

Dosing Amphotericin B in Cryptococcal Meningitis

William G. Powderly

University College Dublin School of Medicine and Medical Science, Dublin, Ireland

(See the article by Bicanic et al. on pages 123–30)

It is salutary to note that, although for the past 50 years of therapeutics, amphotericin B has been the mainstay of antifungal treatment for cryptococcal meningitis, in an era of evidence-based medicine, we remain uncertain regarding the appropriate dose of this drug to use when giving treatment to patients. The article by Bicanic et al. [1] provides some useful insight into this question, but before considering the new data, it is worth reviewing the history of amphotericin B use for treatment of cryptococcal meningitis.

Amphotericin B was available for >20 years before large, randomized trials investigating its use for systemic fungal infection were published. Cryptococcal meningitis was one of the first diseases tackled by the fledging Mycoses Study Group in the 1970s and 1980s (before the era of HIV infection and AIDS). At that time, the Mycoses Study Group's focus was on reducing the dosage and duration of use of amphotericin B as much as possible, and the findings of 2 randomized studies [2, 3] led to the conclusion that a dosage of amphotericin B deoxycholate of

0.3 mg/kg per day was effective when given in combination with flucytosine. In retrospect, the methodology of these trials, which excluded from analysis patients who died early in the course of treatment, may have led to an overly optimistic appraisal of low dosages of amphotericin B. Certainly, initial results in the treatment of AIDS-associated cryptococcal meningitis were not as encouraging.

The Infectious Diseases Society for America's current guidelines [4] for the treatment of cryptococcal meningitis recommend an amphotericin B deoxycholate dosage of 0.7 mg/kg per day. This is derived largely from a large randomized trial of 381 patients who received the agent at this dosage [5]. However, the amphotericin B dosage in that trial was selected rather arbitrarily. An earlier trial of the dosage 0.4 mg/kg per day produced results that were generally regarded as unsatisfactory [6]. Several investigators favored dosages as high as 1.0 mg/kg per day, but there were considerable concerns about toxicity at that dosage. A dosage of 0.7 mg/kg per day was therefore selected, especially because there was some published experience with this dosage [7]. The overall success of a 2-week induction period of amphotericin B deoxycholate, 0.7 mg/kg per day, followed by fluconazole maintenance therapy was believed to be sufficient to become the standard of care. Although concern remains about toxicity—especially nephrotoxicity—amphotericin B is generally well tolerated for 2 weeks. The

advent of effective antiretroviral therapy led to a substantial reduction in the number of new cases of cryptococcal infection in the developed world, and the impetus to investigate further treatment options decreased concomitantly.

Despite advancements made in antiretroviral therapy, cryptococcal meningitis remains a common opportunistic infection in resource-poor settings, particularly in Southeast Asia and Africa. Fluconazole is widely available in generic form; however, there are concerns that fluconazole may not be as effective as amphotericin B for treatment of cryptococcal meningitis. In a small trial, Brouwer et al. [8] demonstrated that amphotericin B (0.7 mg per day) plus flucytosine was more rapidly fungicidal (compared with amphotericin B alone and with amphotericin B plus fluconazole) using an end point that examined the rate of decrease of cryptococcal colony-forming units in the CSF after 14 days of treatment. In the current trial, this study design is used to compare 2 dosages of amphotericin B (0.7 and 1.0 mg/kg per day) administered with flucytosine. The authors convincingly show that higher doses of amphotericin B, when used with flucytosine, lead to a more rapid fungicidal effect. However, their conclusion that these findings should lead to more widespread use of the drug at this dosage (1.0 mg/kg per day) is premature. They may well be correct; however, dosing of a toxic drug is always a balance between clinical benefit and adverse effects, and this study

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Reprints or correspondence: Dr. William G. Powderly, UCD School of Medicine and Medical Science, University College Dublin, Health Sciences Centre, Belfield, Dublin 4, Ireland (head.smmms@ucd.ie).

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is too small to adequately answer this cost-benefit question. There were no differences in survival and toxicity rates between the 2 arms. These were secondary outcomes, and the sample size is too small to conclude that a clinically relevant difference was not missed. The authors' suggestion that toxicities could be managed by an earlier switch to fluconazole is reasonable, but such a strategy might, in a larger trial, lead to differences in efficacy.

Nevertheless, the authors are to be commended for readdressing the question of optimal therapy for cryptococcal meningitis, especially in the context of AIDS. There is little prospect of new antifungal agents on the horizon, so we must best use the available drugs. In the developed world, there are several (expensive) alternative formulations of amphotericin B. There is no evidence that they are better than conventional amphotericin B deoxycholate. A large trial comparing liposomal amphotericin B at 3.0 and 6.0 mg/kg per day with amphotericin B deoxycho-

late, 0.7 mg/kg per day, revealed equivalent outcomes [9]. Scandalously, this trial has not been published—10 years after completion! In resource-poor settings, amphotericin B is expensive, and flucytosine availability is limited. As is true for so many other HIV-related morbidities, the best approach should be wider access to earlier antiretroviral therapy to prevent the occurrence of cryptococcal infections.

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