Comparative Efficacy of Amphotericin B Lipid Complex and Liposomal Amphotericin B for the Treatment of Invasive Fungal Infections in HSCT Recipients and other Immunocompromised Patient Populations with Hematologic Malignancies: A Critical Review

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Abstract: Amphotericin B is an important agent for the treatment of invasive fungal infections in immunocompromised patients because of its broad spectrum. However, its toxicities and the availability of alternative agents limit its application. Lipid-based formulations of amphotericin B, such as amphotericin B lipid complex (ABLC) and liposomal amphotericin B (L-AMB), are less nephrotoxic and as effective as conventional amphotericin B. However, because of their similarities, choosing between the two formulations remains a challenge. The majority of prospective and retrospective comparative studies have shown equivalence in terms of efficacy although some subset analyses favor ABLC over L-AMB. While both drugs penetrate well in the reticuloendothelial system, ABLC gets concentrated in the lungs to a much greater extent. This may have clinical implications because the lungs are the commonest site of invasive fungal infections. L-AMB is associated with less infusion-related adverse effects and less nephrotoxicity than ABLC. ABLC has been shown to be more cost-effective than L-AMB, although this is affected by variable institutional contracts and pricing. The choice between the two drugs should be based upon due consideration of all these factors.

Keywords: Amphotericin B lipid complex, fungal infections, immunocompromised patients.

INTRODUCTION

Invasive fungal infections are a significant cause of morbidity and mortality in severely immunocompromised patients including those with hematologic malignancies and recipients of solid-organ or hematopoietic stem cell transplantation (HSCT). Although *Aspergillus* and *Candida* species remain the most common pathogens, the spectrum of invasive mycoses is changing with emergence of other opportunistic fungal pathogens such as *Fusarium*, *Zygomycetes* and *Scedosporium* [1-4]. While all of these are potentially life-threatening, invasive pulmonary infections with mold (aspergillosis and zygomycosis) tend to be particularly serious [5,6].

Amphotericin B has been the cornerstone of antifungal therapy since its discovery in 1956 due to its broad activity against a wide range of fungi including *Aspergillus* and *Candida* species. However, due to its lack of selective activity against fungal cell membranes, conventional amphotericin B (C-AMB) is toxic [7]; significantly limiting its therapeutic utility. The last 10-15 years have seen the development of several new broad-spectrum antifungal agents, including lipid formulations of amphotericin B, broad spectrum triazoles (voriconazole and posaconazole),

and the echinocandins (caspofungin, micafungin and anidulafungin). All of these agents are very effective against *Aspergillus* and *Candida* species, and have safety profiles that are superior to C-AMB. With the advent of these new agents, the use of amphotericin has declined considerably (Fig. **1**). However, unlike the lipid formulations of amphotericin B, the activity of the new agents against pathogenic zygomycetes is limited [8]. Indeed, there are questions about the activity of posaconazole – a drug thought to be active – against zygomycetes [9] and a case of breakthrough zygomycosis has been reported in a patient receiving posaconazole [10]. Breakthrough infections have been reported with all of the novel agents [11-13].

The development of resistance and the increasing number of invasive mold infections has renewed interest in lipid-based formulations of amphotericin B as a potential therapeutic option in appropriate clinical situations. The decreased nephrotoxicity of these agents allows higher individual and cumulative doses of amphotericin to be given [14]. Amphotericin B lipid complex (ABLC; Abelcet®, Cephalon) and liposomal amphotericin B (L-AMB; AmBisome®, Gilead/Fujisawa), the two commonly used lipid-based formulations, are at least as effective as C-AMB in the treatment of invasive fungal infections, are less nephrotoxic and are associated with a lower risk of infusion-related reactions [15]. The biochemical, pharmacokinetic and pharmacodynamic characteristics of these preparations differ [14,15], and there is considerable debate concerning their comparative clinical effectiveness, tolerability and cost.

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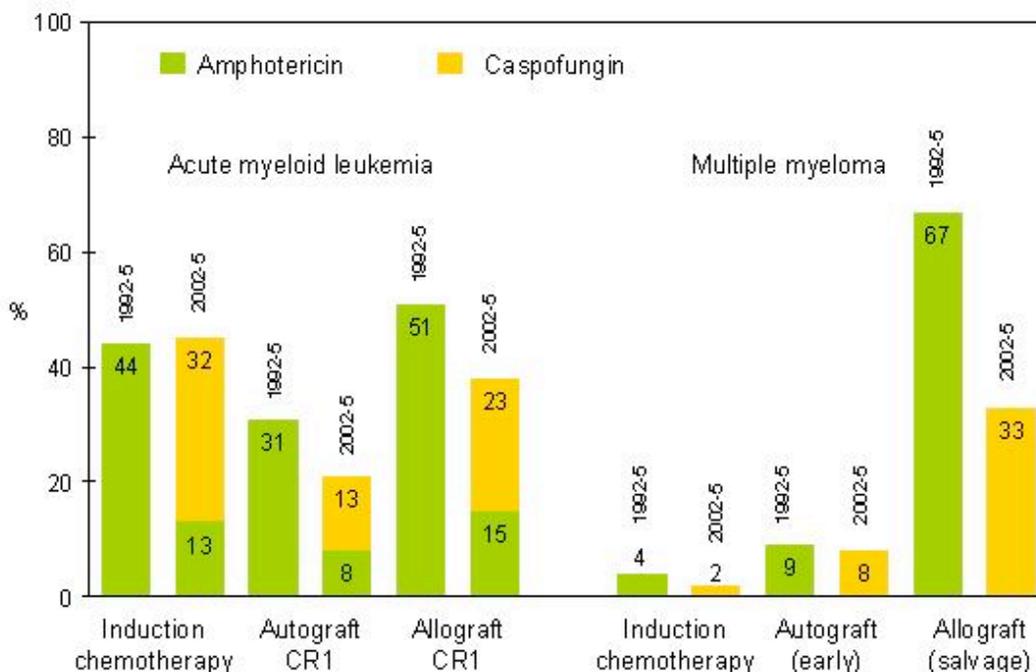
Fig. (1). Changing pattern of amphotericin use. The 1992-95 period represents use of amphotericin (mostly conventional amphotericin B) at the Royal Marsden Hospital, Surrey, UK. The 2002-05 period represents use of amphotericin (ABLC or L-AMB only) at the Northwestern Memorial Hospital, Chicago. The numbers represent the proportion of patients receiving amphotericin or an alternative antifungal agent in acute myeloid leukemia (AML) and multiple myeloma at various stages of therapy: during induction therapy or within the first 6 weeks of an autograft or an allograft. Amphotericin was the sole agent used in the earlier period, and caspofungin was the alternative in the later period. The use of amphotericin declined by 70% in AML and was eliminated in myeloma.

COMPARATIVE EFFICACY OF LIPID-BASED AM-PHOTERICIN B FORMULATIONS AND CONVEN-TIONAL AMPHOTERICIN B

A systematic review comparing lipid-based amphotericin B formulations to conventional amphotericin in the treatment of systemic fungal infections identified 7 randomized comparative studies [15]. The use of lipid-based formulations was found to reduce the all-cause mortality risk significantly compared to C-AMB – odds ratio (OR) 0.72; 95% confidence interval (CI) 0.54-0.97. Moreover, there was no significant difference in efficacy between the different lipid-based formulations and C-AMB (OR 1.21; 95% CI: 0.98-1.49). The review, however, did not include comparative studies of ABLC and L-AMB.

The aim of this review is to examine the key published evidence on the comparative efficacy of ABLC and L-AMB in the treatment of invasive fungal infections in HSCT recipients and other immunocompromised patient populations with hematologic malignancies. Amphotericin B colloid dispersion has been shown to have a higher rate of infusion-related adverse effects than C-AMB in two randomized, blinded studies [16, 17], and has not been dealt with in this review because of paucity of data and limited clinical use.

COMPARATIVE EFFICACY OF ABLC AND L-AMB

An initial search was undertaken in PubMed using the following search terms: "abelcet", "amphotericin B lipid complex", "amBisome", "liposomal amphotericin B" and "drug efficacy". The searches were restricted to clinical

trials, meta-analyses, case reports, and comparative studies published in English, between 1966 and 2011. Other electronic databases and relevant websites were also searched: ClinicalTrials.gov, National Institute for Health and Clinical Excellence (NICE) and Cochrane Collaborations. All clinical studies and reports that compared the efficacy of ABLC and L-AMB in the treatment of invasive fungal infections in HSCT recipients and other immunocompromised patient populations with hematologic malignancies were included. Citations were assessed for inclusion based on the study title and abstract. Papers investigating the use of aerosolised forms of ABLC or L-AMB were excluded, as were studies investigating prophylaxis for visceral leishmaniasis.

In total, 6 published studies were identified that compared the use of ABLC and L-AMB in the treatment of suspected or documented fungal infections or prolonged neutropenic fever (Table **1**) [18-23], one of which was a randomized, double-blind study [19]. The majority of the patients treated in these studies had malignant diseases, were neutropenic and/or immunosuppressed, and a significant proportion were HSCT recipients.

The first study to be published was a small retrospective analysis by Clark *et al.* [18] comparing ABLC at a median daily dose of 4.8 mg/kg with L-AMB at a median daily dose of 1.9 mg/kg for the treatment of suspected or documented fungal infections in 58 adult patients with hematologic malignancies. Lipid-based formulations were used if there was progression of underlying proven or suspected fungal infection, or if there was renal or hepatic impairment. Over

Table 1. Summary of Studies Comparing the Efficacy of ABLC and L-AMB

Author and Year	Study Design	Patients	Treatment Groups	Hematopoietic Stem Cell Transplantation		Response Rate		P
				ABLC	L-AMB	ABLC	L-AMB	
Clark 1998[a]	Retrospective	59; hematologic malignancies	ABLC 4.8 mg/kg/d L-AMB 1.9 mg/kg/d (median doses)	Allograft 39% Autograft 39%	Allograft 63% Autograft 28%	Overall 78% Proven 62% Suspected 83%	Overall 71% Proven 42% Suspected 79%	NS NS NS
Wingard 2000[b]	Randomized, double-blind	244; malignant diseases with neutropenic fever	ABLC 5 mg/kg/d L-AMB 3 mg/kg/d L-AMB 5 mg/kg/d	Allograft 15% Autograft 36%	Allograft 15%/16% (3/5 mg/kg) Autograft 31%/33% (3/5 mg/kg)	*Overall:* 33% *Persistent fever:* 27%	*Overall:* 3 mg/kg/day: 40% 5 mg/kg/day: 42% *Persistent fever:* 3 mg/kg/day: 40% 5 mg/kg/day: 30%	NS NS NS NS
Fleming 2001[c]	Prospective	75; leukemia	ABLC 3 mg/kg/d L-AMB 4 mg/kg/d (median doses)	Not reported	Not reported	Overall 63% Proven 30% Empiric 94%	Overall 39% Proven 29% Empiric 62%	0.03 NS 0.02
Cannon 2001[d]	Observational	67; various, not on dialysis	ABLC 5.3 mg/kg/d L-AMB 4.8 mg/kg/d (mean doses)	22% (2% organ transplants)	29% (5% organ transplants)	Proven 87%	Proven 80%	NS
Mattiuzzi 2004[e]	Prospective, historic control	131; AML and MDS	ABLC 2.5 mg/kg 3x/week L-AMB 3 mg/kg 3x/week	Not reported	Not reported	79% infection-free at 3 weeks	67% infection-free at 3 weeks	0.102
Hachem 2008[f]	Retrospective	158; hematologic malignancies	ABLC 5-10 mg/kg/d L-AMB 5-10 mg/kg/d	Allograft 37% Autograft 6%	Allograft 37% Autograft 6%	12%	12%	NS

ABLC = Amphotericin B lipid complex, AML = Acute myeloid leukemia, L-AMB = Liposomal amphotericin B, MDS = Myelodysplastic syndrome.

[a][18]
[b][19]
[c][20]
[d][21]
[e][22]
[f][23]

50% of patients in each group had received C-AMB previously. Overall response rates were comparable for both groups (ABLC: 78% *vs.* L-AMB: 71%). Response rates for evaluable patients with proven fungal infections were higher in the ABLC group compared with the L-AMB group (62% *vs.* 42%) but the difference was not statistically significant [18]. Other comparative studies have also shown no statistically significant difference in efficacy between the two formulations [19, 21]. Wingard *et al.* [19] assessed the comparative toxicity profiles of ABLC 5 mg/kg/day and L-AMB 3 or 5 mg/kg/day in 244 neutropenic patients with fever persisting after 3 days of antibacterial therapy in a double-blind, randomized, multicenter study. Both treatment groups were comparable at baseline. About half the patients had undergone HSCT and the proportion of allograft recipients was comparable. The majority of patients had received prior antifungal therapy: 89% in the ABLC group and 81% in the L-AMB group. Although primarily designed to compare the safety profiles of the two lipid-based amphotericin B formulations, efficacy data were also collected to ensure that the reduced toxicity associated with these formulations did not compromise their efficacy. ABLC 5 mg/kg was found to be equal to L-AMB 3 mg/kg in terms of the overall response rate (33.3% *vs.* 40.0%; P=NS) and the treatment failure rate due to persistent fever (27% *vs.* 40%; P=NS) [19].

These findings are consistent with those reported by Cannon *et al.* [21] who compared the efficacy of ABLC (mean daily dose 5 mg/kg) with L-AMB (mean daily dose 4.8 mg/kg) in 67 adults and children for the treatment of documented fungal infections or neutropenic fever. The majority of patients (70% ABLC and 90% L-AMB) had cancer. One patient in each treatment group had undergone solid organ transplant, and 22% of the ABLC recipients and 29% of the L-AMB recipients had undergone HSCT. Amongst patients with proven fungal infections, the response rate was 87% for ABLC and 80% for L-AMB. All 12 patients with documented *Candida* infections received ABLC and all responded (25% complete and 75% partial). Amongst patients with non-*Candida* infections, 73% of ABLC recipients and 80% of L-AMB recipients responded. All patients in the ABLC group with febrile neutropenia responded; however, one patient in the L-AMB group with febrile neutropenia developed breakthrough pulmonary zygomycosis after 15 days of therapy.

In contrast, Fleming *et al.* [20] reported significantly higher overall response rates for patients treated with ABLC compared with those treated with L-AMB. In this prospective study of 75 adult leukemic patients with 82 episodes of suspected or proven fungal infections, patients were treated depending on their clinical situation: 3 mg/kg per day for fever of unknown origin (FUO), 4-5 mg/kg per day for

sinusitis, cellulitis, and pneumonia with unknown pathogen, and 5 mg/kg per day for documented fungal infections. Baseline characteristics were similar between the two treatment groups, although a greater proportion of patients receiving ABLC was neutropenic at the start of therapy (93% *vs.* 79%; P=0.07). The median total duration of therapy among responders was longer for L-AMB (13 *vs.* 8 days, respectively; P=0.08). The majority of patients with FUO and disseminated candidiasis were in the ABLC arm, whereas all patients with *Fusarium* infections received L-AMB. The median daily dose of ABLC and L-AMB were 3 mg/kg and 4 mg/kg, range respectively. The mean duration of treatment for responders was 8 days for ABLC and 13 days for L-AMB. Using the intent-to-treat analysis, the overall clinical response rate was 63% *vs.* 39%, respectively (P=0.03). Although the response rate for documented fungal infections was comparable for the two groups (ABLC 30% *vs.* L-AMB 29%), a higher response rate was seen amongst ABLC-treated patients compared with L-AMB-treated patients who received empiric treatment (94% *vs.* 62%; P=0.02)[20].

Limited data are available comparing the efficacy of ABLC and L-AMB as prophylactic agents in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome, or in the treatment of invasive aspergillosis in patients with cancer. Mattuizzi *et al.* [22] reported that ABLC 2.5 mg/kg 3 times per week and L-AMB 3 mg/kg 3 times per week have similar efficacy in the prevention of fungal infections in newly diagnosed patients aged ≥15 years with AML or high-risk myelodysplastic syndrome, with 49% of patients in each treatment group completing therapy without developing a suspected or documented fungal infection. Overall, mortality was similar between the two treatment groups. However, a higher proportion of ABLC recipients remained infection-free at 3 weeks (79% *vs.* 67% with L-AMB), with a trend towards longer time-to-failure with ABLC (P=0.102) [22]. In contrast, markedly lower response rates to those seen in previous comparative trials [18-21] were reported in a retrospective study undertaken by Hachem *et al.* [23] comparing the efficacy of ABLC and L-AMB (5-10 mg/kg per day) used as either primary or salvage therapy in 381 patients with advanced hematologic malign-

nancies and invasive aspergillosis. The overall response rate was approximately 8%.

DRUG DELIVERY TO SITES OF INFECTION

ABLC and L-AMB differ substantially in the way amphotericin interacts with the lipid component. Thus, the structure and pharmacological profile of the two drugs is quite different (Table **2**) [14,24]. ABLC is made up of relatively large lipid structures. The complexes have a mean particle diameter of 2-5 μm and appear as unique ribbon-like structures. L-AMB is a lyophilized formulation of amphotericin incorporated into small, rigid unilamellar liposomes, which are known to have long circulation times in the bloodstream [25].

Effective treatment of fungal infections requires adequate drug penetration and retention at the sites of infection. The large ribbon-like structure of ABLC is taken up rapidly by the mononuclear phagocytes of the reticuloendothelial system, and results in lower circulating amphotericin concentration and enhanced tissue penetration – especially the lungs (Table **3**). Preclinical studies show that ABLC concentrates in the liver, spleen and lungs, and to a lesser degree, in the bone marrow [26,27]. After intravenous administration, most of the amphotericin B in L-AMB is retained in the liver and spleen and less in the lungs and kidney [25,28,29]. Amphotericin B concentration in lung tissue after ABLC administration exceeds that after L-AMB [14, 26-30].

Given the high mortality rate from pulmonary fungal infections, this affinity of ABLC for the lungs may have important clinical implications, particularly when choosing an appropriate therapy for treating fungal infections that primarily involve the lung. This was highlighted by Paterson *et al.* [31] who tested the susceptibilities of 12 strains of *Aspergillus fumigatus* and *Aspergillus flavus* from 11 patients who had failed treatment with C-AMB (n=6) or L-AMB (n=5). They reported that all the strains of *Aspergillus fumigatus* were susceptible to amphotericin (minimum inhibitory concentration: [MIC] 0.25-0.5 μg/ml) as were 3 of the 6 *Aspergillus flavus* strains (MIC 1 μg/ml), while 3 *Aspergillus flavus* strains were less susceptible (MIC 2

Table 2. Molecular Structure of ABLC and L-AMB

Formulation	Liposome Category	Particle Size	Structure	Lipids (Molar Ratio)
ABLC	Multilamellar vesicle fraction	2-5 μm	Lipid ribbon	Dimyristoyl phosphatidylcholine : Dimyristoyl phosphatidylglycerol (7:3)
L-AMB	Small unilamellar vesicles	80 nm	Liposome	Hydrogenated soy phosphatidylcholine : Distearoyl phosphatidylglycerol : Cholesterol (10:5:4)

ABLC = Amphotericin B lipid complex, L-AMB = Liposomal amphotericin B.

Table 3. Pharmacokinetic Characteristics of ABLC and L-AMB

Formulation	Plasma Peak Concentration Compared to C-AMB	Tissue Amphotericin Concentrations Compared to C-AMB		
		Liver	Lung	Kidney
ABLC	Lower	Higher	Higher	Similar
L-AMB	Higher	Higher	Similar	Similar

ABLC = Amphotericin B lipid complex, C-AMB = Conventional amphotericin B; L-AMB = Liposomal amphotericin B.

µg/ml). They used high-performance liquid chromatography to measure amphotericin levels in post-mortem infected lung specimens, normal lung and normal liver from a patient with invasive aspergillosis who had received treatment for 28 days. The levels of amphotericin detected in infected lung were low (0.1 µg/g) while slightly higher levels were achieved in the surrounding normal lung (0.67 µg/g). They concluded that difficulty in treating invasive aspergillosis was likely due to poor tissue penetration of amphotericin rather than resistance to it.

On the other hand, Janoff *et al.* [32] reported that a heart transplant recipient who had received 3 doses of ABLC (5.3 mg/kg) had high tissue amphoterin concentrations (mg/g) at autopsy in the liver (196), spleen (290), and lungs (222), and low concentrations in the heart (5), lymph nodes (8), brain (2), and kidney (7).

Although differences have been observed between ABLC and L-AMB in terms of pulmonary concentrations of active drug and there may be a link between this and the trend towards greater efficacy of ABLC in some studies, the paucity of comparative data means that the conclusions that can be drawn are limited.

COST CONSIDERATIONS

The management of invasive fungal infections, particularly aspergillosis, the most significant fungal infection in immunocompromised patients, is associated with considerable healthcare costs [33]. In a pharmacoeconomic study of fungal infections, aspergillosis accounted for the largest incremental per person hospitalization costs followed by candidiasis [34]. In addition, transplant patients were found to have the highest mean additional hospitalization costs per person attributable to any type of fungal infection [34]. Given increasing healthcare costs and limited healthcare budgets, pharmacoeconomic analyses, which integrate clinical outcomes with data on costs and quality of life, are becoming increasingly important [35]. Therefore, in addition

to efficacy and toxicity, cost-effectiveness is an important consideration when choosing an antimicrobial agent [36]. There are, however, a number of challenges with performing pharmacoeconomic studies in this patient population: a wide variety of invasive fungal infections, small patient populations in some clinical studies limiting the power and capacity to simplify results, and changing patterns of standards of care [37].

Several analyses have been undertaken to investigate the pharmacoeconomics of various antifungal drugs used in the management of invasive fungal infections [33, 35, 38-44], including C-AMB, ABLC and L-AMB in the treatment of invasive pulmonary aspergillosis [33]. A review of comparative studies suggests that ABLC is a cost-effective option compared with C-AMB or other lipid-based formulations of amphotericin B [43]. However, there are limited pharmacoeconomic data on which of the two lipid-based formulations (ABLC or L-AMB) is more cost-effective. Based on the available evidence, a comparative pharmacoeconomic analysis published in 2004 suggested that ABLC was a more cost-effective option than L-AMB [44]. Calculations were based on acquisition costs of the antifungal agents, cost of concomitant therapy, and costs associated with the treatment of adverse events or treatment failure.

TOLERABILITY

Although higher rates of nephrotoxicity have been reported for ABLC in one of the 6 studies [19], nephrotoxicity is comparable in the other studies. The case study below illustrates the clinical course of a patient to show how serum creatinine levels fluctuate – and may explain the higher nephrotoxicity rates seen in the blinded study [19], where it was not specified whether nephrotoxicity reflected peak data or data from baseline to the last drug dose. ABLC is associated with a higher rate of infusion-related reactions, but these can be managed with regulation of the rate of administration and appropriate premedications [45-47]. ABLC and L-AMB are also less nephrotoxic than C-AMB.
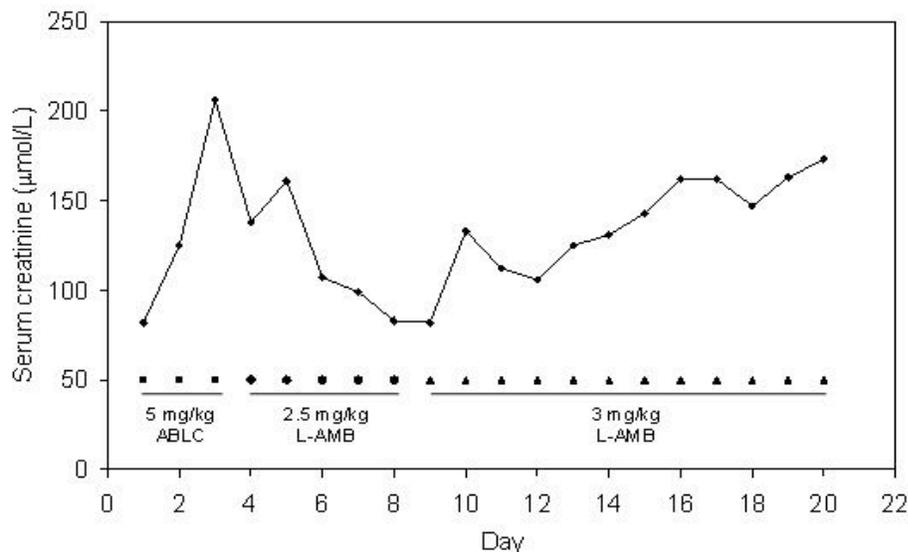
Fig. (2). Effect of ABLC and L-AMB on renal function in a myeloma patient with aspergillosis. Each day's serum creatinine level represents the level before drug administration.

Case Study

A female patient with myeloma was given ABLC at an initial dose of 5 mg/kg/day for the treatment of pulmonary aspergillosis. Blood samples were taken prior to the administration of the antifungal agent and serum creatinine levels were measured daily. Serum creatinine levels increased from 82 µmol/L on Day 1 to 125 µmol/L on Day 2 (Fig. **2**). By Day 3 the patient's serum creatinine levels had more than doubled (206 µmol/L). ABLC was discontinued and on Day 4, the patient was switched to L-AMB at an initial dose of 2.5 mg/kg/day. On Day 4, serum creatinine levels had fallen to 138 µmol/L, which was actually a reflection of the effect of the first 3 days of ABLC therapy rather than the effect of L-AMB therapy, as the bloods were drawn before L-AMB was administered. This was further evidenced by the fact that once the dose of L-AMB was increased to 3 mg/kg/day, the patient's serum creatinine levels started to increase once again from 82 µmol/L on Day 8 to 133 µmol/L on Day 10, peaking at 173 µmol/L by Day 20. This case study suggests that a short-term increase in creatinine may be seen with these drugs, which settle down after a few days.

CONCLUSIONS

The major advantage of lipid-based formulations of amphotericin B is the reduction in the adverse effects associated with C-AMB. When the use of amphotericin is called for, the choice of the lipid amphotericin preparation used should be based on clinical efficacy and then cost. Selecting the most appropriate lipid-based formulation of amphotericin remains a challenge to many clinicians. While high-quality evidence from randomized, controlled trials is limited, and the sample size of the treatment groups in many of the published trials is relatively small, the data from these 6 studies in aggregate indicate that ABLC and L-AMB are effective in the treatment of suspected or documented fungal infections. The poor outcomes observed in the retrospective study in patients with hematologic malignancies and invasive aspergillosis may have been due to the fact that most of the selected patient population in the study either had advanced disease or were critically ill, and approximately one-third of the patients had undergone allogeneic HSCT within the prior year [23].

Although comparative studies have found no or limited significant differences in efficacy between ABLC and L-AMB, when taken together, there appears to be a trend towards higher overall response rates for ABLC. Furthermore, there are theoretical tissue distribution advantages in using ABLC. The advantage seen for ABLC over L-AMB in terms of efficacy in some of the studies should ideally be explored further in a randomized study. In terms of cost, ABLC is less expensive than L-AMB. These potential advantages of ABLC need to be balanced against the better tolerability of L-AMB.

ABBREVIATIONS

ABLC   =   Amphotericin B lipid complex

L-AMB =   Liposomal amphotericin B

HSCT   =   Hematopoietic stem cell transplantation

C-AMB =   Conventional amphotericin B

AML   =   Acute myeloid leukemia

OR   =   Odds ratio

CI   =   Confidence interval

ANC   =   Absolute neutrophil count

FUO   =   Fever of unknown origin

MIC   =   Minimum inhibitory concentration

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