Liposomal amphotericin B: what is its role in 2008?

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ABSTRACT

Although our antifungal armamentarium has been enlarged recently with new azoles (voriconazole and posaconazole) and echinocandins (caspofungin, micafungin, anidulafungin), the polyenes still have an important role in antifungal strategies because of their extended antifungal spectrum and rarity of mycological resistance. The use of conventional amphotericin B deoxycholate is limited by substantial toxicity that is either infusion-related or associated with renal failure. Its lipid derivatives, particularly liposomal amphotericin B (LAmB), are less nephrotoxic while maintaining a broad antifungal spectrum. LAmB is active against most Candida spp., including Candida glabrata and Candida parapsilosis, and against more resistant, emerging yeasts species such as Rhodotorula spp., Geotrichum spp. and Trichosporon spp.. LAmB is also active against Cryptococcus spp. and all dimorphic fungi such as Histoplasma, Blastomyces, Coccidioidomyces, and Paracoccidioidomyces. The antifungal spectrum of LAmB is particularly interesting with regard to filamentous fungi, with marked activity against Aspergillus spp. and agents of zygomycosis. The latter might emerge during long-term treatment with voriconazole or an echinocandin, as these organisms are resistant to these drugs. We review here the role of LAmB in the current antifungal management strategy, which is based on results obtained in prospective trials. LAmB can be retained as first-line treatment for human immunodeficiency virus (HIV)-positive patients with disseminated histoplasmosis and cryptococcosis, even in the setting of renal impairment or concomitant administration of potentially nephrotoxic drugs. In addition, there is sufficient evidence that the drug should be a major consideration for the empirical treatment of persistent febrile neutropenia or as an alternative to for patients with invasive aspergillosis, for those at risk of renal impairment, major drug-drug interaction or liver insufficiency, particularly in the situation of an establishedazole intolerance. The primary licensed indication for LAmB is empirical treatment. When zygomycosis is suspected or has been documented, high doses of LAmB should be prescribed. Finally, LAmB may also be considered as a therapeutic option for the management of candidaemia and remains a cornerstone for the treatment of some visceral localisations during systemic candidosis.

Keywords Liposomal amphotericin B, review

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INTRODUCTION

Although our antifungal armamentarium has been expanded recently with new azoles (voriconazole and posaconazole) and echinocandins (caspofungin, micafungin, anidulafungin), polyenes still have an important role in antifungal management strategies because of their broad antifungal spectrum and rarity of resistance. The use of conventional amphotericin B deoxycholate (AmBD) is limited by substantial toxicity that is either infusion-related or associated with renal failure. Its lipid derivatives, particularly liposomal amphotericin B (LAmB), are less nephrotoxic while maintaining the broad antifungal spectrum. LAmB is active against most Candida spp., including Candida glabrata, which can be less susceptible...
or resistant to fluconazole, and Candida parapsilosis, which appears to be intrinsically less susceptible to the echinocandins. Some emerging yeast species demonstrate greater resistance: Rhodotorula is frequently resistant to fluconazole and voriconazole [1], and Geotrichum is frequently resistant to fluconazole and voriconazole [1]. Kullberg et al. compared voriconazole with AmBD for the treatment of candidaemia in non-neutropenic adults and they also found therapy with AmBD to be more toxic than a voriconazole-based regimen (overall rate of adverse events being 51% vs. 36%) [7]. Such observations point to the conclusion that not insufficient activity, but rather major immediate and/or renal toxicity, constitutes the major limiting factor of AmBD in the management of candidosis.

The efficacy of LAmB was first studied in invasive candidosis in 1991. Twenty-five patients with heterogeneous underlying diseases were treated with LAmB 0.5–5 mg/kg/day as second-line treatment after intolerance of or failure with AmBD; 76% of patients were finally cured [8]. LAmB was further studied in 44 neonates and preterm infants with invasive candidosis, and a 73% response rate was achieved [9]. LAmB was also evaluated in the treatment of systemic candidosis among very low birth weight infants: 24 infants were treated with 2.5–7 mg/kg/day LAmB, and an 83% response rate was achieved at the end of treatment [10]. In another small, non-randomised study, LAmB was compared with AmBD in premature infants with candidaemia. Thirty-four infants with normal renal function were treated with AmBD at a dose of 1 mg/kg/day for at least 14 days; six with altered renal function were given 5 mg/kg/day LAmB, and another 16 with altered renal function received 3 mg/kg/day amphoterin B colloidal dispersion (ABCD). Clearance of fungaemia was achieved in 68% of patients treated with AmBD, as compared to 83% among patients on LAmB and 57% on ABCD [11]. LAmB thus appeared to be at least as efficacious as AmBD in the treatment of candidaemia in neonates and infants.

In a recently published randomised, double-blind non-inferiority trial, 3 mg/kg/day LAmB was compared with 100 mg/day micafungin as first-line treatment of candidaemia and invasive candidosis. Antifungal therapy was given for at least 14 days to 537 neutropenic and non-neutropenic patients [12]. The success rate for both micafungin and LAmB was 90%, and this striking similarity was independent of the Candida spp.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Treatment groups</th>
<th>Patient number</th>
<th>Duration of treatment</th>
<th>Response at end of therapy</th>
<th>Breakthrough fungal infection</th>
<th>Survival</th>
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<tbody>
<tr>
<td>Candidiasis</td>
<td>[8]</td>
<td>IC, second-line treatment</td>
<td>MC</td>
<td>LAmB 0.5–5 mg/kg/day</td>
<td>25</td>
<td>18 days</td>
<td>76% cured</td>
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<tr>
<td></td>
<td>[9]</td>
<td>IC in neonates and preterms, first-line treatment</td>
<td>SC</td>
<td>LAmB 1–5 mg/kg/day</td>
<td>44</td>
<td>22 days</td>
<td>73%</td>
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<td></td>
<td>[10]</td>
<td>IC in very low birth weight infants, first- or second-line treatment</td>
<td>MC</td>
<td>LAmB 25–7 mg/kg/day</td>
<td>24</td>
<td>2 weeks</td>
<td>83%</td>
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<td>Candidaemia and IC, first-line treatment</td>
<td>[12]</td>
<td>SC</td>
<td>LAmB 3 mg/kg/day</td>
<td>202</td>
<td>2 weeks</td>
<td>89.6%</td>
<td>_</td>
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<td>[11]</td>
<td>SC</td>
<td>LAmB 5 mg/kg/day</td>
<td>190</td>
<td>2 weeks</td>
<td>89.5%</td>
<td>_</td>
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<td>Aspergillosis</td>
<td>[8]</td>
<td>Proven IA, second-line treatment</td>
<td>MC</td>
<td>1–5 mg/kg/day</td>
<td>28</td>
<td>29 days</td>
<td>32% cured</td>
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<tr>
<td></td>
<td>[9]</td>
<td>SC</td>
<td>1–5 mg/kg/day</td>
<td>44</td>
<td>2 weeks</td>
<td>64%</td>
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<td></td>
<td>[10]</td>
<td>SC</td>
<td>1–5 mg/kg/day</td>
<td>24</td>
<td>2 weeks</td>
<td>50%</td>
<td>_</td>
</tr>
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<td>[28]</td>
<td>Disseminated in patients with AIDS</td>
<td>MC</td>
<td>LAmB 0.5 mg/kg/day</td>
<td>25</td>
<td>2 weeks</td>
<td>68%</td>
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<tr>
<td>Cryptococcosis</td>
<td>[33,68]</td>
<td>Cryptococcal meningitis and AIDS</td>
<td>MC</td>
<td>LAmB 4 mg/kg/day</td>
<td>32</td>
<td>3 weeks</td>
<td>86%</td>
</tr>
<tr>
<td>Unpublished</td>
<td>Cryptococcal meningitis and AIDS</td>
<td>MC</td>
<td>LAmB 4 mg/kg/day</td>
<td>15</td>
<td>3 weeks</td>
<td>86%</td>
<td>_</td>
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<tr>
<td>Febrile neutropenia</td>
<td>[4949]</td>
<td>Febrile neutropenia</td>
<td>MC</td>
<td>LAmB 3 mg/kg/day</td>
<td>55</td>
<td>2 weeks</td>
<td>88%</td>
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<td>Febrile neutropenia</td>
<td>MC</td>
<td>LAmB 0.5 mg/kg/day</td>
<td>26</td>
<td>3 weeks</td>
<td>84%</td>
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<tr>
<td>IFI prophylaxis</td>
<td>Unpublished</td>
<td>AL</td>
<td>ACST</td>
<td>LAmB 10 mg/kg/day</td>
<td>15</td>
<td>4 weeks</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>[61]</td>
<td>SC</td>
<td>ACST acute GVHD</td>
<td>LAmB 7.5 mg/kg/week</td>
<td>21</td>
<td>8 weeks</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>[62]</td>
<td>AL</td>
<td>ACST children</td>
<td>LAmB 3 mg/kg/day</td>
<td>51</td>
<td>100 days</td>
<td>Dose decrease: 30%</td>
</tr>
<tr>
<td>Visceral leishmaniasis</td>
<td>[65]</td>
<td>VL</td>
<td>ACST</td>
<td>LAmB 4 mg/kg/day, days 1–5, day 10</td>
<td>13</td>
<td>100%</td>
<td>_</td>
</tr>
<tr>
<td></td>
<td>[64]</td>
<td>VL</td>
<td>LAmB 1 mg/kg/day, days 1–4, day 10</td>
<td>24</td>
<td>100%</td>
<td>_</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>[66]</td>
<td>VL</td>
<td>LAmB 5 mg/kg</td>
<td>46</td>
<td>100%</td>
<td>_</td>
<td>91%</td>
</tr>
</tbody>
</table>

MC, multicentre; SC, single centre; R, randomised; DB, double blind; VRZ, voriconazole; LAmB, liposomal amphotericin B; AmBID, amphotericin B deoxycholate; AE, adverse event; IFI, invasive fungal infection; IMI, invasive mycotic infection; IA, invasive aspergillosis; IC, invasive candidiasis; VL, visceral leishmaniasis; AL, acute leukaemia; ASCT, allogeneic stem cell transplant; GVHD, graft vs. host disease; ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; NA, not available; DI, day 1.
involved and the neutropenia status. Survival was similar in both arms of the trial and was 60% at week 12, whereas treatment-related adverse events were seen more frequently in the LAmB group: rigors (0.8% vs. 6.4%), infusion-related reactions (17% vs. 28.8%), and creatinine elevations (10.3% vs. 29.9%); hypokalaemia was also more prevalent in patients receiving LAmB (6.8% vs. 12%).

A study of Wingard and colleagues demonstrated that LAmB is better tolerated than is amphotericin B lipid complex (ABLC), the other widely commercialised amphotericin B lipid formulation in Europe, in relation to both fever (23% vs. 57%) and chills (19% vs. 80%) [13]. Nephrotoxicity was seen more commonly in patients treated with ABLC as compared to LAmB (14% vs. 42% respectively). The authors’ conclusion, highlighting an improved safety profile for LAmB as compared with AmBD, is shared by Ostrosky-Zeichner and colleagues, who argue that LAmB might be used as a better option to treat candidaemia when polyenes are seriously considered as an alternative for fluconazole, i.e., for severe sepsis, and for patients with neutropenia, a history of recent treatment with an azole antifungal and the possibility of fluconazole-resistant Candida spp. [14].

According to the 2004 guidelines published by the Infectious Diseases Society of America (IDSA), fluconazole is recommended for the treatment of candidaemia and disseminated candidiasis as first-line treatment for clinically stable patients who have not recently received azole treatment. For other patients, AmBD and caspofungin are mentioned as preferred treatment options [15]. A dose of 3 mg/kg/day of LAmB is advocated for patients at high risk of being intolerant to AmBD (renal dysfunction or concomitant use of potentially nephrotoxic agents). UK guidelines recommend either fluconazole or AmBD as standard treatment for candidaemia, whereas LAmB is considered to represent a useful alternative [16], whereas French guidelines recommend LAmB for the treatment of candidaemia in cases of renal impairment or administration of at least two concomitant nephrotoxic drugs [17]. Caspofungin can also be used in this context. The 2007 update of the ECIL Guidelines for Antifungal Therapy in Leukemia Patients has given LAmB the highest recommendation (A1), similar to that for caspofungin, where the species had been identified.

Treatment guidelines for meningitis, endocarditis presumably caused by Candida spp. and hepatosplenic candidiasis rely on observational studies. The recommended treatment for meningitis is a combination of AmBD or LAmB with fluconazole. Such a combination has become popular on the basis of the favourable results obtained in cryptococcal meningitis. Endocarditis treatment classically combines heart surgery with either AmBD or LAmB and fluconazole. The recommendations for the initial treatment of hepatosplenic candidiasis are based on AmBD or LAmB, possibly in association with fluconazole for unstable patients, and fluconazole for stable patients [15].

Hence, LAmB still serves as an alternative treatment option for candidaemia in patients with renal impairment or those receiving concomitant nephrotoxic drugs, and in children with candidaemia. For Candida meningitis or endocarditis, an association with fluconazole should be considered.

**LIPOSOMAL AMPHOTERICIN B AND INVASIVE ASPERGILLOSIS (IA)**

Voriconazole has now become the treatment of choice for IA, based on the results of a double-blind multicentre trial that compared voriconazole with AmBD as a first-line treatment for the infection [18]. Voriconazole showed superior efficacy, with response rates at week 12 of 53% vs. 32% and a higher survival rate at the end of treatment of 71% vs. 58% as compared with the group that received AmBD. In addition, among patients who were treated with AmBD as first-line therapy and experienced failure or toxicity, the response rate to second-line antifungal therapy was only 19% [19]. Hence, most experts currently agree that AmBD no longer has a role in the management of IA in immunocompromised hosts.

The first study that evaluated the efficacy of LAmB in the treatment of IA was conducted in 1991 and was in a setting of so-called second-line treatment for patients who failed to respond to or were intolerant of other systemic antifungals. Nine of 28 patients (32%) treated with LAmB, given in doses between 0.5 and 5 mg/kg/day, were cured [8]. Subsequently, LAmB was compared with AmBD as primary therapy for invasive fungal infections (IFIs) in neutropenic patients [20]. Patients in this trial received either
LAmB 5 mg/kg/day or AmBD 1 mg/kg/day for 14 days. Among a total of 53 patients with suspected or documented pulmonary aspergillosis, the response rates were 52% (13/25) and 29% (8/28) in the LAmB and AmBD groups, respectively [20]. In another first-line trial, Ellis and colleagues compared two doses of LAmB, i.e., 1 and 4 mg/kg/day, for the treatment of pulmonary IA in 87 patients, and reported response rates of 64% and 48%, respectively [21]. However, the clinical impact of this study was limited by the small sample size. Under the assumption that higher doses would be more effective, the feasibility of administering very high doses of LAmB for IA has been studied, and a pharmacokinetic analysis of the results revealed that LAmB pharmacokinetics are non-linear and do display a maximal $C_{\text{max}}$ and area under the curve (AUC) at the 10 mg/kg/day dose, which was well-tolerated [22].

The safety and efficacy of LAmB given in a standard dose of 3 mg/kg/day were compared to the effects of a high dose of 10 mg/kg/day for 10 days followed by the standard dose; 95% of the study population suffered from IA, which was localised to the lungs in 90% of cases. The results of this ‘AmBiLoad’ trial were published recently [23]. The response rates at the end of treatment were 46% for those receiving the high loading dose and 50% for those treated with the standard dose. The 10 mg/kg/day dose was associated with a significantly higher rate of hypokalaemia, i.e., 30% vs. 16%, and an increased nephrotoxicity rate of 31% vs. 14%. Therefore, on the basis of this trial, a high-dose LAmB regimen cannot be recommended for first-line treatment of invasive pulmonary aspergillosis. Whether or not higher doses of LAmB might be of benefit in particular cases of IA, such as endocarditis, brain abscesses or bone infections, remains to be determined. Patients with widespread disseminated aspergillosis might well benefit from higher doses of LAmB.

Although comparison of data from two different studies has serious limitations, it is interesting to see that when considering first-line treatment for IA, both the clinical responses for voriconazole (53%) and for LAmB 3 mg/kg/day (50%), and the 3-month survival rates of 71% and 72%, respectively, appear quite similar [18,23]. On the basis of the data available, voriconazole remains the drug of choice for the treatment of IA, but in our opinion the ‘AmBiLoad’ study has validated LAmB at the standard dose of 3 mg/kg/day as a reasonable alternative, at least for patients with a high likelihood of major drug interactions, for patients with liver insufficiency, and for those who are intolerant of azoles [24]. Indeed, the 2008 IDSA Guidelines for aspergillosis recommend that LAmB be used for patients with IA where voriconazole is not appropriate (A1 recommendation).

A recent prospective, randomised study evaluated for the first time the putative efficacy of a combination of two antifungals vs. monotherapy as first-line treatment for IA. In this so-called ‘Combistrat trial’, LAmB at a dose of 10 mg/kg/day was compared with a regimen of LAmB 3 mg/kg/day in combination with caspofungin. Fifteen patients were included in each arm. Response rates at day 14 and week 12 and overall survival rates were similar in both arms of the study, but the response rate at the end of treatment was higher for combination therapy, being 67% vs. 27% for the single agent (Caillot DTA, Herbrecht R et al. Liposomal amphotericin B in combination with caspofungin versus liposomal amphotericin B high dose regimen for the treatment of invasive aspergillosis in immunocompromised patients: randomised pilot study (combistrat trial). Focus Fungal Infect 2006). In the patients who had been treated with high-dose LAmB, more nephrotoxicity (20% vs. 7%) was found, as well as a higher number of infusion-related reactions (20% vs. 0%), whereas there was no difference between both arms in the rates of hypokalaemia. Larger randomised studies are required to explore the real potential of combination therapies. It is of note that echinocandins do not penetrate well into the central nervous system, and this may explain why caspofungin given in combination with ABCD did not enhance the efficacy of the polyene in an immunodeficient mouse model of cerebral aspergillosis [25,26].

**LIPOSOMAL AMPHOTERICIN B AND HISTOPLASMOSIS TREATMENT**

Current treatment recommendations for severe forms of disseminated histoplasmosis, in either human immunodeficiency virus (HIV)-positive or HIV-negative subjects, feature polyenes as first-line therapy instead ofitraconazole. For less...
severe cases, oral itraconazole constitutes an appropriate treatment [25,26]. However, the use of itraconazole is limited by several well-recognised problems such as numerous drug interactions, variable intra- and inter-individual digestive absorption and the lack of an easily available intravenous formulation in Europe.

LAmB 3 mg/kg/day should now be regarded as first-line therapy for induction treatment of disseminated histoplasmosis in AIDS patients. Indeed, LAmB has been evaluated in a multicentre randomised double-blind trial comparing LAmB 3 mg/kg/day (n = 55) with AmBD 0.7 mg/kg/day (n = 26) for 2 weeks in AIDS patients with disseminated histoplasmosis [28]. Induction treatment was followed by 10 weeks of itraconazole consolidation treatment. Patients treated with LAmB had a higher response rate at the end of induction therapy (88% vs. 64%), as well as a lower mortality rate (2% vs. 13%) with fewer infusion-related side-effects (25% vs. 63%) and less nephrotoxicity (9% vs. 37%). Mycological response and response rates at the end of consolidation therapy were similar in both groups [27]. As the number of patients in the study was rather low, the outcome has to be interpreted with due caution. It should be noticed that this study was the first to demonstrate a clear superior activity of LAmB over AmBD in the treatment of invasive mycoses. In addition, LAmB 3 mg/kg/day and itraconazole were studied in a trial that enrolled AIDS patients with a first episode of disseminated histoplasmosis (median CD4 cell count 20/\text{mm}^3; 80% of patients with positive blood culture). Response rates were similar in both groups (86% and 88.5%), but those who were given LAmB showed faster fungal clearance and blood culture sterilisation at week 2 (85% vs. 53%) as compared with patients who received itraconazole. Histoplasma antigen levels also decreased more rapidly under treatment with LAmB (−1.6 U vs. −0.1 U) [28].

LIPOSOMAL AMPHOTERICIN B AND CRYPTOCOCCOSIS TREATMENT

A combination of AmBD 0.7–1 mg/kg/day and flucytosine is generally regarded as the preferred treatment for cryptococcal meningitis in both HIV-positive and HIV-negative patients [29]. When AmBD and flucytosine are used simultaneously, faster fungal clearance of the cerebrospinal fluid (CSF) is seen [29]. This classic finding has been corroborated in a recent prospective study, where it was shown that after 2 weeks of treatment, CSF sterilisation was impaired and delayed in HIV-infected patients with cryptococcal meningitis who did not receive the combination as induction therapy [30]. Furthermore, not giving flucytosine during induction therapy appeared to be associated with a higher subsequent relapse rate [31].

In a randomised trial in a similar category of patients, the efficacy in patients with cryptococcal meningitis of treatment for 3 weeks with AmBD at a dose of 0.7 mg/kg/day (n = 13) was compared with 4 mg/kg/day LAmB (n = 15), followed by a 400 mg/day fluconazole regimen [32]. The preliminary results of this study indicated faster CSF sterilisation in the LAmB group than in the AmBD group, in association with a higher rate of negative CSF cultures at day 7 (40% vs. 8%), day 14 (67% vs. 11%) and day 21 (73% vs. 37%). However, the clinical response rates were similar (86% vs. 80%) in both groups. CSF sterilisation rates were very low, at 67% and 11%, respectively, on day 14.

A still unpublished randomised double-blind trial in 267 AIDS patients with cryptococcal meningitis compared LAmB 3 mg/kg/day with LAmB 6 mg/kg/day or AmBD 0.7 mg/kg/day [34]. Mycological responses were achieved in 64% of patients who were treated with 3 mg/kg/day LAmB, in 54% with 6 mg/kg/day LAmB, and in 54% with AmBD. Thus, the study suggests that LAmB is at least as effective as AmBD in the treatment of cryptococcal meningitis in AIDS patients, while it is better tolerated, as evidenced by a less frequent occurrence of renal failure and immediate infusion-related toxicity in the LAmB group. However, the combination of LAmB with flucytosine has not yet been investigated.

The current IDSA guidelines designate LAmB as being potentially useful in the treatment of cryptococcal meningitis in cases of renal dysfunction [31]. It is our view that LAmB is indicated in the treatment of cryptococcal meningitis and that it should be used, in combination with flucytosine, in cases of pre-existing renal impairment or concomitant use of nephrotoxic agents, as renal toxicity induced by AmBD may facilitate subsequent accumulation of flucytosine, which may lead to serious haematological toxicity.
LIPOSOMAL AMPHOTERICIN B AND ZYGOMYCOSIS TREATMENT

Prospective therapeutic trials on the treatment of zygomycosis have not been reported. However, data in summary form are available, originating from case reports or small retrospective series that used variable and different criteria for evaluation of the response (Table 2). Most of the new antifungals, including echinocandins and voriconazole, are not active against Zygomycetes [33], whereas polyenes and posaconazole display, at least in vitro, activity against organisms belonging to the Zygomycota group [34]. Posaconazole has limited activity against certain of the Zygomycetes. In a murine model of zygomycosis, posaconazole showed partial efficacy against Absidia corymbifera and a dose-dependent response effect in mice infected with Rhizopus microsporus [34]. After its activity against Zygomycetes in vitro and in animals had been established, the clinical potential of posaconazole in patients with zygomycosis was retrospectively evaluated in two studies where the drug was given as second-line therapy in individuals who had been treated with other antifungals that were not tolerated or had an insufficient effect. Response rates of 60% in 91 patients and 79% in 24 patients, respectively, were reported [35,36]. It should be remembered that posaconazole can only be administered orally and carries the risk of drug–drug interactions that are typical for the azole class of antifungal compounds [37]. Moreover, steady-state plasma levels are only obtained after 7–10 days of treatment [38]. Without representative data on first-line treatment, posaconazole should not be used as first-line treatment of zygomycosis. Only when an intravenous formulation becomes available can a clinical trial that compares posaconazole with LAmB be performed, leading to a possible change in the future role of these drugs in the management of zygomycosis.

The options for and limitations of AmBD and LAmB as first-line treatment of zygomycosis have been assessed in several retrospective analyses. The first retrospective series covered the period between 1987 and 2001, comprised 51 patients with haematological malignancies, and showed a 23% response rate among 39 patients treated with AmBD at a dose of 1 mg/kg/day, and a 58% response rate in patients who received LAmB at the standard dose level of 3 mg/kg/day [39]. The second, smaller retrospective series reported a response rate of two of six patients treated with AmBD, while one of two patients treated with LAmB responded [40]. A recent large retrospective survey, which included all cases of zygomycosis that had been described in the literature, reported a 61% survival rate for AmBD as compared with 69% for LAmB [40].

Two other retrospective studies evaluated the efficacy and safety of the alternative lipid formulations of amphotericin B in the setting of second-line treatment of zygomycosis. The series of patients treated with ABLC at a dose of 5 mg/kg/day was characterised by a wide variety of risk-factors and showed a 75% response rate for this drug [41]. ABCD given in doses between 2 and 6 mg/kg/day accomplished an objective response in 60% of cases [42].

In summary, it can be stated that the lipid derivatives of amphotericin B are probably more effective and better tolerated than AmBD in the treatment of zygomycosis. Whether higher dosages of LAmB would be of benefit for this indication remains obscure. Indeed, the AUC of LAmB is maximal at a dose rate of 10 mg/kg/day; at this level, the drug can saturate mononuclear cells and allow a higher accumulation of amphotericin B in the lungs, which are major targets of infection by the agents of zygomycosis [22]. Moreover, high doses of LAmB were able to attain a clinical response in patients who failed to respond to conventional dosages [43,44].

Table 2. Retrospective studies evaluating liposomal amphotericin B during zygomycosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Number</th>
<th>Response</th>
<th>Survival</th>
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<tr>
<td>[40]</td>
<td>First-line treatment</td>
<td>Haematological malignancies</td>
<td>LAmB 3 mg/kg/day</td>
<td>12</td>
<td>58%</td>
<td>20% (month 3)</td>
</tr>
<tr>
<td>[41]</td>
<td>First-line treatment</td>
<td>Haematological malignancies</td>
<td>AmBD 1 mg/kg/day</td>
<td>39</td>
<td>23%</td>
<td>37%</td>
</tr>
<tr>
<td>[68]</td>
<td>First- or second-line treatment</td>
<td>Diverse underlying diseases</td>
<td>LAmB</td>
<td>116</td>
<td>69%</td>
<td>61%</td>
</tr>
</tbody>
</table>

AmBD, amphotericin B colloidal dispersion; LAmB, liposomal amphotericin B
‘Ambiloadd’ trial [23] did not support the possible superiority of 10 mg/kg/day over 3 mg/kg/day LAmB for first-line treatment of invasive filamentous fungal infections, but this trial included only three patients with zygomycoses who received 10 mg/kg/day LAmB. In an attempt to provide an answer to the question of adequate dosing, we have started a prospective national phase II multicentre study (‘Ambizygo’ trial) to evaluate the maximally effective and tolerated dose of LAmB (up to 10 mg/kg/day) as first-line treatment of zygomycosis in adults and children. In our view, LAmB given in high doses represents an effective first-line treatment for zygomycosis.

EMPIRICAL THERAPY IN PATIENTS WITH PERSISTENT FEBRILE NEUTROPENIA

Empirical treatment with AmBD in febrile neutropenic patients became broadly accepted on the basis of the outcome of two randomised trials, and it was believed that such a strategy was able to reduce the frequency of proven invasive fungal infections [45,46]. Pizzo et al. randomised neutropenic patients with persisting unexplained fever despite broad-spectrum antibiotic therapy into three arms: a group in which all antibiotic therapy was terminated; a group that received empirical AmBD as an additional treatment; and a last group that continued antibacterial therapy without any antifungal therapy. Patients who received empirical antifungal therapy had a more favourable clinical course than those in whom antibiotics were continued with respect to resolution of fever (68% vs. 53%) and a lower incidence of IFI (1% vs. 9%) [46]. The second classic trial in an antibiotic-refractory febrile neutropenic population compared the outcome of a group of patients who received AmBD empirically with that of a group who were not given any antifungal. Infections occurred in six of 16 unprotected patients as compared to two of 18 patients who received empirical antifungal treatment [45]. However, both studies have serious limitations, namely: only a small number of patients was included, which did not allow a statistically solid conclusion, and there was no evidence for either an improvement in survival rates or a significant decrease in the incidence of invasive fungal infections. Despite these limitations, empirical antifungal therapy for neutropenic patients with fever that persists despite broad-spectrum antibacterial therapy has become generally accepted. However, with modern diagnostic tools such as testing for the presence of Aspergillus galactomannan antigen, fungal DNA and β-glucan, as well as the utility of high-resolution computed tomography scans, it is possible to diagnose IFI at an earlier stage of development. As a result, a pre-emptive antifungal treatment strategy is a realistic treatment option, particularly among adults, that will figure more prominently in the future [47].

Three major non-inferiority studies have assessed the role of LAmB in the management of persistent fever in neutropenic patients. Initially, LAmB was compared to AmBD in a randomised multicentre trial [48]; 343 patients were treated with 3 mg/kg/day LAmB and 344 patients with 0.6 mg/kg/day AmBD. To be eligible, patients had to be febrile for at least 5 days in spite of adequate antibiotic therapy and neutropenic with a neutrophil count <500/mm³. After enrolment, therapy was continued until resolution of neutropenia. The overall response was evaluated on the basis of a five-point composite score and appeared to be similar in both groups (50% vs. 49%). A sub-analysis revealed that there were fewer breakthrough fungal infections in the LAmB-treated group than in the AmBD group (3% vs. 8%) and strikingly fewer renal toxicity- and infusion-related reactions [48]. In the second multicentre non-inferiority randomised trial, 3 mg/kg/day LAmB was compared to intravenous voriconazole 6 mg/kg twice-daily on the first day, followed by 3 mg/kg twice-daily on subsequent days [49]. Success rates for LAmB and voriconazole (31% vs. 26%), as well as the 7-day survival rate, were similar (94% vs. 92%) for both arms but significantly more breakthrough fungal infections occurred in patients receiving LAmB (5% vs. 2%). The main objective of the trial, i.e., the demonstration of non-inferiority for voriconazole in comparison with LAmB, was not met, and therefore voriconazole failed to qualify as an alternative candidate for the empirical antifungal treatment of neutropenic patients. Finally, a dose of 3 mg/kg/day LAmB was compared to caspofungin at a starting dose of 70 mg on day 1, followed by 50 mg/day in the only
double-blind multicentre non-inferiority randomised trial [50]. Overall success rates, as assessed by composite score, were similar for both groups (34% vs. 34%), with a similar number of breakthrough fungal infections. Caspofungin was better tolerated, was associated with fewer cases of infusion-related toxicity and was less nephrotoxic.

LAmB given for empirical purposes has also been compared to ABLC, the other commonly available lipid formulation of amphotericin B, in a multicentre double-blind randomised trial [13]. Patients with fever and neutropenia received either 3 mg/kg/day LAmB (n = 85), or 5 mg/kg/day LAmB (n = 81), or 5 mg/kg/day ABLC (n = 78). The response rates to the three different drug regimens were similar, namely 42%, 40%, and 33%, respectively. Infusion-related adverse reactions were more frequent when ABLC was given, and amounted to 88%, as compared with 52% and 48% for LAmB, but the differences between the regimens were even more pronounced with respect to nephrotoxicity, as a two-fold increase of creatinine serum level occurred in 14%, 14% and 42% of cases, respectively.

Although LAmB has a broader antifungal spectrum of activity than the other recommended option, caspofungin, caution is required with regard to potential nephrotoxicity, particularly in allogeneic bone marrow transplant recipients. On the other hand, the use of caspofungin has been associated with breakthrough fungal infections caused by rare moulds and yeasts, such as zygomycosis [51], trichosporonosis [52], scedosporinosis [53], Scopulariopsis brevicaulis infection [54], and Aspergillus ustus infection [55]. On the basis of its spectrum of activity and the results obtained in large clinical trials, LAmB has to be counted among the preferred antifungal agents for empirical antifungal treatment in patients with antibacterial-refractory, persisting fever during neutropenia.

LIPOSOMAL AMPHOTERICIN B AS POTENTIAL ANTIFUNGAL PROPHYLAXIS IN HIGH-RISK PATIENTS

Among specific high-risk populations, IFIs may be extremely prevalent and are associated with a high mortality rate. This particularly concerns patients who are treated for acute leukaemia (AL), and allogeneic stem-cell transplant (ASCT) recipients. Over the last 15 years, fluconazole has evolved as the classic antifungal prophylactic drug for the prevention of yeast infections, but this compound does not provide any coverage against mould infections [56]. Although two major recent studies have demonstrated the efficacy of posaconazole prophylaxis in high-risk populations during prolonged neutropenia and graft vs. host disease, the lack of an intravenous formulation and possible drug interaction issues may limit its use [57,58]. For cases where an azole cannot be given, LAmB might offer a reasonable alternative to prevent both yeast and mould infections. To explore the feasibility of this approach, several preliminary studies that evaluated the safety of LamB in a setting of prophylaxis have recently been performed.

An open, prospective multicentre study, the ‘Prophylome trial’, evaluated the tolerance of LAmB given as a weekly infusion at a dose of 10 mg/kg to 15 AL patients for 4 weeks and to eight ASCT recipients for 8 weeks [59]. The AL patients received a mean of three infusions, whereas ASCT recipients only tolerated a mean of 1.5. None of the patients treated for AL required a reduction in dose or withdrawal of the drug, but five of eight ACST recipients required a decrease in dose or a treatment interruption. The mean numbers of adverse events per patient were 2.9 in AL patients and 7.2 in ACST recipients. Obviously, this novel strategy appeared to be better tolerated in AL patients, with transfusion-related reactions in 13% of cases and nephrotoxicity in 20% of cases, than in ASCT recipients, who experienced infusion-related reactions in 37% of cases and nephrotoxicity in 50% of cases. LAmB given at a dose of 7.5 mg/kg/week for prophylactic purposes was also evaluated in another study that included 21 ACST recipients with acute graft vs. host disease requiring corticosteroids 2 mg/kg/day; the investigators classified tolerance as acceptable in 53% of patients who had to stop the treatment because of adverse events [60]. A third study conducted in a paediatric population evaluated the tolerance and efficacy of 3 mg/kg/day LAmB given as prophylaxis over 100 days post-ASCT in 51 children during a hospital construction period. Thirty per cent of
the patients required a decrease of the dose, and in 11% treatment had to be interrupted because of toxicity; 9.7% developed IFIs, four of which were caused by Candida spp. and one by Trichosporon. No invasive mould infections were seen in these children, whereas five patients with a low risk of mould infections who had been nursed in an oncology unit without the protection of a prophylactically administered antifungal developed IA [61].

LAmB is well-tolerated as antifungal prophylaxis in high-risk patients, at least in non-allogeneic bone marrow transplant patients, but the definitive demonstration of its efficacy for this indication is still awaited.

LIPOSOMAL AMPHOTERICIN B AND LEISHMANIASIS

Visceral leishmaniasis (VL) is a major public health concern in some parts of the world, particularly in the Eastern Bihar region of India and in South America. Therapeutic trials in non-immunocompromised patients have mainly been conducted in India. Pentavalent antimony-based drugs have been the classic first-line therapy, but their use is limited by cardiac toxicity, which occurs in 8–17% of patients, and by the development of resistance, which is responsible for a disappointing success rate that presently ranges from 36% to 69% in Bihar [62]. Different schemes for the treatment of VL with LAmB have been studied in HIV-negative patients. The first study compared different regimens of short-course treatment with LAmB in 88 immunocompetent patients. In one study, 13 patients were treated from day 1 to day 5 with 4 mg/kg/day LAmB and showed a 100% cure rate at day 10, when a total dose 24 mg/kg had been given; 42 patients received 3 mg/kg/day for 6 days, with a 98% cure rate at day 10 after a total dose of 18 mg/kg; finally, 32 patients were treated with 3 mg/kg/day from day 1 to day 5, with a 91% cure rate at day 10 and a total dose of 15 mg/kg [63]. On the basis of these results, the authors recommended treating VL with a total dose of LAmB of ≥20 mg/kg, to be given for 5 or more days at a dose rate of 3–4 mg/kg/day [64]. Interestingly, two trials assessed the feasibility of a single high dose of LAmB in HIV-negative patients suffering from VL, and both studies demonstrated a high efficacy in combination with good tolerance of a single dose of LAmB at dose levels of 5 mg/kg/day and 7.5 mg/kg/day, with cure rates of 92% and 96%, respectively [63,65].

The number of studies in HIV-infected patients is more limited. In a first-line therapy study, melamine antimoniate was compared with two ABLC-based regimens at a dose level of 3 mg/kg/day for 5 days and 3 mg/kg/day for 10 days in 57 patients. The cure rates were similar, and amounted to 37%, 33%, and 42%, respectively, but ABLC was less toxic than the antimoniate regimen. The evolution of VL in HIV-infected patients is often complicated by frequent relapses, even when the cellular immunity has been restored [66]. LAmB is recommended as first-line treatment for VL in both HIV positive and HIV-negative patients. Secondary prophylaxis for VL is recommended in HIV-infected patients to reduce relapse rates, even in patients with recent immune reconstitution, but the precise role of LAmB in this context remains to be established.

CONCLUSION

In summary, LAmB can be used as an useful alternative in the treatment of candidaemia in patients with renal impairment or where there is concomitant use of nephrotoxic drugs, as well as for the treatment of Candida meningitis and endocarditis; in the latter cases, a combination with fluconazole appears to be attractive. LAmB is currently the first-line therapy for disseminated histoplasmosis in HIV-positive or HIV-negative patients, and for cryptococcal meningitis treatment in patients with renal impairment. The drug is very useful for the treatment of invasive aspergillosis in cases where there is a risk of potential major drug–drug interactions, and for patients with liver insufficiency or azole intolerance. When zygomycosis is present or likely, a high dose should be administered. Owing to its broad antifungal spectrum, LAmB is perfectly suited for empirical treatment of persisting febrile neutropenia. It is of interest that LAmB tolerance has also been well-demonstrated in paediatric patients, including preterms infants, and the drug is effective against candidaemia in children. In conclusion, based on results of several randomised prospective trials, the LAmB deserves a major place in the 2008 antifungal armamentarium.
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