Review

Emerging Fungal Pathogens, Drug Resistance and the Role of Lipid Formulations of Amphotericin B in the Treatment of Fungal Infections in Cancer Patients: A Review

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ABSTRACT

The incidence of life-threatening invasive fungal infections in immunocompromised patients has increased dramatically in recent years. *Candida* spp other than *C. albicans* are increasingly being isolated, and *Aspergillus* infections also are on the increase, as well as infections due to previously uncommon organisms. It is likely that this phenomenon is multifactorial in origin, although the extensive use of antifungal prophylaxis may have played a role, especially for the emergence of non-albicans *Candida*. Amphotericin B remains the antifungal agent with the broadest spectrum of action available and is thus the standard treatment for immunocompromised patients with proven or suspected fungal infections, especially aspergillosis. However, its potential for nephrotoxicity limits its usefulness. Lipid formulations of amphotericin B may allow therapy to be administered with reduced renal toxicity. Three different lipid formulations of amphotericin B currently are available. These compounds have different pharmacokinetic properties and seem to achieve higher serum or tissue concentrations than amphotericin B. This statement is based on animal models and scattered human data. At present, there are no studies comparing the lipid formulations with each other and only a few randomized trials comparing them with conventional amphotericin B. However, a number of open clinical trials and compassionate-use protocols suggest that lipid-based forms of amphotericin B can achieve good response rates with minimal toxicity in patients with a variety of invasive mycoses, including those who have proved refractory or intolerant to previous therapy with conventional amphotericin B. Unfortunately, the cost of these compounds remains high and may represent a limiting factor to their use.

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The number of patients undergoing potentially life-saving chemotherapy for neoplastic diseases has increased dramatically in recent years. Unfortunately, so has the incidence of life-threatening invasive fungal infections occurring in these patients.[1–3] This is especially true for recipients of bone marrow transplants (BMTs). Based on autopsy studies, it appears that the successful outcome of up to a quarter of all BMTs carried out is jeopardized by such infections.[4] Moreover, the variety of pathogenic fungi observed in this setting is increasing, with the emergence of previously uncommon organisms.[5] Questions of how to manage such patients remain problematic, for several reasons. First, it is frequently difficult to confirm a fungal infection until late in the course of the disease; second, some organisms have intrinsic or acquired resistance to antifungal agents; third, there is a risk of renal and other drug-related toxicity, particularly in BMT patients receiving concomitant therapy for graft-versus-host disease (GVHD); and finally, all therapeutic and prophylactic efforts can be frustrated by the absolute inability of the patient to produce an adequate immunologic response. The clinical approach to mycoses in BMT patients and the general approach to antifungal therapy in cancer patients recently have been reviewed.[3,6] This article reviews the epidemiology and the etiology of fungal infections in cancer patients, and the potential therapeutic role of lipid formulations of amphotericin B in these patient populations.

INCIDENCE AND MORTALITY OF INVASIVE FUNGAL INFECTIONS

According to a large American study,[7] the rate of invasive fungal infections among hospital patients approximately doubled between 1980 and 1990, increasing from 2.0 to 3.8 per 1000 discharges, and the incidence of noso-

Table 1. Correlation between Clinical Subtype and Outcome in 129 Bone Marrow Transplant Patients with Non-*Candida* Fungal Infection

			Dead	
Type of Infection	*n = 129*	*Alive n = 23 (18%)*	*Related to Infection n = 69 (53%)*	*Unrelated to Infection n = 37 (29%)*
Minor skin or soft tissue	6	2 (33)	0	4 (67)
Single organ or site	59	12 (20)	24 (41)*	23 (39)†
Disseminated	54	3 (6)	45 (83)*	6 (11)†
Isolated fungemia	10	6 (60)	0	4 (40)

*Among patients who died of their fungal infection, there were significantly more deaths in those with disseminated infection compared to those with single organ or single site infection ($P < 0.0001$).
†Among patients who died of causes other than their fungal infection, there was no significant difference in numbers of deaths between those with disseminated infection and those with single organ or single site infection ($P = 0.68$).
(Adapted from Morrison et al.[9])

comial candidemia alone increased fivefold. Similar results have been reported in Europe, with one large autopsy study showing an increase in frequency from 1.6% in the period from 1978 to 1982 to 4.1% in 1988 to 1992.[8] Among BMT patients, an American study revealed an incidence of fungal infections of between 15% and 25%.[4] Furthermore, although they are infrequently the cause of the first febrile incident during neutropenia, fungal pathogens have been reported to account for almost half of all superinfections in BMT patients.[2]

The mortality rates resulting from invasive fungal infections are truly frightening, since rates as high as 40% overall and 60 to 85% for patients with invasive aspergillosis have been reported. In an American study involving 1186 BMT patients, 106 of 129 BMT patients with non-*Candida* fungal infections died, including 69 (53%) whose death was directly associated with the fungal infection, despite aggressive antifungal therapy.[9] In this study there also was a strong correlation between the extent of visceral involvement of the infection and the outcome, with 83% of patients with disseminated disease dying of their infection compared to 43% of those with infection located at a single organ or site ($P < 0.0001$) (Table 1). In contrast, there was no significant difference between the numbers of patients with disseminated or nondisseminated fungal disease who died from causes other than their fungal infection, thus showing the independent role attributable to the fungal infection in causing death in this patient population. Cause-specific mortality rates were found to be highest for *Aspergillus*, *Chrysosporium*, *Fusarium*, *Mucor*, and *Scopulariopsis*, all pathogens with a high potential for invasive disease and disseminated infection.[9]

Table 2. Host Factors Associated with Increased or Possibly Reduced Risk of Invasive Fungal Infections in Granulocytopenic Patients

Increased risk
Protracted granulocytopenia
Corticosteroid therapy
Broad-spectrum antibiotics
Relapsed neoplastic disease
Hematologic neoplasia
Previous invasive pulmonary aspergillosis
Central venous catheter
Total body irradiation
Allogeneic BMT, especially with
T-cell depletion
GVHD
Possibly reduced risk
Solid tumors
Remission of neoplastic disease
Recovery from granulocytopenia
Spontaneous
Related to recombinant hematopoietic cytokines*
Related to stem cell reconstitution*
Related to granulocyte transfusion*

*Investigational.
(Adapted from Walsh et al and Viscoli et al.[10,11])

RISK FACTORS

There are multiple reasons for the increase in incidence of invasive fungal infections in cancer patients; primarily, the increased intensity of chemotherapy employed in these patients (Table 2).[10] In BMT patients in particular, the effect of the conditioning regimen associated with the prolonged use of immunosuppressive agents for the prevention and treatment of GVHD (especially in patients receiving allogeneic BMT from mismatched relatives or from matched unrelated donors) may be devastating. Moreover, there is a whole series of additional host factors associated with increased risk, including the use of broad-spectrum antibiotics, indwelling catheters, age, life style and hobbies, and previous infectious history (including infections developed before and after the diagnosis of cancer).[11] The resulting multifactorial deficit in the anti-infective defenses allows some of the less common opportunistic pathogens to take hold, as well as those more commonly seen.

ETIOLOGY OF MYCOSES IN CANCER PATIENTS

Although *Candida* and *Aspergillus* spp remain the most commonly identified pathogens in invasive fungal disease, more unusual organisms increasingly are being isolated.[2,5] *Candida albicans* still remains the most frequently reported of the *Candida* spp as the cause of disease in cancer patients,[12] even if other types of *Candida* (so called non-albicans strains) are reported with increased frequency and sometimes represent the most frequently isolated species of *Candida* (Table 3),[13,14] with an increased likelihood of intrinsic or acquired resistance to the most widely used antifungal agents.[2,12,13,15] In a prospective study of candidemia in a miscellaneous group of immunocompromised patients, the percentage of

Table 3. Predominant *Candida* Pathogens in Oncology Patients during Different Decades

1950s–1970s	*1980s*	*1990s*
C. albicans	*C. albicans* *C. tropicalis*	*C. albicans* *C. tropicalis* *C. glabrata* *C. krusei* *C. lusitaniae* *C. parapsilosis*

(From Wingard.[2])

infection caused by non-albicans *Candida* spp (in decreasing order: *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae*, and *C. pseudotropicalis*) increased from 40% to 53% between June 1990 and June 1994, with increases seen in all four medical centers participating in the study.[13] In a large surveillance study performed by the Invasive Fungal Infection Group of the European Organization for Research and Treatment of Cancer (EORTC), the shift from *C. albicans* to non-albicans *Candida* as cause of candidemia was more relevant in patients with hematologic malignancies than in those with solid tumors. Among patients with hematologic malignancies, a multivariate analysis showed that the occurrence of non-albicans candidemia was significantly correlated with the underlying disease (acute leukemia with respect to lymphoma) and with the administration of antifungal prophylaxis (mainly azole drugs, but also intravenous amphotericin B). Among patients with solid tumors, only neutropenia was significantly associated with non-albicans candidemia.[15] The trend toward the emergence of non-albicans strains also has been confirmed in a recent study at the M.D. Anderson Cancer Center in Houston, Texas, USA.[16] At least in part, the emergence of non-albicans strains might be correlated with the widespread and prolonged use of antifungal prophylaxis, which, while successfully knocking out sensitive organisms, has allowed other pathogens or more or less resistant strains to emerge. However, the situation is probably more complicated than that, since the epidemiologic impact of fluconazole has been noted mostly at single centers, but not confirmed either in prospective multicenter trials or in other single centers observations (E. Castagnola. Personal communication).[19–21] Therefore, the shift in the etiology of *Candida* infections is probably multifactorial in origin.[22]

The rate of *Aspergillus* infection varies among institutions as a result of patient selection and differences in therapeutic regimens as well as the presence or absence of contaminated ventilation systems or hospital construction work.[2,23] In general, invasive *Aspergillus* infections are on the increase in patients treated for acute leukemia or undergoing BMT, with an incidence as high as 25% in some allogeneic BMT populations, such as those receiving BMT from mismatched relatives or from matched unrelated donors.[24] The study in Germany gave more insight into this problem and confirmed that there is a trend toward a decreasing incidence of *Candida* infection and an increasing incidence of infections due to filamentous fungi among immunocompromised patients.[8] The incidence of invasive infections with previously uncommon fungal pathogens, such as *Fusarium*, *Trichosporon, Alternaria*, and species belonging to Zygomycetes (e.g., *Rhizopus*, *Cunninghamella*, and *Absidia* spp), is clearly increasing, especially in patients with profound and prolonged neutropenia.[2,5,8,10,25] In a study performed in a single American hospital,[9] investigators reported non-*Candida* fungal infections occurring in 11%, 70% of which were *Aspergillus* infections, but no fewer than 16 other species were identified (Table 4). However, these findings might just be representative of local situations and cannot necessarily be extrapolated

Table 4. Non-*Candida* Pathogens among BMT Patients with Disseminated Fungal Infection or Fungemia

Fungal Isolate	*Minor Skin & Soft Tissue (n = 7)*	*Single Organ or Single Site (n = 61)*	*Disseminated Infection (n = 58)*	*Isolated Fungemia (n = 12)*	*Total n = 70 (%)*
Acremonium	–	–	–	3	3 (2)
Alternaria	–	6	–	–	6 (4)
Aspergillus	5	49	43	–	97 (70)
Chrysosporium	–	–	1	–	1 (1)
Curvularia	–	1	–	–	1 (1)
Fusarium	–	2	7	1	10 (7)
Hansenula	–	–	–	1	1 (1)
Histoplasma	–	–	3	–	3 (2)
Malassezia	–	–	–	1	1 (1)
Mucor	–	1	2	–	3 (2)
Penicillium	–	–	–	2	2 (1)
Phialophora	–	1	–	–	1 (1)
Phoma	1	–	–	–	1 (1)
Rhodotorula	–	–	–	1	1 (1)
Saccharomyces	–	1	–	1	2 (1)
Scopulariopsis	1	–	1	–	2 (1)
Trichosporon	–	–	1	2	3 (2)

(From Morrison et al.[9])

to other hospitals. Invasive trichosporosis, fusariosis, and mucormycosis all are associated with a poor prognosis and high mortality rates.

Resistance in *Candida* Species

The concept of drug resistance as applied to antifungal drugs is not clear. Indeed, drug resistance can be considered either as clinical failure or as a drug minimum inhibitory concentration (MIC) that is higher than the serum concentration readily obtainable in vivo with the usual dosage of a given drug. Unfortunately, therapeutic failures and successes can be obtained with pathogens that are in vitro-resistant or sensitive (i.e., regardless of the MIC for the pathogen). The clinical scenario that can be envisaged includes (1) the development of resistance during therapy in an isolate that was initially sensitive to a given drug, (2) the selection among a fungal population of a strain or species that is intrinsically resistant to a given drug, or (3) the acquisition de novo of a pathogen that is intrinsically resistant.[26] Simply to identify resistance with clinical failure can be misleading. For example, in a recent study of fluconazole in the management of candidemia in immunocompromised patients, catheter change was found to be a crucial factor for response to treatment. In these cases, failure showed little association with MICs of fluconazole.[27,28] Despite these limitations, it is clear that resistance to azole drugs (and especially to fluconazole, the most widely used antifungal drug in the past 6 years) can occur and is probably increasing.[29-33] However, the development of fluconazole resistance has been uncommon in short-term therapy, such as that administered to cancer patients,[34] whereas development of resistance during therapy in strains that were formerly susceptible has been well described in patients with acquired immunodeficiency syndrome (AIDS) receiving multiple and prolonged courses of low-dose fluconazole for the treatment of oropharyngeal candidiasis.[35] The second type of resistance (i.e., intrinsic resistance) to fluconazole is common in *C. krusei*, with a much higher in vitro MIC compared to most *C. albicans* isolates.[17] *Candida glabrata* infections also tend to require much higher doses of fluconazole for their successful management, to the extent that some strains should probably be considered intrinsically resistant.[18] If these pathogens are present in a mixed population of *Candida* strains, they could be selected by fluconazole use. As recently pointed out by Rex et al,[26] it appears that a MIC of fluconazole (as evaluated by the National Committee for Clinical Standards [NCCLS] methodology) around 16 μg/mL is predictive of a poor response to a dosage of fluconazole of 100 mg per day, and that a MIC higher than 64 μg/mL predicts a poor response to dosages as high as 400 to 800 mg per day. Often, strains resistant to fluconazole also are resistant to other azoles.[29] In patients with serious *Candida* infections, combination therapy with amphotericin B and flucytosine may be synergistic, but carries a relatively increased risk of flucytosine-related toxicity.[36] Although amphotericin B remains the antifungal agent with the broadest spectrum of action available, laboratory studies have identified amphotericin B-resistant strains of *C. albicans*, *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. lusitaniae*, and *C. neoformans*.[29,32,37-40] Furthermore, the duration of prior amphotericin B therapy has been shown to be directly correlated to the minimum lethal concentration of amphotericin B against *Candida* isolates occurring during breakthrough candidemia.[13]

Resistance in *Aspergillus* Species

Aspergillus spp are intrinsically resistant to fluconazole. In contrast, many isolates show in vitro susceptibility to itraconazole. However, bioavailability of the oral form of itraconazole varies among individuals and also may be reduced as a result of damage to the intestinal epithelium caused by intensive chemotherapy.[41] In theory, plasma itraconazole levels should be closely monitored to ensure that appropriate MICs are achieved. Clinical experience indicates that amphotericin B generally is active against *Aspergillus* spp. In vitro studies have identified strains of *A. nidulans*, *A. flavus*, and *A. conicus* that are resistant to amphotericin B, but there is no firm evidence to date that in vitro susceptibility is related to the clinical outcome in aspergillosis.[38] The problem is more likely to be inadequate dosage because of toxicity problems, particularly nephrotoxicity, and severity of the underlying immunosuppression. Flucytosine is inactive against filamentous fungi like *Aspergillus* spp, although it is sometimes recommended in combination with amphotericin B.[36]

Resistance in Other Pathogenic Fungi

Most of the more unusual fungal pathogens referred to above are resistant to azole therapy but may respond to treatment with amphotericin B. However, both *Trichosporon* spp and *Fusarium* spp have been reported to have intrinsic resistance to amphotericin B.[30,38] Many isolates of *Pseudallescheria boydii* and *Trichosporon beigelii* are resistant to amphotericin B, with an in vitro MIC well over 2 mg/L,[25] and it has been suggested that infections with these organisms are best treated with alternative antifungal agents.[29]

MANAGEMENT OF INVASIVE FUNGAL INFECTION

Fluconazole

Fluconazole is a triazole antifungal drug that can be administered once a day either orally or intravenously. Dosages commonly used are 6 to 12 mg/kg per day in children and 400 to 1200 mg per day in adults. Dosages of 19 mg/kg per day in children and 1600 mg per day in

adults have been tolerated. The drug, which diffuses readily in tissues, is eliminated unmodified by the renal route. The spectrum of action includes many strains of *Candida* (with the exception of *C. kruzei* and *C. glabrata*), *Cryptococcus* spp and *T. beigelii*. Unfortunately, fluconazole is not active against filamentous fungi, such as *Aspergillus*. At therapeutic doses, the most frequently reported side effect is hepatotoxicity, which usually disappears at the end of treatment.[3,6] A large comparative clinical trial in non-neutropenic immunocompromised patients showed that fluconazole was as effective as amphotericin B deoxycholate in the treatment of candidemia.[27] Since, in these patients, candidemia is frequently correlated with indwelling catheter colonization, catheter removal is usually considered mandatory.[42]

Itraconazole

Itraconazole is another triazole antifungal drug that can be administered once a day, although only by the oral route. The dosage is 7 mg/kg per day in children and 400 mg per day in adults. Less clinical experience is available for the use of itraconazole at higher doses, although the drug is likely to be well tolerated. There is no intravenous formulation of itraconazole currently available. Absorption by the oral route is erratic and the drug needs to be administered with meals (which is nearly impossible in patients with severe stomatitis, who are unable to swallow any food). A potentially effective, although empirical way of using itraconazole is in sequential therapy, in patients with aspergillosis who have completed an adequate course of amphotericin B (either deoxycholate or lipid-based) and who are able to swallow food and medication. A new formulation of itraconazole associated with cyclodextrine seems to be associated with improved bioavailability and could be useful for the therapy of documented fungal infections in patients able to swallow medications.[3,6]

Amphotericin B Deoxycholate

Although the antifungal activity of amphotericin B is probably concentration-dependent,[43] relation between serum and tissue concentrations, on the one hand, and clinical efficacy and toxicity, on the other, are unclear. Nevertheless, in the clinical setting, amphotericin B remains the drug with the broadest antifungal activity and the lowest risk of development of secondary resistance. Amphotericin B is not absorbed by the oral route and must be administered intravenously to achieve therapeutic blood levels. Orally, it exerts a topical activity that can be important for reducing intestinal colonization and for treating oropharyngeal and gastrointestinal candidiasis. Intravenously, the most appropriate dose of amphotericin B is not established. It is usually administered once a day at dosages of 0.5 to 1.5 mg/kg per day (depending on the pathogen involved and the clinical circumstances) in 5% dextrose in water, in an infusion lasting from 1 to 6 hours (most often 4 hours). Classic teaching suggests that the dosage should be increased slowly, by 0.1 mg/kg daily, but in case of severe infections or in high-risk patients, full dosages must be administered from the first or second day of treatment. In general, amphotericin B should be administered through a central venous access. If such a device is not available, heparin (1000 U) should be added to the solution, to reduce the risk of phlebitis. More than the early toxic reactions (that are rarely severe enough to warrant treatment discontinuation, but that can often limit the daily amount of drug that can be administered), the major drawback of amphotericin B therapy is its renal toxicity. Although this is manageable to some extent by the use of prior fluid and salt loading, it still remains a serious problem. In patients who are already receiving other nephrotoxic agents, such as cyclosporine, the risk is greatly increased and can create a real clinical dilemma: to reduce the immunosuppressive treatment, thus increasing the risk of GVHD, or to reduce the dose, thus increasing the risk of treatment failure? In documented fungal infections with no alternative to amphotericin B, lipid formulations of amphotericin B may help to resolve this dilemma.

Lipid Formulations of Amphotericin B

When dealing with the lipid formulations of amphotericin B, the main problems are (1) the scarcity of pharmacokinetic data; (2) the small number of comparative clinical trials with amphotericin B deoxycholate, especially in documented infections; (3) the absolute absence of comparative studies between each of the lipid formulations; and (4) the fact that, at the time of this writing, some studies have been published in abstract form, which means that little information about the statistical methodology is available and the results are often preliminary. Owing to the shortage of data, there is the risk that the fight for the market share will depend largely on which product is the first to the market and on which product's marketing campaign is the most successful in manipulating physicians' preferences.[44] While waiting for reliable studies, physicians must base their decisions about which would be the best compound in each individual patient with each type of infection more on experimental animal models than on data from randomized, controlled trials in humans.

As recently reviewed,[45] three different lipid formulations of amphotericin B presently are available on the market in most European countries and in the United States: liposomal amphotericin B (LAMB), amphotericin B colloidal dispersion (ABCD), and amphotericin B lipid complex (ABLC). These vary considerably in terms of their structure and bioavailability compared to deoxycholate amphotericin B (DAMB) (Table 5). Their most important feature is that they are less nephrotoxic and

Table 5. Structure and Pharmacokinetics of Three Lipid Formulations of Amphotericin B

Lipid Formulation	*Lipid Configuration*	*Size (nm)*	*Lipids*	*Mean C_{max} in µg/mL (dose)**
Abelcet® (amphotericin B lipid complex)	Ribbon-like	1,600–11,000	DMPC, DMPG	Decreased 0.27 (1.0 mg/kg) 1.10 (2.5 mg/kg)
Amphocil/Amphotec® (amphotericin B colloidal dispersion)	Disk-like	120–140	Cholesteryl sulphate	Decreased 0.84 (0.5 mg/kg) 2.19 (1.0 mg/kg) 2.53 (1.5 mg/kg)
AmBisome® (liposomal amphotericin B)	Small unilamellar vesicle (liposome)	80	Hydrogenated soy PC, DSPG	Increased 7.30 (1.0 mg/kg) 17.20 (2.5 mg/kg) 57.60 (5.0 mg/kg)

Abelcet®, The Liposome Company, Princeton, New Jersey; Amphotec, Sequus Pharmaceuticals, Inc., Menlo Park, California; AmBisome, Fujisawa Healthcare Inc., Deerfield, Illinois, and NeXstar Pharmaceuticals, Inc., Boulder, Colorado.
Decreased or increased in reference to values for conventional amphotericin B.
DMPC = dimyristoyl phosphatidylcholine; DMPG = dimyristoyl phosphatidylglycerol; PC = phosphatidylcholine; DSPG = distearoyl phosphatidylglycerol.
(Adapted from Hiemenz and Walsh.[50])

safer than DAMB, even in patients with renal failure resulting from previous courses of amphotericin B or other nephrotoxic drugs. However, this might not be true for infusion-related events. Indeed, in a recent randomized study of empirical antifungal therapy, these side effects were more common with ABCD than with DAMB.[46] It should be noted that what is known about the pharmacokinetics of the lipid compounds of amphotericin B is based on measurements of the total amount of drug, with no estimate of whether the drug is free or bound.[47]

Pharmacokinetics and Tolerability

All lipid compounds are able to concentrate in the reticuloendothelial system, but present different pharmacokinetic profiles.[47-50] Amphotericin B lipid complex has a short plasma half-life and seems to achieve the highest concentrations in the liver, spleen, and lungs, with lower levels achieved in plasma. Amphotericin B colloidal dispersion also has a short half-life and is concentrated in the liver, whereas LAMB is concentrated in the liver, spleen, and at lower concentrations, lungs. Moreover, LAMB shows a rate of uptake by the reticuloendothelial system that is much slower than that by the other compounds, which provides a reason for its longer half-life and higher blood levels. Some data seem to suggest the existence of a correlation between the improved pharmacokinetics of these compounds and their clinical effectiveness. Indeed, in an animal model, LAMB recently has been shown to achieve cerebral concentrations that are significantly higher than those obtained with DAMB or the other lipid formulations,[51] and surprisingly, a correlation between tissue concentrations and efficacy has been observed with an in vivo model of murine cryptococcosis.[52] All three compounds produce low kidney concentrations of drug, which is probably one of the reasons explaining their reduced renal toxicity. In all but one of the experimental and clinical studies that have been performed,[46] lipid compounds have proved to be less toxic and to have a maximum tolerated dose that is higher than that of DAMB.[53-59] In an American multicenter, open-label, emergency-use protocol,[59] ABLC (administered at a median dose of 4.9 mg/kg/d) was found to be well tolerated overall. Although 9% of the patients had treatment discontinued because of adverse events, there was a significant fall in serum creatinine levels during therapy ($P = 0.03$).[59] Among patients with prior amphotericin B-induced nephrotoxicity or renal dysfunction, the decrease in serum creatinine was particularly pronounced ($P = 0.001$). Furthermore, the subgroup of patients with baseline serum creatinine levels of 2.5 mg/dL showed the most significant decrease of all, from the first week through the sixth week of therapy ($P < 0.0001$). Studies using LAMB indicate that it is well tolerated, even in patients who have already experienced adverse effects on DAMB.[55,56] For example, among 116 neutropenic patients who could not tolerate or did not respond to DAMB, adverse effects during LAMB treatment were infrequent, and there was no significant impact on renal function. Five patients experienced acute reactions, 23 had reversible hepatic dysfunction, and 17 had hypernatremia.[57] Similar tolerability has been shown for ABCD in a trial involving 168 patients with documented or presumed invasive mycosis in whom prior DAMB had proved ineffective or toxic.[58] Even though the dose was increased to as high as 6 mg/kg per day in some patients and the mean cumulative dose was 4 mg/kg per day, serum creatinine values remained unchanged from baseline to the end of the study, with a mean fall of 0.02 mg/dL. In general, the three lipid compounds seem to be equivalent in

Table 6. Response to Amphotericin B Lipid Complex According to Type of Infection in the Open-Label Emergency-Release Protocol

Type of Infection	*Clinical Response (%)*
Candidiasis	65/91 (71)
Aspergillosis	55/130 (42)
Zygomycosis	17/24 (71)
Fusariosis	9/11 (82)

(From Walsh et al.[59])

Table 7. Response to Treatment in Patients with Invasive Candidiasis: Results of a Prospective Randomized Trial of Amphotericin B Lipid Complex versus Amphotericin B

Response to Treatment	*ABLC*	*Amphotericin B*	*P-Value*
Overall	81/124 (65%)	43/70 (61%)	0.642
According to underlying condition			
Hematologic malignancy	14/28 (50%)	2/12 (17%)	0.079
Solid tumor	24/32 (75%)	17/25 (68%)	0.570
Major surgery	16/21 (76%)	7/10 (70%)	1.000
Other	27/43 (63%)	17/23 (74%)	0.421

ABLC = amphotericin B lipid complex.
(From Anaissie et al.[62])

terms of renal toxicity. Infusion-related toxicity also may be a problem with the lipid compounds. Although there are no comparative data, the clinical experience suggests that LAMB and ABLC are well tolerated (with some possible advantage for LAMB over ABLC).[60] Amphotericin B colloidal dispersion seems to have the same or even more immediate adverse effects than DAMB,[46] and should probably be given with premedication.

Efficacy

Several noncomparative studies have been carried out to assess the benefits of administering lipid formulations of amphotericin B to patients with proven refractory mycosis or who were intolerant to previous antifungal therapy, most of which consisted of DAMB.

Candidiasis. Results of the American emergency-use protocol with ABLC showed a complete or partial response rate of 71% among the evaluable patients with disseminated candidiasis (Table 6).[59] A separate analysis for the BMT patients in the study has been performed.[61] Among the 59 such patients evaluable for response to ABLC, 20 had proven candidiasis, 70% of whom responded clinically to therapy. A prospective, randomized, multicenter trial also has been carried out to compare ABLC (5 mg/kg/d) with DAMB (0.6–1 mg/kg/d) for the treatment of invasive candidiasis.[62] In this study, around two thirds of patients in each treatment group responded (Table 7). Although the frequency of adverse events was similar in the two groups, patients receiving ABLC developed less nephrotoxicity than those receiving amphotericin B. Pediatric patients also appear to respond well to ABLC, as shown in a small study carried out at the National Cancer Institute in Bethesda, Maryland, USA.[63] In this study, six children with hepatosplenic candidiasis were treated with ABLC at a dose of 2.5 mg/kg per day. All five patients who were evaluable responded to ABLC, with resolution of lesions as determined by computed tomography and magnetic resonance imaging. In a study in the United Kingdom, 49 adult patients with hematologic malignancies were treated with ABLC 5 mg/kg per day for presumed or proven fungal infection, following failure of previous antifungal therapy or renal dysfunction.[64] The overall response rate was 64% among 39 evaluable empirical courses of ABLC and 71% among the 14 courses given for proven infection, including complete responses in all five patients with confirmed *Candida* infections. In an open-label, compassionate-use trial of ABCD in patients who had failed to respond to DAMB or who had renal insufficiency, 19 (58%) of 33 evaluable patients with candidiasis responded to ABCD at a dose of 3 mg/kg per day.[58]

Aspergillosis. Response rates of up to 77% have been achieved in various studies in patients with invasive aspergillosis who were treated with lipid formulations of amphotericin B (Table 8).[22,57–59,61–67] In the American open-label study of ABLC, there was a clinical response rate of 42% overall (see Table 6).[59] In a study in which LAMB was given to 116 neutropenic patients for 133 episodes of suspected or confirmed fungal infection, there was an overall response rate of 61%. Among the 17 patients with proven aspergillosis in this study, 13 (77%) responded to LAMB even though 11 of them had failed to respond to DAMB.[57] In the open-label, compassionate-use protocol with ABCD, clinical responses were seen in 11 (34%) of 32 aspergillosis patients who were refractory or intolerant to DAMB.[58] In another study, a group of 82 patients with proven or probable aspergillosis treated with ABCD was compared with an historic control group of 261 patients treated with DAMB.[22] The

Table 8. Clinical Response to Various Lipid-Based Forms of Amphotericin B in Patients with Invasive Aspergillosis Refractory or Intolerant to Conventional Amphotericin B

Lipid-Based Form of Amphotericin B	*Number of Patients*	*Response* (%)*	*Reference*
SUVL-AmBisome	17	13 (77)	Mills et al[57]
SUVL-AmBisome	32	21 (66)	Ringden et al[66]
SUVL-AmBisome	5	3 (60)	Chopra et al[67]
ABCD	32	11 (34)	Oppenheim et al[58]
ABCD	82	40 (49)	White et al[22]
ABLC	133†	63 (47)	Walsh et al[59]
ABLC	16†	11 (69)	Lister[65]

*Success or improvement; †patients who had failed to respond to at least 500 mg cumulative dose of prior conventional amphotericin B. ABCD = amphotericin B colloidal dispersion; ABLC = amphotericin B lipid complex.

response rate was significantly higher with ABCD compared to DAMB (49% and 23%, respectively; $P < 0.001$), and patients treated with the lipid preparation also experienced significantly less nephrotoxicity (8% vs. 43%; $P < 0.001$). There is a problem in the evaluation of these studies. The high variability in the diagnostic criteria of aspergillosis could have introduced a bias in the definition of success or failure in the different trials, thus influencing the "success" rates and providing obvious difficulties in the interpretation of the "real" efficacy of the treatment, even when using a pragmatic criterium, such as survival.

Fusariosis. The mortality rate among patients with fusariosis treated with DAMB remains high. Within the American open-label protocol using ABLC, however, 9 (82%) of 11 patients treated achieved a clinical response (see Table 6).[59] This is a promising result, that needs to be confirmed in larger populations. Indeed, survival from disseminated fusariosis seems to be correlated to bone marrow recovery rather than to any kind of antifungal therapy.

Other Infections. In the American open-label protocol with ABLC, there were high clinical response rates among patients with cryptococcosis, zygomycosis, or other fungal infection (see Tables 6 and 7).[56,61] Only a few patients with mucormycosis have been treated with lipid-based forms of amphotericin B, and most of these treatments have been successful,[65] although again it should be remembered that much larger patient numbers are required before definitive conclusions can be drawn.

Empirical Antifungal Therapy

The use of empirical antifungal therapy in persistently febrile granulocytopenic cancer patients, including those receiving BMT, is a popular procedure, even if validated by an observational study and by only one randomized clinical trial performed in a small patient population.[34,68] Deoxycholate amphotericin B is considered the drug of choice for this indication, even if other antifungal drugs, such as fluconazole, might be effective in selected cases.[14,69] Recently, two randomized studies demonstrated that LAMB at 1 mg/kg per day was as effective as DAMB for this indication.[70,71] In the study by Walsh and coworkers,[71] 687 persistently febrile and neutropenic patients received either LAMB or DAMB according to a double-blind, randomized design. The two groups of patients had similar response rates, in terms of survival and rate of defervescence. Patients receiving DAMB experienced a higher rate of infusion-related fevers (44% vs. 17%), episodes of chills and rigors (54% vs. 18%), cardiorespiratory events (46% vs. 13%) and nephrotoxicity (34% vs. 19%). The authors also reported a higher incidence of breakthrough fungal infections in patients receiving DAMB.

CONCLUSIONS

In terms of tolerance, the lipid-based compounds are better tolerated than DAMB, especially because of their reduced renal toxicity. In terms of efficacy, data suggest possible equivalence, although few randomized clinical trials have been performed. The relative merits of the three formulations in terms of comparative efficacy and toxicity are still unknown, since no comparative trial is available. Unfortunately, the acquisition cost of the lipid compounds is far higher than that of DAMB, both because of the intrinsic cost of the drugs and because of the much higher dose required. Costs based on the British National Formulary of the available packages of lipid-based amphotericin B compounds in the United Kingdom per 100 mg are approximately US$136.7 for ABLC, US$464 for LAMB, and US$318.4 for ABCD.[72] According to the 58th Edition of the Italian Directory of Drugs and Manufacturers,[73] the costs in US$for 100 mg of ABLC, LAMB, and ABCD (including the 50% discount on the official cost that drug companies use to apply when selling drugs to public institutions) are about US$128, US$358, and US$296 (dollar rate of July 23, 1998), thus slightly different from the prices in the United Kingdom. The administration schedules approved for the three lipidic compounds are different: ABLC is approved at 5 mg/kg per day, SUVL-AmB is approved at 3 mg/kg per day, and ABCD is approved at 4 mg/kg per day. This might introduce further differences in terms of cost. However, it is unclear why the three compounds should be used at different dosages. Indeed, animal models have shown that the three compounds are equipotent on a per milligram basis and probably 5 mg/kg per day is the most reasonable dosage, at least in documented aspergillosis.[42]

In light of these considerations and waiting for more information about the relative merits of the lipid compounds (especially among themselves), we believe that the lipid formulations of amphotericin B must be considered as an alternative in selected patients with a documented fungal infection that can only be treated with amphotericin B. These include patients whose renal function is primarily or secondarily (after DAMB therapy) severely compromised and those with untreatable immediate side effects (e.g., bronchospasm). At the time of writing, the choice of the lipid-based formulation cannot be based on data from comparative clinical trials, but only on the ratio between dosage and cost and, perhaps, on data coming from animal models. Further randomized studies are needed to determine whether administration of these new agents will improve outcome, and to determine the optimal dosage in terms of maximal efficacy with minimal toxicity and minimal costs, in both adults and children. Moreover, a better knowledge of the different human pharmacokinetic properties of the three lipid-based compounds of amphotericin B might allow physicians to choose the appropriate compound according to the localization of the infection.

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