Editorial Response: Randomized Trial of Lipid-Based Amphotericin B for Invasive Aspergillosis in Neutropenic Hosts Is an Important Step Forward

Fungal infection is a prominent cause of morbidity and death among patients compromised by neutropenia, especially those with acute leukemia and prolonged, therapy-induced bone marrow aplasia [1–4]. The significant incidence of documented fungal infections, coupled with the high mortality when earliest manifestations go untreated, supports the use of early and aggressive therapy with amphotericin B (AmB) in the management of these cases. Many of these invasive infections are commonly caused by *Aspergillus*, which exhibits significant microbiological and clinical resistance to AmB [4, 5]. At least clinically, this intrinsic resistance can be overcome in part by the delivery of high doses of drug.

Investigators at several centers have demonstrated that prompt detection and institution of aggressive fungicidal therapy with high-dose AmB (1.0–1.25 mg/kg · d) alone or in combination with 5-flucytosine result in enhanced survival in cases of infection caused by filamentous organisms such as *Aspergillus* and *Fusarium* species or non–*Candida albicans* yeasts [1, 3–5]. The impact of this approach is most clearly seen in documented infections caused by filamentous fungi, in which delayed institution of antifungal therapy is associated with a 50% decrease in survival rate, relative to when AmB therapy is instituted empirically before definitive diagnosis, often on the basis of nonspecific clinical findings [1].

Early institution of AmB therapy has yielded gratifying results and has been adopted by many investigators as a practical standard of care for definitive or presumed fungal infections (typified by aspergillosis) in the profoundly neutropenic host. Yet, in retrospect, it is unfortunate that there have been no randomized or controlled studies in this complex clinical setting to demonstrate the superiority of aggressive AmB management over a more traditional and conservative approach to diagnosis and therapy.

One obstacle to early and aggressive AmB therapy has been the knowledge that AmB is not a completely benign drug. Over the years, however, it has become possible to blunt many of the toxicities by maintaining renal perfusion, preventing AmB-induced renal artery spasm, and administering agents aimed at inhibiting inflammatory cytokines. Still, AmB-related renal dysfunction adds a layer of complexity to treating the neutropenic patient who requires multiple antibiotics (many of which are renally excreted) or nephrotoxins such as cyclosporine A. In addition, the constitutional symptoms (fever, rigors) that often accompany AmB administration may confound the patient’s overall clinical picture and, at times, can be severe enough to cause hypotension and bronchospasm.

In this light, the development of lipid formulations of AmB (L-AmB) has been greeted with strong enthusiasm. These preparations are designed to deliver higher concentrations of drug to sites of active infection and, at the same time, to spare the host from the well-documented AmB-related multiorgan toxicities (especially renal dysfunction) [2, 6, 7]. Noncomparative studies involving bone marrow and solid organ transplant recipients substantiate that L-AmB preparations are more tolerable and at least as efficacious as traditional AmB, especially for candidiasis.

When used as antifungal prophylaxis during bone marrow transplantation, L-AmB can suppress fungal colonization and reduce the incidence of both presumed and documented fungal infections. Documentation of the efficacy of L-AmB against fusarium infection in the setting of leukemia-associated marrow failure suggests the potential for enhanced efficacy against other traditionally AmB-refractory filamentous fungi, for instance, *Aspergillus* species and other emerging pathogens [6, 7].

Still, the most efficacious usage of these lipid-modified AmB preparations in the armamentarium of antifungal interventions has yet to be defined. To this end, the EORTC presents in this issue a large, prospective, randomized clinical trial that is the first to compare the therapeutic efficacy of two dosages of L-AmB against documented or probable aspergillosis in neutropenic hosts [8]. This is a pioneering effort to obtain biologically and statistically meaningful data before a standard of care is established—indeed, to use scientific principles as a foundation upon which to determine an optimal management approach.

The EORTC has conducted this pivotal trial in the subset of compromised patients with definitive (microbiologically documented) or probable (clinically and radiographically detected) invasive aspergillosis [8]. Such patients are notoriously difficult to study in any trial design, particularly in a randomized fashion. Invasive fungal infections in the neutropenic population evade attempts at early diagnosis for several reasons [1–5]. The lack of inflammatory effector cells in these patients often mutes localizing tissue-specific physical signs, making clinical findings characteristically nonspecific early in the course of infection.

Invasive procedures to definitively establish the diagnosis of deep-tissue involvement are often contraindicated in the clinical setting of deep marrow aplasia and, in part due to a lack of inflammatory changes in the affected tissue, may be unreliable in establishing a specific diagnosis. A lack of positive blood cultures or of colonization at sites that might be predictive of...
systemic infection can further complicate definitive diagnosis. These problems are compounded by the lack of sensitive laboratory tests providing rapid identification of pathogenic fungi and of generally available methods for fungal drug susceptibility testing.

Perhaps it is time for industry and government to support the development and application of surrogate biochemical markers (fungal antigens, metabolites, and nucleic acids, for example) for early detection of fungal infection. Radiographic studies with CT are useful in the early detection as well as the follow-up of deep-tissue invasion but do not provide absolute or specific identification of the responsible pathogen [1, 5, 8]. The epidemiology of fungal infections can be highly variable, as well, since aspergillus infections often occur in clusters, with the precipitating factors and therefore the timing of those clusters being difficult to anticipate. Last, these critically ill patients evince multiple confounding factors, making stratification unmanageable both biostatistically and biologically.

From the data generated, the authors are forced to conclude that more is not necessarily better when it comes to L-AmB. This counterintuitive finding stands in contradistinction to studies demonstrating the enhanced clinical effects of high-dose AmB for the relatively AmB-resistant fungi. However, the apparent paradox might relate to any one of several parameters: (1) the inherent difficulties in diagnosing the presence and magnitude of aspergillus infections in the neutropenic host; (2) the lack of reliable and reproducible in vitro drug susceptibility testing for Aspergillus (and for filamentous fungi in general); (3) our lack of understanding of the pharmacokinetics of AmB, either in its conventional state or in a liposomal form; and (4) a potential alteration in net drug disposition conferred by the liposomal formulation to enhance overall tissue exposure over a prolonged period of time.

Given these unanswered (and unanswerable) questions, it is hard to make any strong statements about the appropriate dosing schedule or the achievement of therapeutic fungicidal levels of drug. And yet, contrary to the authors’ generalized conclusions, the data exhibit a trend toward improved survival for patients with proven aspergillus who received higher doses of L-AmB [8]. This finding supports the dose-response that has been demonstrated for nonlipid AmB in the therapy of proven or probable invasive aspergillosis.

Another implication of this finding may be that cases of presumptive invasive aspergillosis were not due to Aspergillus but instead were caused by other fungal pathogens (e.g., non-albicans Candida) that are less intrinsically AmB-refractory. Alternatively, it may be that the early detection of presumed invasive aspergillosis by radiographic methods was associated with a lower burden of organisms and, as such, may not have required higher doses of L-AmB.

How does L-AmB compare with nonliposomal AmB in terms of clinical antifungal activity? In the ideal world, the study could have been designed to address this issue directly, with use of “anti-Aspergillus” doses of conventional AmB (1–1.25 mg/[kg·d]) as a third arm for randomization. Indeed, nonliposomal AmB at such doses would serve as a useful standard against which to measure the efficacy of these newer AmB preparations. Such comparisons are sorely needed, since the only data available regarding L-AmB preparations have been derived from open-label studies [6, 7], and direct head-to-head comparisons of equivalent doses of conventional AmB and high-dose liposomal preparations have not been performed.

In sum, the EORTC has tackled a number of pivotal issues surrounding the management of aggressive fungal infections in the profoundly neutropenic host. Clinical investigation in this setting is particularly challenging, in part because of the tremendous variability in patient status and in part because of the inherent difficulties in securing a definitive diagnosis promptly and accurately. In addition, the EORTC should be commended for its willingness to include those patients with CT abnormalities in the study, because it is in this subgroup of patients that early institution of aggressive antifungal therapy may make a formative difference in clinical outcome.

EORTC investigators have broken new ground with this study and, by so doing, have raised some provocative issues that need to be addressed if we are to optimize our approaches to these critically ill patients. The EORTC has started a new generation of studies in the arena of antifungal therapy, and we are likely to be busy addressing the complexities of AmB and aspergillosis for a long time to come.

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References