Randomized, Double-Blind Clinical Trial of Amphotericin B Colloidal Dispersion vs. Amphotericin B in the Empirical Treatment of Fever and Neutropenia

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We conducted a prospective, randomized, double-blind study comparing amphotericin B colloidal dispersion (ABCD) with amphotericin B in the empirical treatment of fever and neutropenia. Patients with neutropenia and unresolved fever after ≥3 days of empirical antibiotic therapy were stratified by age and concomitant use of cyclosporine or tacrolimus. Patients were then randomized to receive therapy with ABCD (4 mg/[kg·d]) or amphotericin B (0.8 mg/[kg·d]) for ≤14 days. A total of 213 patients were enrolled, of whom 196 were evaluable for efficacy. Fifty percent of ABCD-treated patients and 43.2% of amphotericin B–treated patients had a therapeutic response (P = .31). Renal dysfunction was less likely to develop and occurred later in ABCD recipients than in amphotericin B recipients (P < .001 for both parameters). Infusion-related hypoxia and chills were more common in ABCD recipients than in amphotericin B recipients (P = .013 and P = .018, respectively). ABCD appeared comparable in efficacy with amphotericin B, and renal dysfunction associated with ABCD was significantly less than that associated with amphotericin B. However, infusion-related events were more common with ABCD treatment than with amphotericin B treatment.

Empirical antimicrobial therapy for patients with chemotherapy-induced neutropenia and fever has become standard practice [1]. In particular, pivotal studies [2, 3] established the addition of amphotericin B as an important therapeutic intervention for patients with persistent fever and neutropenia that did not resolve following 4 to 7 days of empirical antibacterial therapy. However, the administration of amphotericin B is associated with infusion-related and renal toxicity, and amphotericin B–induced nephrotoxicity may be exacerbated by concomitant use of nephrotoxic agents.

Concerns about renal toxicity associated with amphotericin B may preclude empirical initiation and maximal dosing of amphotericin B therapy for the neutropenic, febrile patient. Current intensive chemotherapy and marrow transplant regimens and consequent prolonged episodes of neutropenia frequently lead to sustained exposures to nephrotoxic agents, such as aminoglycosides. In addition, cyclosporine use in cases of allogeneic bone marrow transplantation independently predisposes to renal dysfunction. Reluctance to use amphotericin B in these settings may result in worse outcomes, although this finding has not been demonstrated in clinical trials.

Lipid-associated formulations of amphotericin B were developed to enhance the therapeutic index of the parent compound while maintaining its antifungal activity. Amphotericin B colloidal dispersion (ABCD) is a formulation of equal molar amounts of amphotericin B and sodium cholesteryl sulfate. Results of preclinical [4], uncontrolled [5], and retrospective, controlled clinical trials [6] of this agent have been promising. A major benefit of ABCD appears to be its diminished renal toxicity in comparison with amphotericin B [6]. However, its efficacy and safety relative to amphotericin B have not been established in prospective, controlled clinical trials.

Therefore, a pilot, multicenter, randomized, double-blind comparison trial of ABCD and amphotericin B in the empirical antifungal treatment of febrile, neutropenic patients was conducted.
Materials and Methods

Eligibility Criteria

Patients were eligible for the study if they were neutropenic following chemotherapy for hematologic malignancy or had undergone marrow or stem cell transplantation in the previous 3 months. Patients were anticipated to be neutropenic (absolute neutrophil count, ≤500/mm^3 or ≤1,000/mm^3 and expected to decline to ≤500/mm^3 within 2 days) for ≥7 days. Fever was defined as continued temperatures of ≥38°C following at least 72 hours of empirical broad-spectrum antibacterial therapy or recrudescence of fever (temperature to ≥38°C) on two or more occasions after initial defervescence with antibacterial treatment. The choice of ≥3 days of fever and neutropenia reflected clinical practice at the participating institutions.

Patients were excluded from the study because of the following reasons: prior anaphylactoid reaction to amphotericin B products, amphotericin B therapy in the 2 weeks before the current fever, documented systemic fungal infection within 1 month of study enrollment, or a physician’s unwillingness to discontinue other systemic antifungal therapy. Patients were also excluded because of renal impairment (serum creatinine level three or more times the upper limit of normal), hepatic impairment (serum aspartate aminotransferase or alanine aminotransferase level, ≥4.0 μkat/L [240 U/L]; alkaline phosphatase level, ≥11.50 μkat/L [690 U/L]); and/or total bilirubin level, ≥6.0 mg/dL), life expectancy of <14 days, prior participation in the study, and use of macrophage colony-stimulating factor or granulocyte transfusions.

All participating centers had institutional review board approval of the protocol. Written informed consent was obtained from all patients or from the parent or legal guardian of minors.

Study Design

This was a randomized, double-blind multicenter trial. At enrollment, patients were grouped by age and concurrent use of cyclosporine or tacrolimus: group 1 (adults [16 years of age or older] receiving the agents), group 2 (adults not receiving the agents), group 3 (children [2 years of age or older and younger than 16 years of age] receiving the agents), and group 4 (children not receiving the agents). At each center and within each of these groups, patients were randomized equally to receive either 4.0 mg of intravenous ABCD/(kg·d) (Amphotec [amphotericin B cholesteryl sulfate complex]; SEQUUS Pharmaceuticals, Menlo Park, CA) or 0.8 mg of intravenous amphotericin B/(kg·d) (Fungizone; Bristol-Myers Squibb, Princeton, NJ). Each study site and enrollment group had its own randomization table. At enrollment, investigators contacted the sponsor (SEQUUS Pharmaceuticals) with the eligibility information and group designation; the site pharmacist was then given the randomization assignment. Blinding was simplified by the similar clear yellow appearance of the study drugs.

Patients received the study drug until an end point was reached: an absolute neutrophil count of >500/mm^3 for 48 hours, identification of an infection thought to be the cause of fever, toxicity leading to study drug discontinuation, or a maximum of 14 days of therapy. Exceptions to study drug discontinuation because of recovery of neutrophil count were made at institutions where empirical amphotericin B therapy is discontinued when absolute neutrophil counts are >1,000/mm^3 or where stable, afebrile pediatric patients with absolute neutrophil counts of ≥200/mm^3 are routinely discharged. After study drug discontinuation, patients could receive continued antifungal therapy at the discretion of their physician.

Complete physical examinations and the following laboratory evaluations were performed at baseline, every 3 days during study drug therapy, and at the end of the study: determination of complete blood cell count and serum electrolyte levels, liver and renal function tests, blood cultures, and urinalysis with microscopic examination. Other cultures, radiographic studies, and aspiration or biopsy of suspicious lesions were performed as clinically indicated.

All patients were required to have a follow-up evaluation for detection of suspected or documented fungal infection 7 days after the last dose of the study drug. Patients who received at least seven doses of the study drug and/or discontinued study drug therapy because of an adverse event underwent follow-up evaluations 2, 3, and 4 weeks after study drug discontinuation. Survival was followed up through 4 weeks after the last dose of the study drug.

Drug Administration

After randomization, patients received a 10-mL test dose of the study drug (4 mg of ABCD or 0.8 mg of amphotericin B) that was administered from a prepared solution over 15–20 minutes. If this dose was tolerated, the patient received premedications (acetaminophen and diphenhydramine) before receiving the first therapeutic dose over 4 hours. Infusion-related chills and fever were treated symptomatically. If infusion-related toxicity occurred, hydrocortisone and meperidine could be added to subsequent premedication regimens. Therapy could be discontinued because of severe or recurrent infusion-related reactions.

Study drug administration was interrupted because of any moderately severe toxicity attributable to the study drug. Treatment was resumed if the degree of toxicity lessened, but if toxicity persisted or recurred, study drug therapy was discontinued. Therapy was discontinued because of any severe toxicity possibly or probably caused by the study drug. At the investigator’s discretion, therapy could also be discontinued because of an increase in the serum creatinine level to ≥133 μmol/L (≥1.5 mg/dL) or a doubling of the level from baseline.

Efficacy Evaluation

Eligible patients who received no concomitant systemic antifungal therapy, received at least 7 days of the study drug,
and/or reached a study end point at any time during study drug administration were evaluable for efficacy.

A successful treatment outcome included all of the following criteria: survival for \( \geq 7 \) days after the last dose of the study drug, lack of suspected or documented fungal infection during the study and within 7 days of the last dose of the study drug, lack of study drug discontinuation because of adverse events, and lack of fever on the day of discontinuation of therapy. Fever (temperature, \( \geq 38.0 ^\circ \text{C} \)) that occurred during or within 2 hours of study drug or blood product administration was considered infusion- or transfusion-related. Defervescence was defined as an absence of fever for 48 hours. Sustained defervescence was defined as an absence of fever for 48 hours with no recurrence before the end of study drug administration. Documented fungal infections were defined as described previously [5, 7], but the determination of suspected fungal infections was left to the discretion of the investigator.

Safety Evaluation

All patients who received any amount of the study drug were evaluated for safety. Renal toxicity was defined as any of the following: a doubling in the serum creatinine level from baseline, an increase of 88 \( \mu \text{mol/L} \) (1.0 mg/dL) in the serum creatinine level from baseline, or a \( \geq 50\% \) decrease in the calculated creatinine clearance from baseline during study drug administration. Patients for whom therapy was prematurely discontinued and who did not experience renal toxicity before discontinuation were classified as having no renal toxicity.

Statistical Analysis

The sample size determination was based on the incidence of renal toxicity in the adult enrollment groups. It was estimated that 50\% of patients receiving amphotericin B therapy would experience renal toxicity. Therefore, 60 evaluable patients in each enrollment group (30 per treatment arm), with an 80\% power and a two-sided \( P \) value of .05, would detect a decrease of 35\% in the occurrence of renal toxicity in ABCD recipients. Enrollment to the study was to be stopped once 120 evaluable adult patients (the population more likely to develop renal toxicity) completed the trial.

Treatment differences were tested by using the Cochran-Mantel-Haenszel test [8] after controlling for enrollment group. Time-to-event data were analyzed by means of stratified log-rank tests (stratified by enrollment group). In addition, two-sided 95\% confidence intervals for treatment difference in proportions of successful outcome, defervescence, and sustained defervescence were constructed. All statistical tests were two-sided.

Results

Patient Demographics

A total of 213 patients was enrolled in the study, and 196 patients were evaluable for efficacy. Seventeen patients (eight ABCD recipients and nine amphotericin B recipients) were not evaluable because of study drug discontinuation before reaching a study end point or because of receipt of concomitant systemic antifungal therapy. Six children younger than the age of 2 were enrolled as protocol exceptions.

Demographic and baseline characteristics of evaluable patients are outlined in table 1. There were no significant differences in baseline parameters between the two treatment arms, controlling for enrollment group. For groups 1 and 3, the median baseline cyclosporine dose was 2.86 mg/kg (range, 0.60–11.34 mg/kg) for ABCD recipients and 2.87 mg/kg (range, 0.61–20.16 mg/kg) for amphotericin B recipients. Only four patients received tacrolimus therapy.

The median daily dose of amphotericin B was 4.0 mg/kg for ABCD recipients and 0.8 mg/kg for amphotericin B recipients. The median cumulative dose for ABCD recipients (1,884 mg) was approximately fivefold greater than that for amphotericin B recipients (380 mg). The median duration of treatment for all patients who received study drug was 8.0 days (9.0 days for ABCD recipients and 7.5 days for amphotericin B recipients).

Treatment Outcome

Follow-up information for three ABCD recipients was incomplete; therefore, 193 patients were evaluable for response (table 2). A successful response was noted in 49 (50\%) of 98 ABCD recipients and in 41 (43.2\%) of 95 amphotericin B recipients (\( P = .31 \), controlling for enrollment group). The 95\% confidence interval for treatment difference was \(-7.2 \) to 20.9, where the lower bound was within 10\%. The rates of successful outcome associated with ABCD and amphotericin B in each enrollment group were comparable (data not shown). There was also no significant difference between treatment groups in the percentage of patients who had defervescence, the median number of days to defervescence, and the occurrence of sustained defervescence. In addition, there were no significant differences in the percentage of patients who became afebrile by days 7 and 14 or in the percentage who had sustained defervescence on those days (data not shown).

Of all patients who received treatment, 32 (15 ABCD recipients and 17 amphotericin B recipients) had suspected or documented invasive fungal infection during study drug administration or within 7 days of the end of treatment. Fourteen (14.3\%) of 98 evaluable ABCD recipients had suspected or documented fungal infection. Three infections were documented: in each case, blood or catheter tip cultures were positive for Candida species from 1 to 4 days after the last dose of ABCD. Eleven patients were considered to have suspected fungal infection because of an abnormal finding on a chest radiograph.

Fourteen (14.7\%) of 95 evaluable amphotericin B recipients had suspected or documented fungal infection. Three of these infections were documented, and all occurred while the patient was receiving amphotericin B treatment: yeast structures were
Table 1. Demographic and baseline characteristics of evaluable patients in a trial comparing ABCD and amphotericin B as empirical treatment for neutropenia and fever.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD (n = 42)</td>
<td>AmB (n = 38)</td>
<td>ABCD (n = 33)</td>
<td>AmB (n = 36)</td>
</tr>
</tbody>
</table>
| No. (%) of males | 27 (64) | 25 (66) | 24 (73) | 18 (50) | 3 (38) | 4 (67) | 12 (67) | 8 (53) | .28*
| No. (%) of females | 15 (36) | 13 (34) | 9 (27) | 18 (50) | 5 (63) | 2 (33) | 6 (33) | 7 (47) | .28*
| No. (%) with underlying condition | | | | | | | | |
| Allogeneic BMT | 31 (74) | 28 (74) | 3 (9) | 3 (8) | 7 (88) | 4 (67) | 2 (11) | 0 |
| Autologous BMT | 10 (24) | 7 (18) | 8 (24) | 6 (17) | 0 | 0 | 3 (17) | 5 (33) |
| Allogeneic PBSC | 1 (2) | 2 (5) | 0 | 0 | 0 | 0 | 0 | 0 |
| Autologous PBSC | 0 | 0 | 2 (6) | 4 (11) | 0 | 0 | 7 (39) | 3 (20) |
| Leukemia | 0 | 1 (3) | 17 (52) | 20 (56) | 1 (13) | 1 (17) | 5 (28) | 7 (47) |
| Other | 0 | 0 | 3 (9) | 3 (8) | 0 | 1 (17) | 1 (6) | 0 |
| No. (%) with graft vs. host disease at baseline | | | | | | | | .47¹
| Grade 0 or 1 | 29 (69) | 26 (68) | 3 (9) | 2 (6) | 5 (63) | 4 (67) | 2 (11) | 0 |
| Grade 2 | 1 (2) | 2 (5) | 0 | 0 | 0 | 1 (17) | 0 | 0 |
| Grade 3 or 4 | 0 | 1 (3) | 0 | 0 | 0 | 0 | 0 | 0 |
| NA | 12 (29) | 9 (24) | 30 (91) | 34 (94) | 3 (38) | 1 (17) | 16 (89) | 15 (100) |
| ANC (/mm³) | | | | | | | | .91* |
| ≤100 | 35 (83) | 34 (92) | 26 (79) | 30 (86) | 8 (100) | 6 (100) | 18 (100) | 14 (93) |
| >100–1,000 | 6 (14) | 2 (5) | 5 (15) | 5 (14) | 0 | 0 | 0 | 1 (7) |
| >1,000 | 1 (2) | 1 (3) | 0 | 0 | 0 | 0 | 0 | 0 |
| % with fluconazole use within 1 w of enrollment | 98 | 100 | 70 | 67 | 50 | 50 | 67 | 40 | .40* |
| Median baseline creatinine level (mg/dL) | 0.90 | 0.90 | 0.90 | 0.90 | 0.40 | 0.35 | 0.40 | 0.40 | .74* |
| % with aminoglycoside use | 38 | 47 | 52 | 67 | 75 | 83 | 56 | 60 | .14* |
| Mean maximum temperature (°C) at baseline | 38.5 | 38.6 | 38.8 | 39 | 39.4 | 39 | 39.1 | 38.8 | .82³ |

NOTE. Two AmB recipients had missing ANCs and WBC values at baseline and are not included. Of the remaining 194 patients, 101 had a missing ANC at baseline; therefore, their WBC count was used. Abbreviations: ABCD = amphotericin B colloidal dispersion; AmB = amphotericin B; ANC = absolute neutrophil count; BMT = bone marrow transplant; CMH = Cochran-Mantel-Haenszel; group 1 = adults receiving cyclosporine or tacrolimus; group 2 = adults not receiving cyclosporine or tacrolimus; group 3 = children receiving cyclosporine or tacrolimus; group 4 = children not receiving cyclosporine or tacrolimus; NA = not applicable or not available; PBSC = peripheral blood stem cell transplant.

* CMH general association test, controlling for enrollment group.
² CMH row mean scores test, controlling for enrollment group.

noted upon biopsy of skin lesions in one case, esophageal and colonic lesions associated with fungal forms were found in one, and *Aspergillus flavus* was isolated from a biopsy specimen from a skin lesion adjacent to an indwelling catheter in one. Eleven patients had radiologically suspected pulmonary fungal infection.

Of the 28 evaluable patients with suspected or documented fungal infection, 11 of 14 ABCD recipients and eight of 14 amphotericin B recipients had undergone bone marrow transplantation. There were no significant differences between treatment arms in the incidence of fungal infection, controlling for enrollment group (data not shown).

Eighty-four patients (42 ABCD recipients and 42 amphotericin B recipients) prematurely discontinued study drug therapy because of the following reasons: nonfungal cause of fever (3 ABCD recipients and 2 amphotericin B recipients), suspected or documented fungal infection (12 ABCD recipients and 12 amphotericin B recipients), adverse events (18 ABCD recipients and 20 amphotericin B recipients), other infection as cause of fever at baseline (4 ABCD recipients and 5 amphotericin B recipients).
Table 2. Response of evaluable patients by treatment group in a trial comparing ABCD and amphotericin B as empirical treatment for neutropenia and fever.

<table>
<thead>
<tr>
<th>Response</th>
<th>ABCD</th>
<th>AmB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>49/98 (50)</td>
<td>41/95 (43.2)</td>
<td>.31*</td>
</tr>
<tr>
<td>Fungal infection¹</td>
<td>14/98 (14.3)</td>
<td>14/95 (14.7)</td>
<td>.84*</td>
</tr>
<tr>
<td>Documented fungal infection</td>
<td>3/98 (3.1)</td>
<td>3/95 (3.2)</td>
<td>1.00¹</td>
</tr>
<tr>
<td>Defervescence</td>
<td>54/101 (53.5)</td>
<td>55/95 (57.9)</td>
<td>.63*</td>
</tr>
<tr>
<td>Median no. of d to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>defervescence (range)</td>
<td>7.0 (1–20)</td>
<td>5.0 (1–14)</td>
<td>.58³</td>
</tr>
<tr>
<td>Sustained defervescence</td>
<td>34/101 (33.7)</td>
<td>38/95 (40)</td>
<td>.41*</td>
</tr>
</tbody>
</table>

NOTE. Only evaluable patients for whom all data were available are included. Patients who prematurely discontinued therapy and had not had defervescence before the end of study participation were considered febrile. Unless stated otherwise, data are no. of patients with response/total no. (%). Abbreviations: ABCD = amphotericin B colloidal dispersion; AmB = amphotericin B. * Cochran-Mantel-Haenszel general association test, controlling for enrollment group. ¹ Documented or suspected during study drug administration or within 7 days of study drug discontinuation. ³ Fisher’s exact test.

Table 3. Summary of data on renal safety in a trial comparing ABCD and AmB as empirical treatment for neutropenia and fever.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>ABCD (n = 43)</td>
<td>AmB (n = 43)</td>
<td>ABCD (n = 34)</td>
<td>AmB (n = 35)</td>
<td></td>
</tr>
<tr>
<td>Median change in serum creatinine level (mg/ dl) from baseline to EOT</td>
<td>0.40</td>
<td>0.80</td>
<td>0.20</td>
<td>0.50</td>
<td>0.22</td>
</tr>
<tr>
<td>% change in serum creatinine level</td>
<td>43</td>
<td>88</td>
<td>29</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>No. (%) of patients with renal toxicity during treatment</td>
<td>13 (30)</td>
<td>29 (67)</td>
<td>4 (12)</td>
<td>11 (31)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Median change in serum potassium level (mM) from baseline to EOT</td>
<td>−0.20</td>
<td>−0.40</td>
<td>0.05</td>
<td>−0.15</td>
<td>−0.28</td>
</tr>
</tbody>
</table>

NOTE. Only evaluable patients for whom both a baseline serum creatinine level and at least one subsequent value were obtained. ABCD = amphotericin B colloidal dispersion; AmB = amphotericin B; EOT = end of therapy; NA = median not achieved. * Cochran-Mantel-Haenszel general association test, controlling for enrollment group.
photererin B recipients. However, the percentage increase in the alanine aminotransferase level from baseline to the end of treatment ($P = .006$) was greater for ABCD recipients than for amphotericin B recipients.

All but one of the 213 enrolled patients received at least one dose of premedications before study drug administration. Premedications were used more frequently by ABCD recipients than by amphotericin B recipients. For example, in group 1, the mean duration of premedication use for ABCD recipients was 6.7 days and it was 6.1 days for amphotericin B recipients. The $P$ value for treatment difference for the entire population (controlling for fungal therapy, trials such as the current one would require duration of premedication use for ABCD recipients was .068.

Most patients reported one or more adverse events possibly or probably related to the study drug (99% of ABCD recipients and 92% of amphotericin B recipients, $P = .014$). All adverse events reported by $\geq$10% of subjects in either treatment arm were analyzed. Chills were noted in 87 (79.8%) of 109 ABCD recipients and in 68 (65.4%) of 104 amphotericin B recipients ($P = .018$).

Twenty-nine patients had adverse events classified as hypoxia during the study. Sixteen patients (13 ABCD recipients [one of whom was a child] and three amphotericin B recipients, $P = .013$) reported hypoxic events that were possibly or probably related to the study drug. Of these patients, 12 ABCD recipients had documented oxygen saturation of <90%, as did all three of the amphotericin B recipients. Most hypoxic episodes (11 ABCD recipients and all three amphotericin B recipients) were temporally associated with rigors and fever and required treatment with supplemental oxygen and other medications. All episodes resolved, but one amphotericin B recipient and five ABCD recipients were withdrawn from the study as a result of these events.

Adjustment in cyclosporine dose during study drug administration was assessed for groups 1 and 3. In group 1, the cyclosporine dose was adjusted for 16 (38%) of 42 ABCD recipients and for 14 (33%) of 43 amphotericin B recipients; in group 3, adjustments in cyclosporine dose were made for seven (88%) of eight ABCD recipients and for five (71%) of seven amphotericin B recipients ($P = .45$, controlling for enrollment group). There were also no significant differences in the frequency with which cyclosporine doses were changed for patients at risk for graft-vs-host disease (GVHD) [9] or in the worsening of the GVHD grade (from baseline to 28 days after study assessment) between the two treatment arms (data not shown).

Mortality was assessed from the first dose through 28 days after the last dose of the study drug. Twenty-nine patients died (16 ABCD recipients and 13 amphotericin B recipients); most (59%) died $\geq$7 days after the last dose of the study drug. Two patients (one ABCD recipient and one amphotericin B recipient) died due to documented fungal infection. The death of one patient (an amphotericin B recipient with hypokalemia who died of arrhythmia) was possibly related to the study drug.

Discussion

This double-blind, comparative trial demonstrated no significant difference in therapeutic response to ABCD and amphotericin B in the empirical treatment of patients with neutropenic fever. Renal toxicity associated with ABCD was significantly less frequent than that associated with amphotericin B for both adults and children, but infusion-related reactions and hypoxic events were more common in ABCD recipients than in amphotericin B recipients.

This study was designed as a pilot trial of renal safety for neutropenic patients and does not address the incidence of fungal infection as a primary end point. Because current practice dictates that amphotericin B be included in empirical antifungal therapy, trials such as the current one would require many hundreds of patients to detect modest differences in the relatively low incidence of predicted fungal infections [2, 3]. However, the rates of suspected or documented fungal infections, defervescence, and overall therapeutic response in the two treatment arms of this trial were similar. It is likely that ABCD has an efficacy similar to that of amphotericin B in the empirical antifungal treatment of patients with fever and neutropenia, but this finding cannot be stated definitively.

This study provides convincing evidence that the renal safety profile of ABCD is better than that of amphotericin B. The availability of an effective agent with the broad-spectrum antifungal activity of amphotericin B in a form that can be given with better renal safety has implications for the management of fever and neutropenia. Currently, the initiation of empirical amphotericin B treatment may be delayed for patients with mild to moderate renal insufficiency, and frequent adjustments in amphotericin B dose or schedule for patients with evolving or existing renal insufficiency may impair antifungal efficacy, as well as that of aminoglycosides, cyclosporine, and other medications. These management problems may be ameliorated with a less nephrotoxic agent like ABCD.

In theory, stable renal function during the preengraftment period of bone marrow transplantation should lead to fewer adjustments in cyclosporine dose and to a reduction in the incidence and/or grade of GVHD at a later time. However, analysis of these variables did not reveal a difference in the occurrence of GVHD between the two treatment arms, despite significantly reduced renal dysfunction associated with ABCD administration.

The incidence of infusion-related chills and respiratory distress associated with ABCD was greater than that associated with amphotericin B. Review of the hypoxia episodes revealed a strong correlation with typical infusion-related reactions to amphotericin B, such as fever and chills or rigors. Although most patients (63%) with hypoxic episodes had coexisting pulmonary abnormalities, no clear predictor of respiratory distress due to ABCD or amphotericin B could be discerned.

Respiratory distress characterized by wheezing and shortness of breath is a known complication of amphotericin B infusions. The increased incidence among ABCD recipients may reflect the fivefold higher dose of amphotericin B that was given to patients randomized to receive ABCD therapy. A trial administering 2 mg of ABCD/(kg · d) (one-half the dose used in this trial) is underway to examine this question further. However, dose may not be
the only factor in these infusion-related events: a recently com-
pleted clinical trial [10] involving febrile, neutropenic patients
demonstrated that the frequency of chills and hypoxic events
among patients randomized to receive treatment with another
lipid-associated amphotericin B product was lower than that
among patients randomized to receive conventional amphotericin
B therapy. That lipid product was also administered at five times
the dose of conventional amphotericin B (3 mg/[kg·d] vs. 0.6
mg/[kg·d], respectively), although dose adjustment was permitted
when adverse events occurred.

A cost-effectiveness analysis was not performed during this
study. The expense of new antifungal drugs is an important issue
when deciding among agents. In this regard, it is not possible to
determine if the renal safety benefit of ABCD warrants the cost
of a new formulation of amphotericin B.

In conclusion, notwithstanding the limitations found in the effi-
cacy evaluation in this small trial, ABCD appears to be as effective
as amphotericin B in the empirical treatment of patients with
neutropenia and fever. The renal safety profile of ABCD is clearly
better than that of amphotericin B, most notably for patients re-
ceiving concomitant cyclosporine therapy. This benefit must be
weighed against the greater risk of infusion-related toxicities, in-
cluding hypoxia, when reviewing options for empirical antifungal
therapy for neutropenic patients.

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References

1. Schimpff SC, Satterlee W, Young VM, Serpick A. Empiric therapy with
carbencillin and gentamicin for febrile patients with cancer and granulo-
2. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and
antifungal therapy for cancer patients with prolonged fever and granulo-
3. EORTC International Antimicrobial Therapy Cooperative Group. Empiric
86:668–72.
and nephrotoxicity of amphotericin B colloidal dispersion in experimen-
tal pulmonary aspergillosis. Antimicrob Agents Chemother 1994; 38:
518–22.
study of amphotericin B colloidal dispersion for the treatment of inva-
sive fungal infections after marrow transplant. J Infect Dis 1996; 173:
1208–15.
sion vs. amphotericin B as therapy for invasive aspergillosis. Clin Infect
Dis 1997; 24:635–42.
7. Denning DW, Lee JY, Hostetler JS, et al. NIAID Mycoses Study Group
multicenter trial of oral itraconazole therapy for invasive aspergillosis.
8. Mantel N, Haenszel W. Statistical aspects of the analysis of data from
versus-host disease in human recipients of marrow from HLA-matched
trial of AmBisome (liposomal amphotericin B) in the empirical treat-
ment of persistently febrile neutropenic patients [abstract LM-90]. In:
Program and abstracts of the 37th International Conference on Antimi-
crobial Agents and Chemotherapy (Toronto). Washington, DC: Ameri-
can Society for Microbiology, 1997.