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Aerosolized Amphotericin B Lipid Complex as Adjunctive Treatment for Fungal Lung Infection in Patients with Cancer-Related Immunosuppression and Recipients of Hematopoietic Stem Cell Transplantation

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Abstract

Aerosolized amphotericin B lipid complex (aeABLC) has been successfully used to prevent fungal disease. Experience with aeABLC as treatment of fungal lung disease is limited. We evaluated the safety and efficacy of aeABLC adjunct therapy for fungal lung disease in a retrospective study of 32 immunosuppressed adults. Acute leukemia (69%) and severe neutropenia (63%) were common. The median duration of aeABLC was 185 ± 424 days in patients who underwent allogeneic stem cell transplantation (56%). High-dose corticosteroids were administered during aeABLC in 28% of patients. Fungal lung disease was proven or probable in 41% of patients. Most patients (78%) received systemic antifungal therapy for a median of 14 ± 18 days before aeABLC. The median cumulative aeABLC dose was $1,050 \pm 2,368$ mg, and the median duration of aeABLC therapy was 28 ± 130 days. Most patients (78%) received 50 mg aeABLC twice daily. Partial or complete resolution of fungal lung disease was noted in 50% of patients. In 3 patients (9%) modest cough, mild bronchospasm, and transient chest pain with accompanying nausea and vomiting resolved completely after discontinuation of aeABLC. No patient required hospitalization for drug toxicity or had a serious (grade III or IV) drug toxicity. Treatment with aeABLC was tolerated without serious toxicity and may be considered in the setting of severe immunosuppression, cancer, and/or stem cell transplantation in patients with difficult-to-treat fungal lung disease.

Keywords

Infections; cancer; refractory fungal infection; aerosolized amphotericin B lipid complex; lung disease; hematopoietic transplantation; neutropenia

INTRODUCTION

Fungal lung infections remain a serious complication despite the availability of highly effective antifungal drugs in patients with treatment-refractory hematologic malignancies, persistent neutropenia, allogeneic hematopoietic stem cell transplantation.^{1–3} Restoration of

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immune function would improve the likelihood of achieving a favorable response to antifungal therapy. However, amelioration of the immune dysfunction associated with cancer, cancer treatment, or graft-versus-host disease is often not feasible. New methods of treating fungal disease are urgently needed for immunosuppressed patients. Fungal infection, particularly fungal pneumonia, is associated with an extremely high mortality rate approaching 100% if treatment is not successful.^{1, 4} Various strategies for promoting immune defenses are currently under investigation.^{5, 6} Examples include recombinant myeloid growth factors, Th1 cytokines, and adaptive immunotherapy.^{7–10} High-dose granulocyte transfusions to mitigate severe neutropenia in patients with opportunistic fungal infections have yielded uncertain benefits.¹¹

New modalities of treatment for invasive fungal lung disease may include novel routes of drug delivery. The lungs have a large surface area. Topical therapy to improve mucociliary function and aerosol delivery of drugs to prevent opportunistic lung infections have been successfully used for decades.¹² The use of aerosolized amphotericin B deoxycholate or aerosolized amphotericin B lipid complex (aeABLC) prophylaxis has significantly reduced the frequency of invasive fungal lung disease in patients following heart, lung, or heart-lung transplantation.^{13–17} Similarly, prophylactic aerosolized liposomal amphotericin B (AmBisome®) has been well tolerated with encouraging results in preserving lung function in patients with hematologic malignancies.¹⁸ In a study of neutropenic patients with myeloid or lymphoid cancers, prophylactic aerosolized AmBisome reduced the risk of invasive fungal lung disease by nearly 70% ($P=0.007$) compared with patients not receiving prophylaxis.¹⁹ This protective benefit of aerosolized amphotericin B was not seen in previous studies possibly because the amphotericin B deoxycholate formulation provoked undesirable inflammation of the lower respiratory tract and lungs that counteracted any potential prophylactic efficacy.^{20, 21}

The efficacy of aeABLC for the treatment of established fungal lung infections has not been determined. We previously reported that aeABLC therapy successfully resolved breakthrough pulmonary zygomycosis in a patient with profound immunosuppression.²² In the present study, we assessed the safety and efficacy of aeABLC alone or in combination with other agents in the treatment of established fungal lung disease in a cohort of severely immunocompromised patients at a National Cancer Institute-designated comprehensive cancer center.

PATIENTS AND METHODS

Study Design

A retrospective analysis of all consecutive adult patients (18 years or older) receiving aeABLC for the treatment of established fungal lung infections was conducted at the University of Texas MD Anderson Cancer Center in Houston, Texas, between November 2006 and October 2008. The study was undertaken after obtaining approval from the institutional review board. Patients were identified from the Division of Pharmacy database, and data were collected from electronic medical records. Patients were followed until any of the following conditions occurred: 1) death, 2) relapsed fungal disease or 3) end of the observation period for this study.

The Acute Physiology and Chronic Health Evaluation (APACHE) II score was assessed when aerosolized therapy commenced. All antifungal drugs administered as prophylactic, empiric, preemptive, or disease-specific therapy within 3 months of initiation of aeABLC therapy were recorded. The duration of neutropenia (<500 cells/ μ L) and treatment with systemic corticosteroids within 4 weeks of fungal disease diagnosis were documented. The toxicity of aeABLC was monitored by the nursing staff, respiratory therapists, and

consulting physicians from primary oncology/transplant and infectious diseases services. The respiratory therapy service administered the first dose when aeABLC treatment was started in an outpatient setting. Outpatients were assessed weekly for potential adverse events.

Microbiologic Evaluation

All microbiologic evaluations were performed using standard methods. When applicable, drug-susceptibility testing followed the National Committee on Clinical Laboratory Standards guidelines. Microbiologic documentation included isolation and identification of fungal species associated with invasive disease in samples obtained by bronchoalveolar or sinus lavage or by lung, sinus, skin, brain, or other tissue biopsy or fine needle aspiration when available. All blood cultures positive for yeasts and *Fusarium* species were considered to represent true fungemia.

Aerosolized ABLC

The MD Anderson Cancer Center pharmacy prepared the aeABLC formulation. A commercial ABLC preparation for intravenous use was mixed with normal saline; 10 mL of saline was used for a 50-mg antifungal dose. Small-volume jet nebulizers yielding 80% drug with less than 5- μ m particle size were used. Various systems used during the study period generated similar aerosol particle size and a similar drug-saline suspension particulate inhaled mass.²³ Patients were instructed to take a dose of an inhaled short-acting beta-2 adrenergic receptor agonist bronchodilator, such levalbuterol tartrate, prior to each dose of aerosol antifungal therapy.

Response to aeABLC

The treatment response and adverse events associated with aeABLC were determined by the treating primary hematologist or bone marrow transplant faculty, consulting infectious diseases faculty, pulmonary faculty (when present), and from institutional radiology and microbiology reports. All treatment responses, including infection resolution and progressive invasive fungal disease, were independently reassessed by the study team and the principle investigator.

Therapy with aeABLC was considered successful in patients with complete or partial clinical and radiographic “resolution” of fungal lung disease. These included, but were not limited to, resolution of cough, dyspnea, pleuritic chest pain, and evidence of disease resolution on serial CT scans of chest.^{24, 25} Partial improvement was clinical response with radiographic persistence of infection, whereas complete resolution of clinical and radiographic features of pulmonary fungal disease were regarded as complete clinical response. Therapy was considered a failure if the fungal lung disease remained unchanged or worsened clinically or radiographically despite 7 or more days of aeABLC. Adverse events were captured as reported and were not tracked prospectively. These outcomes were assessed 4 and 12 weeks after aeABLC therapy commenced.

Definitions

Definitions for possible, probable, and proven invasive fungal disease (IFD) were based on recently updated criteria outlined by the European Organization for Research and Treatment of Cancer/Mycoses Study Group.²⁴ Briefly, for probable IFD, we considered host factors and major and minor criteria as strength of evidence for diagnosis of IFD. The demonstration of tissue-invasive mold on histological examination or the presence of fungemia in patients with clinical and radiographic evidence of deep-tissue infection was considered evidence of definite infection. Radiologic diagnosis of invasive fungal lung

disease was based on well-described features including but not limited to peripheral lung nodule(s) with or without a “halo” sign.²⁵ The results of chest computed tomography (CT) scans were evaluated by a radiology specialist and review by the principal investigator. Salvage antifungal therapy was defined as treatment change required for no change in signs and symptoms including appearance on CT scan despite 7 days of initial antifungal therapy, worsening of fungal lung disease despite 7 days of antifungal therapy, or primary antifungal therapy associated with serious adverse events (National Cancer Institute grade III and IV). Serum levels of electrolytes, minerals, creatinine, and liver enzymes were assessed prior to, during, and upon cessation of aeABLC therapy. Standard definitions were used for fever, neutropenia, and high-dose corticosteroid administration (> 600 mg cumulative prednisone equivalent dose), as described elsewhere.^{7, 10} Infection-associated deaths were defined using standard criteria.⁴

Statistical Analysis

We calculated frequencies, percentages, medians, and standard deviations to summarize demographic features and disease characteristics. Univariate analysis was performed using descriptive statistical methods for continuous and discrete variables. Categorical values were analyzed using the chi-square test or Fisher exact test. Continuous variables were analyzed using a t-test; a 2-sided p value < 0.05 was considered statistically significant. A univariate analysis was first conducted with all potential covariates for success vs. failure. The multivariate analysis included all the variables that on the bivariate analysis had a p value 0.2. A multivariate backward logistic regression model was used to identify factors that predicted failure of aeABLC included the following variables: a) leukemia vs. lymphoma vs. solid-organ cancer; b) comorbidity; c) APACHE II score; d) ICU stay at onset of therapy; e) mechanical ventilation at the time aeABLC therapy commenced; f) ICU stay during therapy; g) mechanical ventilation during aeABLC therapy and h) total number of aeABLC doses given. Statistical analyses were performed using SPSS statistical software version 12.0 (SPSS, Inc., Chicago, IL) and SAS software version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients

We identified 32 patients treated with aeABLC for fungal lung infections (Table 1). Most patients had acute leukemia/myelodysplastic syndrome number (69%). Nearly half (47%) had relapsed or refractory cancer. Eighteen allogeneic stem cell transplant recipients (56%) received aeABLC for a median of 185 ± 424 days ($\pm$ standard deviation) following transplantation. Severe neutropenia was common (63%), and the median APACHE II score was 15 ± 4 when aeABLC therapy commenced. High-dose steroids were administered before or during aeABLC in 37% and 28% of patients, respectively. Most patients (78%) were treated with broad-spectrum antifungal drugs prior to receiving aeABLC (median duration: 14 ± 18 days).

Fungal Disease

Characteristics of the fungal lung infections are summarized in Table 2. Probable or proven fungal lung infections were noted in 13 patients (41%). In two patients with candidemia, aeABLC was administered for probable mold fungal lung disease.

Treatment and Outcome

All patients received concurrent systemic antifungal therapy (Table 3). Most patients received aeABLC twice daily. Systemic antifungal therapy included an echinocandin drug

alone (22%) or in combination with mold-active triazole (31%) or lipid amphotericin B preparation (28%).

Clinical and radiographic resolution of fungal disease occurred in 16 patients (50%), none of whom had evidence of fungal lung infection recurrence during a median of 213 ± 189 days of follow-up. Seven patients (22%) died of their fungal disease and/or cancer, and aeABLC therapy was discontinued a median of 77 ± 184 days prior to death in this group. Nine other patients (28%) who failed therapy had stable fungal disease. In these patients, aeABLC therapy was given for a median of 30 ± 176 days. Modest cough, mild bronchospasm, transient chest pain, nausea, and vomiting in 3 patients (9%) resolved completely after aerosolized therapy was discontinued. Treatment with aeABLC was not restarted in these patients. There were no indications of systemic absorption of aeABLC, and electrolyte abnormalities, worsening renal or hepatic function, or evidence of myelosuppression did not occur (Table 3). No patient required hospitalization for drug toxicity or had a serious (grade III or IV) drug toxicity.

Univariate and Multivariate Analyses

Results of univariate analysis are summarized in Table 4. Treatment failures were associated with medical comorbidities ($P = 0.06$), shorter intervals between aeABLC therapy and hematopoietic stem cell transplantation (< 100 days; $P = 0.03$), shorter duration of aeABLC therapy ($P = 0.04$), initiation of aeABLC therapy in the intensive care unit ($P = 0.01$), and the use of mechanical ventilatory support ($P = 0.03$). A higher median cumulative corticosteroid dose prior to ($P = 0.06$) and during aeABLC therapy ($P = 0.1$) was common in patients who failed aeABLC therapy, but a longer duration of systemic steroids was associated with treatment success ($P = 0.05$).

Multivariate logistic regression analysis showed that treatment failure was associated with initiation of aeABLC in the intensive care unit (odds ratio, 14; 95% confidence interval, 1.47–133; $P = 0.02$). No other covariate included in the analysis was significantly associated with failure including the duration of aeABLC therapy.

DISCUSSION

Treatment with aeABLC in severely immunocompromised patients was tolerated without serious toxicity. Most patients had treatment-refractory invasive fungal lung disease. The favorable response in 50% of our patient population was encouraging. It was interesting that a shorter course of treatment with aeABLC significantly increased the risk of failure. However, the only factor that significantly increased probability of treatment failure was initiation of aeABLC therapy in the intensive care unit.

The published data on the safety and efficacy of aerosolized amphotericin B or its lipid preparations in the treatment of established fungal lung disease are from reports based on a limited numbers of patients.^{22, 26} For example, two non-immunocompromised patients with liposomal amphotericin B-resistant necrotizing pseudomembranous *Aspergillus* tracheobronchitis responded to extended therapy with inhaled amphotericin B deoxycholate plus granulocyte-macrophage colony-stimulating factor and interferon-gamma.²⁶ We reported on a favorable response to aeABLC therapy in a patient who had refractory leukemia that relapsed following allogeneic stem cell transplantation and who developed life-threatening caspofungin-breakthrough pulmonary zygomycosis.²² These cases are of interest but do not provide satisfactory information regarding the safety and efficacy of aerosolized antifungal therapy for the treatment of fungal lung disease.

Aerosolized amphotericin B deoxycholate and aeABLC are both effective in preventing fungal disease in the respiratory tract following lung transplantation, although aeABLC is better tolerated.^{27, 28} Similarly, in patients undergoing allogeneic stem cell transplantation, aeABLC has a favorable toxicity profile and provides reasonable protection from fungal lung disease.²⁹

We used aerosolized polyene-based drug therapy in our patients only after conducting an exhaustive review of the published literature on the safety, distribution kinetics, and antifungal potency in immunocompromised animals. In particular, aerosolized amphotericin B showed promising results in animal models of *Aspergillus* lung infections.^{30, 31} Drug composition is known to influence the effectiveness of aerosol drug therapy. In one study, a 6-fold higher lung concentration was achieved in animals given aeABLC than in those given aerosolized amphotericin B deoxycholate.³¹ Furthermore, a dose-dependent survival up to 100% in animals given aeABLC beginning 2 days prior to lung infection with *Aspergillus* species encouraged the use of ABLC over amphotericin B deoxycholate via aerosolized delivery.³²

The choice of drug delivery platform can have a substantial impact on particulate size, thus influencing the distribution and deposition of antimicrobial agents to desired regions in the respiratory tract and/or lungs.³³ In prophylaxis, antifungal drugs are often delivered as liquid aerosols generated by air-jet (pneumatic) nebulizers, which use energy provided by compressed gas flow.³³ In contrast, the new-generation ultrasonic nebulizers with new vibrating mesh devices use electricity to vibrate a piezoelectric crystal at a high frequency delivering 4 times more drug to the lungs than jet nebulizers. Pneumatic systems yield adequate pulmonary deposition of drugs in ambulatory patients, whereas in patients receiving ventilator support, drug deposition by pneumatic nebulizers has been less optimal.^{34, 35} This may partially explain the higher failure rate among patients receiving assisted mechanical ventilation (Table 4), because pneumatic systems used during mechanical ventilation may have been inadequate in delivering the antifungal drug to terminal respiratory tract and lung tissue. The new-generation pneumatic nebulizers such as AeroEclipse that generate aerosol using higher gas flow (7–8 l/min compressed air) have been associated with 2-fold higher deposition of drug in the lungs compared with standard air-jet nebulizers, with the result being that nearly 10% of inhaled ABLC is deposited in the lungs.³⁶ Pulmonary deposition of drugs is further improved by ultrasonic nebulizers, which yield 2 to 3 times higher drug concentrations compared with pneumatic nebulizers.³⁷ Future clinical trials using highly efficient air-jet or ultrasonic nebulizers may reduce drug wasting and improve drug concentrations at the pulmonary infection site.³⁸

One potential limitation of this study, that is inherent in all non-randomized retrospective reviews, includes a risk of selection bias. It is possible that only patients considered likely to have a favorable outcome were given aeABLC. Delayed cumulative benefit of prior systemic antifungal therapy may have played a role in favorable outcomes observed during aeABLC. In addition, we did not include a control group. However, these factors were not likely to have a serious impact on the results of our study because we included patients with multiple predictors for unfavorable outcome, as underscored in Tables 1 and 4, and it is difficult and likely unethical to include a control group of patients who do not receive potentially life-saving salvage therapy for a universally fatal disease.

An exhaustive review of known and possible risk factors for adverse treatment outcomes was conducted prior to conducting this study. All aeABLC-associated adverse events documented by nursing staff, respiratory therapists, and primary and consulting physicians were monitored to follow the most immediate treatment-related adverse events, such as cough, bronchospasm, and hypoxemia. Long-term toxicity and reasons for discontinuation

were obtained from physician and allied health care provider clinic notes and nursing notes from telephone conversations and clinic visits. In our experience with invasive fungal lung disease in severely immunosuppressed patients who have failed conventional systemic antifungal therapy, a delayed spontaneous resolution of infection due to a cumulative antifungal drug response is seldom noted. The size of our cohort of severely immunocompromised patients further strengthens our observations.

In conclusion, our data show that adjunctive treatment with aeABLC was tolerated without serious toxicity and may be considered in the setting of severe immunosuppression, cancer, and/or stem cell transplantation in patients with difficult-to-treat fungal lung disease. Further prospective studies are needed to assess the efficacy of aeABLC as primary and salvage therapy for refractory pulmonary mycoses.

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Table 1

Characteristics of patients, disease, and prior therapy in 32 patients treated with aeABLC for fungal lung disease

Characteristic	No. patients (%) ^a
Age, median $\pm$ standard deviation [range], years	56 $\pm$ 15 [21–72]
Sex, male	17 (53)
Cancer	
Acute leukemia or myelodysplastic syndrome	22 (69)
Chronic leukemia	2 (6)
Lymphoma	5 (16)
Solid-organ cancer	3 (9)
Cancer status during aeABLC therapy	
Relapsed or refractory	15 (47)
Chemotherapy prior to aeABLC therapy	
Median duration $\pm$ standard deviation, days	49 $\pm$ 144
Hematopoietic stem cell transplantation prior to aeABLC therapy	18 (56)
Median interval $\pm$ standard deviation, days ^b	185 $\pm$ 424
Comorbidity during aeABLC therapy	21 (66)
Diabetes mellitus	8 (25)
Renal failure	13 (41)
Systemic corticosteroid prior to invasive fungal disease	21 (66)
Median cumulative dose $\pm$ standard deviation, mg	820 $\pm$ 1481
>600 mg prednisone equivalent steroid dose	12 (37)
Median duration of therapy $\pm$ standard deviation, days	10 $\pm$ 14
Systemic corticosteroid during aeABLC therapy	21 (66)
Median cumulative dose $\pm$ standard deviation, mg	331 $\pm$ 1212
>600 mg prednisone equivalent steroid dose	9 (28)
Median duration of therapy $\pm$ standard deviation, days	10 $\pm$ 30
APACHE II score during aeABLC therapy, median $\pm$ standard deviation	15 $\pm$ 4
Severe neutropenia prior to invasive fungal disease ^c	20 (63)
Median duration of neutropenia $\pm$ standard deviation, days	53 $\pm$ 56
Absolute neutrophil count, median $\pm$ standard deviation, cells/ μ L ^d	1345 $\pm$ 4120
Creatinine at start of aeABLC therapy, median $\pm$ standard deviation, mg/dL	1.0 $\pm$ 0.6
Creatinine at end of aeABLC therapy, median $\pm$ standard deviation, mg/dL	1.0 $\pm$ 0.5
Prior systemic antifungal therapy	25 (78)
Lipid amphotericin B plus anti-mold triazole	2 (6)
Lipid amphotericin B plus echinocandin	9 (28)
Lipid amphotericin B plus anti-mold triazole plus echinocandin	7 (22)
Anti-mold triazole plus echinocandin	7 (22)
Median duration of prior antifungal therapy $\pm$ standard deviation, days	14 $\pm$ 18

^aData are number of patients (%) unless otherwise indicated.

^b Interval from transplantation to diagnosis of invasive fungal disease.

^c Severe neutropenia was absolute neutrophil count < 500 cells/ μ L.

^d At start of aeABLC therapy.

Table 2

Diagnosis and etiology of invasive fungal disease in patients treated with aerosolized ABLC

Diagnosis/fungus	No. patients (%)
Possible fungal pneumonia	19 (59)
Probable fungal pneumonia	9 (28)
Definite fungal pneumonia and sinusitis ^a	2 (6)
Disseminated fungal disease and fungemia plus lung disease	2 (6)
Microbiologic identification of fungi ^b	12 (37)
<i>Aspergillus</i> sp.	7 (22)
<i>Fusarium</i> sp.	2 (6)
<i>Rhizomucor</i> sp.	1 (3)
<i>Scedosporium prolificans</i>	1 (3)
Basidiomycete	1 (3)

^aTwo patients had proven tissue invasive *Aspergillus* and *Fusarium* species infection.

^bIsolated from bronchoalveolar lavage, and/or blood cultures and/or biopsy tissue specimens

Table 3

Aerosolized ABLC (aeABLC) and concurrent antifungal drugs used to treat fungal lung infections in 32 patients

Antifungal drugs	No. patients (%) ^a
AeABLC	32 patients
50 mg twice daily ^b	25 (78)
Median cumulative dose $\pm$ standard deviation, mg	1,050 $\pm$ 2,368
Median duration of aeABLC $\pm$ standard deviation, days	28 $\pm$ 130
Concurrent antifungal drugs	
Systemic liposomal amphotericin B preparation plus echinocandin ^c	9 (28)
Anti- <i>Aspergillus</i> triazole such as voriconazole or posaconazole	6 (19)
Anti- <i>Aspergillus</i> triazole ^c plus echinocandin ^d	10 (31)
Echinocandin ^d	7 (22)

^aData are number of patients (%) unless otherwise indicated.

^bSeven patients (22%) received aeABLC 50mg once daily

^cVoriconazole, posaconazole.

^dCaspofungin, micafungin, or anidulafungin.

Table 4

Univariate comparison of characteristics in patients in whom aeABLC failed versus those in whom aeABLC resulted in a response^a

Characteristic	Failure n=16	Resolution of IFD n=16	P value
Age, median $\pm$ s.d. [range], years	57 $\pm$ 16 [21–72]	55 $\pm$ 16 [31–68]	0.9
Sex, male	9 (56)	8 (50)	0.7
Cancer			
Leukemia or MDS	11 (69)	13 (81)	0.1
Lymphoma	2 (13)	3 (19)	0.1
Solid-organ malignancy	3 (19)	0	0.1
Cancer status during aeABLC			
Relapsed or refractory	8 (50)	7 (44)	0.7
Comorbidity during aeABLC	13 (81)	8 (50)	0.06
Renal failure	13 (81)	8 (50)	0.06
Plus DM, CHF, COPD	9 (56)	4 (25)	NC
Plus DM and CHF	3 (19)	3 (19)	NC
Plus COPD or CHF	1 (6)	1 (6)	NC
Chemotherapy prior to aeABLC, median interval $\pm$ s.d. [range]	33 $\pm$ 103 [1–319]	67 $\pm$ 176 [11–649]	0.4
Stem cell transplantation prior to aeABLC	9 (56)	9 (56)	1
Median interval $\pm$ s.d. [range]	76 $\pm$ 132 [5–317]	258 $\pm$ 513 [32–1367]	0.03
Allogeneic graft	8 (89)	9 (100)	1
Myeloablative conditioning	3 (33)	2 (22)	0.6
Corticosteroid prior to aeABLC	12 (75)	9 (56)	0.4
Median cumulative dose $\pm$ s.d. [range]	1407 $\pm$ 1737 [50–3963]	674 $\pm$ 754 [67–2594]	0.06
High-dose steroids ^b	7 (58)	5 (56)	1
Median duration of therapy $\pm$ s.d. [range]	7 $\pm$ 14 [1–31]	27 $\pm$ 15 [1–42]	0.5
Corticosteroid during aeABLC	11 (69)	10 (63)	1
Median cumulative dose $\pm$ s.d. [range]	900 $\pm$ 1481 [238–4838]	210 $\pm$ 465 [40–1530]	0.1
High-dose steroids ^b	6 (55)	3 (30)	0.4
Median duration of therapy $\pm$ s.d. [range]	7 $\pm$ 14 [1–31]	27 $\pm$ 15 [1–42]	0.05
APACHE II score, median $\pm$ s.d. [range]	16 $\pm$ 4 [9–23]	13 $\pm$ 4 [7–20]	0.1
Severe neutropenia prior to aeABLC	10 (63)	10 (63)	1

Characteristic	Failure n=16	Resolution of IFD n=16	P value
Median duration $\pm$ s.d. [range]	75 $\pm$ 55 [8–150]	42 $\pm$ 59 [14–210]	0.5
Median ANC during aeABLC $\pm$ s.d. [range], k/uL	2821 $\pm$ 5317 [0–17,444]	1110 $\pm$ 1310 [0–4180]	0.03
Lymphopenia prior to aeABLC ^c	13 (81)	11 (69)	0.7
Median duration $\pm$ s.d. [range], days	90 $\pm$ 1085 [3–3990]	33 $\pm$ 67 [10–240]	0.3
Median ALC during aeABLC $\pm$ s.d. [range], k/uL	740 $\pm$ 633 [40–2040]	730 $\pm$ 657 [130–2590]	0.7
Serum creatinine			
Start of aeABLC, median $\pm$ s.d. [range], mg/dL	1.2 $\pm$ 0.6 [0.2–2.0]	1.0 $\pm$ 0.5 [0.5–2.2]	0.7
End of aeABLC, median $\pm$ s.d. [range], mg/dL	0.9 $\pm$ 0.5 [0.2–1.7]	1.2 $\pm$ 0.6 [0.6–2.5]	0.08
Decrease or stable during therapy	10 (63)	5 (31)	0.1
Median decrease $\pm$ s.d. [range], at the end of aeABLC therapy, mg/dL	0.50 $\pm$ 0.51 [0.2–1.4]	0.20 $\pm$ 0.26 [0.1–0.6]	0.3
Prior systemic antifungal therapy	14 (87)	11 (69)	0.4
Anti-mold triazole	1 (4)	1 (9)	NC
ABLC plus triazole	0	1 (9)	NC
ABLC plus echinocandin	5 (36)	3 (27)	NC
Triazole plus echinocandin	4 (29)	1 (9)	NC
Triple antifungal drugs ^c	4 (29)	5 (45)	NC
Median duration of prior antifungal therapy $\pm$ s.d. [range]	21 $\pm$ 23 [3–92]	35 $\pm$ 16 [5–59]	0.7
Fungal disease symptoms prior to antifungal therapy, median $\pm$ s.d. [range]	23 $\pm$ 28 [1–90]	31 $\pm$ 24 [2–77]	0.9
aeABLC therapy			
Median duration $\pm$ s.d. [range]	10 $\pm$ 17 [2–70]	26 $\pm$ 56 [2–219]	0.04
Median total number of doses $\pm$ s.d. [range]	19 $\pm$ 33 [2–140]	30 $\pm$ 181 [11–713]	0.2
Median cumulative dose $\pm$ s.d. [range]	950 $\pm$ 1657 [100–7000]	1400 $\pm$ 38,489 [210–155,650]	0.3
Invasive fungal disease			
Probable and/or proven	7 (44)	6 (37)	1
ICU at start of aeABLC	8 (50)	1 (6)	0.01
Median duration $\pm$ s.d. [range]	12 $\pm$ 6 [8–24]	32	NC
Mechanical ventilation	7 (44)	1 (6)	0.03
Median duration $\pm$ s.d. [range]	11 $\pm$ 6 [8–24]	32	NC
Alive at last follow-up	1 (6)	13 (81)	0.0001
Last follow-up after aeABLC, median $\pm$ s.d. [range]	3 $\pm$ 27 [0–106]	213 $\pm$ 205 [0–605]	0.001

Abbreviations: s.d.: standard deviation; NC: not calculable; DM: diabetes mellitus; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; ICU, intensive care unit.

^aData are number of patients (%) unless otherwise indicated. All durations are in days and drug doses are given in milligrams.

^b>600 mg prednisone equivalent steroid dose; cells/ μ l

^cAnti-mold triazole plus echinocandin plus systemic lipid amphotericin B preparation