Efficacy and Toxicity of Caspofungin in Combination with Liposomal Amphotericin B as Primary or Salvage Treatment of Invasive Aspergillosis in Patients with Hematologic Malignancies

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BACKGROUND. Caspofungin (CAS) as salvage therapy for refractory invasive aspergillosis (IA) had a response rate of 45% among a heterogeneous group of patients. The use of CAS with other agents is appealing given its unique mechanism of action. Therefore, the authors retrospectively evaluated the efficacy and toxicity of CAS plus liposomal amphotericin B (LipoAMB) in patients with documented (definite or probable) or possible IA.

METHODS. Patients were evaluable for outcome if they received CAS/LipoAMB for at least 7 days. Patients who received CAS and LipoAMB sequentially were excluded. All patients were evaluable for toxicity. Outcome was assessed weekly and at the end of therapy. Stable disease and progression were considered treatment failures.

RESULTS. Forty-eight patients with documented ($n = 23$) or possible ($n = 25$) IA were identified between March 2001 and December 2001. The majority of the patients (65%) received CAS/LipoAMB as salvage therapy for progressive IA despite 7 or more days of previous LipoAMB monotherapy. The overall response rate was 42%. No significant toxic effects were seen. Factors associated with failure at the end of therapy were documented IA ($P = 0.03$), significant steroid use before the study ($P = 0.02$), and duration of combination therapy for less than14 days ($P = 0.01$). The response rate in patients with progressive documented IA was low (18%).

CONCLUSIONS. The CAS/LipoAMB combination is a promising preemptive therapy for IA and was generally well tolerated. This combination might have limited benefit as salvage therapy for documented IA. ***Cancer* 2003;98:292–9.**

KEYWORDS: caspofungin, liposomal amphotericin B, combination therapy, aspergillosis.

Invasive aspergillosis (IA) is a leading cause of infectious death in patients with hematologic malignancies.[1,2] Pneumonia is the most frequent clinical manifestation of this opportunistic mycosis.[1] The efficacy of current antifungal therapies against IA is suboptimal. The disease has a mortality rate of 60–80% among patients with acute leukemia and among bone marrow transplant (BMT) recipients.[1–3] The availability of promising new agents that have different mechanisms of action,[4] such as the echinocandins and new generations of triazoles, has received renewed interest. In particular, the clinical validity of novel combinations that, when administered either con-

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comitantly or sequentially, result in additive or synergistic effects[5] is an important focus of ongoing investigations.[6]

Caspofungin (CAS) is a novel echinocandin that inhibits cell wall biosynthesis, an essential fungus-specific drug target.[4,7] This drug has shown promise as salvage therapy for documented IA and has been approved for the treatment of documented IA in patients whose disease is refractory to or who are intolerant of other therapies (i.e., amphotericin B [AMB], liposomal AMB [LipoAMB], and/or itraconazole).[8] Whether CAS performs best as monotherapy or as part of a combination therapy regimen for IA remains to be determined. For example, there is preclinical evidence that the echinocandins augment the efficacy of AMB against *Aspergillus* species.[9–13]

Since CAS became available in March 2001, it has been used in combination with LipoAMB for primary or salvage therapy for proven, probable, or possible IA in our leukemia and BMT patients. Consequently, we have evaluated retrospectively our initial experience regarding the efficacy and toxicity of this combination in patients with IA.

MATERIALS AND METHODS

We identified 101 patients who received the combination of CAS and LipoAMB from March to December 2001 in The University of Texas M. D. Anderson Cancer Center (MDACC) pharmacy database. We extracted the following information from their medical records: age, gender, underlying malignancy, BMT type (autologous or allogeneic), presence of graft versus host disease (GVHD), presence of pulmonary or extrapulmonary diseases, degree of lung involvement (unilateral vs. bilateral disease), severity of the underlying immunosuppression (e.g., duration and degree of neutropenia, steroid use within 1 month of the initiation of the combination), and recovery from neutropenia. Patients were considered in two groups: combination therapy given initially (primary therapy) and CAS added to LipoAMB when the latter drug was considered to be ineffective alone. The global response was assessed at the end of therapy (EOT) by the principal investigator (D. P. K.). If the subject continued to receive long-term antifungal therapy, the global response assessment was made immediately before the time at which the investigator considered the goal of further therapy to be secondary prophylaxis. In cases of possible IA (fungal pneumonia based on the clinical and radiologic picture without histopathologic or culture confirmation), we excluded patients who had a concomitant pulmonary or systemic documented infection that could confound the evaluation of the response. Patients were evaluable for efficacy if they received the CAS/LipoAMB combination for at least 7 days. All of the patients who received the combination for at least 1 day were evaluated for toxicity.

Definitions

The IA cases were defined as proven, probable, or possible according to the guidelines recently published by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases (EORTC/MSG criteria).[14] For probable and possible IA cases, we recorded the strength of evidence for the diagnosis as evidenced by the number of host factors and major and minor clinical criteria. De novo IA was defined as an infection in the absence of previous antifungal therapy. Breakthrough IA was defined as an infection in a patient receiving systemic prophylactic antifungals with known activity against *Aspergillus spp.* (e.g., itraconazole, AMB deoxycholate, or LipoAMB) for at least 7 days before the onset of IA. The EOT was defined as the point of discontinuation of the CAS/LipoAMB combination by the primary physician based on evidence of progressive infection or a satisfactory response with the completion of the combination. Progressive IA was defined as clinical and radiologic progression of the infection after at least 7 days of systemic antifungal therapy. Response was defined as the resolution or major improvement of symptoms and signs of IA (including radiologic changes on chest X-rays or computed tomography [CT] scans, if available) and as the requirement of no further systemic antifungal treatment as judged by the treating physician. Failure was defined as the deterioration or a lack of significant improvement of these same parameters (including death of the subject or drug withdrawal with evidence of infection still present) after 7 days of therapy. Invasive aspergillosis was considered a contributory cause of death if there was histopathologic involvement of a major organ at autopsy and antemortem evidence of severe dysfunction of the affected organ or, when an autopsy was not performed, if a microbiologically documented infection was present at the time of death. Patients who died of other causes during therapy were considered to have responded to CAS/LipoAMB if the signs and symptoms of IA had resolved before death or if there was no evidence of infection at autopsy (if performed).

The combination of CAS/LipoAMB was defined as concomitant administration of both agents (each started within 72 hours of the other) for at least 7 days. Caspofungin was given intravenously as a 70-mg loading dose on Day 1 followed by a daily dose of 50 mg,

whereas LipoAMB was given at a dose of 5 mg/kg per day as initial therapy. The two drugs were infused at different times each day. Unanticipated side effects were defined as an adverse experience not expected to occur based on the clinical safety profile of each of the antifungals (CAS, LipoAMB) included in the combination therapy as described in its product information. Patients with a serum creatinine level equal to or greater than 2.5 mg/dL were considered to have mild to moderate renal insufficiency. Neutropenia was defined as an absolute polymorphonuclear cell count less than 1000/μL, whereas severe neutropenia was defined as an absolute polymorphonuclear cell count less than 500/μL.

Statistical Analysis

Descriptive and inferential statistics were obtained for the parameters associated with success or failure. For categoric data, we used the Fisher exact text. For numerical data, we used the Student *t* test and the Wilcoxon rank sum test. We also used logistic regression analysis with stepwise backward elimination to determine multiple discriminators between the CAS/LipoAMB combination and predictors of response. Significance was assigned for *P* values of 0.05 or less. No adjustments were made for multiple comparisons. All analyses were performed using the SAS/STAT software program (Version 8; SAS Institute Inc., Cary, NC).

RESULTS

Of the 101 consecutive patients who received CAS and LipoAMB during the study period, 53 were not evaluable for the following reasons: sequential but not concomitant use of the 2 drugs (n = 31), pneumonia that was attributed to a bacterium or virus (n = 10), other fungal disease (n = 7), a noninfectious cause of pulmonary infiltration (n = 3), lack of failure of initial monotherapy with LipoAMB (n = 1), and the use of a combination of 3 antifungal drugs (n = 1). Table 1 shows the characteristics of the 48 evaluable patients. Thirty-one patients (65%) had CAS added to LipoAMB for progressive IA (documented in 17 patients, possible in 14 patients) and 17 patients (35%) received the combination as initial therapy for IA (documented in 6, possible in 11 patients). The median duration of LipoAMB therapy before the addition of CAS was 9 days (range, 7–35 days). Almost one-half of the patients were given the combination for documented IA (definite in 5 patients, probable in 18 patients). Of the 25 patients with possible IA, 5 (20%) had 1 host factor criterion plus 1 major criterion, whereas the remaining 20 patients (80%) had 1 host factor criterion plus 2 minor clinical or radiologic criteria as outlined by the EORTC/MSG definitions (Table 1).

TABLE 1
Characteristics of Patients who Received the Combination of Caspofungin and Liposomal Amphotericin B for Documented or Possible Invasive Aspergillosis (n = 48)

Characteristic	Total no. (%)
Documented IA	23/48 (48)
Definite	5/23 (22)
Probable	18/23 (78)
Possible IA[a]	25/48 (58)
Indication for combination	
Progression on LipoAMB	31/48 (65)
Definitive/probable	17/31 (55)
Possible	14/31 (45)
Primary therapy	17/48 (35)
Definitive/probable	6/17 (35)
Possible	11/17 (65)
Median age, ys (range)	56 (3–75)
Gender (male/female)	24/24
Underlying disease	
Leukemia[b]	35/48 (73)
Myeloma/lymphoma	13/48 (27)
BMT	24/48 (50)
Allogeneic	20/24 (83)
Autologous	4/24 (17)
Grade III–IV GVHD	8/20 (40)
Systemic steroids	39/48 (81)
Neutropenia at onset of treatment with CAS/LipoAMB	30/48 (63)
< 1000 PMN	8/30 (27)
500–101 PMN	12/30 (40)
< 100 PMN	10/30 (33)
APACHE II score at the onset of treatment	
≥ 16	16/48 (33)
< 16	32/48 (67)
ICU transfer at onset of combination	7/48 (15)
Need for subsequent ICU transfer	20/48 (42)
Culture positive for *Aspergillus spp.*	23/48 (48)
A. fumigatus	7/23 (30)
Other *Aspergillus*[c]	14/23 (61)
Polyfungal *Aspergillus* pneumonia[d]	2/23 (9)
Chest X-ray/CT findings	
Diffuse infiltrates at onset	36/48 (75)
Unilateral focal infiltrate at onset	12/48 (25)
Breakthrough IA	33/48 (69)
PMN recovery	17/30 (57)
Median length (days) of combination therapy (range)	20 (7–180)
Median duration (days) of LipoAMB monotherapy (range)	9 (7–35)
Total mortality	17/48(35)

IA: invasive aspergillosis; LipoAMB: liposomal amphotericin B; BMT: bone marrow transplant; GVHD: graft vs. host disease; CAS: caspofungin; PMN: polymorphonuclear leukocytes; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; CT: computed tomographic scan.

[a] Five patients had at least 1 host factor criterion plus 1 major criterion, whereas 20 patients had 1 host factor criterion plus 2 minor clinical or radiologic criteria.

[b] Acute myelogenous leukemia in 19 patients, chronic lymphocytic leukemia and chronic myelogenous leukemia each in 5 patients each, myelodysplastic syndrome in 4 patients, and acute lymphoblastic leukemia in 2 patients.

[c] *A. terreus* in 6 patients; *A. flavus* in 5 patients; and *A. niger, A. versicolor,* and not speciated in 1 patient each.

[d] *A. fumigatus* plus *A. terreus* in one patient, *A. fumigatus* plus *A. terreus* plus *A. flavus* in one patient.

The underlying malignancy in the majority of the patients was leukemia (acute myelogenous leukemia [AML] in 19 patients, chronic lymphocytic leukemia and chronic myelogenous leukemia in 5 patients each, myelodysplastic syndrome in 4 patients, and acute lymphoblastic leukemia in 2 patients). The median age of the patients was 56 years (range, 3–75 years) and they were divided evenly by gender. One-half of the patients were BMT recipients (allogeneic in 20 patients, autologous in 4 patients). Eight of the 20 allogeneic BMT recipients (40%) had evidence of Grade III–IV GVHD. Thirty patients (63%) were neutropenic at the onset of combination treatment, 22 (73%) of whom had severe neutropenia. Thirty-nine patients (81%) had received adrenal corticosteroids within 1 month before the onset of this treatment. Among these patients, information about the cumulative total dose of prednisone equivalent was available for 30 patients, 12 of whom (40%) had received chronic high-dose corticosteroids (more than 600 mg of cumulative prednisone equivalent).

Of the 30 patients with neutropenia, 47% had neutrophil recovery during the course of treatment using CAS/LipoAMB. Fifty-six percent of the patients either were in the intensive care unit (ICU) at the onset of treatment using the combination regimen (7 patients) or had to be transferred to the ICU later due to their infection (20 patients). Thirty-three percent of the patients had an Acute Physiology and Chronic Health Evaluation (APACHE II) score equal to or higher than 16 at the onset of their therapy. In addition, of the 23 patients with microbiologically documented IA, 14 (61%) had IA due to the presence of a species other than *Aspergillus fumigatus*. More than one *Aspergillus spp.* was recovered from two patients. Invasive aspergillosis was considered a breakthrough infection during administration of systemic antifungals with activity against *Aspergillus spp.* in 33 of the 48 patients (69%). All of the patients had pulmonary IA, with 3 patients (6%) having concomitant extrapulmonary involvement. Involvement of both lungs was seen on a chest Xray or CT scan in most of the patients (75%).

The median duration of administration of the CAS/LipoAMB combination was 20 days (range, 7–180 days). The median total dose of LipoAMB administered was 8063 mg (range, 920–59,150 mg). The median follow-up period was 66 days (range, 9–452 days). Seventeen of the 48 patients died (Table 1), 4 of whom underwent an autopsy. The overall response rate was 42% (22% in patients with documented IA and 60% in patients with possible IA; Table 2). Among patients whose infection had progressed while receiving LipoAMB alone, the response rate was 57% in those with possible IA and 18% in those with docu-

TABLE 2
Outcome of the Caspofungin/Liposomal Amphotericin B Combination in Fungal Pneumonia

Characteristics	Responses (%)	*P* value	OR (95% CI)[b]
Documented IA	5/23 (22)	0.01	0.19 (0.05–0.66)
Definite	2/5 (40)		
Probable	3/18 (17)		
Possible	15/25 (60)		
Indication for combination			
Progression on LipoAMB	11/31 (35)		
Definitive/probable	3/17 (18)	0.03	0.16 (0.03–0.82)
Possible	8/14 (57)		
Primary therapy	9/17 (53)		
Definitive/probable	2/6 (33)	NS	
Possible	7/11 (64)		
Underlying malignancy			
Leukemia[a]	10/20 (50)		
Lymphoma	3/4 (75)		
BMT			
No	13/24 (54)	NS	
Yes	7/24 (29)		
Allogeneic	6/20 (30)		
Autologous	1/4 (25)		
GVHD Grade III–IV	2/8 (25)		
Steroids			
No	7/9 (78)	0.02	0.14 (0.03–0.79)
Yes	13/39 (33)		
Neutropenia			
No	9/18 (50)	NS	
Yes	11/30 (37)		
< 1000	3/8 (38)	NS	
< 500–101	5/12 (42)		
< 100	3/10 (30)		
PMN recovery			
No	5/13 (38)	NS	
Yes	6/17 (35)		
ICU at onset of treatment with CAS/LipoAMB			
No	18/41 (44)	NS	
Yes	2/7 (29)		
Need for subsequent ICU transfer			
No	16/28 (57)	0.02	0.18 (0.05–0.71)
Yes	4/20 (20)		
Aspergillus spp.			
A. fumigatus	0/7 (0)	NS	
Other *Aspergillus*	4/14 (29)		
Polyfungal *Aspergillus* pneumonia[a]	1/2 (50)		
Chest X-ray/CT findings at onset of treatment		NS	
Diffuse infiltrate	14/36 (39)		
Unilateral focal infiltrate	6/12 (50)		
Breakthrough IA			
No	9/15 (60)	NS	
Yes	11/33 (33)		
Therapy duration (days)			
< 14	1/12 (8)	0.008	0.08 (0.009–0.70)
≥ 14	19/36 (53)		

OR: odds ratio; CI: confidence interval; IA: invasive aspergillosis; LipoABB: liposomal amphotericin B; NS: not significant; BMT: bone marrow transplant; GVHD: graft vs. host disease; PMN: polymorphonuclear leukocytes; CAS: caspofungin; ICU: intensive care unit; CT: computed tomographic scan.

[a] No BMT.

[b] Each odds ratio and its 95% confidence interval was defined as the ratio of the odds of response if the risk factor was present to the odds of response if the risk factor was absent. For all statistically significant outcomes, the odds ratios and confidence intervals all are less than 1.0.

mented IA (Table 2). The EOT mortality rate was 61% (17 of /28 patients) in the nonresponders versus 0% in the 20 patients who responded to the CAS/LipoAMB combination ($P < 0.0001$). Thirteen patients remained persistently neutropenic during the study period. Five of these patients (38%) responded to the CAS/LipoAMB combination despite experiencing continuous neutropenia. A survival analysis of the time from the initiation of the CAS/LipoAMB combination to treatment failure in documented and possible IA showed that all patients who failed to respond to the combination therapy did so within the first week of therapy, regardless of the indication for combination (primary vs. salvage therapy, data not shown). Factors associated with a lack of response to the CAS/LipoAMB combination at the EOT as determined using univariate analysis are shown in Table 2. In particular, documented IA ($P = 0.01$; odds ratio [OR] for response, 0.19; 95% confidence interval [CI], 0.05–0.66), previous use of steroids ($P = 0.02$; OR, 0.14; 95% CI, 0.03–0.79), and a need for subsequent transfer to the ICU ($P = 0.02$; OR, 0.19; 95% CI, 0.05–0.71) were associated with failure of the combination therapy. The median duration of CAS/LipoAMB therapy was higher in the responders than in the nonresponders (35 vs. 17 days; $P = 0.01$). The CAS/LipoAMB combination was more successful as a primary therapy than as a salvage therapy although the response rates were not statistically significant (53% vs, 35%; $P = 0.36$). Documented IA ($P = 0.003$; OR for response, 0.07; 95% CI, 0.01–0.41) and duration of therapy (less than 14 days; $P = 0.01$; OR for response, 0.06; 95% CI, 0.006–0.56) were independent factors of poor outcome in a multivariate logistic regression analysis model.

Toxicity

Mild to moderate renal insufficiency while receiving the combination therapy developed in 7 (15%) of the 48 patients and was attributed to the use of LipoAMB. Four of these seven patients required cessation of therapy with LipoAMB. In addition, significant hypokalemia was observed in 3 (6%) of the 48 patients. One patient had fever associated with the administration of CAS, whereas another had hepatic dysfunction of multifactorial origin. In no patient was the CAS/LipoAMB combination withheld due to unanticipated side effects.

DISCUSSION

The efficacy of antifungal therapy for invasive IA is poor. Greater than 50% of all patients experience failure of first-line therapies.[1–3,15] Therefore, empirical administration of combination antifungal regimens for presumed or documented IA may be an important strategy to improve outcome for this relatively refractory mycosis. However, no prospective clinical trials to date have evaluated the use of these regimens against IA in humans.[5] This is not surprising because these studies are difficult to perform for a variety of reasons. For example, the relative infrequency of IA is a confounder of the true efficacy of antifungal combinations, as are a multitude of host factors associated with the IA (e.g., underlying conditions, subtle presentation of infection, concomitant opportunistic infections, and neutrophil recovery). In addition, the lack of reliable laboratory surrogate markers for predicting the clinical outcome of an antifungal combination, slow enrollment, expense, lack of uniform agreement about definitions/end points, and determining the optimal approved comparator of the combination are all difficult problems to resolve in a study design. Finally, and most importantly, the optimal timing of these interventions is unclear.[5]

Very few retrospective studies have tried to address combination antifungal therapy for IA. Denning and Stevens[3] reviewed 2121 cases of IA. In their study, 63 patients received a combination of AMB and flucytosine and 26 patients received a combination of AMB and rifampin. The AMB response rates in the patients who underwent treatment for more than 7 days were comparable with those of AMB in combination with either flucytosine or rifampin. Popp et al.[16] reviewed outcomes in 21 patients with definite or probable IA at Memorial Sloan-Kettering Cancer Center (MSKCC). Of the 11 patients who received combination therapy with itraconazole and AMB, 9 (82%) experienced a clinical cure, compared with 5 of the 10 patients (50%) who received only AMB. Their results suggested that the simultaneous administration of itraconazole and AMB may be beneficial. In contrast, data from our institution (MDACC) suggest that AMB/itraconazole combinations have little effect on the outcome of IA in severely immunosuppressed patients. Specifically, Hachem et al.[17] reviewed our experience with 67 patients with documented IA who had hematologic malignancies or BMT (period, 1995–1998).[17] The overall failure rate of antifungal therapy (10 or more days of treatment) in these patients was 85%.[17] No differences in outcome were noted in patients who underwent monotherapy with AMB or its lipid formulations or AMB in combination with oral itraconazole.[17]

The recent availability of CAS, a drug with promising efficacy against IA, has stimulated interest in its use in combination with other agents. Because the mechanisms of action of CAS (inhibition of cell-wall biosynthesis) and AMB (intercalation of the fungal membrane and the development of transmembrane pores differ both in terms of the site and rapidity of the

antifungal action,[4] combining these two drugs may result in potentiation of antifungal efficacy. In vitro and animal studies support this concept.[9–13] However, it may be challenging to determine whether the combination enhances the efficacy of each drug alone against human IA. For example, a comparison of the results of the salvage therapy trial that used CAS as monotherapy with the results of the combination of CAS/LipoAMB in our study is difficult for many reasons. In particular, the CAS salvage therapy trial was a multicenter study with inevitable differences in the patient population unlike our single-center experience. In the current study, patients with IA who received the CAS/LipoAMB combination had worse prognostic factors compared with the patients enrolled in the CAS salvage therapy trial. For example, 43% of our 17 patients with documented progressive IA were allogeneic BMT recipients and 55% of them had neutropenia. In comparison, only 22% and 26% of patients, respectively, in the CAS salvage therapy trial had these underlying conditions. A more meaningful comparison, despite its limitations, would be the comparison of the efficacy of the CAS/LipoAMB combination to our recent experience with the efficacy of the lipid formulations of AMB for documented IA. Another comparison would be the efficacy of the CAS/LipoAMB combination versus the analogous experience with the use of CAS in combination with AMB in other tertiary-care oncology centers that care for a large number of patients at high risk for death due to IA. The efficacy of the lipid formulations of AMB given as initial therapy in a select group of 30 patients with documented IA at MDACC in the same period (i.e., 1998–2001) was 30%.[18] In a previous study at MDACC, the efficacy of lipid formulations of AMB with or without itraconazole for the treatment of documented IA in 67 patients from 1995 to 1998 was only 16%.[17] Aliff et al.[19] reported their experience with the CAS/AMB combination in the treatment of progressive IA in 30 patients with leukemia at MSKCC, most of whom (67%) had presumed pulmonary IA. An overall favorable response was seen in 60% of the patients, which is comparable with the response rate of 57% in our cohort of patients with possible IA who received the CAS/LipoAMB combination for progressive infection.

The current study allowed the clinical assessment of the combination of CAS/LipoAMB in a relatively homogeneous patient population (all of the patients had hematologic cancer and the majority had evidence of progression of IA after at least 7 days of LipoAMB use). Our study demonstrated the spectrum of CAS use in combination for primary or salvage therapy for documented or possible IA. The indicators of poor outcome that were identified were not surprising. Documented IA carried a worse prognosis than presumed IA, perhaps because the fungal burden in documented IA is higher. It is noteworthy that the CAS/LipoAMB combination had a 38% response rate among patients with persistent neutropenia and (presumed) IA. The MSKCC group also reported success of the CAS/AMB combination therapy despite the presence of active leukemia or the administration of reinduction chemotherapy.[19] Therefore, this combination performs well in certain patient populations with poor prognostic features for response, such as patients with neutropenia or refractory leukemia. This is in contrast to the results of previous studies with the azole/AMB combination therapy at MDACC.[17] In addition, the patients who received the combination for more than 2 weeks had a better outcome in the current study. However, the bias caused by the selection of survivors of the more acute forms of IA probably undermined such an association. Finally, we confirmed the remarkable safety of CAS, even in very ill patients, and that its use in combination with LipoAMB does not result in unforeseen short-term toxic effects.

The current study had several limitations, including the fact that it was retrospective, had a relatively small number of subjects, and lacked a comparative group. The response data should be viewed with caution because the choice of the combination and decisions about duration of therapy were not controlled but made according to each physician's discretion. We did not evaluate the responses of possible IA to the CAS/LipoAMB combination in relation to concomitant changes in antibacterial therapy, which may have affected favorably the outcome or stratified responses according to the number of previously failed antifungal therapies. It is possible that some cases of possible IA were instead caused by other nonfungal pathogens. In addition, it was difficult to provide an accurate evaluation of toxicity because the entire clinical scenario was not always complete at the time of assessment. The limited number of patients who underwent autopsies did not allow us to discriminate effectively between attributable mortality of IA and all-cause mortality. Finally, our study did not provide a long follow-up duration that would allow estimation of the risk of recurrence of IA in the setting of subsequent intensification of immunosuppression or possible delayed toxicities.

Since the completion of our study, the availability of voriconazole has provided new options for the treatment of IA at MDACC. This broad-spectrum triazole has impressive activity when used as a primary or salvage therapy of IA.[20,21] However, there is no consensus yet about voriconazole being the drug of choice to treat IA.[22–25] Other antifungal combinations in the

treatment of IA that are worth future exploration include the echinocandins/triazoles. Emerging preclinical evidence suggests that combined or sequential use of these two classes of antifungal drugss might be beneficial.[26] However, the clinical data so far consist only of anecdotal case reports.[27] Whether antifungal combinations would provide a cost-effective advantage over antifungals given as monotherapy (e.g., voriconazole) is unknown because there are no data to address this important issue.

In conclusion, our results suggest that the CAS/LipoAMB combination warrants further evaluation especially as primary therapy for documented or possible IA. The results of the current study may assist in the design of future prospective studies that evaluate the clinical utility of the combination of a lipid formulation of AMB with an echinocandin. Because of the uncertainty of the probability of IA in the possible cases, it is imperative that future clinical studies in combination antifungal therapy of IA should have careful patient selection criteria and should use firm and validated definitions of what constitutes a IA infection.[14] Finally, because the cost of care for IA patients is not a trivial issue,[28] future studies should also address the cost-effectiveness of antifungal combinations. It is noteworthy that in less than a year, more than 100 patients received combination therapy at MDACC even though there were no clinical data to support this more expensive approach. These studies will provide more rational use of LipoAMB and CAS for IA.

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