. The area under the concentration-time curve from 0 to 24 h ( $AUC_{0-24h}$ ) was calculated by trapezoidal estimation. Maximum concentration in whole blood ( $C_{max}$ ) was determined directly from patient concentration-time profiles. Total body clearance (CL) and average concentration over the dosing interval ( $C_{ave}$ ) were determined by using standard noncompartmental equations (6). CL was calculated as  $dose/AUC_{0-24h}$ , and  $C_{ave}$  was calculated as  $AUC_{0-24h}/dosing\ interval$ .

**Analytical methods.** Whole blood concentrations of ABLC were determined by reversed-phase high-performance liquid chromatography (HPLC). Two-hundred microliters of whole blood sample or standard (The Liposome Co., Princeton, N.J.) was transferred to a microcentrifuge tube, followed by the addition of 600  $\mu$ l of extraction solvent. The extraction solvent consisted of 30% chloroform (Fluka Chemical Corp., Ronkonkoma, N.Y.), 30% acetonitrile (J. T. Baker, Phillipsburg, N.J.), and 40% dimethyl sulfoxide (Sigma Chemical Co., St. Louis, Mo.). The samples were vortexed and centrifuged (International Equipment Co., Needham Heights, Mass.) at room temperature at  $1,000 \times g$  for 10 min. After centrifugation, three layers were formed: the chloroform layer, the erythrocyte layer, and the aqueous layer. The upper aqueous layer was transferred to HPLC autosampler vials for injection.

The chromatographic apparatus consisted of a series II 1090 liquid chromatograph (Hewlett-Packard Corp., Palo Alto, Calif.) with an autosampler compartment, a solvent delivery system, and a diode array UV absorbance detector. The absorbance wavelength was 405 nm with a reference wavelength of 500 nm. The mobile phase consisted of 5.6% 0.1 M  $Na_2EDTA$  (Sigma Chemical Co.), 58.4% deionized water (Milli-QUV Plus; Millipore Corp., Bedford, Mass.), and 36.0% HPLC-grade acetonitrile (J. T. Baker) and was run at a flow rate of 1 ml/min. A Waters Nova-Pak  $C_{18}$  guard column was placed in line prior to the analytical column. The sample was injected onto a reversed-phase column (Waters Bond-Pak  $C_{18}$ , 3.9 by 150 mm; Millipore Corp., Milford, Mass.), which was maintained at ambient room temperature. ABLC had a retention time of approximately 6 min within a total run time of 12 min. The chromatographic peak area was used for quantitation by linear regression analysis. The lower limit of detection for the assay was 250 ng/ml. The interassay coefficient of variation for whole blood concentrations was less than 11.4% within the range of 250 to 5,000 ng/ml. Five (6%) of 91 samples were below the limit of quantitation. These missing points did not appear to result in any changes in the pharmacokinetic parameters.

**Monitoring of antifungal response.** All patients were monitored by serial physical examinations, blood and urine cultures for fungi, CT scans, MRI scans, chest radiographs, and fundoscopies. CT scans, MRI scans, and chest radiographs were performed at weeks 3 and 6 while the patients were receiving ABLC. Follow-up CT scans, MRI scans, and chest radiographs were obtained at 1, 2, 3, 6, 9, and 12 months after the completion of therapy.

A complete clinical response was defined as the resolution of all symptoms and physical findings referable to HSC. A partial clinical response was defined as improvement but not resolution of symptoms and physical findings referable to HSC. Clinical failure was defined as no improvement of symptoms and physical findings referable to HSC. A complete radiologic response was defined as resolution of lesions of HSC, a partial radiologic response was defined as improvement but not resolution of lesions, and radiologic failure was defined as no

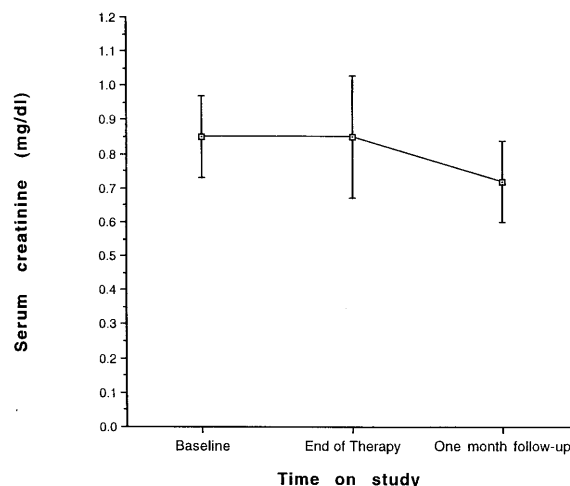


FIG. 1. Mean serum creatinine at baseline, at the end of 6 weeks of therapy, and at 1-month follow-up in six children with HSC treated with ABLC. Error bars represent standard errors.

improvement. Patients were evaluated for an overall response based upon the combination of radiographic and clinical parameters described above.

The chronological trend of resolution of hepatic and splenic lesions was quantified by using a modified scoring system previously applied to the therapeutic monitoring of pulmonary lesions in experimental invasive aspergillosis by ultrafast CT scanning (24). The responses in liver and spleen were separately evaluated by both CT and MRI scans. The scoring system is based upon a semiquantitative estimate of lesions being better, worse, or the same in comparison to the previous scan. The lesion score in a given tissue is initially zero. Improvement, stabilization, or worsening in the subsequent scan are then scored as -1, 0, or +1, respectively, and added at that time to the previous score. The mean lesion score for a given time point represents the mean of all scores for patients at a given time point in the study. Progression of infection is represented by a positive slope, improvement is represented by a negative slope, and stabilization is represented by a zero slope. Separate evaluations were performed for CT scans with contrast of the liver and of the spleen and for MRI scans with gadolinium of the liver and the spleen. Patient 4 had a history of CT contrast-induced renal impairment and consequently was evaluated only by MRI with gadolinium.

## RESULTS

**Patients.** There were four females and two males with a mean age of 10 years (range, 4 to 17 years). Five patients had acute leukemia and one had neuroblastoma. All patients were evaluable for safety and tolerance, and five patients were evaluable for efficacy. One patient was unable to continue on the study due to relapse of acute leukemia; this patient was evaluable for safety, tolerance, and pharmacokinetics. Three children were evaluable for pharmacokinetics. The other three children were not eligible for pharmacokinetic sampling due to their having received conventional amphotericin B desoxycholate within 2 weeks before enrollment in the study.

**Safety and tolerance.** Administration of ABLC was not complicated by dose-limiting nephrotoxicity. As depicted in Fig. 1, there was no significant change in mean serum creatinine in the study population throughout the 6-week course of infusion of the 105 mg/kg dosage. One-month follow-up evaluation revealed a downward trend of the mean serum creatinine, which was slightly lower than the mean serum creatinine values at baseline and at the end of therapy.

Hypokalemia (serum potassium < 3.5 meq/ml) was present in none of the six patients at baseline, in one of six during administration of ABLC, and in none at the end of therapy or at 1-month follow-up. Hypomagnesemia (serum magnesium < 0.75 mM) was present in two of six patients at baseline, two of six during administration of ABLC, and one of five at the end

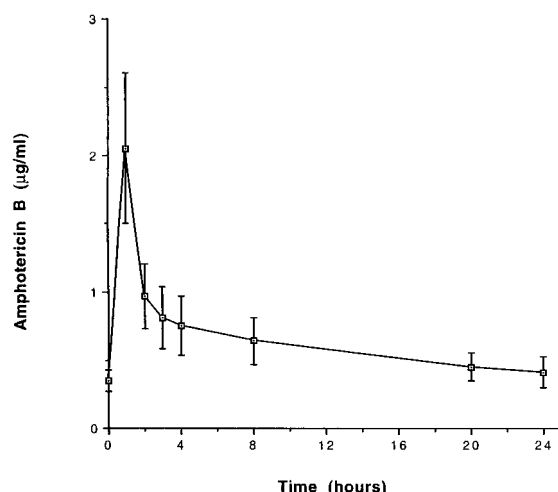


FIG. 2. Multiexponential concentration-time curve of ABLC in three children with HSC on day 7 of treatment. Error bars represent standard errors.

of therapy and at 1-month follow-up. There were no abnormalities in serum transaminases, bilirubin, alkaline phosphatase, or hematological parameters attributable to ABLC.

Infusion-related toxicity was assessed on the first dose of ABLC (2.5 mg/kg infused over 2 h) before the administration of premedications. There were no reactions to the test dose. Five (83%) of six patients manifested infusion-related toxicity to the first 2.5-mg/kg dose. Fever developed in four (67%) children, chills or rigors in five (83%), headache in one (17%), and nausea in four (67%). Symptoms were graded according to the World Health Organization common toxicity criteria, using a symptom scale of 1 to 4, with 4 being the worst grade of toxicity. The range of toxicity for fever was 1 to 2, the range for chills or rigor was 2 to 3, the range for headache was 3, and the range for nausea was 1 to 2. The infusion-related adverse reactions were well controlled thereafter by conventional premedications, including acetaminophen, diphenhydramine, meperidine, and lorazepam.

**Pharmacokinetics.** Following intravenous administration, ABLC concentrations exhibited a multiexponential decline (Fig. 2). Maximum concentrations were attained at the end of the infusion; however, a second peak was observed in one patient, suggesting a possible redistribution of the drug back into the central compartment via release from a peripheral site(s). Pharmacokinetic parameters are detailed in Table 1.  $C_{ave}$  and  $AUC_{0-24h}$  increased between the first and seventh doses but were similar between doses 7 and 42. These findings suggest that steady state is achieved by day 7 of therapy.

**Response to antifungal therapy.** Five patients were evaluable for efficacy. During the course of administration of ABLC

infusion and the follow-up period, there was no progression of HSC, breakthrough fungemia, or posttherapy recurrence. Three patients had complete overall responses, and two had partial responses and died before completion of follow-up; one patient withdrew from the study due to tumor relapse and was not evaluable for therapeutic response. A complete clinical response was obtained in all patients. Five patients had resolution of symptoms and physical findings, consisting of fever in five and abdominal pain with tenderness in two. The incomplete radiologic responses occurred in two patients who died due to their underlying neoplastic diseases before follow-up was completed. At the time of their deaths, their HSC was clinically resolved and the lesions were radiologically resolving.

The therapeutic response of lesions in the liver and spleen monitored by CT and MRI scans are depicted in Fig. 3. Both CT and MRI scans demonstrated comparable sensitivity in detection and therapeutic monitoring of lesions. Similar rates of resolution in response to ABLC were found in the liver and the spleen. Lesions were more numerous and more intensively concentrated in the spleen than in the liver. Consequently, lesions continued to decline in number over a longer period of time in the spleen in comparison to those in the liver, which resolved earlier, as reflected by a leveling of the radiologic response curve of the liver.

## DISCUSSION

This study is the first, to our knowledge, which investigates the safety, tolerance, and pharmacokinetics of ABLC in children. ABLC administered for a total dose of 105 mg/kg was free of dose-limiting nephrotoxicity. Infusion-related side effects were common but were well controlled with conventional premedications. Pharmacokinetic analysis appeared to indicate that steady state was attained within 7 days of daily administration of ABLC. A complete clinical response was obtained in all patients, and a complete radiologic response was observed in three patients. There was no progression of HSC, breakthrough fungemia, or posttherapy recurrence.

ABLC is a lipid complex (not a liposome) which consists of amphotericin B in a 30% molar ratio with dimyristoylphosphatidylglycerol (DMPG) and dimyristoylphosphatidylcholine (DMPC) in a 3:7 ratio (9). The lipid formulation of amphotericin B known as ABLC was developed by Janoff et al. (9), who found that a ribbon-like component of a 5% mixture of amphotericin B in a formulation of multilamellar vesicles and ribbon-like complexes was highly active and less nephrotoxic than the multilamellar vesicles alone. Paradoxically, as amphotericin B was added into the ribbon-like component of the DMPG and DMPC lipids, nephrotoxicity diminished. These chemical properties of ABLC distinguish it from other lipid formulations of amphotericin B (8).

This study found no dose-limiting nephrotoxicity of ABLC. Mean serum creatinine in the children in our study did not

TABLE 1. Pharmacokinetic parameters of ABLC in children<sup>a</sup>

Day of therapy	$AUC_{0-24h}$ ( $\mu\text{g} \cdot \text{h/ml}$ )	$C_{ave}$ ( $\mu\text{g/ml}$ )	$C_{max}$ ( $\mu\text{g/ml}$ )	CL (ml/min/kg)
1	$8.9 \pm 3.9$ (2.4–16.2)	$0.37 \pm 0.16$ (0.10–0.67)	$1.09 \pm 0.25$ (0.83–1.59)	ND <sup>b</sup>
7	$15.3 \pm 3.8$ (9.5–22.5)	$0.64 \pm 0.16$ (0.40–0.94)	$2.05 \pm 0.55$ (0.95–2.62)	ND
42	$11.9 \pm 2.6$ (9.3–14.6)	$0.50 \pm 0.11$ (0.39–0.61)	$1.69 \pm 0.75$ (0.93–2.44)	$3.64 \pm 0.78$ (2.86–4.43)

<sup>a</sup> The data from the three children evaluable for pharmacokinetics are presented as the mean  $\pm$  standard error of the mean (range). The other three children in this study were not eligible for pharmacokinetic sampling due to their having received conventional amphotericin B desoxycholate within 2 weeks before enrollment in the study.

<sup>b</sup> CL was derived from washout of ABLC after the last day of infusion and thus was not determined (ND) on days 1 and 7.

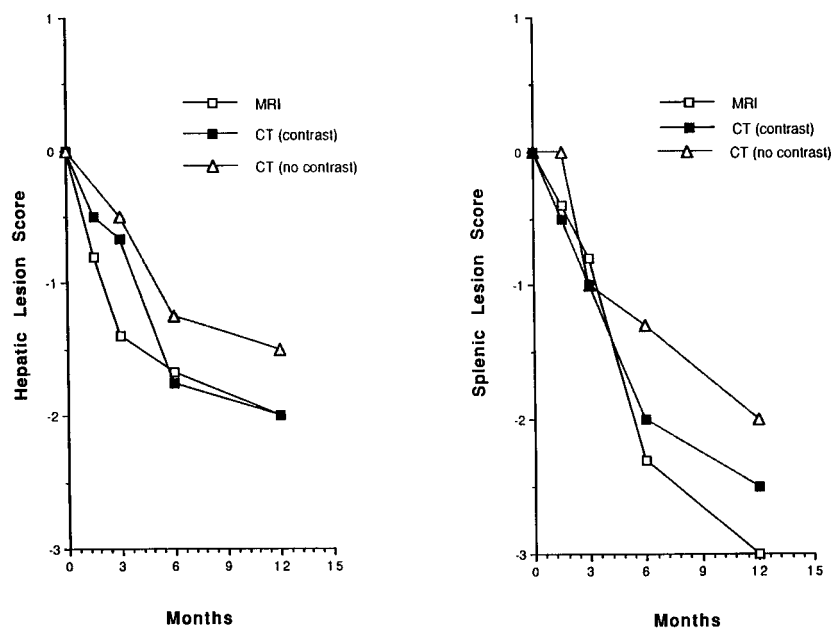


FIG. 3. Radiologic response of lesions in liver (left panel) and spleen (right panel) monitored by CT and MRI scans in five children treated with ABLC for HSC. The therapeutic response score is based upon a semiquantitative assessment of lesions being better, worse, or the same in comparison to the previous scan. The lesion score is initially zero. Improvement, stabilization, or worsening in the subsequent scan are then scored as  $-1$ ,  $0$ , or  $+1$ , respectively, and added at that time to the previous score. Progression of infection is represented by a positive slope, improvement is represented by a negative slope, and stabilization is represented by a zero slope.

change during the course of ABLC treatment, despite their receiving 105 mg/kg over 6 weeks (Fig. 1). Consistent with this observation are experimental and early clinical data demonstrating that larger doses of amphotericin B in the form of ABLC can be safely administered with minimal nephrotoxicity in the treatment of invasive fungal infections (2, 7–9, 26). An open-label compassionate trial of ABLC in patients intolerant of or refractory to conventional antifungal therapy found that the serum creatinine of these patients significantly declined during the course of treatment (26). A randomized clinical trial of ABLC versus amphotericin B for treatment of invasive candidiasis in adults demonstrated significantly reduced nephrotoxicity but equivalent antifungal activity (2). Among the possible mechanisms for reduced nephrotoxicity for ABLC are (i) selective affinity of ABLC for fungal cell membranes versus mammalian cell membranes, (ii) initial increased uptake of the ABLC by the liver and the spleen with concomitantly decreased concentrations in the kidneys, and (iii) organism-mediated phospholipase-induced release of amphotericin B from the lipid complex (8, 9, 18).

Amphotericin B-induced nephrotoxicity consists of glomerular and renal tubular injury, which is reflected by azotemia and hypokalemia, respectively (12). Whether the reduction of azotemia is paralleled by protection from renal tubular toxicity has not been well studied. Two patients entering into this study initially required large dosages of potassium supplements due to previous amphotericin B therapy. Their potassium requirements diminished during ABLC therapy. On the other hand, the remaining four patients required potassium supplementation during their course of therapy. None of these patients sustained dose-limiting hypokalemia, which may occur with conventional amphotericin B despite potassium supplementation. Thus, while ABLC may cause tubular dysfunction resulting in the need for supplemental potassium, it may be less severe than that of conventional amphotericin B.

Infusion-related toxicity appeared to be similar to that observed with conventional amphotericin B. These infusion-related side effects were medically well controlled with subsequent administration of conventional premedications, and ABLC was not withheld for these events. Patients who received amphotericin B prior to enrollment in this study reported that the infusion-related side effects of ABLC were similar to or less intense in quality than those of amphotericin B. Hence, there appears to be a dissociation between the paucity of nephrotoxicity and the occurrence of infusion-related toxicity for ABLC.

We did not observe several previously reported adverse events associated with lipid formulations of amphotericin B. Specifically, there was no transaminase elevation attributable to ABLC, as was previously reported in normal adult volunteers (10), nor was there any pulmonary toxicity, as was previously described for a multilamellar formulation of amphotericin B in an immunocompromised adult (14).

The pharmacokinetic profile of ABLC at a dosage of 2.5 mg/kg/day in the children enrolled in this study demonstrated a somewhat lower mean  $C_{max}$  and greater mean clearance than those reported in children receiving lower dosages of conventional amphotericin B (3, 12, 20). For example, the  $C_{max}$  of ABLC at a dosage of 2.5 mg/kg/day was  $2.05 \pm 0.55$   $\mu\text{g/ml}$  in comparison to the previously reported mean  $C_{max}$  of conventional amphotericin B at a dosage of 1 to 1.5 mg/kg/day, which was  $3.53 \pm 1.63$   $\mu\text{g/ml}$  (3). Conversely, the mean clearance for ABLC was greater, at  $3.64 \pm 0.78$   $\text{ml/min} \cdot \text{kg}$ , than that of conventional amphotericin B, at  $0.66 \pm 0.21$   $\text{ml/min} \cdot \text{kg}$ . The comparatively lower mean  $C_{max}$  for ABLC may be attributable to its extensive accumulation within the reticuloendothelial system, particularly the Kupffer cells and splenic macrophages.

This accumulation of ABLC within hepatic and splenic macrophages results in high tissue concentrations and provides a rationale for reticuloendothelial loading; i.e., administration of ABLC in large dosages which results in a sustained antifungal

effect after discontinuation of administration of the compound. This effect was demonstrated experimentally when rabbits with experimental HSC were treated with a relatively brief but intense course (5 mg/kg/day for 4 days) of ABLC (13). Serial monitoring of these rabbits after discontinuation of ABLC resulted in sustained clearance of cultures and lesions. As demonstrated in Fig. 3, hepatic and splenic lesions continued to resolve after completion of the course of ABLC. These findings are consistent with the preclinical studies which demonstrated sustained response after discontinuation of ABLC.

These patients would have been unlikely to have resolved their lesions spontaneously. The natural history of HSC in children is one of persistent fever and refractory lesions (1, 11, 15, 17, 21–23, 27). Infection may progress despite administration of conventional therapy, including conventional amphotericin B or fluconazole. Premature discontinuation of therapy may be associated with relapses. Moreover, five of these children were considered by their referring physicians to be refractory to conventional therapy. At the time of enrollment, all of the children had recovered from any previous chemotherapy-induced neutropenia, and thus, recovery from neutropenia had little role in their response to ABLC.

The treatment of HSC may require a protracted course of 6 to 12 months (17, 21–23). The total dosage of 105 mg/kg in this study was predicated upon an estimate of the total dosage of conventional amphotericin B required for treatment over a duration of 6 months with a dosage of 0.6 mg/kg/day. This dosage of amphotericin B in the form of ABLC was able to be administered over 6 weeks due to the reduced nephrotoxic potential of this formulation. Of course, this is just one dosage regimen; the optimal dosage regimen for treatment of HSC in children is not yet established. The study reported here does not attempt to define the optimal treatment of HSC. Indeed, there are several approaches to management of HSC in children, including conventional amphotericin B (4, 17, 21–23, 27), fluconazole (1, 11), and other lipid formulations of amphotericin B (15, 19, 21, 27). We conclude that ABLC (2.5 mg/kg/day for 6 weeks) in these children with HSC was safe, was characterized by a steady state attainable within 1 week of therapy, and was effective in the treatment of chronic disseminated candidiasis.

#### ACKNOWLEDGMENTS

We thank the following physicians for referral and follow-up of patients enrolled in this study: Richard Axtell, Butterworth Hospital; Pedro deAlarcon, University of Virginia Health and Science Center; Alan Gamis, Children's Mercy Hospital; Mary Anne Jackson, Children's Mercy Hospital; Doug Taylor, Dana-Farber Cancer Institute; Sarah Strandjord, University of Oregon Health Sciences Center; Peter Waldron, University of Virginia Children's Medical Center. We also thank the staff of the Pediatric Branch for their devoted and outstanding patient care.

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