THE USE OF LIPID FORMULATIONS OF AMPHOTERICIN B IN CANCER PATIENTS
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Introduction
Cancer patients, especially stem cell transplantation recipients and patients with leukemia, constitute a high-risk group for the development of life-threatening systemic fungal infections. Candidiasis represents the most commonly reported fungal infection in cancer patients. Candidemia alone is associated with a mortality rate above 50% in this patient population.\(^1\) Even more challenging than the management of systemic yeast infections is the treatment of Aspergillus and other molds. In the case of Aspergillus pneumonia, the historical mortality rate in cancer patients has exceeded 80%.\(^2\) Additional fungal pathogens including Trichosporon, Fusarium, Muco, Alternaria, Bipolaris, Curvularia, etc. continue to be identified in this immunosuppressed population. Risk factors for the development of mycotic infection in cancer patients include neutropenia, chronic corticosteroid use, broad-spectrum antibiotic therapy, chemotherapy- or radiation therapy-induced mucositis, and central venous catheterization.\(^3,4\)

Management of these life-threatening fungal infections has been difficult due to the limited available pharmacological antymycotic armamentarium. Fluconazole, an azole antifungal, has been used effectively in the treatment of Candida infections in the immunocompromised host.\(^5\) However, the use of fluconazole for both prophylaxis and treatment of candidiasis has been limited by the development of resistant yeast strains of Candida krusei and Torulopsis glabrata.\(^6\) Fluconazole is also lacking in ef-icacy against molds, including Aspergillus.\(^6\) Itraconazole, an azole antifungal with improved Asper-gillus activity, has displayed limited clinical utility to date due to unreliable oral absorption of the capsule formulation\(^6\) and the lack of a commercially available intravenous formulation. Itraconazole oral solution has pharmacokinetic advantages over the capsule formulation,\(^7,8\) but its role in systemic fungal infections of cancer patients is as yet undefined. In addition, azole antifungal agents are limited to fungisstatic as opposed to fungicidal activity.\(^6\) For all of these reasons, one antifungal agent has dominated the treatment of systemic mycoses for 40 years -- amphotericin B (AMB).

This article focuses on the newest development in antifungal therapy, lipid formulations of AMB designed to maintain antymycotic efficacy while reducing toxicity.

Case Report
A 53-year-old man with a history of stage IV low-grade non-Hodgkin’s lymphoma in first relapse had a partial response to salvage chemotherapy. High-dose cyclophosphamide/carmustine/etoposide chemotherapy was followed by an allogeneic bone marrow transplant from his HLA-identical sister. The posttransplantation course was complicated by chronic graft-vs-host disease involving the skin and liver (requiring cyclosporine and prednisone), chronic renal insufficiency, and multiple infections including Pseudomonas aeruginosa bacteremia, cyto megalovirus pneumonia, recurrent mucocutaneous herpes simplex infections, and presumed anaerobic sacriolic joint osteomyelitis. On day +301 status following bone marrow transplantation, the patient complained of a one-week history of productive cough, progressive weakness, and chest discomfort but no fever. Chest radiograph demonstrated a left upper lobe infiltrate. Laboratory studies yielded the following values: white blood cell count, 4,660 cells/µL; blood urea nitrogen (BUN), 44 mg/dL; serum creatinine, 2.3 mg/dL; albumin, 4 g/dL; total bilirubin, 2 mg/dL; alkaline phosphatase, 210 U/L; serum glutamic-oxaloacetic transaminase (SGOT), 54 U/L; serum glutamic-pyruvic transaminase (SGPT), 142 U/L. He was admitted, and empiric antibiotic therapy consisting of intravenous ciprofloxacin, piperacillin/tazobactam, and fluconazole was initiated. Cyclo-sporine dose was decreased from 225 mg po BID to 100 mg po BID due to renal dysfunction. Computed tomography (CT) scan of the chest revealed a left upper lobe infiltrate as well as a nodular right upper lobe infiltrate (Fig 1). Fluconazole was discontinued and oral itraconazole solution was begun pending a definitive diagnosis. Fiberoptic bronchoscopy was performed on day +302 with no immediate positive diagnostic findings. On day +304, a CT-guided biopsy of the right upper lung nodule demonstrated one filamentous fungal element consistent with Aspergillus pneumonia. Itraconazole solution was discontinued, and Abecel (AMB lipid complex; The Liposome Co, Princeton, NJ) was instituted at 5 mg/kg per day intravenously. At this point, the patient’s BUN was 20 mg/dL and the serum creatinine level was 2 mg/dL. Viral cultures from bronchoalveolar lavage grew cytomegalovirus, and respiratory syncytial virus (RSV) was reported as positive on day +306. Ganciclovir and intravenous immunoglobulin were instituted at this time for cytomegalovirus therapy. RSV treatment was deferred due to improving pulmonary status. Ciprofloxacin and piperacillin/tazobactam were then discontinued. The patient did well clinically during the remainder of the hospitalization. Renal dysfunction remained an issue with a BUN level of 49 mg/dL and a serum creatinine level of 2.5 mg/dL at discharge on day +316. By day +319, his BUN level rose to 49 mg/dL, and serum creatinine level to 3.4 mg/dL, requiring discontinuation of cyclosporine. Abecel was reduced to 3 mg/kg every 48 hours, which resulted in the gradual improvement of renal function. On day +346, with a BUN level of 33 mg/dL, and a serum creatinine level of 1.7 mg/dL, Abecel was discontinued, and itraconazole oral solution 200 mg po BID was started as antifungal prophylaxis during the remainder of corticosteroid therapy. On day +504, all immunosuppressants have been discontinued with no evidence of recurrent infection.
Amphotericin B

AMB was first isolated at Squibb Laboratories in 1953 as a byproduct of Streptomyces nodosus fermentation. Initial data on its antifungal activity were published three years later. Amphotericin B (Fig 2) was so named due to its amphoteric chemical properties: it forms soluble salts under acidic and basic conditions but is insoluble in water. Therefore, commercial AMB for injection requires the addition of sodium deoxycholate, which produces a soluble colloidal dispersion (Fungizone, Bristol Myers-Squibb Co, Cherry Hill, NJ, available in generic form). AMB is a polyene macrolide antifungal that adheres to ergosterol in the fungal cell wall producing increased membrane permeability and leading to cell death by leakage of cell contents. AMB also has the benefit of a broad antifungal spectrum including Candida species, Torulopsis glabrata, Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans, Paracoccidioides brasiliensis, and Histoplasmosa capsulatum, as well as Sporothrix species. Variable activity has been reported against Aspergillus, Fusarium, and Mucor. Due to its superior fungal spectrum and the potential of fungicidal activity, AMB remains the mainstay of the management of systemic fungal infections. Due to the high risk of fungal superinfections, empiric use of AMB in the setting of prolonged neutropenic fevers following 5 to 7 days of broad-spectrum antibiotic therapy is indicated.

Despite the value of AMB and the importance of early initiation upon clinical suspicion of fungal infection, AMB has often been underutilized in clinical practice. AMB earned its nickname, "amphoterrible," from its unfavorable toxicity profile. Patients often complain of the infusion-related toxicity that produces fever and shaking chills in the majority of patients receiving this agent. The severity of this syndrome can range from barely noticeable to completely intolerable. Prompt treatment of rigors with meperidine 25 to 50 mg IV push will usually alleviate the rigors. Premedication with acetaminophen 650 mg PO, diphenhydramine 25 to 50 mg IV push, and/or hydrocortisone 25 to 50 mg IV push may benefit some particularly insensitive patients. Infusion-related reactions generally decline in severity with time. Of more concern to the clinician than the infusion-related toxicity is the frequent complication of renal toxicity. AMB exerts its nephrotoxic effects by reducing glomerular filtration rate and renal blood flow in addition to interfering with proximal and distal electrolyte reabsorption. The clinical result may include evidence of renal tubular acidosis, casts in the urine, azotemia, oliguria, and magnesium and potassium wasting. Reversible renal impairment will be detected in greater than 80% of patients within two weeks. Irreversible renal damage has been reported, particularly after treatment with high cumulative doses. Sodium supplementation (150 mEq per day) appears to reduce the frequency of nephrotoxicity. Nonetheless, renal damage remains the most significant risk of AMB therapy. Recent advancements in lipid pharmaceutical technologies have led to three new formulations with reduced nephrotoxicity: amphotericin B lipid complex (Abelcet), amphotericin B cholesteryl sulfate (Amphotec, Sequus Pharmaceuticals, Inc, Menlo Park, Calif), and liposomal amphotericin B (AmBisome, Fujisawa Healthcare, Inc, Deerfield, Ill, and NeXstar Pharmaceutical, Inc, Boulder, Colo).

Pharmaceutical Use of Lipid Technology

Liposomes are vesicles composed of spherical arrangements of bilayered phospholipid molecules (Fig 3). In an aqueous medium such as the human body, hydrophilic "heads" face outward protecting the hydrophobic "tails" from contact with water. Hydrophobic chemicals such as AMB can be incorporated into the lipid bilayer. Liposomal and related lipid complexes will affect drug delivery due to selective uptake by the reticuloendothelial system, which results in altered drug distribution. Specifically, the drug is concentrated in the liver, spleen, lymph nodes, and bone marrow. Phagocytosis of these lipid complexes may lead to enhanced concentration at sites of active infection or inflammation.
While the liposome serves as a model for understanding the selectivity of the lipid formulations of AMB, each agent has its own distinct molecular structure (Figs 4-6). These variations result in profound pharmacokinetic differences that could result in clinically important differences. Abelcet consists of a 1:1 ratio of AMB in combination with a 7:3 ratio of dimyristoyl phosphatidylcholine to dimyristoyl phosphatidylglycerol. The resulting complex forms a tightly packed ribbon structure, approximately 250 nm in diameter, the largest of the three lipid formulations. Amphotec is a colloidal dispersion produced by a 1:1 molar ratio of AMB and cholesteryl sulfate. The resulting disc-like structure measures 122 nm in diameter with a thickness of 4 nm. AmBisome is produced by the incorporation of AMB into a single liposomal bilayer composed of hydrogenated soy phosphatidylcholine, cholesterol, and distearoyl phosphatidylglycerol in a 10:5:4 ratio. AmBisome has the simplest and smallest lipid structure with a diameter of 60 to 70 nm.

**Pharmacokinetics**

The various lipid formulations of AMB have proven to produce dramatically different pharmacokinetic properties (Table 1). Of note, all available pharmacokinetic data are based on total serum concentrations of AMB and therefore include both complexed and free drug. This is particularly significant for AmBisome, which displays a much slower rate of uptake by the reticuloendothelial system than either Abelcet or Amphotec due to its smaller size and negative charge. This results in higher plasma levels and a significantly lower volume of distribution, which is a reflection of the extent and rate of tissue penetration. More clinically relevant than total AMB plasma concentrations may be tissue AMB levels as measured by various animal studies. All three formulations are concentrated in the liver and spleen in a dose-dependent fashion, while renal amphotericin levels are comparable to those obtained with conventional AMB. In contrast to Amphotec and AmBisome, Abelcet achieves higher pulmonary concentrations than AMB deoxycholate. Central nervous system penetration is another potentially important area of drug distribution. In a
study of noninfected, catheterized rabbits, Groll and colleagues found undetectable amphotericin cerebrospinal fluid levels following 7 days with standard doses of conventional AMB, Abelcet, Amphotec, or AmBisome. Clinically relevant brain tissue concentrations, however, were achieved most notably with AmBisome, which obtained levels 4 to 7 times higher than the other formulations. Clinical trials are needed to determine if Abelcet is in fact superior in pulmonary infections or if AmBisome is superior in central nervous system infections.

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<th>Area Under the Curve (µg x hr/mL)</th>
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<th>Clearance (mL/hr/kg)</th>
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**Table 1. Pharmacokinetic Properties of Amphotericin B Formulations**

A small series of six children with hepatosplenic candidiasis treated with Abelcet 2.5 mg/kg intravenously for 6 weeks was reported by Walsh et al. One of the six children could not be evaluated for efficacy due to early death related to relapsed leukemia. All children were evaluated for safety, tolerance, and pharmacokinetics. No nephrotoxicity was encountered. Complete clinical responses were achieved in all five evaluable patients and were confirmed by regressin liver and spleen lesions by CT and magnetic resonance imaging scans. A subset analysis of emergency-use trials of Abelcet revealed that 73 of 556 patients were treated with doses of <=3 mg/kg per day. Patients with yeast infections were more likely to be treated with a low dose (21% of patients with candidiasis) than those with mold infections (6% of patients with aspergillosis). The overall response rate for this group was 82%, with insufficient power to identify differences in efficacy by organism. Treatment with Abelcet appears to be effective at doses lower than 5 mg/kg per day intravenously in sensitive organisms, including many *Candida* species. Prospectively designed clinical trials should be performed to confirm this concept.

**Amphotec**

Initial phase I data regarding AMB cholesteryl sulfate in 75 bone marrow transplant patients with fungal infections were reported by Bowden and associates. Dose escalation in this trial established the maximum tolerated dose of 7.5 mg/kg per day via intravenous infusion. Beyond this dose, infusion-related toxicity (fevers, chills, rigors, and hypotension requiring vasoressor use) became intolerable. Renal toxicity, defined as a serum creatinine level at 150 to 200% baseline or up to 2.5 mg/dL, occurred in 17% of patients and may have been largely due to their underlying disease state. Severe renal toxicity, defined as serum creatinine greater than 200% baseline or 2.5 mg/dL, was not reported in this trial.

Amphotec was approved by the FDA on open-label use in *Aspergillus* infections compared to concurrent historical controls treated with conventional AMB. White et al. evaluated 82 patients treated with Amphotec 0.5 to 8 mg/kg per day intravenously and 261 treated with AMB 0.1 to 1.4 mg/kg per day intravenously. Those using Amphotec were required to meet one of the following criteria: (1) refractory to >=15 mg/kg cumulative dose of AMB, (2) nephrotoxicity with AMB defined as doubling of serum creatinine or an increase of =>1.5 mg/dL, above baseline, (3) pre-existing renal dysfunction defined as serum creatinine =>2 mg/dL, or (4) participation in the phase I trial in bone marrow transplant patients. Clinical response rates for Amphotec vs AMB were as follows: 48.8% vs 23.4%, respectively, overall (*P < 0.001*); 35.9% vs 19.5%, respectively, in bone marrow transplant patients (*P = 0.049*), and 75% vs 18.6%, respectively, in patients with hematological malignancies (*P < 0.001*). Survival showed similar trends: 50% vs 71.6%, respectively, of patients died during treatment for aspergillosis (*P < 0.001*). Ampho-tec also displayed less nephrotoxicity: 43.1% vs 8.2%, respectively (*P < 0.001*). While these results suggest clinical superiority of Amphotec over AMB, the retrospective and uncontrolled methodology limits the conclusions to reduced toxicity with at least equivalent efficacy. These same open-label trials also demonstrated activity of Amphotec in the treatment of infections with *Candida, Cryptococcus, Mucor,* and *Fusaria.*

White and colleagues also studied Amphotec 4 mg/kg per day intravenously vs AMB 0.8 mg/kg per day intravenously for the empiric treatment of 194 cases of febrile neutropenia >=72 hours after initiation of broad-spectrum antibiotics. In this trial reported in abstract form, success was defined as survival 7 days after study drug, defervesence, no evidence of emerging fungal infection, and study drug tolerance. Patients were divided into cohorts based on age and exposure to cyclosporine or tacrolimus and were on study for a median of 8 to 11.5 days. There was no statistically significant difference in terms of engraftment, clinical success, or survival. All groups displayed a statistically significant reduction in renal toxicity.

**AmBisome**

Unfortunately, no clinical trials have been published that directly compare two or three lipid formulations in the same patient populations. Instead, most clinical data are based on compassionate-use trials or comparisons between conventional and lipid formulations of AMB.

**Abelcet**

AMB lipid complex was approved based primarily on compassionate-use trials in patients with life-threatening fungal infections (candidiasis, aspergillosis, cryptococcosis, zygomycosis, fusariosis, etc). These patients failed AMB therapy (cumulative dose >=1000 mg) or other antifungals, they developed AMB-induced nephrotoxicity (serum creatinine level >=2.5 mg/dL in adults), or they had equivalent renal disease at baseline. They were treated with Abelcet 5 mg/kg per day intravenously for four weeks. In a cohort of 228 cases, the overall clinical response rate was 69% with a 55% mycological response rate. Candidiasis proved to be somewhat more sensitive than aspergillosis (78% vs 60% clinical response rate, respectively). Serum creatinine levels declined from a mean baseline of 3.69 to 2.06 mg/dL at week 4 (*P < 0.0001*) in the group enrolled for nephrotoxicity. In this uncontrolled trial, Abelcet demonstrated clinical efficacy as well as reduced nephrotoxicity.
As with Abelcet and Amphotec, data for AmBisome treatment of patients with documented fungal infections (Aspergillus, Candida, Cryptococcus) have been extrapolated from open-label compassionate-use protocols primarily for refractory or intolerant cases. At the time of this writing, these data have not been reported in full. AmBisome 3 to 5 mg/kg per day intravenously was provided for 140 infectious episodes in 133 patients, with 53 episodes evaluable for mycological response and 91 episodes evaluable for clinical outcome. Clinical success and mycological eradication occurred in some patients with documented aspergillosis, candidiasis, and cryptococcosis.16

The largest published series of AmBisome-treated patients with documented or suspected fungal infections was reported by Mills et al.25 They described 133 episodes in 116 neutropenic patients. The majority of these patients (74%) received AmBisome after AMB therapy either for intolerance (66 of 99 patients) or for evidence of progressive infection (32 of 99 patients). Most of those receiving AmBisome first-line either had recurrence of previous AmBisome–requiring infections (16 of 34 patients) or had pre-existing renal dysfunction (8 of 34 patients). The median duration of therapy was 12 days with a median total dose of 1684 mg. AmBisome was well tolerated clinically, but the authors reported a 17% incidence of hepatic function test abnormalities possibly related to AmBisome use. Of 21 patients with documented aspergillosis, 13 (62%) obtained a clinical response. Eleven (52%) of these 21 patients had progressive disease after AMB therapy, of whom 7 (64%) responded. Thirty-six patients with suspected aspergillosis displayed a 53% complete or good partial eradication of their signs of infection, including eight patients who had progressive disease following AMB. Overall, 61% of patients achieved a clinically successful outcome, including 13 patients with proven aspergillosis and 39 patients with evidence of candidiasis.

Prentice et al26 reported the results of two open-label, randomized trials of AmBisome 1 or 3 mg/kg per day intravenously vs AMB 1 mg/kg per day intravenously in persistently febrile neutropenic patients. The adult trial enrolled 43, 42, and 45 patients, respectively, while the pediatric trial included 7 patients at each dose level. Success was defined as fever resolution for 3 days with no new fungal infections. When both trials were combined, the groups using AmBisome and AMB 1 mg/kg per day displayed similar efficacy (58% vs 49%, respectively). AmBisome 3 mg/kg per day was slightly more effective than AMB (64% vs 49%, respectively). Insufficient power existed to prove a significant difference when the results were evaluated in age subgroups. AMB toxicities (eg, hypokalemia, infusion reactions, nephrotoxicity) were least common with AmBisome 1 mg/kg per day, followed by AmBisome 3 mg/kg per day, then AMB 1 mg/kg per day. Doubling of serum creatinine levels occurred in 10%, 12%, and 24% of patients, respectively. Of note, this trial used an aggressive dose of conventional AMB. Less nephrotoxicity may have occurred if a more standard neutropenic fever dose of AMB (0.5 to 0.6 mg/kg per day intravenously) had been used.

H. Lee Moffitt Cancer Center participated in a multicenter trial to evaluate AmBisome 3 to 6 mg/kg per day intravenously vs AMB 0.6 to 1.2 mg/kg per day intravenously in the empirical treatment of patients with neutropenic fevers after at least 96 hours of broad-spectrum antibiotics. This randomized, double-blind, comparative trial enrolled 687 patients (343 using AmBisome and 344 using AMB). Therapeutic success was defined as defervescence, absence of emerging fungal infection, survival for at least 7 days following therapy, tolerance of study drug, and resolution of any entry fungal infection. Overall success was achieved in 49.9% of patients using AmBisome vs 49.1% of those using AMB with no differences in any safety or efficacy endpoints. Both groups had similar incidence of discontinuation of study drug due to toxicity or lack of efficacy (14.3% vs 18.6%, respectively). AmBisome and AMB were found to be equivalent for the empirical therapy of persistent febrile neutropenia.16

**Adverse Effects**

Anaphylaxis has been reported with an incidence of less than 0.1% in patients receiving both conventional and lipid formulations of AMB.14–16 AMB 1 mg intravenous test doses have been widely used but do not reliably screen for anaphylaxis.6 Epinephrine, oxygen, intravenous corticosteroids, and airway management should be immediately administered as indicated. Direct comparison among lipid formulations is difficult as no such parallel trials have been reported. Table 2 reflects the most commonly reported adverse effects and their incidence. Table 3 summarizes the most common drug interactions encountered with AMB formulations. Table 4 summarizes recommended dosing and administration guidelines for the AMB formulations.

Nephrotoxicity was defined differently in each trial. For Abelcet, nephrotoxicity indicates doubling of serum creatinine.11 For Amphotec, nephrotoxicity was defined as doubling of serum creatinine, an increase of serum creatinine by at least 1 mg/dL, or a 50% decrease in calculated creatinine clearance.12 The AmBisome definition requires doubling of serum creatinine with minimum peak serum creatinine of 1.2 mg/dL.16

In summary, the various lipid formulations of AMB are capable of producing all of the toxicities associated with conventional AMB. Clearly, nephrotoxicity is reduced with all of these formulations. Although this has not been directly compared in a head-to-head clinical trial, Amphotec appears to exhibit a higher incidence of infusion-related toxicities than its competitors.11,12,14,16 In order to minimize this toxicity, Amphotec must be infused at a slower rate of 1 mg/kg per hour, requiring a five-hour infusion for maximal dosing vs a two-hour infusion for either Abelcet or AmBisome. This slower infusion rate can cause difficulties in terms of central line access, nursing administration and monitoring time, as well as clinic or home health care time for outpatients.

**Drug Interactions, Dosage, and Administration**

Table 3 summarizes the most common drug interactions encountered with AMB formulations. Table 4 summarizes recommended dosing and administration guidelines for the AMB formulations.

| Table 2. -- Adverse Effects of Amphotericin B Formulations11,12,14-16 |
|--------------------------|----------------|----------------|----------------|----------------|
| **Adverse Effect**       | **Abelcet**   | **Amphotec**  | **AmBisome**  | **AMB**        |
| Chills/rigors            | 18%           | n/a           | 77%           | 53%            | 20.0%          | 56.0%          |
| Fever                    | 14%           | n/a           | 49%           | 43%            | 18.0%          | 43.0%          |
| Nausea                   | 9%            | n/a           | 8%            | 6%             | 13.0%          | 10.0%          |
| Vomiting                 | 8%            | n/a           | 8%            | 6%             | 6.0%           | 7.0%           |
| Dyspnea                  | 12%           | 8%            | 8%            | 4%             | 4.7%           | 7.3%           |
| Hypertension             | 0%            | 0%            | 0%            | 6%             | 7.9%           | 16.3%          |
| Hypotension              | 0%            | 0%            | 0%            | 12%            | 3.5%           | 8.1%           |
| Tachycardia              | 5%            | 0%            | 6%            | 4%             | 2.3%           | 12.5%          |
| Hypokalemia              | 5%            | 0%            | 17%           | 20%            | 42.9%          | 50.6%          |
| Hyponatremia             | n/a           | 0%            | 6%            | 0%             | 20.4%          | 25.6%          |
| Nephrotoxicity           | 28%           | 17%           | 8%            | 43%            | 18.7%          | 33.7%          |

| Table 3. -- Drug Interactions of Amphotericin B Formulations14-16,28 |
Cost Evaluation

Toxicity issues have traditionally limited the use of conventional AMB. The limiting factor for use of the lipid formulations of AMB may prove to be the difficulty in determining the most cost-effective use of these extremely expensive antifungal agents. Table 5 reports drug costs based on average wholesale price.27 Due to wide contractual variations, these figures may or may not accurately reflect the actual pharmacy cost or patient charge in any given institution. Given the increasing frequency of managed care precapitated contracts, the clinician must strive to weigh the benefits of these agents against their high cost.

| Table 5. -- Drug Costs of Therapy With Amphotericin B Formulations |
|-----------------------|-----------------------|-----------------------|-----------------------|
| **Formulation**      | **Cost per 100 mg**  | **Cost for 35 mg (~0.5 mg/kg) QD x 4 wks** | **Cost for 70 mg (~1 mg/kg) QD x 4 wks** |
| Conventional         | $57.76                | $1,132.10             |
| AmBisome             | $57.76                | $1,132.10             |

Cost Evaluation

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Conclusions

The various lipid formulations of AMB have demonstrated antifungal efficacy at least equivalent to the conventional product with significantly reduced nephrotoxicity. Despite pharmacokinetic differences among these products, available clinical data support the use of similar dosage regimens for each of these three products for similar indications. Empiric therapy of persistent febrile neutropenia may be treated with 3 to 4 mg/kg per day intravenously, while documented, life-threatening, systemic fungal infections require 5 to 6 mg/kg per day intravenously. Abelcet and AmBisome appear to have an advantage over Amphotec in terms of frequency and severity of infusion-related toxicity, and they also allow more rapid infusion.14-16 Currently, no data exist to suggest that any one of these agents exhibits a greater efficacy than the others.

Determining the most cost-effective use of these highly expensive but clinically useful agents remains a challenge. Current clinical data strongly suggest that even the most draconian of formularies should allow for the use of one of these agents for the treatment of life-threatening fungal infections when conventional AMB is contraindicated. This would include patients whose infections have progressed despite adequate doses of conventional AMB treatment, patients who experience significant nephrotoxicity secondary to AMB therapy, or patients with significant pre-existing renal impairment. This policy essentially uses the emergency-use trial inclusion criteria as drug-use criteria.

Patient populations at high risk for AMB nephrotoxicity such as allogeic bone marrow transplant recipients on cyclosporine or tacrolimus or patients with multiple myeloma may require a lower threshold. Many specialists in infectious disease are beginning to encourage first-line use of lipid formulations for systemic mold infections (such as Aspergillosis) due to the high dose intensity needed to successfully treat these patients. The creation of cost-effective yet caring guidelines for the use of these expensive but clinically important agents will no doubt continue to be a challenge for years to come.

Dr Quiliz is a Speakers’ Bureau member for The Liposome Company and for Nexstar Pharmaceuticals, Inc.

References


