EDITORIAL

Amphotericin B and invasive aspergillosis – how do the data guide us?

The escalating incidence of invasive aspergillosis (IA) in immunocompromised patients coupled to the staggering overall case fatality ratio in excess of 50% [1, 2] reminds us that our therapeutic outcomes are suboptimal. Conventional amphotericin B (CAB) is toxic, which limits compliance. In an attempt to control severe systemic reactions, patients are exposed to potentially harmful opiates, corticosteroids, dopamine and subtherapeutic antifungal dosing. In a recent study, 30% of 707 patients treated with CAB developed acute renal failure, resulted in a three-fold excess mortality, 8 days extra hospitalisation and an increased adjusted health care cost of 30000 US dollars per patient [3]. Despite the repeated documentation of such facts, hospital purchasing departments think purely in terms of acquisition costs when budgeting for antifungal agents. Yet amphotericin B has been dubbed the emperor of antifungal drugs – an allusion largely founded on its excellent in-vitro activity.

Therefore, in keeping with many contemporary royalties, amphotericin B is changing its habits. The liposomal preparation (LAB, trade name AmBisome) has the lowest incidence of infusion-related adverse events. Nephrotoxicity is reduced dramatically from around 80% to 5%. It makes LAB currently the strongest candidate among the three commercially available lipid formulations of amphotericin B (the other two being ABLC and ABCD). Clinical trials and a Cochrane Review of all the lipid-soluble formulations [4] confirm this opinion.

The contentious issues of initiation and dosing quantitation, efficacy [5] and repeated concerns over economics remain. Debates over the design of clinical trials are well known and rehearsed – heterogeneity of patients, variable case definitions, etc. – and will not be repeated here. A recent systematic review of the literature updating the case fatality rates in IA concluded that the mortality of this condition remained high despite the newer formulations of amphotericin B [2]. That review discarded 172 of 222 papers and even the 50 remaining ones had high heterogeneity. Any benefit of lipid formulations would be lost in the jungle of papers. So we should look more carefully at statements such as ‘our data suggest a trend for lower case-fatality rates with lipid formulations of amphotericin B’ [2].

Controlled animal models provide one perspective for this exercise. There is strong evidence for a substantially superior effect of lipid preparations over CAB; e.g., Allende et al. [6] demonstrated a two-fold increased survival with ABCD 1–5 mg/kg/day, Leenders et al. [7] showed a 2–4-fold decrease in dissemination of Aspergillus with LAB 1–10 mg/kg/day. Open-label salvage studies confirm a parallel human phenomenon in that patients failing treatment with CAB responded to the various lipid preparations [5]. Controlled studies also support the impression of heightened efficacy for LAB over CAB: improved resolution of fever in patients with antibiotic unresponsive neutropenic fever [8], reduction in breakthrough fungal infections [9], and a better response in patients with fungal infections [10]. The human clinical literature is biased towards the larger experience with LAB; controlled data supporting superior clinical performance of ABLC and ABCD over CAB has yet to be demonstrated convincingly. Furthermore, no convincing head-to-head clinical efficacy comparison trials of any of the lipid preparations have yet been performed, but one toxicity study showed substantially and significantly increased safety of LAB over ABLC [11].

What dose to use – a maximum tolerated or a minimum effective? Are these the same? Here animal studies reveal a non-parallelism [6, 7, 12]. Although bigger doses (over a range 1–10 mg/kg/day) of either ABCD or LAB sterilise Aspergillus-infected tissues better, this has not translated into clinically meaningful improved survival figures. For example, in Allende’s model survival was 55–64% for 1 mg and 5 mg of ABCD [6] (and was actually reduced to <30% at 10 mg). This mycologic-survival dissociation phenomenon suggests that factors other than the dosages used impact on survival. The first published prospective randomised clinical efficacy trial of antifungal agents in IA showed no apparent difference in survival when either 1 mg or 4 mg of LAB was used [13]. Heterogeneity of patient characteristics was a characteristic feature of this study, and although both treatment arms were balanced in that regard, the overall analysis could not even detect a trend in favour of the higher dose. However, more patients in a small subgroup with definite IA responded and survived with the higher dose of LAB, suggesting that a better response with a higher dose could be possible. An
alternative explanation for the apparent outcome equivalence is that dosages in excess of 4 mg are needed to optimise response. This alternative explanation has some support from studies in neutropenic mice with candidosis, where survival was increased from 40% with 5 mg to 100% at the maximum tolerated dose of 29 mg [14].

There are other pertinent observations which support both the use of higher doses of LAB and administering LAB at the earliest stage in the clinical evolution of IA. It is generally accepted that both CAB and LAB have concentration-dependent antifungal activity, and this is linked to clinical efficacy [15]. MICs of LAB for several Aspergillus species range up to 2.5 mg/L [16, 17]. Steady-state plasma concentrations indicate that even at a dose of 1 mg, the Cmax is 12.2 mg/L [18]. However, the more relevant pharmacokinetic parameter is likely to be the lung tissue concentration. At 1 mg of LAB that is only 1.8 mg/kg and this measurement was made in healthy tissue [17]. The levels will be lower in infected tissue, and below the MICs. However, at 5 mg the level is 10.3 mg/kg [17]. Superior antymycological activity of LAB at higher doses has already been alluded to earlier in this article. Treatment failure has been linked to the poor tissue penetration of amphoterin C into infected lung tissue. In one study the level of CAB in infected tissue was three times lower (0.2 mg/kg) than in healthy lung tissue, in a patient who died from IA [19]. This strongly suggests that poor tissue penetration may result in treatment failure. Histopathological studies reveal that the IA lesions are lung infarcts secondary to the vascular lesions, producing the central necrotic nodules surrounded by a haemorrhagic peripheral ring. Antifungal drug penetration is compromised in such tissue. These early nodular lesions, visible on CT scanning [20], rapidly progress to larger fungal masses such as the wedge-shaped pleural-based lung infarcts, cavitory masses and abscesses, confounding the problem of effective drug delivery.

Early and serial computed tomography (CT) scanning is a highly effective modality for diagnosing invasive pulmonary aspergillosis in neutropenic patients [20]. Galactomannan determination is becoming another important early diagnostic tool. Early diagnosis is linked to better survival because amphoterin B treatment is started earlier [21], at a time when fungal burden is relatively small. At some variance with IDSA guidelines [22], many clinical mycologists would give treatment at the earliest possible stage of IA with a dose which would provide a concentration at an infected site in excess of the MIC. LAB at a dose of ≥ 5 mg/kg should be capable of meeting this expectation because there would be small chance of dose interruption, no need for test dosing or gradual incremental dose increasing, and assurance that the drug physically homes in on the site of fungal disease [23].

Support for such a strategy will not be found in the large meta-analysis type of reviews. It will come from reports from individual institutions. We recently reviewed our experience in Tawam Hospital, the UAE’s tertiary referral centre for leukaemia, following adoption of a linked policy of early diagnosis and administering modestly high doses of LAB. There were 21 cases of IPA over the last 2 years in patients with chemotherapy-induced neutropenia; 20 of the 21 patients had halo signs. LAB was given at a mean daily dose of 4.4 SD 2.2 mg/kg, starting within 1 week of ARNF, and for a mean cumulative dose of 5.7 g. Attributable mortality from IA was 9.5%. In the two patients who died, the daily dose of LAB was low at 1.5 and 3 mg. These are encouraging findings when compared with current literature figures of responses of 54% and attributable mortalities of at least 19%. This does not prove that LAB resulted per se in a good outcome for the patients. It does suggest that the use of modestly high doses of LAB, given early as first-line treatment, in a setting of an experienced dedicated unit using optimal support measures, are strongly associated with a favourable outcome from IA.

We have to refine our diagnostics and explore ways of maximising options for treatment of IA. Meanwhile, it is hard to dispove the heightened efficacy of the lipid amphoterinics, in particular LAB. Cost is a factor, but there is much to support the contention that, although drug acquisition costs are higher, overall final costs are lower and lives are saved. We should pursue what we believe to be the current best treatment option for our patients.

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References


