Amphotericin B as Primary Therapy for Cryptococcosis in Patients with AIDS: Reliability of Relatively High Doses Administered over a Relatively Short Period

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Thirty-one consecutive AIDS patients with cryptococcal disease were enrolled in a study of the efficacy and safety of short-course primary treatment with a relatively high dose of amphotericin B (1 mg/[kg · d] for 14 days); 26 patients also received flucytosine (100–150 mg/[kg · d], given either intravenously or orally). Twenty-five patients had cryptococcal meningitis confirmed by culture, three had presumed cryptococcal meningitis, and three had disseminated extrameningeal cryptococcosis. After successful primary treatment, all patients were given oral itraconazole or fluconazole as suppressive therapy, and their lifelong clinical and mycologic follow-up was planned. Successful primary therapy was defined as the resolution of symptoms and the documentation of negative cultures of cerebrospinal fluid and/or blood 2 months after the initial diagnosis. Therapy was successful in 29 (93.5%) of all 31 cases and in 26 (92.8%) of the 28 cases of culture-proven or presumed cryptococcal meningitis. Nephrotoxicity developed as a result of amphotericin B administration in seven cases; this adverse reaction required a reduction of the dose in two cases and the discontinuation of therapy in five. No deaths due to cryptococcosis were documented during primary therapy. Treatment failed in two cases. During a mean observation period of 10.7 months, three relapses of the underlying infection occurred. Our results indicate that an aggressive approach to the primary treatment of cryptococcosis in AIDS patients, with the administration of a relatively high dose of amphotericin B for a relatively short period, is effective and well tolerated.

Cryptococcosis is the most common life-threatening fungal disease among patients with AIDS. Studies indicate that 5%–10% of human immunodeficiency virus (HIV)–infected patients in Western countries and up to 30% of those in sub-Saharan Africa develop cryptococcosis at some point [1, 2]. The fatality rate during initial therapy is 10%–25% [3–5], and the 12-month overall survival rate is 30%–60% [3, 4]. Although involvement of the CNS is the most frequent feature at presentation and altered mental status is the most reliable predictor of acute-phase mortality [4], the median survival interval and the rate of relapse seem to be similar regardless of meningeal involvement [3]. In the absence of chronic suppressive therapy, the main features of cryptococcosis in patients infected with HIV type 1 are a poor outcome and a high relapse rate (50%–60%) [5, 6] after the discontinuation of primary therapy. Lifelong maintenance therapy to prevent relapse therefore is currently recommended as standard practice after successful primary therapy [1]. Acute cryptococcosis is presumed to be caused by newly acquired primary infection [7]; some evidence indicates that relapses arise from the persistence of the original cryptococcal strain [8, 9]. Moreover, after primary therapy, a considerable number of patients (~27% [4]) develop "quiescent disease," which is characterized by clinical improvement with an incomplete mycologic response.

Standard primary therapy for cryptococcosis in AIDS patients still consists of amphotericin B (AmB) either alone or combined with flucytosine [10]. The optimal dosage of AmB and the optimal duration of its administration remain controversial, as do the relative efficacies of AmB alone and the AmB/flucytosine combination. Regimens of AmB ranging from 0.3 to 0.7 mg/kg daily or on alternate days for 3–22 weeks—either alone or combined with 75–150 mg of flucytosine/(kg · d)—have been suggested [3, 4, 6, 11, 12]. Triazole antifungal agents are still of questioned value when compared with AmB for the initial treatment of cryptococcal disease [4, 12, 13]; for maintenance therapy, these agents are as effective as AmB and are less toxic [5, 14]. Currently, an aggressive approach to the initial treatment of cryptococcal disease with AmB, either alone or combined with flucytosine, seems to be favored [7, 15].

In 1991 we began an uncontrolled trial on the initial treatment of cryptococcosis in AIDS patients with a relatively high dose of AmB (1 mg/[kg · d]) plus flucytosine (100 mg/[kg · d]) for periods as short as 2 weeks. The aim of this ongoing study is to evaluate the efficacy and tolerability of this short-course, high-dose primary therapy for cryptococcal meningitis (CM) and extrameningeal disseminated cryptococcosis (EMC) in AIDS.

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Materials and Methods

From June 1991 onward, samples of blood, urine, sputum, and CSF from all AIDS patients with suspected cryptococcosis at our institution were cultured for *Cryptococcus neoformans;* bronchoalveolar lavage and chest radiography were also undertaken if the lungs were involved. The cryptococcal latex agglutination antigen (CLAA) test (Latex-Crypto Antigen Detection System, Immuno-Mycologics, Norman, OK) was performed with both serum and CSF.

All patients with HIV infection (confirmed by a positive result in an anti-HIV ELISA and by western blot) and with culture-documented *C. neoformans* infection were enrolled in the study. These patients were monitored for cryptococcal infection at the end of initial therapy and at months 2, 4, 6, and 12 thereafter.

CM was defined by a CSF culture positive for *C. neoformans* or—when the culture was negative—by a positive CSF CLAA test (titer, $\geq$1:8) and a positive blood culture. In the latter case, the diagnosis of CM was only presumed to be accurate. At enrollment, patients with CM were evaluated in terms of mental status (normal status, confusion, lethargy, or obtundation), duration of illness, and biocytochemical characteristics of CSF (protein levels, glucose concentration, and white blood cell [WBC] count). EMC was recognized in AIDS patients by a blood culture positive for *C. neoformans* and a negative CSF culture combined with a CSF CLAA titer of <1:8.

All patients were scheduled to receive the full regimen of AmB: 1 mg/(kg · d) for 14 days. The dosage of AmB and the length of treatment were reconsidered if drug-related toxicity developed. AmB therapy was continued beyond 14 days if the clinical outcome was poor. Administration of the full dosage was preceded by a test dose (1 mg in 100 mL of 5% glucose iv), with progression to the maximal dose by 48–72 hours.

AmB was injected over 4–6 hours once a day in either 250 mL of Intralipid (Intralipid 20%; Kabivitrum AB, Stockholm) or 500 mL of 5% glucose solution. Flucytosine (100–150 mg/kg) was given orally (or iv, in the event of coma) in four daily doses. The dosage and length of treatment were adjusted for flucytosine as for AmB. After completion of primary therapy, patients were randomized to receive either fluconazole (300 mg/d) or itraconazole (300 mg/d) orally as lifelong maintenance treatment. Monitoring for the potential adverse effects of AmB and flucytosine was conducted three times a week in a complete hematologic and biochemical evaluation.

In cases of CM, therapeutic success was defined as the resolution of symptoms plus a negative CSF culture coupled with a fall in CSF CLAA titer 2 months after diagnosis. In cases of EMC, a favorable outcome was defined as clinical improvement plus a negative blood culture and a decrease in serum CLAA titer after 2 months of therapy. A lack of clinical improvement and/or the failure to clear *C. neoformans* from blood or CSF by the end of initial therapy or within the first 2 months after diagnosis was defined as a failure of treatment. Relapses were defined as the reemergence of clinical symptoms of cryptococcosis in the presence of a positive blood or CSF culture and/or an increase in serum and/or CSF CLAA titer after the first 2 months of therapy. Survival periods were calculated from the date of diagnosis.

Results

Thirty-one consecutive AIDS patients (29 men and 2 women, 25–56 years old; median age, 35.4 years) were enrolled in the study. The baseline characteristics of these patients are summarized in table 1. Twenty-five patients (80.6%) had CM proven by CSF culture, 3 (9.7%) had presumed CM, and 3 (9.7%) had EMC.

The mean full-regimen AmB dose administered was 0.91 mg/(kg · d) for a mean of 11.6 days (range, 6–19 days). The mean overall AmB dosage administered was 750.4 mg (range, 440–1,316 mg).

AmB-related nephrotoxicity—as reflected by a serum creatinine level of >2.4 mg/dL (normal value, 0.5–1.2 mg/dL)—developed in seven cases. In five instances AmB therapy had to be discontinued because of the severity of this reaction; i.e., serum creatinine levels were >4 mg/dL and/or blood urea levels were >40 mg/dL (normal value, <22 mg/dL) on day 6 (one case), day 7 (two cases), or day 8 (two cases). The dosage was reduced in the remaining two cases. Minor electrolyte disturbances did not require adjustment of the dosage. In cases requiring the discontinuation of treatment with AmB, primary therapy with azoles (itraconazole, 400–600 mg/d, or fluconazole, 600 mg/d) was administered for 2 additional weeks before the conversion to maintenance therapy. Predictors of poor outcome (e.g., abnormal mental status, a CLAA titer of >1,024 in CSF, and a WBC count of <20/mm^3 in CSF) that were detected at enrollment are shown in table 1.

Flucytosine was not administered in four cases—because of concomitant potentially granulocytopenic therapy (with sulfadiazine plus pyrimethamine) in one case and because of a low baseline WBC count in three cases. The 27 patients treated with flucytosine were given a mean of 117.1 mg/(kg · d) for a mean of 11 days.

Therapy was successful in 29 (93.5%) of the total of 31 cases and in 26 (92.8%) of the 28 cases of culture-proven or presumed CM. One patient died with signs and symptoms of CM 7 weeks after diagnosis; in this case, therapy with AmB had been discontinued after 7 days because of nephrotoxicity. The second patient in whom treatment failed also had CM. This patient's clinical condition progressively deteriorated during initial treatment, with the persistence of India ink–positive CSF at day 14; 0.25 mg of AmB was therefore administered intrathecally on alternate days for 13 days, and

Table 1. Baseline characteristics of 31 AIDS patients with cryptococcal disease who were enrolled in a study of primary treatment with high-dose, short-course amphotericin B and supplemental flucytosine.

Characteristic	Value for indicated group*		
	Cryptococcal meningitis (n = 28[†])	Extrameningeal disseminated cryptococcosis (n = 3)	Total (n = 31)
$CD4^+$ lymphocyte count	46.1 (5–201)	39.6 (9–59)	45.4 (5–201)
Abnormal mental status[‡]	13	. . .	13
WBC count of <20/mm^3 in CSF	16	0	16
CLAA[§] titer in CSF	3,272 (4–8,192)	. . .	. . .
CLAA titer of >1,024 in CSF	16	0	16
CLAA titer in serum	4,288 (64–8,192)	2,069 (64–4,096)	4,073 (64–8,192)

* Values are either numbers of patients or means (ranges) of counts or titers, as indicated under "Characteristics."

[†] Three of these 28 patients had presumed (as opposed to definite) cryptococcal meningitis; see text.

[‡] Lethargy, dizziness, confusion.

[§] Cryptococcal latex agglutination antigen.

fluconazole was given iv at a dose of 1,000 mg/d. Major neurological signs persisted despite the fact that culture did not yield *C. neoformans*. Concomitant toxoplasmic encephalitis and a generally poor clinical condition made this patient difficult to evaluate.

As of February 1994 (mean observation period, 10.7 months), three relapses (10.3%) had been documented among the 29 patients whose therapy succeeded. Two patients who had relapses 6 months after diagnosis were successfully retreated with AmB and flucytosine. A third patient had a relapse 4 months after treatment and died of EMC despite retreatment. Of the 31 patients monitored over the study's duration (mean follow-up period, 12.5 months; range, 49 days to 30 months), 19 died; 17 of these deaths were due to opportunistic infections other than cryptococcal disease. Two patients were lost to follow-up at months 16 and 20, respectively. Ten patients are still alive (mean follow-up period, 5.9 months; range, 2–13 months).

Discussion

The currently recommended dosage of AmB for the primary treatment of cryptococcosis in AIDS patients does not exceed 0.7 mg/(kg·d) [10]; higher dosages (1.0–1.5 mg/[kg·d]) are administered for devastating fungal diseases, such as mucormycosis [16]. To our knowledge, no experience has previously been reported with short-course, high-dose AmB for initial treatment of cryptococcosis in AIDS patients. The foremost limitations of AmB are its toxic effects (mainly nephrotoxicity), whose development is strongly correlated with prolonged use and the resultant high cumulative total dosage; significant infusion-associated morbidity due primarily to bacterial superinfection has also been reported [17]. The availability of triazole antifungal agents, which can be administered as long-term maintenance therapy without important adverse effects, has reduced the need for prolonged administration of AmB. We prefer an aggressive approach to primary therapy for cryptococcosis in AIDS, with relatively high doses of AmB given in combination with flucytosine over a fairly short period. Our results show a generally rapid mycologic response together with early clinical improvement, even in patients at risk of a poor outcome. Only one early death occurred (at 7 weeks after diagnosis). A second case whose treatment was classified as a failure was actually difficult to evaluate, since the patient also had toxoplasmic encephalitis and still had India ink–positive CSF at the end of initial therapy despite cultures negative for *C. neoformans*. During follow-up, the observed relapse rate was 10.3% among the 29 patients receiving itraconazole or fluconazole as maintenance therapy. Our experience suggests that, in the event of relapse, retreatment with the same regimen used for primary therapy is appropriate.

Nephrotoxicity has been documented in 30%–80% of patients given this drug [18, 19]. In our study, a reduction in dosage or the discontinuation of therapy due to nephrotoxicity was necessary in 22.6% of cases. In no case did flucytosine-associated myelotoxicity require the discontinuation of therapy.

Our data appear to support an aggressive approach to the treatment of meningeal or extrameningeal cryptococcosis in AIDS patients. Relatively high doses of AmB, perhaps combined with flucytosine, can be administered over a short period (e.g., 2 weeks) for this purpose. Early mycologic and clinical responses make it possible to convert to less toxic therapy (i.e., with triazoles) that can be continued on a life-

long basis. Relapses should be retreated with the regimen used for primary therapy.

Although our study included only a small number of patients, all favorable clinical and mycologic responses were confirmed 2 months after the completion of therapy. Furthermore, in light of the extensive follow-up period, our data seem comparable to those of other controlled trials with much larger groups of patients.

Note Added in Proof

Since the submission of this manuscript, four additional patients with AIDS and CM were treated with the same therapeutic regimen (AmB and flucytosine). All patients completed primary therapy successfully. No side effects due to AmB or flucytosine therapy were detected.

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