TREATMENT OF HIV-ASSOCIATED CRYPTOCOCCAL MENINGITIS IN SOUTH AFRICA: THE CASE FOR AMPHOTERICIN B OVER CONVENTIONAL DOSE FLUCONAZOLE FOR INITIAL THERAPY

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Cryptococcal meningitis is a major cause of morbidity and mortality in African AIDS patients, accounting for between 13% and 17% of deaths in Ugandan HIV-infected individuals[1,2] and 44% of deaths in a cohort of HIV-seropositive South African miners.[3] This burden of disease is a result of high incidence, especially in southern and East Africa, and high acute mortality.[4-6] In much of Africa, fluconazole rather than amphotericin B was, and still is, widely used as initial therapy, for a variety of reasons. These include the availability of fluconazole through free access programmes and in generic form, and the attractiveness of an easy to use, safe oral regimen over a difficult to administer intravenous drug with significant side-effects, requiring inpatient admission and close laboratory monitoring. In addition, in the absence of antiretroviral therapy, treatment of cryptococcal meningitis has in the recent past been palliative rather than curative, reducing the rationale for more aggressive therapy, if this is associated with increased side-effects. However, what data there are suggest that outcomes with fluconazole at conventional dosage (up to 400 mg/d) as initial therapy are poor. In addition, the cost of amphotericin B, previously considerable in South Africa, has been reduced.[7] More importantly, increasing access to antiretroviral therapy (ART) now means that the long-term prognosis of patients with cryptococcal meningitis is good, *provided* they survive the acute infection.[8] We summarise the evidence that a factor contributing to high acute mortality in cryptococcal meningitis is the inadequacy of fluconazole at up to 400 mg/d as an induction regimen, and present the case for initial treatment with amphotericin B in South Africa, where feasible.

OUTCOMES OF INITIAL THERAPY

Current treatment guidelines, which advocate amphotericin B as induction therapy, are based on a large randomised controlled trial (RCT) from the USA that compared initial therapy with amphotericin B (0.7 mg/kg/d) plus or minus flucytosine for 2 weeks, followed by 8 weeks of consolidation treatment with either fluconazole (400 mg/d) or itraconazole (400 mg/d).[9] The overall mortality rate was 9.4% in the first 10 weeks, the lowest of any published trial, with flucytosine associated with lower relapse rates and a trend toward a higher proportion of negative cerebrospinal fluid (CSF) cultures at 2 weeks. Fluconazole was superior to itraconazole as consolidation therapy. However, the sickest patients, notably those with a decreased level of consciousness, were excluded from the study. A 10-week mortality rate of 26% has been reported in a less selected US series of amphotericin B-treated patients,[10] and the rate was 33% in a Cape Town cohort of patient receiving amphotericin B 1 mg/kg/d for a median of 7 days.[11] Even compared with these unselected series, results with fluconazole monotherapy (200 - 400 mg/d) as initial therapy are disappointing. One small RCT found that fluconazole 400 mg/d was inferior to amphotericin B 0.7 mg/kg/d plus flucytosine,[12] and although a larger RCT comparing fluconazole 200 - 400 mg/d with amphotericin B 0.4 - 0.5 mg/kg/d found no significant difference between groups in overall mortality, there were trends in favour of amphotericin B: the mortality in the first 2 weeks was higher in the fluconazole treatment arm (15% v. 8%), and the median time to culture-negative CSF was 64 days for fluconazole versus 42 for amphotericin.[13] Overall mortality in both treatment groups of this study was high, and the dosage of

amphotericin B, which has concentration-dependent activity, was less than currently recommended, making interpretation difficult.

African studies also show unfavourable outcomes with initial fluconazole treatment at 200 - 400 mg/d. In a series from Zambia the median survival with fluconazole 200 mg/d monotherapy was 19 days compared with10 days in untreated patients.[5] Mortality with fluconazole 200 mg/d in a Ugandan trial was 40% in the first 2 weeks and 64% at 2 months.[14] Schaars *et al.* demonstrated a 10-week mortality of approximately 50% with either 200 or 400 mg/d in a study in Cape Town.[6] This is almost certainly an underestimate given the retrospective nature of the study. Of note, although many of these studies were carried out prior to availability of ART, two studies suggest that access to ART does not affect the acute, 10-week mortality from cryptococcal meningitis.[11,15] The evidence therefore suggests that the 10-week mortality in unselected patients treated with fluconazole at up to 400 mg/d is significantly more than 50% in most African settings.

FUNGISTATIC VERSUS FUNGICIDAL TREATMENT

In contrast to amphotericin B, which is fungicidal, standard dose fluconazole is effectively fungistatic. Time to culture negativity has consistently been shown to be longer with fluconazole than with amphotericin-based regimens.[11,12] In the RCT of fluconazole 400 mg versus amphotericin 0.7 mg/kg plus flucytosine the mean time to CSF sterilisation was 41 days with fluconazole and 16 days with amphotericin B.[12] Recent work in Cape Town, using serial quantitative cultures to measure the rate of clearance of cryptococcal colony-forming units from the CSF (also called early fungicidal activity or EFA), has further demonstrated that the clearance of cryptococci from the CSF over the first 2 weeks is significantly faster with amphotericin (given for 1 week at a dosage of 1 mg/kg/d) than fluconazole (400 mg/d), fluconazole being almost fungistatic over this time period (Fig. 1).[11]

There is evidence that the rapidity of CSF sterilisation is related to clinical outcome. Two-week CSF culture status has been shown to be associated with outcome at 10 weeks by multivariate analysis.[10] In addition, by pooling data from patients studied with serial quantitative CSF cultures in Thailand, Cape Town and Uganda, we have increasing evidence that rate of clearance of infection is associated with mortality, independent of altered mental status at presentation and baseline organism load, the other two major prognostic factors (author's unpublished data).

DRUG RESISTANCE

The fungistatic nature of fluconazole as initial therapy may promote the development of drug resistance because of ongoing high fungal burdens and drug exposure over prolonged periods. Surveillance data from South Africa have shown an increase in the percentage of *Cryptococcus neoformans* isolates with fluconazole resistance.[16,17] In a prospective study in Cape Town looking at symptomatic relapse of cryptococcal meningitis in patients who had received initial fluconazole therapy (400 mg/d), two-thirds of relapses were culture positive. Over half of these were associated with *C. neoformans* isolates with high-level resistance to fluconazole (Fig. 2). Outcomes in these patients were poor, with prolonged hospital admissions and considerable mortality despite prolonged treatment with amphotericin B.[16]

CRYPTOCOCCAL MENINGITIS IMMUNE RECONSTITUTION SYNDROME

A further concern resulting from the prolonged high fungal burden associated with fluconazole therapy is the possibility of predisposition to immune reconstitution syndromes (IRIS) following initiation of ART. Cryptococcal IRIS has been reported in up to 30% of patients with cryptococcal meningitis following ART,[18,19] and high rates, with associated mortality, have been reported in South African cohorts treated with initial fluconazole therapy.[20] An association between high rates

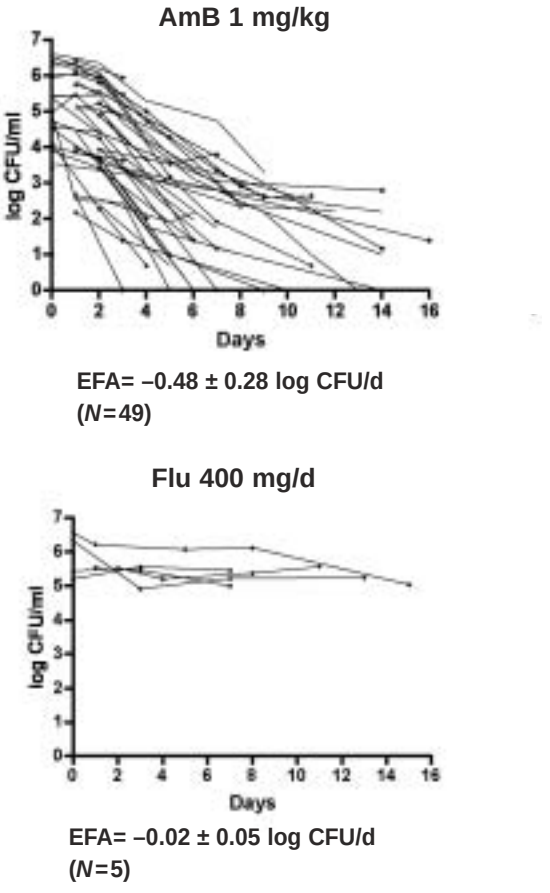

Fig. 1. Decrease in CSF Cryptococcus neoformans *colony-forming units (CFU) over time, by treatment group. The decrease in log CFU per ml of CSF per day was calculated for each patient using the slope of the linear regression of log CFU against time. For each treatment group, early fungicidal activity (EFA) is shown as the mean±SD rate of decrease in log CFU counts. EFA was significantly greater for amphotericin B, compared with fluconazole (*p=0.001 *(from Bicanic* et al.,[11] *with permission).*

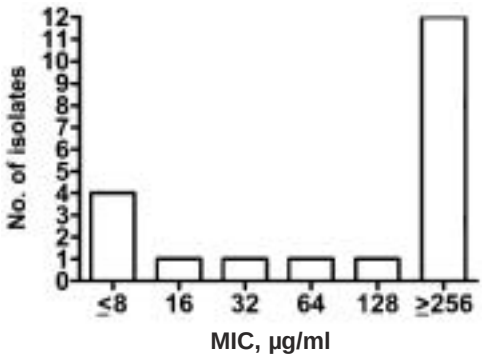

Fig. 2. Minimum inhibitory concentrations (MICs) of fluconazole for 20 Cryptococcus neoformans *isolates recovered from patients with culture-positive relapse of cryptococcal meningitis. For 1 isolate from a patient with culture-positive relapse, sensitivity data were not available (from Bicanic* et al.,*[16] with permission).*

of cryptococcal IRIS and fluconazole as initial treatment as opposed to amphotericin B has not been demonstrated, but would be consistent with the existing data on risk factors for the development of IRIS. Cryptococcal IRIS is associated with a high fungal burden at baseline (high antigen titres and disseminated disease), early introduction of ART (within 1 - 2 months of diagnosis of cryptococcal disease, when fungal burdens are likely to be higher), and persistently positive CSF cultures after 2 weeks.[18,19] Experience from Cape Town suggests that the rates of cryptococcal IRIS may have declined since the introduction of amphotericin B as initial therapy.[20,21]

CONCLUSIONS

The balance of evidence suggests that amphotericin B (0.7 - 1 mg/kg/d)-based regimens are superior to fluconazole 400 mg/d as induction therapy for HIV-associated cryptococcal meningitis. Amphotericin B induction therapy should be used where possible, with sodium and fluid loading, equivalent to 1 litre normal saline per day, if there are no contraindications, and the patient is carefully monitored for anaemia, renal impairment and electrolytes, and receives potassium replacement therapy as required. In the absence of flucytosine, a dosage of 1 mg/kg/d for up to 2 weeks is usually tolerated. Significant side-effects, if they occur, usually do so in the second week, by which time the organism load will have been significantly reduced and patients can be switched early to fluconazole if necessary.[8,11,22] In the many settings (especially common in the rest of Africa) where amphotericin B therapy is still not feasible, fluconazole should be used at a dosage of at least 800 mg/d, pending the results of studies, currently under way, to optimise oral treatment regimes in such settings. There is a linear plasma level-dose relationship with fluconazole doses up to 2 g/d,[23] and some evidence for a dose-response effect with higher fluconazole doses, in terms of time to sterilisation of CSF.[12,13,24,25] Dosages up to 1 600 mg/d have been used in limited numbers of patients without serious side-effects.[23,26]

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