Successful Use of Amphotericin B Lipid Complex in the Treatment of Cryptococcosis

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The efficacy and renal safety of amphotericin B lipid complex (ABLC) injection were assessed in 106 patients with cryptococcal infection. Eighty-three patients (78%) had a central nervous system (CNS) infection. Of these patients, 20 initiated azole therapy concomitantly with ABLC therapy, and 7 had received prior azole therapy, which continued during administration of ABLC. Clinical response (cured or improved) was achieved in 67 (66%) of 101 patients whose results could be evaluated. Response rates were 65% (51/78) for patients with a CNS infection and 70% (16/23) for patients without a CNS infection. The response rate for patients with HIV infection was 58% (30/52). Response rates were 56% (19/34) for patients who were refractory to prior antifungal therapy, 65% (11/17) for patients who were intolerant of prior antifungal therapy, 60% (3/5) for patients with underlying renal disease who received prior antifungal therapy, 76% (25/33) for patients with underlying renal disease who did not receive prior antifungal therapy, and 73% (8/11) for patients with no renal disease who did not receive prior antifungal therapy. A mean serum creatinine level decrease of 0.02 mg/dL occurred. ABLC was an effective treatment for cryptococcal infection in immunocompromised patients.

Cryptococcus neoformans is a fungus found in soil and bird droppings in almost all areas of the world. Infection in humans follows inhalation of infectious spores or yeasts. Exposure to the spores or yeasts is probably common, but cryptococcosis occurs infrequently in humans [1]. Although apparently healthy hosts can become infected, the fungus causes disease more frequently and with greater severity in patients with compromised immune systems.

Since the beginning of the AIDS pandemic in the early 1980s, HIV infection has been the predisposing factor in >80% of patients with cryptococcal infections [2]. Although antiretroviral therapy has resulted in a steady decrease in the prevalence of cryptococcosis among HIV-positive patients [3], cryptococcosis remains a serious concern in other populations, given the increasing utilization of organ transplantation and immunosuppressive therapies.

Amphotericin B deoxycholate (AmB) and/or azoles are generally efficacious for treating cryptococcal infections, but comparative studies of both humans and animal models have demonstrated that therapy with AmB results in more-expeditious antifungal activity than does therapy with azoles [4, 5]. The utility of AmB and/or azoles is limited, however, because these agents may not be well tolerated or may fail to control the infection. The nephrotoxicity associated with AmB is of particular concern in patients with underlying HIV infection, because they may experience renal insufficiency due to HIV nephropathy [6]. Similarly, antirejection drugs (e.g., cyclosporine or tacrolimus) administered to transplant recipients are often nephrotoxic, and utilization of AmB in these patients may result in additive renal toxicity.

A lipid-based alternative to treatment with AmB is amphotericin B lipid complex (ABLC) injection (Enzon Pharmaceuticals), which has been demonstrated to provide fungicidal activity comparable to that of the conventional formulation, with less nephrotoxicity. The reduction in nephrotoxicity permits administration of higher doses of ABLC than AmB over a longer duration of therapy [7]. ABLC may therefore be beneficial in the
Table 1. Sites of infection in patients with cryptococcosis.

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>No. (%) of patients (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>83 (78)</td>
</tr>
<tr>
<td>Blood</td>
<td>31 (29)</td>
</tr>
<tr>
<td>Lung</td>
<td>15 (14)</td>
</tr>
<tr>
<td>Skin</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Genitourinary tract/bladder</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Peritoneum/ascites</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Bone</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sputum</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

*a Thirty-six patients (33.9%) were reported as having multiple sites of infection.

initial treatment of cryptococcal infection, particularly when renal dysfunction is present, or as second-line therapy when amphotericin-induced nephrotoxicity occurs. However, there has been no systematic trial of the use of ABLC in these settings. Experience with other lipid-based amphotericin B products has been favorable, thus making the use of ABLC in this setting worthy of investigation.

METHODS

The Collaborative Exchange of Antifungal Research (CLEAR) database was queried to identify patients with cryptococcal infection who were treated with ABLC. The complete methods used in CLEAR for data collection and analysis are explained in the introduction to this supplement [8], including the definitions for patient status prior to therapy with ABLC and for clinical outcomes of cured, improved, stable, deteriorated, and indeterminate. In addition to the standard methodology, supplemental information gleaned from the database that is relevant to the population of patients with cryptococcal infection included subanalyses of response rates among HIV-infected patients and those with CNS infection. A favorable response to therapy was defined as cure or improvement at the end of therapy with ABLC.

RESULTS

Of the 3514 patients enrolled in the CLEAR database, 106 (3%) were diagnosed with cryptococcosis. The diagnosis and confirmation of cryptococcal infection were arrived at on the basis of multiple methods, with >1 method used for most patients. The 2 most common methods used for diagnosis were fever and clinical signs and symptoms and serologic testing.

Thirty-five patients (33%) were female, and 70 (66%) were male, with a median age of 43 years. The sex of 1 patient was not reported. The mean weight was 70.1 kg (range, 30.0–175.0 kg). In terms of treatment status prior to enrollment, 38 patients (38%) had underlying renal disease, 34 (34%) were refractory to prior antifungal therapy, and 17 (17%) were intolerant of prior antifungal therapy. Eleven patients (11%) had received no prior antifungal therapy and did not have renal disease. One patient’s status at enrollment is not known. Of the 38 patients with underlying renal disease, 33 received no prior antifungal therapy, resulting in a total of 44 patients (44%) who received ABLC as first-line therapy. Twenty patients (19%) initiated therapy with an azole concomitantly with administration of ABLC, and 7 patients (7%) had received prior azole therapy, which then continued during administration of ABLC. Fifty percent of the 106 patients had AIDS as an underlying condition, and 26% had received a solid-organ transplant. The mean daily dose of ABLC was 4.4 mg/kg/day (range, 0.2–10.0 mg/kg/day) for a mean duration of 16 days (range, 1.0–132.0 days).

The most frequent sites of cryptococcal infection were the CNS (78%), blood (29%), lungs (14%), and skin (8%) (table 1). Thirty-six patients (34%) were reported to have multiple sites of infection. Twenty-five patients had 2 sites of infection, 10 had 3 sites, and 1 had 4 sites. Nine patients (9%) were coinfected with another pathogen, mainly Candida species (5 patients) and Aspergillus species (3 patients). One patient had an unspecified yeast infection, and 1 pathogen was unidentified.

Clinical response data could be evaluated for 101 (95%) of 106 patients (figure 1). The overall favorable response, defined as cured or improved, was 66% (67/101 patients).

In patients with cryptococcal infection of the CNS, the favorable response rate was 65% (51/78). The response rate for patients with underlying HIV infection was 58% (30/52). Response rates by status prior to enrollment were 56% (19/34)

Figure 1. Favorable response (cured or improved) in patients with cryptococcosis whose results could be evaluated (n = 101).
DISCUSSION

Although the incidence of cryptococcal meningitis is decreasing, it remains the most common systemic mycosis in patients with HIV infection and is associated with significant morbidity and mortality [9–11]. The current standard of care for patients with cryptococcal infection, including cryptococcal meningitis, is AmB (with or without flucytosine) followed by a course of fluconazole therapy.

Although AmB is considered to be the standard of care, many clinicians are questioning the appropriateness of initiating therapy with this agent [12]. When AmB was introduced in 1959, it was viewed as a lifesaving drug, and randomized studies designed to demonstrate its efficacy and safety were deemed to be unnecessary. It appears, however, that the nephrotoxicity of this agent was underestimated. A recent study reported a 30% incidence of acute renal failure among general hospital patients treated with AmB and a corresponding effect on mortality rates [13]. The financial impact of the increased mortality, length of hospital stay, and estimated additional costs to treat nephrotoxicity amounted to ~$30,000/patient. A previous study of patients receiving AmB for invasive aspergillosis reported qualitatively similar results [14]. In addition, a pharmacoeconomic analysis demonstrated that a less nephrotoxic lipid formulation of amphotericin B is more cost effective than AmB, even when the higher cost of the lipid formulations is taken into consideration [15].

Azole antifungals have been investigated as a potential alternative to AmB. Although azoles produce fewer and less-severe infusion-related events, comparative efficacy studies with AmB in treatment of cryptococcal meningitis have demonstrated a more rapid mycological response to AmB therapy in both human and animal models [4, 5]. In one such study, 194 patients with AIDS-associated cryptococcal meningitis, randomized to receive fluconazole or AmB, were evaluated for antifungal efficacy, safety, and outcomes [4]. Although there was no significant difference in response rate between AmB (40%; 25/63 patients) and fluconazole (34%; 44/131 patients), there was a discernible difference in median time to first negative CSF culture (42 days for AmB vs. 64 days for fluconazole).

In a recent study evaluating the efficacy, tolerability, and safety of voriconazole in 273 patients who were refractory to or intolerant of prior antifungal therapy (including azoles), a subset of the study population (n = 18) with diagnosed cryptococcosis was evaluated for pathogen-specific efficacy. This trial suggested a relatively poor response to voriconazole treatment, with a satisfactory global response reported in only 39% (7/18) of the patients [16]. However, of the 11 patients who did not have a satisfactory outcome, 10 had stable disease at the end of treatment, as judged by stable serological values. In contrast, analysis of response rates of patients with cryptococcosis enrolled in the CLEAR registry by pretreatment status resulted in response rates of 56% (19/34) for patients who were...

Table 2. Summary of clinical response in patients with identified Cryptococcus infection whose results could be evaluated, by prior status.

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>Refractory to prior antifungal therapy (n = 34)</th>
<th>Underlying renal disease/prior antifungal therapy (n = 5)</th>
<th>Underlying renal disease/no prior antifungal therapy (n = 33)</th>
<th>Intolerant of prior antifungal therapy (n = 17)</th>
<th>No prior antifungal therapy/no renal disease (n = 11)</th>
<th>Unknown/other (n = 1)</th>
<th>Total (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>3 (9)</td>
<td>...</td>
<td>4 (12)</td>
<td>1 (6)</td>
<td>1 (9)</td>
<td>...</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Improved</td>
<td>16 (47)</td>
<td>3 (60)</td>
<td>21 (64)</td>
<td>10 (59)</td>
<td>7 (64)</td>
<td>1 (100)</td>
<td>58 (57)</td>
</tr>
<tr>
<td>Stable</td>
<td>8 (24)</td>
<td>3 (64)</td>
<td>15 (45)</td>
<td>3 (18)</td>
<td>1 (9)</td>
<td>...</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>7 (21)</td>
<td>...</td>
<td>3 (9)</td>
<td>1 (9)</td>
<td>2 (18)</td>
<td>...</td>
<td>15 (15)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients.
refractory to prior antifungal therapy and 65% (11/17) for patients who were intolerant of prior antifungal therapy.

Lipid formulations of amphotericin B allow for administration of higher doses of AmB with comparable efficacy and reduced toxicity in animals and humans [17–19]. In immunocompromised hosts with cryptococcal meningitis, the optimal therapeutic goal is rapid host tissue sterilization. Given the need for rapid antifungal activity with low nephrotoxicity, dose selection becomes extremely important.

In a dose-comparative study conducted by Perfect and Wright [7], immunocompromised rabbits with cryptococcal meningitis received AmB (1 mg/kg/day) or ABLC (1 or 10 mg/kg/day). A test dose of 3 mg/kg/day of AmB with rapid infusion produced significant infusion-induced mortality and was therefore not included in the comparison. All 3 treatment regimens proved to be effective. AmB was more potent initially than was ABLC at equal doses; however, the higher ABLC dose demonstrated more-expeditious antifungal activity with no signs of apparent toxicity.

A comparative study of AmB lipid formulations evaluated the efficacy of ABLC, liposomal amphotericin B (LAmB), and amphotericin B colloidal dispersion (ABCD) in CD-1 female mice [20]. The study resulted in 100% survival among the mice receiving LAmB and ABCD (5 and 10 mg/kg/day, respectively), compared with 50% and 90% survival among the mice receiving ABLC (5 and 10 mg/kg/day, respectively). Only 20% of mice receiving ABLC (10 mg/kg/day) were deemed to be free from infection. In contrast, the study by Perfect and Wright [7] reported that 42% of immunosuppressed rabbits (8/17 rabbits) receiving ABLC (10 mg/kg/day) had sterile CSF culture after 7 days of treatment.

Efficacy studies of humans that compared various lipid formulations with AmB in the treatment of cryptococcal meningitis have produced mixed results. In a comparative evaluation of LAmB (4 mg/kg/day) and AmB (0.7 mg/kg/day) for the treatment of cryptococcal meningitis in HIV-infected patients, researchers were able to demonstrate similar response rates among LAmB recipients, compared with conventional therapy [21]. In a study comparing ABLC (5 mg/kg/day) and AmB (0.7–1.2 mg/kg/day) for treatment of cryptococcal meningitis in HIV-infected patients, a superior clinical response of 86% (18/21 patients) was observed in ABLC recipients, compared with 65% (11/17 patients) for AmB recipients [22]. In both studies, there were no significant differences in mycological response between the lipid formulations and AmB.

Clinical response to ABLC has been reported for 556 patients with various fungal infections, including 11 patients with cryptococcosis, treated under a compassionate-use protocol [23]. These patients were refractory to or intolerant of AmB or had preexisting nephrotoxicity. The complete or partial response rate was 64% (7/11 patients), and serum creatinine levels improved for many patients. Although the number of patients with cryptococcosis studied in this trial was small, the results parallel those presented here from the CLEAR database.

The CLEAR database does not include information on markers typically evaluated in cryptococcal meningitis, such as rate of CSF sterilization and intracranial pressure; however, the results from CLEAR parallel previously published studies [22, 23] indicating that ABLC is effective and renal-sparing when used to treat Cryptococcus infections. We have determined that, among patients enrolled in CLEAR, ABLC was effective when used in those with impaired renal function, underlying HIV infection and its associated renal insufficiency, and cryptococcal infection of the CNS, which can be difficult to manage successfully.

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Table 3. Summary of clinical response in patients with identified Cryptococcus infection whose results could be evaluated, by first-line versus second-line treatment with amphotericin B lipid complex (ABLC).

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>First-line therapy with ABLC (n = 44)</th>
<th>Second-line therapy with ABLC (n = 56)</th>
<th>Unknown/other (n = 1)</th>
<th>Total (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>5 (11)</td>
<td>4 (7)</td>
<td>...</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Improved</td>
<td>28 (64)</td>
<td>29 (52)</td>
<td>1 (100)</td>
<td>58 (58)</td>
</tr>
<tr>
<td>Stable</td>
<td>6 (14)</td>
<td>13 (23)</td>
<td>...</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>5 (11)</td>
<td>10 (18)</td>
<td>...</td>
<td>15 (15)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients.
References


